Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests

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Report of the
Secretary's Advisory Committee on Genetics, Health, and Society

April 2010

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DEPARTMENT OF HEALTH & HUMAN SERVICES

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March 31, 2010

The Honorable Kathleen Sebelius
Secretary of Health and Human Services
200 Independence Avenue, S.W.
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Dear Secretary Sebelius:

In keeping with our mandate to provide advice on the broad range of policy issues raised by the development and use of genetic technologies as well as our charge to examine the impact of gene patents and licensing practices on access to genetic testing, the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) is providing to you its report *Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests*. The report explores the effects of patents and licensing practices on basic genetic research, genetic test development, patient access to genetic tests, and genetic testing quality and offers advice on how to address harms and potential future problems that the Committee identified. It is based on evidence gathered through a literature review and original case studies of genetic testing for 10 clinical conditions as well as consultations with experts and a consideration of public perspectives.

Based on its study, SACGHS found that patents on genetic discoveries do not appear to be necessary for either basic genetic research or the development of available genetic tests. The Committee also found that patents have been used to narrow or clear the market of existing tests, thereby limiting, rather than promoting availability of testing. SACGHS found that patients have been unable to obtain testing when a patent-protected sole provider does not accept particular payers, particularly state Medicaid insurance. SACGHS also found that when there is a patent-enforcing sole provider, patients cannot obtain independent second-opinion testing, and sample sharing as a means of ensuring the quality of testing is not possible. The substantial number of existing patents on genes and methods of diagnosis also pose a threat to the development of multiplex testing, parallel sequencing, and whole-genome sequencing, the areas of genetic testing with the greatest potential future benefits.

The six recommendations contained in this report identify steps that the Department of Health and Human Services could take to help address existing harms and to help eliminate potential barriers to development of promising new testing technologies. The statutory changes the Committee has proposed are narrowly tailored to directly address the identified problems without altering patent rights for therapeutics.

We appreciate the opportunity to serve you and the Department and hope the report will help you and the Department in achieving equitable access to health care and stimulating progress in health care technology.

Sincerely,

Steven Teutsch, M.D., M.P.H.
SACGHS Chair

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Over the course of the lifetime of the Task Force, technical experts from the Federal Government included Scott Bowen, Deputy Director of the National Office of Public Health Genomics at the Centers for Disease Control and Prevention; Martin Dannenfelser, then-Deputy Assistant Secretary for Policy and External Affairs at the Administration for Children and Families; Claire Driscoll, Director of the National Human Genome Research Institute (NHGRI) Technology Transfer Office; Jonathan Gitlin, a science policy analyst with NHGRI; Ann Hammersla, Director of the Division of Policy of the National Institutes of Health (NIH) Office of Technology Transfer (OTT); John LeGuyader, Director of the U.S. Patent and Trademark Office's (USPTO's) Technology Center 1600; Laura Lyman Rodriguez, Acting Director, NHGRI Office of Policy, Communication and Education; and Mark Rohrbaugh, Director of NIH OTT. In addition, Brian Stanton was a technical expert from the government until he retired and then he continued on the Task Force as an *ad hoc* member.

The Committee thanks Dr. Robert Cook-Deegan and his team of researchers at the Center for Genome Ethics, Law & Policy at Duke University, who conducted the original case studies that informed the report and provided assistance to the Committee throughout the study. Dr. Cook-Deegan's work was part of a comprehensive project conducted under the auspices of the Center for Public Genomics, a Center of Excellence in Ethical, Legal, and Social Implications (ELSI) Research supported by NHGRI. The Committee also thanks Mark Rohrbaugh and Stephen Finley of NIH OTT and consultant Lori Pressman for their efforts to examine the effects of different statutory schemes on technology development.

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Emeritus, Stanford Law School; and Christina Sampogna, Senior Project Leader for Patents and Biotechnology, Organisation for Economic Co-operation and Development.

The Committee also thanks all of the individuals and organizations that responded to the Committee's request for public comments on an earlier draft of the report (see Appendix C for a list of public commenters). The Committee carefully considered each submitted comment; this input from the public greatly helped with the development of the report and recommendations.

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PREFACE

SACGHS was first chartered in the fall of 2002 to formulate advice and recommendations on the range of complex and sensitive medical, ethical, legal, and social issues raised by new technological developments in human genetics, including the development and use of genetic tests. One of the specific issues that the charter calls on SACGHS to examine is "current patent policy and licensing practices for their impact on access to genetic technologies." Accordingly, during the development of its first study agenda in 2003-2004, the Committee identified the role that gene patenting and licensing practices may play in patient access to genetic tests as a priority issue.

SACGHS' predecessor, the Secretary's Advisory Committee on Genetic Testing (SACGT),[1] also looked into the issue of the impact of gene patents on patient access. In 2000—following consultations with representatives from the Federal Government, industry, academia and patient communities; legal experts; clinicians; and ethicists—SACGT concluded that further data and analysis were needed to determine whether certain patenting and licensing approaches (a) have adverse effects on access to and the cost and quality of genetic tests, (b) deter laboratories from offering tests beneficial to patients because of the use of certain licensing practices, (c) affect the training of specialists who offer genetic testing services, or (d) affect the development of quality assurance programs. In a letter to the Secretary of Health and Human Services, SACGT also acknowledged that gene patents can be critical to the development and commercialization of gene-related products and services. In an August 8, 2001, reply to SACGT, the Acting Principal Deputy Assistant Secretary for Health concurred with the need for additional data.

SACGHS' exploration of gene patents began in earnest in 2006 when the National Research Council (NRC) completed a study commissioned by NIH on the granting and licensing of intellectual property rights for discoveries relating to genetics and proteomics and the effects of these practices on research and innovation. The NRC report, *Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation, and Public Health,*[2] was released in fall 2005 and published in 2006.

Because of the relevance of the NRC work, SACGHS thought it best to review its findings before proceeding further. After reviewing the NRC report, SACGHS agreed with its general thrust—particularly the conclusion that although the evidence to date suggests that the number of difficulties created for researchers by human DNA and gene patenting is currently small, the complexity of the patent landscape is worrisome and may become "considerably more complex and burdensome over time."[3] SACGHS also noted the report's recommendation that Federal research funding agencies should continue their efforts to encourage the broad exchange of research tools and materials.

Since the NRC report focused on the effects of intellectual property practices on innovation and research rather than on clinical issues, SACGHS concluded that NRC's work was of limited

[1] SACGT was chartered between 1998 and 2002.
[2] NRC. (2006). *Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation, and Public Health.* Washington, DC: National Academies Press.
[3] Ibid., p. 3.

relevance to the impact of patents and licensing practices on patient access. Only one of its recommendations dealt with the clinical dimension, and that recommendation pertained to a concern about the barriers that patents and exclusive licensees might represent to the independent validation of test results—a quality issue. SACGHS decided that more information was needed regarding the effects of gene patents and licenses on patient and clinical access to diagnostic and predictive genetic tests. At its June 2006 meeting, SACGHS held an informational session on gene patents. At that meeting, SACGHS also decided to form a task force. The task force that was created was composed of SACGHS members, nongovernmental experts appointed as *ad hoc* members, and technical experts from relevant Federal agencies. The individual task force members possessed relevant expertise and diverse perspectives on the topic of gene patents and licensing.

The task force's role was to guide the development of an in-depth study assessing whether gene patenting and licensing practices affect patient and clinical access to genetic tests, and if so, how. The study involved a review of the literature, original case studies, consultations with experts, including experts on gene patent policy in other countries, and the gathering of public perspectives.

The task force presented a public consultation draft report to the full Committee for review in December 2008. The draft report summarized the Committee's findings and conclusions from the case studies, literature review, and expert consultations and presented a range of policy options for public consideration. SACGHS agreed that the draft report should be released to the public for comment. After revisions were made to the report to reflect the Committee's discussion, the consultation draft was released for comment through the *Federal Register*, the SACGHS Web site, and the SACGHS listserv. The public comment period ran from March 9, 2009, to May 15, 2009.

In summer 2009, the SACGHS task force considered the public comments and developed a revised version of the report for the Committee's consideration. The revised draft report and proposed recommendations were extensively discussed by the Committee at its October 2009 meeting. The Committee made modifications to the recommendations and, with 14 voting members present, by an overall vote of 12 to one, with one abstention, approved the six recommendations. The Committee also called for further changes to be made to the report to incorporate a more extensive discussion of the public comments received during the public consultation process and at the October meeting. The Committee also wanted revisions that would clarify the basis for the Committee's conclusions. The report was revised for presentation at the February 4-5, 2010, meeting. During the revision period, three members wrote a statement of dissent, which appears at the end of this report. At its February 4-5, 2010, meeting, the Committee unanimously approved a motion to close the report and send it forward to the Secretary of Health and Human Services.

EXECUTIVE SUMMARY

A. Introduction

The development of and equitable access to clinically useful, high-quality genetic tests has been a central concern of the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) since its first meeting in June 2003. Given this focus of SACGHS, in 2004 the Committee noted conflicting viewpoints concerning whether gene patents and licensing practices benefit or harm genetic research and genetic test development, patient access to these tests, and genetic test quality. At that time, the Committee decided to undertake a study of these issues to determine whether the weight of the evidence pointed to net benefits or net harms for patients.

In this report, "patent claims to genes" and similar expressions, such as "patents on genes," refer to claims to isolated nucleic acid molecules whose sequences correspond to human genes, mutations, fragments of genes or mutations, or intergenic DNA. The expression also refers to claims to processes for the detection of specific nucleic acid sequences. "Association patent claims" and equivalent phrases refer to claims to processes of simply associating a genotype with a phenotype.

B. Findings

In examining the effect of patents on patient access to genetic tests, the Committee recognized that patient access to a high-quality test necessarily depends upon, first, basic genetic research that generates insights into the genetic basis of particular diseases and, second, efforts to translate those discoveries into clinically useful, widely available tests. Thus, in addition to looking at how patent enforcement has directly affected patient access to tests, the Committee examined how patents and licensing practices can affect basic genetic research and genetic test development. The Committee also considered the effect of patents on test quality given the Committee's longstanding efforts to ensure that patients have access to those tests that are analytically and clinically valid. This section, thus, highlights relevant findings for these three issues: (1) the effect of patents and licensing practices on genetic research and genetic test development; (2) how patent enforcement has affected patient access to genetic tests; and (3) the effects of patents and licensing practices on the quality of genetic tests.

1. Effect of Patents and Licenses on Genetic Research and Test Development

The Committee found that the prospect of patent protection of a genetic research discovery does not play a significant role in motivating scientists to conduct genetic research. Scientists typically are driven instead by factors such as the desire to advance understanding, the hope of improving patient care through new discoveries, and concerns for their own career advancement.[4]

Although the prospect of patent protection does not significantly motivate individual scientists to conduct genetics research, this prospect does stimulate some private investment in basic genetic

[4] JM Golden. (2001). Biotechnology, technology policy, and patentability: natural products and invention in the American system. *Emory Law Journal* 50:101-191.

research. Nevertheless, the Federal Government is likely the major funder of basic genetic research.[5] Thus, patents are not needed for much of U.S. basic genetic research to occur. In addition, for that basic research that is funded privately, the investors may be motivated by the prospect of developing therapeutic applications as much, if not more so, than the potential for diagnostic applications. Therefore, the prospect of patenting therapeutic applications may be sufficient to motivate this private investment.

Importantly, the Committee found that patents can also harm genetic research. Although the patent law requirement of disclosure and description of a claimed invention is meant to expand the public storehouse of knowledge and stimulate follow-on research, there is evidence to suggest that patents on genes discourage follow-on research.[6] Moreover, patents on genes are not needed to stimulate the disclosure of research discoveries. The norms of academic science encourage disclosure of research results, and scientists have strong incentives to publish and present their discoveries.[7] Finally, patents are not needed to encourage disclosure in industry because a new health care product or service will not be accepted by the clinical community unless there is disclosure and because products such as genetic diagnostic test kits can be easily reversed engineered.

The Committee found that, although a patent or exclusive license may at times stimulate its holder to develop a genetic test, SACGHS found no cases in which possession of exclusive rights was necessary for the development of a particular genetic test, including test kits and tests for both common and rare genetic diseases. For example, more than 50 private and public entities offer testing for cystic fibrosis (CF), a common genetic disease, in the United States under a nonexclusive license.[8] Similarly, lack of exclusive rights to testing for Huntington disease, a rare genetic disease, has not discouraged more than 50 academic and commercial laboratories from developing and offering genetic testing for that disease.[9] In contrast, when exclusive rights are successfully enforced, there is only one provider of a genetic test, such as in the case of genetic testing for breast cancer (a common disease) and spinocerebellar ataxia, a rare set of disorders.

Furthermore, exclusive rights do not result in faster test development. In none of the cases studied was a patent-protected test the first to market. Rather, tests were quickly developed without patent protection by multiple laboratories and when patent rights were subsequently granted, they were used to narrow or clear the market of already-developed competition, thus limiting access.

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[5] The Federal Government is the major funder of basic research and, therefore, likely the major funder of basic genetic research. The Federal Government funded 59 percent of basic research in 2006. Science and Engineering Indicators 2008. National Science Foundation, available at http://www.nsf.gov/statistics/seind08/c4/c4h.htm#c4hs.

[6] KG Huang and FE Murray. (Forthcoming). Does patent strategy shape the long-run supply of public knowledge? Evidence from human genetics. *Academy of Management Journal*.

[7] KR Fabrizio and A Diminin. (2008). Commercializing the laboratory: faculty patenting and the open science environment. *Research Policy* 37:914-931; MA Bagley. (2006). Academic discourse and proprietary rights: putting patents in their proper place. *Boston College Law Review* 47:217-274; RK Merton (1973). The Sociology of Science.

[8] S Chandrasekharan, C Heaney, T James, C Conover, and R Cook-Deegan. (2009). Impact of gene patents and licensing practices on access to genetic testing for cystic fibrosis. Appendix A, p. C-7.

[9] NRC. (2006). *Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation, and Public Health*. Washington, D.C.: National Academies Press. p. 67. A patent covering testing for this disease has not been licensed or enforced.

In addition to examining the effects of patents and licensing practices on currently existing tests, the Committee and public commenters were concerned about the future of genetic testing, which will certainly depend on the growing capacity to analyze multiple genes simultaneously. As such, the Committee considered how patents and licensing practices will affect the development of these technologies and found that patents on genes and associations threaten the development of new and promising testing technologies—in particular, multiplex tests, parallel sequencing, and whole-genome sequencing. Because a substantial number of patents claim gene molecules or methods of associating the gene with a phenotype, developing multiplex tests and parallel sequencing will depend on acquiring rights to multiple patents on genes and associations. Similarly, developing whole-genome sequencing likely depends on acquiring multiple rights to association patents and may require rights to patents on genes. Negotiating licenses to all relevant patents would be expensive, and, under current law, there is little to prevent the holder of a needed patent from refusing to deal[10] or from charging exorbitant rates. Even if all patent holders provide a reasonably priced license, the cumulative cost of multiple licenses could make products unmarketable.

These concerns are more than hypothetical. Patents are already hindering the development of multiplex tests. Laboratories utilizing multiplex tests are already choosing not to report medically significant results that pertain to patented genes for fear of liability.

The prospect that patent holders will work together to solve these problems appears dim. Patent pools that aggregate patent rights and provide a single license to the bundled rights have been used in other areas to permit the development of technologies that infringe multiple patents. However, in the cases in which pools formed, no single patent holder could market a product without patent rights held by others. In contrast, the holder of patent rights to one critical gene or a few related critical genes can develop a test for those genes without the need for other patents on genes. As a result, questions remain concerning the likelihood that patent holders will voluntarily form a patent pool for the development of multiplex tests, parallel sequencing, and whole-genome sequencing. For the same reasons, doubts remain concerning the viability of a royalty-collection clearinghouse as a means of addressing the patent thicket in genetics.

2. Effects of Patents and Licensing Practices on Patient Access to Existing Tests

Where patents and licensing practices have created a sole provider of a genetic test, patient access to those tests has suffered in a number of ways. First, patients are unable to obtain insurance-covered access to a sole provider's test when the provider does not accept the patient's insurance. For example, participants in a particular state's Medicaid program cannot obtain covered access if the sole provider refuses to accept that particular Medicaid program. In this situation, patients have had to forgo testing because they cannot afford the test. Second, patients who desire second-opinion testing from an independent laboratory cannot obtain it when there is a sole provider. Other access problems may have occurred; in particular, the lack of availability of familial long QT syndrome (LQTS) testing during an 18-month period due to patent

[10] See *Verizon Communications Inc. v. Law Offices of Curtis V. Trinko, L.L.P.*, 540 U.S. 398 (2004).

enforcement prevented testing of any patients who needed testing for this life-threatening condition during that time.[11]

3. Effects of Patents and Licensing Practices on Test Quality

The most robust method for assuring quality in laboratory testing is through the comparison of results obtained on samples shared between different labs. Moreover, the presence of multiple laboratories offering competing genetic testing for the same condition can also lead to improvements in the overall quality of testing through innovation in developing novel and more thorough techniques of testing. Neither sample sharing nor competition is possible when an exclusive-rights holder prevents others from providing testing. As a result, significant concerns about the quality of a genetic test arise when it is provided by a patent-protected sole provider.

C. Recommendations

Based on the above findings, a majority of the Committee made the following six recommendations.[12] Three SACGHS members issued a statement of dissent from the report's conclusions and recommendations; that statement is provided at the back of this report.

Recommendation 1: Support the Creation of Exemptions from Infringement Liability

The Secretary of Health and Human Services (HHS) should support and work with the Secretary of Commerce to promote the following statutory changes:

A. *The creation of an exemption from liability for infringement of patent claims on genes for anyone making, using, ordering, offering for sale, or selling a test developed under the patent for patient-care purposes.*

B. *The creation of an exemption from patent infringement liability for those who use patent-protected genes in the pursuit of research.*

The exemption is narrowly tailored to address identified problems without altering the enforceability of gene patents for therapeutic applications. The continued ability to exclude others from therapeutic uses of these gene molecules preserves the incentive such patents create for basic genetic research and any incentive they provide for the development of therapeutics.

If enacted, the first recommended statutory change would enable multiple providers to offer tests that are currently available only from an exclusive-rights holder. Under these circumstances, a patient would have a better chance of finding at least one provider who accepts his or her health insurance. The change will also permit second-opinion testing and the sharing of samples to ensure the quality of testing.

[11] M Angrist, S Chandrasekharan, C Heaney, and R Cook-Deegan. (2009). Impact of patents and licensing practices on access to genetic testing for long QT syndrome. Appendix A, F-26.

[12] With 14 voting members present, the recommendations were approved by a vote of 12 to one, with one abstention.

The second recommended statutory change would remove the risk of liability from using patented genes in research to develop genetic tests or in basic genetic research.

The Committee also urges the Secretary to use current authority to discourage the seeking, the granting, and the invoking of any patents on simple associations between a genotype and a phenotype. As with patent claims to genes, association patent claims threaten the availability of existing genetic tests and are a significant potential barrier to the development of testing innovations, such as microarrays and whole-genome sequencing.

The Committee believes the changes described in Recommendation 1 offer the most direct way of promoting the development of high-quality genetic tests and patient access to them. Recommendations 2 and 3, below, propose changes that could be more easily implemented by the Secretary. They are intended as stopgap measures prior to any statutory changes. The remaining recommendations call for changes that would have benefits regardless of whether the statutory changes are made.

Recommendation 2: Promote Adherence to Norms Designed to Ensure Access

Using relevant authorities and necessary resources, the Secretary should explore, identify, and implement mechanisms that will increase adherence to current guidelines that promote nonexclusive licensing of diagnostic genetic/genomic technologies.

The Secretary should convene stakeholders—for example, representatives from industry and academic institutions,[13] researchers, and patients—to develop a code of conduct that will further broad access to such technologies.

Since many of the problems identified in this report are associated with exclusive licensing, greater adherence to the guidelines would avert these problems in the future.

Recommendation 3: Enhance Transparency in Licensing

Using relevant authorities and necessary resources, the Secretary should explore, identify, and implement mechanisms that will make information about the type of license and the field of use for which rights were granted readily available to the public.[14]

If this change were made, prospective test developers would be able to easily determine whether particular patent rights are available for licensing, a task that is difficult at present and represents a significant burden for test developers.

[13] Representation of academic institutions should not be limited to university technology transfer professionals, but should include academic researchers.

[14] Because of the public importance of this information, the Committee advocates that it not be regarded as suitable for protection as trade secrets.

Recommendation 4: Establish an Advisory Body on the Health Impact of Gene Patenting and Licensing Practices

The Secretary should establish an advisory body to provide ongoing advice about the health impact of gene patenting and licensing practices. The advisory body also could provide input on the implementation of any future policy changes, including the other recommendations in this report.

This advisory body would be available to receive information about patient access to genetic tests from the public and medical communities to assess whether problems are continuing and, if so, to what extent.

Recommendation 5: Provide Needed Expertise to U.S. Patent and Trademark Office (USPTO)

The Secretary should work with the Secretary of Commerce to ensure that USPTO is kept apprised of scientific and technological developments related to genetic testing and technology.

The Committee believes experts in the field could help USPTO in its development of guidelines on determinations of such matters as nonobviousness and subject matter eligibility in this rapidly changing field.

Recommendation 6: Ensure Equal Access to Clinically Useful Genetic Tests

Given that genetic tests will be increasingly incorporated into medical care, the Secretary should ensure that those tests shown to have clinical utility are equitably available and accessible to patients.

One way to achieve equitable access would be to ensure all payers include clinically useful genetic tests in their covered benefits.

I. INTRODUCTION

A. SACGHS' Longstanding Commitment to Technical Innovation and Access

The development and accessibility of validated, clinically useful genetic tests has been a central concern for SACGHS since its first meeting in June 2003. This concern has led SACGHS to explore a variety of issues that it thought to be of central importance in determining the cadences of scientific discovery and the processes by which these discoveries are transformed into effective clinical and public health interventions. Coupled with this focus on supporting technical progress, SACGHS has also had a longstanding commitment to ensure equity in the availability of useful genetic tests and services and that they act to reduce, and not exacerbate, social disparities in health outcomes.

SACGHS has long recognized the need for federal policy to facilitate the development in both the private and public sectors of new genetic technologies and their application for improving human health. Accordingly, the Committee has published a series of comprehensive reports that recommend actions the Secretary can take to eliminate barriers to the development of reliable, effective tests and access to them. Reports that concern obstacles to the development of quality genetic tests include the Committee's 2008 report on the oversight of genetic testing, in which the Committee recommended specific improvements in federal regulatory policies as part of an effort to create a favorable environment for developing and assuring the quality of new genetic technologies. Also in 2008, the Committee issued a report on the promise of pharmacogenomics, which underscored the role of federal policies in facilitating private sector development of new technologies in this rapidly growing field.

SACGHS' concern for the equitable provision of new genetic capabilities has been a primary consideration in all its deliberations and reports, and the Committee addressed this issue directly in several ways. Reports focused on access to genetic tests include the Committee's 2006 report, "Coverage and Reimbursement of Genetic Tests and Services." In that report, the Committee identified steps the Secretary could take to reduce financial barriers to access to appropriate genetic technologies. In other communications with the Secretary, the Committee has consistently underscored the importance of equitable access to genetic tests and services as a means of advancing various health-reform goals, including reducing health disparities and improving public health. The Committee has also promoted access to genetic tests by strongly supporting efforts to prevent discrimination based on genetic information and seeking ways to expand the education and training of health professionals in genetics so that these professionals will adopt and appropriately use new genetic tests and services.[15]

B. The Relevance of Gene Patents and Licensing Practices to Patient Access

Given its concerns about the development of clinically useful, reliable genetic technologies and timely, equitable access to these technologies, the Committee took note of reports in the literature discussing concerns that gene patents could create barriers that limited the development

[15] SACGHS Reports and Recommendations are posted on the SACGHS website at http://oba.od.nih.gov/SACGHS/sacghs_documents.html

of these tests, their quality, and patient access to them. The Committee also reviewed scholarly work suggesting that the dispersed ownership of gene patents might block the development of (and therefore access to) new multi-gene testing innovations. As a result, in 2004, the Committee formally identified as one of its priority topics the potential effects of patenting and licensing practices on genetic test development and patient access to genetic tests. The Committee focused on the concerns that arise after patents are issued, particularly the effect of patents on patient access. In so doing, SACGHS was also fulfilling an explicit charge within its charter: namely, examining current patent policy and licensing practices for their impact on access to genetic and genomic technologies.[16]

The importance of this priority topic has only increased in the years since 2004. During this time, genomic research has resulted in new insights into health and disease and created the potential for new genetic tests that may provide guidance to physicians in tailoring preventive strategies and treatments to individual patients. The importance of patents and licensing to the mandate of SACGHS was reaffirmed in its assessment of the most important issues confronting federal policy on genetics and, consequently, is one of the central priorities for the Committee's deliberations.[17]

Much is at stake with regard to gene patents and genetic testing, and controversy exists as to whether gene patents are promoting or blocking beneficial innovations in genetic testing and whether gene patents promote or restrict patient access to established genetic tests. Strongly held opposing viewpoints on these issues were expressed throughout the Committee's inquiry by members of the public, including clinicians, technology transfer professionals, industry representatives, and patient advocates.

The Committee recognized the controversies inherent in these issues as well as the difficulties in assessing these complex questions without more data. Therefore, a multi-pronged study plan was developed to find out whether patents and licensing practices are beneficial in promoting the development of and access to genetic tests and whether patents and licensing practices cause harms related to the quality of genetic tests, the availability of these tests to patients at reasonable prices, and the ability of clinical, research, and commercial communities to develop new or improved genetic tests.

C. A Comprehensive Analytical Approach

This study consisted of a literature review, consultation with experts, the solicitation of public comments, and original case studies. The case studies were conducted by the Center for Genome Ethics, Law & Policy, which is part of Duke University's Institute for Genome Sciences & Policy. After consultation with NHGRI's ELSI Research Program, this team was selected because it had been awarded a Centers for Excellence in ELSI Research (CEER) award by the ELSI Program of NHGRI (P50 HG 003391) to develop a Center for Public Genomics, a Center

[16] Charter for the Secretary's Advisory Committee on Genetics, Health, and Society. http://oba.od.nih.gov/oba/SACGHS/sacghs_charter.pdf

[17] See SACGHS Report on the Integration of Genetic Technologies into Health Care and Public Health at: http://oba.od.nih.gov/oba/SACGHS/SACGHS%20Progress%20and%20Priorities%20Report%20to%20HHS%20Secretary%20Jan%202009.pdf

specifically focused on research on genomics and intellectual property. With the permission of NHGRI, the researchers at the Center, led by Dr. Robert Cook-Deegan used funds from this grant to conduct the case studies. While some of the researchers involved with this project receive salaries from Duke University, their salaries did not fund any of the research for the case studies. Overall, the focus of the Duke Center's research is to gather and analyze information about the effects of publication, data and materials sharing, patenting, database protection, and other practices on the flow of information in genomics research. The Center's work on this project also served NHGRI's interest in promoting research on intellectual property issues surrounding access to and use of genetic information. In particular, NHGRI is funding research that examines the impact of laws, regulations, and practices in the area of intellectual property on both the development and commercialization of genomic technologies and derived products and access to and use of such technologies and information by researchers and the public.[18]

The Center conducted eight case studies of genetic testing for 10 clinical conditions and how exclusive rights or lack thereof has affected test development, access, and quality. The case studies were selected by the Duke group in consultation with the SACGHS gene patents task force and the full SACGHS Committee. Each case involves a Mendelian (inherited) disorder or a cluster of disorders associated with a clinical syndrome for which genetic tests are available. The case studies focused on

1. inherited susceptibility to breast/ovarian cancer and colon cancer;
2. hearing loss;
3. cystic fibrosis (CF);
4. inherited susceptibility to Alzheimer disease;
5. hereditary hemochromatosis (HH);
6. spinocerebellar ataxias (SCA);
7. familial long QT syndrome (LQTS); and
8. Canavan disease and Tay-Sachs disease.

The cases were chosen in part because they involve different and contrasting patenting strategies and licensing schemes; they also include common and uncommon conditions. They include data from the literature and other sources regarding the effect of patents and licensing practices on the cost, availability, accessibility, and quality of particular genetic tests. The case studies were peer-reviewed, and subjects interviewed for the case studies had an opportunity to review draft case study reports and to correct factual inaccuracies.

The case studies cover developments that began more than a decade ago but also include very recent events. For example, the case studies' data on the price of genetic tests comes from a survey of laboratories conducted in 2007 and 2008. The case study on LQTS covers the licensing situation before 2002 through the present. The study of access to genetic testing for hereditary breast, ovarian, and colon cancers includes events occurring as recently as 2009. The case study on Alzheimer disease covers new testing introduced in 2008. The CF case study discusses changes to medical practice in 2002, 2005, and 2006 that affect how intellectual property is used. The case study of genetic testing for hearing loss discusses business deals in 2008 and 2009 affecting intellectual property as well as the latest trends in technology platforms. The HH case

[18] ELSI Research Priorities, NHGRI website, http://www.genome.gov/10001618.

study also documented changes in licensing practices between 2002 and 2008. A compendium of the eight case studies can be found in Appendix A of this report, and a summary box for each case study appears when the case study is first mentioned in the narrative of the report.

During the course of work on the case studies, and to complement the case study approach, the Duke investigators recommended that a second study be undertaken on the impact on technology development of licensing approaches under two different statutory frameworks for patenting and licensing: the Stevenson-Wydler Act, which applies to Federal laboratories, such as the NIH intramural research program, and the Bayh-Dole Act, which applies to Federal grantees and contractors. This work is still underway but preliminary results are summarized in Appendix B, and further discussion appears later in this report. Duke University is funding the remaining work on this study through grant support.

SACGHS also gathered information and perspectives on its draft report through a solicitation of public comments that was published in the *Federal Register* and disseminated through the SACGHS Web site and the SACGHS listserv. The public consultation draft also asked for feedback on a broad spectrum of policy options, ranging from simply calling for stakeholder advocacy efforts to fundamental statutory changes that would apply to Government-owned and funded inventions as well as private-sector inventions. The statutory options themselves ranged from making no changes to a prohibition on patent claims to nucleic acid molecules relevant to human health.

A total of 77 public comments were received on the public consultation draft report. Among the commenters were 11 professional associations, 16 technology transfer offices or technology transfer professionals, five academics, five health and disease advocacy groups, two industry trade groups, nine life science companies, nine health care providers, four commercial laboratories, and 12 private citizens.

In addition to these public comments, the Committee heard presentations from experts during the course of its study to gain a broad perspective on the topic. The experts included a patent attorney from a law firm; a federal technology transfer office attorney; an attorney with a company that makes products relating to genetic testing; an academic expert in policy issues relating to patents on genes; a judge with the U.S. Court of Appeals for the Federal Circuit, a federal court that has exclusive jurisdiction over appeals in patent cases; and several academics and a representative of the Organisation for Economic Co-Operation and Development who provided information on how international bodies and foreign countries have addressed concerns about patents on genes.

All of the information gathered through this multi-pronged study afforded the Committee an expansive view of the patent landscape for genetic tests and enabled the Committee to evaluate the effects of patents and licensing practices on genetic test development, access, and quality.

D. Developing Constructive Recommendations

The SACGHS mandate is to develop recommendations considered helpful in improving federal strategies to use genetic discoveries to improve human health. Therefore, the analysis of the

benefits and harms associated with current gene patent and licensing policies was undertaken to inform the development of specific recommendations for the Department of Health and Human Services. However, before the Committee could formulate recommendations, it also had to consider patent law developments and determine whether these developments address or stand to address any identified problems. The Committee also reviewed U.S. technology transfer laws and policies to evaluate existing mechanisms for promoting a balance between access and innovation. Germane policy studies were also reviewed to evaluate the findings and recommendations of other groups. Finally, the Committee reviewed foreign patent laws to determine whether other countries' legal provisions provided a model for legal changes that could be recommended in the United States.

The recommendations in this report call for focused changes designed to minimize observed harms in patient access, to eliminate barriers to test development and testing innovations, and to preserve benefits of gene patents for the development of genetically based therapeutics. These recommendations reflect the considered judgments of the Committee based on all of the information gathered and its continued dual commitment to technical progress and equitable access to the technologies in a rapidly evolving health care environment.

E. Study Scope and Terminology Used in the Report

In previous reports, SACGHS has described the wide array of genetic tests currently in use, which rely on biochemical, cytogenetic, and molecular methods or a combination of these methods to analyze DNA, ribonucleic acid (RNA), chromosomes, proteins, and certain metabolites.[19] The scope of this study and report, however, is on those genetic tests that rely on analysis of nucleic acid molecules to determine human genotype, whether used for diagnostic, predictive, or other clinical purposes. When the term "genetic test" is used in this report, it implies the broadest definition of nucleic acid tests, such as those called "genomic tests" or even whole-genome sequencing and is not limited to the single-gene tests classically used for medical genetic diagnosis. The report does not address protein-based genetic tests or patent claims on isolated proteins.

Nor does this report explore questions about the legitimacy of granting patents on human genes or the morality of doing so—e.g., whether such patenting leads to the "commodification" of the human body. Other groups have explored this issue in depth,[20] and current court cases are pending that will address the patentability of isolated gene molecules. The Committee recognizes that many people have moral objections to gene patents, while many others see no fundamental moral issue or regard the benefits of patenting as outweighing other moral concerns.

The Committee gathered information on both *clinical access* and *patient access* to such tests. As used in this report, *clinical access* means the ability of a health care professional or laboratory to

[19] In particular, see SACGHS. (2008). U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services.

[20] Other reports have explored this issue in depth. See, for example, U.S. Congress, Office of Technology Assessment. (1989). New Developments in Biotechnology: Patenting Life-Special Report, OTA-BA-370; Nuffield Council on Bioethics. (2002). The ethics of patenting DNA; and World Health Organization. (2005). Genetics, genomics and the patenting of DNA: review of potential implications for health in developing countries.

obtain or provide genetic tests for patients. *Patient access* means the ability of a patient to obtain genetic testing.

In some sections of the report, a distinction is made between laboratory-developed tests and genetic test kits. Laboratory-developed tests are tests developed by commercial and academic laboratories for use solely in the test developer's laboratory; these tests are not sold or distributed commercially.[21] A genetic test kit is a commercial product that is developed for purchase and distribution to multiple laboratories. A laboratory that conducts its testing using a test kit purchased from a company is not using a laboratory-developed test.

Another distinction between laboratory-developed tests and test kits is that they are currently subject to different oversight schemes. Test kits are subject to premarket review by the Food and Drug Administration (FDA). Most laboratory-developed tests are not subject to FDA review. Oversight of laboratories using test kits and/or laboratory-developed tests is provided through regulations under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), except for those States that are CLIA-exempt.[22]

Sections of this report also refer to multiplex testing, which involves the simultaneous testing of multiple genetic markers in a single test. Multiplex testing can involve testing one condition involving multiple markers or testing multiple conditions, with each condition determined by one or more genetic markers. More information on multiplex testing is provided later in the report. A multiplex test could be either a laboratory-developed test or a test kit.

The phrases "exclusive rights holder" or "patent rights holder," as used in this report, refer to the party that has rights to use and enforce the patent and could be either the patent owner or the exclusive licensee.

F. Patent Law Basics and Types of Patents Associated with Genetic Tests

According to section 101 of the 1952 Patent Act, patents may be obtained for several types of inventions: processes (a series of steps "to produce a given result"[23]); machines (apparatuses[24]); manufactures (articles made from raw or prepared materials but given new forms or properties[25]); compositions of matter (synthesized chemical compounds and composite articles[26]); and "any new and useful improvement thereof [a process, machine, manufacture, or composition of matter.]"[27] In addition to showing that the invention is patentable subject matter, the inventor must demonstrate that the invention is novel, useful, and nonobvious.[28] More information on what makes an invention nonobvious is provided in a later section. A patent provides a grant of "the right to exclude others from making, using, offering for sale, or selling

[21] Examples of commercial laboratories include Myriad Genetics Laboratories and Bio-Reference Laboratories.
[22] The Secretary may exempt those states that enact clinical laboratory requirements equal to or more stringent than those required under CLIA. 42 U.S.C. § 263a(p)
[23] *Cochrane v. Deener*, 94 U.S. 780 (1877).
[24] *Nestle-Le Mur Co. v. Eugene, Ltd.*, 55 F.2d 854 (6th Cir. 1932).
[25] *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).
[26] Ibid.
[27] 35 U.S.C. § 101.
[28] These criteria are laid out in 35 U.S.C. §§ 101-103.

the invention throughout the United States or importing the invention into the United States" until 20 years after the date of the patent application.[29]

The types of patent claims that can serve as the basis for exclusive rights to a genetic test generally fall into several categories. One category is compositions of matter/manufacture claims to isolated nucleic acid molecules. The claimed isolated molecules may have sequences that correspond to human genes, mutations, and fragments of the genes or mutations. An example of such a patent is patent 5,622,829, which claims complementary DNA (cDNA) forms of various tumorigenic *BRCA1* alleles and fragments of those alleles. cDNA is DNA that has been made from the messenger RNA (mRNA) transcript of a gene. A cDNA sequence, like a mature mRNA sequence, differs from a gene sequence in that it lacks the noncoding regions of the gene. Because testing for the *BRCA1* mutated alleles typically involves using probes or primers that are fragments of those alleles, the patent holder's exclusive rights over the mutated allele fragments enables it to exclude others from performing testing. To avoid infringing these particular claims of the patent while testing for *BRCA1* mutant alleles, a test developer would have to devise a method of testing that did not use or make the claimed isolated fragments or alleles.

Patent claims to processes for the detection of particular nucleic acid sequences or mutations using probes, primers, or some other method are another category of patents that protect genetic tests. An example of a patent claim to a process or method of detecting a particular mutation associated with hearing loss is claim six of patent 5,998,147:

> A method of detecting a deletion of a guanosine at position 30 of the connexin 26 [*GJB2*] gene in a biological sample containing DNA, said method comprising:
>
> a) contacting the biological sample with a pair of oligonucleotide primers under conditions permitting hybridization of the pair of oligonucleotide primers with the DNA contained in the biological sample, said pair of oligonucleotide primers capable of amplifying a region of interest in the connexin 26 gene;
>
> b) amplifying said region of interest in the connexin 26 gene; and
>
> c) detecting the deletion of a quanosine at position 30 of the connexin 26 gene.

[29] 35 U.S.C. § 154.

Another example of a patent claim to a method of detecting a mutation is claim one of patent 5,753,441:

> A method for screening germline of a human subject for an alteration of a BRCA1 gene which comprises comparing germline sequence of a BRCA1 gene or BRCA1 RNA from a tissue sample from said subject or a sequence of BRCA1 cDNA made from mRNA from said sample with germline sequences of wild-type BRCA1 gene, wild-type BRCA1 RNA or wild-type BRCA1 cDNA, wherein a difference in the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA of the subject from wild-type indicates an alteration in the BRCA1 gene in said subject.

With patents such as these, the patent holder's exclusive rights to the method would be infringed by any genetic test that detects the designated mutation through the patented method.

Another category of patent claims that protect genetic tests are claims to processes involving simply associating a genotype with a phenotype. An example of such a patent claim is patent 5,693,470, which claims

> 1. A method of determining a predisposition to cancer comprising:
>
> testing a body sample of a human to ascertain the presence of a mutation in a gene identified as hMSH2 (human analog of bacterial MutS and Saccharomyces cerevisine MSH2) which affects hMSH2 expression or hMSH2 protein function, the presence of such a mutation indicating a predisposition to cancer.
>
> 2. The method of claim 1 wherein the sample is DNA.
>
> 3. The method of claim 1 wherein the sample is RNA.
>
> 4. The method of claim 1 wherein the sample is isolated from prenatal or embryonic cells.

The first claim, which does not specify a particular testing method, could be interpreted as giving exclusive rights to any method of testing that involves detecting the mutation and correlating it with cancer.

A significant distinction between composition of matter/manufacture claims to isolated nucleic acid molecules and method claims is that claims to molecules cover all uses of the molecule, including uses outside of diagnostics, while a claim to a method of using a molecule would not prohibit one from using that molecule for another method.

Other types of patents associated with genetic tests include claims to genetic test kits and claims to platform technologies used for genetic testing.

Throughout this report, where the Committee refers to "patent claims on genes" and similar expressions, such as "patents on genes," it means patent claims to isolated nucleic acid molecules whose sequences correspond to human genes, intergenic DNA (DNA located between genes), or mutations that occur in the human body; the phrase also refers to patent claims to methods of detecting particular sequences or mutations and claims to primers, probes, and other nucleic acid molecules useful for the detection of a particular gene, mutation, or sequence of importance. Where reference is made to "association patent claims," the Committee means patent claims upon the act of simply associating a genotype with a phenotype. Composition of matter/manufacture claims to isolated nucleic acid molecules that correspond to naturally occurring genes are commonly referred to as "gene patents," although this phrase, in some forms, can include patent claims upon the act of simply associating a genotype with a phenotype. For that reason, this report generally avoids the phrase "gene patents" in order to avoid confusion.

In some cases, a genetic test may be protected by multiple patent claims, including claims to DNA primer molecules, claims to methods of using fragment probes for mutation detection, and claims to methods involving the act of simply associating a genotype with a phenotype.

It is generally difficult if not impossible to "invent around" patent claims on genes and associations. Inventing around a technology involves making an invention that accomplishes the same thing as the original patented invention but that does not infringe the patented invention. To invent around patent claims on a gene associated with a particular disease and fragments of that gene to create a genetic test for that disease, one might use probe or primer molecules corresponding to a second gene that is also associated with the disease, but unpatented. In this way, one would in theory have avoided using the patented molecules and still accomplished the end of the first invention—testing for the disease. However, such a strategy of utilizing only freely accessible genes in a diagnostic test without the ability to use the patent-protected gene would, by definition, result in an incomplete and clinically unacceptable test since all of those individuals with the disease who have a mutation in the patented gene would go undetected and undiagnosed. For a diagnostic test to be useful, it must encompass all (or at least most) of those particular genes associated with a disorder. A test that fails to assay even one gene that can cause a given disease is, by definition, an incomplete clinical test. Moreover, given the number of existing patents protecting genes, in some cases an unpatented substitute may not be available. In other cases, a particular gene or genetic marker that is patent-protected may well be the only unique sequence related to the underlying condition, eliminating completely the possibility to invent around it. As discussed later in this report, it is also not possible to invent around patents on genes and associations by testing for unpatented genetic markers that are in linkage disequilibrium with the patented molecules. Finally, because association patent claims often claim a method of associating a particular genetic marker with a phenotype, in the absence of a substitute marker it is impossible to invent around an association patent claim.

A recent study confirms that a substantial number of patents relating to genetic testing will be difficult to invent around.[30] In that study, researchers from the Centre for Intellectual Property Rights and the Centre for Human Genetics in Belgium evaluated U.S. and European patent

[30] I. Huys, N Berthels, G Matthijs, and G Van Overwalle. (2009). Legal uncertainty in the area of genetic diagnostic testing. *Nature Biotechnology* 27:903-909.

claims relating to genetic testing to determine how many could be circumvented or invented around.[31] The researchers reviewed patents relating to the 22 inherited diseases most frequently tested for in Europe and identified 267 patent claims relating to genetic testing for these conditions.[32] For these 267 claims, 38 percent claimed methods of testing for particular conditions, 25 percent claimed isolated gene molecules, 23 percent claimed primers or probe molecules, and 14 percent claimed genetic test kits.[33]

Analyzing these 267 claims to ascertain whether they could be invented around, the researchers determined that "[n]early half of the claims can be regarded as difficult to circumvent."[34] Claims that are difficult to circumvent, according to the researchers, can only be circumvented after "a substantial investment of money and time, as well as a large amount of inventiveness."[35] Fifteen percent of the claims were considered "impossible to circumvent" or blocking, while the remaining 36 percent were considered easy to circumvent.[36] Thus, 64 percent of the patent claims were either difficult or impossible to circumvent.[37]

The researchers also found that claims to methods of testing for particular sequences were more often blocking or impossible to circumvent than claims to isolated genes.[38] In particular, for those claims directed to isolated gene molecules (25 percent of the 267 patent claims), 3 percent were impossible to circumvent and about half were difficult to circumvent. On the other hand, 30 percent of claims to methods of detecting particular sequences (38 percent of the 267 patent claims) were impossible to circumvent, and a total of 77 percent of these method claims were either difficult or impossible to circumvent.[39]

It should be noted, however, that the authors' terminology differs from that used in this report. The authors' definition of method claims, for example, includes some of the patents this report defines as claims on genes and association patent claims. Despite this difference, the researchers' finding that 64 percent of patent claims are at least difficult to circumvent is consistent with SACGHS' conclusion that patents associated with genetic tests are often difficult, and sometimes impossible, to invent around.

G. Licensing Basics[40]

Patent law does not comprehensively address licensing practices, and USPTO does not regulate licensing practices.

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[31] Ibid.
[32] Ibid.
[33] Ibid.
[34] Ibid., p. 906. Subtracting, from 100, the total percentage of patents that were either easy to circumvent or blocking indicates that, when the authors say that "nearly half" of the patents were difficult to circumvent, the exact percentage of difficult-to-circumvent patents was 49 percent.
[35] Ibid., p. 905.
[36] Ibid., p. 906.
[37] Ibid.
[38] Ibid., p. 906-907.
[39] Ibid., p. 906-907.
[40] Consultant Lori Pressman contributed much of the content in this section.

A patent does not allow or compel a patent owner to take any action whatsoever— including using the technology themselves. Rather, it grants the patent holder the right to exclude others from making, using, selling, offering for sale, or importing the invention, for a term of 20 years from the date of filing of a patent application. All patent licenses by their nature constitute an agreement that the patent holder will not exclude the licensee from practicing the claimed invention. Some patent licenses include terms requiring the licensee to practice the invention. Licenses can convey the patent owner's exclusionary right to another party in whole, in part, or not at all. The various types of licenses are discussed in more detail below.

An *exclusive-all-fields-of-use* license conveys the patent owner's exclusionary right to another party in whole. The licensee typically has the right, although usually not the obligation, to enforce the patent rights and the right to sublicense the patent rights to others. Typically, the licensor requires the licensee to use or develop the invention. An *exclusive-by-field-of-use* license conveys the patent owner's exclusionary right to one other party in a well-defined "field." A particular field can be a country, a market area, a technology, or any other mutually agreed upon term. For example, a license could be "exclusive in New Jersey," "exclusive in ophthalmology," "exclusive when the analyte is a nucleic acid," "exclusive when the analyte is a protein," "exclusive for vaccines," or "exclusive for multiplex tests that analyze 20 or more loci at once." Within the defined field, the patent holder agrees not to grant other licenses, but may grant licenses outside of the defined field. Typically, within the field, the licensee may further sublicense the patent rights. The right to enforce is negotiated on a case-by-case basis. In general, the narrower the scope of the field, the more likely the patent owner is to retain control of enforcement. *Exclusive-by-field-of-use* licenses can also contain a requirement to use or develop the invention within the field or risk losing exclusivity or the entire license.

A *co-exclusive license* restricts the number of additional licenses the patent owner can grant. Unless this license is also restricted by field, the starting assumption is that the license is for all fields. The patent holder can agree to grant no more than one, or two, or any specified finite number of additional licenses. Co-exclusivity can also be combined with field-of-use exclusivity. Generally, the licensee would have sublicensing rights, but probably not the right to enforce without coordination with the patent owner. These licenses also generally contain a requirement to use or develop the invention or risk losing license rights.

A *nonexclusive license* places no restrictions on the number of additional licenses the patent holder can subsequently grant. This license can also be restricted by field, although the starting assumption is that the license is for all fields. Typically, the licensee does not have sublicensing rights, does not have the right to enforce the patent, and there is no requirement to use or develop the invention.

Table 1 summarizes these concepts.

Table 1: Key Features of Licensing Types

License Characterization	Number of other licenses which the patent holder can grant	Requirements to use and develop the technology, or the exclusivity terminates, or the license terminates	Rights to enforce the patent against infringers	Rights to sublicense the patent
Exclusive, All Fields of Use	0	Generally Yes	Generally Yes	Generally Yes
Exclusive, By Field of Use	Within the field, 0. Outside the field, unlimited	Generally Yes	Sometimes	Generally Yes, in the Field
Co-exclusive (no additional restriction on Field)	A defined number: 3, 10, etc…	Generally Yes	Unlikely without coordination with patent holder	Probable
Nonexclusive	Unlimited	Generally No	Generally No	Generally No

Those holding patents protecting genetic tests may use any of the above licensing approaches. When a genetic test would be applicable to different diseases or could be used in multiple contexts (e.g., newborn screening and carrier screening), field of use licenses, either exclusive, co-exclusive, or nonexclusive, may be used.

Licensees often prefer exclusive licenses because they eliminate the risk of competition from other licensees. Exclusivity is seen as especially important when the licensee will be required to make considerable investments of its own to bring the product to market (or to prosecute the patent). On the other hand, a licensor might favor co-exclusive licenses where the market is so large that one licensee alone could not satisfy it or might favor licenses exclusive by field where the invention's market has multiple fields or territories. Where the market is sufficiently large, co-exclusive licenses can in fact increase introduction of a technology because multiple providers leads to competition, and competition lowers prices, improves access, and increases the size of the patent holder's market. Although market size can in theory guide licensing decisions, in reality patent holders and prospective licensees have difficulty assessing the particular market conditions their technology will face.[41]

What is given in return to receive a license varies. For example, the licensee may agree to pay a lump sum up front, based on projected benefits. In other cases, the licensee may agree to pay running royalties based on actual sales of the license-associated product or service. The licensee may also grant the licensor access to state-of-the art equipment or related technologies. A combination of payments is also possible. In still other cases, two parties may issue one another cross licenses and collaborate to develop a technology that relies on both their inventions.

[41] PW Heisey, JL King, KD Rubenstein, and R Shoemaker. (2006). Government patenting and technology transfer. USDA Economic Research Report No. (ERR-15), available at http://www.ers.usda.gov/publications/err15/.

As noted in Table 1, in exchange for granting a license, a licensor may also require the licensee to achieve certain milestones in developing the technology, with failure to reach any milestone being grounds for termination of the license; terms in the licensing contract that require the licensee to achieve such milestones are known as diligence conditions or terms. What a patent holder will accept from the licensee in exchange for granting a license can depend on the stage of development of the product. A patent holder who licenses a technology that requires considerable development to a small company usually will not require upfront payments that would hinder the company's development efforts, but will seek later royalty payments and/or a transfer of stock ownership.

II. EFFECTS OF PATENTS AND LICENSES ON PROMOTING THE DEVELOPMENT OF GENETIC TESTS

According to the U.S. Constitution, the purpose of the U.S. patent system is to promote "the progress of science and useful arts . . . ."[42] While the patent system may well fulfill that function overall, the Committee's task was to determine whether there were circumstances associated with genetic research and genetic test development that impaired the ability of the U.S. patent legal system to promote progress in this area or that rendered patents in this area unnecessary. Because patents may promote progress through three different means—by stimulating invention, disclosure, or investment in post-discovery development—this analysis had three sub-parts.

A. Patents as an Incentive for Invention

The idea that patents stimulate inventive activity is based on the premise that without patents, people would not pursue inventions, because any inventions they might create could be copied by others.[43] These copyists, or "free riders," could sell the product just as easily as the original inventor, and such competition would lower the invention's price "to a point where the inventor receives no return on the original investment in research and development."[44] The right of exclusion promised by a patent in effect reassures the would-be inventor or investor that any invention that is created cannot be copied during the patent term. Reassured in this way, the would-be inventor presumably decides to pursue invention, while the would-be investor presumably becomes willing to fund such pursuits, should outside funds be needed.

Scholars have pointed out, however, that biotechnology researchers have strong incentives to invent that are independent of patents. Academic and industry researchers, who make up the "inventor class" in genetics and biotechnology, often are motivated principally by the desire to advance understanding, help their patients by developing treatments for disease, advance their careers, and enhance their reputations.[45] Scientists'enjoyment of research and solving complex problems also naturally leads to invention.[46]

This understanding of the motivations of scientists is consistent with the findings from the case studies that appear in this report. Scientists interviewed as part of the case studies stated that they would have pursued their research even if their discoveries were not patent-eligible. For example, most of the Alzheimer disease researchers "expressed ambivalence about patenting and

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[42] *Kewanee Oil Co. v. Bicron*, 416 U.S. 470 (1974). This utilitarian view of patents "is distinct from moral arguments for patent protection advanced in some European countries . . . ." The drafters of the Constitution did not believe that "inventors have a natural property right in their inventions." RS Eisenberg. (1989). Patents and the progress of science: exclusive rights and experimental use. *University of Chicago Law Review* 56:1017-1086, p. 1025.

[43] R Eisenberg, op. cit.

[44] Ibid., p. 1025.

[45] JM Golden, op. cit. Golden acknowledges, though, that the vast majority of funding for university scientists comes from the Federal Government, which is interested in both advancing knowledge and seeing that inventions reach the public. For the latter goal, government, through the Bayh-Dole Act, encourages patenting and licensing of inventions by funded researchers.

[46] J Thursby and M Thursby. (2007). Knowledge creation and diffusion of public science with intellectual property rights. *Intellectual Property Rights and Technical Change, Frontiers in Economics Series*, Vol. 2, Elsevier Ltd.

none attributed the intensity of the races [to discover genes associated with Alzheimer disease] to patent priority. Rather, they stated that the races were driven by wanting priority of scientific discovery, prestige, scientific credit, and the ability to secure funding for additional research based on scientific achievement."[47] Nor did the prospect of a patent encourage the researcher who discovered the Tay-Sachs gene, *HEXA*, or the researchers who discovered the gene associated with CF, *CFTR*.

Box: Genetic Testing for Alzheimer Disease

Alzheimer disease (AD) as currently classified has several forms, of which two are relevant to genetic testing. A very small percentage of AD cases arise in family clusters with early onset. Familial early-onset AD (EOAD) is usually caused by an autosomal dominant mutation in one of three genes: *PSEN1* (chromosome 14), *PSEN2* (chromosome 1), or *APP* (chromosome 21). A person with one of these fully penetrant mutations will contract the disease if they live long enough, usually developing symptoms before age 60. These families are quite rare, but the 50 percent risk for each child of an affected member to carry the causative mutation means that these tests can be important for those at risk. In contrast to early onset Alzheimer Disease, variants of the *APOE* gene confer increased risk of developing the form of AD most commonly seen in the general population. Unlike the risk variants for EOAD, variants in *APOE* that confer increased risk of AD are very common in the general population.

Patents relevant to genetic testing for all four genes have been granted in the United States. The patenting landscape is complex. The *APOE* gene and mutations or polymorphisms of this gene are not patented. However, testing to predict the risk of Alzheimer disease is the subject of three "methods" patents issued to Duke University and licensed exclusively to Athena Diagnostics. The method claims are based on *APOE* genotype (both direct and indirect determinations) and "observation" of AD risk. A combination of method and composition of matter claims relating to the *PSEN1* and *PSEN2* genes have been patented and exclusively licensed to Athena Diagnostics. Athena offers genetic testing for *PSEN1*, *PSEN2*, *APP*, and *APOE*. Athena Diagnostics has sent several cease-and-desist letters[48] to laboratories offering *APOE* testing. The company charges $475 for *APOE* testing and $1,675-$2,750[49] for *PSEN1* and/or *PSEN2* testing.

Source: Case study prepared for SACGHS by the Duke University Center for Genome Ethics, Law & Policy; see Appendix A.

Box: Genetic Testing for Tay-Sachs Disease and Canavan Disease

Tay-Sachs disease and Canavan disease are both neurological autosomal recessive conditions that predominantly but not exclusively affect the Ashkenazi Jewish population. Carrier screening and genetic diagnosis for Tay-Sachs are mainly through enzyme assay, with DNA-based testing for ambiguous cases, or in situations like pre-implantation genetic diagnosis where only a DNA test is possible, or for diagnostic confirmation. DNA-based analysis is the mainstay for both screening and diagnostic confirmation of Canavan disease. Nonprofit research institutions obtained patents on both relevant genes, first the gene that when mutated causes Tay-Sachs (the *HEXA* gene encoding the enzyme hexosaminidase A) and later for Canavan disease (the *ASPA* gene encoding aspartoacylase). The inventor for the *HEXA* patent worked at the NIH laboratory and her Tay-Sachs patent was never licensed. That discovery was, therefore, effectively in the public domain, and the genetic test is broadly available. The patents relevant to Canavan disease, in contrast, were licensed by the Miami Children's Hospital, which initially enforced

[47] K Skeehan, C Heaney, R Cook-Deegan. (2009). Impact of gene patents on access to genetic testing for Alzheimer disease. Appendix A, p. B-14.

[48] In a letter submitted to SACGHS after the approval of this report, Athena Diagnostics indicated that these letters were patent notice letters.

[49] In a letter submitted to SACGHS after the approval of this report, Athena Diagnostics indicated that the price range for this test is $1,970.

its patent rights and planned to issue limited licenses. This decision was highly controversial and led to litigation in which patient advocates were plaintiffs. The lawsuit was about fair access and distribution of benefits, not commercialization per se. The patents were eventually nonexclusively licensed at least 20 times.

Source: Case study prepared for SACGHS by the Duke University Center for Genome Ethics, Law & Policy; see Appendix A.

Box: Genetic Testing for CF

Approximately 30,000 Americans have CF. It is the most common severe recessive genetic disorder among Caucasians. The disease is caused by mutations in the *CFTR* gene, which encodes a transmembrane chloride ion channel. One mutation, ΔF508, is responsible for approximately 70 percent of cases (~50 percent of CF patients are homozygous for this mutation) in Caucasian populations. Other mutations are far rarer. Mutation and carrier rates vary by ethnicity.

The University of Michigan, the Hospital for Sick Children in Toronto, and Johns Hopkins University hold patents covering *CFTR* mutations and methods for detecting them. The University of Michigan's patent portfolio includes the important ΔF508 mutation. Currently, at least 63 U.S. laboratories test for the *CFTR* gene. Testing by numerous laboratories is possible in part because the three academic institutions that hold the patents license them nonexclusively. The initial fee for kit licenses is $25,000, which has not changed in more than 15 years. The annual fees too have remained unchanged since the initial license was granted in 1993. The cost of full sequencing tests ranges from $40 to $86 per amplicon (ranging from 29 to 50 amplicons) depending on the laboratory. Mutation testing is also available on several platforms.

Source: Case study prepared for SACGHS by the Duke University Center for Genome Ethics, Law & Policy; see Appendix A.

Several public commenters also stated that scientists are motivated by concerns apart from patents. The president of PreventionGenetics wrote, "DNA patents are not needed as motivation for identification of disease genes. Nearly all disease genes are identified not by private industry, but by researchers working at non-profit institutions. These researchers are motivated primarily by competition with their peers for faculty positions at top ranked institutions, for publication space in top journals, and for grants. Profit motive from patents plays only a very minor motivational role at best."

Comments on the draft report from the pharmaceutical company Sanofi-Aventis U.S. echoed these views: "patents do not generally affect research done in this area. We agree that most of this research is done in a university/academic setting. There is a need for academic researchers to perform research and publish their work in order to obtain recognition from their colleagues and to advance their careers."

The Wisconsin Alumni Research Foundation (WARF), the intellectual property management organization for the University of Wisconsin, also agreed in its comments to the draft report that most gene discoveries are not patent-driven, pointing out that most gene discoveries arise from basic research and "are not commercially or patent driven but driven by the curiosity of individual scientists whose interest and focus is on exploring disease, health or nutritional states through observations of symptomatic conditions and the desire to trace the origins of those symptoms. Hence, it would be expected that genetic research is not patent driven."

Taken together, this information suggests that scientists are motivated to conduct genetic research by reasons other than patents, suggesting that discoveries will be sought regardless of the availability of intellectual property rights.

1. Does the Prospect of Patents Stimulate Investment in Genetic Research?

In considering whether patents promote progress by stimulating research and inventive activity, the Committee also weighed the role of patents in stimulating investment to fund such research. Several public commenters discussed the role of patents in stimulating private investment in genetics research. For example, Celera, a manufacturer of diagnostic products, wrote,

> Even though the Draft Report suggests that scientists who search for gene-disease associations may not be motivated by the prospect of receiving a patent, they cannot conduct this type of research without considerable capital and resources. In our experience, meaningful gene-disease associations are confirmed only if the initial discoveries are followed by large scale replication and validation studies using multiple sample sets, the costs of which are prohibitive for many research groups. Private investors who provide funding for such research invariably look to patents that result from such work as a way of protecting their investment.

The case studies and literature review support these commenters' assertions that patents attract investment to fund genetic research. Both the case studies and literature review reveal that when researchers or companies sought private funds to initiate or advance their genetic research, investors were willing to provide funding because of the prospect of patents being granted as a result of the research. For example, according to a policy paper, Eli Lilly agreed to fund Myriad Genetics' ongoing efforts to find genes associated with breast cancer "in return for licensing privileges for diagnostic kits and therapeutic products on *BRCA1*." [50] This agreement was based on the assumption that Myriad would in fact be the first to discover the gene and that the company would then patent the gene.[51] The rights promised to Eli Lilly would then be derived from that patent.

Box: Genetic Testing for Breast/Ovarian Cancer and Colon Cancer

Specific mutations in the *BRCA1* and *BRCA2* genes can dramatically increase patients' risks for breast and ovarian cancers in women with a family history of these cancers. Myriad Genetics holds broad U.S. patents on both of these genes and their mutations and is the sole provider of full-sequence *BRCA* testing in the United States. Because Myriad is the only testing service in the U.S. market, its practices are a *de facto* standard. In 2002, Myriad launched testing for the five most common rearrangements in the *BRCA1* and *BRCA2* genes (accounting for about a third of all rearrangements in these genes) and simultaneously began developing a test for all large rearrangements (BART®), which it launched in 2006. Myriad states that it has not enforced patents for services it does not provide (such as paraffin-embedded tissues) and that it has sublicensed *BRCA* testing to three laboratories offering pre-implantation genetic diagnosis. For *BRCA*, Myriad charged $3,120 in 2009, or $38.05 per amplicon (including separate testing for common rearrangements). A 2003 survey of laboratory directors demonstrates nine instances of patent enforcement by Myriad on its *BRCA* patents. In addition, there have been two lawsuits concerning the

[50] RE Gold and J Carbone. (2008). Myriad Genetics: in the eye of the policy storm. *International Expert Group on Biotechnology, Innovation and Intellectual Property*. p. 8.
[51] V Berridge and K Loughlin. (2005). Medicine, the market and the mass media: producing health in the twentieth century. Volume 19 of the Routledge Studies in the Social History of Medicine. p. 267

BRCA patents. Adoption by third-party payers is becoming more common.

In May 2009, a group of health professional organizations and patients sued USPTO, Myriad Genetics, and the University of Utah Research Foundation over Myriad's *BRCA1* and *BRCA2* patents.[52]

Genetic tests for hereditary nonpolyposis colorectal cancer (HNPCC) focus on three genes: *MLH1*, *MSH2*, and *MSH6*. Testing for *MLH1* and *MSH2* is protected by claims to an association between the mutated forms of the gene and HNPCC and claims to oligonucleotide probes (small nucleic acid molecules) capable of hybridizing with mutated forms of *MLH1* and *MSH2* (see patent 7,022,472). This patent has not been enforced, and there are multiple providers, both nonprofit and for-profit, including Myriad, for full-sequence tests on both genes. Some of these providers test for a third gene—*MSH6*—but whether patents protect testing for this gene is "unclear" according to the case study.

Genetic testing for familial adenomatous polyposis (FAP), another type of colon cancer, focuses on the *APC* gene. Patent 5,352,775 contains claims to the cDNA form of the *APC* gene and probes that are complementary to *APC*. This patent has been nonexclusively licensed, and Myriad and four nonprofits offer full-sequence analysis of the *APC* gene.

Although the patents associated with colon cancer genetic testing are either unenforced or non-exclusively licensed, Myriad charges more per amplicon for its full-sequence tests of HNPCC and FAP than for its full-sequence analysis of BRCA.

Source: Case study prepared for SACGHS by the Duke University Center for Genome Ethics, Law & Policy; see Appendix A.

The prospect of patents also attracted investment in Mercator Genetics, which discovered the gene associated with HH, *HFE*. According to the case study, "The prospects of patents and revenue from diagnostic testing for HH probably stimulated research at Mercator Genetics. However, Dr. Dennis Drayna, co-founder of Mercator Genetics, notes that the company was conceived and initially funded on an agenda much broader than hemochromatosis gene discovery or diagnostic testing alone."[53]

Box: Genetic Testing for HH

HH is an autosomal recessive disorder that results most often from mutations in the *HFE* gene, which regulates iron absorption. Mutations in the *HFE* gene increase the risk for developing symptomatic HH, an iron metabolism disorder that leads to excess iron absorption from the diet. Since the body lacks a natural way to rid itself of the excess iron, in the presence of *HFE* mutations, iron accumulates and can cause organ damage, particularly in the heart, liver, and pancreas. Currently, diagnosis of HH often is based on first-level biochemical tests, followed by second-level genetic testing. Biochemical methods are simple, fast, and inexpensive. Bio-Rad Laboratories holds most of the patents relating to the *HFE* gene and HH genetic testing. In 1999, Bio-Rad bought many of those intellectual property rights from Progenitor, which had retained the rights to HH genetic testing following its merger with Mercator, the company that first isolated the *HFE* gene. Mercator scientists first identified the *HFE* gene in 1995–1996, along with two gene mutations, C282Y and H63D, which were present in more than 80 percent of people with HH. In 1995 and 1996, Mercator applied for patents related to *HFE* and its mutations. Several patents were granted between 1998 and 2000 and cover the whole *HFE* gene sequence, methods for detecting the C282Y and H63D mutations in the *HFE* gene, and a test kit. Other patents in the same

[52] Judge Robert Sweet of the U.S. District Court for the Southern District of New York held in a written decision issued on March 29, 2010, that the patents-in-suit were invalid for claiming unpatentable subject matter.

[53] S Chandrasekharan, E Pitlick, C Heaney, and R Cook-Deegan. (2009). Impact of patents and licensing practices on access to genetic testing for hereditary hemochromatosis. Appendix A, p. E-3.

patent family and with the same group of inventors issued between 2000 and 2006 and were assigned to Bio-Rad. These patents included diagnostic methods for a panel of less prevalent mutations. They also covered polypeptides related to the *HFE* gene and the associated proteins. Some other patents covering additional mutations in *HFE* are not controlled by Bio-Rad but are far fewer in number than the patents controlled by Bio-Rad. Progenitor's exclusive licensing of patents to SmithKline Beecham Clinical laboratories as a sole source provider of *HFE* testing was controversial. However, since 2000, BioRad has nonexclusively licensed its patents to kit and single-gene test (Analyte-Specific Reagent, or ASR) providers.

Bio-Rad offers two HH ASRs as well, both of which provide for 24 tests at a cost of $2,016, or $84 per test. A purchase of the ASRs comes with a sublicense from Bio-Rad to perform the test. As of May 2007, the GeneTests Laboratory Directory[54] listed 37 U.S. laboratories performing targeted mutation analysis for HH. Prices for targeted mutation analysis at 17 of those 37 laboratories ranged from $125 to $467.

Source: Case study prepared for SACGHS by the Duke University Center for Genome Ethics, Law & Policy; see Appendix A.

Public comments from Axial Biotech and Juneau Biosciences, two companies pursuing the development of genetic diagnostics for, respectively, diseases of the spine and diseases that predominately affect women, also indicated that the prospect of patent protection stimulated investment into the companies' initial genetic research.

Patents can attract not only outside investment, but also can motivate established companies to invest their own existing resources in pursuing particular lines of genetic research. For example, the case study concerning colon cancer found that the prospect of patents, most likely on a therapeutic agent, motivated Human Genome Sciences to conduct genetic research involving sequencing cDNAs encoding receptor proteins.[55] Researchers at John Hopkins who were at the time searching for colon cancer genes decided to partner with Human Genome Sciences to search through the company's database of cDNAs, and the combination of Hopkins' research and the information provided by the database resulted in the discovery of the *MLH1* gene involved in colon cancer.[56]

Although these examples show that patents can stimulate private investment into basic gene-disease research, the Federal Government is the major funder of basic research and likely the major funder of basic genetic research.[57] However, definitive data on Federal Government versus private sector investment in basic genetic research are not available.

Public comments also highlighted the role that disease advocacy groups have played in funding of disease-specific genetic research and contributing needed tissue samples. The executive director of the Claire Altman Heine Foundation, an organization focused on the prevention of

[54] GeneTests Laboratory Directory can be found at http://www.ncbi.nlm.nih.gov/sites/GeneTests/lab?db=GeneTests
[55] Robert Cook-Deegan, corresponding author for "Impact of patents and licensing practices on access to genetic testing for inherited susceptibility to cancer: comparing breast and ovarian cancers to colon cancers," personal communication
[56] R Cook-Deegan, C DeRienzo, J Carbone, S Chandrasekharan, C Heaney, and C Conover. (2009). Impact of patents and licensing practices on access to genetic testing for inherited susceptibility to cancer: comparing breast and ovarian cancers to colon cancers. Appendix A, A-27. N Angier. (1994). Competing research teams find new colon cancer clue. *The New York Times*, March 17, 1994.
[57] The Federal Government funded 59 percent of basic research in 2006. Science and Engineering Indicators 2008. National Science Foundation, available at http://www.nsf.gov/statistics/seind08/c4/c4h.htm#c4h3.

spinal muscular atrophy (SMA), wrote in a public comment, "In the case of SMA, the patent holder did not even bear the financial burden of the discovery, rather an advocacy group and patients and families suffering from the disease donated funds and tissue samples to a researcher who then patented her discovery and sold it." The chief executive of Parent Project Muscular Dystrophy also indicated that an advocacy group had contributed funding for muscular dystrophy genetic research: "The patent on the dystrophin gene [the gene responsible for muscular dystrophy] was awarded to Boston Children's Hospital at the time of the discovery, made by Louis Kunkel, Ph.D., Eric Hoffman, Ph.D., and another researcher in Dr. Kunkel's laboratory. Funding was provided by the Muscular Dystrophy Association as well as private funders."

In sum, the role of patents in stimulating genetic research thus appears to be limited to stimulating private funding that is supplemental to the significant Federal Government funding in this area. Those willing to invest in the research appear to be rarely focused exclusively on diagnostics. In one case, the company hoped the research generated both a diagnostic and a therapeutic, while another company was most likely interested in only a therapeutic. Moreover, as noted in the conclusion to the prior section, the individual scientists conducting this research are strongly motivated by many factors other than patents. The role of patents in stimulating the investment of capital and resources to translate genetic research discoveries into laboratory-developed tests or test kits is discussed after the following section.

B. Patents as an Incentive for Disclosure of Discoveries

A second way that patents may promote the progress of useful arts is through the required disclosure of the new invention.[58] In exchange for the patent right of exclusion, an inventor must publicly disclose his or her invention in a manner that enables one of ordinary skill in the inventive field to make the invention.[59] Public disclosure of an invention promotes the progress of useful arts by adding to the public storehouse of knowledge.[60] Furthermore, it is assumed that the disclosure of a new invention will stimulate ideas that lead to the development of other advances.[61]

The concept that patents provide an incentive to disclose is based on the premise that if inventors could not patent their inventions, they would try to maintain them as trade secrets.[62] Such secrecy is undesirable because the public is denied new knowledge.[63] The public also might waste resources duplicating the discovery.[64] The patent system, therefore, can act to ensure that discoveries are revealed and not sequestered.

Although patents are seen as a means of ensuring disclosure, it is doubtful that inventors would keep genetic discoveries secret if they could not patent them. Academic researchers in genetics—as well as academic scientists in general—have strong incentives to publish and present their discoveries, because the norms of science encourage sharing research results, and publication is

[58] R Eisenberg, op. cit.
[59] 35 U.S.C. § 112.
[60] R Eisenberg, op. cit.
[61] *Kewanee Oil Co. v. Bicron*, 416 U.S. 470 (1974).
[62] R Eisenberg, op. cit.
[63] Ibid.
[64] Ibid.

also necessary to achieve reputational gains.[65] Furthermore, because prizes for research are based on priority of discovery, they stimulate researchers not only to disclose their discoveries, but to disclose them as early as possible. In addition, scientists funded by NIH are expected, under an agency data-sharing policy, to share and release in a timely manner "final research data from NIH-supported studies for use by other researchers."[66] (See further discussion later in this report.)

A public comment submitted by The Innovation Partnership, a nonprofit intellectual property consultancy, also cast doubt on the idea that patents promote disclosure: "The argument that patents promote progress through the required disclosure of the new invention is not substantiated by empirical evidence. Patent specifications are drafted for the specific purpose of supporting patent claims. They are thus drafted as broadly as possible while disclosing little. Most scientists admit they rarely consult patents to identify useful information. Scientifically relevant disclosures are made in scientific journals."

There are also data from the literature suggesting that patents may actually diminish the production of public genetic knowledge. For example, Kenneth G. Huang and Fiona E. Murray have found that "gene patents" negatively affect follow-on public research about those genes.[67] In their study, Huang and Murray looked at gene discoveries that were both published in an academic journal and patented.[68] They then used "publication citations to each gene paper (i.e. peer-reviewed publications citing the focal paper) as a proxy for follow-on [research and] public knowledge accumulation."[69] In particular, they examined the number of forward citations to 1,279 gene papers describing particular human genes with the number of forward citations predicted by a mathematical model of citing trends without patents.[70] After conducting the analysis, Huang and Murray found that the actual number of forward citations was 5 percent less than the number of forward citations predicted by their most stringent model.[71] The results were starker in cases where the genes were strongly linked to human disease; in those cases, the drop in public research was almost 10 percent.[72] These results suggest that gene patents can have a negative impact on follow-on public research, which results in less public knowledge than would occur if the patented genes were only published and not patented.[73]

With regard to the idea that patents are needed to discourage secrecy, Rebecca Eisenberg has pointed out that secrecy is not a viable option for many inventors, because their inventions could be reverse engineered—that is, reproduced without the benefit of the original design plans.[74] In the area of genetics particularly, Randal J. Kirk and his coauthors have observed that "trade

[65] KR Fabrizio and A Diminin, op. cit.; MA Bagley, op. cit.; RK Merton, op. cit.
[66] Final NIH Statement on Sharing Research Data, February 26, 2003.
[67] KG Huang and FE Murray, op. cit., p. 40.
[68] Ibid., p. 23-24.
[69] Ibid., p.22.
[70] Ibid., p. 26.
[71] Ibid., p. 40.
[72] Ibid., p. 38.
[73] Ibid.
[74] R Eisenberg, op. cit., p. 1029.

secret protection is largely impractical for biotechnology and genetic material due to . . . the ease with which these products can be reverse engineered."[75]

In the specific area of genetic tests, test kits could often be easily reverse engineered, while laboratory-developed tests could not be practically maintained as trade secrets. In the case of a test kit, the most common technique necessary for reverse engineering would be ascertainment of the DNA sequences of the nucleic acid components of the test kit—a process that is typically straightforward. A laboratory that uses a laboratory-developed test for its test, on the other hand, does not have a physical product that can be obtained and studied for reverse engineering. As such, the provider of a laboratory-developed test could offer a test for a genetic disease without publicly revealing the exact gene being tested. As a practical matter, however, the medical community would be unlikely to give such a test much credence without disclosure of the relevant gene, which suggests that laboratory-developed tests could not be practically maintained as trade secrets. Given that trade secret protection does not appear to be a practical option for either test kits or laboratory-developed tests, the use of patents to discourage trade secret protection of gene-disease associations seems unnecessary.

In sum, it appears that scientists have sufficient reasons independent of patents to disclose gene-disease associations and that patent claims to genes may be diminishing research that builds on disclosed genetic discoveries.

C. Patents as an Incentive for Investment in Test Development

Legal and economics scholars recognize a third possible mechanism by which patents could promote progress. According to this view, as explained by Wolrad Prinz zu Waldeck und Pyrmont, the patent system "is not so much needed to stimulate inventive activity; rather, it facilitates investment into costly and risky development processes that are necessary to transform a 'mere' invention into a marketable product."[76] Biotechnology industry representatives assert that patents in fact operate in this way, helping small biotechnology companies attract the venture capital needed to further develop promising discoveries.[77] The Bayh-Dole Act is also based on this understanding of how patents operate.[78] Although prior to the Act, individual federal agencies, including NIH and the National Science Foundation, permitted contractors to patent inventions resulting from federally funded research, the Bayh-Dole Act established a uniform policy among federal agencies that academic institutions may patent inventions arising from federally supported research and license them to companies.[79] The law was based on the

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[75] RJ Kirk, JL Hung, SR Horner, and JT Perez. (2008). Implications of pharmacogenomics for drug development. *Experimental Biology and Medicine* 233:1484-1497, footnote 8.

[76] W Prinz zu Waldeck und Pyrmont. (2008). Research tool patents after *Integra v. Merck*—have they reached a safe harbor? *Michigan Telecommunications Technology Law Review* 14:367-446, p. 372. Under this understanding of the patent system, the incentive provided by a patent operates after a patent has been issued. Conversely, any patent incentives to invent (and to fund inventive activity) and to disclose operate or exist before the patent issues. R Eisenberg, op. cit.

[77] Ibid. See also Federal Trade Commission. (2003). To promote innovation: the proper balance of competition and patent law and policy, http://www.ftc.gov/os/2003/10/innovationrpt.pdf.

[78] 35 U.S.C. § 201 et seq.; American Bar Association. (2002). The economics of innovation: a survey, http://www.ftc.gov/opp/intellect/0207salabasrvy.pdf.

[79] L Rudolph. (1994). Overview of Federal technology transfer. *Risk: Health, Safety, and Environment* (available at http://www.piercelaw.edu/risk/vol5/spring/rudolph.htm)

premise that, absent exclusive rights from licenses, companies would not invest resources to develop an invention into a product because free riders could copy the finished product.[80]

Many trade groups and university technology transfer offices that submitted public comments also stated that patents help attract the investment needed for further development of genetic discoveries. For example, the American Intellectual Property Law Association suggested that patents stimulate commercialization and public distribution of inventions.

The Biotechnology Industry Organization (BIO) expressed similar views:

> Patents play a significant role in the investment of capital in the biotechnology markets. Investors measure opportunities in the biopharmaceutical sector through potential sales of the drug/product, the strength of market protection from patents, and other forms of exclusivity (such as orphan drug exclusivity). The patent plays a critical role in helping the innovator take his initial discovery to fruition.

Likewise, WARF contrasted its statement that genetic research is not patent-driven with its view that patents may provide a major incentive for test development because of the protection they afford for the expenditure of risk monies.

In addition to these comments concerning the general idea of whether patents stimulate investment to develop genetic tests, some commenters identified particular tests under development that they said would not be commercialized without the exclusive rights provided by patent protection. The Vice President for Research and Technology Management at Case Western Reserve University stated that a genetic test aimed at detecting early-stage colon cancer is being commercially pursued because the university was able to exclusively license the associated patent rights.

The Director of Licensing at the University of Michigan described a similar situation, stating that an exclusive license to practice a patent protecting a five-gene panel test for lupus erythematosis will motivate the licensee to "invest in both further university research as well as in clinical trials to validate the use of this DNA panel." The director added that because of the exclusive license "[t]he public will become the beneficiary of this testing procedure sooner rather than possibly not at all."

Axial Biotech and Juneau Biosciences, the two companies referenced earlier, also pointed out in their comments that patents had influenced outside investors. Protecting their genetic tests through the patent system has been "a major factor" in persuading investors that their tests could one day be sold at a profit.

On the other hand, the existence of a patent claiming a mutation involved in a rare hereditary disorder may discourage test development. This viewpoint was articulated in a public comment on the draft report from the president of Gene Dx, a company focused on the development of genetic tests for rare hereditary disorders. The company president explained,

[80] Ibid.

> For a rare disorder . . . it may take several years for a laboratory to recover the initial development costs due to the small number of individuals who will be tested. The additional expense associated with negotiating a license of a patent, and paying the up-front and ongoing royalties, can be a strong disincentive to a commercial laboratory in its selection of genetic tests to develop and offer to the community.

The Gene Dx president went on to say that

> [g]ene patents have a severe negative impact on the development, and thus the availability, of genetic testing for rare disorders. . . I can assure the committee that any gene on which there is patent protection falls to the very bottom of my quite extensive list of genetic tests in which my company is interested.

Taken together, this information suggests that patents may stimulate investment in the development of genetic test kits and some laboratory-developed tests, but may discourage investment in the development of tests for rare hereditary disorders.

D. Are Patents Needed for Test Development?

Although patents may sometimes encourage development of genetic tests and at other times discourage development, it is important to consider a related question: namely, are patents needed for test development?

Weighing in on this issue, several commenters suggested that patents are not needed to create laboratory-developed tests because such tests are often developed without patents.[81] According to the American College of Medical Genetics, for example, "genetic tests are typically well-developed and being delivered BEFORE patent holders seek to control the testing. Therefore, it is self-evident that gene patents are not needed to stimulate the development of tests."

The president of a PreventionGenetics, a clinical DNA testing laboratory, made similar points:

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[81] Although they did not refer to tests that have been developed without a patent, law professors Joshua Sarnoff, Jonathan Kahn, and Lori Andrews expressed doubt about the necessity of patents: "Given existing incentives for gene-based science and medical discoveries, there are good reasons to believe that patents are not needed to incentivize DNA-based therapeutic (as well as diagnostic) innovations."

Questions as to the role of patents in stimulating the development of therapeutics were outside the scope of the Committee's study. The Committee notes only that there appears to be a diversity of opinion on this issue. In contrast to the view expressed by these professors, the American College of Medical Genetics wrote in their submission, "In high investment areas such as the development of therapeutics, patents are critical to the long and expensive process of bringing a product to the marketplace." Gold and Carbone have noted that viewpoints on either side of this issue are based on subjective beliefs and that there is no clear empirical evidence to say which position is right: "There are few examples of . . . [therapeutics] being commercialized without intellectual property, but it is unclear whether this is because nobody has tried to do so or whether intellectual property is, in fact, essential to the effort." RE Gold and J Carbone., op. cit., p. 47-48.

> DNA patents are . . . not needed to induce the development of clinical DNA tests. Hundreds of clinical DNA testing laboratories throughout the world are developing thousands of new clinical DNA tests each year. The vast majority of these tests are for genes that are not patent protected. Labs [such as ours] will continue to develop tests at a rapid pace regardless of whether they hold exclusive patent licenses.

The College of American Pathologists also pointed out that unpatented tests have been developed through the work of pathologists in clinical laboratories who have introduced and improved upon the majority of molecular tests largely without patent protection.

Consistent with these comments, the case studies show that laboratories lacking exclusive rights associated with genetic testing for particular conditions have regularly developed genetic tests for those conditions. In particular, patents were not needed to develop genetic tests for hearing loss, SCA, breast cancer, LQTS, Canavan disease, and HH. Indeed, all of these tests were on the market before the test offered by the relevant patent-rights holder.[82]

Box: Genetic Testing for Hearing Loss

Inherited DNA mutations account for more than half of all hearing loss cases. Genetic hearing loss can be classified as "syndromic" or "nonsyndromic," depending on whether there are associated clinical features beyond hearing loss (syndromic) or not (nonsyndromic). Mutations in many different genes have been implicated in genetic hearing loss. Mutations in a few genes are the most commonly tested: *GJB2*/*Connexin 26*, *GJB6*/*Connexin 30*, *SLC26A4*/*PDS*, *MT-RNR1*, and *MT-TS1*. Most hearing loss genes identified to date are not patented. *GJB2* patents have been exclusively licensed, apparently with territory-of-use restrictions, to the for-profit company Athena Diagnostics for testing in the United States, Canada, and Japan.

The majority of laboratories currently providing tests for genetic hearing loss are academic health centers. Prices vary for *GJB2* full-sequence analysis, ranging from $140 to $430 per amplicon. Athena charges $472-$575[83] for *GJB2* testing. Genetic tests for *GJB2* and *MT-RNR1*, which are patented, and for *GJB6*, *SLC24A6*, and *MT-TS1*, which are not patented, have been developed and are offered by several providers at similar prices. Several providers have in fact developed test panels that include both the patented *GJB2* and *MT-RNR1* genes as well as the unpatented *GJB6* and *MT-TS1* genes. The acquisition of an exclusive license for *GJB2* diagnostic testing in the United States was presumably integral to Athena Diagnostics' plan to commercialize these tests. While Athena has intermittently enforced its exclusive rights to test for *GJB2* against other service providers, it is not the sole provider of testing. Costs of hearing loss tests do not appear to correlate strongly with patent status. For instance, the price of the most expensive test can be attributed mostly to the costs of sequencing a large gene.

Source: Case study prepared for SACGHS by the Duke University Center for Genome Ethics, Law & Policy; see Appendix A.

Box: Genetic Testing for SCA

SCA is not a single condition, but a group of progressive neurological genetic disorders with common

[82] In a letter submitted to SACGHS after the approval of this report, Athena Diagnostics indicated that this statement is inaccurate. To clarify, the tests that are referenced in this statement are those that were the subject of the case studies. In none of the case studies was the test developed by the exclusive rights holder the first to market.

[83] In a letter submitted to SACGHS after the approval of this report, Athena Diagnostics indicated that the lower end price of this test is $340.

symptoms and disparate genetic causes. SCA is a relatively rare syndrome. Genetic testing plays a direct role in identifying the molecular defect in some cases. There are currently 15 variants of SCA for which genetic testing is available. Athena Diagnostics holds the patent or has exclusive license to 12 patents that identify mutations in six SCA-associated genes (*ATXN1*, *ATXN2*, *ATXN3*, *CACNA1A*, *ATXN7*, *ATXN8OS*) and two other hereditary ataxias (Friedreich ataxia and early-onset ataxia) included in their Complete Ataxia Panel. Mutations in these genes account for roughly 60 to 80 percent of known SCA cases, depending on the patient's country of origin. Athena was also granted a nonexclusive license by Baylor Medical College for methods for detecting mutations in *ATXN10*, and Athena also does testing for *SPTBN2*, *KCNC3*, *PRKCG*, and *TBP* mutations. Of the 12 patents listed by Athena, half are licensed from the University of Minnesota. Athena Diagnostics has enforced its exclusive licenses and is widely assumed to be the sole licensed laboratory for the above tests. Athena's legal department has sent "cease-and-desist" letters to some laboratories performing SCA genetic tests for which Athena has exclusive patent rights.[84] SCA genetic tests can be performed individually for as little as $400, for the least expensive single-locus test, or as much as $2,335[85] for the most expensive full-sequence gene test.[86] The lower-cost tests are for known mutations in subsequent family members, once a proband case in that family is characterized. Athena also offers the Complete Ataxia Panel, a compilation of 18 tests that cover the most commonly identified SCA mutations for the price of $7,300. Athena offers a "Patient Protection Program" that caps out-of-pocket payments at 20 percent of the price for cases where Athena directly bills the patient's insurer.

Source: Case study prepared for SACGHS by the Duke University Center for Genome Ethics, Law & Policy; see Appendix A.

Box: Genetic Testing for Familial LQTS

Familial LQTS affects one in 3,000 newborns. It is a Mendelian condition in which patients' hearts do not recharge appropriately after heartbeats and can lead to life-threatening arrhythmias. Mutations in 12 susceptibility genes account for some 75 percent of familial LQTS; of that 75 percent, mutations in three genes account for most cases. Genetic testing for familial LQTS is important because knowing which gene (and which part of that gene) is mutated can have a direct bearing on decisions regarding preventive measures and drug treatments. The major familial LQTS susceptibility genes were discovered at the University of Utah in the mid-1990s. The University of Utah Research Foundation began licensing patents on familial LQTS susceptibility genes in the late 1990s. Until 2009, at any one time there was never more than a single licensee of the major intellectual property attached to the three genes that predispose to the majority of familial LQTS.

Some Utah patents were initially licensed exclusively to DNA Sciences, which sent out "cease-and-desist" letters to laboratories offering genetic testing of the genes to which the company had exclusive rights. DNA Sciences also sued GeneDx; GeneDx settled and withdrew from the market. For a period of one to two years, DNA Sciences was not offering testing, but other laboratories that were offering testing withdrew from the market due to its patent enforcement. The exclusive rights to the Utah patents subsequently changed hands twice with corporate mergers and acquisitions, from DNA Sciences to Genaissance and from Genaissance to PGxHealth. From 2005 through 2008, PGxHealth (a Clinical Data subsidiary) was the sole U.S. provider of licensed testing for the five most common long-QT mutations, although it granted international licenses in Australia, New Zealand, and Europe, and a research license to a company in Utah.

[84] In a letter submitted to SACGHS after the approval of this report, Athena Diagnostics indicated that these were patent notice letters.
[85] In a letter submitted to SACGHS after the approval of this report, Athena Diagnostics indicated that the price for this test is $1,170.
[86] In a letter submitted to SACGHS after the approval of this report, Athena Diagnostics indicated that this is the largest full-sequence gene test for SCA.

The situation changed in 2009 when GeneDx once again began offering familial LQTS and related gene testing. This market re-entry was enabled by GeneDx acquiring exclusive licenses for some familial LQTS susceptibility genes held by the University of Utah. In 2008, Bio-Reference Laboratories (BRLI, which owns GeneDx) obtained an exclusive license for several patents, giving it rights to test for familial LQTS type 3, which accounts for approximately 10 to 15 percent of inherited familial LQTS. BRLI also aggregated intellectual property related to Jervell and Lange-Nielsen syndrome and to familial LQTS susceptibility genes *KCNQ1*, *KCNH2*, *KCNE1*, *KCNE2*, and *KCNJ2*. Both GeneDx and PGxHealth now offer testing for more than 10 genes.

Source: Case study prepared for SACGHS by the Duke University Center for Genome Ethics, Law & Policy; see Appendix A.

When relevant patents were granted, the patent-rights holder enforced their patent rights to narrow or clear the market of these competing tests. For example, the hearing loss case study indicates that there have been intermittent enforcement efforts by the exclusive licensee, Athena Diagnostics, of patents protecting testing for *GJB2*, with the result that some laboratories have stopped testing. The case study also found that Boston University's Center for Human Genetics stopped offering *GJB2* and *MT-RNR1* testing following Athena's enforcement of patents protecting those genes. Athena has also enforced its rights with regard to patents protecting SCA testing; the case study on SCA concluded that Athena is now assumed to be the sole provider of SCA testing.

Similarly, Myriad enforced its patents to stop provision of breast cancer genetic testing by laboratories that had been offering it since before the patents issued.[87] The case study on familial LQTS also describes enforcement actions by exclusive licensees that led providers to discontinue testing.

In the case of genetic testing for Canavan disease, the patent holder initially offered infringing laboratories a license to continue performing testing. The case study does not indicate how many laboratories refused the license and discontinued testing.

Finally, patent enforcement has also stopped the provision of HH testing by laboratories that were offering it. In particular, Jon F. Merz and his coauthors reported "that many US laboratories began genetic testing for haemochromatosis before the [relevant] patents were awarded, but 30 percent of those in our survey reported discontinuing or not developing genetic testing in the light of the exclusive license granted on the patents covering clinical-testing services."[88]

The development of unpatented tests prior to patent enforcement suggests that developers were driven by considerations other than the promise of a patent and were not dissuaded from test development by the threat of free riders copying their tests. The hearing loss case study suggests that what motivated the laboratories was not profit, but clinical need and demand. That study found that for patented and unpatented genes, demand for testing was the primary factor that determined whether diagnostic testing was offered.

[87] B William-Jones. (2002). History of a gene patent: tracing the development and application of commercial BRCA testing. *Health Law Journal* 10:123-146.

[88] J Merz, AG Kriss, DGB Leonard, and MK Cho. (2002). Diagnostic testing fails the test: the pitfalls of patents are illustrated by the case of haemochromatosis. *Nature* 415:577-579.

The costs of developing these laboratory-developed tests appear to be relatively modest. According to one group of clinical geneticists, the cost of developing a sequencing-based genetic test is $1,000 per exon.[89] Given that the average gene has 8-10 exons (or coding regions),[90] the cost of developing a laboratory-developed genetic test that relies on gene sequencing as opposed to probe hybridization to detect a single mutation is, on average, between $8,000 and $10,000.

Although the costs of developing a laboratory-developed genetic test are low, a public comment from Celera suggested that the same is not true of test kits. To market a test kit, the developer must obtain approval of the kit as a medical device under the Food, Drug, and Cosmetic Act, a process that, according to Celera, involves considerable cost:[91]

> A product manufacturer must design, validate, and manufacture each diagnostic product in compliance with FDA's Quality System Regulation, which includes good manufacturing practices and design control requirements that are costly to implement. In addition, diagnostic products submitted for FDA registration must be accompanied by data from clinical trials which are also costly undertakings. Thus, patent protection is a necessary incentive to investors in mitigating their risk in funding companies that engage in research and development of genetic tests [marketed as test kits].

This claim—that the cost of developing a test kit are so high that patent protection is needed to fund test kit development—was one the Committee had heard from other parties and that it examined. Two case studies contain facts relevant to whether the patent incentive is needed for test kit development. First, the case study on Tay Sachs indicates that a company expressed interest in developing a test kit for genetic testing in Tay Sachs, but would do so only if the gene was patented. However, when the gene was patented, the patent holder—NIH—decided not to enforce it or license it; no test kit has been developed to date, although laboratory-developed tests are in use, and testing is broadly available. Although the one company described in the case study indicated that the patent was necessary for it to pursue test kit development, it is not clear why other companies have not pursued development of a test kit. Whether other companies are discouraged by the lack of an exclusive license or some factor unrelated to patents, such as their perception of low demand for the test, is unknown.

The second relevant case study in this area—the case study on genetic testing for CF—suggests that exclusive rights are not necessary for the development of a test kit for a common genetic condition. Specifically, the CF case study shows that multiple parties have obtained a nonexclusive license to develop a test kit for CF testing. At the time of the case study's writing, two licensees had obtained FDA approval for their test kits, and other companies were in the process of seeking FDA approval of their test kits.[92] The fact that these licensees will have to compete against one another has not dissuaded any of them from pursuing test kit development.

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[89] S Das, SJ Bale, and DH Ledbetter. (2008). Molecular genetic testing for ultra-rare diseases: models for translation from the research laboratory to the CLIA-certified diagnostic laboratory. *Genetics in Medicine* 10:332-336, p. 336.
[90] MK Sakharkar, VT Chow, and P Kangueane. (2004). Distribution of exons and introns in the human genome. *In Silico Biology* 4:387-393.
[91] 21 U.S.C. § 321(h); 21 C.F.R. Part 809.
[92] Robert Cook-Deegan, one of the authors for "Impact of gene patents and licensing practices on access to genetic testing for cystic fibrosis," personal communication.

The case study indicates that 63 American laboratories perform CF Testing: "The majority of those labs are academic medical centers or hospital-based genetic testing laboratories that use CF test kits developed under these licenses."[93]

Based on all of the above information, patent-derived exclusive rights are neither necessary nor sufficient conditions for the development of genetic test kits and laboratory-developed tests. In the area of laboratory-developed tests particularly, where development costs are not substantial, patents were not necessary for the development of several genetic tests. This conclusion is revisited in the Conclusions section of this report, where the necessity of patents is examined in light of a potential change in the regulatory oversight of genetic tests.

[93] S Chandrasekharan, C Heaney, T James, C Conover, and R Cook-Deegan. (2009). Impact of gene patents and licensing practices on access to genetic testing for cystic fibrosis. Appendix A, p. C-7.

III. OTHER POSSIBLE BENEFITS OF PATENTS AND LICENSES

Public comments and the case studies make reference to other possible benefits of patents associated with genetic tests. The breast cancer case study, for example, suggests that exclusive rights holders have significant incentives to educate physicians and patients and that such patent-driven educational efforts can have the benefit of increasing awareness of the test. However, there are concerns that in addition to benefits, marketing (promotion) of tests may lead to overutilization, inappropriate testing, and patient harm. In response to these concerns, Myriad has stated, according to the case study, that it is not trying to expand testing to inappropriate patients, but merely to saturate testing among high-risk families.

Nevertheless, greater federal regulation of advertising claims made about laboratory-developed tests would provide further assurance that companies that advertise these tests do not make inappropriate claims. A separate paper under development by the Committee on direct-to-consumer genetic testing will address how the Federal Government can improve regulation of advertising claims made by providers of laboratory-developed tests.

Another possible benefit of patents the Committee considered was whether patents provide an important incentive to pursue insurance coverage for a test. BIO, for example, stated during a public comment session at the October 2009 Committee meeting that patents in this area have this benefit. The case study on breast cancer, however, suggests that both sole providers and nonexclusive providers have an equal incentive to obtain coverage: "[c]ompanies offering genetic testing have incentives to negotiate the complex coverage and reimbursement landscape on behalf of patients using their services."[94] Furthermore, having multiple providers pursuing coverage should lead to greater cumulative coverage than the coverage obtained by one provider, particularly if that provider has decided not to accept particular insurers or insurance programs.

The Committee also considered whether patents associated with genetic tests have the benefit of ensuring that genetic testing is limited to patients for whom it is clinically useful. That is, because a patent-derived license can be used to limit the use of patent rights to only those situations where testing is clinically useful, can the use of licenses in this way be counted as benefit of patents? An example of using a license to enforce clinical guidelines is described in the Alzheimer disease case study. According to that case study, the discoverer of the patented *APOE* gene said the reason that Duke chose to license the patent exclusively was to ensure that *APOE* testing was done in compliance with professional standards, which recommended that the test be used only in patients with confirmed dementia.[95]

Notwithstanding the license's[96] possible salutary effect in this case, there is no guarantee that

[94] R Cook-Deegan, C DeRienzo, J Carbone, S Chandrasekharan, C Heaney, and C Conover. (2009). Impact of patents and licensing practices on access to genetic testing for inherited susceptibility to cancer: comparing breast and ovarian cancers to colon cancers. Appendix A, p. A-8.

[95] In a letter submitted to SACGHS after the approval of this report, Athena Diagnostics, the licensee, indicated that the patent license contains no restriction about the use of the test, but the test requisition form Athena uses indicates that the test is to be ordered for patients symptomatic of dementia.

[96] Ibid.

other holders of patents protecting genetic tests will adopt this approach to licensing. Patent law does not require the holders of genetic-testing-related patents to devise licenses that enforce clinical guidelines. As such, the use of patents to enforce clinical guidelines cannot be viewed as a system-wide benefit of patents protecting genetic tests. Moreover, given the evolving evidence base on the clinical validity and utility of genetic tests, licensing provisions outlining clinical guidelines may quickly become outdated. For example, recent data now suggest that *APOE* testing for Alzheimer disease risk prediction might indeed be desirable in a number of clinical situations, contrary to the assumed stipulations of the license.[97] Thus, there may be more effective ways of enforcing clinical guidelines than through terms of a patent-derived license.

[97] RC Green et al. (2009). Disclosure of APOE genotype for risk of Alzheimer's disease. *New England Journal of Medicine* 361:245-254.

IV. THE EFFECT OF PATENTS AND LICENSING PRACTICES ON CLINICAL AND PATIENT ACCESS TO GENETIC TESTS

As the Introduction to this report suggests, the patent system involves a trade-off between the potential benefits of patents and the potential social harms that can result from rewarding a patent holder exclusive rights.[98] Having evaluated one side of this trade-off in Sections II and III—specifically, the benefits of patents associated with genetic tests—Sections IV, V, and VI examine whether such patents are causing social harms by creating barriers to clinical and patient access, test quality, and the development of new testing innovations.

A. Patents and Licensing Practices and the Price of Genetic Tests

One way patents associated with genetic tests might limit clinical or patient access is by raising prices above what would exist in a competitive market. Although the case studies attempted to evaluate how patents and licensing practices affect the price of genetic tests, some case studies did not yield definite conclusions because of difficulties in obtaining relevant data and challenges in determining the relative contribution of various factors, including overhead costs, to price.

One of the case studies where there was a definite conclusion was the one concerning breast and colon cancer testing, where it was found that the per-unit price of the full-sequence *BRCA* test, which often is cited as being priced very high, was actually quite comparable to the price of full-sequence tests done on colon cancer, for which associated patents are nonexclusively licensed. On the other hand, the case study on LQTS suggests that the price of the patent-protected test was higher than it would have been had the test been unpatented, with the potential that this premium is reducing patient utilization of the test. In that case study, the authors write, "[W]e believe that a competitive presence could have accelerated the test to market and lowered the cost from its current $5,400."[99]

In addition, it appears that the test developers of the Canavan disease genetic test used their patent monopoly to establish restrictive license conditions and sought license fees that exceeded what laboratories offering similar tests for Tay-Sachs disease were willing to pay. A consortium of the Canavan Foundation, the National Tay-Sachs and Allied Diseases Association (NTSAD), the National Foundation for Jewish Genetic Diseases, and the Canavan Research Fund organized against the patent holder, initiated a lawsuit roughly a year after the license terms were first proposed, and negotiated a sealed and confidential settlement that altered the license terms in a way that the plaintiffs apparently considered acceptable. Even after the settlement, however, there was an average price difference between genetic tests for Canavan disease and tests for Tay-Sachs disease. The case study concludes that "the average price per amplicon for Tay-Sachs

[98] R Mazzoleni and RP Nelson. (1998). The benefits and costs of strong patent protection: a contribution to the current debate. *Research Policy* 27:273-284.

[99] M Angrist, S Chandrasekharan, C Heaney, and R Cook-Deegan. (2009). Impact of patents and licensing practices on access to genetic testing for long QT syndrome. Appendix A, p. F-4.

. . . is $111.50 while the price per amplicon for Canavan disease is $199.58: a significant difference that could reflect a patent premium."[100]

In addition to these findings from the case studies, a number of commenters claimed that patents affect the price of genetic tests, but they did not provide concrete evidence of such patent price effects. Nor did any articles reveal evidence of exclusive rights resulting in an inflated price for a genetic test.

In sum, although the case studies identified patents and exclusive licenses that appear to be causing high prices for some genetic tests, no evidence was found that patents and exclusive licenses have consistently led to higher prices for genetic tests.

B. Clinical Access to Existing Genetic Tests

Based on its review of the literature, case studies, and public comments, the Committee found that the patenting and licensing of genetic tests has limited the ability of clinical laboratories to offer genetic testing. This limitation, in turn, can affect patient access, the quality of testing, and efforts to innovate. The effect of patents and licensing practices on the quality of genetic tests and innovations in testing are discussed in greater detail in later sections. Committee findings in support of the conclusion that patents and licensing practices have affected the ability of clinical laboratories to offer genetic tests are presented below.

In 2002, Merz and his coauthors reported that approximately 30 percent of laboratories discontinued or did not offer the test for HH, in light of the exclusive license for the test given to and enforced by SmithKline Beecham Clinical Laboratories. [101] Among these 36 laboratories, 22 of them stated that patents were the reason they had stopped, while 10 reported that patents were one of several reasons why they discontinued or did not develop a test.[102] Merz and his coauthors concluded that the narrowing of the market had implications for test quality and patient access, because there was little opportunity for validation and confirmation studies and limited ability to incrementally innovate or develop clinical expertise.[103]

With regard to patient access, however, the HH case study found that any initial problems were solved through a later broadening of licensing practices:

> In 2007 and 2008, compared to 2002, we found little controversy surrounding *HFE* genetic testing and the licensing model has evolved to include several providers and sublicensing for use on different platform technologies. The past licensing practices of SmithKline Beecham Clinical Laboratories (SBCL) (exclusive licensing model) were controversial, but the current owner of patent

[100] A Colaianni, S Chandrasekharan, and R Cook-Deegan. (2009). Impact of patents and licensing practices on access to genetic testing and carrier screening for Tay-Sachs and Canavan disease. Appendix A, p. H-11.
[101] J Merz, AG Kriss, DGB Leonard, and MK Cho, op. cit.
[102] Ibid.
[103] Ibid.

> rights, Bio-Rad, Ltd., appears to have a broad sub-licensing model that has resulted in broader clinical and patient access and less public conflict.[104]

Researchers followed up on the 2002 study with a more comprehensive survey of the effect of patents and licensing practices on laboratories' performance of genetic tests. Specifically, in 2003, Mildred Cho and her coauthors surveyed directors of laboratories conducting clinical genetic testing, making the following key findings:

> Twenty-five percent of respondents reported that they had stopped performing a clinical genetic test because of a patent or license. Fifty-three percent of respondents reported deciding not to develop a new clinical genetic test because of a patent or license. In total, respondents were prevented from performing 12 genetic tests, and all of these tests were among those performed by a large number of laboratories. We found 22 patents that were relevant to the performance of these 12 tests. Fifteen of the 22 patents (68%) are held by universities or research institutes, and 13 of the 22 patents (59%) were based on research funded by the United States Government.[105]

The survey found little support for the value of patenting among laboratory directors, and the authors concluded that "patents and licenses have a significant negative effect on the ability of clinical laboratories to continue to perform already-developed genetic tests" and continued by stating that "we do not know whether patients who were denied access to these tests had testing performed by another laboratory . . . ."[106]

The case studies found other instances of exclusive rights being enforced to prevent clinical laboratories from offering testing:

- The exclusive rights Myriad Genetics holds on the *BRCA* genes have been used to stop other laboratories from conducting breast cancer genetic testing.
- Athena Diagnostics has intermittently used its exclusive rights to various hearing loss genes to stop some laboratories from testing.
- Athena has also enforced patents associated with Alzheimer disease testing to reduce alternative providers.
- DNA Sciences used its exclusive rights to familial LQTS genes to attempt to clear the market.
- Miami Children's Hospital enforced its patent on the Canavan disease gene, resulting in laboratories stopping testing or paying a royalty fee to continue performing testing.

The case study on SCA genetic testing also provides a lengthy discussion of the effect on clinical access of Athena Diagnostics' enforcement of patents covering SCA genes:

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[104] S Chandrasekharan, E Pitlick, C Heaney, and R Cook-Deegan. (2009). Impact of gene patents and licensing practices on access to genetic testing for hereditary hemochromatosis. Appendix A, p. E-2

[105] MK Cho et al. (2003). Effects of patents and licenses on the provision of clinical genetic testing services. *Journal of Molecular Diagnosis* 5(1):3-8., p. 3.

[106] Ibid., p. 8.

> Athena's legal department has sent "cease-and-desist" letters[107] to some laboratories performing SCA genetic tests[108] for which Athena has exclusive patent rights. In another instance, the Diagnostic Molecular Pathology Laboratory at the University of California Los Angeles stopped offering testing for SCA over two years ago, after receiving a "cease-and-desist" letter[109] from Athena Diagnostics. According to Dr. Wayne Grody, Director of the Laboratory, the terms of the sublicense offered by Athena Diagnostics were not economically viable for the laboratory. Attempts to negotiate terms of a sublicense have not been successful to date. It is unclear to what extent cessation of testing at UCLA has affected patient access to SCA testing. Dr. Grody indicated that samples are now sent to Athena Diagnostics for clinical testing. Several other laboratories are also listed on GeneTests.org for adult SCA diagnoses. Comprehensive Genetics Services offers a complete panel of SCA tests but did not respond to questions about patents or licensing in phone interviews. We recently became aware that Boston University reached a settlement with Athena Diagnostics regarding testing for SCA and several other conditions and no longer offers SCA testing.[110]

Several public commenters also provided information relating to clinical access. Two public comments stated that clinical laboratories offering multiplex testing do not report medically relevant results relating to patent-protected genes included in the array for fear of liability. For example, the technical director of a medical laboratory wrote,

> Multiplex assays are being used clinically at least in the constitutional area for individuals with birth defects and/or developmental issues and autism; areas of arrays where patented genes lie must be identified and masked, so that if a patient has a copy change (deletion or duplication) present, the information cannot be reported by the lab performing the test unless they have paid license fees (if even available) for the gene(s). This is expensive to labs to spend resources keeping up with which genes are patented and which are not and which genes are licensed and which are not and how, and altering work-flow so as to not report data regarding certain sequences—this cost will be passed on to the patient and the insurers. This also has the potential for patients to remain undiagnosed for certain conditions, if someone has an alteration that cannot be reported by a particular testing lab, even after having spent large sums of money for their diagnostic testing.[111]

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[107] In a letter submitted to SACGHS after the approval of this report, Athena Diagnostics indicated that these were patent notice letters.

[108] In a letter submitted to SACGHS after the approval of this report, Athena Diagnostics indicated that these letters were only sent to laboratories performing commercial SCA genetic tests.

[109] In a letter submitted to SACGHS after the approval of this report, Athena Diagnostics indicated that this was a patent notice letter.

[110] A Powell, S Chandrasekharan, and R Cook-Deegan. (2009). Spinocerebellar ataxis: patient and health professional perspectives on whether and how patents affect access to clinical genetic testing. Appendix A, p. G-6.

[111] While it may be that not reporting test results prevents the patent holder from becoming aware of the use of patent-protected genes or probe molecules, performance of the test is still infringement so long as the probe molecules used in the test are claimed by the patent or equivalent to what the patent claims.

Another public comment stated that the exclusive licensee of a patent covering the detection of the leukemia-associated *FLT3* gene has stopped several laboratories, including the Mayo Clinic, from performing such testing. The commenter, the medical director of molecular oncology at a blood center, stated that physicians have complained of a slow turnaround time in receiving testing results from the exclusive licensee. The commenter added, "If true, this delay in receiving test results could have a negative impact on patient management."

In sum, some patents associated with genetic tests and exclusive licensing practices have limited clinical access to genetic tests. Some patent holders have used their property rights to prevent other laboratories from offering testing, thereby becoming in some cases the sole provider of the test. Nonexclusive licenses can also limit clinical access if laboratories cannot afford or are unwilling to pay the royalty fees associated with the nonexclusive license. It is important to note, however, that limitations in clinical access do not necessarily limit patient access. For instance, the nonexclusive licensing fees providers have to pay to offer HH testing do not appear to be affecting patient access to the test.

C. Patient Access to Existing Genetic Tests

The case studies generally found that for patented tests that were broadly licensed there was no evidence of patient access problems. However, in those cases where an exclusive-rights holder narrowed or cleared the market of competing tests through patent enforcement, some problems did occur. For example, in the case of testing for familial LQTS, two successive exclusive licensees enforced their patent rights from 2002 to 2004 even though they were not yet offering a commercial test. This action resulted in a period of 18 months when testing was only available from academic research laboratories and not from clinical laboratories certified by CLIA.[112] While acknowledging that the evidence is incomplete, the case study concludes that some patients during this period (2002-2004) may have been prevented from receiving testing for this potentially lethal disorder. The case study describes the effect as "small but tangible" and suggests that "this negative effect would likely have been larger had there been greater awareness, understanding and acceptance of genetic testing on the part of cardiologists and electrophysiologists at that time."[113]

Enforcement of patent rights has also created access problems when the exclusive-rights holder does not accept a particular insurance, including Medicaid or Medicare. Patients who are covered by these payers must either forgo a needed test or pay out of pocket for it. For example, Athena Diagnostics, which has exclusive rights to patents related to the hearing loss gene *GJB2*, has enforced its rights to narrow the market of other tests.[114] Because Athena does not accept

[112] CLIA requires certification of clinical laboratories that perform laboratory examination of materials derived from the human body. 42 U.S.C. § 263a. As explained in the Committee's report on the oversight of genetic testing, "Genetic testing laboratories must undergo inspections (also called surveys) every 2 years to assess their compliance with CLIA quality requirements such as personnel qualifications and responsibilities, quality control (QC) standards, PT [proficiency testing], QA [quality assurance], and record keeping." SACGHS. (2008). U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services.

[113] M Angrist, S Chandrasekharan, C Heaney, and R Cook-Deegan. (2009). Impact of patents and licensing practices on access to genetic testing for long QT syndrome. Appendix A, p. F-1.

[114] The case study indicates that even though Athena has enforced its patent rights, it does not appear to have completely cleared the market of competing tests.

MediCal, the California Medicaid program, access for MediCal patients may have suffered as a result.

Athena, which is also the sole provider of SCA testing and *APOE* and *PSEN2* testing relating to Alzheimer disease, is not a participating provider in any Medicaid program.[115] Medicaid patients, however, can apply for a discount of up to 80 percent through Athena's Financial Assistance Program.[116] To request this discount, a Medicaid patient must submit payment, a completed Financial Assistance Program Application, proof of Medicaid eligibility, proof of household income with tax documentation, and documentation of total medical bills in the last 12 months.[117] Knowledgeable clinicians, including Committee members, have not observed wide uptake of this program by patients and regularly see patients simply forgoing testing. Clinicians may be observing low participation in Athena's program because even with the 80 percent discount, the costs of some tests are so high—in the range of $10,000—that patients would still have to pay a considerable amount.

Clinicians who submitted public comments on the draft form of this report have also observed access problems when an exclusive rights holder does not accept a particular insurance, but enforces its patents to narrow or clear the market. For example, two genetic counselors from Emory University wrote in their public comment,

> Unfortunately, there are also labs [that are exclusive licensees or patent holders] that choose not to contract with Medicaid or Medicare at all. The end result is that access to a genetic test can be largely influenced by a patient's socioeconomic status and geographical location. Given the fact that approximately 50% of Georgia births are covered by Medicaid, this represents a major problem in our state.

A legal complaint challenging the *BRCA* patents held by Myriad Genetics also alleges access problems resulting from Myriad's decision not to accept particular insurers. According to that complaint, one plaintiff covered by MediCal and another plaintiff covered by MassHealth, the Massachusetts Medicaid program, cannot afford to pay for the full cost of *BRCA1*/*BRCA2* testing out-of-pocket and have had to forgo recommended testing because Myriad did not accept their insurance, even though MassHealth would cover *BRCA* genetic testing.[118] Although Myriad, according to the case study, has reduced "the number of self-pay patients to single-digit percentages of its clientele[,]"[119] allegations such as these suggest that patient access problems are occurring.

While an exclusive rights holder's refusal to accept a particular insurance can cause access

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[115] Athena Diagnostics web site. Ordering & Billing section. http://www.athenadiagnostics.com/content/ordering/
[116] Ibid.
[117] Ibid. See in particular the linked Financial Assistance Program Application.
[118] Association for Molecular Pathology Compl. ¶¶ 21, 24, available at http://www.aclu.org/images/asset_upload_file939_39568.pdf
[119] R Cook-Deegan, C DeRienzo, J Carbone, S Chandrasekharan, C Heaney, and C Conover. (2009). Impact of patents and licensing practices on access to genetic testing for inherited susceptibility to cancer: comparing breast and ovarian cancers to colon cancers. Appendix A, p. A-32. The case study indicates that Myriad has established contracts with—or accepts—over 300 insurance carriers.

problems for some patients, an exclusive rights holder's clearance of the market denies all patients of the ability to access a confirmatory genetic test from a different laboratory. The ability to obtain a confirmatory test from a second laboratory is important because genetic test results can have implications for major medical decisions, such as whether to have a mastectomy or surgical removal of the ovaries. Confirmatory testing by another laboratory is the laboratory equivalent to the time-honored practice of obtaining a second opinion from a clinician. The legal complaint filed against Myriad names one plaintiff who would have liked a second opinion on her *BRCA1/BRCA2* genetic test results but instead had to make major medical decisions based on the Myriad test results alone.[120]

Other types of access problems can arise when a patent rights holder has cleared the market of other laboratories that were offering the genetic test provided by the patent rights holder. For example, patients who want to test their fetuses for particular conditions may not be able to if the sole provider refuses to conduct its test on fetal samples, as is the policy of the sole provider of familial LQTS testing. Although it is not clear whether there are patients who want prenatal testing for familial LQTS, such testing was at one time offered but subsequently stopped because of patent enforcement. The availability of—and therefore access to—carrier testing or newborn screening for particular conditions could also be prevented if a rights holder has cleared the market but lacks the ability—or the willingness—to conduct these tests. This concern was raised by the Association for Molecular Pathology (AMP). In particular, AMP was concerned that the exclusive licensee of patents relating to spinal muscular atrophy (SMA) testing, Athena, and its sublicense would be unable to handle the volume of testing that would be generated from carrier testing for SMA.

In sum, the Committee found that access to genetic tests for significant segments of the population—especially indigent patients—has been impeded when a patent rights holder does not accept all insurers or insurance programs and uses its patent rights to prevent other laboratories from offering the test. Patients covered by the unaccepted insurers or insurance programs cannot afford testing and choose to forgo it. If other laboratories could offer the genetic tests in question, these patients would have a greater chance of obtaining access because it would be likely that at least one of the other laboratories would accept their particular insurance.

Access to confirmatory testing is completely impeded when a patent-enabled sole provider exists. That is, patients who desire a confirmatory test from a second laboratory are unable to obtain this second-opinion test in those cases where the patents right holder has cleared the market of other laboratories offering the test.

Other access problems may have occurred or may be occurring. In particular, the lack of availability of familial LQTS testing during an 18-month period due to patent enforcement caused access problems if there were patients seeking the test at that time. Whether there were such patients is not documented. Now that familial LQTS testing is available, access to testing of fetal samples may be suffering because the sole provider will not perform the test on fetal samples. Here again, however, it is unclear whether there are any patients who desire prenatal testing.

[120] ACLU Compl. ¶ 23, available at http://www.aclu.org/images/asset_upload_file939_39568.pdf.

Finally, another lesson that was drawn from the Committee's study—specifically the case study on Canavan disease testing—is that controversies concerning patient access to patent-protected genetic tests are more likely to occur when the interests of medical practitioners and patients are not taken into consideration during the process of licensing the relevant patents.

D. Are Patient Access Problems Better Addressed Through Health Insurance Reform?

Discussion by both the patents task force and the Committee at its October 2009 meeting raised the issue of whether the patient access problems described here were better addressed through changes in health insurance law and policy rather than changes in patent law and policy. A public comment submitted by Celera on the public consultation draft of this report made a similar point: "issues related to clinical and patient access . . . may be better addressed through . . . coverage and reimbursement systems for such services."

However, it is not clear how legal changes affecting the practices and policies of health insurers could solve these patient access problems because these problems are caused not by any behavior by health insurers, but by an exclusive rights holder's decisions. It is the decision of a rights-holding sole provider not to accept particular health insurance that has caused access problems for some patients, just as it is the decision by an exclusive rights holder not to permit other laboratories to offer testing that has prevented second-opinion testing. Likewise, it is the decision by the company offering familial LQTS testing not to offer prenatal testing that may be denying access to prenatal testing.

Insurance law changes also would not eliminate the barrier patents present to the development of new testing innovations, a situation described in section VI. Furthermore, health insurance reforms would not address the problems that patents can cause in the quality of genetic tests. Neither of these problems is caused by health insurers' policies or practices.

V. THE EFFECTS OF PATENTS AND LICENSING PRACTICES ON THE QUALITY OF GENETIC TESTS

Concerns have been raised about the quality of genetic tests provided by exclusive rights holders. For example, in 2006, a commentary in the *Journal of the American Medical Association* (JAMA) and testimony before Congress questioned the quality of Myriad Genetics' test for breast cancer susceptibility, pointing to its inability to detect genomic rearrangements, insertions, and deletions. While Myriad Genetics was already working on addressing these deficiencies, the case study on breast cancer genetic testing suggests that the *JAMA* article may have accelerated Myriad's efforts.

A public comment submitted in response to the draft version of this report also revealed concerns about the quality of Athena's test for the dystrophin gene. In the public comment, the chief executive of Parent Project Muscular Dystrophy explained the context within which concerns about the test have been raised:

> [C]linical trials are in process and in development targeted to specific mutations within the dystrophin gene. Because these strategies are targeted to specific subsets of patients, genetic testing becomes a critical factor in terms of screening patients, participation in trial, and ultimately an approved therapy for . . . [muscular dystrophy]. This makes the quality of testing an extremely important issue for our families. We have been contacted by several families with concerns about the accuracy of their test results. We have also been contacted by clinicians with concerns about test results and the lack of laboratories to provide confirmatory testing and to evaluate cases where a mutation is not detected by Athena.[121]

While this comment should not be taken as evidence of actual quality problems in Athena's test, it suggests that an effective way to address concerns about laboratory quality or test accuracy would be to ensure independent confirmatory testing.[122] Moreover, the only way to assess whether concerns about quality are founded or not would be through such independent testing.

In addition to these specific concerns about the Myriad and Athena tests, some public commenters argued that the quality of genetic testing for a condition improves when there are multiple providers. For example, in a comment submitted to the Committee, a clinician stated that greater competition for certain genetic tests that are currently exclusively provided by an exclusive rights holder would improve their quality:

> In all aspects of my medical practice aside from genetic testing, if a consultant or laboratory fails to provide adequate service, doesn't provide optimal interpretation of results, makes routine errors, or has unwieldy paperwork requirements, I have

[121] In a letter submitted to SACGHS after the approval of this report, Athena Diagnostics indicated that alternative providers of this test are in fact available.
[122] Ibid.

> options to seek out a different laboratory or consultant to optimize care for my patients. In the area of genetic testing for neurologic disorders, I often have no such options. One laboratory has exclusive rights to diagnostic testing. There is no oversight group that is capable of insuring quality care. The marketplace can, however, drive quality. In speaking with my colleagues at national meetings about this issue, it is clear that our experiences regarding quality are highly congruent. However, each individual has only a few problems per year, and limited time to try to interest any oversight organization in addressing them. If we had a choice of labs for genetic tests, a marketplace message would quickly be sent and patient care overall would be improved.

Another medical doctor who submitted a comment stated that competition can improve the overall quality of genetic testing for a condition:

> The greater the number of laboratories performing such analyses, the better the possibilities for advances in assay performance. This is true even if all available tests are of high quality and subject to excellent quality control procedures.

The LQTS case study takes a similar view, concluding that more competition might have brought about greater progress in understanding the complicated genetics of familial LQTS; greater understanding of the disease in turn would improve testing for the disease.

In contrast to the view that having multiple providers is the best way to ensure test quality, a medical professional society concerned with clinical laboratory science submitted a comment stating that CLIA should remain the primary vehicle for ensuring the quality of testing. A manufacturer of diagnostic products in its public comments also favored existing oversight systems as the best means of addressing test quality: "quality may be better addressed through the evaluation of the regulation and oversight of genetic tests . . . ."[123]

While these commenters suggest that testing quality depends on regulatory oversight, Kathleen Liddell and her coauthors have suggested that quality depends on the number of providers—and that having fewer providers may be preferable to having many. In particular, Liddell and her coauthors argue that

> there are certain technical advantages of centralising the provision of genetic tests with a small number of laboratories. It is far easier to ensure a consistent quality of testing across one or two labs, than to produce a standardised kit suited to wide deployment. This is particularly so for complex tests, which may be difficult to turn into a standardised kit which can be used in multiple labs, and which may best be carried out by major reference laboratories until consistent sampling procedures are established. One respondent [in the authors' survey] also pointed out that monopoly provision of genetic services does not run wholly against the

[123] It should be noted, however, that CLIA does not require CMS to assess a test's clinical validity, which is an important component of a test's quality. Clinical validity refers to a test's ability to detect or predict the associated disorder (phenotype).

> grain. The "reference lab" model is well accepted as a way of improving the quality of rare disease genetic tests.[124]

Despite this suggestion that quality is best addressed by limiting the number of providers of a genetic test and other suggestions that quality is best addressed through regulatory oversight, as the Committee evaluated the totality of evidence, it concluded that the best means to ensure the quality of genetic tests is by allowing laboratories to independently verify results and share samples. The Committee's conclusion is echoed by laboratory directors and is consistent with standard mechanisms currently used to ensure test quality. The Committee also concluded that competition among laboratories is a potent mechanism for ensuring quality as it provides clinicians with alternatives and thus harnesses market forces for continued quality improvement.

Finally, there have been calls (e.g., by NRC in their report *Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation, and Public Health*) for a provision to allow verification or second opinion testing when a sole provider exists.[125] Although the Committee does not disagree with the spirit of the NRC recommendation, it believes that such a narrow provision would not produce the intended effect because there would be little incentive, and many disincentives, for a laboratory to develop and maintain a test simply to provide second opinions or verification requests. Moreover, the volume of such requests could be insufficient to ensure optimal test quality.

[124] K Liddell, S Hogarth, D Melzer, and RL Zimmern. (2008). Patents as incentives for translational and evaluative research: the case of genetic tests and their improved clinical performance. *Intellectual Property Quarterly* 3:286-327, p. 293.
[125] See Recommendation 13 of the report.

VI. THE POTENTIAL EFFECT OF PATENTS AND LICENSING PRACTICES ON GENETIC TESTING INNOVATIONS

In examining the effects of patents and licensing practices on genetic tests, the Committee has been concerned not only with existing effects, but also with the potential impact of patents and licensing on future innovations in testing. A recent innovation in genetic testing is multiplex testing, which involves simultaneously testing multiple genetic markers. This efficient form of testing could be used in various contexts, including in newborn screening. It is anticipated that such screening might eventually be done by affordable whole-genome sequencing—an innovation that is likely to develop in the coming years.[126] These innovations and others—and the challenges to their development and use posed by patents and licensing practices—are discussed below.

A. The Potential Effect of Patents and Licensing Practices on the Development of Multiplex Tests

Several technologies have been developed for simultaneously testing multiple genetic markers (either genes or sequences of phenotypic relevance outside of genes) with a single test. Such multiplex testing can be useful when a condition involves multiple genetic factors or when one wants to simultaneously test for multiple conditions that have one or more potential genetic causes. In the past, when multiple genetic markers had to be tested, each genetic marker would be tested in a separate test, making testing complex, time-consuming, and expensive. As such, multiplex testing is seen as more efficient and potentially less costly.

Because multiplex tests involve multiple genes, concerns have been raised that multiplex tests would violate multiple patent claims to genes and associations.[127] That is, although it is possible that a multiplex test might represent a patentable advance, for the patent holder to practice the invention, rights to all patented genes associated with the test would have to be acquired or licensed. If the relevant patents (or licenses to them) are not all held by the test developer, the development of these tests may not be pursued and their promise could go unrealized. The validity of these concerns is examined in this section.

The first issue to consider in judging whether patents pose a barrier to the development of multiplex tests is whether multiplex methods of testing would likely infringe patent claims to genes and associations. To evaluate that issue, one must understand how multiplex tests are

[126] The President's Council on Bioethics. (2008). The changing moral focus of newborn screening: an ethical analysis by the President's Council on Bioethics. Chapter Three: The Future of Newborn Screening. For a discussion of the technological development of affordable whole-genome sequencing, see RF Service. (2006). Gene sequencing: the race for the $1000 genome. *Science* 311:1544-1546.

[127] See, for example, D Nicol. (2009). Navigating the molecular patent landscape. *Expert Opinion on Therapeutic Patents* 18(5):461-472, p. 468. See also S Soini, S Aymé, and G Matthijs. (2008). Patenting and licensing in genetic testing: ethical, legal and social issues. *European Journal of Human Genetics* 16:S10-S50, p. S12.; TJ Ebersole, MC Guthrie, and JA Goldstein. (2005). Patent pools as a solution to the licensing problems of diagnostic genetics. *Intellectual Property & Technology Law Journal* 17:6-13.

designed. The most common multiplex platform is the gene microarray, which consists of a substrate upon which specific nucleic acid molecules are placed or "spotted." These spotted molecules, which have sequences that correspond to partial gene sequences or sequences of phenotypic relevance outside of genes, will hybridize or combine with complementary patient DNA fragment molecules. This hybridization can be detected by a variety of methods, thus revealing the presence or absence of specific sequences in the patient's genome. A related method of multiplex testing involves microbeads. Like microarrays, microbead systems involve attaching onto beads DNA molecules with partial gene sequences or sequences of phenotypic relevance outside of genes.

For both microarray and microbead forms of multiplex testing, the probe molecules used to detect gene sequences would infringe corresponding patented genes if the probe molecules are identical or equivalent to the claimed isolated genes. The probe molecules would also infringe any claims to identical or equivalent oligonucleotide molecules useful as probes.[128] Similarly, those spotted molecules whose sequences correspond to DNA sequences of phenotypic relevance outside of genes would infringe patent claims to such molecules. Multiplex testing would also infringe association patent claims. Association patent claims, a phrase used in this report to refer to claims of a simple association between a genotype with a phenotype, may not reference a particular method for detecting the genotype. For example, patent 5,693,470 claims "[a] method of determining a predisposition to cancer comprising: testing a body sample of a human to ascertain the presence of a mutation in a gene identified as hMSH2." Because this patent claims "testing" generally, any testing method, including any multiplex testing that "ascertains the presence" of a mutation in *hMSH2*, probably would infringe this patent claim, so long as the method was used for determining, among other things, a predisposition to cancer. Thus, association patent claims of this nature—which do not specify a particular method for detecting the genotype—likely would be infringed by multiplex testing.

Because multiplex testing methods would infringe typical patent claims on genes and associations, to market a multiplex test without being sued for infringement, a test developer would need to license those patents infringed by the particular molecules used in the multiplex test. The alternative of leaving patented genes out of a multiplex test or not reporting the results pertaining to those genes undermines the very clinical utility of multiplex analysis.[129]

The number of licenses a microarray developer would need would depend on how many genes the developer intended to include in the test and how many of those genes are protected by patents. But, assuming the developer wanted to test for multiple conditions involving many genes or multiple genes causing one condition, the developer would likely need many licenses given that many human genes are protected by patents. Although studies conducted so far have not been able to determine exactly how many genes in the genome are patented, these studies provide related information that is useful in getting a general sense of just how much of the genome is covered by patents. For example, one study found that 20 percent of the genes

[128] Patent 5,622,829 contains claims to such fragments.
[129] While it may be that not reporting test results prevents the patent holder from becoming aware of the use of patent-protected genes or probe molecules, performance of the test is still infringement so long as the probe molecules used in the test are claimed by the patent or equivalent to what the patent claims.

identified so far in the human genome are referenced in the claims of patents.[130] This percentage corresponds to 4,382 genes of the 23,688 genes in the National Center for Biotechnology Information's RefSeq and Entrez Gene databases as of 2007.[131] The authors of this study, Kyle Jensen and Fiona E. Murray, determined these numbers by first searching for all patents that include nucleotide sequences in the claims (the claims section of a patent describes what is precisely claimed as the invention) and correlating the sequences with mRNAs from the human genome—mRNAs are nucleic acid molecules that are made from genes and have a sequence complementary to a gene.[132] The genes referenced in the claims are distributed over 4,270 patents "owned by 1,156 different assignees (with no adjustments for mergers and acquisition activity, subsidiaries, or spelling variations)."[133] Of these patents, 63 percent are assigned to private firms.[134] The limitation of this study is that even when a patent claim contains a nucleotide sequence, it does not necessarily mean that the isolated nucleic acid molecule that corresponds to that sequence is the actual patented invention. In some cases, the patent may be claiming the isolated molecule as the invention, but in other cases, the patent could be claiming something else, such as a process for using the molecule.[135]

Although the Jensen and Murray study cannot be extrapolated to conclude that precisely 20 percent of human genes are either patented as isolated molecules or protected through association patent claims, the study does suggest that a substantial number of genes are protected by patents. Furthermore, ownership of these patents is spread over a large number of assignees. The existence of so many patents protecting genes, spread among various assignees, creates a "patent thicket"— "a dense web of overlapping intellectual property rights that a company must hack its way through in order to actually commercialize new technology."[136] To hack through this thicket to develop a multiplex test, a developer would face several challenges. The developer first would have to identify all the patents requiring licenses. This effort would involve a costly search for relevant patents and an analysis of their claims to determine whether the proposed multiplex test would infringe each particular claim. Once the patents relevant to the test were identified, the developer would have to determine whether licenses were available for each patent. The case studies revealed that such licensing information often is difficult to obtain. Finally, the developer would have to separately negotiate licenses with each individual patent holder.[137]

Assuming the developer could obtain all of the needed licenses, their cumulative cost might make the product unprofitable. As a practical matter, the developer's anticipation of such "royalty stacking" and the transaction costs described above may discourage him or her from

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[130] K Jensen and F Murray. (2005). Intellectual property landscape of the human genome. *Science* 310:239-240, p. 239. These databases can be found at http://www.ncbi.nlm.nih.gov/RefSeq/ and http://www.ncbi.nlm.nih.gov/gene
[131] Ibid.
[132] Ibid. The researchers specifically conducted a search of the patent database looking for the phrase "SEQ ID NO" in the claims. This phrase stands in for the particular nucleotide sequence that is disclosed later in the patent.
[133] Ibid.
[134] Ibid.
[135] Ibid.
[136] C Shapiro. (2001). Navigating the patent thicket: cross licenses, patent pools, and standard setting. *Innovation Policy and the Economy* 1:119-150.
[137] I Ayres and G Parchomovsky. (2007). Tradable patent rights: a new approach to innovation. *Scholarship at Penn Law*. Paper 183. available at http://lsr.nellco.org/upenn_wps/183

pursuing the development of the multiplex test in the first place, with the result that this innovation is not realized for the benefit of patients and that more costly and time-consuming gene-by-gene testing remains the practice.

Instead of trying to obtain multiple licenses, an innovator could ignore the blocking patents, develop the product, and then respond to infringement suits if they ensue. However, this is not an advisable alternative approach. As Ian Ayres and Gideon Parchomovsky have observed, "By sinking money into the commercialization of an infringing product, the cumulative innovator only makes herself an easier prey for patent holders. After an innovation has been commercialized and put to large scale production, patentees can seek far greater royalties by threatening to shut down production."[138]

It can also be difficult for a company to determine whether a product or service will infringe existing patents. This problem is particularly prevalent in the information technology field.[139] Choosing to proceed with a product involves the risk of being sued, and the expense of defending against suits that arise diverts funds that could otherwise be used for innovation.

When there are many patents that must be licensed for a technology to be commercialized, there is also the risk of a licensing holdout delaying or blocking commercialization. That is, a patent holder on one small component of the technology may threaten to enjoin the use of his or her patent unless granted a royalty that far exceeds the value of his or her component to the overall product.[140] The developer must either grant the high licensing fee or challenge the motion to enjoin.

The Supreme Court's decision in *eBay v. MercExchange, L.L.C.*, 547 U.S. 388 (2006), may have minimized a holdout's chances of obtaining such an injunction. Prior to that decision, the U.S. Court of Appeals for the Federal Circuit had been applying a rule "that courts will issue permanent injunctions against patent infringement absent exceptional circumstances."[141] The Supreme Court rejected this rule, holding that a four-part test applies to decisions whether to grant permanent injunctions.[142] Under that test,

> A plaintiff must demonstrate: (1) that it has suffered an irreparable injury; (2) that remedies available at law, such as monetary damages, are inadequate to compensate for that injury; (3) that, considering the balance of hardships between

[138] Ibid., p. 17.
[139] Testifying before the Federal Trade Commission, a representative of Cisco systems stated that "the large number of issued patents in our field [information technology] makes it virtually impossible to search all potentially relevant patents, review the claims, and evaluate the possibility of an infringement claim or the need for a license." Federal Trade Commission. (2003). To promote innovation: the proper balance of competition and patent law and policy, http://www.ftc.gov/os/2003/10/innovationrpt.pdf.
[140] MA Lemley and C Shapiro. (2007). Patent holdup and royalty stacking. *Texas Law Review* 85:1991-2049. A threat to enjoin involves a threat to petition the court for an injunction; an injunction is a declaration by the court requiring a party to do or not do some particular act. In this case, the patent holder would threaten to seek an injunction declaring that the developer could not use the patented component.
[141] *MercExchange, L.L.C. v. eBay, Inc.*, 401 F.3d 1323, 1339 (Fed. Cir. 2005).
[142] *eBay v. MercExchange, L.L.C.*, 547 U.S. 388 (2006).

> the plaintiff and defendant, a remedy in equity is warranted; and (4) that the public interest would not be disserved by a permanent injunction.[143]

In a concurring opinion in *eBay*, Justice Kennedy recognized the phenomenon of holdouts seeking to extract exorbitant licensing fees and suggested that injunctive relief may not be appropriate in such cases: "When the patented invention is but a small component of the product the companies seek to produce and the threat of an injunction is employed simply for undue leverage in negotiations, legal damages may well be sufficient to compensate for the infringement and an injunction may not serve the public interest."[144]

Despite this encouraging language, how the *eBay* four-factor test would be applied to a patent holder who sought to enjoin commercialization of a multiplex test is unclear. This uncertainty has a chilling effect; that is, under *eBay* a multiplex developer does not learn until after lengthy and expensive litigation is concluded whether an injunction will issue. The risk that the test developer will be enjoined is likely to discourage investment in such tests.

Holdouts create problems not only when they threaten an injunction for the purpose of negotiating a higher licensing fee, but also when they refuse to license at all. Faced with such a situation, a multiplex test developer likely would have little legal recourse. Such a developer might be inclined to sue the holdout on the theory that his refusal to license was an antitrust violation. However, based on the U.S. Supreme Court's ruling in *Verizon Communications Inc. v. Law Offices of Curtis V. Trinko, L.L.P.*, 540 U.S. 398 (2004), trial courts likely would not find such a refusal to license to be anticompetitive under section two of the Sherman Act.[145] For that reason as well, the Federal Government is unlikely to prevail in court if it seeks criminal or civil sanctions for anticompetitive behavior against a holdout that refuses to license. Therefore, any threat by the Government to bring criminal or civil sanctions against a holdout that refused to license would probably not be credible or effective in motivating the holdout to license.

Thus, the thicket of patents on genes and associations presents multiple challenges that may prevent the development of multiplex tests. Several scholars and companies have echoed these concerns. For example, Dianne Nicol has highlighted several of the challenges discussed here:

> Companies involved in the development of microarray technology, which allows for multiple tests to be undertaken, are likely to face the greatest level of complexity. If such companies wish to ensure freedom to operate, they have to undertake onerous search obligations to ascertain which patents contain relevant claims and then enter into multiple licensing negotiations. The risks of royalty stacking . . . in such an environment are particularly high. It is not surprising that leaders in the field such as Affymetrix rail against gene and related patents.[146]

[143] Ibid.
[144] Ibid.
[145] MA Carrier. (2006). Refusals to license intellectual property after *Trinko*. *DePaul Law Review* 55:1191-1210.
[146] D Nicol, op. cit., p. 468.

Affymetrix is a company that has developed a platform microarray for multiplex tests.[147] Another company involved in developing platforms for multiplex testing, Illumina, also raised concerns in a public comment about patents affecting the development of multiplex tests. In its public comment on the draft of this report, the company expressed support for gene patenting, but pointed out that "[d]ealing with such vast amounts of genetic information has the potential to raise a whole host of unique intellectual property challenges . . . ."

Gert Matthijs, Ségolčne Ayme, and Sirpa Soini, writing on behalf of the European Society of Human Genetics, have also expressed concerns: "Biochip development will enable rapid detection of hundreds of genetic mutations, but practicing this might also violate hundreds of patents."[148]

What some scholars call a patent thicket is described by others as an "anticommons problem." The term "anticommons" is a shorthand reference to the phrase "the tragedy of the anticommons," which itself is a play on the older expression "the tragedy of the commons." The scholar who coined the phrase, Michael Heller, explained the derivation this way:

> In a commons, by definition, multiple owners are each endowed with the privilege to use a given resource, and no one has the right to exclude another. When too many owners have such a privilege of use, the resource is prone to overuse—*a tragedy of the commons*. Canonical examples include depleted fisheries, overgrazed fields, and polluted air.
>
> In an anticommons, by my definition, multiple owners are each endowed with the right to exclude others from a scarce resource, and no one has an effective privilege of use. When there are too many owners holding rights of exclusion, the resource is prone to underuse—*a tragedy of the anticommons*.[149]

Rebecca Eisenberg recently wrote about the possibility of an anticommons problem in multiplex testing: "some DNA diagnostic products, such as microarrays that include many different genes and mutations, could face an anticommons problem if the burden of negotiating many necessary licenses [from each patent owner] consumes too much of the expected value of the product. This may be why microarray developer Affymetrix has been an outspoken opponent of patents on DNA sequences."[150]

Indeed, as articulated earlier in this report, the numerous existing patent claims on genes are already affecting the use, if not the development, of multiplex tests in that clinicians are not reporting the results for patent-protected genes in multiplex tests for fear of inviting a lawsuit.

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[147] See the following page from Affymetrix's Web site for further information about their microarrays: http://www.affymetrix.com/estore/browse/level_one_category_template_one.jsp?parent=35796&category=35796

[148] S Soini, S Aymé, and G Matthijs. op. cit.

[149] MA Heller. (1998). The tragedy of the anticommons: property in the transition from Marx to markets. *Harvard Law Review* 111:621-688.

[150] R Eisenberg. (2008). Noncompliance, nonenforcement, nonproblem? Rethinking the anticommons in biomedical research. *Houston Law Review* 45:1059-1099, p. 1072.

1. Earlier Patent Thickets and Approaches to Addressing Them

The thicket of patents on genes and associations is not the first thicket to arise during the history of the U.S. patent system. One of the earliest documented patent thickets arose in the 1850s when various patents on components of the sewing machine temporarily prevented its development.[151] Eventually, the various patent holders formed a patent pool to consolidate their rights so that they could proceed with development of the sewing machine.[152]

Cumulative technologies such as the sewing machine—that is, inventions made up of several components or elements—often result in patent thickets because different parties may have patented the various components. Other examples of cumulative technologies where patent thickets developed include radio and airplanes in the early 20th century.[153] In the case of radio, Robert Merges and Richard R. Nelson explain that "the presence of a number of broad patents, which were held by different parties and were difficult to invent around, interfered with the development of the technology."[154] In the end, the various patent holders formed Radio Corporation of America (RCA) to break the deadlock.[155] In the case of the airplane patent thicket, the Secretary of the Navy had to intervene, working out a deal to allow automatic cross-licensing.[156] This solution, according to a group of officials with USPTO, "was crucial to the U.S. Government because the two major patent holders, the Wright company and the Curtiss Company, had effectively blocked the building of any new airplanes, which were desperately needed as the United States was entering World War I."[157]

Patent pools are thus one possible solution to patent thickets. Birgit Verbeure and her coauthors have defined a patent pool as an agreement "between two or more patent owners to license one or more of their patents as a package to one another, and to third parties willing to pay the associated royalties."[158] Because members of the pool or outsiders can obtain all needed patents with one license, the problem of royalty stacking is solved.[159] The ability to obtain all patents with one license also reduces the transaction costs that would result if a developer had to separately negotiate multiple licenses. The members of the pool agree to a formula for distributing royalties among themselves from licenses.[160] Other benefits of patent pools include the avoidance of costly litigation over patent rights and the sharing of technical information among the members of the pool.[161]

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[151] A Mossoff. (2009). A stitch in time: the rise and fall of the sewing machine patent thicket. *George Mason University Law and Economics Research Paper Series*, 09-19. p. 4.
[152] Ibid., p. 38-39.
[153] RP Merges and RR Nelson. (1990). On the complex economics of patent scope. *Columbia Law Review* 90:839-916.
[154] Ibid., p. 892-893.
[155] Ibid., p. 893.
[156] Ibid., p. 891.
[157] J Clark, J Piccolo, B Stanton, and K Tyson. (2000). Patent pools: a solution to the problem of access in biotechnology patents? Report from the United States Patent and Trademark Office.
[158] B Verbeure, E van Zimmeren, G Matthijs, and G Van Overwalle. (2006). Patent pools and diagnostic testing. *Trends in Biotechnology* 24(3):115-120, p. 117.
[159] J Clark, J Piccolo, B Stanton, and K Tyson. op. cit.
[160] B Verbeure, E van Zimmeren, G Matthijs, and G Van Overwalle. op. cit.
[161] Ibid.

Patent pools have proven successful in solving patent thickets in the field of electronic technologies, a field in which the need to standardize technologies for interoperability creates an incentive to pool that does not exist in biotechnology.[162] Nonetheless, a few patent pools have formed in biotechnology, particularly in the agricultural arena, including one pool involving crucial patents for Golden Rice.[163] But even in agriculture, pools have yet to provide a full solution to the patent thicket problem.[164]

Patent pools have also formed when no single patent holder could bring a product to market without licenses from all of the other patent holders; these circumstances, for example, led to the formation of the patent pool for radio, as described earlier. However, the holder of an important patent claim on a gene or association can often exploit the patent on its own, making and offering a genetic test protected by the patent. Such a patent holder's refusal to participate in a pool could prevent its formation or limit its usefulness.[165] And, as noted earlier, because of *Verizon Communications Inc. v. Law Offices of Curtis V. Trinko, L.L.P.,* threats to sue a holdout for anticompetitive activity in such a situation likely would not be effective.

Although the holder of a patent on an particular gene can exclusively market a genetic test for the condition or conditions that gene is associated with, such a patent holder, according to Ted Ebersole, Marvin Guthrie, and Jorge Goldstein, would have an incentive to join a patent pool if patents on other genes involved in the particular condition were held by others.[166] Goldstein and his coauthors elaborate that if, under these circumstances, an organization such as the American College of Medical Genetics (ACMG) defined the particular genes that should be tested for the specific condition, the holders of patents on these important genes would "recognize how crucial it is that all of these mutations be tested simultaneously and offer assistance [to one another] by agreeing to participate in a patent pool."[167]

Although the existence of these circumstances would seem to create an incentive to join a patent pool, these circumstances were generally not found in the case studies. For example, Myriad Genetics has patent rights to all those breast cancer mutations that, for the moment, appear relevant for testing. Similarly, one party, Athena Diagnostics, holds patents rights on two mutations frequently associated with hearing loss, while other common mutations that have been discovered are not patented. As such, Athena is in a position to test for all common mutations, but prevent anyone else from doing so. Unlike the patents on mutations associated with breast cancer and hearing loss, patents on mutations associated with familial LQTS are now held by two different parties. Cross-licenses, rather than a patent pool, would seem to be a straightforward solution to permit each rights holder to offer complete testing, but it is not clear yet if this agreement will happen.

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[162] Ibid.
[163] Ibid.
[164] BD Wright and PG Pardey. (2006). Changing intellectual property regimes: implications for developing country agriculture. *International Journal of Technology and Globalisation* 2:93-114.
[165] Ibid.
[166] TJ Ebersole, MC Guthrie, and JA Goldstein. op. cit.
[167] Ibid., p. 11.

Another challenge to setting up a patent pool is that it must not be anticompetitive in operation. The Department of Justice and the Federal Trade Commission have issued guidelines on what kinds of pooling practices qualify as competitive and anticompetitive.[168]

In sum, patent pooling shows some promise as a solution to the patent thicket that threatens the development of multiplex testing. However, there has been little progress to date in demonstrating the utility of the approach and thus doubts remain about the viability of patent pooling as a solution in the area of genetic testing.

A royalty-collection clearinghouse has also been proposed by Birgit Verbeure and her coauthors as a potential solution to patent thickets in genetics.[169] A patent clearinghouse would involve patent owners granting the clearinghouse the right to set license terms; the clearinghouse would then set a standard patent licensing fee, which would eliminate transaction costs because there would be no negotiation..[170] The clearinghouse would collect royalties from the licensees, paying patent holders according to an agreed-upon formula after deducting administrative costs.[171] To solve the royalty stacking problem, a clearinghouse could use "royalty stacking clauses" in their licensing agreements that would reduce or cap royalties for those who took many licenses.[172]

To be effective, clearinghouses must involve an entire branch of industry or many patent holders.[173] This challenge as well as others led Verbeure and her coauthors to conclude that it "remains to be seen whether patent proprietors with a strong portfolio would be willing to voluntarily participate in such a far reaching model, where patent holders no longer have ultimate control over all transactions with regard to their patented technologies managed by the clearing house."[174] Thus, as with patent pools, questions remain concerning the viability of this approach to addressing patent thickets.

[168] J Clark, J Piccolo, B Stanton, and K Tyson. op. cit.
[169] G Van Overwalle, E van Zimmeren, B Verbeure, and G Matthijs. (2007). Dealing with patent fragmentation in ICT and genetics: patent pools and clearinghouses. *First Monday* 12(6). Available at http://firstmonday.org/htbin/cgiwrap/bin/ojs/index.php/fm/article/view/1912/1794
[170] CM Nielsen and MR Samardzija. (2007). Compulsory patent licensing: is it a viable solution in the United States? *Michigan Telecommunications Technology Law Review* 13:509-539, p. 532.
[171] E van Zimmerman, B Verbeure, G Matthijs, and G Van Overwalle. (2006). A clearing house for diagnostic testing: the solution to ensure access to and use of patented genetic inventions? *Bulletin of the World Health Organization* 84(5). Available at http://www.scielosp.org/scielo.php?pid=S0042-96862006000500013&script=sci_arttext
[172] Ibid.
[173] Ibid.
[174] G Van Overwalle, E van Zimmeren, B Verbeure, and G Matthijs. op. cit.

B. The Potential Effect of Patents and Licensing Practices on Clinical Whole-Genome Sequencing

As noted in the introduction to this section, affordable clinical whole-genome sequencing is on the horizon. Once it is developed, clinicians hope to use a patient's genomic information to guide near-term preventive strategies and treatment decisions. Given the promise of affordable whole-genome sequencing, the Committee explored whether a patent thicket could delay or prevent the development of this technology. In other words, would whole-genome sequencing infringe the majority of existing patents on isolated genes and association patent claims?

To answer that question, one must consider how whole-genome sequencing is accomplished. A variety of methods exist, but most rely on the massively parallel amplification and analysis of small sections of the genome and then assembly of the resulting sequences by sophisticated information technology algorithms.[175]

The question then becomes whether such a process would infringe typical claims to isolated genes and association patent claims. Although it is difficult to generalize, claims to isolated genes typically claim the isolated gene and various complementary probes; the gene might be claimed either in its cDNA form or as a whole gene sequence, including noncoding sequences, or both.

At this time, there is uncertainty in the legal community concerning whether whole-genome sequencing would infringe patent claims on genes. Furthermore, differences in claim language among patent claims on genes may lead to differing infringement determinations. However, because of the distinct possibility that some patent claims on genes will be infringed by whole-genome sequencing, these patents remain a concern as a potential barrier to the development of whole-genome sequencing.

Although uncertainty exists as to whether patent claims on specific isolated genes would be infringed by whole-genome sequencing, one can be more confident that association patent claims would be infringed by whole-genome sequencing. Association patent claims can be quite broad. Consider the first two claims in U.S. patent 5,508,167, relating to a protein associated with the development of Alzheimer disease:

> 1. A method of detecting if a subject is at increased risk of developing late onset Alzheimer's disease (AD) comprising directly or indirectly: detecting the presence or absence of an apolipoprotein E type 4 isoform (ApoE2) in the subject; and observing whether or not the subject is at increased risk of developing late onset AD by observing if the presence of ApoE4 is or is not detected, wherein the presence of ApoE4 indicates said subject is at increased risk of developing late onset AD.
>
> 2. A method according to claim 1, wherein said detecting step is carried out by collecting a biological sample containing DNA from said subject, and then

[175] E Mardis. (2008). The impact of next-generation sequencing technology on genetics. *Trends in Genetics* 24(3):133-141.

determining the presence or absence of DNA encoding ApoE4 in said biological sample.

These claims do not refer to particular molecular methods of detecting a gene or protein's presence. Thus, the claims could be interpreted as protecting multiple, unspecified methods, which would include whole-genome sequencing (as well as multiplex testing). Whole-genome sequencing and multiplex testing would appear to infringe these claims because, consistent with dependent claim 2, both methods would involve collecting a biological sample and determining the presence of DNA encoding ApoE4. The infringement of this claim, however, would further depend on using the presence of the gene to infer that the patient was at increased risk for late-onset Alzheimer disease. If other association patent claims have a breadth similar to the above claims, association patent claims may create a patent thicket that challenges the development of whole-genome sequencing.[176]

Finally, before whole-genome sequencing is performed routinely in the clinical diagnostic laboratory, it is likely that parallel sequencing of multiple genes will be routinely performed. This process relies on oligonucleotides that include partial or complete gene sequences that are typically protected by patent. Therefore, the use of these oligonucleotides may well infringe patent claims on probe molecules or genes, and these patents may create a thicket that prevents or delays the development of parallel sequencing of multiple genes.

As in the case of multiplex tests, patent pools and clearinghouses are potential solutions to any thickets that arise in the area of whole-genome sequencing or parallel sequencing of multiple genes, but questions remain as to the viability of these potential solutions.

C. Test Developers Have Limited Protection from Infringement Liability

The challenges patents pose to innovations in testing are not limited to patent thickets and their associated problems. Patents can also constrain developers' ability to conduct research needed to create new innovations.

Existing exemptions from liability for patent infringement provide only limited protection to those who wish to use patent-protected isolated gene molecules or associations during research and experimentation to develop improved genetic tests. First, the common law experimental use exemption most likely would not protect test developers from liability for using patent-protected isolated gene molecules or associations in the course of developing a new test. The narrow exemption is limited to "actions performed 'for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry.'"[177] The exemption does not extend to research and experiments that have "definite, cognizable, and not insubstantial commercial purposes."[178] Furthermore, the

[176] Unlike patents on associations, patents on platform technologies for sequencing and algorithms used to correctly order the sequence data can be invented around. So, these patents do not appear to pose as substantial a barrier to clinical access to whole-genome sequencing. That is, a laboratory that was not licensed rights to a particular patented platform could rely on another platform or develop its own platform for whole-genome sequencing. Indeed, several competing proprietary whole-genome sequencing platforms already exist.

[177] *Madey v. Duke University*, 307 F.3d 1351 (Fed. Cir. 2003) (quoting *Embrex, Inc. v. Service Engineering Corp.*, 216 F.3d 1343 (Fed. Cir. 2000)).

[178] *Embrex, Inc. v. Service Engineering Corp.*, 216 F.3d 1343 (Fed. Cir. 2000).

Federal Circuit has held that, regardless of whether the use is ultimately for commercial gain, any experimental use "in keeping with the legitimate business of the alleged infringer does not qualify for the experimental use defense."[179] In *Madey v. Duke University*, the Federal Circuit described Duke University's legitimate business as "educating and enlightening students and faculty participating in . . . [research] projects."[180]

Given these limitations on the experimental use exception, neither academic medical centers nor companies are likely to be able to invoke it to protect any infringing acts they committed in the course of experiments to develop a new genetic test. An example is provided by a developer creating a multiplex test that includes a patented gene fragment. Experiments to develop and validate this test might involve testing patients or known samples to verify the test's performance. Such experiments would necessarily involve the use of the patent-protected gene fragment. Validation of the test by testing patients would also likely infringe any patent claims to testing patients and associating the designated gene with a phenotype. In the case of an academic medical center, such uses of the patented gene fragments and associations would be arguably commercial in nature because any test that was ultimately developed from these experiments would be offered as a laboratory-developed test. Even if this use somehow was not commercial, one could argue that the use of the gene fragment or association to develop a genetic test would not be eligible for the exemption because it would relate to the legitimate business of an academic medical center in developing clinically useful diagnostics that improve patient care. In the case of companies using a patented gene fragment in the course of experiments to develop tests that involve those fragments, such experimental use would almost certainly be commercial in purpose and related to the company's business of developing biotechnology products or services; in that case, the company would not be entitled to the exemption.

One jurist has observed that such limitations on research are at odds with the role of patents in disclosing knowledge:

> The purpose of a patent system is not only to provide a financial incentive to create new knowledge and bring it to public benefit through new products; it also serves to add to the body of published scientific/technologic knowledge. The requirement of disclosure of the details of patented inventions facilitates further knowledge and understanding of what was done by the patentee, and may lead to further technologic advance. The right to conduct research to achieve such knowledge need not, and should not, await expiration of the patent. That is not the law, and it would be a practice impossible to administer. Yet today the court disapproves and essentially eliminates the common law research exemption. This change of law is ill-suited to today's research-founded, technology-based economy.[181]

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[179] *Madey v. Duke University*, 307 F.3d 1351 (Fed. Cir. 2003). Even if one were to argue that *Madey's* interpretation of experimental use was confined to research tools such as the invention used in *Madey*, genes claimed in some patent claims can serve as research tools in some contexts.

[180] Ibid.

[181] *Integra Lifesciences I, Ltd. v. Merck KGaA*, 331 F.3d 860, 873 (Fed. Cir. 2003) (Newman, J., dissenting). The case did not involve the common law research exemption—instead, it was about the statutory research exemption, which is discussed in subsequent paragraphs of this report.

While the common law experimental use exemption likely would not provide any protection to genetic test developers, a statutory experimental use exemption likely provides only limited protection. This statutory exemption is found in the Hatch-Waxman Act and provides an exemption from patent infringement liability for using a patented invention for the purpose of developing and submitting information under a Federal law regulating drugs.[182] Given the conditions needed to invoke this exemption, it appears that only test kit developers, and not creators of laboratory-developed tests, may be able to invoke it because test kits, unlike most laboratory-developed tests, are subject to review by FDA as medical devices under the Food, Drug, and Cosmetic Act (FDCA).[183] As part of the review process, the test developer would have to demonstrate the test's analytical validity, which could involve performing the kit's genetic test on patients.[184] Because in this case the performance of the genetic test would be related to submitting information under the FDCA for review of the test kit, the use of the patented isolated gene molecules and patented associations would likely be exempt from infringement liability.[185] However, once the genetic test kit was FDA-cleared or -approved and then marketed, the use of the patented isolated gene molecules and patented associations without a license would no longer be exempt from infringement.

In contrast to the process of developing a test kit, research to create a laboratory-developed test generally would not involve submission of information under the FDCA. Laboratories that provide laboratory-developed tests are presently regulated under CLIA, 42 U.S.C. § 263a. It seems unlikely that CLIA would be considered a "Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products," as required by the exemption.[186] Therefore, any clinical testing done as research to develop a laboratory-developed test likely would not fit within the Hatch-Waxman exemption.[187]

The majority of genetic tests are offered as laboratory-developed tests, rather than as testing kits.[188] Unless this trend changes, very few genetic test developers (i.e., only those creating kits) will able to conduct developmental research on patents without being liable for infringement.

In sum, it appears that test manufacturers are eager to develop—and clinicians are eager to use—multiplex tests, rather than single-gene tests, to carry out genetic testing. These tests would be more efficient than conducting a series of individual tests. Patent claims on isolated genes and association patent claims, however, appear to have already created a thicket of intellectual property rights that may prevent innovators from creating these multiplex tests. Similar concerns arise when envisioning the clinical application of whole-genome sequencing. Such scenarios threaten to diminish the usefulness of these promising technologies and their application to patient care. The creation of a patent pool or clearinghouse is a possible, but uncertain, solution to the patent thicket facing multiplex tests and whole-genome sequencing.

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[182] 35 U.S.C. § 271(e)(1).
[183] 21 U.S.C. § 321(h); 21 C.F.R. Part 809.
[184] See FDA Guidance on Pharmacogenomic Tests and Genetic Tests for Heritable Markers, available at http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077862.htm#8
[185] See EM Kane. (2008). Patent-mediated standards in genetic testing. *Utah Law Review* 2008:835-874, p. 843.
[186] 35 U.S.C. § 271(e)(1).
[187] Kane, op. cit., p. 844.
[188] Ibid., p. 839.

Finally, more information is needed on patent holders' licenses: particularly the types of licenses that have been issued and whether they are restricted to a particular field of use. Such information would enable technology developers to more easily determine the necessary licenses for planned innovations. As multiplex testing and whole-genome sequencing become commonplace in medicine, challenges to innovators in obtaining access to licensing information may discourage the development of advanced tests and their application to medicine.

VII. RELEVANT LEGAL DEVELOPMENTS

The Committee also considered legal developments in the patent arena and how they might affect the identified issues. Several public commenters were of the view that recent legal decisions have obviated any need for change; others suggested that the decisions did not alter what were viewed as existing threats to patient access.

A. Plaintiffs Challenge the Patentability of Nucleic Acid Molecules

AMP and other plaintiffs, represented by the American Civil Liberties Union (ACLU) and the Public Patent Foundation, filed a lawsuit in May 2009 against Myriad Genetics, USPTO, and other defendants that challenges the idea that isolated nucleic acid molecules are patentable subject matter. The case, *Association for Molecular Pathology, et al. v. United States Patent and Tradmark Office, et al.*, will be the first to squarely consider whether such molecules are patentable subject matter.[189]

Congressional committee reports accompanying the Patent Act of 1952 indicate that Congress intended patentable statutory subject matter under § 101 to "include anything under the sun that is made by man."[190] On the other hand, things that are not made by humans—such as laws of nature (for example, the law of gravity), natural phenomena, and abstract ideas—are not patentable subject matter under § 101.[191] This exclusion extends to products of nature, such as minerals.[192] Based on this legal principle, the genes found in nature—the genes within a human's cells, for example—cannot be patented. However, USPTO began issuing patents on isolated nucleic acid molecules whose sequences correspond to genes in 1992 and, in response to public comments, has expressed its belief that these isolated molecules are patentable as compositions of matter or as manufactures because they do not exist in a purified, isolated form in nature.[193]

Among the cases USPTO cites in support of its conclusion is the 1911 case *Parke-Davis & Co. v. H.K. Mulford & Co.*, 189 F. 95 (C.C.S.D.N.Y. 1911). In that case, Judge Learned Hand held that adrenaline purified from a gland was patentable. In finding the invention patentable, Judge Hand reasoned that purified adrenaline differed "not in degree, but in kind" from the adrenaline

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[189] The case was decided in March 2010 after the approval of this report.

[190] *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).

[191] Ibid. No major opinion apparently has addressed whether the exclusion of laws of nature from patent-eligibility is constitutionally mandated, although this may be the case, because patents on laws of nature would not serve to promote the progress of useful arts. For a fuller discussion of this issue, see RS Gipstein. (2003). The isolation and purification exception to the general unpatentability of products of nature. *Columbia Science and Technology Law Review* 4, available at http://www.stlr.org/html/volume4/gipstein.pdf. Justice Breyer, in his dissent from the denial of certiorari in *Lab. Corp. v. Metabolite*, 548 U.S. 124 (2006), implied that the exclusion of laws of nature from patentability is constitutionally mandated.

[192] *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).

[193] "The first patented gene was the retinoblastoma tumor suppressor gene . . . ." C Koss. (2007). Oysters and oligonucelotides: concerns and proposals for patenting research tools. *Cardozo Arts & Entertainment Law Journal* 25:747-773, p. 753, note 40. The U.S. Patent and Trademark Office's (USPTO's) utility guidelines reveal the basis for the USPTO's belief that isolated, purified DNA molecules are patentable. The guidelines are available at http://www.uspto.gov/web/offices/com/sol/og/2001/week05/patutil.htm. Purification and isolation here refer not to absolute purity, but to the general absence of other large molecules and biological substances. See A Chin. (2006). Artful prior art and the quality of DNA patents. *Alabama Law Review* 57:975-1039.

found in glands and was "for every practical purpose a new thing commercially and therapeutically."[194]

Since *Parke-Davis*, other courts have found inventions derived from nature to be patentable.[195] In *Diamond v. Chakrabarty*, 447 U.S. 303 (1980)—another case cited by USPTO in support of its conclusion—the U.S. Supreme Court considered a different inquiry: whether a living thing that did not occur naturally was patentable. A case that was closely watched by the biotechnology community, *Charkrabarty* concerned the patentability of a bacterium that had been genetically altered by introducing plasmids that enabled it to degrade oil.[196] The Supreme Court held that the bacterium qualified as a patentable manufacture or composition of matter because it was "a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility."[197] The Court continued, "[The inventor's] discovery is not nature's handiwork, but his own; accordingly it is patentable subject matter under § 101."[198]

The *Chakrabarty* decision signaled to the biotechnology community that genetically altered organisms could be patented. No case, however, has squarely considered the question of whether isolated, purified nucleic acid molecules are patentable subject matter.[199]

John Conley and Roberte Makowski have critiqued USPTO's conclusion that purified DNA molecules are patentable for suggesting that the purification of naturally occurring substances automatically confers patentability.[200] Conley and Makowski argue that the focus of the patentability inquiry, as established in *Parke-Davis* and *Charkrabarty*, is not on purification *per se*, but on whether an invention derived from nature differs "in some substantial and material

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[194] *Parke-Davis & Co. v. H.K. Mulford & Co.*, 189 F. 95 (C.C.S.D.N.Y. 1911).

[195] For example, in *Merck & Co., Inc. v Olin Mathieson Chemical Corporation*, 253 F.2d. 156 (4th Cir. 1958), vitamin B12, extracted from the liver of cattle, was found to be patentable. At least some cases before *Parke-Davis* that considered whether claimed inventions derived from nature were patentable found that they were not patentable—see, for example, *American Wood-Paper Co. v. Fibre Disintegrating Co.*, 90 U.S. 566 (1874) (holding that pulp purified from wood and other sources was not a new manufacture). Even some cases after *Parke-Davis* found such inventions not to be patentable—see, for example, *General Electric Co. v. DeForest Radio Co.*, 28 F.2d 641 (3d. Cir. 1928) (holding that purified tungsten was not patentable, even though it has ductility and strength that natural tungsten oxide lacks). Different perspectives on the evolution of "products of nature" jurisprudence can be found in Gipstein, op. cit.; JM Conley and R Makowski. (2003). Back to the future: rethinking the product of nature doctrine as a barrier to biotechnology inventions (Part I). *Journal of the Patent & Trademark Office Society* 85:301-334; JM Conley and R Makowski. (2003). Back to the future: rethinking the product of nature doctrine as a barrier to biotechnology inventions (Part II). Journal of the Patent & Trademark Office Society 85:371-398; and L Andrews and J Paradise. (2008). Genetic sequence patents: historical justification and current impacts. Paper presented at the Conference on Living Properties: Making Knowledge and Controlling Ownership in the History of Biology. Berlin, Germany, available at http://www.kentlaw.edu/islat/pdf/GeneticSequencePatents.pdf. A complete review of these cases is beyond the scope of this report.

[196] *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).

[197] Ibid.

[198] Ibid.

[199] JM Conley and R Makowski (Part II), op. cit.; H Berman and R. Dreyfuss, op. cit. In a case that came close to this question but that did not address it, the Federal Circuit considered various other challenges to a patent claiming a purified and isolated DNA molecule. *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200 (Fed. Cir. 1991).

[200] For such a critique, see JM Conley and R Makowski (Part II), op. cit.

way from the natural version."[201] In other words—using the language from *Parke-Davis*—the invention must be different "in kind." Therefore, according to Conley and Makowski, purification "is a basis for patentability only if it creates a material difference between the claimed product and its natural precursor."[202] Conley and Makowski point to arguments that could be made both for and against the patentability of isolated nucleic acid molecules and have called for the courts to conduct a "fact-specific inquiry into the materiality of the differences that are created by the processes such as isolation, purification, and synthesis."[203]

AMP's lawsuit against Myriad Genetics and the other defendants presents an opportunity for the Federal courts to undertake this inquiry, as well as to consider whether association patent claims are patentable.[204] The plaintiffs are challenging the validity of patents associated with two genes used in breast cancer genetic testing, specifically *BRCA1* and *BRCA2*.[205] In the complaint filed with the U.S. District Court, Southern District of New York, the plaintiffs argue that patents on isolated nucleic acid molecules and association patent claims violate "long established principles that prohibit the patenting of laws of nature, products of nature, and abstract ideas."[206]

At this writing, this case has not been decided.[207] If the defendants prevail, the Committee's recommendation will still be relevant because gene patents and associations will remain enforceable. But even if the plaintiffs prevail, the decision would not lead to the automatic invalidation of all existing patents on genes and associations.[208] Depending on how the decision is framed, there may be a continuing need to challenge patenting strategies.

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[201] Ibid., p. 379. See also DS Chisum. *Chisum on Patents* (2001 & Supps.) (recognizing that in *Parke-Davis,* the focus of the patentability inquiry is on whether the pure compound differs in kind). See also H Berman and R Dreyfuss, op. cit. (recognizing that, to be patentable, an invention derived from nature must be different in kind from the product of nature). Conley and Makowski's statement that the invention must have material differences over the product of nature is simply a way of rephrasing the *Parke-Davis* requirement that the invention differ in kind from the product of nature.

[202] JM Conley and R Makowski (Part II), op. cit.

[203] Ibid., p. 393-394.

[204] The case is not limited to those Myriad patents claiming isolated DNA molecules. It also challenges patents that claim methods of associating a genotype with a phenotype. For example, claim 2 of patent 6,033,857 claims "[a] method for diagnosing a predisposition for breast cancer in a human subject which comprises comparing the germline sequence of the BRCA2 gene or the sequence of its mRNA in a tissue sample from said subject with the germline sequence of the wild-type BRCA2 gene or the sequence of its mRNA, wherein an alteration in the germline sequence of the BRCA2 gene or the sequence of its mRNA of the subject indicates a predisposition to said cancer." Judge Robert Sweet of the U.S. District Court for the Southern District of New York held in a written decision issued on March 29, 2010, that the claims-in-suit were invalid for claiming unpatentable subject matter. *Assoc. for Molecular Pathology v. USPTO* (S.D.N.Y. March 29, 2010).

[205] Gene Patents Stifle Patient Access To Medical Care And Critical Research. ACLU Press Release, May 12, 2009, available at http://www.aclu.org/freespeech/gen/39572prs20090512.html

[206] ACLU Compl. ¶ 4, available at http://www.aclu.org/images/asset_upload_file939_39568.pdf

[207] After the approval of this report, Judge Robert Sweet of the U.S. District Court for the Southern District of New York held in a written decision issued on March 29, 2010, that the claims-in-suit were invalid for claiming unpatentable subject matter. *Assoc. for Molecular Pathology v. USPTO* (S.D.N.Y. March 29, 2010).

[208] As the attorney for the plaintiffs explained in a recent interview, "Success in this case will encourage new lawsuits regarding any or all of those [existing] patents. Theoretically, the facts in each instance are sufficiently different so that there would be no across-the-board invalidation of the patents. Each case would be separate." S Albainy-Jenei. (2009). Bulletproof: Interview with ACLU attorney Chris Hansen over gene patents. Patent Baristas web site, November 12, 2009. http://www.patentbaristas.com/archives/2009/11/12/bulletproof-interview-with-aclu-attorney-chris-hansen-over-gene-patents/

B. Recent Case Law Relevant to Association Patent Claims

During its 2010 term, the U.S. Supreme Court is expected to release a decision on *Bilski v. Kappos*, which may bear on the patentability of association patent claims. Before reviewing this case, this section provides some background on these patents and the controversy they have provoked.

As noted in the Introduction, novel, useful, and nonobvious processes are eligible for patents. Relying on this ability to patent processes or methods, researchers who have discovered associations between particular gene variants and disease have obtained patent claims upon processes involving simply associating a genotype with a phenotype.

Critics of the patenting of such associations argue that process claims of this nature should not be patent-eligible because they involve unpatentable fundamental laws of nature—namely, the relationship or association between a particular genetic sequence and a disease. Furthermore, it can be argued that such processes involve mental steps that are not subject to protection.[209] Whether the courts will agree with these arguments is unclear at the moment. In a recent case, *In re Bilski*, 545 F.3d 943 (Fed. Cir. 2008), the Federal Circuit Court of Appeals defined the test that governs whether a process qualifies as patent-eligible subject matter under 35 U.S.C. § 101 or is unpatentable as a law of nature. Citing U.S. Supreme Court precedent, the Federal Circuit first recognized that processes that involve a specific application of an abstract idea or natural law are patent-eligible, even though abstract ideas and natural laws themselves are not patentable.[210] The Federal Circuit then elaborated that a process is limited to a specific application of an abstract idea or natural law (and thus patentable) if (1) it is tied to a particular machine or apparatus or (2) it transforms a particular article into a different state or thing.[211]

The patented process in question in *Bilski* was not a process for simply associating a genotype with a phenotype, but "a method of hedging risk in the field of commodities trading."[212] Whether a typical claim to a method of diagnosis based on associating a genotype with a phenotype would pass the "machine-or-transformation" test is an open question. The answer will depend on how patent examiners and courts interpret the precise meaning of "machine" and "transformation." The *Bilski* court indicated that future decisions will refine "the precise contours" of what qualifies as a machine or apparatus.[213] Attorneys have indicated that guidance from the Federal Circuit is needed as well on what qualifies as a transformation.[214]

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[209] "Mental processes" is a phrase that has been used by the Federal Circuit in referring to unpatentable processes based solely on mental operations. *In re Comiskey*, 499 F.3d 1365 (Fed. Cir. 2007).
[210] *In re Bilski*, 545 F.3d 943 (Fed. Cir. 2008).
[211] Ibid.
[212] Ibid.
[213] Ibid.
[214] *Patentable Subject Matter: In re Bilski*, Edwards Angell Palmer & Dodge Client Advisory, December 2008, http://www.eapdlaw.com/newsstand/detail.aspx?news=1435

Although the majority opinion in *Bilski* did not reference diagnostic tests, Judge Rader filed a separate opinion in which he commented on the patentability of association patent claims.[215] First, however, Judge Rader rejected the majority's "machine-or-transformation" test.[216] He argued that the test imposes conditions on the patentability of processes that have no basis in the Patent Act.[217] He elaborated, "[T]he only limits on eligibility [for patents] are inventions that embrace natural laws, natural phenomena, and abstract ideas."[218] Rader then went on to explain that although biological relationships cannot be patented because they are natural laws, processes that employ these relationships for a specific useful end can be.[219]

Therefore, under Judge Rader's analysis, a process for diagnosing a disease based on the biological relationship between a gene and a disease would be patentable. Since his views were in a separate opinion, they do not establish legal precedent. As such, for the moment, no court decision has directly answered whether association patent claims qualify as patentable subject matter or are unpatentable laws of nature.

Following the Federal Circuit's decision, the patent applicants in *Bilski* petitioned the U.S. Supreme Court for a writ of certiorari—that is, they petitioned the Court to review the appellate court's decision.[220] The petitioners asked the Court to decide whether the Federal Circuit's "machine-or-transformation" test for patentable processes was in error.[221] On June 1, 2009, the Court granted the petition, and on November 9, 2009, the Court heard oral argument; the Court is expected to issue a decision by June 2010.[222]

The principles of the Court's decision may be applicable to association patents, and, even if they are not, the Court's decision may offer *dicta*—nonbinding statements not needed for the decision—on whether association patent claims are patentable.

To date, the only Supreme Court opinion to comment on the patentability of association patent claims was a 2006 dissent by Justice Stephen Breyer. Breyer filed his dissent to the Court's decision to pass on deciding a case, *Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 370 F.3d 1354 (2004), that concerned the validity of an association patent claim.[223] The association patent claim in question in *Lab. Corp.* consisted of assaying a body fluid for homocysteine and then correlating an elevated level of homocysteine with a vitamin B deficiency.[224] The university doctors who patented this process had discovered the biological relationship between these two substances.[225] When the case was before the Federal Circuit Court of Appeals, the Federal Circuit did not reach the issue of the patentability of the process, deciding the case on other

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[215] *In re Bilski*, 545 F.3d 943 (Fed. Cir. 2008).
[216] Ibid.
[217] Ibid.
[218] Ibid.
[219] Ibid.
[220] *Bilski v. Kappos*, Petition for a Writ of Certiorari, available at http://www.patentlyo.com/bilskipetition.pdf
[221] Ibid.
[222] *In re Bilski,* 545 F.3d 943 (Fed. Cir. 2008), cert. granted sub nom., *Bilski v. Kappos*, 129 S.Ct. 2735 (U.S. June 1, 2009) (No. 08-964). IP Update – Bilski v. Kappos, http://www.finnegan.com/IPUpdateBilskivKappos/
[223] *Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124 (2006). The Court granted the writ of certiorari, heard oral arguments, and then dismissed the writ of certiorari as improvidently granted.
[224] Ibid.
[225] Ibid.

grounds.[226] LabCorp sought review of the case by the U.S. Supreme Court, but the Court dismissed the petition after initially granting review and hearing oral arguments.[227] Justice Breyer, joined by Justice Stevens and Justice Souter, dissented from the dismissal. In his dissent, Breyer addressed the patentability of the process in *Lab. Corp.* and argued that the diagnostic process was nothing more than an unpatentable natural phenomenon.[228] (Rader's separate opinion in *Bilski* was in part a rebuttal to Breyer's opinion.) As with Rader's opinion, Breyer's opinion is not precedential.

The Supreme Court must also decide whether to grant review of *Prometheus Labs., Inc., v. Mayo Collaborative Servs.*, a September 2009 Federal Circuit Court of Appeals decision that applied the *Bilski* machine-or-transformation test to a patented medical diagnostic process. The patented process in *Prometheus* was a method for adjusting the dose of a drug based on the blood concentration of the drug's active metabolite after the drug is first given to a patient. The Federal Circuit determined that the process satisfied the transformation prong of the test because the first step of administering the drug results in "the various chemical and physical changes of the drug's metabolites that enable their concentrations to be determined."[229] If the Supreme Court decides to review this case, it will have a chance to directly address the patentability of diagnostic methods, which could bear on the patentability of association patent claims.

Given the importance of addressing existing patient access problems in a timely manner, the Committee's recommendations should be considered before this case is resolved.

C. The Nonobviousness Standard for Patents on Nucleic Acid Molecules

An invention cannot be patented if it would have been obvious to one of ordinary skill in the particular inventive field.[230] Patents were not designed to protect marginal improvements to technology that are obvious and to be expected.[231] For an invention to be patentable, then, it must be nonobvious. In judging nonobviousness, one compares the prior art—the prior knowledge and technology in a particular field—to the claimed invention, assesses the ordinary level of skill in the field, and then determines whether the invention represents an advance over the prior knowledge that is beyond the capacity of the ordinary artisan.[232]

With respect to patents claiming DNA molecules, the United States' test for nonobviousness has changed since two seminal cases in the mid-1990s, *In re Bell*, 991 F.2d 781 (Fed. Cir. 1993) and *In re Deuel*, 51 F.3d. 1552 (Fed. Cir. 1995). In *Bell*, which is substantially similar to *Deuel*, the Federal Circuit considered an appeal from USPTO's rejection, on obviousness grounds, of patent applications claiming DNA molecules. The particular DNA molecules in question corresponded to insulin-like growth factor (IGF) proteins.[233] The prior art the USPTO examiner had reviewed to make the obviousness determination consisted of two important pieces of information: the

[226] Ibid.
[227] Ibid.
[228] Ibid.
[229] *Prometheus Labs., Inc., v. Mayo Collaborative Servs.,* Case No. 2008-1403 (Fed. Cir. Sept. 16, 2009).
[230] 35 U.S.C. § 103.
[231] Adelman et al., op. cit.
[232] *Graham v. John Deere Co.*, 383 U.S. 1 (1966).
[233] *In re Bell*, 991 F.2d 781 (Fed. Cir. 1993).

amino acid sequence of IGF proteins and a published laboratory procedure.[234] That laboratory procedure provided instructions for taking a protein sequence, creating a DNA probe from it using the genetic code, and then using that probe to obtain the protein's gene.[235] The patent applicants in *Bell* had used the known IGF amino acid sequence, created a DNA probe from it, and then used the probe to obtain the *IGF* gene.[236] As a final step, the patent applicants sequenced this gene, with that sequenced molecule claimed as an invention.[237] USPTO believed that based on the prior art, it would have been obvious to an ordinary molecular biologist to "find the nucleic acid when the amino acid sequence is known . . . ."[238]

The Federal Circuit Court of Appeals disagreed, holding the invention was nonobvious.[239] The Federal Circuit acknowledged that "one can use the genetic code to hypothesize possible structures for the corresponding gene and that one thus has the potential for obtaining that gene."[240] Nonetheless, because the genetic code is degenerate, with most amino acids corresponding to at least two different possible nucleotide sequences, the actual sequence of the gene could never be predicted.[241] In essence, the Federal Circuit found that the inability of one to predict on paper the gene's sequence made the resulting molecule, when sequenced, nonobvious.

Arti Rai has critiqued the Federal Circuit's analysis, arguing that the focus of the inquiry should be whether the laboratory procedures to obtain the gene would be obvious—not whether one could know beforehand, on paper, the gene's exact sequence.[242] However, this view was directly rejected by the Federal Circuit in *Deuel*. There, the Federal Circuit noted that even though it might have been "obvious to try" a standard method to obtain a gene from a protein, "'obvious to try' has long been held not to constitute obviousness."[243]

However, in *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007), the U.S. Supreme Court recently held, contrary to *Deuel*, that "the fact that a combination was obvious to try might show that it was obvious."[244] Although *KSR* did not involve a biotechnology invention, the Board of Patent Appeals and Interferences recently relied on it in deciding a case with facts similar to *Deuel*. In *Ex parte Kubin*, the Board rejected as obvious a DNA molecule whose

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[234] Ibid.
[235] Ibid.
[236] Ibid.
[237] Ibid. The court decision does not list the sequencing step, but this can be inferred from the patent applicant's possession of a sequence.
[238] Ibid.
[239] Ibid.
[240] Ibid.
[241] Ibid. As explained in a footnote to the decision, "A sequence of three nucleotides, called a codon, codes for each of the twenty natural amino acids. Since there are twenty amino acids and sixty-four possible codons, most amino acids are specified by more than one codon. This is referred to as 'degeneracy' in the genetic code."
[242] AK Rai. (1999). Intellectual property rights in biotechnology: addressing new technology. *Wake Forest Law Review* 34:827-847; see also BC Cannon. (1994). Toward a clear standard of obviousness for biotechnology patents. *Cornell Law Review* 79:735-765 for a critique of Federal Circuit nonobviousness jurisprudence in biotechnology cases.
[243] *In re Deuel*, 51 F.3d. 1552 (Fed. Cir. 1995).
[244] The Supreme Court's principal holding in *KSR*, which did not involve a biotechnology invention, was to reaffirm the test of nonobviousness first laid out by the Court in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966).

sequence was derived from a known protein.[245] The Board reasoned that for an ordinary molecular biologist with a protein in hand, it would be obvious to isolate and sequence the corresponding DNA.[246] In other words, such sequencing would be "obvious to try." Although the Board asserted that *Deuel* was not relevant to the case, insofar as *Deuel* might be considered relevant, the Board found that the *KSR* decision overruled the *Deuel* principle that obvious to try does not constitute obviousness.[247]

The inventors appealed this decision, and on April 3, 2009, the Federal Circuit Court of Appeals decided *In re Kubin*, upholding the Board's decision that the claimed DNA molecule was obvious.[248] Based on this decision, a patent examiner can now find obviousness where the combination of certain elements was obvious—where, for example, it was obvious to combine knowledge of a protein's sequence and standard methods to find a gene based on a protein's sequence.

Prior to this Federal Circuit decision, USPTO had issued "Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex, Inc.*"[249] These guidelines signal that the patent office will consider obvious and unpatentable any applications that claim a DNA molecule derived from a known protein.[250] But even nucleic acid molecules derived through other means may be unpatentable after *KSR* and *In re Kubin*, according to Janis Fraser's assessment: "As a practical matter, if obviousness of a gene hinges on whether there was a known technique that could have been used to clone the gene, few if any gene inventions will pass muster."[251] In addition, existing patents on nucleic acids are now subject to *KSR's* and *In re Kubin's* obviousness standard and challenges against existing patents' validity will likely be brought.[252] Any party can challenge a patent's validity through a reexamination procedure.[253] In addition, a defendant in an infringement lawsuit can challenge the validity of a patent, and a party with standing can challenge a patent's validity through a declaratory judgment action.[254]

Although the Committee recognizes that *In re Kubin* may have weakened the ability of many patentees of nucleic acid molecules to enforce their patents, it is difficult to know for certain

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[245] *Ex Parte Kubin & Goodwin*, No. 2007-0819, 2007 WL 2070495 (Bd.Pat.App. & Interf. May 31, 2007).
[246] Ibid.
[247] Ibid.
[248] *In re Kubin*, No. 2008-1184 (Fed. Cir. Apr. 3, 2009).
[249] Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex, Inc.*, effective October 10, 2007, http://www.uspto.gov/web/offices/com/sol/og/2007/week45/patgide.htm.
[250] Ibid.
[251] JK Fraser. (2008). U.S. gene patents in legal limbo for now. *Genetic Engineering and Biotechnology News*, April, 1, http://www.genengnews.com/articles/chitem.aspx?aid=2422
[252] RG Stern, KC Bass, JE Wright, and MJ Dowd. (2007). Living in a post-*KSR* world, working paper created for The Sedona Conference on Patent Litigation VIII, http://64.237.99.107/media/pnc/1/media.121.pdf.
[253] The reexamination procedure can be found in Chapter 30 of United States Code Title 35. Some legal commentators have learned that the USPTO is working on establishing standards for determining when a reexamination challenge to an issued patent claiming a nucleic acid molecule raises "a substantial new question of patentability," as required by 35 U.S.C. § 303(a). It seems that challengers will not be able to merely cite *KSR* and ask for a re-review of the cited prior art. RG Stern, KC Bass, JE Wright, and MJ Dowd. op. cit.
[254] The declaratory judgment action is made under 28 U.S.C. § 2201.

whether the genes claimed in older patents were discovered by means that would have been obvious to an ordinary person in the field at the time of their discovery (thereby making these older patents vulnerable to invalidation).[255] In addition, it is difficult to predict whether holders of patents on genes, regardless of the objective validity or invalidity of their patents, will conclude that their patents are invalid and stop enforcing them or whether they will operate under the belief that their patents are valid and continue to enforce them. Even if patent holders largely concluded their patent claims on genes were unenforceable, association patent claims would remain as a means of protecting genetic tests unless *Bilski v. Kappos* alters their patentability. Given the uncertainty surrounding the impact of recent decisions as well as pending and possible future cases, the Committee believes that its recommendations are the best way to address the problems and concerns identified in this report.

D. Clinicians are not Exempt from Liability for Infringing Biotechnology Patents

No existing law provides a safe harbor for clinicians who infringe patents when performing genetic tests. In 1996, U.S. patent law was amended to exempt medical practitioners from infringement liability for using patented medical or surgical techniques in medical practice.[256] Under the revised law, a court could decide that a physician had infringed a medical process patent but could not order that physician to pay damages or to stop using the technique. The liability protection was not extended to "the practice of a patented use of a composition of matter in violation of such patent, or . . . the practice of a process in violation of a biotechnology patent[,]" or "the provision of pharmacy or clinical laboratory services (other than clinical laboratory services provided in a physician's office) . . . ."[257]

In 2002, Representative Lynn Rivers (D-MI) introduced the Genomic Research and Diagnostic Accessibility Act of 2002, which included a provision to allow researchers and medical practitioners to use patented genes sequences for noncommercial research purposes and a provision to exempt clinicians performing genetic tests from patent infringement liability.[258] The bill did not become law.[259]

[255] The obviousness or nonobviousness of a discovery is evaluated by considering what would have been obvious at the time the invention was made. *Environmental Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984).
[256] 35 U.S.C. § 287(c). This is sometimes referred to as the Frist-Ganske medical procedures exemption statute.
[257] 35 U.S.C. § 287(c).
[258] NIH Office of Legislative Policy and Analysis, http://olpa.od.nih.gov/legislation/107/pendinglegislation/9gene.asp.
[259] See http://www.govtrack.us/congress/bill.xpd?bill=h107-3967.

VIII. BALANCING ACCESS AND INNOVATION: GUIDANCE FROM U.S. LAW AND POLICY, PREVIOUS POLICY STUDIES, AND OTHER LEGAL FRAMEWORKS

In considering what recommendations to make to the Secretary, SACGHS reviewed three other broad areas. First, the Committee looked at existing technology transfer laws and policies, evaluating the mechanisms they provide for addressing patient access problems. The Committee also reviewed a study of licensing practice outcomes for DNA patents under two different policy frameworks, a framework created by the Patent and Trademark Amendments of 1980 (35 U.S.C. §§ 200-212, also known as the Bayh-Dole Act), which applies to academic institutions, and a framework created by the Stevenson-Wydler Technology Transfer Act of 1980, which applies to research conducted by NIH intramural scientists (i.e., Federal Government employees) (see further discussion below). The Committee also reviewed the findings and recommendations of other groups that have looked at the effect of patents and licensing practices on patient access to genetic tests. Finally, the Committee considered the international patent and licensing landscape to see how other countries have tried to balance potential incentives from exclusive rights and public access to genetic tests.

A. The Bayh-Dole Act

The Federal Government supports a significant amount of biomedical research. Prior to 1980, there was no Government-wide policy for the patenting and licensing of inventions made by the Government's grantees and contractors. The Government retained ownership of most inventions created with Federal funding, and very few of these were developed successfully into useful products or services. In 1980, the Federal Government held title to more than 28,000 patents, and fewer than five percent of these were licensed to industry for commercial development.[260]

The Bayh-Dole Act was signed into law in December of 1980 and became effective July 1, 1981. It was enacted to increase U.S. competitiveness and economic growth by promoting the transfer of inventions made with Federal Government funding by Federal Government grantees and contractors to the private sector for development into commercial products and services that would be beneficial and become available to the public. The Bayh-Dole Act established a uniform policy that Federal contractors and grantees may elect title to and patent their inventions that are conceived of or first actually reduced to practice in the performance of a Federal grant, contract, or cooperative agreement. The Act's policy and objectives include promoting "the commercialization and public availability of inventions made in the United States . . . ."[261]

With respect to any invention that the contractor or grantee elects title to, the Federal Government is granted a "nonexclusive, nontransferable, irrevocable, paid-up license . . . ."[262]

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[260] U.S. General Accounting Office (GAO) Report to Congressional Committees. (1998). *Technology Transfer: Administration of the Bayh-Dole Act by Research Universities*.
[261] 35 U.S.C. § 200.
[262] 35 U.S.C. § 202(c)(4).

On November 1, 2000, the Bayh-Dole Act was amended to ensure that inventions made under it were used "without unduly encumbering future research and discovery."[263] Regulatory provisions associated with the enactment of the Bayh-Dole Act of 1980 stipulated the need for all grantees or contractors to report on the utilization of inventions that result from federally funded research.[264]

To facilitate compliance with these legal requirements, the Interagency Edison (iEdison) tracking system and database was designed, developed, and implemented in 1995. This system facilitates and enables grantee and contractor organizations to directly input invention data as one means of fulfilling the reporting requirement. Since 1997, iEdison participation has grown to more than 1,300 registered grantee or contractor organizations supported by any of more than 29 Federal agency offices. Use of iEdison, however, is voluntary for inventions and patents developed under Federal funding agreements.

Under the Bayh-Dole Act, NIH may limit a grantee's right to elect title or NIH may elect title itself "in exceptional circumstances when it is determined by the agency that restriction or elimination of the right to retain title to any subject invention will better promote the policy and objectives" of the Bayh-Dole Act.[265] If NIH believes such "exceptional circumstances" are involved, it must file a statement with the Secretary of Commerce justifying its determination of exceptional circumstances.[266] If the Secretary of Commerce agrees with the determination, the grantee can file an appeal with the U.S. Court of Federal Claims, and the determination of exceptional circumstances is to be held in abeyance until the appeal is resolved.[267]

Arti Rai and Rebecca Eisenberg have argued that the requirement that agencies withhold patenting rights only "in exceptional circumstances" is too burdensome, potentially deterring NIH and other agencies from invoking the procedure when needed.[268] Rai and Eisenberg call for deleting this language from the statute, so that agencies such as NIH will have more discretion in controlling patenting rights.[269] NIH would use its discretion judiciously, they argue, because the agency recognizes the value of patenting in promoting commercial development of technology and would only withhold patenting rights from a grantee when it served the aims of the Bayh-Dole Act.[270] Rai and Eisenberg also recommend allowing research on the subject grant/award to proceed during the appeal of a determination.[271]

In addition to permitting the Government to elect title to an invention in exceptional circumstances, the Bayh-Dole Act permits a Federal agency to "march in" and secure broader rights from the holder of a patent that was funded by the Federal Government.[272] The four

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[263] 35 U.S.C. § 200.
[264] The regulatory provisions are found at 37 C.F.R. Part 401.
[265] 35 U.S.C. § 202.
[266] Ibid.
[267] Ibid; 35 U.S.C. § 203(b).
[268] AK Rai and RS Eisenberg. (2003). Bayh-Dole reform and the progress of biomedicine. *Law & Contemporary Problems* 66:289-314.
[269] Ibid.
[270] Ibid.
[271] Ibid.
[272] 35 U.S.C. § 203.

limited circumstances under which the Government can use its "march-in" rights are as follows: (1) when the grantee or contractor has not taken and is not expected to take within a reasonable time effective steps to achieve practical application of the subject inventions; (2) when such action is necessary to alleviate health or safety needs that are not reasonably satisfied by the contractor, assignee, or licensee; (3) when such action is necessary to meet requirements for public use that are not reasonably satisfied; and (4) when such action is necessary to provide preference for U.S. industry or "because a licensee of the exclusive right to use or sell any subject invention in the United States is in breach of such agreement."[273] In using its "march-in" authority, the Government can either require the grantee or contractor to grant a nonexclusive, partially exclusive, or exclusive license in any field of use to a responsible applicant or applicants or the Government can grant such a license itself.[274]

Christopher Holman has proposed march-in as an option to remedy any potential problems that arise in patient access to genetic diagnostics.[275] However, Rai and Eisenberg have questioned the usefulness of the procedure, viewing it as just as burdensome as the administrative procedures involved in declaring exceptional circumstances.[276] In fact, as they explain, "the administrative obstacles are sufficiently cumbersome that NIH has never exercised these rights."[277] Although NIH has considered three different march-in petitions, NIH in each case elected not to initiate march-in proceedings.[278]

In an article written in 1999, a former deputy director of NIH OTT, Barbara M. McGarey, and HHS Office of General Counsel attorney Annette C. Levey also characterize the march-in administrative process as burdensome.[279] In their view, if a situation arose where march-in was justified by a health care emergency, "the administrative process would likely not be expeditious enough to address the situation."[280]

In a report released by the Government Accountability Office (GAO) in July 2009, officials from the Department of Defense, Department of Energy, the National Aeronautics and Space Administration, and NIH also observe that the administrative processes when considering march-in are detailed and time-consuming and may make it difficult to initiate march-in.[281] However,

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[273] 37 C.F.R. § 401.14.
[274] 37 C.F.R. § 401.14(j).
[275] CH Holman. Recent legislative proposals aimed at the perceived problem of gene patents. American Bar Association Biotechnology Section, available at http://www.abanet.org/scitech/biotech/pdfs/recent_legislative_chris_holman.pdf
[276] AK Rai and RS Eisenberg, op. cit. To lessen the current administrative hurdles, Arti Rai and Rebecca Eisenberg called for changing "the requirement that march-in authority be held in abeyance pending exhaustion of all court appeals by the government contractor . . . ." These legal scholars argue that allowing agencies to proceed with march-in more expeditiously seems appropriate, given that march-in in some cases may be needed to alleviate health or safety needs.
[277] Ibid.
[278] The three march-in petition determinations are available here: http://ott.od.nih.gov/policy/cellpro_marchin.pdf; http://www.ott.nih.gov/policy/March-In-Xalatan.pdf; and http://www.ott.nih.gov/policy/March-in-norvir.pdf
[279] BM McGarey and AC Levey. (1999). Patents, products, and public health: an analysis of the CellPro march-in petition. *Berkeley Technology Law Journal* 14:1095-1116.
[280] Ibid., p. 1110.
[281] GAO. (2009). Information on the Government's Right to Assert Ownership Control over Federally Funded Inventions. GAO-09-742.

"some officials also acknowledged that because the regulations are detailed, they ensure that appropriate and fair processes are followed during march-in proceedings."[282]

Given the administrative hurdles involved with march-in, McGarey and Levey suggest that alternative laws would be more effective if there is a public health need for an invention.[283] For instance, under 28 U.S.C. § 1498(a), the Government can practice an invention without a license if that practice is by or for the United States.[284] Despite the drawbacks of invoking the march-in provision, including the possibility that its frequent use would discourage licensing of federally funded inventions, McGarey and Levey recognize its value as a "threat . . . to federal funding recipients to ensure appropriate commercialization of the inventions."[285]

Threatening march-in could be used to address the situation in which a holder of a patent on a federally funded invention refused to license or to grant a particular type of license. Assuming such refusal created one of the four conditions needed for march-in, the Government could credibly threaten march-in to induce licensing or actually march in to compel licensing. As such, although a Government threat to bring civil and criminal sanctions for anticompetitive behavior against a patent holder who refused to license is unlikely to be effective after the *Trinko* decision, a threat to bring march-in likely would be effective, but could only be used where the patented invention was developed with Federal funding.

B. NIH Policies Relating to Data Sharing

The *NIH Principles and Guidelines on Sharing Biomedical Research Resources* encourage sharing of research tools developed by NIH-funded grant and contract recipients. [286] The document states that the goal of public benefit should guide those who are receiving NIH funds. The NIH also encourages grantees and contractors to comply with the 2005 guidance document *NIH Best Practices for the Licensing of Genomic Inventions* (see Box A). [287] For certain NIH-funded programs, compliance with the Best Practices policy is a term and condition of the grant or contract award. However, since the Best Practices encourage but do not force nonexclusivity, a grantee or contractor can still choose to license a genomic invention exclusively. In order to meet NIH programmatic and research goals, NIH has also determined that certain research findings, such as those involving full-length cDNA sequences from humans, rats, and mice, must be made available to the research community in named databases.

[282] Ibid.
[283] BM McGarey and AC Levey, op. cit.
[284] Ibid.
[285] Ibid., p. 1096.
[286] HHS. (1999). NIH Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources: Final Notice. *Federal Register* 64(246). December 23. Notices. P. 72090, http://ott.od.nih.gov/pdfs/64FR72090.pdf.
[287] See http://ott.od.nih.gov/policy/genomic_invention.html.

Box A: Excerpt from NIH Best Practices for the Licensing of Genomic Inventions

The optimal strategy to transfer and commercialize many genomic inventions is not always apparent at early stages of technology development. As an initial step in these instances, it may be prudent to protect the intellectual property rights to the invention. As definitive commercial pathways unfold, those embodiments of an invention requiring exclusive licensing as an incentive for commercial development of products or services can be distinguished from those that would best be disseminated nonexclusively in the marketplace.

Whenever possible, nonexclusive licensing should be pursued as a best practice. A nonexclusive licensing approach favors and facilitates making broad enabling technologies and research uses of inventions widely available and accessible to the scientific community. When a genomic invention represents a component part or background to a commercial development, nonexclusive freedom-to-operate licensing may provide an appropriate and sufficient complement to existing exclusive intellectual property rights.

In those cases where exclusive licensing is necessary to encourage research and development by private partners, best practices dictate that exclusive licenses should be appropriately tailored to ensure expeditious development of as many aspects of the technology as possible. Specific indications, fields of use, and territories should be limited to be commensurate with the abilities and commitment of licensees to bring the technology to market expeditiously.

For example, patent claims to gene sequences could be licensed exclusively in a limited field of use drawn to development of antisense molecules in therapeutic protocols. Independent of such exclusive consideration, the same intellectual property rights could be licensed nonexclusively for diagnostic testing or as a research probe to study gene expression under varying physiological conditions.

License agreements should be written with developmental milestones and benchmarks to ensure that the technology is fully developed by the licensee. The timely completion of milestones and benchmarks should be monitored and enforced. Best practices provide for modification or termination of licenses when progress toward commercialization is inadequate. Negotiated sublicensing terms and provisions optimally permit fair and appropriate participation of additional parties in the technology development process.

Funding recipients and the intramural technology transfer community may find these recommendations helpful in achieving the universal goal of ensuring that public health consequences are considered when negotiating licenses for genomic technologies.

PHS [The Public Health Service] encourages licensing policies and strategies that maximize access, as well as commercial and research utilization of the technology to benefit the public health. For this reason, PHS believes that it is important for funding recipients and the intramural technology transfer community to reserve in their license agreements the right to use the licensed technologies for their own research and educational uses, and to allow other institutions to do the same, consistent with the Research Tools Guidelines.

Available in full at: http://ott.od.nih.gov/policy/lic_gen.html.

NIH also encourages data sharing from genome-wide association studies, which are aimed at identifying common genetic factors that influence health and disease. Data sharing policies are also in place for the International HapMap Project, the goal of which is to compare the genetic sequences of different individuals from varying ancestries to identify chromosomal regions where genetic variants are shared. By making this information freely available, the project aims to help biomedical researchers find genes that play a role in disease and in drug responses.

In addition, the Genetic Association Information Network project, a public-private partnership between NIH and the private sector, also uses the approach set out in the *Best Practices* document. Collaborators have adopted an intellectual property policy that all of the data from

this effort will be placed in a public database so that it can be shared with other investigators. This practice prevents third parties from taking inappropriate ownership and can reduce the overall cost of research by eliminating the need for others to duplicate the research to gain access

Box B. Excerpt of NIH Policy for Sharing Data Obtained in NIH Supported or Conducted Genome-Wide Assocation Studies (GWAS)

V. Intellectual Property

It is the hope of the NIH that genotype-phenotype associations identified through NIH-supported and NIH-maintained GWAS datasets and their obvious implications will remain available to all investigators, unencumbered by intellectual property claims. The NIH discourages premature claims on pre-competitive information that may impede research, though it encourages patenting of technology suitable for subsequent private investment that may lead to the development of products that address public needs.

The NIH will provide approved GWAS data users with certain automated calculations (described under the Data Access section) as a component of the GWAS datasets distributed through the NIH GWAS data repository.

The NIH expects that NIH-supported genotype-phenotype data made available through the NIH GWAS data repository and all conclusions derived directly from them will remain freely available, without any licensing requirements, for uses such as, but not necessarily limited to, markers for developing assays and guides for identifying new potential targets for drugs, therapeutics, and diagnostics. The intent is to discourage the use of patents to prevent the use of or block access to any genotype-phenotype data developed with NIH support. The NIH encourages broad use of NIH-supported genotype-phenotype data that is consistent with a responsible approach to management of intellectual property derived from downstream discoveries, as outlined in the NIH's Best Practices for the Licensing of Genomic Inventions and its Research Tools Policy.

Available in full at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-088.html

to the same genomic data for data analysis and follow-on research.

C. NIH's Technology Transfer Policies for Intramural Inventions

On October 21, 1980, two months before the Bayh-Dole Act was enacted, the Stevenson-Wydler Technology Transfer Act of 1980 was passed by Congress, and, in 1986, the Federal Technology Transfer Act (FTTA) of 1986 amended the Stevenson-Wydler Act. Similar to the purpose of the Bayh-Dole Act, FTTA's purpose is "[t]o promote United States technological innovation for the achievement of national economic, environmental, and social goals, and for other purposes."[288] FTTA authorizes Federal agencies to transfer federally owned technology to the private sector for product development and authorizes the use of cooperative research and development agreements between Federal laboratories and nonFederal entities. Although there are similarities between the Bayh-Dole Act and FTTA, the latter has several distinct features, including the following: (1) a license may be granted only if the applicant has supplied a satisfactory plan for development and/or marketing of the invention;[289] (2) notices are published in the *Federal Register* of exclusive or partially exclusive licenses for federally owned inventions that include the prospective licensee's name and a period of time for objection;[290] and, (3) the granting of exclusive, co-exclusive, or partially-exclusive licenses is contingent, not only upon notice in the

[288] 15 U.S.C. § 3701.
[289] 37 C.F.R. § 404.5(a)(1).
[290] 37 C.F.R. § 404.7(a)(1)(i).

Federal Register, but also upon a determination by the Federal agency that the grant of a license will not tend to substantially lessen competition.[291] The FTTA also limits the term and scope of exclusivity to not greater than reasonably necessary to provide the incentive for bringing the invention to practical application or otherwise promoting the invention's utilization by the public.[292]

NIH's intramural patent policy has been developed to be consistent with the Stevenson-Wydler Act and its amendments. The policy, applying to inventions developed in its intramural research programs, provides for the use of patents and other technology transfer mechanisms (such as license agreements, material transfer agreements, and research-only licenses) for biomedical technologies only when a patent facilitates the availability of the technology to the public for preventive, diagnostic, therapeutic, research, or other commercial uses. When commercialization and technology transfer can best be accomplished for intramural-made inventions without patent protection, such protection typically is not sought. NIH licensing policy for intramural-developed technologies seeks to promote the development of each technology for the broadest possible application and requires that commercial partners expeditiously develop the licensed technology. NIH only uses partially exclusive or exclusive licensing for its intramural-developed inventions when exclusive rights are a reasonable and necessary incentive for the licensee to risk capital and resource expenditures to bring the invention to practical application or otherwise promote the invention's utilization.[293] If it is determined by NIH that a grant of an exclusive or partially exclusive license is necessary for further development of the technology, the terms and conditions of such exclusivity are narrowly tailored and are not greater than reasonably necessary.[294]

To optimize the number of new products that will reach the market, NIH licenses its technology through nonexclusive licenses, exclusive licenses in narrowly defined fields of use, or exclusive licenses. Since 1990, the agency has also required that its licensed technology be made available for noncommercial research by for-profit, Government, and nonprofit researchers. Most NIH patent commercialization licenses are nonexclusive (80 percent), some are co-exclusive, and the few that are exclusive, in areas such as therapeutics or vaccines, are quite narrow (limited to a particular field of use, disease indication, or technology platform). As noted earlier, NIH grants exclusive licenses when it determines that they are a reasonable and necessary incentive for the licensee to risk capital and expenditures to bring the invention to practical application.[295]

D. Results of a Comparison of Licensing Under Two Statutory Frameworks

Since license exclusivity is often a topic of policy recommendations, a comparison of commercialization outcomes under different policy frameworks, one enabling more exclusivity in its licenses than the other, was undertaken.[296] NIH OTT patents and licenses inventions from

[291] 37 C.F.R. § 404.7(b)(1)(iii).
[292] 37 C.F.R. § 404.7(C).
[293] 37 C.F.R. § 404.7 (a)(1)(ii)(B).
[294] 37 C.F.R. § 404.7(a)(1)(ii)(C).
[295] C Driscoll, Director, Technology Transfer Office, National Human Genome Research Institute (NHGRI). Presentation to SACGHS. March 27, 2007.
[296] This study is still underway because the study authors plan to analyze additional data (76 licenses, including licenses for genes to detect pathogens such as HIV).

the NIH intramural research program under the Stephenson-Wydler Act. This Act favors nonexclusive licensing, requires a public notice period before granting licenses with exclusivity, and does not grant all-fields-of-use exclusive licenses.[297] The data for inventions developed by academic institutions were obtained in 2003 and 2004, and the data on NIH inventions extend through 2006.[298] For technical reasons, the data were not as comparable as had been anticipated. Also, there were no detailed product data for the academic institutions as those data were not part of the 2003 study. The differences in data may be due to the differing statutory frameworks and missions.

One of the preliminary findings of the study is that there are no marked differences between the NIH and academic institution in terms of the frequency and type of exclusivity in licenses. This result was surprising given that the NIH OTT licensing framework under Stevenson-Wydler favors nonexclusive licensing relative to the academic institutions under Bayh-Dole. Another finding is that OTT maintains more never-licensed patents as a percentage of its total than do academic institutions operating under the Bayh-Dole Act (see Appendix B). In addition, more DNA patents managed by academic institutions are licensed, overall, than those managed by the NIH OTT. One possible explanation for this result might be the differing statutory frameworks that academic institutions and the NIH are subject to or differences in the nature of inventions licensed by NIH.

The report also reaches the tentative conclusion that the elapsed time between patent filing, which in the biotechnology sector is generally a reasonable estimate of invention publication, and the first revenue from the license is somewhat longer under the NIH OTT practice framework than under the academic practice framework. That is, patented inventions licensed by academic institutions reached the market sooner than those licensed by the NIH. This finding suggests that exclusivity may create development incentives, as the time from licensing to the introduction of a product on market appears shorter with exclusivity than without it.

There are many caveats to this finding that exclusively licensed technologies bear royalty income sooner on average than those that are licensed nonexclusively. First and foremost, because the study was focused only on royalty-generating tests, the study necessarily missed the large percentage of genetic tests that are developed without a patent or royalty-generating license soon after a published genetic finding. Therefore, this study finding does not imply that exclusively licensed tests reach the market faster than tests developed without exclusive rights. In fact, in the case studies where there were (or are) exclusive licensees—for patents associated with testing for breast cancer, hearing loss, HH, SCA, LQTS, and Canavan disease—those that lacked patent protection reached the market with tests before the exclusive licensee. In those cases, the patent was simply used to narrow or clear the market of tests that were already available.

Second, factors other than the differing licensing approach may explain why NIH inventions generate royalty payments later. For example, the study cites research showing that university

[297] 15 U.S.C. §§ 3701 et seq.
[298] L Pressman et al. (2006). The licensing of DNA patents by U.S. academic institutions: an empirical survey. *Nature Biotechnology* 24:31-39

inventors are more involved in the technology transfer process than are NIH inventors.[299] This greater involvement by university inventors could explain why their exclusively licensed inventions reach the market faster.

Third, the limited number of data points and wide variance between them created large standard deviations for the data on university-owned inventions. As a result, the difference between the two licensing approaches for university-owned patents has not been demonstrated to be statistically significant.

A separate finding from this study was that it was difficult to determine from examining issued patents whether rights associated with that patent came to be licensed for use in genetic testing. Neither a search algorithm nor scientists with biology expertise could reliably identify, when looking at patents alone, those patents whose rights had been licensed for use in a genetic test. This finding suggests that policy recommendations relating to patents and genetic tests should not focus on the patents themselves, but on their uses or their licensing.

In fact, none of the Committee's recommendations focus on the patents themselves; they instead concern the use of patents on genes—as defined in this report—for testing and research.

E. Nine Points to Consider in Licensing University Technology

In 2007, a group of research universities and the Association of American Medical Colleges issued points to consider in managing intellectual property in the academic environment (see Box C). The Board of the Association of University Technology Managers has endorsed these points. Despite these guidelines, problems in patient access to patent-protected genetics have arisen, as described in this report.

[299] The study cites C Jansen and HF Dillon. (1999). Where do the leads for licenses come from? Source data from six institutions. *Journal of the Association of University Technology Managers* 11:51-66; and V Ramakrishnan, J Chen, and K Balakrishnan. (2005). Effective strategies for marketing biomedical inventions: lessons learned from NIH license leads. *Journal of Medical Marketing* 5(4):342-352.

Box C: "In the Public Interest: Nine Points to Consider in Licensing University Technology"

Point 1: Universities should reserve the right to practice licensed inventions and to allow other nonprofit and governmental organizations to do so.

Point 2: Exclusive licenses should be structured in a manner that encourages technology development and use.

Point 3: Strive to minimize the licensing of "future improvements."

Point 4: Universities should anticipate and help to manage technology transfer related conflicts of interest.

Point 5: Ensure broad access to research tools.

Point 6: Enforcement action should be carefully considered.

Point 7: Be mindful of export regulations.

Point 8: Be mindful of the implications of working with patent aggregators.

Point 9: Consider including provisions that address unmet needs, such as those of neglected patient populations or geographic areas, giving particular attention to improved therapeutics, diagnostics and agricultural technologies for the developing world.

Source: Available in full at: http://www.autm.net/Nine_Points_to_Consider.htm

F. Previous Policy Studies

Four previous policy reports addressing the issue of patenting genes or biotechnology inventions merit attention, because they contain sections specific to genetic tests. These studies were conducted by the Nuffield Council on Bioethics (a group in the United Kingdom), the Australian Law Reform Commission (ALRC), NRC, and the Organisation for Economic Co-Operation and Development (OECD). In addition, the U.S. Federal Trade Commission has issued a report on patent policy that included discussion of biotechnology patents.

Nuffield Council. The Nuffield Council on Bioethics, which is funded by two nonprofit charities and the U.K.'s Medical Research Council, issued *The Ethics of DNA Patenting* in 2002. The report urged raising the bar for obviousness and utility when granting DNA patents in the United Kingdom. The Council also advocated for limiting a patent's scope to identified uses:

> In our view, when patent examiners consider that a patent application that asserts rights over a naturally-occurring DNA sequence meets the criteria for patenting, the applicants could be required in some cases to disclose the specific uses to which they have demonstrated that the sequence can be put. The scope of protection would then be limited to these particular uses. In this way, at the very least, rights over entirely unrelated uses could not be subsequently asserted. The scope of the monopoly awarded would, therefore, be commensurate with the actual contribution by the inventor.[300]

[300] Nuffield Council on Bioethics. (2002). The ethics of patenting DNA. p. 65.

The Council also raised the possibility of compulsory licensing of diagnostic patents so that public health needs would be met.[301]

Australian Law Reform Commission. ALRC, an advisory body to the government, issued a major report addressing biotechnology and patents, devoting more attention to patents associated with genetic tests than any other government group. [302] With regard to Australian law and practices, the final 2004 ALRC report found "no clear evidence of any adverse impact, as yet, on access to medical genetic testing, the quality of such testing, or clinical research and development."[303] The report noted, however, that "some people in the Australian public health sector harbor genuine and serious concerns about the implications of gene patents. . . . There are arguments suggesting that the exclusive licensing of patents relating to medical genetic testing may have adverse consequences, depending on the behavior of licensees."[304] Among its recommendations, the Commission called for an experimental use exemption that would not be precluded by a commercial objective in undertaking the research.[305]

Organisation for Economic Co-operation and Development. OECD, a forum in which the governments of 30 countries work together to address the economic, social, and environmental challenges of globalization, issued *Guidelines for the Licensing of Genetic Inventions* in 2006.[306] These guidelines were developed in response to a 2002 workshop that investigated the impact of patents and licensing strategies of genetic inventions on access to information, products, and services for researchers, clinicians, and patients. Broadly speaking, the OECD guidelines support licensing practices that foster innovation, that promote dissemination of information and developments related to genetic inventions, and that encourage access to and use of genetic inventions for the improvement of human health. Best Practice 2.2 references genetic testing and states, "Rights holders should license genetic inventions for health applications, including diagnostic testing, on terms and conditions that seek to ensure the widest public access to, and variety of, products and services based on the inventions."

In October 2003, the **Federal Trade Commission** issued a report, *To Promote Innovation: the Proper Balance of Competition and Patent Law and Policy*,[307] suggesting that broad patents may have anticompetitive effects and block innovation in certain high-technology industries, such as computers and biotechnology. The report makes a number of recommendations aimed at restoring the balance between competition and patent policy and improving patent quality (e.g., by reducing the number of obvious patents). The report also recommends new mechanisms to make it less onerous to challenge invalid patents and new procedures to allow increased access to pending patents for the purpose of business planning and avoiding infringement.

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[301] Ibid., p. 48-56.
[302] ALRC. *Genes and Ingenuity: Gene Patenting and Human Health June 2004*. Australia: SOS Printing Group, http://www.austlii.edu.au/au/other/alrc/publications/reports/99/index.html.
[303] Ibid., p. 503, point 20.72.
[304] Ibid., p. 504, point 20.77.
[305] Ibid., List of Recommendations, 13-1
[306] See http://www.oecd.org/document/26/0,3343,en_2649_34537_34317658_1_1_1_1,00.html.
[307] Federal Trade Commission. (2003). To promote innovation: the proper balance of competition and patent law and policy, http://www.ftc.gov/os/2003/10/innovationrpt.pdf.

NRC. As discussed earlier, the NRC's 2006 report, *Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation, and Public Health*, was an immediate precursor to the current SACGHS study. The NRC committee commissioned three lines of inquiry, and staff conducted additional research. The committee drew on the DNA Patent Database for aggregate data on U.S. patents, worked with USPTO Examining Group 1600, which reviews patent applications in the areas of biotechnology, pharmaceuticals, and organic chemistry, and commissioned a survey of scientists that explored research access to patented materials.[308] The NRC committee also performed its own analysis of specific cases, including some U.S.-European comparisons and the patents and licensing practices associated with genetic testing for breast cancer, Canavan disease, and Huntington disease (HD). The Committee's review of the HD story indicates that researchers who discovered the gene associated with HD sought to patent a method of using the gene for diagnosis because they "believed they might use the patent to control the testing process."[309] They also discussed using licenses associated with the patent on the isolated gene molecule to enforce testing and counseling protocols. However, to date, the patent assignee has not enforced its patent rights nor issued any licenses, and the HD test is available "from more than 50 academic and commercial laboratories in the United States."[310] The NRC report notes that the broad availability of the test allows verification of test results and that laboratories have collaborated to ensure the quality of testing:

> Once the HD gene was cloned, academic and commercial laboratories interested in testing took it upon themselves to develop the proper test methodology to ensure quality control. They shared test samples representing normal and variably sized expanded alleles in order to ascertain that all the laboratories were using the same techniques and getting comparable results. . . . Testing quality control by sending around test samples has been done periodically ever since.[311]

Most of the NRC report and recommendations focus on the impacts of intellectual property law and policies on research, but, as discussed earlier in this report, one of the recommendations calls for Congress to consider a limited statutory exemption from patent infringement liability for clinical verification testing:

> Recommendation 13: Owners of patents that control access to genomic- or proteomic-based diagnostic tests should establish procedures that provide for independent verification of test results. Congress should consider whether it is in the interest of the public's health to create an exemption to patent infringement liability to deal with situations where patent owners decline to allow independent verification of their tests.[312]

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[308] JP Walsh, C Cho, and WM Cohen. (2005). View from the bench: patents and material transfers. *Science* 309**:**2002-2003. JP Walsh, C Cho, and WM Cohen. (2005). Material Transfers and Access to Research Inputs in Biomedical Research (Final Report to the National Academy of Sciences' Committee on Intellectual Property Rights in Genomic and Protein-Related Research Inventions).
[309] NRC, op. cit., p. 66.
[310] Ibid., p.67.
[311] Ibid.
[312] Ibid., p. 18.

G. International Comparisons

As part of its study, SACGHS reviewed some of the patent law provisions of other countries to see whether they permit the patenting of genes and how these countries have responded to concerns about the effect of these patents on patient access to genetic tests.

According to an OECD report, all OECD countries allow patents on gene molecules:

> Although the appropriateness of granting patents on DNA and other nucleotide sequences continues to be publicly debated, the position of the official patent authorities in OECD countries has been more or less stable for some time. Assuming that a DNA sequence is novel (not previously publicly known or used in a public manner) and that the other criteria of patentability are also met (utility, inventiveness/non-obviousness), the substance of the DNA itself can be patented. To be precise, the claims concern not the sequence as abstract information, but a molecule which has the defined sequence and function.[313]

Moreover, a 1998 European Union Directive requires that all members of the European Union (EU) allow gene patenting in their national patent laws.[314] When Germany implemented the controlling EU directive into its national patent law, it added the limitation that a patent claiming a gene molecule would be limited to those industrial applications disclosed in the patent.[315] France has a similar provision in its patent law.[316] The effect of these provisions is that researchers do not need license rights to conduct research on a patented gene, and anyone whose discovers a new application of the gene may patent that application.[317] It is not clear, however, whether a gene patented for diagnostic application could be freely used by others for the kind of research described in this report—that is, using a gene in test runs of an improved genetic test. Interpretation of German and French law is beyond the expertise of the Committee; nor were any articles found discussing this narrow question.

According to German policy analyst Ingrid Schneider, in enacting these provisions, Germany and France

> argued that patents which were "too broad" in scope would "over-compensate" the inventor, would be counterproductive both scientifically and economically because of their potential to stifle the generation of new scientific knowledge, and would reduce the incentives for inventors working downstream in research and development.[318]

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[313] Organization for Economic Co-operation and Development. (2002). *Genetic Inventions, Intellectual Property Rights and Licensing Practices: Evidence and Policies*, http://www.oecd.org/dataoecd/42/21/2491084.pdf. p. 28.
[314] Council Directive 98/44, On the Legal Protection of Biotechnological Inventions, 1998 O.J. (L213) 13 (EC) at art. 5.2.
[315] C Ann. (2006). Patents on human gene sequences in Germany: on bad lawmaking and ways to deal with it. *German Law Journal* 7:279-292, p. 286.
[316] I Schneider. (2005). Civil society challenges biopatents in the EU. PropEur Newsletter. Summer 2005. No. 1 p. 3.
[317] E Bryan. (2009). Gene protection: how much is too much? Comparing the scope of patent protection for gene sequences between the United States and Germany. *Journal of High Technology Law* 9:52-65; C Ann, op. cit.
[318] I Schneider, op. cit.

France has also passed a law permitting the government to issue compulsory licenses for patents protecting diagnostic methods, devices, and products.[319] Like France, Belgium, in implementing the EU directive, added provisions designed to mitigate the potential negative effects of biotechnological inventions on health care.[320] One provision is an expanded research exemption that makes clear that a patent holder's rights do not extend to research on or with the subject matter of the invention.[321] The scope of this research exemption is wider than that of other European countries, which permit only research on a patented invention.[322] The other Belgian provision allows for the government to grant nonexclusive compulsory licenses for public health reasons to patents protecting diagnostic methods, devices, and products.[323] According to Geertrui Van Overwalle and Esther van Zimmeren, this provision "was largely inspired by the restrictive licensing policy of the company Myriad Genetics, which refused to grant reasonable licenses to centres for genetic testing and hospitals."[324] These compulsory license provisions are broader than the U.S.'s march-in rights under the Bayh-Dole Act because they apply to patents that result from privately funded research, not just patents secured after partial or full government funding of research.

H. Would Legal Changes Relating to Patents on Genes and Associations Violate TRIPS?

Countries that belong to the World Trade Organization (WTO), such as the United States, do not have unfettered discretion regarding their patent laws. Rather, they must afford at least as much patent protection as is required by the minimum standards enunciated in the WTO's Agreement on Trade-related Aspects of Intellectual Property Rights (TRIPS). Therefore, one question that arose during Committee discussions was whether legal changes affecting either the patent-eligibility of genes and associations or the enforceability of patents on genes and associations would be inconsistent with the U.S. obligations under TRIPS.

The Committee determined that there is no cause for concern as there is ample authority in the Agreement to support changes that promote access to, and research on, genetic testing. First, nations may elect to exclude from patentability diagnostic methods for the treatment of humans, plants, and animals other than microorganisms.[325] They can also exclude "inventions, the prevention within their territory of the commercial exploitation of which is necessary to protect ordre public or morality . . . including to protect human . . . health."[326] It thus appears that broader steps than those advocated here—namely the exclusion of genes or diagnoses based on genotype-phenotype associations from patent-eligibility—would be compatible with TRIPS.

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[319] JP Love. (2007). Recent examples of the use of compulsory licenses on patents. *Knowledge Ecology International.*
[320] G Van Overwalle and E van Zimmermen. (2006). Reshaping Belgian patent law: the revision of the research exemption and the introduction of a compulsory license for public health. Chizaiken Forum 64:42-49.
[321] Ibid.
[322] Nuffield Council on Bioethics, op. cit., p. 60.
[323] G Van Overwalle and E van Zimmermen, op. cit.
[324] Ibid., p. 43.
[325] Article 27.3(a), TRIPS, http://www.wto.org/english/tratop_e/trips_e/t_agm3c_e.htm#5.
[326] Article 27.2, TRIPS, http://www.wto.org/english/tratop_e/trips_e/t_agm3c_e.htm#5.

Second, TRIPS permits members to define for themselves what constitutes an "invention."[327] Applying this principle, Argentina, Bolivia, Brazil, Columbia, Ecuador, Peru and Venezuela have chosen to classify isolated gene molecules as discoveries rather than inventions.[328] Similarly, should *Bilski* determine that simple associations are not patentable subject matter, the decision would not violate the TRIPS Agreement any more than the European Patent Convention's exclusion of programs for computers or diagnostic methods.[329]

Third, Article 30 of the TRIPS agreement indicates that

> [m]embers may provide limited exceptions to the exclusive rights conferred by a patent, provided that such exceptions do not unreasonably conflict with a normal exploitation of the patent and do not unreasonably prejudice the legitimate interests of the patent owner, taking account of the legitimate interests of third parties.[330]

Admittedly, this provision received a rather stingy interpretation in the only WTO case interpreting the Agreement in relation to a health care-related measure, *Canada–Patent Protection of Pharmaceutical Products*.[331] In that case, a dispute resolution panel held that the phrases in Article 30 are cumulative, requiring the respondent nation to justify an exception under each clause separately. In addition, the challenged measure was separately examined under Article 27 of the TRIPS Agreement, which requires members to make patents available "for any inventions . . . in all fields of technology."[332]

Canada-Pharmaceuticals was, however, decided by a WTO panel—the WTO analogue of a trial court. The Appellate Body (the WTO's "Supreme Court") has yet to address any of the exemption provisions found in the TRIPS Agreement.

More important, *Canada-Pharmaceuticals* was decided before the Doha Round of WTO negotiations. In that Round, a Ministerial Declaration emphasized that TRIPS must be interpreted "in a manner supportive of public health."[333] Furthermore, a separate Declaration on TRIPS and Public Health stated that

> the TRIPS Agreement does not and should not prevent members from taking measures to protect public health. Accordingly, while reiterating our commitment to the TRIPS Agreement, we affirm that the Agreement can and should be

[327] A Heath. (2005). Preparing for the genetic revolution—the effect of gene patents on healthcare and research and the need for reform. *Canterbury Law Review* 11:59-90
[328] Ibid.
[329] European Patent Convention, art. 52(1)(c) and 52(4), http://www.epo.org/patents/law/legal-texts/html/epc/1973/e/ar52.html.
[330] Article 30, TRIPS, http://www.wto.org/english/tratop_e/trips_e/t_agm3c_e.htm#5.
[331] WT/DS114/R (March 17, 2000).
[332] Article 27.1, TRIPS, http://www.wto.org/english/tratop_e/trips_e/t_agm3c_e.htm#5.
[333] Doha Ministerial Declaration, WT/MIN(01)/DEC/1, 20 November 2001, paragraph 17, http://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_e.htm.

> interpreted and implemented in a manner supportive of WTO members' right to protect public health . . . .[334]

The Declaration continues, "In this connection, we reaffirm the right of WTO members to use, to the full, the provisions in the TRIPS Agreement, which provide flexibility for this purpose."[335] As Alison Heath has suggested, the Declaration "may mean that a dispute regarding a gene patent measure aimed at improving access to healthcare will be approached with some leniency."[336] As explained further below, the Committee's proposals are consistent with this approach to the Agreement.

1. Changes in the Enforceability of Patents on Genes

A change in law making patents on genes unenforceable for diagnostic uses would create a limited exception. Since such a legal change would not interfere with the enforceability of these patents for therapeutics and would further the legitimate interests of doctors and their patients, it appears that it would comply with Article 30 of the TRIPS Agreement, particularly when interpreted in light of the Doha Declaration.

Whether the provision would also have to comply with the technological neutrality principle of Article 27 is another issue. Now that the Ministerial Conference has confirmed the special treatment to be accorded to patents involving health care, a neutrality requirement no longer makes sense. But even if Article 27 continues to be applicable, *Canada-Pharmaceuticals* suggests that a provision could be framed in a way that passes muster. The law challenged in that case appeared to be nonneutral in that it was devised to permit generic drug companies to develop premarket clearance data during the patent period. Nonetheless, the panel reasoned that because any industry that was subject to premarketing approval could avail itself of the measure, Canada met the neutrality requirement of the Agreement.[337]

Although the analysis in this report was limited to gene patents, if Congress is concerned about meeting the requirements of Article 27, it could frame the exemption more broadly so that it provides relief to any industry experiencing the same problems that prompted this recommendation (for example, the impossibility of inventing around and the potential for deep patent thickets).[338]

2. Creation of a Statutory Research Exemption

Because most countries have broad research exemptions,[339] it is unlikely that any WTO member would challenge the research exemption proposed by the Committee as outside the scope of

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[334] World Trade Organization. Declaration on the TRIPS agreement and public health. http://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.htm
[335] Ibid.
[336] A Heath, op. cit., p. 74.
[337] Panel Report, Canada—Patent Protection of Pharmaceutical Products, WT/DS114/R (Mar. 17, 2000) at ¶ 7.102.
[338] G Dinwoodie and R Dreyfuss. (2007). Diversifying without discriminating: complying with the mandates of the TRIPS Agreement. *Michigan Telecommunications and Technology Law Review* 13:445-456.
[339] See the discussion in this report under International Comparisons.

Article 30. Since the proposed exemption is, however, limited to gene patents, a challenge could be brought on technological neutrality grounds. But as explained above, such a challenge is not likely to succeed in the health care arena.

More importantly, Congress could avoid a challenge by casting the exemption broadly—for example, by reversing the Federal Circuit's decision in *Madey v. Duke* and restoring a general research exemption. Since the Committee's analysis was limited to gene patents, it could not propose such an exemption itself. But such an exemption has been urged by many commentators.[340] While there is empirical research suggesting that research is not hampered by the absence of a research defense, the findings suggest that scientists have persevered by developing a norm of ignoring patents.[341] An exemption that legitimized existing practice would promote the rule of law. Because patent holders' current revenue stream does not include payments for research uses, an exemption would not conflict or prejudice patent holder interests and thus would not, as Joshua Sarnoff and Henrik Holzapfel have concluded, violate Article 30.[342] Also, it would be technologically neutral.

[340] JR Thomas. (2004). Scientific research and the experimental use privilege in patent law. Congressional Research Service Report for Congress. See also KJ Strandburg. (2004). What does the public get? Experimental use and the patent bargain. *Wisconsin Law Review* 2004:81-153; MA O'Rourke. (2000). Toward a doctrine of fair use in patent law. *Columbia Law Review* 100:1177-1250; JM Mueller. (2001). No "dilettante affair": rethinking the experimental use exception to patent infringement for biomedical research tools. *Washington Law Review* 76:1-66; RS Eisenberg, op. cit. (1989).

[341] See RS Eisenberg. (2006). Patents and data-sharing in public science. *Industrial and Corporate Change* 15:1013-1031, p. 1018-1019; JP Walsh, C Cho, and W M Cohen. (2005). View from the bench: patents and material transfers. *Science* 309:2002-2003.

[342] See H Holzaphel and J Sarnoff. (2008). A cross-Atlantic dialog on experimental use and research tools. Washington College of Law Research Paper No. 2008-13, p. 46-50; S Musungu. (2007). Access to ART and other essential medicines in sub-Saharan Africa: intellectual property and relevant legislations. Report Commissioned by the United Nations Development Programme (UNDP) Regional Service Centre for Eastern and Southern Africa.

IX. CONCLUSIONS

SACGHS has a long-standing interest in recommending policies that will ensure the development of clinically useful genetic technologies, including genetic tests, and equitable access to these technologies. These concerns led the Committee to study the effect of patents on genetic test development and patient access. The Committee also studied the effect of patents on the quality of genetic tests because the reliability of a test is a fundamentally important component of any test. The conclusions and recommendations presented here reflect the consensus of the majority of the Committee. The views of three dissenting members are outlined in a statement at the end of this report.

The Committee found that a near perfect storm is developing at the confluence of clinical practice and patent law. The cost of genetic analysis is decreasing dramatically, while knowledge about the genetic foundations for health, illness, and responsiveness to medicine is growing exponentially. There is now substantial potential for improving health using these new technologies. With genetic tests, physicians may be better able to identify their patients' genetic predispositions and help patients take steps to avoid—or at least minimize—the effects of their vulnerabilities. Genetic information can also be used by pharmaceutical and biotech companies to develop therapeutics targeted to subpopulations with specific genetic variations, while physicians can use this information to identify those patients who will benefit from these targeted therapeutics.

Trends in patent law appear, however, to pose serious obstacles to the promise of these developments. Patenting has moved upstream; instead of covering only commercial products, patents can now control foundational research discoveries, claiming the purified form of genes. Fragmented ownership of these patents on genes by multiple competing entities substantially threatens clinical and research use. While new technologies enable simultaneous evaluation of multiple genes through multiplex testing, parallel sequencing, and whole-genome sequencing, fragmented ownership may create a host of problems such as patent thickets, blocking patents, high transaction costs, royalty stacking, and holdouts. Some of these problems have already come to light. In particular, some laboratories using multiplex tests have chosen not to report to patients or ordering clinicians the results for certain patent-protected genes for fear of being sued.[343] In short, the evidence indicates that patents have already limited the potential of these tests.

U.S. law has decreasing capacity to mitigate these problems. Unlike many other countries, the United States does not have compulsory licensing rules to deal with problems of blocking or holdouts. In addition, its research exemption is nominal; it essentially shields from infringement liability only research required to develop information needed for review by FDA. Also, antitrust law does not set limits on a patentee's power to refuse to sell or license its technologies.

[343] While it may be that not reporting test results prevents the patent holder from becoming aware of the use of patent-protected genes or probe molecules, performance of the test is still infringement so long as the probe molecules used in the test are claimed by the patent or equivalent to what the patent claims.

In other fields of technology, these shortcomings in U.S. law have not caused overwhelming problems because patents in other fields can be invented around. But patent claims to genes and associations often claim (or come close to claiming) fundamental principles of nature; therefore, it is frequently not possible to invent around these patents to produce materials of equivalent diagnostic and research value. In fact, for all conditions that are caused by a single mutation, inventing around the patented mutation to create a genetic test is very difficult if not impossible. Even when inventing around is possible, it is inadvisable. For example, in the case of single-gene conditions, although it is sometimes possible to design around a patent on a gene or association by using an unpatented marker that is linked to the gene through the phenomenon of linkage disequilibrium, the vast majority of single-gene diseases do not demonstrate linkage disequilibrium due to underlying genetic heterogeneity.[344] Therefore, in the majority of cases, this strategy for avoiding patent infringement in clinical testing is unavailable. Furthermore, even when an associated marker is available and unpatented, using the associated marker for testing will, due to inherent genetic constraints, necessarily lead to more false positives and false negatives than directly testing for mutations that cause the disorder. Because these false positives and false negatives can only be discovered by analyzing the gene(s) involved in the disorder, clinicians who relied on a marker test alone would make diagnostic errors unbeknownst to them that could cause significant management consequences. Thus, using an associated marker to invent around a patented gene does not produce a genetic test of equivalent value to direct analysis of the gene in question.

Because of these issues, U.S. patent law not only threatens medical progress, it may also drive valuable genetic research to countries with a more hospitable legal climate. For example, Belgium has a broad research exemption that makes research on or with isolated gene molecules exempt from infringement.

If patents on genes were necessary to stimulate research and genetic test development, it might be necessary to tolerate the social harms identified in this report. However, patents do not appear to be necessary to stimulate research and genetic test development; most troubling in the diagnostic realm, patent rights have been used to clear the market after broad testing was developed by multiple entities. As demonstrated by the research and analysis in this report, scientists have strong nonpatent incentives to engage in research on the genetic basis of diseases; scientists are principally motivated to conduct research by their curiosity, career ambitions, and desire to advance understanding of health and disease. Moreover, the Federal Government and nonprofits fund much of this research. Similarly, laboratories have sufficient non-patent incentives to develop genetic tests: clinical need and demand drive development, and development costs are minimal. Even when development costs are more substantial—as they are for development of a FDA-reviewed test kit—a lack of exclusive rights has not prevented multiple companies from investing in test development.

Furthermore, patents are not needed to encourage disclosure. In academia and medicine, disclosure of discoveries is encouraged and rewarded, and trade secrecy is not a feasible option.

[344] R Nussbaum, R McInnes, and H Willard. (2007). Thompson & Thompson Genetics in Medicine. W.B. Saunders. 8th edition.

A. Analysis of Potential Approaches to Addressing Problems in Test Development and Patient Access

The Committee evaluated a variety of potential approaches to address the identified problems in genetic test development and patient access, seeking a solution that was complete, narrowly tailored, and that could be accomplished expeditiously. A number of considered approaches failed to meet at least one of these criteria.

For example, the Committee considered whether to recommend that Government use its march-in rights under the Bayh-Dole Act to address existing problems. Under this Act, an agency that funded genetic research that resulted in a patented gene or association could require the patent holder to grant nonexclusive licenses to other laboratories and companies or could grant these licenses itself. However, the procedures involved in marching in are complex and make pursuit of this option to obtain rights inefficient. While commentators have proposed changes to the Bayh-Dole Act to lessen the administrative burdens involved in marching in, the Committee chose not to recommend these changes because, even if march-in were more efficient for each individual case, pursuing separate march-in proceedings for each federally funded patented gene or association that is exclusively licensed would be a time-consuming and burdensome process. Moreover, because march-in can only be used against patents on inventions that resulted from Federal funding, it could not remedy problems caused by patents on inventions that were not federally funded, including, among others, some of the patents that protect molecules and methods used for breast cancer genetic testing and a patent that protects molecules and methods used for testing for a hearing loss gene.[345] Thus, this approach would not be expeditious and would fail to address all problems.

Similarly, it has been suggested that existing problems could be addressed by strengthening NIH guidelines relating to technology transfer. But once again, such changes would affect only federally funded inventions. While there are also nonNIH guidelines that seek to promote nonexclusive licensing, the Committee chose not to recommend stronger promotion of these guidelines as its principal recommendation since such nonbinding guidelines have existed for some time and have not prevented the identified problems from occurring.

The Committee likewise rejected recommending a ban on patenting genes or associations. A bill that would have established such a ban was, in fact, introduced by Congressman Xavier Becerra in 2007. The bill called for amending patent law so that "no patent may be obtained for a nucleotide sequence, or its functions or correlations, or the naturally occurring products it specifies."[346] The legal changes called for in proposed legislation, however, would not have applied to a patent issued before the bill's enactment.[347] Thus, it would not have solved the problems identified in this report, which involve existing patents. Although a ban that was both retroactive and prospective would solve these problems by eliminating exclusive rights to genetic testing, it would also eliminate exclusive rights to therapeutic uses of genes. The importance of

[345] See Myriad patents 5,693,473; 5,709,999; 5,837,492; and 6,033,857. Patent 5,998,147 claims a purified nucleic acid molecule whose sequence corresponds to the mutated form of the connexin 26 gene, which accounts for up to half of all non-syndromic recessive hearing loss cases.
[346] H.R. 977, 110th Cong. § 2 (2007).
[347] Ibid.

exclusive rights to genes for the development of therapeutics was not studied by the Committee, so it seemed prudent not to alter the availability of these rights without knowing whether it would have harmful effects for therapeutic development. The Committee instead wanted an approach that was narrowly tailored to improve genetic test development and patient access without affecting patent rights in other areas.

The Committee also rejected an approach targeted only at sole-source providers. This approach would have involved a legal change that gave the Government the authority to compel licensing or grant a license itself if a sole-source provider refused to license voluntarily. A shortcoming of this approach is that testing providers might satisfy the requirement of licensing by only licensing to one other laboratory, and a duopoly would not guarantee a solution to patient access problems.

B. The Potential Impact of Recent and Pending Legal Decisions

A number of new cases relating to patents on genes and/or patents on associations also were reviewed to determine whether they would eliminate existing problems in test development and patient access. One potentially salutary legal development is a recent change in the standard for determining whether an isolated nucleic acid molecule is nonobvious.[348] Although existing patents on genes can now be challenged on obviousness grounds under the revised standard established in *In re Kubin*, it is far from certain whether all or most of these patents will be vulnerable to invalidation. Even if they are, the process of challenging each of these patents separately would be extremely time-consuming and costly.

A pending case goes further than *In re Kubin* by challenging the patentability of genes and associations. That case, *Association for Molecular Pathology, et al. v. USPTO, et al.*,, gives the federal courts the first opportunity to directly address whether the isolated gene molecules and associations claimed in some patents are unpatentable products or principles of nature; the case particularly concerns patents protecting breast cancer genetic testing. Although this case stands to solve some of the problems in access to breast cancer genetic testing, its outcome is uncertain.[349] Furthermore, even if the plaintiffs prevail, this would not lead to the automatic invalidation of all existing patents on genes and associations.[350] Depending on how the decision is framed, there may be a continuing need to challenge patenting strategies.

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[348] *In re Kubin*, No. 2008-1184 (Fed. Cir. Apr. 3, 2009).

[349] Judge Sweet of the District Court of the Southern District of New York held in a March 29, 2010, decision in *Association for Molecular Pathology, et al, v. United States Patent and Trademark Office, et al.* (S.D.N.Y. 2010) that a number of patent claims relating to breast cancer genetic testing were invalid for claiming unpatentable products of nature. The invalidated claims were to nucleic acid molecules containing nucleotide sequences relating to *BRCA1* and *BRCA2* and to various methods of comparing *BRCA1* and *BRCA2* gene sequences for the purpose of mutation detection or diagnosis. The decision does not bind other courts, which may determine that similar patent claims are patentable.

[350] As the attorney for the plaintiffs explained in a recent interview, "Success in this case will encourage new lawsuits regarding any or all of those [existing] patents. Theoretically, the facts in each instance are sufficiently different so that there would be no across-the-board invalidation of the patents. Each case would be separate." S Albainy-Jenei. (2009). Bulletproof: Interview with ACLU attorney Chris Hansen over gene patents. Patent Baristas web site, November 12, 2009. http://www.patentbaristas.com/archives/2009/11/12/bulletproof-interview-with-aclu-attorney-chris-hansen-over-gene-patents/

Another case, *Bilski v. Kappos*, anticipated to be decided by the U.S. Supreme Court by June 2010, may also have implications for the patentability of gene-disease associations, although not patents on genes. The Court is considering as well a petition to review *Prometheus Labs., Inc., v. Mayo Collaborative Servs.,* a case that concerned the patentability of a diagnostic method. If the Supreme Court decides to review this case, its decision may bear upon the patentability of associations.

In *eBay v. MercExchange,* the Supreme Court also limited the strength of patent protection by giving courts discretion over awards of injunctive relief and suggesting that injunctions can be denied when there is an important public interest at stake. There is, however, substantial uncertainty regarding how this case will be interpreted. Although permitting infringement of certain inventions might serve a public interest in free availability of those inventions, it is unlikely that courts will generally deny injunctive relief as this would diminish patent incentives for invention. Courts may instead award permanent injunctions but suspend the application of the award in order to give defendants enough time to invent around.[351] While this approach may solve holdout and thicket problems in the software and business sectors, where it is possible to invent around, it would not help those who wish to use genetic information that cannot be invented around.

Rather than wait on cases that in the end may not fully address identified problems, the Committee recommended actions that address these problems directly and expeditiously.

C. Health Care Reform

As this report was being finalized, Congress was debating changes in health care insurance law.[352] It remains uncertain whether health care insurance reforms will be enacted and, if they are, what form they would take.[353] However, none of the changes under consideration appear to address the problems identified in this report. Moreover, it is not clear how changes affecting health insurers could solve access problems caused by a sole provider's decision not to accept a particular insurance. To solve these access problems, a legal change would have to require the sole provider to accept all insurers. Even if this legal change were made, it would not solve other problems associated with patent-protected sole providers—namely, the inability of patients to obtain second-opinion testing from independent providers and concerns about the quality of tests. Finally, this legal change also would not address the barrier that patent thickets present to the development of new testing technologies, such as multiplex testing.

D. Recommended Changes to Improve Test Development and Patient Access

The Committee identified two narrowly tailored statutory changes that, if enacted, would solve the identified problems in an expeditious manner.

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[351] See, for example, *i4i L.P. v. Microsoft Corp.,* No. 2009-1504 (Fed. Cir. Dec. 22, 2009).
[352] In late March 2010, the Patient Protection and Affordable Care Act and the Health Care and Education Affordability Reconciliation Act of 2010 were enacted after passing in Congress.
[353] Ibid.

1. First Recommended Statutory Change

One of the principal legal changes that the Committee proposes is an exemption from liability for anyone who infringes a patent on a gene while making, using, ordering, offering for sale, or selling a genetic test for patient care purposes. If this change is enacted, tests that under the current system are offered by only an exclusive rights holder could be offered by multiple providers. One can reasonably expect that multiple laboratories and companies would pursue development of these tests, given that when there are nonexclusive rights and free market conditions, multiple laboratories actively develop needed tests. For example, although patents protect genes involved in hereditary nonpolyposis colorectal cancer, the patents have not been enforced, and at least 15 different U.S. laboratories have developed genetic testing for this condition.[354] Similarly, exclusive rights to testing for Huntington disease are not being enforced, and multiple laboratories have developed genetic tests for that disease. The evidence thus suggests that free market conditions, unencumbered by patent-enabled exclusivity, are conducive to the development of genetic tests. Where exclusivity does not prevail, as in the cases of CF, Huntington disease, hereditary nonpolyposis colorectal cancer and myriad others, a thriving market appears in which laboratories—both public and private—compete on the basis of service and quality. Indeed, it is when patents are used in the diagnostic arena to limit access and suppress free market conditions that the problems documented in this report arise.

By restoring free market conditions, the recommended statutory change would eliminate patient access problems. If multiple providers can offer tests that under the current system are offered by only a single exclusive-rights holder, patients are much more likely to find that at least one of the providers accepts their particular insurance. The existence of multiple providers for a particular test would also permit second-opinion testing and the sharing of samples to ensure the quality of testing. In addition, the recommended statutory change would permit the wider development of new testing technologies, such as multiplex tests. Developers who wish to create these tests will no longer face the difficult prospect of acquiring rights to multiple patents.

The proposed statutory change does not eliminate gene patents. Rather, it is narrowly tailored and applies only to diagnostic use of gene patents in the context of patient care. Privately funded genetic research, which is supplemental to Government-funded genetic research, is often driven by the desire to develop a therapeutic, whether in the form of a drug or a gene-based therapeutic. Because patents on genes would remain available and enforceable for therapeutic uses with this statutory change, the prospect of a patent on a gene or on a therapeutic would still serve to stimulate private investment in basic genetic research. The narrow tailoring of the exemption also leaves undisturbed the ability to enforce patent rights to test kits, platform technologies, and methods of genetic analysis that do not rely on specific patent claims on human genes.

2. Exemption is Advisable Even if FDA Begins to Regulate Laboratory-Developed Tests

Under the current oversight system for genetic tests, most laboratory-developed tests are not subject to FDA premarket review, and thus the costs associated with an existing laboratory launching a laboratory-developed test are relatively low—roughly $8,000 to $10,000 for each

[354] As of December 2009, GeneTests.org lists 14 laboratories that perform this test; the case study on breast and colon cancer indicates that Myriad Genetics also offers this test.

gene sequenced. There have been increasing calls in recent years, however, for FDA to increase regulation of laboratory-developed genetic tests.[355] In fact, this Committee has recommended that the FDA "address all laboratory tests in a manner that takes advantage of its current experience in evaluating laboratory tests."[356] The Committee elaborated that the FDA should "optimize the time and cost of review without compromising the quality of assessment."[357] In other words, the review process should be sufficient to ensure the quality of the test without being so daunting that companies are discouraged from pursuing test development.

If in the future the FDA takes a larger role in the oversight of laboratory-developed genetic tests, the cost of developing such tests, which would undergo FDA premarket review, may become more substantial, similar to the costs of developing an FDA-reviewed test kit. Whether academic laboratories will have sufficient resources to pursue such FDA premarket review is unclear. However, even if these laboratories cannot pursue FDA premarket review, the case study on CF reveals that multiple entities are willing to pursue FDA approval of a genetic test—in that case a test kit—even though they lacked exclusive rights to test kit development. Therefore, at least for common conditions, multiple companies lacking exclusive rights likely will still invest in creating laboratory-developed tests even if they have to participate in FDA premarket review. As such, the expectation of increased FDA oversight of laboratory-developed tests is not a reason to reject the many benefits presented by the exemption the Committee proposes. This exemption will lead to wider test development, not less test development, even if the FDA expands its oversight of laboratory-developed tests.

3. Second Recommended Statutory Change

The second principal legal change that the Committee proposes is the creation of an exemption from patent infringement liability for those who use patent-protected genes in the pursuit of research. This change—which, like the first recommendation, does not eliminate gene patents—is narrowly focused on permitting scientists to use genes in research efforts to develop new genetic tests and therapeutics; research on genes could also yield insights that lead to the development of new methods of prognosis and risk assessment. It is not clear whether patent-rights holders have consistently sought to enforce their patent rights to prevent such research, but even if patents have not been enforced against such research, an exemption from liability would provide complete assurance to scientists that such research is permissible. Finally, in the Committee's view a research exemption is entirely consistent with the aim and intent of the patent system—that is, the promotion of the progress of useful arts.

Since the Committee's focus is strictly on addressing potential impediments to the development of and patient access to genetic tests, it did not evaluate the appropriateness of, nor recommend, a general research exemption in all areas of science. However, if Congress is concerned that a research exemption limited to patents on genes violates Article 27 of TRIPS, which requires that "patents shall be available and patent rights enjoyable without discrimination as to . . . the field

[355] B Kuehn. (2009). Growing calls in United States, Europe to improve regulation of genetic testing. *Journal of the American Medical Association* 302:1405-1408.
[356] SACGHS. (2008). U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services.
[357] Ibid.

of technology[,]"[358] Congress could broaden the exemption from infringement for research on all patents or research involving all upstream patents.

The Committee's narrow focus on nucleic-acid-based genetic tests limits its recommendations in other ways as well. Specifically, the Committee's recommendations do not extend to patents on proteins. These patents were excluded from the scope of the study because most genetic tests detect genetic sequences rather than proteins. However, if there are any concerns about the effects of protein patents on the development of and access to protein-based genetic tests, other groups may wish to undertake a study of this issue and may well find that analogous recommendations are appropriate.

Finally, the Committee is cognizant of the fact that patent and licensing practices should not be changed lightly or without sufficient cause. Indeed, in the realm of commodities or consumer electronics it may well be that dramatic harms and a profound lack of benefit should be required to compel any recommendation for change. But genetic tests affect patients' lives and health. Thus, the current system's net negative effects on test development and patient access to these tests argue strongly for the narrowly tailored changes that are proposed.

[358] Article 27.1, TRIPS, http://www.wto.org/english/tratop_e/trips_e/t_agm3c_e.htm#5

X. RECOMMENDATIONS

Recommendation 1: Support the Creation of Exemptions from Infringement Liability

The Secretary of Health and Human Services (HHS) should support and work with the Secretary of Commerce to promote the following statutory changes:

A. *The creation of an exemption from liability for infringement of patent claims on genes for anyone making, using, ordering, offering for sale, or selling a test developed under the patent for patient-care purposes.*

B. *The creation of an exemption from patent infringement liability for those who use patent-protected genes in the pursuit of research.*

SACGHS believes the changes described in Recommendation 1 offer the most expeditious and straightforward way of addressing the identified problems and promoting patient access to emerging genetic advances.

If enacted, the first recommended statutory change would allow service providers to offer gene-based diagnostic testing unimpeded by fear of infringing patent claims on genes and would apply to both commercial and noncommercial laboratories. It would also allow test kit manufacturers to make, offer for sale, and sell genetic test kits without the need to obtain licenses to any patented nucleic acid molecules included in kits. The ability of multiple providers to offer tests that currently are available from only one source should solve the patient access problems identified in this report. With more providers, a patient will have a better chance of finding at least one who accepts their health insurance. The change will also permit second-opinion testing, the development of new forms of existing tests, the development of multiplex tests, and the sharing of samples to ensure the quality of testing. This narrowly tailored exemption permits the holders of patents on genes to continue to enforce their exclusive rights to therapeutic uses of the claimed molecules, thereby preserving the incentive such patents create for the development of therapeutics. Moreover, by preserving the right to patent genes and enforce those patents for therapeutic applications, this exemption maintains the strong incentive patents create for privately funded basic genetic research, which is often ultimately driven by the hope of developing a therapeutic.

The second recommended statutory change—providing an exemption from infringement for research on or with genes—is designed to permit research that can generate insights into disease, genetic tests, and therapeutics.

In addition to these formal recommendations, the Committee also urges the Secretary to use current authority to discourage the seeking, the granting, and the invoking of any patents on simple associations between a genotype and a phenotype. Association patent claims threaten the availability of existing genetic tests and are an anticipated barrier to the development of testing innovations, such as microarrays and whole-genome sequencing.

The steps called for in Recommendations 2 and 3 below can likely be accomplished more quickly than the statutory changes required in Recommendation 1, given that, even when there is political support for a particular legal change, law-making can proceed at a slow pace. Nonetheless, the Committee regards the statutory changes as the most effective means of addressing the identified problems.

The actions called for in Recommendations 4 through 6 will foster progress, regardless of whether Congress enacts the proposed statutory changes.

Recommendation 2: Promote Adherence to Norms Designed to Ensure Access

Using relevant authorities and necessary resources, the Secretary should explore, identify, and implement mechanisms that will increase adherence to current guidelines that promote nonexclusive licensing of diagnostic genetic/genomic technologies.

The Secretary should convene stakeholders— for example, representatives from industry and academic institutions,[359] researchers, and patients—to develop a code of conduct that will further broad access to such technologies.

The Committee supports guidelines that encourage broad licensing and broad access to diagnostic genetic/genomic tests.[360]

The National Institues of Health's *Best Practices for the Licensing of Genomic Inventions* and the *Organisation for Economic Co-operation and Development Guidelines for Licensing of Genetic Inventions* discourage exclusive licensing for genetic/genomic inventions. Points Two and Nine of the Nine Points to Consider in Licensing University Technology, including their explanatory text, are also relevant for genetic tests. In particular, the explanatory text under Point Two recognizes that "licenses should not hinder clinical research, professional education and training, use by public health authorities, independent validation of test results or quality verification and/or control."

In identifying mechanisms that will promote adherence to the guidelines, HHS may need to determine the scope of its authority under existing statutes. For example, the Department may have to clarify whether the Bayh-Dole Act gives agencies authority to influence how grantees license patented inventions.

If it is determined that the HHS has this authority, one way the HHS Secretary could promote adherence to the licensing guidelines would be to direct NIH to make compliance with them an important consideration in future grant awards.

[359] Representation of academic institutions should not be limited to university technology transfer professionals, but should include academic researchers.

[360] Such guidelines include NIH's Best Practices for the Licensing of Genomic Inventions; the Organisation for Economic Co-Operation and Development's (OECD's) Guidelines for Licensing of Genetic Inventions; the NIH Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-wide Association Studies; and In the Public Interest: Nine Points to Consider in Licensing University Technology.

Alternatively, the Secretary could promulgate regulations that enable the Department's agencies to limit the ability of grantees to exclusively license inventions resulting from Government funding when they are licensed for the genetic diagnostic field of use. Exceptions could be considered if a grantee can show that an exclusive license is more appropriate in a particular case—for example, because of the high costs of developing the test.

Recommendation 3: Enhance Transparency in Licensing

Using relevant authorities and necessary resources, the Secretary should explore, identify, and implement mechanisms that will make information about the type of license and the field of use for which rights were granted readily available to the public.[361]

As a means to enhance public access to information about the licensing of patents related to gene-based diagnostics, the Secretary should also direct NIH to amend its *Best Practices for the Licensing of Genomic Inventions* to encourage licensors and licensees to include in their license contracts a provision that allows each party to disclose non-financial information about its licenses (particularly such factors as type of license, field of use, and scope) in order to encourage next-generation innovation.

The case studies discovered that it is often difficult for parties to obtain information on the scope of licenses. Such license information could reveal whether any rights to use the patented invention remain available. Test developers need such information to effectively plan what innovations to pursue. For example, if a license reveals that a particular gene has been exclusively licensed in all fields and may not be sublicensed, a developer would then know not to pursue innovations that require use of that gene. The recommended actions would make relevant licensing information more readily available.

Recommendation 4: Establish an Advisory Body on the Health Impact of Gene Patenting and Licensing Practices

The Secretary should establish an advisory body to provide ongoing advice about the health impact of gene patenting and licensing practices. The advisory body also could provide input on the implementation of any future policy changes, including the other recommendations in this report.

This advisory body would be available to receive information about patient access to genetic tests from the public and medical community. The body could review new data collected on patient access and identify whether problems are occurring and, if so, to what extent.

One of the advisory body's missions would also be to recommend what additional information should be systematically collected through iEdison so that iEdison can be used to determine whether grantees are complying with the guidelines mentioned in recommendation #2.

[361] Because of the public importance of this information, the Committee advocates that it not be regarded as suitable for protection as trade secrets.

The advisory body could also explore whether approaches to addressing patent thickets, including patent pools, clearinghouses, and cross-licensing agreements, could facilitate the development of multiplex tests or whole-genome sequencing.

The advisory body should consist of Federal employees and outside experts from a broad array of areas; for example, the body could be made up of clinical geneticists, patent law experts, researchers, consumers, representatives from the diagnostic kit industry, commercial laboratory directors, technology transfer professionals, laboratorians, and Federal employees from USPTO and NIH.

Such an advisory body could be established within a relevant existing committee.

Recommendation 5: Provide Needed Expertise to USPTO
The Secretary should work with the Secretary of Commerce to ensure that USPTO is kept apprised of scientific and technological developments related to genetic testing and technology.

The Committee believes experts in the field could help USPTO in its development of guidelines on determinations of such matters as nonobviousness and subject matter eligibility, particularly the patent-eligibility of methods that rely on the association between a genotype and phenotype.

Recommendation 6: Ensure Equal Access to Clinically Useful Genetic Tests

Given that genetic tests will be increasingly incorporated into medical care, the Secretary should ensure that those tests shown to have clinical utility are equitably available and accessible to patients.

Such uniformity in coverage would ensure that all insured patients, regardless of geographic location or economic status, obtain access to clinically useful genetic tests.

Our advocacy for equal access here is part of this Committee's long-standing concern about ensuring equity in the provision of genetically related tests and services. Earlier SACGHS reports and recommendations have called attention to the importance of equitable access to genetic testing.

Appendix A: Compendium of Case Studies Prepared for SACGHS by the Duke University Center for Genome Ethics, Law & Policy*

*The case studies presented here were provided in final form to SACGHS in February 2009. They were updated and republished by the study authors in the journal *Genetics in Medicine*, which is available at http://journals.lww.com/geneticsinmedicine/toc/2010/04001.

Impact of Patents and Licensing Practices on Access to Genetic Testing for Inherited Susceptibility to Cancer: Comparing Breast and Ovarian Cancers to Colon Cancers

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Executive Summary

A natural case study in the field of cancer genetics enables us to compare the development of testing for inherited susceptibility to colorectal cancers to inherited breast and ovarian cancers. Specific mutations in the *BRCA1* and *BRCA2* genes can dramatically increase patients' risks for breast and ovarian cancers; Myriad Genetics, Inc., holds broad patents on both of these genes and their mutations in the United States. Similarly, specific mutations in several other genes can give rise to two inherited conditions highly-associated with developing colorectal cancer, known as Lynch Syndrome (or Hereditary Non-Polyposis Colorectal Cancer, HNPCC) and Familial Adenomatous Polyposis (FAP), but the involved gene patents are predominantly held by non-profit institutions, and licensed non-exclusively. Myriad is the sole provider of full-sequence *BRCA* testing in the U.S. For FAP, Myriad and four non-profits offer full-sequence analysis of the FAP-associated *APC* gene (and from some testing services, another gene, MYH). For Lynch Syndrome, Myriad, Quest Diagnostics, Huntington Diagnostic Laboratories and four non-profits offer full-sequence analysis for three HNPCC-causing genes (*MLH1, MSH2*, and *MSH6*).

The clinical decision tree and the role of full-sequence genetic testing differs between BRCA and colon cancer predisposition (and details about exactly how best to do genetic testing for colorectal cancer are particularly unsettled). But for purposes of comparing the impact of patents and licensing practices, those uncertainties about clinical practice do not directly interfere with expected effects attributable to patents and licensing.

Basic and Clinical Research

- As of September 2008, Myriad has submitted over 18,000 entries (>80% of total entries) for over 2600 unique mutations to the Breast Cancer Information Core database and cites over 4,300 follow-up publications on *BRCA1* and *BRCA2* (as of Feb. 2005) and more than 100 individual research projects (including a 1999 Memorandum of Understanding with the NCI) as evidence that it supports research.[1]
- Some argue that Myriad's definition of infringing research is too broad. Specifically, Myriad asserted that even though Genetic Diagnostics Laboratory (GDL) limited testing to patients in NCI research

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[1] William Rusconi, Myriad Genetics. *Patenting and Licensing of the Breast Cancer Susceptibility Genes - BRCA1 and BRCA2.* PowerPoint. Given February 11, 2005, to National Acadmies of Science. Email from William Rusconi to Christopher Heaney, January 15, 2009.
A search of the Breast Cancer Information Core for mutations catalogued as deposited by Myriad Genetics revealed 8,826 mutations in BRCA1 and 9,891 mutations in BRCA2. (*Breast Cancer Information Core.* National Human Genome Research Institute. See http://research.nhgri.nih.gov/bic/ [accessed September 25, 2008].)

- NCI Director Richard Klausner signed a December 1999 Memorandum of Understanding (MOU) that included an explicit definition of genetic testing for research.[3] That MOU provided deeply discounted testing for any NCI-funded project with no reach-through rights to new discoveries. Under this definition, researchers could perform research testing within their institutions without a license from Myriad.
- A 2005 Lewin Group report concluded that, based on incentive effect theory, Myriad's exclusive patents on the *BRCA* genes stifled further basic research; however, few empirical data support or refute the Lewin Group's conclusion.[4]
- While Myriad maintains it has not enforced its patents against researchers, neither has it publicly stated that it would not do so in a written, actionable form except in the NCI MOU. This ambiguity may itself be a factor in stifling further research to the extent that this has occurred.
- Myriad responds that it collaborates with many academic groups, and they simply have to contact Myriad. This is only a partial remedy, however, as contacting Myriad would alert the patent-holder about actions it could regard as infringement.
- A recent controversy in Australia, precipitated when Myriad's licensee Genetic Technologies Ltd. announced it would reverse its 2003 announcement allowing testing laboratories to do BRCA testing without a license, led it to clarify that its license does not cover research testing, and so any enforcement for research use would be from Myriad or the University of Utah (neither of which has indicated any intention to enforce against research use in Australia).

Development

- A 2003 French study on the cost-effectiveness of full-sequence *BRCA* testing versus other methods stated:

> The results of our cost-effectiveness analysis strongly suggest that negative [monopolistic] effects of this kind are occurring in the case of *BRCA1*…. [Such monopoly control] may prevent health care systems from identifying and adopting the most efficient genetic testing strategies.[5]

- The same study found that:

> "…there exist alternative strategies for performing BRCA1 diagnosis: prescreening techniques such as FAMA [fluorescent assisted mismatch analysis] and, potentially, DHPLC [denaturing high performance liquid chromatography] or DGGE [denaturing gradient gel electrophoresis], based on the current estimates of their sensitivity, would minimize the cost of diagnosis while also ensuring a comparable level of effectiveness to that of applying DS [direct sequencing] to the

[2] Parthasarathy S. Architectures of genetic medicine: comparing genetic testing for breast cancer in the USA and UK. *Social Studies of Science* 2005 (February). 35(1):5-40, at 24.
[3] The crucial definition was Definition 2.4 "Research Testing Services" of a December 1999 Memorandum of Understanding between Myriad Genetics and the U.S. National Cancer Institute (signed on 10 December by Gregory Critchfield, President of Myriad Genetic Laboratories, Inc., and 14 December by Richard Klausner, NCI Director): "part of the grant supported research of an Investigator, and not in performance of a technical service for the grant supported research of another (as a core facility, for example). Research Testing Services are further defined as paid for solely by grant funds, and not by the patient or by insurance."
[4] The Lewin Group. *The Value of Diagnostics*: *Innovation, Adoption, and Diffusion into Health Care*. 2005, 62-3.
[5] Sevilla C et al. Impact of gene patents on the cost-effective delivery of health care: the case of *BRCA1* genetic testing. *International Journal of Technology Assessment in Health Care* 2003. 19:287-300.

entire gene."[6]

These uncertainties for BRCA testing parallel the uncertainty about which genetic testing protocols are optimal for colorectal cancer susceptibility, except that in the case of BRCA testing, Myriad is the only testing service in the US market and so its practices are a *de facto* standard, whereas practices for colon cancer vary among health care providers.

- Myriad notes that its sequencing technologies are a gold standard method, as alternatives are confirmed by sequence analysis.[7] Some health systems outside the US have chosen to use a diagnostic decision tree that uses full-sequence analysis later in the process and more selectively to reduce expenses. We know of no head-to-head comparison studies on health outcomes. The comparable comparative studies for colon cancer testing found no clear "winner" strategy among four examined, one of which was initial full-sequence testing of multiple genes.[8]
- Using multiplex ligation-dependent probe amplification (MLPA), a 2006 study published in the *Journal of the American Medical Association* (JAMA) noted that Myriad's testing strategy (short-range PCR followed by genomic sequencing) missed up to 12% of large genomic deletions or duplications.[9] This led to criticism of the Myriad test algorithm. In congressional testimony on October 30, 2007, Drs. Marc Grodman and Wendy Chung attributed this problem to Myriad's sole provider status and patent monopoly, concluding, "It was only after considerable pressure from the scientific community that the company added methods to detect these deletions, insertions, and re-arrangements in 2006, over 10 years after they first introduced clinical genetic testing, and barred anyone else from performing the tests. In a competitive marketplace, this delay never would have occurred."[10]
- Myriad disagrees with this characterization. Myriad notes it launched testing for the five most common rearrangements (accounting for about a third of all rearrangements) in 2002—and simultaneously began developing testing for all large rearrangements (BART®) that it launched in 2006 for the higher risk patients (similar to the JAMA paper's criteria) as part of its BRAC*Analysis*™. This technology was the subject of poster presentations in 2004.[11] Myriad notes

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[6] Ibid.

[7] William Rusconi, Myriad Genetics. *Patenting and Licensing of the Breast Cancer Susceptibility Genes - BRCA1 and BRCA2.* Op. cit.

[8] Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome relatives. *Genetics in Medicine* 2009. 11(1):35-41.
Palomaki GE, McClain MR, Melillo S, Hampel HL, Thibodeau SN. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. *Genetics in Medicine* 2009. 11(1):42-65.

[9] Walsh T et al. Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer. *Journal of the American Medical Association* 2006 (March). 295(12):1379-1388.

[10] Dr. Marc Grodman, testimony before the House Judiciary Committee, Subcommittee on the Courts, the Internet and Intellectual Property; oversight hearing on "Stifling or Stimulating?—The role of gene patents in research and genetic testing," October 30, 2007, 2237 Rayburn House Office Building, Washington, DC. Oral testimony and written statement of Marc M. Grodman, CEO of BioReference Laboratories, Inc., at 5. Quote taken from Appendix A, October 25, 2007, supplementary written statement from Dr. Wendy Chung, Columbia University, at 3.

[11] After the Walsh et al. paper was published, Myriad issued Clinical Update, Vol. 4, No. 5, "Testing for Hereditary Breast and Ovarian Cancer Syndrome," in September 2006. It cited ongoing work and intention to have a test for large-scale rearrangements by later that year. An abstract submitted Feb. 2004 and a poster presented fall 2004 that report on Myriad efforts to detect large-scale rearrangements were cited in that update. Judkins T, Hendrickson BC, Gonzales D et al. Detection of large rearrangement mutations in *BRCA1* and *BRCA2* in 528 high risk families from North America by quantitative PCR based gene dose analysis. Abstract from 2004 American Society of Human Genetics annual meeting. [See http://www.ashg.org/genetics/abstracts/abs04/f518.htm [accessed 11 July 2008]]. Hartmann C, John AL, Klaes R et al. Large *BRCA1* gene deletions are found in 3% of German high-risk breast cancer families. *Human Mutation* 2004 (December). (Mutation in Brief #762.) 24(6): 534.) Presentations were: Hendrickson BC, Judkins T, Deffenbaugh AM, Pyne K, Ward BE,

that rearrangement testing it was already conducting would have detected roughly 1/3 of the "missing" cases reported in the JAMA article, so the problem was overstated, and Myriad incorporated more extensive testing for rearrangements in 2006, the year the JAMA article appeared.

- The congressional testimony also alluded to limits on availability of BRCA tests in forms that Myriad itself does not perform. This includes testing of paraffin-embedded samples or pre-implantation genetic diagnosis. Some patients and families lack access to a relative's blood (but potentially with access to a deceased relative's preserved paraffin-embedded tumor sample). Myriad states it has not enforced patents for services it does not provide (such as paraffin-embedded tissues), and has sublicensed BRCA testing to three laboratories offering pre-implantation genetic diagnosis.[12]

Commercialization

- A centralized testing service offers some benefits, including Myriad's ability to provide free testing to first-degree relatives once a mutation has been identified to further characterize uncertain variants. Testing is CLIA-certified and reportedly has faster turn-around time than most other laboratories, and Myriad's reports are characterized as clear and detailed.
- Based on available data as described in the text (derived primarily from phone calls to testing laboratories and online pricing guidelines), calculating the price for each genetic test per DNA segment amplified by PCR (an "amplicon") yields a rough estimate of Myriad's patent premium:
    - For *BRCA*, Myriad charges $3,120 total, or $38.05 per amplicon (including separate testing for common rearrangements).
    - For FAP – where Myriad has four competitors – Myriad charges $1,795 or $40.80 per amplicon (including Southern Blot rearrangement and insertion-deletion testing plus two common mutations of the MYH gene).
        - Non-profit competitors' prices range from $1,200 to $1,675 ($28.57 to $ 39.88 per amplicon) though rearrangement testing is generally not included in this price.
    - For HNPCC – where Myriad has six competitors – Myriad charges $2,950 or $49.17 per amplicon (for three genes, which includes Southern Blot testing for insertions, deletion and rearrangements).
        - Non-profit competitors' prices range from $1,800 to $ 4,646.16 ($30.00 to $ 77.44 per amplicon) and generally does not include rearrangement testing.

Scholl T. Recurrent intragenic rearrangement mutations in the tumor suppressor gene *BRCA1*: prevalence results from 12,272 patients at high risk for breast and/or ovarian cancers and methods of biochemical analysis. 40th Annual Meeting of the American Society of Clinical Oncology, New Orleans, LA, June 2004 (Poster); Judkins T, Hendrickson BC, Gonzales D, Eliason K, McCulloch J, Ward BE and Scholl T. Detection of large rearrangement mutations in *BRCA1* and *BRCA2* in 528 high risk families from North America by quantitative PCR based gene dose analysis. *54th Annual Meeting of the American Society of Human Genetics*, Toronto, Canada, Poster, Program Number 518, October 2004. The first year's experience at Myriad with large-scale rearrangment testing was summarized in a poster for the 2007 American Society for Human Genetics meeting: Spence WC, Ludkins T, Schoenberger J et al. Clinical testing experience for large genomic rearrangements in the BRCA1 and BRCA2 genes for hereditary breast and ovarian cancer.

[12] Harmon A. The DNA age: couples cull embryos to halt heritage of Cancer. *New York Times* 2006 (September 3). The article quotes William Hockett, MD, of Myriad Genetics and states that preimplantation BRCA testing had been licensed to three fertility clinics. A search of genetests.org shows several foreign BRCA prenatal testing services (not necessarily PGD, but Myriad does not offer any form of prenatal testing) and two US services, at the University of Calfornia, San Francisco and Boston University. Online research also found two services offering preimplantation BRCA mutation detection, at Reproductive Genetics Institute in Chicago and Genesis Genetics Institute in Detroit.

- These data show little consistent *price* effect of the BRCA patents, based on two-step logic: (1) comparing intra-laboratory cost per amplicon for Myriad' s testing of BRCA versus colon cancer genes, and (2) comparing Myriad's price for full-sequence testing of colon cancer genes compared to other (competitor) services. [13]

- An analysis done in three French public hospitals showed the incremental costs of testing an additional family member with a previously identified *BRCA* mutation is only 17% of the price charged by Myriad.[14] An alternative technology of two-dimensional electrophoretic mutation scanning was claimed to be highly sensitive but possible as a screening test, estimated at $70/test and perhaps possible to reduce to $10/test direct costs.[15]
- Alternative low-cost testing methods may be used in some health systems, but not in the United States; these low-cost alternative methods have not been adopted widely for colon cancer testing either, and effects are therefore not specific to BRCA testing or patent status. Any failure to adopt alternative technologies cannot be directly attributed to the BRCA patents or sole-provider status. Patent impediments to adoption of inexpensive technologies cannot be excluded entirely, however, because colon cancer sequences and testing methods are also patented.
- A controversy about BRCA testing in Australia erupted in July 2008, when Genetic Technologies Ltd. (GTG), the BRCA licensee in Australia and New Zealand, announced it would enforce its patents against unlicensed laboratories in Australia. GTG sent "cease and desist" letters with an initial deadline of October 2008, then extended to November 2008. On 31 October, GTG announced it "suspended any enforcement activity pending the outcome of further dialogue with all relevant stakeholders."[16]
- Myriad mainly benefits from the *volume* it receives as a monopoly-provider of *BRCA* testing. Myriad can direct all US full-sequence *BRCA* tests to its laboratories, and we have learned of European reference laboratories that also use Myriad, either directly or through its licensed foreign laboratories, because of turnaround time and reliability. Any price effect attributable to patent status is equivocal; the volume effect is unequivocal.

Communication/Marketing

- Marketing can increase awareness of *BRCA* mutations in the general and at-risk patient populations.
- A survey of 300 women following Myriad's 2002 public advertising campaign noted 85% "would contact their physician regarding *BRCA* testing" and 62% would switch providers to find one who

[13] The comparison of BRCA and FAP/HNPCC testing is confounded by several variables that are not controlled, so it is inexact. Different laboratories use somewhat different methods, and different numbers of amplicons, and different degrees of testing for insertions, deletions, and rearrangements. FAP and HNPCC genes do have patents on them, and prices may include licensing fees, so this is not a "patented versus nonpatented gene" pricing comparison. The rearrangement testing is included in total prices, but the details of those aspects of testing differ between BRCA and colon cancer predisposition mutations. The data cannot rule out a monopoly price effect, but only suggest that any such effect is buried in the counfounding variables. One other powerful constraint on pricing is reimbursement practices for genetic tests, which tend to start from per-amplicon unit prices and are negotiated for specific tests from that baseline.

[14] Sevilla C et al. Impact of gene patents on the cost-effective delivery of health care: the case of *BRCA1* genetic testing. Op. cit.

[15] van Orsouw NJ, Dhanda R, Elhaji Y, Narod S, Li F, Eng C, Vijg J. A highly accurate, low cost test for *BRCA1* mutations. *Journal of Medical Genetics* 1999. 36(10):747-753.

[16] Genetic Technologies Ltd. *Further clarifications on BRCA testing.* (Public announcement "for personal use only.") October 31, 2008. See http://www.gtg.com.au/index.asp?menuid=060.070.130&artid=10740&function=NewsArticle [accessed November 8, 2008].

offered the test.[17]

Adoption by Clinical Providers and Testing Laboratories

- Provider, lab, and third-party payer metrics of testing services are only rough proxies for patient access.
- A 2003 survey of laboratory directors demonstrates nine instances of patent enforcement by Myriad on its *BRCA* patents. The same directors noted two FAP patent enforcements and zero Lynch Syndrome (HNPCC) patent enforcements.[18]
- BRCA accounted for 2 cases of gene patent litigation and colon cancer genes for none (out of 31 collected gene patent litigation cases, 5 of which were related to diagnostics).[19] Two gene patent lawsuits between OncorMed and Myriad (accounting for two cases in Holman's count, a suit and counter-suit) were consolidated into a single case, and then settled out-of-court, with Myriad gaining control of Oncormed's BRCA patent rights. The other Myriad-University of Pennsylvania lawsuit over BRCA testing was settled even earlier in the process.

Adoption by Third-Party Payers

- Based on available data and authors' calculations, if gene patents conferred a premium of $750, this would reduce the likelihood of third party coverage by 11 percentage points.[20]
- In one study, only 59% of women undergoing full sequence *BRCA* analysis filed a health insurance claim (99% of whom had insurance).[21] A second study found that 15% of women seeking *BRCA* analysis chose to self-pay for their services and that every woman did so in fear of insurance or employment discrimination.[22]
- The published data do not reflect two major trends. One is the May 2008 enactment of the Genetic Information Nondiscrimination Act, which may reduce fear of BRCA testing having consequences for health insurance and employment. The other is Myriad's current experience with third-party payers, with self-pay reported as having dropped to approximately 5 percent as more insurers and health plans cover testing in high-risk patients. Average reimbursement pays for over 90 percent of charges (so average co-pay is less than 10 percent).[23]
- Adoption by third-party payers is becoming more common. Individuals who are not covered either are uninsured (some of whom qualify for Myriad's financial assistance program), or are covered by state Medicaid plans for which reimbursement is evolving (and some Medicaid programs have been

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[17] Parthasarathy S. *Building Genetic Medicine: Breast Cancer, Technology, and the Comparative Politics of Health Care.* Cambridge: MIT Press, 2007.
[18] Cho M et al. Effect of patents and licenses on the provision of clinical genetic testing services. *Journal of Molecular Diagnostics* 2003 (February). 5(1):3-8. NB: FAP and HNPCC "patent enforcements" are more unlikely given non-exclusive licensing and multiple rights-holders.
[19] Holman CM. The impact of human gene patents on innovation and access: a survey of human gene patent litigation. *UMKC Law Review* 2007. 76(2):295-361, at 347-348. For a draft, see http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1090562 [accessed March 28, 2008].
[20] Schoonmaker M et al. Factors influencing health insurers' decisions to cover new genetic technologies. *International Journal of Technology Assessment in Health Care* 2000. 16: 78-189.
[21] Lee S et al. Utilization of BRCA1/2 genetic testing in the clinical setting. *Cancer* 2002 (March 25). 94(6):1876-85.
[22] Peterson E et al. Health insurance and discrimination concerns and BRCA1/2 testing in a clinic population. *Cancer Epidemiology Biomarkers & Prevention* 2002 (January). 11:79-87.
[23] Figures estimated by William Rusconi, Myriad Genetics. Personal communication to Robert Cook-Deegan, May 29, 2008.

slow to adopt BRCA testing). A small percentage (5-10%) of private insurance plans fail to cover any kind of genetic testing (whether it is BRCA, HNPCC or even CF). This is often due to policy or blanket exclusions on the molecular diagnostic CPT codes[24] through which genetic tests are reimbursed.

Consumer Utilization

- Consumers may pay a different price for a given genetic test depending on whether or not insurance covers it, which holds true for both Myriad Genetics and non-profit providers.
- While early publications estimated that as many as 19-74% of at-risk individuals who could benefit from *BRCA* testing were not being tested,[25] no systematic evaluation of this question has been conducted as coverage and reimbursement have become more common. The Genetic Information Nondiscrimination Act of 2008 will take effect in 2009 (health insurance provisions) and 2010 (employer provisions), and this may also affect use of genetic testing, including breast and ovarian cancer as well as family risk of colon cancer.
- Companies offering genetic testing have incentives to negotiate the complex coverage and reimbursement landscape on behalf of patients using their services.
- In one study, nearly 70% of patients eligible for free *BRCA* testing elected to get tested; however, cost certainly matters since only 22% of self-pay patients in the same sample chose to be tested.[26] These data are out-of-date as Myriad reports only approximately 5 percent self-pay in recent experience.
- Any price effect of the BRCA patents is buried in the noise once prices are normalized, first by comparing Myriad's prices for BRCA to its price for colon cancer gene testing and then by comparing Myriad's prices for colon cancer gene testing to other providers. Myriad's costs per unit are lower for BRCA full-sequence testing than for colon cancer gene tests. Its prices are higher than some nonprofit colon cancer testing services for FAP, though Myriad includes rearrangement testing and comparison services that other providers price differently. Myriad is mid-range among providers of Lynch Syndrome (HNPCC) testing (and low relative to the one for-profit HNPCC testing service). This makes it impossible to calculate a meaningful price premium for BRCA testing or to conclude that BRCA patents have led to prices far above comparable tests for other conditions provided by other laboratories.
- It is therefore difficult to attribute reduced access to BRCA testing to patents. We cannot exclude the possibility that patent holder's investments in education about hereditary breast and ovarian cancer (HBOC) and testing have actually had the opposite effect of increasing access to testing.

Introduction

One natural case study in the field of cancer genetics can address whether and to what degree intellectual property law affects patients' access to genetic testing. The parallel discovery of inherited mutations for two classes of cancer: breast, ovarian and some other cancers associated with BRCA 1&2 genes, compared to a cluster of genes in which mutations predispose to cancer of the colon and rectum. Specific mutations in genes known as *BRCA1* and *BRCA2* can dramatically increase patients' risks for breast cancer and ovarian cancer (and more rarely, some other cancers). Similarly, specific mutations in other

[24] CPT codes are billing codes for reimbursement of health services. CPT® is formally a trademarked term that refers to a system of Current Procedural Terminology maintained by the American Medical Association.
[25] William Rusconi, Myriad Genetics. Personal communication to Robert Cook-Deegan, May 29, 2008.
[26] Ibid.

genes can give rise to two inherited conditions highly associated with developing colon cancer, known as Familial Adenomatous Polyposis (FAP) and Lynch Syndrome (sometimes called Hereditary Non-Polyposis Colorectal Cancer, or HNPCC).

Mutations in all six cancer susceptibility genes were discovered in the 1990s, and genetic tests to detect them were patented over a four-year period. Myriad Genetics, Inc., a for-profit company, gained control over the U.S. patents on genetic tests for *BRCA1* and *BRCA2*. The patents for inherited colon cancer family syndromes remain more broadly distributed, with some key patents held by Johns Hopkins University, Oregon Health Sciences University, Dana Farber, and other non-profit entities. The licensing patterns for these tests vary, again providing a natural case-study to compare for-profit patenting and licensing practices versus non-profit patenting and licensing practices. Finally, as of early 2006 there were 62 genetic tests for cancer available for clinical use but only five used for primary prevention, including the tests for BRCA, FAP, and Lynch Syndrome (HNPCC) discussed in this case study.[27]

Background: Breast Cancer, Ovarian Cancer and *BRCA1* / *BRCA2*

According to the American Cancer Society (ACS), over 178,000 American women were diagnosed with invasive breast cancer in 2007, and another 62,000 with *in situ*, or non-invasive breast cancer. This made breast cancer the most common cancer diagnosis after skin cancer for women. Finally, over 40,000 women were expected to die from breast cancer in 2007, second only to lung cancer.[28]

In 2007, the ACS also projected 22,430 women were diagnosed with ovarian cancer, accounting for 3% of all cancers among women. Furthermore, 15,280 women were projected to die from ovarian cancer in 2007, more than any other cancer of the female reproductive tract.[29]

Both breast and ovarian cancer are associated with age–ovarian cancer incidence peaks around age 70,[30] while 95% of new breast cancer cases and 97% of breast cancer deaths occur in women over the age of 40.[31] Obesity is also a risk factor for both breast and ovarian cancers, and both cancers correlate with family history.

Approximately 20% of women with breast cancer have either a first-degree or a second-degree relative with breast cancer.[32] Scientists have identified several genes associated with elevated risk of breast cancer. Two of these are powerful cancer susceptibility genes, meaning mutations can be traced through families in a classic Mendelian dominant inheritance pattern: *BRCA1* and *BRCA2*. Breast cancers arising from *BRCA1* and *BRCA2* mutations account for between 5 and 10 percent of all breast cancers,[33] or between 20,000 and 40,000 cases annually. Overall, the relative lifetime risk of breast cancer is 2.7 to 6.4 times greater for those with *BRCA* mutations compared to other women (Appendix 1). For ovarian cancer the relative risk for *BRCA* positive women rises 9.3 to 35.3 times (Appendix 1).

Though the Agency for Healthcare Research and Quality (AHRQ) notes that *BRCA1* and *BRCA2* mutations occur at a frequency of around 1 in 300-500 in the general population, the risk of inheriting one of these mutations is much higher in some ethnic groups. For example, specific mutations have been

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[27] AHRQ Technology Assessment Program. *Genetic Tests for Cancer*. January 9, 2006. See http://www.ahrq.gov/clinic/ta/gentests/gentests.pdf [accessed May 5, 2007].
[28] American Cancer Society. *Cancer Facts and Figures, 2007*. See http://www.cancer.org [accessed March 2007].
[29] Ibid.
[30] Ibid.
[31] American Cancer Society. *Breast Cancer Facts and Figures, 2005-2006*. See http://www.cancer.org [accessed March 2007].
[32] AHRQ. Genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility. Evidence synthesis 37. September 2005.
[33] American Cancer Society. *Breast Cancer Facts and Figures, 2005-2006*. Op. cit.

identified in the Ashkenazi Jewish population, and certain families in the Netherlands, Iceland, and Sweden have a high frequency of *BRCA1* or *BRCA2* mutations.[34]

Background: Colorectal Cancer and FAP / Lynch Syndrome (HNPCC)

According to the ACS, colorectal cancer is the third most common cancer among both men and women in the United States. Over 150,000 Americans will be diagnosed with colorectal cancer and over 52,000 Americans will die of colon cancer in 2007, accounting for 10 percent of all cancer deaths.[35] Risk factors for developing colorectal cancer include age, diet, obesity, smoking, physical inactivity, and family history.[36]

Almost one-third of colorectal cancer cases are thought to be related to family history, of which two major conditions have been correlated with specific genetic mutations. Combined, these two conditions are thought to account for between 3 to 5 percent of all US colorectal cancers.

Familial adenomatous polyposis (FAP)

FAP accounts for approximately 1% of all colorectal cancers. The disease is inherited in an autosomal dominant fashion. More than 90% of FAP cases are associated with mutations in the *adenomatous polyposis coli* gene, or *APC* gene. The *APC* gene encodes a tumor-suppressing protein, analogous to the tumor suppressing gene p53 which is found mutated in many kinds of cancer. The percent of individuals with FAP who develop colorectal cancer approaches 100% - or 16.7 times the risk of the general population (Appendix 1) – with most affected individuals developing cancer around age 40.[37] A milder and less common form of FAP is attributed to mutations in the MYH gene.

Lynch Syndrome (Hereditary nonpolyposis colorectal cancer, or HNPCC)

Lynch Syndrome accounts for 1-3% of colorectal cancer in the United States, and mutations are inherited in an autosomal dominant pattern. Lynch syndrome is rapidly becoming a disease category defined by DNA characterization, caused by mutations in genes that encode enzymes that repair DNA base-pair mismatches during DNA replication. This molecular definition replaces the traditional symptomatic and descriptive label hereditary nonpolyposis colorectal cancer, or HNPCC.

The most recent review of evidence about genetic testing in this condition defined Lynch Syndrome as a "predisposition to colorectal cancer and certain other malignancies as a result of a germline mismatch repair gene mutation—including those with an existing cancer and those who have not yet developed cancer." [38] Mutations in specified genes are thus becoming the basis for disease classification, replacing and refining previous clinical criteria. Lynch Syndrome is becoming the preferred term for those who have these mutations, although we also use HNPCC to refer to the clinical findings in this review.

Individuals must inherit a copy of one mutated gene from either their mother or their father to develop the HNPCC disease. The genes already known to give rise to Lynch Syndrome when mutated include: MLH1, PMS1, PMS2, MSH6, TFGBR2, and MLH3.[39] Of these, mutations in MSH2 account for

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[34] Ibid.
[35] American Cancer Society. *Cancer Facts and Figures, 2007*. Op. cit.
[36] Ibid.
[37] Kaz A, Brentnall TA. Genetic testing for colon cancer. *Nature Clinical Practice: Gastroenterology & Hepatology* 2006 (December). 3(12):670-679.
[38] Palomaki GE et al. Op. cit. at 42.
[39] Online Mendelian Inheritance in Man. Entry 120435. See http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=120435 [accessed January 19, 2009].

approximately 60% of cases, and MLH1 another 30%.[40] "Mismatch repair proteins are responsible for correcting errors that occur during DNA replication, typically the addition or deletion of one or more nucleotides."[41] Patients with Lynch Syndrome have an approximately 80% lifetime risk of developing colorectal cancer–or over 13 times the risk of the general population (Appendix 1)–though the specific risk varies by mutation.[42] There is significantly higher risk of developing endometrial (uterine) cancer and ovarian cancer as well in women with these mutations. In fact, about half of women with Lynch Syndrome who develop cancer present with one of these gynecological cancers as their first malignancy.

Patents and Licensing

Breast Cancer

Myriad Genetics owns or has licensed the patents for both *BRCA* genes and their mutations. Some BRCA1 patents are co-assigned to the University of Utah and US Department of Health and Human Services, as the research was supported in part by NIH grants (governed by the Bayh-Dole Act) and intramural research at the National Institute of Environmental Health Sciences (governed by the Stevenson-Wydler Act). While NIH investigators were listed a co-inventors on some patents, NIH assigned administration of those patents to the University of Utah. The BRCA patents have been administered by the University of Utah, with exclusive licensing to Myriad, and Myriad in effect controls the patent rights. We therefore refer to them as "Myriad patents."

Myriad's first patent, U.S. 5753441, is on *BRCA1* testing and includes both method claims and a testing kit. Its second patent, U.S. 6051379, is on *BRCA2* and includes parts of the *BRCA2* gene in oligonucleotide sequences, method claims, and kits. According to Dr. Shobita Parthasarathy, Myriad purchased this patent along with testing services from OncorMed in 1998 for an "undisclosed sum."[43] Patent rights were included in $525,000 paid to OncorMed, reported in its Securities and Exchange Commission (SEC) quarterly report from June 30, 1998.[44] (For more information on patents, see Appendix 4.)

Having sold off its BRCA assets, OncorMed entered into a reorganization agreement in which the company Gene Logic, Inc., bought OncorMed for a sum "not to exceed approximately $38 million."[45] OncorMed registered its termination with the SEC on September 30, 1998.[46]
Myriad became the sole-provider for both *BRCA1* and *BRCA2* full-sequence tests in the United States, as shown in Appendix 1. "To perform *BRCA* 1/2 mutation analysis, Myriad Genetics and its licensees only use direct sequencing of the whole genomic DNA (DS [double-stranded]) of both genes

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[40] Ibid.
[41] Kaz A, Brentnall TA. Genetic testing for colon cancer. *Nature Clinical Practice: Gastroenterology & Hepatology* 2006 (December). 3(12):670-679.
[42] Ibid.
[43] Parthasarathy S. *Building Genetic Medicine: Breast Cancer, Technology, and the Comparative Politics of Health Care.* Op. cit. at 117.
[44] Oncormed, Inc. *SEC EDGAR Filing Information: Form 10-Q - Quarterly Report 1998-30-06*. Page 11. See http://www.sec.gov/Archives/edgar/data/922821/0000950133-98-003049.txt [accessed June 2007]. The document which contains the following statement: "On May 18, 1998, the Company [OncorMed] and Myriad Genetics, Inc. ("Myriad") settled all outstanding lawsuits… [T]he Company granted to Myriad exclusive rights to all current and pending Company patents in the field of *BRCA1* and *BRCA2*… [T]he Company recorded a $525,000 gain related to the sale of the breast cancer testing service, which includes certain customer lists, databases and other intangible assets."
[45] Oncormed, Inc. *SEC EDGAR Filing Information: Form 8-K - Current Report 1998-07-07.* Page 4. See http://www.sec.gov/Archives/edgar/data/922821/0000950133-98-002539.txt [accessed June 2007].
[46] Oncormed, Inc. *SEC EDGAR Filing Information: Form 15-12B - Securities registration termination 1998-30-09.* See http://www.sec.gov/Archives/edgar/data/922821/0000936392-98-001309.txt [accessed June 2007].

(BRACAnalysis®)."[47] In 2003 the *Journal of Molecular Diagnostics* noted that of the twelve tests that laboratory directors across the United States were called on to stop performing by patent enforcers, Myriad's *BRCA* testing tied for first with nine labs reporting enforcement efforts.[48]

Lynch Syndrome (HNPCC)

Multiple gene patents cover the major genes involved in Lynch Syndrome (HNPCC). The first patent, U.S. 5922855, covering the *MLH1* gene, was filed by Oregon Health Sciences University and Dana Farber in 1999. The second patent application, U.S. 5591826, was filed by Johns Hopkins in 1997. It covers the *MSH2* protein. Johns Hopkins also later patented a diagnostic method to find mutations in the *MSH2* gene (U.S. 5693470). There are multiple providers, both non-profit and for-profit, for full sequence tests on both genes (see Appendix 1). Neither patent was noted by laboratory directors as having been enforced.[49] Finally, some providers add a third gene to their test – *MSH6* – but the patent situation for *MSH6* is unclear.

FAP

One patent, U.S. 5352775, covers the *APC* gene and was filed by Johns Hopkins in 1994. Again, multiple non-profit entities and one for-profit provider offer full sequence testing for *FAP* as described in Appendix 1. Finally, Dr. Cho and her colleagues note Johns Hopkins enforced its patent on at least two of the laboratories surveyed in 2001.[50]

Genetic Tests

Breast Cancer

For patients suspected to have one of the *BRCA* mutations–based on strong family history and an early age of onset among cancer-developing family members–two types of genetic testing are available. First, if the patient comes from an ethnic group already known to have specified mutations, or a mutation known from another member of that family, several non-profit university laboratories and one commercial laboratory can perform a targeted genetic test. These tests range in cost from $325 to $2,975.[51] If the patient is not a member of a known risk-group, or if her physician believes full DNA sequencing analysis is necessary, Myriad Genetic Laboratories is the United States' sole provider of full DNA sequencing for the *BRCA* genes. [52]

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[47] Sevilla C et al. Impact of gene patents on the cost-effective delivery of health care: the case of *BRCA1* genetic testing. Op. cit. at 289.
[48] Cho M et al. Op. cit.
[49] Ibid.
[50] Ibid.
[51] AHRQ. Genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility. Evidence synthesis 37. Op. cit.
[52] The patent story outside the United States is more complicated, and described in a separate case study by E. Richard Gold and Julia Carbone. (Gold ER, Carbone J. *Myriad Genetics: In the Eye of the Policy Storm.* 2008. International Expert Group on Biotechnology, Innovation and Intellectual Property, Centre for Intellectual Property Policy, McGill University. See http://www.theinnovationpartnership.org/data/ieg/documents/cases/TIP_Myriad_Report.pdf [accessed January 15, 2008].) For example, patents have been obtained but the patents are being ignored by provincial health systems in Canada. In Australia and the UK, Myriad's licensee permitted use by health systems, but announced a change of plans in August 2008. Only a single mutation has been patented in Myriad's lone European-wide patent, although some patents remain under review of an opposition proceeding. In effect, the United States is the only jurisdiction where Myriad's strong patent position has conferred sole-provide status. (See also Parthasarathy S. *Building Genetic Medicine: Breast Cancer, Technology, and the Comparative Politics of Health Care*. Op. cit.)

AHRQ reports that Myriad's tests have "analytic sensitivity and specificity both >99%"[53] and Myriad's price for "full sequence analysis," which also includes rearrangement testing, is $3,120.[54] Myriad performs redundant testing of each amplicon in both the forward and reverse direction to reduce PCR failure from DNA sequence variants in PCR primers. Myriad resequences any amplicon in which a mutation is detected twice and offers free sequencing of family members to characterize variants of uncertain clinical significance. Finally, when new information is found about a mutation (i.e., an uncertain variant reclassified as a mere polymorphism or as deleterious mutation), Myriad sends an amended report to the ordering physician of every patient in whom this variant has been found.[55] Myriad performs the same variant characterization services for Lynch Syndrome (HNPCC) and FAP testing.

One report in the *European Journal of Human Genetics* questions the cost-effectiveness of using full-sequence analysis testing as a screening method for at-risk women (defined as women with two first-degree relatives with breast cancer) noting that their "results on genetic testing for breast cancer show that [direct DNA sequencing] is not the most cost-effective method available" and that "The monopolist approach of the firm which owns the patents on the [*BRCA1* and *BRCA2*] genes may, therefore, limit the use of the most cost-effective strategies."[56]

Lynch Syndrome (HNPCC)

Several laboratories offer full-sequence analysis for Lynch Syndrome, including both non-profit centers and two commercial labs. With the exception of the price listed for Quest Diagnostics, prices are list prices for insurance companies. Prices were collected in 2008.

- Baylor: $1,150 per gene or $3,200 for the *MLH1*, *MSH2* and *MSH6* genes[57]
- Boston University: $2,995 for all three genes (*MLH1*, *MSH2* and *MSH6*)[58]
- City of Hope: $1,771.20 for *MLH1*, $1,474.56 for *MSH2*, $1,400.40 for *MSH6*[59]
- Harvard: $2,700 for all three genes (*MLH1*, *MSH2* and *MSH6*)[60]
- Huntington Laboratory: $1,200 for two genes (*MLH1* and *MSH2)* plus $600 for *MSH6* ($1,800 for all three genes)[61]
- Mayo Clinic: $2,000 for two genes (*MLH1* and *MSH2*) and $ 1,100 for *MSH6* ($3,100 for all three genes) [62]

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[53] AHRQ. Genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility. Evidence synthesis 37. Op. cit.
[54] Karen (refused last name). Receptionist, Myriad Genetics, via phone May 4, 2007.
Confirmed by "List of Services" (price list) effective April 15, 2008, Myriad Genetics.
[55] William Rusconi, Myriad Genetics. *Patenting and Licensing of the Breast Cancer Susceptibility Genes - BRCA1 and BRCA2.* Op. cit.
[56] Sevilla C et al. Testing for *BRCA1* mutations: a cost-effectiveness analysis. *European Journal of Human Genetics* 2002. 10:599-606.
[57] Baylor College of Medicine Medical Genetics Laboratories. *Prices and CPT Codes.* See http://www.bcm.edu/geneticlabs/cptcodes.html [accessed June 6, 2008].
[58]Alison Nicoletti. Boston University Center for Human Genetics, via phone June 11, 2008. (617)-638-7083
[59] Email from Dr. Juan-Sebastian Saldivar, City of Hope Clinical Molecular Diagnostic Laboratory, to Christopher Heaney, July 8, 2008. Prices effective August 1, 2008.
[60] Harvard Medical School. *MLH1, MSH2, and MSH6 Sequencing and Deletion/Duplication Analysis for Hereditary Non-Polyposis Colorectal Cancer (HNPCC) and HNPCC-like Syndromes.* See http://www.hpcgg.org/LMM/comment/HNPCC_info.jsp [accessed June 20, 2008].
[61] Faye A Eggerding. Huntington Medical Research Institutes, via phone June 11, 2008.
[62] Marie (refused last name). Mayo Medical Laboratories via phone June 18, 2008.

- University of Pennsylvania: $1,360 for *MLH1*, $740 for *MSH2* and $740 for *MSH6* ($2,840 for all three genes)[63]
- Quest Diagnostics: $2,940.00 for full sequencing of both *MLH1* and *MSH2* and $1820.00 for *MSH6* ($4,760 for all three genes)[64]

Among for-profit testing laboratories, Myriad charges $2,950 for its COLARIS® test which includes full-sequencing of the *MLH1*, *MSH2* and *MSH6* genes as well as testing for major rearrangements[65] Rearrangement testing complicates the picture further, as each laboratory has its own price:

- Baylor: Rearrangement testing for either *MLH1* and *MSH2* is $625, rearrangement testing for *MSH6* is not available[66]
- Boston University: Rearrangement testing is included in the cost of $2,995 for sequencing *MLH1, MSH2,* and *MSH6*[67]
- City of Hope: Rearrangement testing and dosage analysis for 7 exons in *MSH2* is $547.56, rearrangement testing and dosage analysis for all exons in *MSH 6* is $658.80[68]
- Harvard: Rearrangement testing for *MLH1* or *MSH2* is $600, rearrangement testing for both is $800[69]
- Huntington Laboratory: Rearrangement and gene dosage analysis for both *MLH1* and *MSH2* is $600[70]
- Mayo: Rearrangement testing is included in the above prices[71]
- Quest Diagnostics: Rearrangement testing for both MLH1 and MSH2 is $540.00; Rearrangement testing for MSH6 is not available[72]

A representative of the University of Pennsylvania Medical Center's lab stated that while rearrangement testing for all of the colon cancer genes discussed here, rearrangement testing is not available as a listed service but can be done on a research basis.[73] Finally, the reported sensitivity of these tests ranges from 50-70%.[74]

FAP

Four non-profit organizations offer direct DNA sequencing for FAP, as does Myriad Genetics:

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[63] Susan Walther, University of Pennsylvania Medical Center, via phone June 23, 2008.
[64] Email from Sam Garetano, Quest Diagnostics, to Christopher Heaney, July 18, 2008.
[65] Karen (refused last name), Receptionist, Myriad Genetics, via phone May 4, 2007; confirmed by "List of Services" (price list) effective April 15, 2008, Myriad Genetics.
[66] Patricia Ward. Medical Genetics Laboratories, Baylor College of Medicine, via phone June 23, 2008.
[67] Alison Nicoletti. Boston University Center for Human Genetics, via phone June 11, 2008.
[68] Email from Dr. Juan-Sebastian Saldivar, City of Hope Clinical Molecular Diagnostic Laboratory, to Christopher Heaney, July 8, 2008. Prices effective August 1, 2008.
[69] Harvard Medical School. *MLH1, MSH2, and MSH6 Sequencing and Deletion/Duplication Analysis for Hereditary Non-Polyposis Colorectal Cancer (HNPCC) and HNPCC-like Syndromes.* Op. cit.
[70] Faye A Eggerding. Huntington Medical Research Institutes, via phone June 11, 2008.
[71] Marie (refused last name). Mayo Medical Laboratories via phone June 18, 2008.
[72] Email from Sam Garetano, Quest Diagnostics, to Christopher Heaney, July 18, 2008.
[73] Susan Walther, University of Pennsylvania Medical Center, via phone June 23, 2008.
[74] Kaz A, Brentnall TA. Op. cit.

- Baylor: $1,675 for full sequence analysis; rearrangement testing $625.[75]
- Harvard: $1,500 for full-sequence analysis; rearrangement testing $600.[76]
- Huntington Laboratory: $1,200 for full-sequence analysis; gene dosage and rearrangement testing $600[77]
- University of Pennsylvania: $1,360 for full-sequence analysis[78]
- Boston University: full-sequencing analysis $1,675; rearrangement testing $495[79]
- Mayo Clinic: Full sequencing $1,300; includes rearrangement testing[80]

Among commercial laboratories, Myriad charges $1,795 for its COLARIS AP® test, providing a full-sequence analysis for the *APC* gene as well as major rearrangements and two mutations of MYH.[81] The reported sensitivity for these FAP tests ranges from 80-90%.[82]

MYH

In addition to Myriad, four other providers test the MYH gene for cancer-related mutations.

- Baylor: $1,150 full-sequence analysis, 2 mutation analysis $300, no rearrangement testing available[83]
- Huntington Laboratory: $600 full-sequence analysis, no rearrangement testing available; 2 mutation analysis available for $250[84]
- University of Pennsylvania: Full sequencing $500; targeted mutation for 2 mutations $600[85]
- Mayo: Testing for 2 mutations $306.60[86]

Summary of Costs

Table 1 notes the approximate sizes of each of the genes discussed above. Table 2 gives the number of "amplicons" used by Myriad Genetics for its BRCA and hereditary colon cancer tests.[87] We use these

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[75] Baylor College of Medicine Medical Genetics Laboratories. *Prices and CPT Codes.* See http://www.bcm.edu/geneticlabs/cptcodes.html [accessed June 18, 2008].
[76] Harvard Medical School. *APC Gene Sequencing and Deletion/Duplication Analysis for Familial Adenomatous Polyposis (FAP) and FAP-like Syndromes.* See http://www.hpcgg.org/LMM/comment/*APC*_info.jsp [accessed July 14, 2008].
[77] Faye A Eggerding. Huntington Medical Research Institutes, via phone June 11, 2008.
[78] Susan Walthers. University of Pennsylvia, via phone June 24, 2008.
[79] Alison Nicoletti. Boston University Center for Human Genetics, via phone June 11, 2008.
[80] Marie (refused last name). Mayo Medical Laboratories via phone June 18, 2008.
[81] Karen (refused to give last name), Receptionist, Myriad Genetics, via phone call May 4, 2007; confirmed by "List of Services" (price list) effective April 15, 2008, Myriad Genetics.
[82] Kaz A, Brentnall TA. Op. cit.
[83] Patricia Ward. Medical Genetics Laboratories, Baylor College of Medicine, via phone June 23, 2008.
[84] Faye A Eggerding. Huntington Medical Research Institutes, via phone June 11, 2008.
Email from Faye Eggerding to Christopher Heaney, July 20, 2008.
[85] Susan Walthers, University of Pennsylvia, via phone July 15, 2008.
[86] Mayo Medical Laboratories. *84304 Overview: MYH Gene Analysis for Multiple Adenoma, Y165C and G382D*. See http://www.mayomedicallaboratories.com/test-catalog/print.php?unit_code=84304 [accessed July 15, 2008].
[87] The full-sequencing tests are done by choosing PCR primers that flank exons or subsections of exons, amplifying the DNA that spans the relevant exonic sequences, and sequencing those stretches of DNA. The "amplicons" include the protein-coding regions of the genes, plus a small amount of flanking sequence for each unit. Amplicons may span an entire (short) exon, or may break a protein-coding region into segments that can be amplified by PCR (so long exons are represented by several amplicons). At Myriad Genetics, each amplicon is amplified from two sets of PCR primers, so that each amplicon is sequenced twice. We

figures because Myriad, as sole provider of the BRCA test, is the only laboratory for which we can compare prices for BRCA and colon cancer testing. For other laboratories, we assume that they are using comparable methodology, although they do not use the same PCR primers, likely use a somewhat different number of amplicons, and may not use exactly the same protocols for testing. The comparisons are therefore only rough benchmarks, and the overall price is the main metric. Myriad Genetics is on the high side of pricing for colon cancer testing in overall price (and the only provider for breast cancer testing), but Myriad also includes rearrangement testing and (for FAP and Attenuated FAP) tests common mutations in a gene, MYH, that some other laboratories price as separate tests but do not necessarily analyze with the standard FAP full-sequence test. Table 2 uses these gene sizes to determine the approximate total number of base pairs sequenced per genetic test for both breast and ovarian cancer, as well as colorectal cancers tests, then estimates charge per kilobase (one thousand base-pairs) for each test as well.

Table 1: Approximate Sizes of Genes[88]

Gene	Amplicons*	Size (Base-pairs)
BRCA1[89]	35	81,155
BRCA2[90]	47	84,193
APC [91]	42	108,353
MLH1[92]	19	57,359
MSH2[93]	16	80,098
MSH6[94]	25	23,807

* Amplicons used by Myriad for its "full sequence" analysis

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did not obtain details of laboratory procedure at other testing services, because we did not need to make intra-laboratory comparisons.

[88] The number of amplicons is based on Myriad Genetics' method of "full sequence" analysis, based on publicly available data from Myriad's technical specification sheets for its tests, and confirmed by phone conversations with Myriad staff. This allows rough comparison of BRCA versus colon cancer gene tests at Myriad. The amplicons and testing protocols are different from other laboratories, but for those laboratories the overall cost is the relevant metric. The objective of the table for hereditary colon cancer susceptibility testing is to compare *inter*-laboratory prices for hereditary colon cancer susceptibility, so overall price is the relevant measure, and per-amplicon cost is merely a rough indicator marginal price per unit among laboratories. Gene sizes are taken from the National Center for Biotechnology Information database, and cross-checked with the Genome Browser, University of California Santa Cruz. Full-length gene sizes do not reflect the number of bases sequenced in the actual gene tests, because actual genetic tests sequence neither the entire genomic sequence nor the cDNA sequence (with introns edited out) of the genes, but rather "amplicon" fragments of the gene that can be amplified by PCR.

[89] NCBI Sequence Viewer. *Homo Sapiens Breast Cancer 1*. See http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=NG_005905.1&from=10511&to=91665&dopt=gb [accessed June 2007].

[90] NCBI Sequence Viewer. *Homo Sapiens Chromosome 13, Reference Assembly*. See http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=NC_000013.9&from=31787617&to=31871809&dopt=gb [accessed June 2007].

[91] NCBI Sequence Viewer. *Homo Sapiens Chromosome 5, Reference Assembly.* See http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=NC_000005.8&from=112101483&to=112209835&dopt=gb [accessed June 2007].

[92] NCBI Sequence Viewer. *Homo Sapiens Chromosome 3, Reference Assembly*. See http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=NC_000003.10&from=37009983&to=37067341&dopt=gb [accessed June 2007].

[93] NCBI Sequence Viewer. *Homo Sapiens Chromosome 3, Reference Assembly*. See http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=NC_000002.10&from=47483767&to=47563864&dopt=gb [accessed June 2007].

[94] NCBI Sequence Viewer. *Homo Sapiens Chromosome 2, Reference Assembly*. See http://www.ncbi.nlm.nih.gov/entrez/viewer.fcgi?val=NC_000002.10&from=47863790&to=47887596&dopt=gb [accessed June 2007].

Table 2: Comparison of Cost-per-Base-Pair among Genetic Tests

Disease	Genetic Test	Total Amplicons	Test Provider	Provider's Charge*	*Charge per Amplicon*
Breast / Ovarian Cancer	*BRCA1* and *BRCA2* full sequencing	35 + 47 = **82**	Myriad*	$3,120	***$38.05***
FAP	*APC* full sequencing	**42**	Baylor	$ 1,675	***$ 39.88***
			Boston	$1,675	***$39.88***
			Harvard	$1,500	***$35.71***
			Huntington	$1,200	***$28.57***
			Univ. of PA	$ 1,360	***$ 32.38***
			Mayo Clinic	$1,300	***$30.95***
			Myriad$^{\Psi}$ (44 amplicons)	$1,795	***$40.80***
Lynch Syndrome (HNPCC)	*MLH1*, *MSH2*, and *MSH6* full sequencing	19 + 16 + 25 = **60**	Baylor	$ 3,200	***$ 53.33***
			Boston Univ.	$2,995	***$49.92***
			City of Hope	$ 4646.16	***$ 77.44***
			Harvard	$2,700	***$45.00***
			Huntington	$1,800	***$30.00***
			Mayo Clinic$^{\vartheta}$	$ 3,100	***$ 51.67***
			Myriad$^{\vartheta}$	$2,950	***$49.17***
			U. Pennsylvania	$ 2,840	***$ 47.33***
			Quest Diagnostics	$4,760	***$79.33***

Notes: Cost per base-pair represents authors' calculations based on costs reported by the testing facilities and the size of each gene as reported by NCBI.

* Includes major rearrangement testing (5 common insertions/deletions and analysis for any other rearrangements in high-risk individuals)

$^{\Psi}$ Includes Southern Blot analysis for rearrangements and 2 MYH mutations (an additional 2 PCR amplicons) with full sequence of MYH if one of the 2 common mutations is detected.

$^{\vartheta}$ Includes rearrangement analysis

As Table 2 shows, Myriad's charge per amplicon varies over the three tests it offers, ranging from $38.05 for its *BRCA1&2* test, to $40.80 for its FAP test, to $49.17 for its Lynch Syndrome (HNPCC) test. Myriad's charge per amplicon is actually lower for its *BRCA1&2* tests, which are done under exclusive provider status associated with Myriad's dominant patent position, compared to the colon cancer tests, despite there being multiple providers and lack of dominant patent position for the various hereditary colon cancer susceptibility tests. This shows no clear *price* premium for the BRCA full-sequence tests.

Myriad's normalized price for colon cancer testing is at the high end for FAP (but that includes two mutations in another gene, MYH, as well as rearrangement testing), and is in the middle of the range for Lynch Syndrome (HNPCC) testing for the three DNA repair genes in that pathway, MLH1, MSH2, and MSH6. All laboratories offering colon cancer testing are presumably paying comparable licensing fees to the patent-holders, although the licensing arrangements are not public information so we do not know details.

The result is somewhat different if normalization is done on cost "per base pair," rather than per PCR amplicon. Calculated per base pair of the full length native gene, BRCA testing price is 15 to 48 percent higher than for colon cancer testing ($18.87 per kilobase of gene sequence for BRCA1 and 2, compared to $16.57 for APC, and $12.71 for the MLH1, MSH2 and MSH6 test). The "length of gene" basis for

normalization is not as relevant for normalization, however, because the test is done by sequencing gene fragments as PCR amplicons, and the unit cost is more related to number of amplicons than total gene size. The price comparisons may be surprising to some, as normalized prices show little if any price premium. **This, in turn, suggests the main market impact of the BRCA patents is not on price but rather on volume, by directing BRCA full-sequence testing in the United States to Myriad, the sole provider.**

Current Genetic Testing Guidelines

Breast Cancer

Though in 2005 the United States Preventative Services Task Force (USPSTF) recommended against routine genetic testing for the *BRCA1 / BRCA2* mutations, the USPSTF does recommend testing for women with "certain specific family history patterns" suggesting *BRCA1* or *BRCA2* risk.[95] Specifically, the USPSTF recommends that women with family histories suggestive of *BRCA1/BRCA2* mutations be referred for appropriate genetic counseling, stating "the benefits of referring women with an increased-risk family history to suitably trained health care providers outweigh the harms."[96]

In terms of clinical algorithms, the National Comprehensive Cancer Network (NCCN) publishes and maintains guidelines on its website http://www.nccn.org/. The NCCN clinical algorithms for breast and ovarian cancer are attached as Appendix 2, and were updated in early 2007.

Colorectal Cancer

The Evaluation of Genomic Applications in Practice and Prevention Working Group (EGAPP) published recommendations for genetic testing among newly diagnosed individuals with colorectal cancer.[97] They examined four genetic testing strategies and found no decisive winner. All four protocols involve genetic testing, but the methods, cost, and selection criteria for which patients get which kind of test differ. The most expensive but also most sensitive method is full-sequence testing, the pathway most comparable to Myriad's BRCA testing. The EGAPP recommendations are based on a January 2009 supplementary evidence review.[98] That review, in turn, builds on a massive 2007 evidence review by the Tufts-New England Medical Center Evidence-Based Practice Center.[99] The NCCN has published its clinical guidelines on testing for FAP and HNPCC, reproduced in Appendix 3. And a joint committee of the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer and the American College of Radiology (ACS/MSTFCRC/ACR) produced a consensus statement on screening and surveillance for colorectal cancer and polyps in May 2008, with Table 3 recommending genetic testing in individuals from high-risk families included in Appendix 3.[100]

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[95] United States Preventative Services Task Force. Genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility. *Ann Intern Med* 2005. 143: 355-61.
[96] Ibid.
[97] Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Op. cit.
[98] Palomaki GE et al. Op. cit.
[99] Bonis PA, Trikalinos TA, Chung M, Chew P, Ip S, DeVine D, Lau J. Hereditary nonpolyposis colorectal cancer: diagnostic strategies and their implications. Evidence report/technology assessment No. 150 (Prepared by Tufts-New England Medical Center Evidence-based Practice Center under Contract No. 290-02-0022). AHRQ Publication No. 07-E008. Rockville, MD: Agency for Healthcare Research and Quality. May 2007. Available at http://www.ahrq.gov/downloads/pub/evidence/pdf/hnpcc/hnpcc.pdf (accessed 4 June 2008).
[100] Levin B et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer and the American College of Radiology. *CA: A Cancer Journal for Clinicians* 2008. 58:130-160.

New EGAPP analysis, in addition to sifting through evidence and assessing four genetic testing strategies, also shifts the framework for genetic testing away from family history, and toward genetic testing of those newly diagnosed with colorectal cancer. This is a significant change, indicating the many individuals who do not know about cancer in relatives or when they are the first individuals in their families identified with the mutations that can now be identified as conferring risk. That is, clinical practice appears to be shifting from genetic testing only when family risk is evident to using genetic testing to identify new individuals and families at risk. This is mainly because many individuals carrying mutations will be missed if family history is a threshold criterion for testing. It is worth noting that if genetic testing becomes less expensive and more widely available, and as more mutations associated with cancer risk are identified, DNA analysis could move higher up the clinical decision tree, not just in Lynch Syndrome but in other cancers as well.

NCCN guidelines specify the following inclusion criteria to consider genetic testing for any of the various inherited colorectal cancers:

- Early-onset colorectal cancer (age < 50), or
- Clustering of same or related cancer in close relative, or
- Multiple colorectal carcinomas or >10 adenomas in the same individual, or
- Known family history of hereditary cancer syndrome with our without mutation.[101]

From here, the NCCN guidelines split between FAP and HNPCC

FAP

In patients with the FAP phenotype (more than 100 colorectal polyps), genetic testing is recommended to establish the diagnosis. From there, the NCCN recommends:

> Genetic testing in individuals with familial polyposis should be considered before or at the age of screening. The age for beginning screening should be based on the patient's symptoms, family phenotype and other individual considerations.[102]

In the event that a familial mutation is unknown, the NCCN further recommends:

> In some families, APC mutations cannot be found with available testing technology, recognizing that the sensitivity to identify APC mutations is currently only about 80%. In other families, affected individuals have died or are not immediately available. Under these circumstances, APC testing should be considered for at-risk family member. If the mutation responsible for FAP within a family is not found, it is important to remember the limitations of interpreting a gene test in a presymptomatic individual. Evaluating presymptomatic individuals at risk in these families presents a difficult problem, since the mutation responsible for FAP within the family is not known. Certainly, a positive test in a presymptomatic person is informative even when the familial mutation has not been previously identified. But interpreting a test in which "no mutation is found" in a presymptomatic person is not the same as a "negative test."[103]

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[101] National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology – Colorectal Cancer Screening.* V.1.2007. See http://www.nccn.org/professionals/physician_gls/PDF/colorectal_screening.pdf [accessed May 2007].
[102] Ibid.
[103] Ibid.

The ACS/MSTFCRC/ACR guideline identifies those with a genetic diagnosis of FAP or suspected FAP without genetic testing as "high risk" and recommends considering genetic testing (if not already done). It recommends monitoring starting age 10 to 12, with an annual flexible sigmoidoscopy exam. If genetic testing is positive, "colectomy should be considered."[104]

HNPCC

The NCCN only recommends HNPCC genetic testing only for certain patients:

- Individuals in families meeting either the Amsterdam I or II criteria, and
- Affected individuals meeting Revised Bethesda guidelines.[105]

The 2008 ACS/MSTFCRC/ACR guideline recommends offering genetic testing for all first-degree relatives of a confirmed case. Monitoring for those with confirmed or at increased risk of HNPCC should begin at age 20 to 25, or a decade before the youngest case in a family (whichever is younger), with colonoscopy every 1-2 years.[106]

The 2007 Tufts Evidence-Based Practice Center report noted a major gap in knowledge about how best to do the genetic testing and differing views on test algorithms in the literature. The report also noted that sequencing was the "method of choice" for mutation detection, but with many different technologies for doing such sequencing and a need to supplement it with rearrangements/insertion/deletion testing. No clear, consistent "winner" was found among technologies.

Regarding test utility, the report concluded:

> Pre-test genetic counseling had good efficacy in improving knowledge about HNPCC and resulted in a high likelihood of proceeding with genetic testing, satisfaction in the decision to undergo genetic testing, and decreasing depression and distress levels among family members of HNPCC probands with cancer and among asymptomatic individuals from HNPCC families.
>
> Identification of HNPCC mutations was associated with an increase in the likelihood that family members of probands with CRC [colorectal cancer] would undergo cancer-screening procedures. HNPCC family members who underwent cancer-screening procedures had a lower risk of developing HNPCC-related cancers and lower mortality rates than those who did not take actions.[107]

These conclusions will now be updated by the January 2009 EGAPP recommendations, which do not choose among the four genetic testing strategies, but do recommend genetic testing in newly diagnosed colorectal cancer.[108] The trend appears to be moving towards genetic testing earlier in the diagnostic process, in order to guide treatment and to identify others in families who might be at risk but do not know it.

If a tumor sample is available, the NCCN recommends testing for both immunohistochemistry and microsatellite stability testing first rather than beginning with DNA sequencing. The results of either of

[104] Levin B et al. Op. cit. At Table 3, p. 154.
[105] National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology – Colorectal Cancer Screening.* Op. cit.
[106] Ibid.
[107] Bonis PA, Trikalinos TA, Chung M, Chew P, Ip S, DeVine D, Lau J. Op. cit. at p. vi.
[108] Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Op. cit.

these preliminary tests can direct a clinician to the appropriate gene to sequence for "germline analysis," thus avoiding the shotgun-like approach of a full-sequence analysis on all three genes.[109]

Non-genetic screening options

Breast Cancer

The USPSTF currently recommends mammography for all women once every 1-2 years after the age of 40.[110] AHRQ reports that the Cancer Genetic Studies Consortium recommended annual mammography for women beginning between the ages of 25 and 35, with annual clinical breast exams also beginning between ages 25 and 35 and monthly self breast exams beginning between ages 18 and 21.[111] AHRQ also notes that the USPSTF does not currently recommend screening women at any age for ovarian cancer.[112] The American Cancer Society issued guidelines in April 2007 calling for MRI screening, in addition to mammography, for women carrying BRCA mutations and first-degree relatives of those with BRCA mutations.[113]

Colorectal Cancer

Beginning at age 50, the American Cancer Society recommends:

- Fecal occult blood testing (FOBT) annually, or
- Flexible sigmoidoscopy every five years, or
- Annual FOBT plus flexible sigmoidoscopy every five years, or
- A double-contrast barium enema every five years, or
- A colonoscopy every 10 years.[114]

However, according to the USPSTF:

> The USPSTF found good evidence that periodic fecal occult blood testing (FOBT) reduces mortality from colorectal cancer and fair evidence that sigmoidoscopy alone or in combination with FOBT reduces mortality. The USPSTF did not find direct evidence that screening colonoscopy is effective in reducing colorectal cancer mortality; efficacy of colonoscopy is supported by its integral role in trials of FOBT, extrapolation from sigmoidoscopy studies, limited case-control evidence, and the ability of colonoscopy to inspect the proximal colon. Double-contrast barium enema offers an alternative means of whole-bowel examination, but it is less sensitive than colonoscopy, and there is no direct evidence that it is effective in reducing mortality rates.[115]

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[109] Ibid.
[110] AHRQ. *U.S. Preventive Services Task Force: Screening for Breast Cancer Summary of Recommendations*. Published February 2002. See http://www.ahrq.gov/clinic/uspstf/usps*BRCA*.htm [accessed May 2007].
[111] AHRQ. Genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility. Evidence synthesis 37. Op. cit.
[112] Ibid.
[113] Saslow D et al. American Cancer Society Guidelines for breast screening with MRI as an adjunct to mammography. *CA: A Cancer Journal for Clinicians* 2007. 57(2):75-89.
[114] American Cancer Society. *Cancer Facts and Figures, 2007*. Op. cit.
[115] AHRQ. *U.S. Preventive Services Task Force: Screening for Colorectal Cancer Summary of Recommendations.* July 2002. See http://www.ahrq.gov/clinic/uspstf/uspscolo.htm [accessed May 2007].

Interpreting Test Results / Options for Prophylactic Treatment

Breast and Ovarian Cancer

The clinical utility of *BRCA1* and *BRCA2* screening may be summarized as follows:

- For those testing positive, there are cost-effective approaches to chemoprevention (prophylactic tamoxifen for breast cancer and oral contraceptives for ovarian cancer), screening, and surgery (prophylactic mastectomy, prophylactic salpingo-oophrectomy or tubal ligation), all of which result in gains in both life expectancy and quality-adjusted life years (QALYs) relative to watchful waiting.[116]
- For high-risk patients who test negative, there may be reduced anxiety about the future risks of breast or ovarian cancer. These gains must be balanced against the losses experienced by those who test positive, including elevated anxiety, depression and guilt.[117]
- Finally, though $50,000 per QALY is the conventional benchmark for cost-effectiveness analysis,[118] some authors do argue for a standard of $100,000 - $150,000 per QALY.[119, 120]

According to AHRQ, interpretation of the test results for *BRCA1* and *BRCA2* genetic testing can be difficult. For example, if a patient with known positive family history for a specific mutation tests negative, she can be "reassured about her inherited risk." On the other hand, a negative test is "less useful if her relatives have cancer but no detected deleterious mutations." Finally, AHRQ noted that up to 13% of tests produce results of "uncertain clinical significance."[121] More recent (2008) data are that variants of uncertain clinical significance are found in fewer than 6% of cases (with the highest rate of "variants of unknown significance" among African Americans, at 11%).[122]

When women do test positive, the USPSTF first noted in 2002 that women at high risk for breast cancer should consider taking chemoprevention (e.g., tamoxifen)[123] but then noted in 2005 that there is "insufficient evidence to determine the benefits of chemoprevention or intensive screening in improving

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[116] Goldman N et al. Screening and primary and secondary interventions for patients at high risk for ovarian cancer. *Women's Oncology Review* 2003 (December). 3(4):269-274.
[117] Higashi M et al. Managed care in the genomics era: assessing the cost effectiveness of genetic tests. *American Journal of Managed Care* 2003. 9(7):493-500
[118] Carroll A et al. Comprehensive cost-utility analysis of newborn screening strategies. *Pediatrics* 2006 (May). 117(5):S287-S295.
[119] Cutler D et al. *Intensive Medical Care and Cardiovascular Disease Disability Reductions*. National Bureau of Economics Research Working Paper No. 12184. November 16, 2006.
[120] Murphy K et al. The economic value of medical research. In: *Measuring the Gains from Medical Research: An Economic Approach.* Chicago: University of Chicago Press, 2003.
[121] AHRQ. Genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility. Evidence synthesis 37. Op. cit.
[122] Saam J, Burbidge LA, Bowles K, Roa B, Pruss D, Schaller J, Reid J, Frye C, Wenstrup RJ. Decline in rate of *BRCA1/2* variants of uncertain significance: 2002-2008. Abstract for presentation at National Society of Genetic Counselors annual meeting. Fall 2008. The crucial data are: "Overall, the VUS [Variants of Unknown Significance] rate decreased from 12.8% in 2002 to 5.9% in 2006, a 54% reduction, including decreases of 50.1% (Western European), 58.3% (African), and 48.6% (Asian). From 2006 to 2008 the identification of variants of uncertain significance continued to decline to 5.1% of tests performed. This continued decrease was observed in all ethnic groups, with the largest decline in the African American population where the VUS rate declined from 38.6% in 2002 to 10.9% in 2008."
[123] AHRQ. *U.S. Preventive Services Task Force: Chemoprevention: Breast Cancer*. July 2002. See http://www.ahrq.gov/clinic/uspstf/uspsbrpv.htm [accessed May 2007].

health outcomes."[124] The ACS recommends that women positive for *BRCA1/BRCA2* mutations consider tamoxifen therapy.[125] See Table 3 for a break-down of the results found in three different cost-effectiveness studies on chemoprevention in at-risk women.

Table 3: Cost Effectiveness Studies Comparing Chemoprevention to Surveillance Alone

Study	Context	Results (Cost per QALY)
Grann (2000)[126]	Positive *BRCA* test	30 year old women = $990 40 year old women = $1,800 50 year old women = $3,600
Hershman (2002)[127]	Two-or-more first-degree relatives diagnosed with breast cancer	30 year-old women = $45,000 50 year-old women = $89,000 60 year-old women = $140,000
Eckermann (2003) [128]	Hypothetical cohort of healthy women at high risk of breast cancer	5 yrs of tamoxifen / 5 yrs of benefit = $32,000 5 yrs of tamoxifen / 10 yrs of benefit = $16,000 5 yrs of tamoxifen / no reduced incidence at 10 yrs = $170,000

Notes: QALY = "Quality Adjusted Life Year"

Surgical options. Both the ACS and the USPSTF note that prophylactic surgery (e.g., bilateral mastectomy and bilateral oophorectomy) significantly decreases the chances of developing cancer in *BRCA* mutation-positive women and should be strongly considered.[129,130] Table 4 shows the results from two cost-effectiveness studies on prophylactic surgery.[131]

Table 4: Cost Effectiveness Studies Comparing Prophylactic Surgery to Surveillance Alone

Study	Context	Results (Cost per QALY)
Grann (1998)[132]	Positive *BRCA* test in 30-year-old women at high-risk	Prophylactic Oophorectomy and Mastectomy = Dominated Prophylactic Oophorectomy = $5,600
Tengs (2000)[133]	High-risk 30-year-old women assuming varying risks of mutation	*BRCA* testing then oophorectomy if positive by mutation probability: *High Risk* *BRCA1* (p=0.5) and *BRCA2* (p=0.0) = $3,900 *BRCA1* (p=0.25) and *BRCA2* (p=25) = $4,700

[124] United States Preventative Services Task Force. Genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility. *Ann Intern Med* 2005. 143: 355-61.
[125] American Cancer Society. *Breast Cancer Facts and Figures, 2005-2006*. Op. cit.
[126] Grann V et al. Prevention with tamoxifen or other hormones versus prophylactic surgery in *BRCA1*/2-positive women: a decision analysis. *Cancer J Sci Am* 2000. 6:13-20.
[127] Hershman D et al. Outcomes of tamoxifen chemoprevention for breast cancer in very high-risk women: a cost-effectiveness analysis. *J Clin Oncol* 2002. 20(1):9-16.
[128] Eckermann S et al. The benefits and costs of tamoxifen for breast cancer prevention. *Aust N Z J Public Health* 2003. 27(1): 34-40.
[129] United States Preventative Services Task Force. Genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility. Op. cit.
[130] American Cancer Society. *Breast Cancer Facts and Figures, 2005-2006.* Op. cit.
[131] For a complete cost-effectiveness analysis of all preventative strategies surrounding positive *BRCA* findings, please see: Anderson K et al. Cost-effectiveness of preventive strategies for women with a *BRCA1* or a *BRCA2* mutation. *Annals of Internal Medicine* 2006 (March 21). 144(6): 397-407.
[132] Grann VR et al. Decision analysis of prophylactic mastectomy and oophorectomy in *BRCA1*-positive or *BRCA2*-positive patients. *J Clin Oncol* 1998. 16:979-85.
[133] Tengs T et al. The cost effectiveness of testing for the *BRCA1* and *BRCA2* breast-ovarian cancer susceptibility genes. *Disease Management and Clinical Outcomes* 2000. 1:15-24.

BRCA1 (p=0.0) and *BRCA2* (p=0.5) = $5,400

Moderate Risk
BRCA1 (p=0.1) and *BRCA2* (p=0.1) = $17,000

Slight Risk
BRCA1 (p=0.05) and *BRCA2* (p=0.05) = $42,000

Average Risk
BRCA1 (p=0.0006) and *BRCA2* (p=0.0002) = $1,600,000

Notes: "QALY" = Quality Adjusted Life Year. "Dominated" means that prophylactic mastectomy and oophorectomy in the Grann article actually saved money compared to surveillance alone.

Colon Cancer

According to the American Gastrological Association (AGA), patients with Lynch Syndrome should receive subtotal colectomy (removal of almost the entire colon, sparing the rectum) with ileorectal anastomosis. This surgical method can preserve some bowel-function by fusing the small intestine to the rectum and creating a "pouch" out of small intestine. Thus, patients should not require a permanent colostomy. The AGA recommends the same surgical approach for patients Lynch Syndrome, both those who already have colon cancer and those who are positive for a mutation but have yet to develop any detectable colon tumors or known symptoms. After surgery, patients should still be followed with regular rectal screening for additional rectal polyps.[134]

We were unable to find cost-effectiveness studies of prophylactic colectomy, but two decision analyses have been published on clinical effectiveness. The first paper was published in *Gastroenterology* in 1996 and demonstrated that compared to a colonoscopic surveillance program, prophylactic colectomy for a 40 year-old male with positive HNPCC mutation yields a life expectancy benefit of 8 months to 1.5 years. For a thirty-year old male with positive HNPCC mutation, this benefit increased to between 1 and 2 years.[135] However, the authors did not analyze quality of life and did not analyze the subtotal colectomy option.

The second clinical effectiveness paper was published in the *Annals of Internal Medicine* in 1998 and addressed both life-expectancy and quality of life. This paper demonstrated that immediate prophylactic surgery (e.g., either total proctocolectomy or subtotal colectomy) extended overall life-expectancy compared to surveillance alone (defined as "colonoscopy every 3 years if no surgical intervention had been performed and flexible sigmoidoscopy of the remaining rectal segment every 3 years after subtotal colectomy" plus segmental resection if cancer was found)[136] in a hypothetical cohort of twenty-five year-olds with HNPCC mutations. However, in terms of quality-adjusted life-years (QALYs) both methods of prophylactic surgery actually fared worse than surveillance:

> Surveillance leads to the greatest quality-adjusted life expectancy compared with all colectomy strategies. Surveillance led to a gain of 14.0 quality-adjusted life-years (QALYs) compared with no surveillance, 3.1 QALYs compared with immediate proctocolectomy, and 0.3 QALYs compared with immediate subtotal colectomy.

[134] American Gastroenterological Association. AGA technical review on hereditary colorectal cancer and genetic testing. *Gastroenterology* 2001 (July). 121(1):198-213.
[135] Vasen H et al. Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis. *Gastroenterology*1996 (April). 110(4): 1020-7.
[136] Syngal S et al. Benefits of colonoscopic surveillance and prophylactic colectomy in patients with hereditary nonpolyposis colorectal cancer mutations. *Annals of Internal Medicine* 1998 (November 15). 192(10):787-796.

> Incorporation of quality adjustments resulted in greater quality-adjusted life expectancies for all subtotal colectomy strategies compared with proctocolectomy strategies, with benefit ranging from 0.3 QALYs if colectomy was performed when colorectal cancer was diagnosed to 2.8 QALYs if colectomy was performed at 25 years of age.[137]

For FAP, the American Gastrological Association (AGA) recommends that patients who are positive for FAP receive immediate total proctocolectomy (removal of the colon and rectum) to minimize the potential for malignancy except in certain "life-style" choices. For example, the AGA would accept delaying surgery in teenagers with minimally-concerning polyps (small and non-villous) to accommodate "work and school schedules."[138] Appropriate follow-up should include endoscopic monitoring any remaining colon (e.g., if a subtotal colectomy is performed) every 6 months as well as additional endoscopic monitoring of the upper gastrointestinal tract with biopsies (including the stomach and small intestine) every 6 months to 4 years.[139] In contrast, the guidelines state "use of chemoprevention as primary therapy for colorectal polyposis is not proven and is not recommended."[140]

Lessons Learned

This comparison was selected because it provides a natural case-study to compare for-profit testing and exclusive licensing practices for BRCA versus a mix of for-profit and non-profit patenting with nonexclusive licensing practices for colon cancer susceptibility genes. Using the conceptual framework developed for a parallel literature synthesis, we now consider what lessons might be learned from this case.

For both breast cancer and colon cancer, the genetic tests discussed above have two major implications. First, genetic tests can distinguish genetic (and thus inheritable) susceptibility from non-genetic cancers in the original patient. Thus, if the original patient tests positive other family members can then test themselves and know with relative certainty whether or not they have inherited the same mutation as their cancer-suffering relative. Second, BRCA and colon cancer genetic tests guide treatment decisions for the original patient as well alerting relatives that they may also be at risk (and can be tested for the same mutation at much lower cost and with greater specificity).

Basic Research

As of August 2008, Myriad has submitted over 18,000 entries (>80% of total entries) for over 2,600 unique mutations to the Breast Cancer Information Core http://research.nhgri.nih.gov/bic database. As of February 2005, over 4,300 follow-up publications on *BRCA1* and *BRCA2* resulted from more than 100 collaborations between Myriad and independent investigators.[141] Patent rights are much narrower in Europe, although details of the recent European patent re-issue have not yet been made public. Europe also differs because several countries have explicit research exemptions and diagnostic use exemptions from patent infringement liability that would cover clinical research testing in several European countries.

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[137] Ibid.
[138] Church J et al. Practice parameters for the treatment of patients with dominantly inherited colorectal cancer (familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer). *Diseases of the Colon and Rectum* 2003 (August). 46(8):1001-1012.
[139] Ibid.
[140] Ibid.
[141] William Rusconi, Myriad Genetics. *Patenting and Licensing of the Breast Cancer Susceptibility Genes - BRCA1 and BRCA2.* Op. cit.
Personal communication to Robert Cook-Deegan 29 May 2008.
A search of the Breast Cancer Information Core for mutations catalogued as deposited by Myriad Genetics revealed 8,826 mutations in BRCA1 and 9,891 mutations in BRCA2. (*Breast Cancer Information Core.* National Human Genome Research Institute. See http://research.nhgri.nih.gov/bic/ [accessed September 25, 2008].)

Research, and in some countries also genetic testing, have therefore proceeded in Europe with less concern about patent infringement.

Some argue that even in the United States, Myriad's definition of infringing research is too broad. Specifically, in 1998 Myriad asserted that even though Genetic Diagnostics Laboratory (GDL) limited testing to patients in NCI research protocols, GDL was performing a patent-infringing third-party service in which it charged other laboratories and rendered clinical services. As Parthasarathy summarizes Myriad's reasoning, "So long as GDL disclosed results to the patient, [it provided] a commercial service and violat[ed] the patent."[142] The 1999 NCI/Myriad Memorandum of Understanding established ground rules permitting use of BRCA testing within a research institution, and discounted testing for research clinical testing contracted to Myriad.[143]

According to a 2005 Lewin Group Report published for AdvaMed:

> An unintended effect of patents is that they may slow further innovation by blocking R&D efforts along avenues patented by other companies. This was the case with genetic testing for the *BRCA1* and *BRCA2* genes [mutations], the presence of which are [is] associated with an elevated risk for developing breast or ovarian cancer. The US Patent and Trademark Office (USPTO) issued patent rights for *BRCA1* and *BRCA2* to a privately owned diagnostics firm. These rights included the gene sequences and any resulting applications developed from them, including laboratory tests and targeted drug therapies. The patents allow the firm to control breast cancer susceptibility testing and research.[144]

Though the Lewin Group concluded that Myriad's exclusive patents on the *BRCA* genes stifled further basic research based on this theory, we found few data either to support or to refute this conclusion. The Gold and Carbone case study did identify a decision not to report some BRCA mutation analysis by Canadian researchers.[145] The researchers were cautioned not to leave a public trace that they had done BRCA testing without a license, and this meant they did not contribute their research results that would have been of general interest.

Myriad maintains it has never enforced its patents against researchers, and does not enforce its patents against laboratories providing BRCA testing services in a form it does not do itself (such as pre-implantation genetic diagnosis and real-time PCR of DNA amplified from paraffin-embedded tissues). Myriad notes it permitted rearrangement testing, and even referred patients to Mary-Claire King and others until it began to offer such testing itself. Myriad says it has never even threatened to take action against basic researchers or those doing pre-implantation diagnostic testing.

A chilling effect, however, does not take hold only when each and every instance of potential infringement is the subject of patent enforcement. Moreover, Myriad never publicly stated its *de facto* research use exemption policy. Myriad either passed on an opportunity to demonstrate its intentions publicly in written form, or avoided comment to keep legal options open. And keeping options open

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[142] Parthasarathy S. Architectures of genetic medicine: comparing genetic testing for breast cancer in the USA and UK. Op. cit. at 24.

[143] Memorandum of Understanding between Myriad Genetics and the U.S. National Cancer Institute (signed on 10 December 1999 by Gregory Critchfield, President of Myriad Genetic Laboratories, Inc., and 14 December by Richard Klausner, NCI Director).

[144] The Lewin Group. Op. cit. at 62-3.

[145] Gold ER, Carbone J. Op. cit. at 40. Specifically, at a November 2006 workshop in Edmonton, researchers from a Canadian university reported that they had refrained from reporting BRCA testing results to the public database because they had been advised by their university's general counsel that it could alert Myriad to infringing activity.

equates to a chilling effect in zones of uncertainty. Myriad therefore cannot fully elude responsibility for any chilling effect on research, because the company could fully anticipate that others would refrain from research for fear of being sued for infringement. Requesting "simple notification" to Myriad is not a full remedy, as it requires notifying the very party that might, at its option, take legal action once alerted. That is, for Myriad to make credible claims of being fully supportive of unfettered research, it would need to express that policy in a form that could be the basis for others' actions, and not passively rely on others to ask them for permission. Other laboratories would need to know what activities Myriad would and would not pursue as infringement, specified in a way that courts could interpret. Ambiguity may itself stifle basic or clinical research as researchers either avoid the work altogether or are wary of publicly reporting results.

We have not found similar evidence of a chilling effect in the basic science arena for either FAP or HNPCC. This may be due to three related features: (1) lack of enforcement actions, (2) patent holders are academic institutions, and (3) licenses are nonexclusive.

Development

The Lewin report concluded that Myriad's patents "also were found to affect development and provision of potentially more cost-effective testing strategies."[146] More specifically, a French study found that:

> …there exist alternative strategies for performing BRCA1 diagnosis: prescreening techniques such as FAMA [fluorescent assisted mismatch analysis] and, potentially, DHPLC [denaturing high performance liquid chromatography] or DGGE [denaturing gradient gel electrophoresis], based on the current estimates of their sensitivity, would minimize the cost of diagnosis while also ensuring a comparable level of effectiveness to that of applying DS [direct sequencing of the whole genomic DNA] to the entire gene.[147]

When compared to the most cost-effective mutation detection strategy analyzed (in common use in French testing labs), the average cost per mutation detected using the Myriad approach was 5 times as high.[148] That is, leaving aside the issue of pricing, the costs entailed—including consumable supplies, equipment and personnel—to carry out the Myriad approach was much higher than alternative approaches that had been developed and were in use in Europe. This criticism suggests that Myriad has eschewed cheaper testing methods because as a monopoly provider it has little incentive to support them. It is difficult to judge this assertion. The comparison to colon cancer genetic testing suggests, however, that (1) Myriad is well within range in its pricing of colon cancer tests compared to other providers, and (2) its cost per unit for BRCA testing is in the same range as colon cancer testing and, if anything, a bit less expensive. Moreover, the analysis of genetic testing strategies has low-cost and high-cost options analogous to BRCA testing, and it is not clear which strategy is optimal.[149]

The technologies for testing are not qualitatively different among these different genes, so if Myriad has failed to shift to cheaper testing technology, then so have other providers for comparable colon cancer tests. Both BRCA and colon cancer susceptibility genes are large and complex, and there are hundreds of documented mutations in them that cannot be predicted in advance except in subpopulations (such as Ashkenazim).

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[146] The Lewin Group. Op. cit. at 62-3.
[147] Sevilla C et al. Impact of gene patents on the cost-effective delivery of health care: the case of *BRCA1* genetic testing. Op. cit. at 296.
[148] Ibid.
[149] Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Op. cit.
Palomaki GE et al. op. cit.

The pricing data do **not** address whether early resort to full-sequence testing in high-risk families is optimal for a health system. Myriad believes it is, and in the United States with Myriad as sole provider, that becomes policy *de facto*. In other countries, Myriad can still supply full-sequence testing, but health systems may adopt testing algorithms that resort to full-sequence testing later in the process, and use other tests as screens. **Myriad's patent position in effect allowed it to establish the standard of care in the United States, but in other countries it did not.**

Those in human genetics and cancer also tell of a patent race between Johns Hopkins University and Oregon Health Sciences University-Dana Farber Cancer Institute for the HNPCC gene *MLH1*. Both Oregon Health Sciences and Johns Hopkins hold patents claiming *MLH1*. The Oregon patent is shared with Dana Farber. It was filed December 9, 1994, and was issued as U.S. 6191268 on February 20, 2001 (Oregon Health Sciences and Johns Hopkins later filed two method patents as well). The Johns Hopkins patent, on the other hand, is shared with the for-profit firm Human Genome Sciences. The Hopkins/Human Genome Sciences patent application was filed on June 6, 1995 and issued as U.S. 6610477 on August 26, 2003. Though the details of this race do not appear in the literature, clearly patenting and ultimately test development played a role in the search for *MLH1* as Johns Hopkins ultimately partnered with a for-profit corporation to complete its work.

Dr. Merz notes the additional concern that Myriad's patents could allow it to collect license royalties as new mutations are sequentially patented, in effect extending the patent term. Dr. Merz writes:

> Think of it this way: new mutations are continually being found in the *BRCA1* and *BRCA2* genes. Assuming that patent applications are continually being filed on them, then the patent holders may have an effective monopoly on testing for the period extending from the grant of the first patent for the first discovered mutation until the end of the patent term on the last discovered mutation. If the patentee were to license the patents, royalties could only be collected for the term of each individual patent (the courts would invalidate attempts to extend the patent term by contract or to tie licenses of the patented and off-patent tests). Thus, by monopolizing the testing service, the patentee undermines the time limitation on the grant of monopoly.[150]

Another critique of patenting centers on reduced incentives of a monopoly provider to introduce newer, cheaper, or otherwise better alternative tests. For example, there is an alternative diagnostic technique to *BRCA* called multiplex ligation-dependent probe amplification, or MLPA, a molecular way to detect genetic variations, including *BRCA1* and *BRCA2* mutations, under development at University of Washington.[151] Using MLPA, a 2006 study published in the *Journal of the American Medical Association* found that Myriad's testing strategy missed up to 12% of large genomic deletions or duplications.[152] The authors noted that the missed mutations were not due to a technical error in Myriad's testing, but a flaw in the testing strategy. That is, the rearrangements were missed not because of sequencing errors in the amplicons, but because sequencing fragments of BRCA as amplicons did not detect large-scale chromosome rearrangements and deletions. The paper noted "many mutations are inherently not detectable by short-range polymerase chain reaction (PCR) followed by genomic sequencing."[153] Drs. Grodman and Chung state in their testimony before the House Subcommittee on Intellectual Property that

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[150] Merz J. Disease gene patents: overcoming unethical constraints on clinical laboratory medicine. *Clinical Chemistry* 1999. 45(3):324-330.
[151] Doheny K. Genetic tests for cancer not perfect. *HealthDay* 2006 (March 21). See http://www.healthfinder.gov/news/newsstory.asp?docID=531683 [accessed May 2007].
[152] Walsh T et al. Spectrum of mutations in BRCA1, BRCA2, CHEK2, and TP53 in families at high risk of breast cancer. Op. cit.
[153] Ibid., 1380.

this testing deficit was only corrected after "considerable pressure from the scientific community,[154] but Myriad notes it began testing for the 5 most common rearrangements (accounting for about a third of all rearrangements) in 2002 and would have detected one-third of those the JAMA paper reported as "missing"—and simultaneously began developing a test for large rearrangements (BART®) that it launched in August 2006 for the higher risk patients (similar to the JAMA article's criteria) as part of BRACAnalysis®. Myriad's claim that it was already working on BART® before the JAMA paper appeared is corroborated by poster presentations on large-scale rearrangement testing in 2004, a chronology that does not fit with the characterization of Myriad responding "under considerable pressure" only after the JAMA paper. The JAMA publication no doubt accelerated Myriad's efforts to introduce the new BART® test, however, as indicated by Myriad's Clinical Update of September 2006. [155]

In her written statement to the House Judiciary Committee, Dr. Chung noted that she believed, "In a competitive marketplace, this delay would have never occurred."[156] Myriad does not agree, and asks: "Could a cost-effective, high throughput, scientifically valid assay be designed and used clinically? It must be noted that the MLPA kits are not FDA approved and are labeled for research use only."[157]

Rearrangements are also common in colon cancer susceptibility genes, and are included as part of such testing at Myriad and many other laboratories. However, we found no literature about a major controversy among test providers for colon cancer comparable to the very public brouhaha over breast/ovarian genetic testing.

Dr. Chung's written statement for the October 30 House Judiciary hearing states that Myriad's decision not to test paraffin-embedded tissue has hampered availability of that type of testing in instances where it might be clinically useful.[158] According to Myriad's technical specifications sheet available online, Myriad isolates only the white blood cells from each sample to extract and purify DNA for testing.[159] Without market pressure to innovate, Dr. Chung notes that Myriad has little incentive to develop techniques to analyze samples other than blood samples, thereby "leaving families at risk with no remedy."[160] Myriad responds that it refers such cases to known testing services with relevant technical capacity when it learns of instances where such testing is needed. And it notes that in most cases where paraffin-embedded testing is relevant, the living person (or persons) at risk could be directly tested using full-sequence analysis, followed by mutation-specific testing for others in the family. Myriad states it has never enforced its patents against a provider offering testing in a form Myriad does not offer itself, such as pre-implantation diagnosis, prenatal diagnosis, or real-time PCR of paraffin-embedded tissue

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[154] Grodman, Marc. Statement before House Judiciary Subcommittee on Courts, the Internet and Intellectual Property in Connection with its hearing on "Stifling or Stimulating – The Role of Gene Patents in Research and Genetic Testing." October 30, 2007.

[155] Myriad Genetics, 2006. Clinical Update, Vol. 4, No. 5. Testing for Hereditary Breast and Ovarian Cancer Syndrome. An abstract submitted Feb. 2004 and a poster presented fall 2004 report on Myriad's BART test for large-scale rearrangements. (Judkins T, Hendrickson BC, Gonzales D et al. Op. cit. Hartmann C, John AL, Klaes R et al. Op. cit.) For presentations, see those listed in note 10.

[156] Grodman, Marc. Statement before House Judiciary Subcommittee on Courts, the Internet and Intellectual Property in Connection with its hearing on "Stifling or Stimulating – The Role of Gene Patents in Research and Genetic Testing." Op. cit.

[157] MRC Holland. "SALSA MLPA Kit P002-B1 BRCA1" specification sheet. April 8, 2008.

[158] See written statement provided by Wendy Chung, MD, Columbia University, to accompany the written statement and oral testimony of Marc Grodman, CEO of Bio-Reference Laboratories, Inc., before the Judiciary Committee, U.S. House of Representatives, in a hearing "Stifling or Stimulating - The Role of Gene Patents in Research and Genetic Testing," 30 October 2007, 2237 Rayburn House Office Building, Washington, DC, 2 p.m. (at page 4 of her statement).

[159] Myriad Genetic Laboratories. *BRACAnalysis® Technical Specifications.* August 29, 2005. See http://www.myriadtests.com/provider/doc/tech_specs_brac.pdf [accessed December 19, 2007].

[160] See written statement provided by Wendy Chung, MD, Columbia University, to accompany the written statement and oral testimony of Marc Grodman, CEO of Bio-Reference Laboratories, Inc., before the Judiciary Committee, U.S. House of Representatives, in a hearing "Stifling or Stimulating - The Role of Gene Patents in Research and Genetic Testing," 30 October 2007, 2237 Rayburn House Office Building, Washington, DC, 2 p.m. (at page 4 of her statement).

samples.[161] The implication is that Myriad would not enforce its patents in such circumstances, although again, as in research, there is no public written statement of that policy. Myriad has licensed three laboratories to perform preimplantation diagnosis, for example.[162] While this may be a policy, we did not find a public statement to this effect on Myriad's website (indeed it took some digging to find this information). Thus, individuals likely would not know about this policy unless they contacted Myriad, thereby alerting them of their intention to test, and alerting Myriad of the option of taking legal action to prevent patent infringement.

Finally, the U.S. Food and Drug Administration has also approved an investigational device exemption study for a breast cancer risk test developed by InterGenetics called OncoVue®. Billed as "the next-generation genetic breast cancer risk test," OncoVue® reports it is "the nation's first genetic-based breast cancer risk test to undergo the FDA approval process."[163] Opaldia plans to release OncoVue® in the U.K. and Ireland under an exclusive agreement.[164]

These are not isolated counter-examples: AHRQ estimated that for all three areas of cancer included in this case study there are more genetic tests for cancer in the pipeline than are currently available. While we cannot be certain of what this picture would have looked like absent patents, it appears that gene patents notwithstanding, the genetic testing for inherited risk of cancer is moving in the direction of an even more bountiful range of clinical genetic tests.

	Breast	Colorectal	Ovarian
Currently Available	**15**	**15**	**7**
Under Development	**22**	**19**	**14**
Primary prevention	1	1	0
Detection	0	8	7
Prognosis	2	0	0
Diagnosis	12	8	4
Management	7	2	3

Compiled by author based on raw data presented in AHRQ, Genetic Tests for Cancer, January 9, 2006.

The foregoing also is a reminder that patent protection never guarantees permanent protection from competition. It remains to be seen whether these developments culminate in Myriad's having to reduce its price or relax its licensing well before its patent expires, and to offer new testing modalities. And the same competitive effects may enter colon cancer genetic testing, for which there is no single provider with a dominant patent position.

BRCA and colon cancer genes also differ in measures of patent enforcement activity. Dr. Cho's 2003 survey of laboratory directors demonstrates nine instances of patent enforcement by Myriad Genetics on its *BRCA* patents; by comparison, Johns Hopkins enforced its *APC* patent for FAP genetic testing twice, and no laboratory directors reported enforcement of the HNPCC patents.[165]

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[161] William Rusconi, Myriad Genetics. *Patenting and Licensing of the Breast Cancer Susceptibility Genes - BRCA1 and BRCA2*. Op. cit.
[162] Harmon A. Op. cit. quoting William Hockett, MD, of Myriad Genetics and stating that preimplantation BRCA testing had been licensed to three fertility clinics.
[163] Page D. FDA approves study for breast cancer risk test by InterGenetics. *The Oklahoma City Journal Record.* September 20, 2006.
[164] First genetic-based breast cancer risk test available in the U.K. and Ireland. *Genetic Engineering & Biotechnology News* 2007 (March 1). See http://www.genengnews.com/news/bnitem.aspx?name=13573820 [accessed May 2007].
[165] Cho M et al. Op. cit.

In a paper reviewing litigation over U.S. gene patents, Christopher Holman found 31 total cases of litigation (covering an estimated 1 percent of gene patents). Two of those cases centered on BRCA patents, compared to none for patents associated with colon cancer genes.[166] One case entailed a suit and counter-suit between OncorMed and Myriad, which was settled out-of-court. The other BRCA case was between Myriad and University of Pennsylvania, which was also settled out-of-court.

Commercialization

Myriad's centralized testing service does provide some benefits to patients, including Myriad's ability to provide free testing to first-degree relatives to elucidate variants of uncertain clinical significance.

This case study demonstrates several major implications of patents on access:

First, the main effect of the patent appears to be on volume rather than price.

1. Any price effect attributable to patents is buried in noise and confounding variables.

2. Myriad's patent position has made it in effect a sole provider of clinical BRCA testing in the United States, and indeed BRCA testing in clinical research except when such testing is conducted at the same research institution as the research.

Based on per-amplicon charges, price data—comparing mutation testing for colon and breast cancer at Myriad and comparing BRCA testing to colon cancer predisposition testing—suggest a small price effect, if any, and suggest the main impact of patenting is to drive volume to Myriad for BRCA testing. The price data constitute an imperfect comparison for many reasons. Colon and BRCA cancer testing does not compare patented to unpatented sequences, but rather a group of patents aggregated by Myriad genetics compared to colon cancer gene tests nonexclusively licensed by several academic institutions that are presumably collecting royalties. Moreover, one major constraint on pricing is the reimbursement system, which codes genetic tests and limits price flexibility. The price comparison does, however, at least provide a benchmark and shows any price effects of patents in these two kinds of genetic testing are not of the magnitude associated with therapeutic pharmaceuticals and some other technologies, for which patents command dramatic price premiums for a patented versus generic product.

The downstream costs of a positive test can be far greater than the test itself, including counseling and potential surgical action.[167] Thus, for any patient contemplating the combined costs of the test and surgery in the event of a positive test, the cost of genetic testing would be a relatively small share of the total.

Second, the coverage and reimbursement practices of insurers and other payers are crucial. Anecdotal reports from interviews with laboratory employees note that many non-profit centers charge patients up front for genetic testing. These anecdotal reports note that insurance companies are slow to respond to claims for genetic tests, and that such tardy reimbursements induced non-profit centers to either charge differential rates for cash-paying and third-party tests or to drop the third-party payer option altogether (so that payment is paid out-of-pocket up front, and patients seek reimbursement for themselves from their insurer or health plan). For its part, Myriad provides a wide variety of payment options as noted on its "Reimbursement Assistance Program" website, both insurance-based and cash-based.[168] Myriad reports that initial inconsistency of coverage and reimbursement is less of an issue now. A much larger number

[166] Holman CM. Op. cit. at 347-348.
[167] Phillips K et al. Genetic testing and pharmacogenomics: issues for determining the impact of healthcare delivery and costs. *American Journal of Managed Care* 2004 (July). 10(7):425-432.
[168] Myriad Genetics. *Myriad Reimbursement Assistance Program*. See http://myriadtests.com/mrap.htm [accessed July 12, 2008].

of agreements and more consistent coverage and reimbursement have reduced the number of self-pay patients to single-digit percentages of its clientele. Myriad has established contracts or payment agreements with over 300 carriers and has received reimbursement from over 2500 health plans.[169]

Finally, as the monopoly provider for *BRCA* testing Myriad will benefit from receiving the entire volume of *BRCA* tests through its laboratories no matter what it charges, though that volume will certainly vary with the price-point. The price comparison we made is compatible with a scenario in which Myriad, as a monopolist, maximizes its profit through price discrimination in which it charges the highest price to those women who most value the test. According to standard economic analysis of monopolist behavior, such discrimination in pricing for different customers would be expected, and paradoxically can enable the monopolist to lower prices for those with lower willingness or ability to pay (in Myriad's case, through its patient access programs). This flexibility is, however, entirely at the discretion of the company. Thus, the patent premium depends on both the price-elasticity of demand for *BRCA* testing and on how Myriad has chosen to set its price point for different purchasers, including consumers with lower ability to pay.

Other firms may enter the breast cancer susceptibility testing market. Myriad is not alone in building a dedicated testing facility around its gene patents. InterGenetics, Inc., is developing OncoVue®, the "next-generation" genetic breast cancer risk test that will be available through a network of breast care centers.[170] How this facility will affect the *BRCA* market is yet to be seen. OncoVue-BRE® tests genes that, when combined, confer a moderately increased risk. The target population is the general population rather than those with family history. Effectively, this test seeks to determine risk for those not in the BRCA risk category. So, the tests are more complementary than competitive. In September 2008, Perlegen announced that it will release a breast cancer diagnostic panel intended to guide treatment choices as well as provide risk stratification, in which case it would compete with Myriad's testing.[171] Many of the "personal genomics" firms offering genome-wide scans, such as 23andMe, Navigenics, SeqWright, Knome, and deCODEme also include some analysis of cancer risk, including breast and colon cancers. None of these genome-wide cancer risk-assessment tests, however, offers comprehensive analysis of BRCA, FAP, or HNPCC genes, and so genome-wide scans are not comparable to those genetic testing services for high-risk families. The exception is the full-sequence Knome service. If a cancer susceptibility mutation were identified in the Knome full genomic sequence, it would require re-testing for the identified mutation in a CLIA-certified laboratory to ensure reliability of the result, which the patient could obtain by referral, or which Knome might bundle with its initial price as a subcontracted service.[172]

What's Going on in Australia?

As this case study was being prepared, a controversy over BRCA testing erupted in Australia. This was precipitated when Genetic Technologies Ltd. (GTG), Myriad's licensee in Australia and New Zealand, sent "cease and desist" letters to laboratories testing for BRCA in its licensing territory.[173] GTG had

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[169] William Rusconi, Myriad Genetics, comments on review draft of case study to SACGHS, September 2008.

[170] InterGenetics builds DNA analysis and genotyping laboratory; laboratory essential to commercialization of nation's first genetic-based breast cancer risk predictive test applicable to all women. *Business Wire* 2005 (September 7). See http://findarticles.com/p/articles/mi_m0EIN/is_2005_Sept_7/ai_n15346276 [accessed May 2007].

[171] Winnick E. Perlegen eyes first-half '09 launch of breast cancer Dx panel. *GenomeWeb News*. See http://www.genomeweb.com/issues/news/149640-1.html [accessed September 30, 2008].

[172] The price on Knome's website was originally $350,000 for full-genome, full-sequence analysis. The website now asks prospective customers to call for individualized pricing, but Steven Pinker reported it to be $99,000 in his January 2009 article in the New York Times Magazine. (Pinker S. My genome, my self. *New York Times Magazine* 2009 (January 7). See http://www.nytimes.com/2009/01/11/magazine/11Genome-t.html?_r=1&scp=1&sq=pinker&st=cse [accessed January 21, 2009].) The idea of subcontracting to CLIA-approved laboratories was discussed by Duke research assistant professor Misha Angrist and Knome CEO and founder Jorge Conde in November 2008.

announced in 2003, when it secured the license, that it would allow unlicensed testing as "gift" to the people of Australia. It changed this policy and decided to enforce its patent rights, and the policy change became public in July 2008 when it was widely covered in the Australian public media.[174] On October 31, as the November 6 deadline it had set in the cease and desist letters loomed, GTG announced it would refrain from enforcing its patent rights pending discussions with "all the relevant stakeholders."[175] It is now the subject of an Australian Senate inquiry.[176] The decisions about enforcement of licensing for BRCA testing may have stemmed from financial pressures GTG, a need to generate revenues, and some disarray in the company's governance.[177] While not directly relevant to US policy, the developments in Australia did spill over to coverage in the United States; GTG actions in Australia also indicate that companies under financial stress may turn to patent assets as revenue sources when their company's survival is being threatened.

Communication/Marketing

Myriad's position as sole US provider of BRCA testing increases its incentives for communication and marketing up to the point of market saturation. The incentive to advertise the service and broaden the market is stronger for a monopoly provider than in a shared market because a monopolist will gain the full benefit of market expansion. In a competitive market, advertising may increase market *share* of a given provider, or it can expand the size of the market, but the expansion effect spills over to benefit competitors as well, and so the incentive to advertise is weaker. Once a market is saturated, a monopolist no longer gains from advertising to expand market (but may advertise for other reasons).

For the same reason, communication and marketing incentives are also strong to educate health professionals who order the tests, because any increase in orders results in higher volume of testing for Myriad. Again, this increase is not shared with other providers; Myriad gets the full benefit of any market expansion. The downside of this incentive is that Myriad's financial incentive is to expand testing, not just appropriate testing. Myriad makes money off of any test, regardless of whether the person is actually at risk. The incentive is not just for appropriate testing; the risk is overutilization.

There are some checks on overutilization. Medical societies establish guidelines for their membership which, in turn, form the basis for payer coverage criteria. Insurers and other payers work not to reimburse for tests when patients do not meet clinical appropriateness criteria. One further check is the bottleneck of

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[173] O'Connor M. Genetic technologies and breast cancer. *Courier-Mail* (Queensland), 2008 (27 October).
Shanahan L. Call to act on breast cancer test. *The Age* (Australia), 2008 (28 October).
Macey J. Company seeks to monopolise breast cancer test. *The World Today*, ABC News Radio, 2008 (23 October).
GenomeWeb. Genetic technologies to enforce BRCA test rights in Australia, New Zealand. July 21, 2008. See http://www.genomeweb.com/issues/news/148308-1.html [accessed 8 November 2008].

[174] The public media reported on GTG's enforcement action in July. (See, for example, Cresswell A. A price on your genes. *The Australian* 2008 (30 July). The story was also covered in most of the major dailies in Melbourne, Sydney, Canberra, and elsewhere in Australia.) Controversy flared up again in late October as GTG's announced deadline neared. See, for example, Jennifer Macey's coverage on ABC radio Australia at http://www.abc.net.au/worldtoday/content/2008/s2399139.htm (accessed November 8, 2008).

[175] Genetic Technologies Ltd. *Further Clarifications on BRCA Testing*. Op. cit.

[176] *Community Affairs Committee. Examination of Budget Estimates 2008-2009. Additional Information Received.* Incomplete Consolidated Volume 5. Health and Ageing Portfolio. December 3, 2008. At 6-18.
Transcript of Senate Standing Committee on Community Affairs Estimates. Australian Senate. October 22, 2008. At CA14-CA17.

[177] According to NASDAQ pricing data, GTG's stock price drifted downward during the year from a high of $5.00 per share on 29 November 2007 to $0.66 on 4 November 2008. In addition to the July 2008 change of policy about BRCA testing, the company also announced its intention to remove five of seven directors at its 19 November 2008 Board meeting, leaving only two directors, which would cause it to fall out of compliance with its corporate bylaws. The proposed new Board member declined to serve, leading to a proposal for an interim board appointment. (Genetic Technologies Ltd. *Intention to Appoint a Director*. November 3, 2008. See http://www.gtg.com.au/index.asp?menuid=060.070.130&artid=10741&function=NewsArticle [accessed 8 November 2008].)

determining eligibility for testing. The limited pre-test counseling resource is used to fulfill specific payer criteria for high-risk patients eligible for coverage and reimbursement. Low-risk candidates can clog the pre-test filters of counseling and coverage determination, occupying them with cases that would not ultimately lead to testing, or if tested, would not be reimbursed by third parties.

In the context of breast cancer testing, Myriad has a strong incentive to "get the word out" about genetic testing for inherited risk of breast cancer. That incentive is stronger for BRCA testing, for which Myriad is sole US provider, than for colon cancer testing, where there are alternative providers. This may be one reason Myriad's past direct-to-consumer advertising—both the 2002 pilot in Denver and Atlanta and the 2007-8 campaign in the northeastern states–focused on breast-ovarian cancer testing rather than Myriad's colon cancer testing services. The social benefit from this incentive is more public knowledge of test availability. The potential harms are overutilization of BRCA genetic testing, and public fear of genetic risk of breast cancer amplified by advertising.

Caulfield and Gold note in their 2000 article from *Clinical Genetics* that:

> Myriad Genetics, a commercial testing company that holds patent rights underlying the [*BRCA1* and *BRCA2*] test, does not exclude women without any family history of breast or ovarian cancer from taking its test. This contrasts sharply with the Working Group with Stanford's Program in Genomics, Ethics and Society, which recommends that 'for most people, testing for *BRCA1* and *BRCA2* mutations is not appropriate.' While all genetic testing policies are undoubtedly motivated by a degree of self-interest, it is hard to deny the strong, and possibly adverse, impact of the profit motive in this context.[178]

Myriad states it does not want to expand inappropriate testing, but rather to saturate testing among high-risk families. Myriad's "television, radio, and print advertising campaign" in September 2002, included ER, *Oprah* and *Better Homes and Gardens*.[179] A follow-up survey on 300 women who had seen the ads noted that "85 percent would contact their physician regarding *BRCA* testing and 62 percent would go so far as to switch health care professionals in order to find one who would help them gain access to the test."[180] This interest can include spurious demand for the tests, and consumes the time of health professionals in filtering out such spurious demand and explaining the complicated genetics of cancer susceptibility to many not actually at elevated risk.

A CDC survey done during the 2003 direct-to-consumer pilots in Denver and Atlanta compared experience in those DTC campaign cities to Raleigh-Durham and Seattle, which did not experience regionally targeted advertising. CDC found an increase in test requests and questions about testing among women, an increase in test-ordering among physicians and providers, and no difference in levels of reported anxiety.[181] CDC concluded that:

> Advertisements might have motivated women interested in learning more about BRCA1/2 testing to talk to their physicians and request testing. Findings from the consumer survey suggest that women in the pilot cities were more aware of BRCA1/2 testing than those in the comparison

[178] Caulfield T, Gold ER. Genetic testing, ethical concerns, and the role of patent law. *Clinical Genetics* 2000 (May). 57(5):370-375, at 371.
[179] Parthasarathy S. *Building Genetic Medicine: Breast Cancer, Technology, and the Comparative Politics of Health Care.* Op. cit. at 120-129.
[180] Ibid., 129.
[181] Centers for Disease Control and Prevention. Genetic testing for breast and ovarian cancer susceptibility: evaluating direct-to-consumer marketing--Atlanta, Denver, Raleigh-Durham, and Seattle, 2003. *Morbidity and Mortality Weekly Report* 2004 (July 16, 2004). 53(27): 603-606.

cities. No evidence suggested an increased interest in the test among women most suited for BRCA1/2 testing (i.e., those having a first-degree relative).[182]

Judy Mouchawar and colleagues did the most systematic studies of consumer, provider, and health plan responses to the Denver DTC advertising campaign. They surveyed health professionals and consumers and assessed impact on health systems in the advertising market (Denver Kaiser Permanente) and in a comparison city (Detroit) and health system (Henry Ford) not exposed to the advertisements. The number of women at high risk who got referred went up by 2.38 times, from 100 to 238, suggesting that over 100 women at high risk got tested who otherwise might not have known about the test. The number of women contacting the systems about testing rose 3.46 times (from 144 to 499) with advertising, including a higher fraction of women not at high risk and therefore not warranting testing (the fraction at high risk dropped from 69 to 48 percent).[183] Thus the number of women at risk who might benefit from testing went up, but there was also a dilution of such high-risk women among an even greater increase of contacts about testing. There was no increase in actual testing among women with low risk *in the population studied*. This caveat is important, because Kaiser Permanente has practice guidelines for BRCA testing, and it cooperated with Myriad to prepare for a surge in demand during the DTC advertising period. Physician surveys showed a modest effect on physicians, with 3 percent reporting significant patient anxiety, 19 percent reporting significant increase in time spent explaining and another 23 percent a little extra time, and 7 percent reporting significant and 8 percent a little strain on the doctor-patient relationship.[184] Eighty-two percent reported the DTC campaign had no effect on their relationship with patients.

Consumers reporting "any anxiety" varied from 28 percent (low family risk) to 55 percent (high risk). Anxiety was most pronounced among Latina/Hispanic women (65 percent), and much more common in low-income (62 percent among those making less than $30,000) than high-income women (30 percent among those making over $80,000).[185] Among those exposed to the ad, 63 percent reported no anxiety at all, but 65 percent reported feeling somewhat or very concerned. It is hard to fully interpret the answers to various questions. Physicians were asked to assess the effect overall on their practice, and 6 percent were positive or very positive, 14 percent were negative or very negative, and 79 percent reported no effect.[186]

The overall impact of the DTC ad campaign on the Kaiser Permanente health system in Denver was a more than two-fold increase in number of women in the high risk category getting tested, a more than three-fold surge in contacts about testing, a moderate increase in anxiety among consumers and a mixed reaction among physicians, but with the vast majority reporting no effect. A comparison between the experience of physicians and women in Kaiser Permanente to other parts of the health system in Denver at the same time would have been immensely useful, as the Kaiser Permanente system is much more organized for genetic services than general medical care. The Mouchawar studies are illuminating as a "best case" of a health system prepared for a surge and with practice guidelines in place; it is very unlikely to represent the effects of the ad campaign elsewhere in Denver (or anywhere else) with a less organized and prepared genetic services program and with physicians less educated about how to triage testing.

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[182] Ibid., 606.
[183] Mouchawar J, Hensley-Alford S, Laurion S, Ellis J, Kulchak-Rahm A, Finucane ML, Meenan R, Axell L, Pollack R, Ritzwoller D. Impact of direct-to-consumer advertising for hereditary breast cancer testing on genetic services at a managed care organization: a naturally occurring experiment. *Genetics in Medicine* 2006 (March). 7: 191-197, at Table 3.
[184] Mouchawar J, Laurion S, Ritzwoller DP, Ellis J, Kulchak-Rahm A, Hensley-Alford S. Assessing controversial direct-to-consumer advertising for hereditary breast cancer testing: reactions from women and their physicians in a managed care organization. *American Journal of Managed Care* 2005. 11(10):601-608, at Table 4.
[185] Ibid., Table 2.
[186] Ibid., Table 4.

Myriad Genetics' marketing campaign both to providers and patients is concisely summarized in Dr. Parthasarathy's book (pages 120-129).[187] Myriad aggressively marketed its *BRCA* genetic tests to providers through a "Professional Education Program," through continuing education accredited by the American Medical Association and at various professional meetings. Highlighting the importance of reaching providers with such educational campaigns, one study showed that high-risk women—those eligible for BRCA testing based on family history—were three times as likely to get tested following a physician recommendation as those who did not get such a recommendation.[188]

On September 10, 2007 Myriad announced it would begin a new "public awareness campaign" throughout the northeastern United States to spread the word about *BRCA* testing.[189] This campaign concluded in March 2008. Myriad's quarterly report through March 2008 reported a jump in molecular diagnostic revenue from $38 million to $59 million, and attributed the 55 percent jump to its northeast advertising campaign.[190] Given these financial results, it is not surprising Myriad is said to be contemplating similar DTC advertising initiatives in Texas and Florida or elsewhere.[191] This clearly illustrates the link between status as a single provider and incentives for direct-to-consumer advertising, with single provider status in this case associated with exclusive patent rights for BRCA testing.

We have not found similar marketing campaigns launched by Myriad or other groups on behalf of other tests. However, a future research project could compare *BRCA* testing uptake in the Denver and Atlanta markets in 2002 or in the northeast 2007-8, where Myriad's advertising was concentrated, to utilization in other regions. This could be done through a large health-insurer's database or using billing records of Medicare/Medicaid for relevant CPT codes matched to clinical indications. The link between DTC advertising and patenting is mediated by the monopoly incentive for advertising noted above. Dynamics in genetic testing markets have changed considerably since 2002. The growing number of physicians ordering genetic tests, the greater availability of third party coverage, the accumulating experience in using genetic tests to manage hereditary cancer risk, and the greater consumer awareness about genetic testing all suggest the 2003 surveys may not predict current or future behavior. Moreover, the increasing conspicuousness and commercial interest in personal genomics may also change perceptions and behaviors. DTC advertising is not directly related to access *per se* although it is highly relevant to projections of demand and perceptions of access.

Adoption by Third-Party Payers

Myriad has a strong incentive to develop the infrastructure to handle billing and payment for BRCA testing because it captures all the revenues from market expansion. This benefits the company, but it also benefits patients to the degree it relieves them of the hassle and paperwork of dealing with health plans and insurers, and it benefits providers by relieving them of those duties as well as legal liability for test inaccuracies. The countervailing force here is that Myriad as a sole-source provider requires providers to send samples, track paperwork, and bill for services providers might otherwise handle at their own institution through internal billing and administrative procedures. The comparison to colon cancer testing is suggestive here. Most colon cancer genetic testing is done by the handful of laboratories set up to offer this complex set of tests, and the test algorithms for BRCA and colon cancer susceptibility genes appear

[187] Parthasarathy S. *Building Genetic Medicine: Breast Cancer, Technology, and the Comparative Politics of Health Care.* Op. cit. at 120-129.
[188] Schwartz M et al. Utilization of *BRCA1*/*BRCA2* mutation testing in newly diagnosed breast cancer patients. *Cancer Epidemiology Biomarkers and Prevention* 2005 (April). 14:1003-1007.
[189] Myriad Genetics. *Myriad Genetics Launches Awareness Advertising Campaign to Educate Women About Hereditary Risks of Breast and Ovarian Cancers*. See http://www.myriad.com/news/release/1049527 [accessed December 19, 2007].
[190] Myriad Genetics. Myriad Genetics reports results for third quarter of fiscal 2008. May 6, 2008.
[191] Suggestions of future DTC advertising plans were reported to us, but were neither confirmed nor denied by Myriad staff.

to have comparable costs and decision pathways. It thus appears there is some advantage to consolidating testing at a few laboratories that can attain sufficient volume to justify sunk costs in developing the test and resources to ensure quality and reduce legal liability for errors. In the case of colon cancer testing, this has resulted in an oligopoly, BRCA patents have made testing a Myriad monopoly in the United States.

The US monopoly on BRCA testing may not be absolute; there is no legal barrier to sending samples abroad, and US courts would be unlikely to interpret merely sending results from tests performed abroad (information) back to the United States an infringement. Myriad would have grounds for infringement liability only if the invention (making and using the patented sequences and methods) were performed abroad in a jurisdiction where those activities are claimed in patents, and Myriad would have to sue in those jurisdictions. Laboratories in countries with diagnostic use exemptions would not face infringement liability.

Regarding third-party payers, at least one study noted in the Lewin Group report showed that as of late 1995, "only 4% of insurance providers… had granted coverage of *BRCA* testing[, and] 55% of respondents cited concerns about the high cost of *BRCA* testing, averaging $2,400 per patient."[192] As noted above, these data no longer represent practices for BRCA testing, which Myriad reports now generally is covered for roughly 95% of those requesting tests, and reimbursed to cover 90% of their charges. The same study cited by the Lewin Group had two other findings of relevance to patented gene tests. First only 6 percent of the decision-makers for private health insurance plans would cover *BRCA* testing if were extended to all women in the general population, whereas 48% would offer it if it were restricted only to women with a positive family history who were enrolled in an approved research trial. Second, the proclivity to offer coverage was sharply dependent on cost: 25% were willing to cover it if the testing cost were $250, but only 14% would cover if the cost rose to $1,000 (it was $2400 at the time). Taken at face value, the figures imply that even if gene patents confer a premium of $750 this would only reduce the likelihood of third party coverage by 11 percentage points. However, the low response rate (22%) and early timing of this study limit the current usefulness of this study.[193]

In 1998, Myriad reported that over 300 different insurers covered *BRCA1* and *BRCA2* testing; they further stated that 94.3% of processed claims for *BRCA1* and *BRCA2* testing had resulted in at least partial payment from insurance companies (suggesting the test was covered to some extent).[194] As of 2002, 38% of testers said they had no problems in getting coverage for genetic services from their insurance plan. But a more telling statistic was that only 59% of women[195] undergoing full sequence *BRCA* analysis in one study filed health insurance claims.[196] Furthermore, 15% of women in a second study undergoing *BRCA* analysis chose to self-pay, and each of those women did so in fear of insurance or employment discrimination.[197] As noted above, Myriad states that only approximately 5 percent of patients now self pay, and more than 2500 payers and health plans have reimbursed testing with Myriad. Finally, the enactment of the Genetic Information Nondiscrimination Act of 2008, and its implementation in 2009 and 2010, may reduce fears of discrimination in employment and health insurance.

In the most recent study to address reimbursement for genetic testing, 56% of non-testers from a sample who had received genetic counseling services and declined testing said they could not afford all costs of the test or their share not covered by insurance, yet more than half also reported income of over $70,000

[192] The Lewin Group. Op. cit. at 153.
[193] Schoonmaker M et al. Op. cit.
[194] Shappell H et al. Writing effective insurance justification letters for cancer genetic testing: a streamlined approach. *Journal of Genetic Counseling* 2001 (August). 10(4):331-341.
[195] Of note, 99% of women in the study did actually have health insurance.
[196] Lee S et al. Op. cit.
[197] Peterson E et al. Op. cit.

annually.[198] Of only 77 individuals for whom insurance status was reported, 42% had insurance that provided no coverage for testing, 25% had partial coverage and the remainder had full coverage. But this was not a random sample of the population, since no one was reported as uninsured. Nationally, 18.8% of women age 19-64 are uninsured,[199] so if we assume the same is true of women with *BRCA* mutations and that 42% of the remainder are insured but have no coverage for *BRCA* testing, this would imply that roughly half of the at-risk group had no insurance coverage for this test at that time.

One conclusion from multiple studies is that when payment is out-of-pocket, price has a strong and direct impact on testing utilization, and thus affects patient access. People do forego potentially beneficial genetic tests when they are expensive and not covered by health plans or insurance. Access is thus linked tightly to coverage and reimbursement policies, which are far more important than any direct patent effects. Patent status matters to the degree it affects price, where high prices require payers to assess a specific new test. Patent status may also affect likelihood to create a bargaining impasse with payers, if patent-holders and payers simply cannot agree on reimbursement. The BRCA experience suggests that over ten years, the vast majority of payers have decided to cover most of the cost of a test when its use is restricted to those at high risk. For those who are not covered by such payers, access is still a problem, in part because of price.

Problems in access may still occur with: 1) Medicaid programs, 2) insurance policies that exclude all genetic testing, and 3) practices and health plans (e.g., in southern California) where there is a strong financial incentive to minimize utilization. These access constraints, however, do not appear to be keyed to patent status, but rather blanket policies focused on cost containment and contractual transaction costs.

Coverage for Risk-Reducing Surgery

A national study on coverage for prospective mastectomy or oophorectomy showed that 10-11% of private insurers and 48 to 50% of public health plans had policies that specifically denied coverage for risk-reducing surgery for women with BRCA mutations; 52 to 64% of private insurers and 40% of public carriers had no identifiable policy regarding coverage of either form of surgery for such women.[200]

A retrospective analysis of 219 Memorial Sloan-Kettering Cancer Center patients with known BRCA1/2 mutations found that of 35 women undergoing 39 risk-reducing mastectomies or oophorectomies, 97% were covered in full (minus applicable deductibles and coinsurance). The single instance in which an indemnity plan refused to provide coverage occurred in 1997 when there were few data about the efficacy of prophylactic oophorectomy.[201] This study is now eight years old, however, and clinicians with whom we have spoken believe that prophylactic surgery in mutation-positive women is broadly covered, although we have no empirical data to corroborate that impression.

Adoption by third-party payers as well as providers and testing laboratories is only a rough proxy for patient access. If possible, future research should focus on getting at direct patient access data, or at least at utilization rather than highly indirect measures such as number of providers or price.

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[198] Kieran S et al. The role of financial factors in acceptance of clinical *BRCA* genetic testing. *Genetic Testing* 2007 (March). (11)1:101-110.

[199] Economic Research Initiative of the Uninsured. *Table 2 – CPS Adult Population (Age 19-64) Calendar Year 2005*. University of Michigan. See http://www.umich.edu/~eriu/fastfacts/cps2005_2.html [accessed May 2007].

[200] Kuerer H et al. Current national health insurance coverage policies for breast and ovarian cancer prophylactic surgery. *Annals of Surgical Oncology* 2000. 7(5):325-332.

[201] Kauff N et al. Insurance reimbursement for risk-reducing mastectomy and oophorectomy in women with *BRCA1* or *BRCA2* mutations. *Genetics in Medicine* 2001 (November/December). 3(6):422-425.

Consumer Utilization

In studies done several years ago, 19-74% of at-risk individuals who could benefit from BRCA testing were not being tested.[202] Cost was not the only consideration: nearly 70% of patients eligible for free BRCA testing elected to get tested; however, cost certainly mattered since only 22% of self-pay patients in the same sample chose to be tested.[203] The financial barriers to individual patients appear to have been reduced considerably for those who have health plans so the financial access questions reduce to how many have such coverage, which as shown above, is still a grey area in terms of hard numbers. In the RAND Health Insurance Experiment, the price elasticity of demand for outpatient health services for those with high cost-sharing was -0.31.[204] If the patent premium on BRCA were 50 percent, for example, this would predict 15.5% fewer high-risk patients without coverage would purchase the test. Any reduction in access due to cost, however, is difficult to attribute to BRCA patents because of the absence of a clear price effect of the patents. Our data do not allow us to tease out any price-utilization effects attributable to patents *per se*.

Finally, Appendix 1 notes the difference in number of providers for the three genetic tests, with Myriad as the sole *BRCA* full-sequence provider, nine providers for the Lynch Syndrome tests, and five for the FAP test. This sole-provider status of Myriad for BRCA testing in the United States is clearly attributable to patent status, although differences in patent status and patent enforcement outside the United States have resulted in Myriad not being sole provider in other jurisdictions.

Acknowledgements

We wish to thank David Ridley, Tracy Lewis, and Wesley Cohen of the Fuqua School of Business for their helpful comments. The case study was also reviewed by William Rusconi, Faye Eggerding, and Michael Hopkins for the Secretary's Advisory Committee on Genetics, Health and Society.

Research for this case study funded under grant P50 HG03391 from the National Human Genome Research Institute (National Institutes of Health) and the US Department of Energy.

[202] Kieran S et al. Op. cit.
[203] Ibid.
[204] Liu S et al. Mathematica Policy Research, Inc. *Price and Income Elasticity of the Demand for Health Insurance and Health Care Services: A Critical Review of the Literature.* March 26, 2006. See http://www.mathematica-mpr.com/publications/pdfs/priceincome.pdf [accessed June 2007].

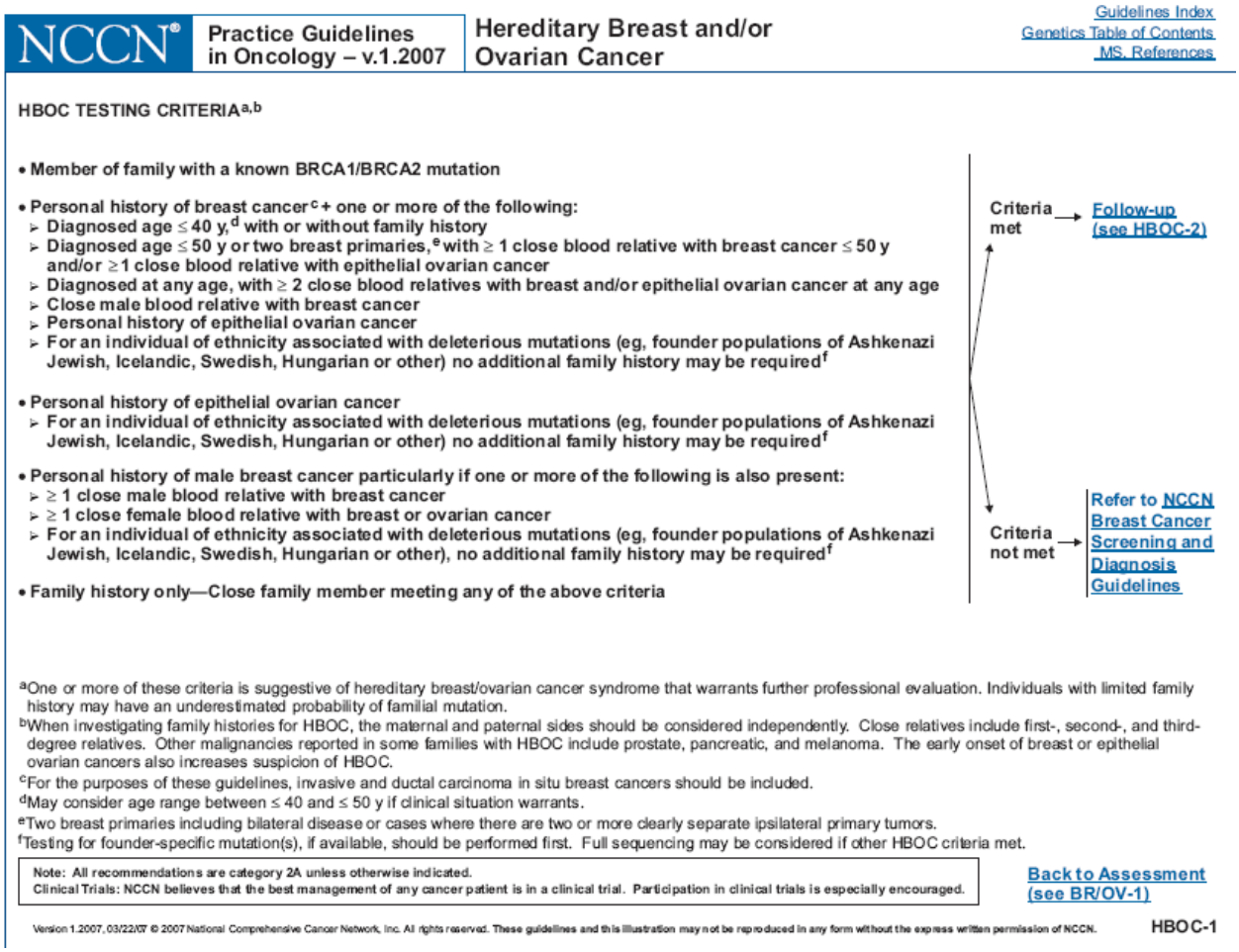
Appendix 1: Summary Table[205]

<table>
<tr><th>Measures</th><th colspan="2">Breast / Ovarian Cancer
BRCA1 / BRCA2</th><th colspan="2">Colorectal Cancer
HNPCC / FAP</th></tr>
<tr><td rowspan="2">Total annual number of new diagnoses (deaths)</td><td>Breast</td><td>178,480 (40,910)</td><td rowspan="2">Colorectal</td><td rowspan="2">153,760 (52,180)</td></tr>
<tr><td>Ovarian</td><td>22,430 (15,280)</td></tr>
<tr><td>Percent of cancers caused by mutation</td><td>Breast and Ovarian</td><td>5-10%</td><td>Colorectal</td><td>~5%</td></tr>
<tr><td rowspan="2">Lifetime percent risk if positive for mutation</td><td>Breast</td><td>35 – 85%</td><td>HNPCC</td><td>80%</td></tr>
<tr><td>Ovarian</td><td>16 – 60%</td><td>FAP</td><td>~100%</td></tr>
<tr><td rowspan="2">Lifetime relative risk if positive for mutation</td><td>Breast</td><td>2.7 – 6.4</td><td>HNPCC</td><td>13.3</td></tr>
<tr><td>Ovarian</td><td>9.4 – 35.3</td><td>FAP</td><td>16.7</td></tr>
<tr><td rowspan="2">Patent holder</td><td colspan="2" rowspan="2">Myriad Genetics, 1998
U.S. 5753441 (BRCA1)
U.S. 6051379 (BRCA2)*
*Purchased from OncorMed in 1998
(See Appendix 4 for more patent information.)</td><td>HNPCC</td><td>MLH1 gene: Oregon Health Sciences Univ. and Dana-Farber, 1999[6] – U.S. 5922855
MSH2 protein: Johns Hopkins, 1997 – U.S. 5591826</td></tr>
<tr><td>FAP</td><td>APC gene: Johns Hopkins, 1994 U.S. 5352775</td></tr>
<tr><td>U.S. licensees</td><td colspan="2">Myriad Genetics</td><td>HNPCC</td><td><u>Non-profit</u>
Baylor College of Medicine, Boston University School of Medicine, City of Hope National Medical Center, Harvard-Partner’s Center for Genetics and Genomics, Huntington Medical Research Institutes, Mayo Clinic, University of Pennsylvania School of Medicine</td></tr>
<tr><td colspan="3"></td><td><u>For profit</u>
Myriad Genetics, Quest Diagnostics</td></tr>
</table>

[205] Based on AHRQ. Genetic risk assessment and *BRCA* mutation testing for breast and ovarian cancer susceptibility. Evidence synthesis 37. September 2005. Op. cit.
National Cancer Institute. *Learning about Colon Cancer.* August 2006. See http://www.genome.gov/10000466 [accessed February 2007].
Kaz A, Brentnall TA. Op. cit.
Centers for Disease Control. Colorectal cancer test use among persons aged >50 years --- United States, 2001. *MMWR* 2003 (March 14). 52(10):193-196.
Myriad Genetics, via phone call March 2007.
Cho M et al. Op. cit.
Patents obtained via standard Delphion Patent Database search. According to GeneTests.org – limited search to “Analysis of the entire coding region: Sequence analysis.”
Parthasarathy S. *Building Genetic Medicine: Breast Cancer, Technology, and the Comparative Politics of Health Care.* Op. cit. at 117.

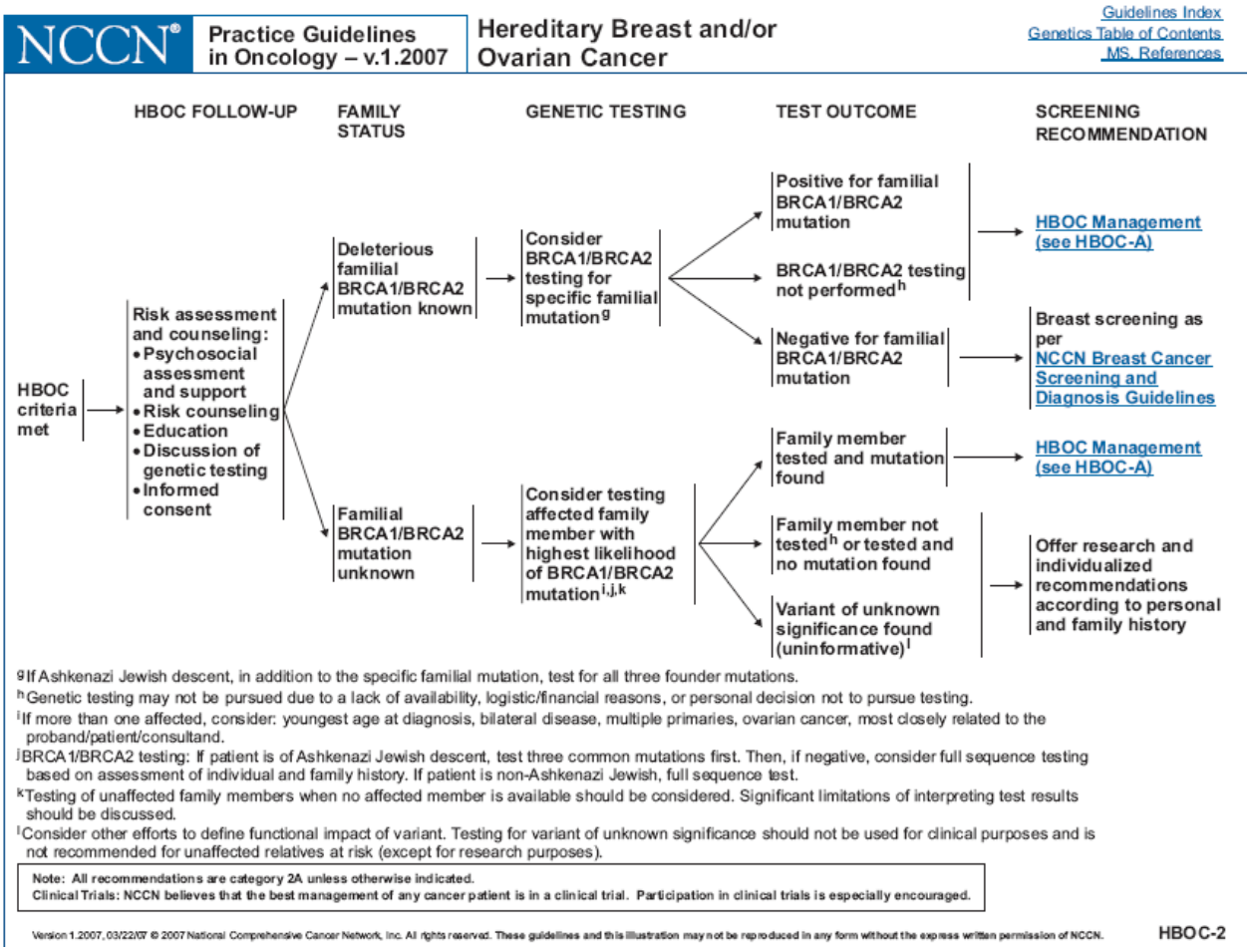
		FAP	*Non-profit* Baylor College of Medicine, Harvard-Partner's Center for Genetics and Genomics, Huntington Medical Research Institutes, University of Pennsylvania School of Medicine *For profit* Myriad Genetics
Cost of genetic test	**$3,120 for two genes**	***HNPCC***	**$600 - $1,800 for one gene** **$1,200 to $2,000 for two genes** **$2,050 to $2,995 for three genes**
		FAP	**$1,200 - $1,800 for one gene**

Appendix 2: Clinical Algorithm for *BRCA1* / *BRCA2* Genetic Testing[206]



[206] Source**:** National Comprehensive Cancer Network. "NCCN Clinical Practice Guidelines in Oncology – Genetic/Familial High-Risk Assessment: Breast and Ovarian." V.1.2007. Accessed May 2007 at: http://www.nccn.org/professionals/physician_gls/PDF/genetics_screening.pdf

Appendix 2 (Cont.): Clinical Algorithm for *BRCA1* / *BRCA2* Genetic Testing



[g] If Ashkenazi Jewish descent, in addition to the specific familial mutation, test for all three founder mutations.

[h] Genetic testing may not be pursued due to a lack of availability, logistic/financial reasons, or personal decision not to pursue testing.

[i] If more than one affected, consider: youngest age at diagnosis, bilateral disease, multiple primaries, ovarian cancer, most closely related to the proband/patient/consultand.

[j] BRCA1/BRCA2 testing: If patient is of Ashkenazi Jewish descent, test three common mutations first. Then, if negative, consider full sequence testing based on assessment of individual and family history. If patient is non-Ashkenazi Jewish, full sequence test.

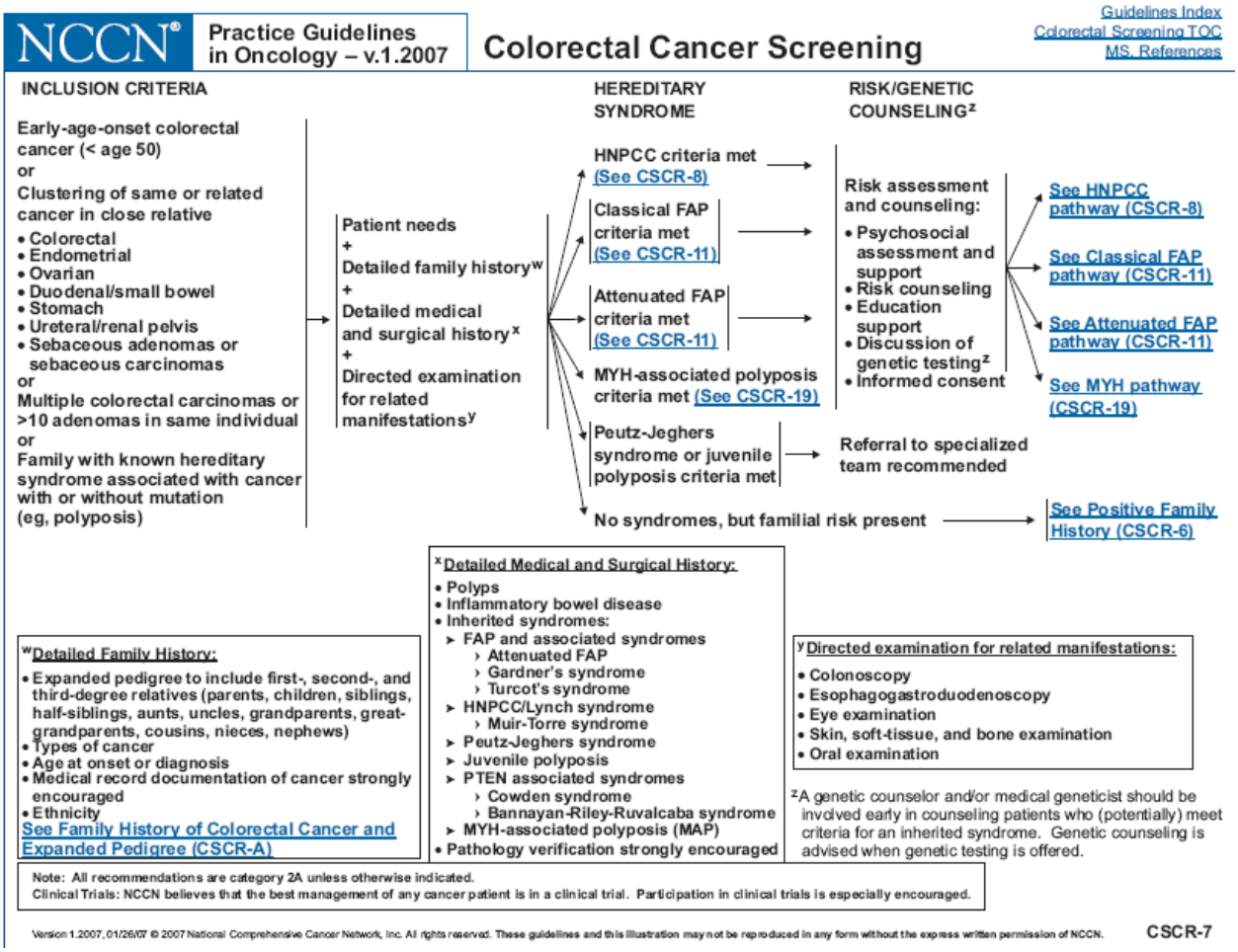
[k] Testing of unaffected family members when no affected member is available should be considered. Significant limitations of interpreting test results should be discussed.

[l] Consider other efforts to define functional impact of variant. Testing for variant of unknown significance should not be used for clinical purposes and is not recommended for unaffected relatives at risk (except for research purposes).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

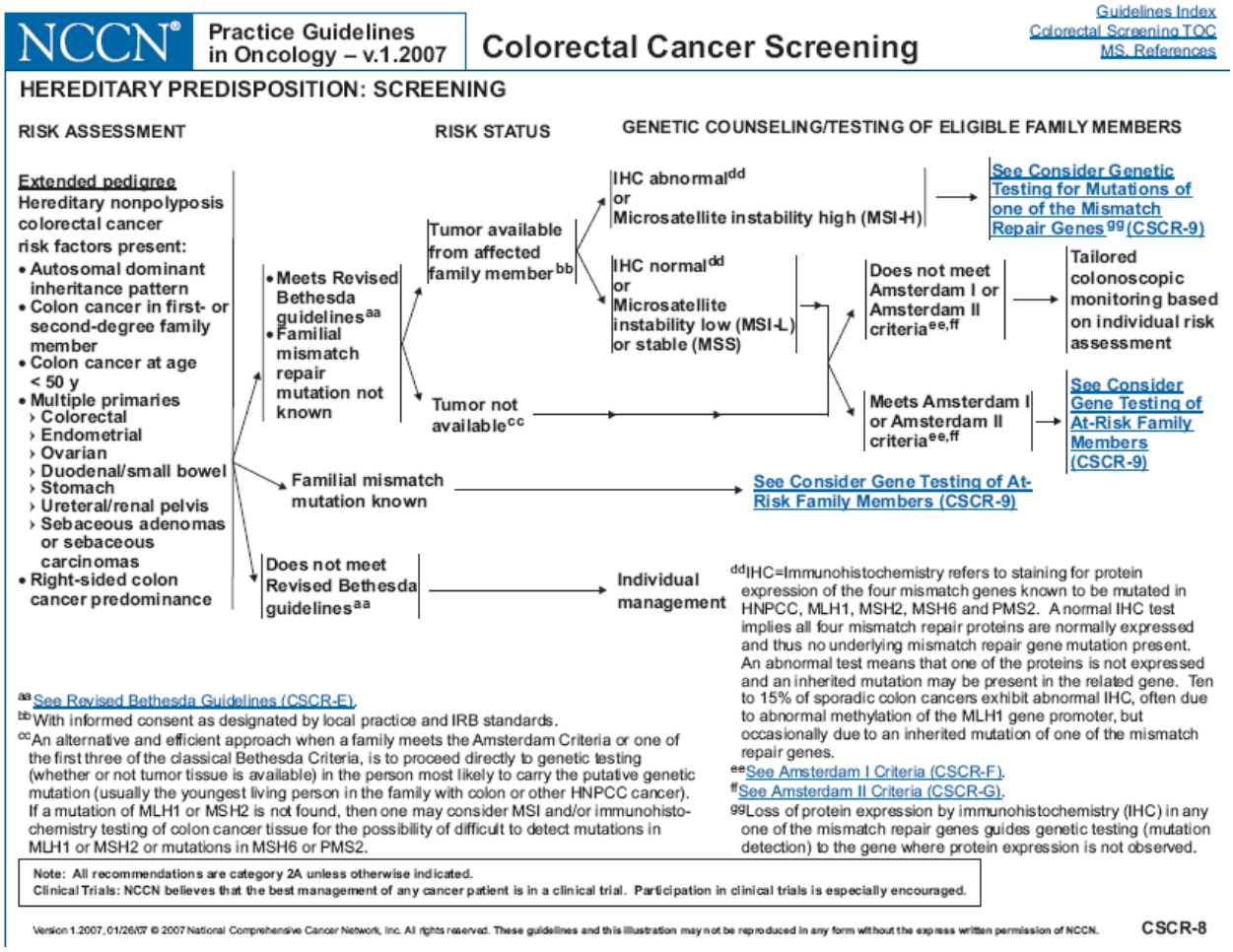
HBOC-2

Appendix 3: Clinical Algorithm for FAP / HNPCC Genetic Testing[207]

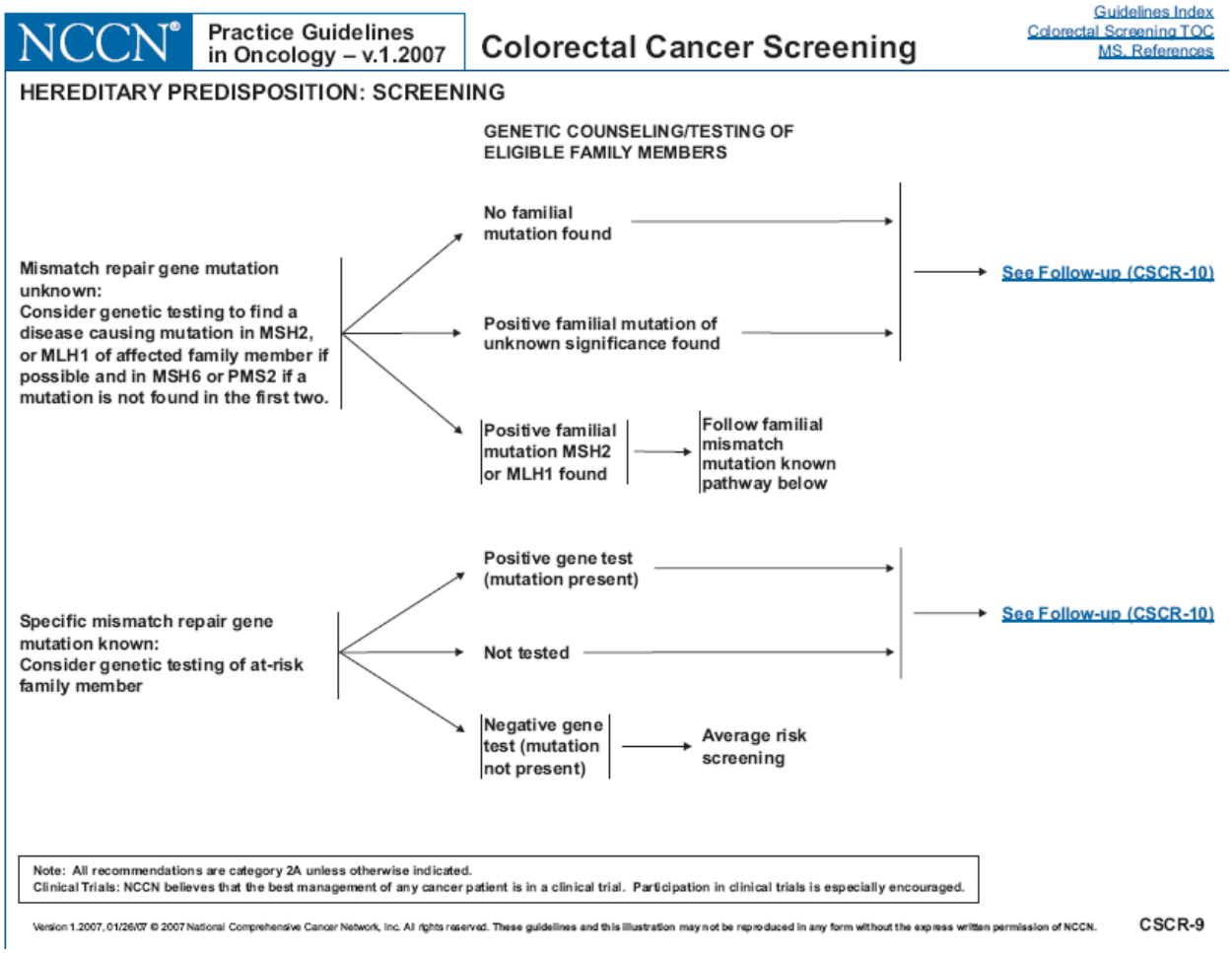


[207] National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology – Colorectal Cancer Screening.* V.1.2007. See http://www.nccn.org/professionals/physician_gls/PDF/colorectal_screening.pdf [accessed May 2007]

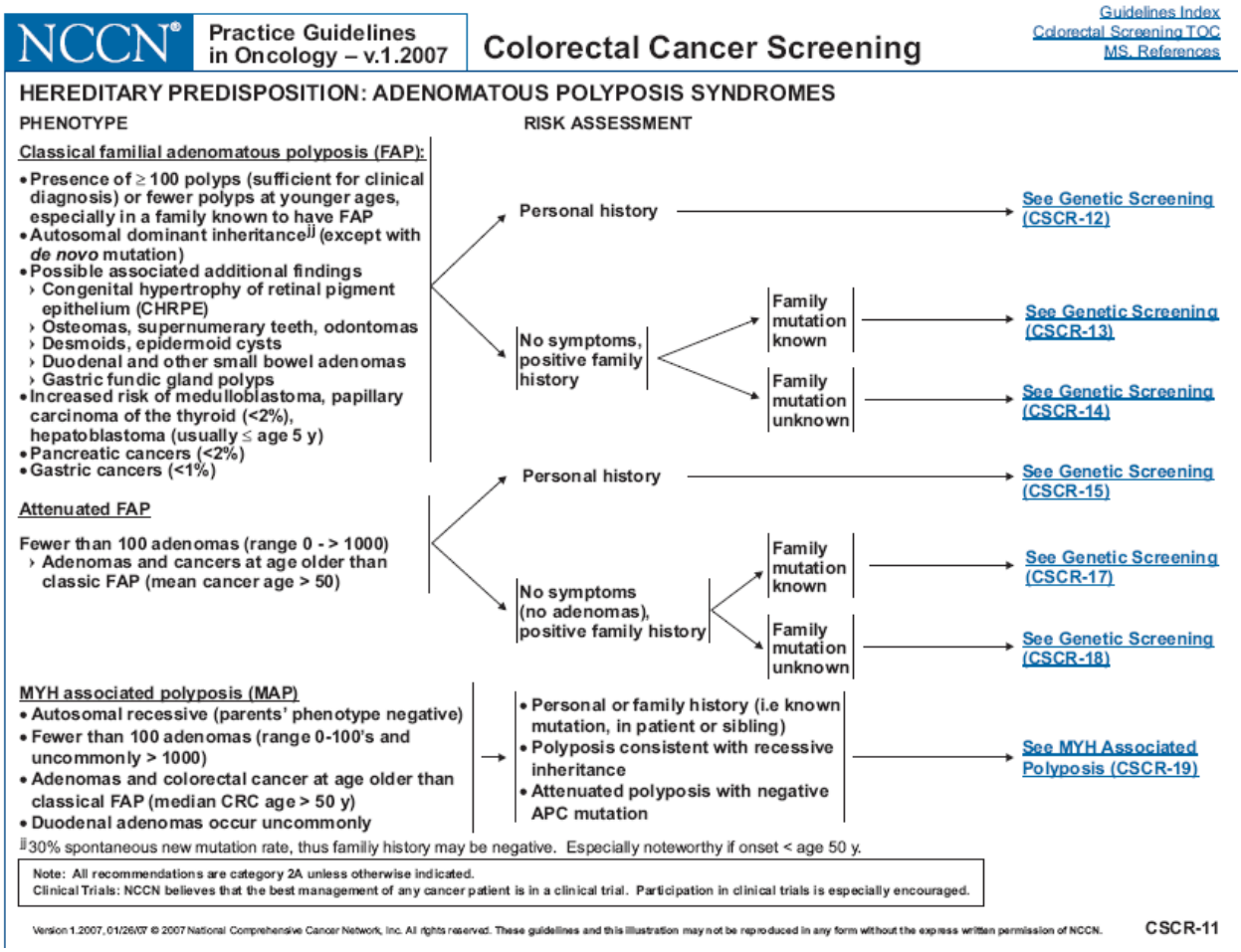
Appendix 3 (Cont.): Clinical Algorithm for FAP / HNPCC Genetic Testing



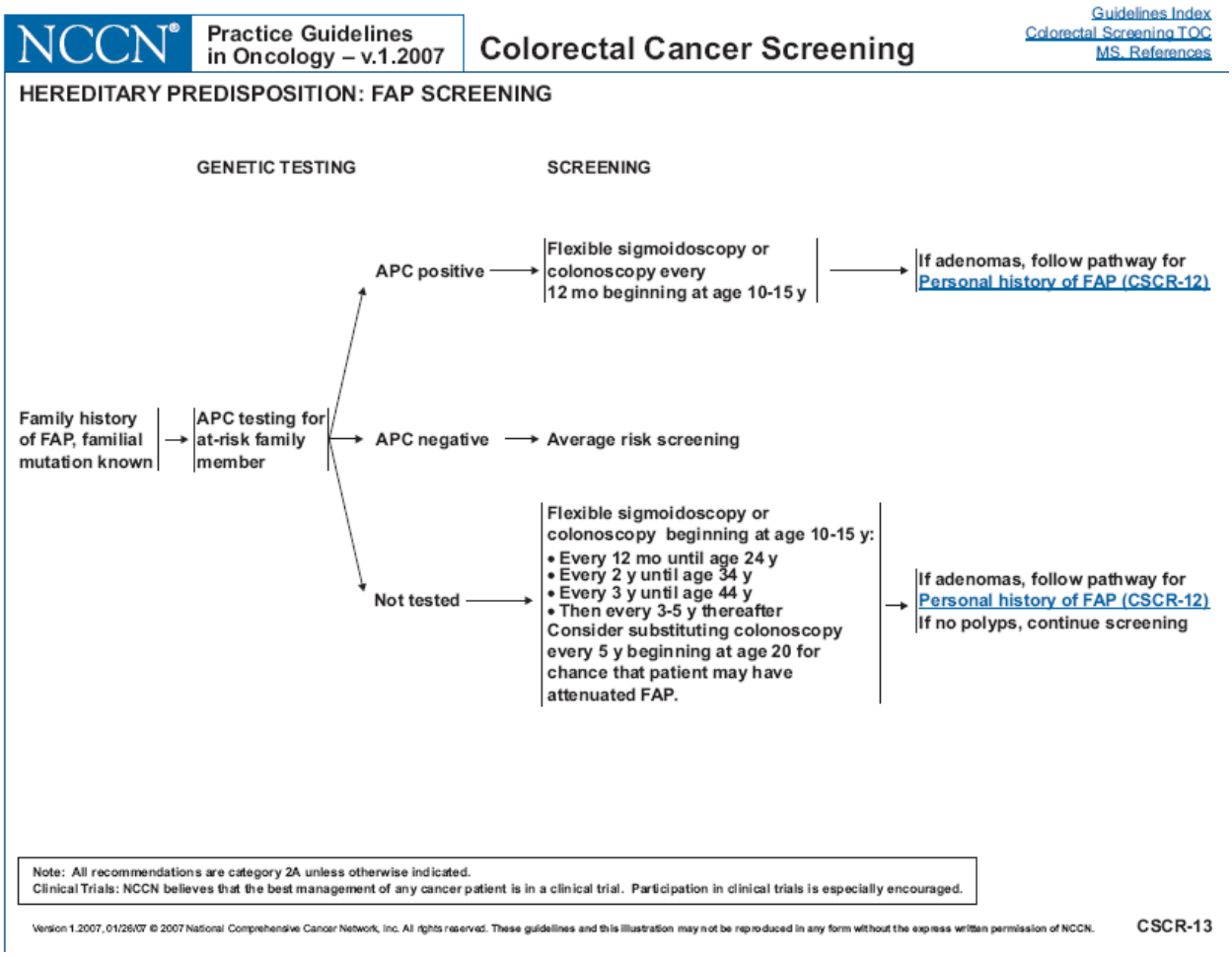
Appendix 3 (Cont.): Clinical Algorithm for FAP / HNPCC Genetic Testing



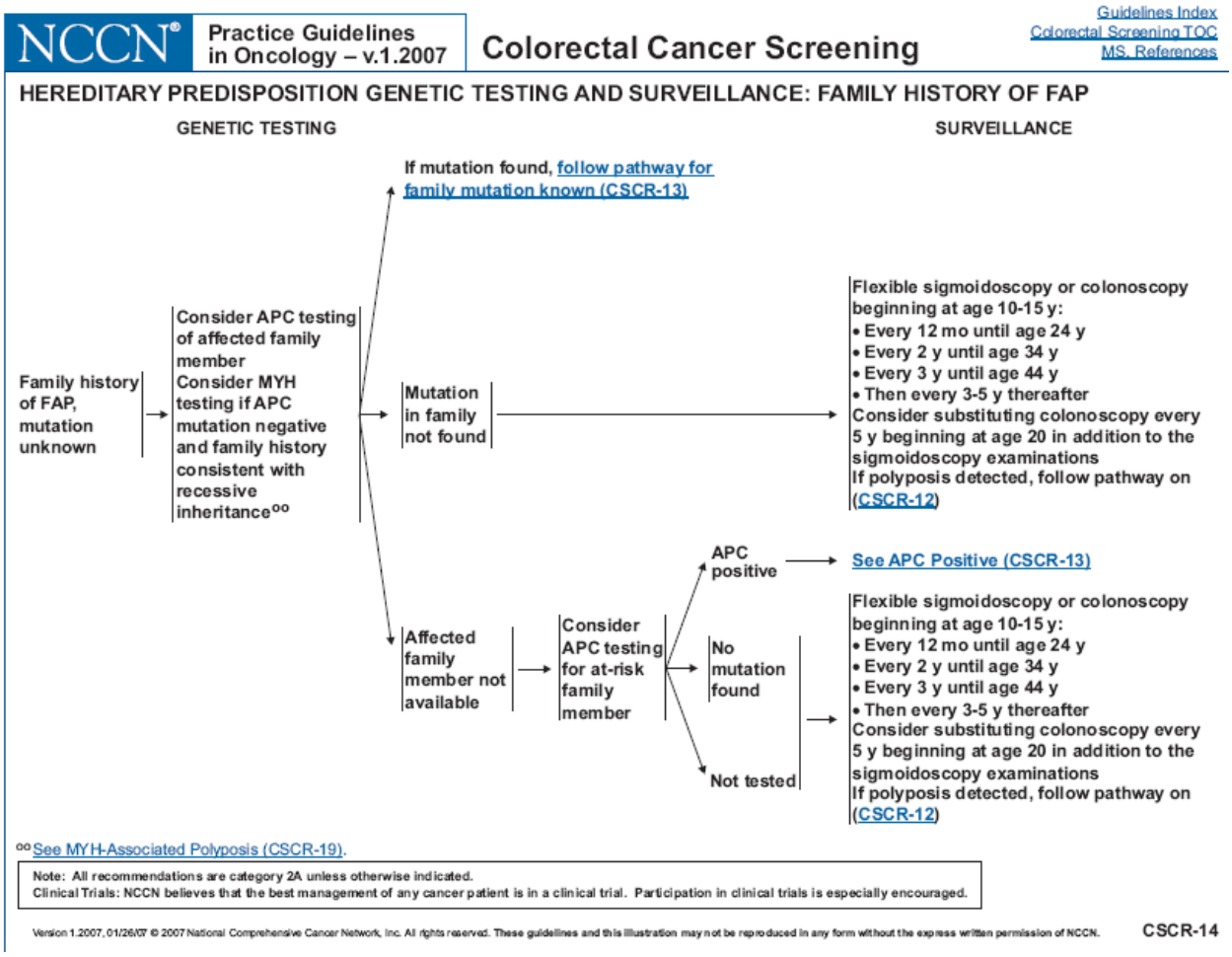
Appendix 3 (Cont.): Clinical Algorithm for FAP / HNPCC Genetic Testing



Appendix 3 (Cont.): Clinical Algorithm for FAP / HNPCC Genetic Testing



Appendix 3 (Cont.): Clinical Algorithm for FAP / HNPCC Genetic Testing



Appendix 4: *BRCA1* and *BRCA2* Patents

US Patent	Nature of Claims	Assignee	US Licensee
5654155	Consensus cDNA sequence for BRCA1, method for detecting *BRCA1* mutations	OncorMed	Rights acquired by Myriad
5622829	Mutant allele probes and methods for BRCA1	University of California	OncorMed (acquired by Myriad)
5693473	*BRCA1* mutations	Myriad Genetics; Centre du Recherche du Chul; Tokyo Cancer Institute	Myriad Genetics
5709999	Method for detecting *BRCA1* mutations	Myriad Genetics; Centre du Recherche du Chul; Tokyo Cancer Institute	Myriad Genetics
5710001	Method for detecting BRCA1 mutations in tumors	Myriad Genetics, University of Utah Research Foundation, and the United States of America	Myriad Genetics
5747282	cDNA sequence for *BRCA1,* cloning vectors containing *BRCA1* cDNA, kit for detecting mutations in *BRCA1*, and method for screening for therapeutics for cells with *BRCA1* mutations	Myriad Genetics, University of Utah Research Foundation, and the United States of America	Myriad Genetics
5750400	cDNA sequence for *BRCA1 and* methods for detecting *BRCA1* mutations	OncorMed	Rights acquired by Myriad
5753441	Method and kit for detecting *BRCA1* germline mutations	Myriad Genetics, University of Utah Research Foundation, and the United States of America	Myriad Genetics
5837492	*BRCA2* sequence and methods	Myriad Genetics, Endo Recherche, HSC (Hospital for Sick Children) Research & Development Limited Partnership, and Trustees of the University of Pennsylvania	Myriad Genetics
6045997	*BRCA2* sequences and methods	Duke University and Cancer Research Campaign (UK)	Expired
6051379	Probes, methods, and kits for detecting *BRCA2* mutations and rearrangements	Myriad Genetics, University of Utah Research Foundation, and the United States of America	Myriad Genetics
6130322	cDNA sequence for segments of *BRCA1*	Gene Logic	*
6162897	Amino acid sequence translated from *BRCA1*	Myriad Genetics, University of Utah Research Foundation, and the United States of America	Myriad Genetics
6686163	*BRCA1* mutations and cloning vectors	Gene Logic	*

	containing mutations		
6720158	*BRCA1* sequence for splicing variations	Philadelphia Health & Education Corp. (now assigned to Drexel University) **	Unlicensed
6838256	*BRCA1* consensus coding sequences, mutations, vector comprising sequence, methods for detecting mutations	Gene Logic	*
6951721	Method for determining functional sequence variations in *BRCA1*	Gene Logic	*

*Duke University researchers requested licensing information from Gene Logic but to date have not received licensing information.

**Drexel University Office of Technology Commercialization, via phone October 20, 2008. (215) 895-0304.

Information compiled by authors.

Impact of Patents and Licensing Practices on Access to Genetic Testing for Alzheimer's Disease

Katie Skeehan, Christopher Heaney, and Robert Cook-Deegan, MD[1]

Introduction

As the most common form of dementia, Alzheimer's Disease (AD) currently afflicts over 5 million Americans, a number expected to increase to 16 million by 2050.[2] Total estimated costs of healthcare for AD were $33 billion in 1998; rising to $61 billion by 2002.[3] Because it strikes so many and costs so much, it is important to understand whether and how patenting and licensing practices might affect the millions of people who will be concerned about genetic risks associated with Alzheimer's disease.

Alzheimer's disease as currently classified has several forms. Two are relevant to genetic testing. A very small percentage of AD cases arise in family clusters with early onset. Familial early-onset AD (EOAD) is usually caused by an autosomal dominant mutation in one of three genes: PSEN1 (chromosome 14), PSEN2 (chromosome 1), or APP (chromosome 21). A person with one of these fully penetrant mutations will contract the disease if they live long enough, usually developing symptoms before age 60. These families are quite rare, but the 50% risk of each child of an affected member means these tests can be important for those at risk.

The vast majority of people who develop AD have the late-onset form (LOAD), which has only one clearly established and robust genetic risk factor known as APOE (the gene that encodes the protein apolipoprotein E). Those who inherit the ε4 allele from one parent have an elevated risk of developing AD, and those who inherit ε4 alleles from both parents have a markedly elevated risk (up to an odds ratio of 16 relative to the population average for Caucasian males, for example). Recent studies based on genome-wide association with markers suggest there may be other genetic risk factors, but the next most significant locus after APOE, on chromosome 12, is many, many orders of magnitude less predictive.[4] The high-risk ε4 genotype is not necessary to predict or diagnose AD. While the APOE genetic test is used in a relatively small fraction of LOAD cases, the much larger number of late-onset AD cases means it is more frequently used than the genetic tests for PSEN1, PSEN2, or APP in high-risk families.

Patents relevant to genetic testing for all four genes have been granted in the United States. The patenting landscape is complex. The APOE gene itself is not patented, nor are mutations or polymorphisms, but testing to predict Alzheimer's risk is the subject of three "methods" patents issued to Duke University and licensed exclusively to Athena Diagnostics. PSEN1 and PSEN2 gene sequences and their variants have been patented and exclusively licensed to Athena Diagnostics. APP is the subject of several patents for making animal models, but not of a sequence patent *per se*. Athena offers genetic testing for PSEN1, PSEN2, APP, and APOE. When this case study was first being prepared in summer 2007, testing for PSEN2 and APP was not listed on Athena's website, and clinicians did not know of a CLIA-certified laboratory offering such testing, but starting February 2008, these tests were offered by Athena.

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[1] Center for Genome Ethics, Law & Policy, Institute for Genome Sciences & Policy, and Sanford Institute of Public Policy, Duke University

[2] Alzheimer's Association. *Alzheimer's Disease Facts and Figures 2007.* 2007. See http://alz.org/national/documents/Report_2007FactsAndFigures.pdf [accessed November 14, 2008], at 5.

[3] Ibid., 14.

[4] Beecham GW et al. Genome-wide association study implicates a chromosome 12 risk locus for late-onset Alzheimer disease. *Am J Hum Gen* 2009 (January 9). 84:35-43.

Direct-to-consumer APOE testing was available March-October 2008 through Smart Genetics.[5] Smart Genetics ceased offering APOE risk assessment for Alzheimer's disease to consumers in October 2008.[6] Direct-to-consumer APOE testing remains advertised through Graceful Earth's website, and APOE ε4 status is indirectly assessed by at least one of the "personal genomics" firms (see below).

Background

AD accounts for 50% to 70% of all cases of dementia. Even without genetic factors, the lifetime risk of AD in the general population is estimated at 15%, with prevalence of the disease doubling every five years after the age of 65 so that nearly 40% of the population aged 85 and older has AD.[7] The most common symptom is gradually worsening memory loss, especially short-term memory, learning, and new memory formation. As the disease advances, victims typically experience confusion and disorientation, impaired judgment, and difficulty speaking and writing. Eventually AD patients lose their ability to do simple everyday tasks like bathing, dressing, and eating. Ultimately those with AD reach a point where they no longer recognize family and friends, lose the ability to communicate, and become bed-bound.[8] AD is incurable and fatal, though the average patient can expect to live 8 to 10 years beyond the initial appearance of symptoms.[9] Some live far longer.

The neuropathology of AD consists of plaques of beta-amyloid protein deposited in the brain and neurofibrillary tangles of another protein called tau inside nerve cells.[10] Scientists and clinicians debate whether the plaques and tangles are the cause or the result of cell death. Most researchers now ascribe to the "amyloid cascade" hypothesis, which postulates that the accumulation of A-beta amyloid is toxic to nerve cells. Elucidating the pathogenic pathway and developing new leads for treatment are extremely active areas of research. Other abnormalities in the brain of a person with AD can include inflammation and oxidative stress.[11] While correct diagnosis of AD has improved greatly since its discovery (it is now at near or beyond 90% in academic centers[12]), the gold standard for AD is autopsy confirmation, when the brain can be examined for the telltale plaques and tangles, combined with a clinical history of dementia. [13]

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[5] Athena initially sublicensed the APOE patents to Smart Genetics, which began offering direct-to-consumer genetic risk assessment for AD in March 2008. The test was widely advertised, including a 28 March "survey" of consumers' willingness to undergo genetic testing through *Parade Magazine*, the most widely circulated publication in the nation. Allen Roses was asked to become a consultant of Smart Genetics, refused, and notified Duke University that it was his understanding the license for the patents on which he is first inventor permitted APOE testing only for those with a physician's certification of a diagnosis of dementia. Smart Genetics ceased operations in October 2008 (Smart Genetics shuts its doors. *Eye on DNA.* See http://www.eyeondna.com/2008/10/06/smart-genetics-shuts-its-doors/ [accessed November 14, 2008]. Genetic testers Smart Genetics closes. *Philadelphia Business Journal*. See http://www.bizjournals.com/philadelphia/stories/2008/09/29/daily42.html [accessed November 14, 2008]).

[6] Hayden EC. Alzheimer's Tests Under Fire. *Nature* 2008. 455: 1155.

[7] Post SG, Whitehouse PJ, Binstock RH, Bird TD, Eckert SK, Farrer LA, Fleck LM, Gaines AD, Juengst ET, Karlinsky H, Miles S, Murray TH, Quaid KA, Relkin NR, Roses AD, St George-Hyslop PH, Sachs GA, Steinbock B, Truschke EF, Zinn AB. The clinical introduction of genetic testing for Alzheimer disease. An ethical perspective. *JAMA* 1997. 277, (10): 832-6.

[8] See Alzheimer's Association. *Alzheimer's Disease Facts and Figures 2007*. Op. cit. at 3.

[9] Small GW, Rabins PV, Barry PP, Buckholtz NS, DeKosky ST, Ferris SH, Finkel SI, Gwyther LP, Khachaturian ZS, Lebowitz BD, McRae TD, Morris JC, Oakley F, Schneider LS, Streim JE, Sunderland T, Teri LA, Tune LE. Diagnosis and treatment of Alzheimer disease and related disorders. Consensus statement of the American Association for Geriatric Psychiatry, the Alzheimer's Association, and the American Geriatrics Society. *JAMA* 1997. 278, (16): 1363-71.

[10] Bird TD. Genetic Aspects of Alzheimer Disease. *Genetics in Medicine* 2008. 10, (4): 231-39.
Schutte DL, Holston EC. Chronic Dementing Conditions, Genomics, and New Opportunities for Nursing Interventions. *Journal of Nursing Scholarship* 2006. 38, (4): 328-34.

[11] Ibid.

[12] Bertram L, Tanzi RE. Alzheimer's disease: one disorder, too many genes? *Human Molecular Genetics* 2004. 13, (Review Issue 1): R135-R41.

[13] Bird TD. Genetic Aspects of Alzheimer Disease. *Genetics in Medicine* 2008. 10, (4): 231-39.231 – 232.

Early-onset AD

EOAD accounts for fewer than 3% of all AD cases, which amounts to less than 50,000 people in the U.S.[14] Some inherited cases are missed. Early-onset cases lacking family history may truly lack inherited risk, or the family history may have missed past cases for one of many reasons. Current classifications have only been in place for the past three decades in a disease with onset late in life, and with few autopsies performed to give definitive diagnosis. Until recent decades, premature deaths (before usual AD onset) were common, so those dying might have developed dementia had they lived long enough. Or affected cases may have died with dementia but it was not reported as the cause of death, nor recorded in family records. Moreover, expectations of "senility" were common, so that those developing symptoms often were not understood to have disease-related dementia. Family history of past cases is thus even more uncertain than for most other conditions.

Familial EOAD (or EOFAD) is usually caused by autosomal dominant mutations in the APP, PSEN1 or PSEN2 genes, although there are additional families with autosomal dominant inheritance pattern in which no mutation has yet been identified. [15] In families with autosomal dominant EOAD, each child of an affected parent has a 50% chance of also having the mutant gene, and therefore developing EOAD if they live long enough. Upon genetic testing, sometimes a new EOAD family reveals a mutation in one of the three known genes; other times no mutation is found to explain the inheritance pattern and testing is inconclusive.[16] In one of the larger studies of EOAD families to date, mutations in the PSEN1 gene accounted for 66% of EOAD families, mutations in APP for another 16%, and 18% were unknown.[17] (Note these numbers are for familial cases, not sporadic ones. EOAD is not always inherited and genetic testing has a very low yield in nonfamilial cases.)

APP

The amyloid precursor protein (APP) was discovered in the 1980s.[18] A mutation in the gene encoding this protein was the first to be linked with AD, in 1991.[19] The APP gene resides on chromosome 21 and contains at least 36 mutations, of which 30 are believed pathogenic.[20] However, this is an extremely rare cause of AD, affecting only approximately 30 known families worldwide. Age of onset ranges from 39 to 67 years. APP-related disease can be influenced by the individual's APOE genotype, the gene that plays a role in late-onset AD.[21] Those with an APP mutation and the ε4 high-risk allele of APOE generally have an even earlier age of onset than relatives with APOE-ε2 or ε3.[22]

PSEN1

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[14] Ibid. 232.
Strobel G, *What Is Early-onset Familial Alzheimer Disease (eFAD)?*, 9 April 2007 2007, Alzheimer Research Forum. See: http://www.alzforum.org/eFAD/overview/essay2/default.asp, July 16 2007].
[15] Bird TD. Genetic Aspects of Alzheimer Disease. *Genetics in Medicine* 2008. 10, (4): 231-39. At 233.
[16] Ibid.
[17] Raux G, Guyant-Marechal L, Martin C, Bou J, Penet C, Brice A, Hannequin D, Frebourg T, Campion D. Molecular diagnosis of autosomal dominant early onset Alzheimer's disease: an update. *Journal of Medical Genetics* 2005. 42: 3.
[18] Glenner G, Wong C. Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. *Biochemical and Biophysical Research Communications* 1984. 120, (3): 885-90.
Glenner G, Wong C. Alzheimer's disease and Down's syndrome: sharing of a unique cerebrovascular amyloid fibril protein. *Biochemical and Biophysical Research Communications* 1984. 122, (3): 1131-35.
[19] Goate A, Chartier-Harlin M-C, Mullan M, Brown J, Crawford F, Fidani L, Giuffra L, Haynes A, Irving N, James L, Mant R, Newton P, Rooke K, Roques P, Talbot C, Pericak-Vance M, Roses A, Williamson R, Rossor M, Owen M, Hardy J. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature* 1991. 349, (6311): 704-06.
[20] *Alzheimer's Disease and Frontotemporal Dementia Mutation Database*. See http://www.molgen.ua.ac.be/ADMutations/default.cfm?MT=1&ML=1&Page=MutByGene [accessed October 18, 2008].
[21] Blacker D. New insights into genetic aspects of Alzheimer's disease. *Postgraduate Medicine* 2000. 108, (5): 119-29.
[22] Strobel, *What is Early-Onset Familial Alzheimer Disease (Efad)?* Op. cit.

Presenilin-1 mutations are the most common among the three known EOAD-associated genes. PSEN1 mutations account for the majority of EOAD cases where onset is before age 50. Discovered in 1992, PSEN1 is located on chromosome 14 and harbors over 180 different mutations, of which 173 are believed pathogenic.[23] Victims of such mutations generally have more severe clinical syndromes, such as earlier onset of seizures and language disturbance, than those with mutations in APP or PSEN2 genes.[24] AD associated with PSEN1 has onset between ages 28 and 64, with an average age of onset of 45 years. [25]

PSEN2

The PSEN2 gene that encodes the presenilin-2 protein was discovered quickly after PSEN1 because of its similar DNA sequence. It is known as "the Volga German gene" since mutations in PSEN2 were isolated on chromosome 1 in a group of apparently related German families that settled in the Volga River region of Russia before coming to the U.S., where their mutation was subsequently discovered.[26] Mutations in PSEN2 are extremely rare, having only been identified in one familial group. The average age of onset is 52 years (with a wide range from 40 to 75 years) with APOE ε4 again associated with somewhat earlier onset.[27] Twenty-two mutations in PSEN2 have been reported, fourteen of which are deemed pathogenic.[28]

Late-onset AD

LOAD is associated with both genetic and other risk factors. While the primary risk factors are age and family history, other factors such as susceptibility genes, exposure to toxins, previous head injury, female gender, and low level of education may also play a part.[29]

APOE

Apolipoprotein E is a cholesterol transport protein (generally written APOE for the gene, and ApoE or apoE for the protein). ApoE protein is encoded by a gene on chromosome 19. There are three common alleles, ε2, ε3, and ε4. In the general population, APOE ε4/4 represents approximately 2%; 3/4 represents 21%; 3/3 represents 60%; 2/3 represents 11%; 2/4 represents 5%; and 2/2 represents less than 0.5%.[30]

APOE ε4 is associated with an increased risk of AD, while APOE ε2 acts as a mildly protective factor. Persons with APOE ε4/ ε4 have increased risk—more than sixteen-fold higher among Caucasian males at peak relative risk—and they have earlier age of onset than individuals with only one ε4 (three-fold higher risk in Caucasian males). Individuals with only one ε4 have a higher risk and earlier onset, in turn, than those with no ε4 alleles. (There are some variants among the ε3 alleles themselves also, although risk

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[23] *Alzheimer's Disease and Frontotemporal Dementia Mutation Database*. Op. cit.
[24] Post SG, Whitehouse PJ, Binstock RH, Bird TD, Eckert SK, Farrer LA, Fleck LM, Gaines AD, Juengst ET, Karlinsky H, Miles S, Murray TH, Quaid KA, Relkin NR, Roses AD, St George-Hyslop PH, Sachs GA, Steinbock B, Truschke EF, Zinn AB. The clinical introduction of genetic testing for Alzheimer disease. An ethical perspective. *JAMA* 1997. 277, (10): 832-6.
[25] Blacker D. New insights into genetic aspects of Alzheimer's disease. Postgraduate Medicine 2000. 108, (5): 119-29. At 120.
[26] Pollen D, *Hanah's Heirs: The Quest for the Genetic Origins of Alzheimer's Disease* (New York: Oxford University Press, 1993).
[27] Ibid.
Bird TD. Genetic Aspects of Alzheimer Disease. *Genetics in Medicine* 2008. 10, (4): 231-39. At 234.
[28] *Alzheimer's Disease and Frontotemporal Dementia Mutation Database.* Op. cit.
[29] Small GW, Rabins PV, Barry PP, Buckholtz NS, DeKosky ST, Ferris SH, Finkel SI, Gwyther LP, Khachaturian ZS, Lebowitz BD, McRae TD, Morris JC, Oakley F, Schneider LS, Streim JE, Sunderland T, Teri LA, Tune LE. Diagnosis and treatment of Alzheimer disease and related disorders. Consensus statement of the American Association for Geriatric Psychiatry, the Alzheimer's Association, and the American Geriatrics Society. *JAMA* 1997. 278, (16): 1363-71.
[30] Roses AD. Apoliopoprotein E alleles as risk factors in Alzheimer's disease. *Annu. Rev. Med.* 1996. 47: 387-400.

curves for sub-subgroups have not been developed for clinical use in detail.) The median onset among those homozygous for ε4 (ε4 /ε4) is before age 70, while among those who develop AD with the ε2/ε3 genotype, the median age of onset is over 90.[31]

Ashford estimates that approximately 50% of the risk of AD is attributable to APOE genotype.[32] Yet APOE is *neither necessary nor sufficient* to predict or diagnose AD.[33] "Although Alzheimer's disease occurs in many patients who carry the [APOE ε4] allele, a significant number of carriers do not get the disease. In addition, only about half of patients with late-onset Alzheimer's disease have the [APOE ε4] allele."[34] By age 90, it is rare to identify ε4/ε4 individuals without onset of dementia. Relative odds of developing AD based on the three alleles differ according to sex and race.[35]

Other Possible Genetic Influences

Because AD affects so many people, research in the field is abundant, to the point that in 2004, Bertram and Tanzi reported "more than 10 genes are reported to show either positive or negative evidence for disease association *per month*."[36] In 90 studies reporting 127 association findings in 2003, only 3 associations between candidate genes and AD were confirmed by three or more independent studies. These loci occurred at chromosomal locations 6p21, 10q24, and 11q23.[37] The recent turn to genome-wide association methods has turned up some signals, but all are far weaker than the APOE genotype.[38] Nothing conclusive has been determined, however, so APOE remains the only established clinically significant susceptibility gene for late-onset AD.

The vast majority of contributions to the Human Genome Mutation Database and Alzheimer and FTD Mutation Database, which catalog AD mutation research, come from academic research centers, and not from Athena Diagnostics, in contrast to the heavy contribution of Myriad Genetics to the analogous mutation database for BRCA1/2 mutations. Athena Diagnostics presumably tracks utilization of its various genetic tests as part of its royalty agreements, but these data are not publicly reported. The system of studying AD thus relies primarily on clinicians and academic researchers rather than family studies conducted or carried out by Athena.

Patents and Licensing

Athena Diagnostics has exclusive licenses to three APOE patents, all of which were granted to Duke University: U.S. 5508167, U.S. 5716828, and U.S. 6027896. The first and third patents have methods claims and the second claims a testing kit. The methods claims are based on APOE genotype (both direct and indirect determinations) and "observation" of AD risk. These may be claims of the type that the October 2008 decision of the Court of Appeals for the Federal Circuit (CAFC) *In re Bilski* cast into doubt.[39] The CAFC states an invention is patent-eligible under section 101 of the patent statute if "(1) it

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[31] Ibid.;
Bird TD. Genetic Aspects of Alzheimer Disease. *Genetics in Medicine* 2008. 10, (4): 231-39.234 – 235.
[32] Ashford JW. APOE Genotype Effects on Alzheimer's Disease Onset and Epidemiology. *Journal of Molecular Neuroscience* 2004. 23, (3): 157-65.
[33] Ibid. 235.
[34] Blacker D. New insights into genetic aspects of Alzheimer's disease. *Postgraduate Medicine* 2000. 108, (5): 119-29. At 120.
[35] Farrer L, et al. Effects of Age, Sex, and Ethnicity on the Association Between Apolipoprotein E Genotype and Alzheimer Disease: A Meta-analysis. *JAMA* 1997. 278, (16): 1349-56.
Bird TD. Genetic Aspects of Alzheimer Disease. *Genetics in Medicine* 2008. 10, (4): 231-39. At 234.
[36] Bertram L, Tanzi RE. Alzheimer's disease: one disorder, too many genes? *Human Molecular Genetics* 2004. 13, (Review Issue 1): R135-R41.
[37] Ibid.
[38] Beecham GW et al. Op. cit.
[39] *In Re Bilski*, F.3d (Fed. Cir. 2008)(*en banc*).

is tied to a particular machine or apparatus, or (2) transforms a particular article into a different state or thing."[40] Duke's patents have not been challenged under this standard.

According to Dr. Allen Roses, first inventor on the patents, the patents were sought because of well known chicanery in publication and reviewing in academic AD research at the time. The gene hunts for PSEN1, PSEN2, and APP were characterized by competitive races and nasty controversies, including conflicting claims of scientific priority. [41] Dr. Roses' solution was to file a patent application for APOE screening to establish a documentary record. The Duke APOE patents were exclusively licensed to ensure that the genotyping was only done "for physicians who confirmed a finding of dementia… [and] we felt that we could monitor the activity better with one license."[42] Because APOE is neither necessary nor sufficient to diagnose AD, Dr. Roses indicated the intention was to use the patent license from Duke to ensure APOE testing would not be used as a presymptomatic screening test; it could only be used for patients already clinically diagnosed with dementia.

We have not been able to confirm these licensing terms, although we submitted questions to both Duke's Office of Licensing and Ventures and to Athena Diagnostics.[43] An October 2008 report in *Nature* corroborates the cessation of Smart Genetics risk-assessment testing, and attributes it to licensing terms between Duke and Athena, although the licensing terms between Duke and Athena are not public.[44] Athena Diagnostics has sent several cease-and-desist letters to laboratories offering APOE testing, including one to the University of Pennsylvania to stop APOE testing (Appendix 1).[45]

Athena also licensed two patents for the presenilin genes. U.S. 5840540 covers the PSEN2 gene and mutations and U.S. 6194153 includes methods claims for PSEN1. These are two patents in a series of five on PSEN1 and PSEN2, four of which were assigned to the Hospital for Sick Children (Toronto) and the University of Toronto. They include U.S. 5986054 (covering the proteins of PSEN1), U.S. 6194153 (which Athena licensed), U.S. 6117978 (covering the proteins of PSEN2), and U.S. 6485911 (covering the methods of PSEN2). The remaining patent is U.S. 5840540, which Athena also licensed. It was assigned only to the Hospital for Sick Children. What is noteworthy here is that Athena only licensed two of the patents and that the patents are two different types of patents. Athena exclusively licensed the gene (sequence) patent for PSEN2 and the methods patent for PSEN1. The Toronto group, under lead inventor-scientist Peter St. George-Hyslop, has another patent that appears to cover the PSEN1 sequence,

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[40] Ibid.

[41] Interview with Dr. Allen Roses, July 5, 2007. In races for other Alzheimer genes, there were allegations of papers in review being held up while reviewers geared up to claim contemporary discovery, disputes over agreements to share or not to share data and materials, use of family pedigrees and clinical materials without permission, withholding such permission arbitrarily for competitive purposes, and other shenanigans. These are recounted, in somewhat muted form, in two books: Pollen D, *Hanah's Heirs: The Quest for the Genetic Origins of Alzheimer's Disease* (New York: Oxford University Press, 1993). The race is also recounted in Tanzi RE, Parson AB, *Decoding Darkness: The Search for the Genetic Causes of Alzheimer's Disease* (Cambridge: Perseus, 2000). According to Roses, the first APP717 mutation reported in *Nature* in 1991 used two families, the larger of which was provided by the Roses Laboratory, but the patenting of the discovery and the submitted publication did not acknowledge this; similarly, the Roses Laboratory provided approximately one-fourth of the patients for discovery of the PSEN1 locus, but was excluded from authorship of the publication.

[42] Email from Dr. Roses, received July 24, 2007.

[43] In an email from Robert Cook-Deegan to Rose Ritts, director of Duke's Office of Licensing and Ventures, on 10 February 2008 (repeated 18 October 2008), ten questions were posed, with an invitation to share the questions with Athena Diagnostics, the Duke licensee. The text of the email is in Appendix 5. Dr. Michael Henry of Athena Diagnostics has had verbal opportunities to answer the same questions but has not done so as of November 1, 2008.

[44] Hayden EC. Alzheimer's Tests Under Fire. *Nature* 2008. 455: 1155. "The test was never intended to be used for wholesale screening of non-cognitively impaired individuals,' adds Alan Herosian, director of corporate alliances for Duke University. He says he has contacted Athena many times in recent months to press this point. Michael Henry, Athena's vice-president of business development, wouldn't comment on whether the company agreed with this interpretation of its licence. But Smart Genetics is no longer taking new orders for Alzheimer's Mirror."

[45] Leonard D. Presentation to Secretary's Advisory Committee on Genetics, Health, and Society (2006). See http://oba.od.nih.gov/oba/SACGHS/meetings/June2006/Leonard3.pdf [accessed January 14, 2009].

called the Alzheimer's Related Membrane Protein in their patent (U.S. 6531586), but this does not appear on Athena's list of exclusively licensed patents.[46]

Another patent, U.S. 6248555, was assigned to the General Hospital Corporation (Massachusetts General Hospital's holding trust for patents) in Boston. This patent covers a mutant PSEN1 gene. Athena did not license it. Instead, another pharmaceutical licensing partner originally paid for its prosecution. When the licensing partner's interest terminated, Massachusetts General Hospital (MGH) abandoned the patent, allowing it to enter the public domain.[47] MGH did so because at that point, the patent had less than half its life left and thus had very limited licensing potential and no immediate licensee options. MGH chose to conserve their patent resources and concentrate efforts on newer technologies.

Finally, an April 2008 search of patents found 355 US patents with claims mentioning an Alzheimer's-specific term.[48] Many of these are clearly for research methods, transgenic animal models, and other purposes, and do not bear directly on genetic testing. A few, however, are of clear interest. Perlegen, for example, has a patent application for "Genetic Basis of Alzheimer's Disease and Diagnosis and Treatment Thereof" that claims a collection of polymorphic sites (US 2006/0228728 A1/WO06083854A2). Its initial claim is for an AD genotype profile, which includes APOE and APP along with many other loci associated with AD risk. Even though the patent application may not be granted, it indicates that multiplex testing for AD is being commercially pursued and is the subject of patent applications.

International Patent Landscape

For APOE, a patent application assigned to Duke University was filed with the World Intellectual Property Organization (WIPO), WO/1994/009155: Methods of Detecting Alzheimer's Disease. This application lists over 60 countries, but appears to have lapsed, been abandoned or rejected in most nations. There are patents in New Zealand, Canada, Germany, and UK. The US patents claim increased risk assessment in individuals, while the WIPO application claims "a method of diagnosing or prognosing Alzheimer's disease in a subject, wherein the presence of an apolipoprotein E type 4 (ApoE4) isoform indicates said subject is afflicted with Alzheimer's disease or at risk of developing Alzheimer's disease."[49] The Canadian Intellectual Property Office (CIPO) issued patent number CA 2142300 in August 2005, 12 years after the application was filed.[50]

Three patent applications for the presenilin genes were filed with the World Intellectual Property Organization (WIPO): WO/1996/034099, WO/1997/027296, and WO/1998/001549. The first two were assigned to both the Hospital for Sick Children (HSC) and the University of Toronto, while the last patent was assigned only to the University. Four patents were granted in Canada. The first, CA 2200794, was assigned only to the University but the remaining three – CA 2219214, CA 2244412, CA 2259618 – were assigned to both HSC and the University of Toronto.

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[46] *Test Catalog*. See http://www.athenadiagnostics.com/content/test-catalog/ [accessed November 14, 2008].
[47] Email from Dr. Colm Lawler, Senior Licensing Associate, MGH, received July 31, 2007.
[48] On April 13, 2008, Robert Cook-Deegan performed a search for patents granted with "presenilin or PSEN1 or PSEN2 or Alzheimer or 'amyloid precursor'" in the claims. That search returned 355 granted US patents. The same text terms returned 5,172 patents and applications when the search was broadened to all fields, all jurisdictions in the Delphion database, and to both patents and applications.
[49] WIPO Patent WO/1994/009155, claim 1. Gathered from WIPO online database.
[50] From CIPO online database. See http://patents.ic.gc.ca/cipo/cpd/en/introduction.html [accessed December 10, 2008].

Genetic Tests

In the United States, AD testing is provided almost exclusively by Athena Diagnostics, which tests for LOAD using APOE, as well as EOAD using PSEN1, PSEN2 and APP genes. Athena has offered PSEN1 testing based on sequence analysis since 1997. The PSEN1 genotype test is priced at $1,675.[51] Prices for APP and PSEN2 are not public.[52]

Using targeted mutation analysis, Athena offers APOE testing for $475. The Duke license to Athena gives worldwide exclusive rights for the Alzheimer's ApoE patents.[53] Within the past year, the Saint Louis University Health Science Center has offered APOE testing for cardiovascular purposes for $365. As of June 2007, some parties expressed interest, but none pursued testing.[54] Because the indication is for cardiovascular risks and not AD, this use does not infringe Athena's patents (recall that Duke could not patent the DNA sequence, only the association with AD). Genotyping for cardiovascular risk thus does not infringe the Duke patents licensed to Athena Diagnostics. Several knowledgeable clinicians indicated in interviews and emails that APOE genotyping can be obtained through laboratories other than Athena, even when it is being used to assess AD risk.

In Canada, McGill University Health Center and Sunnybrook Molecular Genetics Laboratory both offer APOE testing for AD. McGill charges $100 (US dollars) and Sunnybrook $120 (Canadian dollars).[55] McGill has offered the test since 1993 by physician referral only, as the individual needs to exhibit realistic pre-test probability of having the disease. Sunnybrook also only offers testing for individuals with documented cases of AD.

Smart Genetics announced on February 7, 2008, that it entered an agreement with Athena Diagnostics to offer direct-to-consumer genetic testing for APOE.[56] Part of the service, called "Alzheimer's Mirror," included educational materials, a saliva sampling kit, a post-test phone session with a genetic counselor, and ongoing support for managing test results. Initially priced at $399 and later dropped to $249, the test incorporated data on ethnicity, gender, family history, and APOE genotype to assess an individual's AD risk. The testing was performed at a CLIA-certified laboratory.[57] While not claiming to predict with certainty whether or not one would develop AD, it was the only direct-to-consumer AD genetic test that included genetic counseling and further support for users. As of October 2008, the Alzheimer's Mirror website was still open, but the company apparently ceased operations early that month, and the website was unavailable by January 2009.[58]

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[51] Phone interview with Athena Diagnostics Customer Service Representative, June 19, 2007.
[52] In phone interviews in May 2008 with Duke research assistant Christopher Heaney, various Athena employees declined to provide test price information.
[53] Email from Rose Ritts, Director, Duke Office of Licensing and Ventures, February 1, 2008, to Robert Cook-Deegan.
[54] Phone interview with St. Louis University Health Science Center representative, June 19, 2007.
[55] Phone interview with McGill University Health Center, June 19, 2007.
Phone interview with Sunnybrook Molecular Genetics Laboratory, November 19, 2008.
[56] *Smart Genetics Announces Plans to Launch New Alzheimer's Risk Assessment Service*. See http://www.smartgenetics.com/index.php/News/Latest/alzm-press-release.html [accessed November 14, 2008].
[57] *Smart Genetics Launches New Alzheimer's Risk Assessment Service For Customers*. See http://www.smartgenetics.com/news/press/sg-alzmirror-launch.html [accessed November 14, 2008].
[58] Smart Genetics, *Alzheimer's Mirror*. See http://www.alzmirror.com/order-your-test.php [accessed October 18, 2008]. As of October 18, 2008, the final webpage for ordering a test reported: "We're sorry, but due to high demand for Alzheimer's Mirror we are currently unable to process new orders. To be added to our waiting list and notified as we become able to process new orders, please fill out the form below." The 6 October "Eye on DNA" and the Philadelphia Business Journal both reported that Smart Genetics closed its doors (Smart genetics shuts its doors. *Eye on DNA*. See http://www.eyeondna.com/2008/10/06/smart-genetics-shuts-its-doors/ [accessed November 14, 2008]. Genetic testers Smart Genetics closes. *Philadelphia Business Journal*. See http://www.bizjournals.com/philadelphia/stories/2008/09/29/daily42.html [accessed November 14, 2008]. By 19 January 2009, the website was no longer operating.

For $280, Graceful Earth, Inc., an online health alternatives website, promises "a genetic test…to accurately evaluate your risk for Alzheimer's Disease and Atherosclerosis."[59] This is a direct-to-consumer test that does not require physician approval. Consumers send Graceful Earth a saliva sample. Genetic counseling is not listed as a service on the company's website. There is no indication of a license from Duke or a sublicense from Athena Diagnostics on the Graceful Earth website.

Insurance Coverage and Reimbursement

In general, private insurers deem genetic testing as medically necessary when the following conditions are met: (1) family history shows a high likelihood of inherited AD risk; (2) sensitivity of the test is known; (3) the results have direct impact on treatment for the patient; (4) the diagnosis would be unclear without testing; and (5) in some cases, if pre- and post-test counseling is provided.[60] In the case of AD, the largest roadblocks to insurance coverage occur with the issues of direct impact on treatment (since AD is incurable). For late-onset AD (LOAD), APOE genotyping has an unclear value for diagnosis. Insurance coverage would presumably increase if APOE genotyping became important in deciding among drug or other treatment choices. The cost of genotyping would then be offset by avoiding the use of drugs or treatments that would not benefit people with particular genotypes.[61]

While approximately a dozen insurers have policies on testing for genetic markers of familial AD, none of the policies formally and explicitly covers the test.[62] BlueCross/BlueShield considers genetic testing to be investigational.[63] Aetna also does not distinguish between EOAD and LOAD genetic testing. It concludes that all genetic testing for AD is experimental and investigational because the tests have not been shown to improve clinical outcomes of AD.[64] In 2007 Kaiser Permanente stated that it would cover

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[59]Graceful Earth APOE genotyping service available at http://www.gracefulearth.com/index.asp?PageAction=VIEWPROD&ProdID=3&HS=1 [accessed January 19, 2009].

[60] Schoonmaker M. Presentation to Secretary's Advisory Committee on Genetics, Health, and Society (2004). See http://oba.od.nih.gov/oba/sacghs/meetings/March2004/FullDay030104.pdf [accessed January 16, 2009], at 81.

[61] The possibility of using APOE as a pharmacogenomic test is suggested by some developments in AD drug development:
Risner M, Saunders A, Altman J, Ormandy G, Craft S, Foley I, Zvartau-Hind M, Hosford D, Roses AD, Rosiglitazone in Alzheimer's Disease Study Group. Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease. *Pharmacogenomics Journal* 2006. 6, (4): 9.
Roses AD, AM S, Y H, J S, KH W, RW M. Complex disease-associated pharmacogenetics: drug efficacy, drug safety, and confirmation of a pathogenetic hypothesis (Alzheimer's disease). *The Pharmacogenomics Journal* 2007. 7: 10-28.
Roses AD. Commentary on 'A roadmap for the prevention of dementia: The inaugural Leon Thal Symposium meeting report.' An impending prevention clinical trial for Alzheimer's disease: Roadmaps and realities. *Alzheimer's and Dementia* 2008. 4: 3.
Risner et al. reported in 2005 that rosiglitazone appeared effective in AD patients who lacked an ε4 allele in a 24 week monotherapy clinical trial involving 511 patients. These data were reviewed with the FDA at a Voluntary Genomic Data Submission in December 2005 and formed the basis for a 48 week Phase III program including a second monotherapy trial and two adjuvant therapy trials. Two of these clinical trials with thousands of patients conclude in 4q08. Notable in the Phase III clinical trial designs is the role of APOE testing to test and determine the dose for patients without an ε4 allele [2 mg] and with an ε4 allele [4-8 mg]. If these Phase III trials are positive and approved, than APOE testing may be necessary to determine proper dose of therapy, not as a diagnostic for AD, but as a prognostic for effective treatment. The 2 mg dose is almost homeopathic with a drug experience of 8 mg in more than 1 million people. As such, it is anticipated that the drug label would contain the relevant pharmacogenetic information, and APOE genotypying would be linked to therapy and therefore much more likely to become a standard of care for those considering use of this drug. This also has relevance for potential prevention study designs which would include normal individuals at genotype-specific ages of increased probability of becoming symptomatic and, portentially APOE would thus become part of an intervention to delay age of onset.

[62] Schoonmaker M. Op. cit. at 82.

[63] *BlueCross BlueShield Plans Comprising the Regence Group.* (Approved December 18, 2007, effective January 1, 2008.) See http://www.regence.com/trgmedpol/lab/lab21.html [accessed November 14, 2008].
BlueCross BlueShield of Rhode Island. (Last updated September 2, 2008, effective June 15, 2008). See https://www.bcbsri.com/BCBSRIWeb/plansandservices/services/medical_policies/GeneticTesting.jsp [accessed November 5, 2008].

[64] *Clinical Policy Bulletin: Alzheimer's Disease: Diagnosis, Number: 0349.* (Last reviewed May 23, 2008, effective September 13, 1999.) See http://www.aetna.com/cpb/medical/data/300_399/0349.html [accessed November 14, 2008].

genetic testing if a doctor deemed it medically necessary.[65] As of November 2008, the company website says, "Most experts do not consider ApoE-4 testing a necessary or useful part of evaluating a person with suspected Alzheimer's disease."[66] CIGNA HealthCare currently does not cover APOE genotyping because it is considered experimental, investigational, or unproven.[67] Alzheimer's Mirror was not covered by insurance and, according to Smart Genetics, was priced for out-of-pocket payment.[68]

In summary, testing for the rare early onset familial forms is sufficiently rare that it appears to be usually handled case by case; testing for APOE has not apparently become a standard of care with regular coverage and reimbursement under health plans. If APOE genotyping predicted response to drugs or other treatments, then its use might substantially increase, it would become incorporated into clinical standards, and coverage and reimbursement would become routine.

Current Genetic Testing Guidelines

EOAD

A 1998 consensus statement, based on work from Stanford University, states, "Predictive or diagnostic genetic testing for highly penetrant mutations (such as APP, PS1 or PS2 mutations) may be appropriate for adults from families with a clear autosomal dominant pattern of inheritance, particularly those with a family history of early onset of symptoms. Testing is an option that should be discussed, and that could reasonably be accepted or declined."[69] Tests must be ordered by a physician.

LOAD

Testing is much more controversial for LOAD because of its inconclusive nature. Originally, Athena marketed the APOE testing as a predictor of AD but then backed away from it when several professional societies judged such testing as inappropriate. All scientific and governing bodies that have reviewed the matter advise against APOE genotyping as a predictive or screening test, especially for asymptomatic individuals.[70] These groups include the American College of Medical Genetics/American Society of Human Genetics Working Group, the United Kingdom Alzheimer's Disease Genetics Consortium, the Medical and Scientific Advisory Committee of Alzheimer's Disease International, the National Institute on Aging and the Alzheimer's Disease and Related Disorders Association.[71] A 2008 literature review

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[65] Phone interview with Kaiser Permanente Customer Service representative, July 12, 2007.
[66] *Apolipoprotein E-4 Genetic (DNA) Test*. See https://members.kaiserpermanente.org/kpweb/healthency.do?hwid=hw135696&sectionId=hw135696-sec&contextId=hw136623 [accessed November 14, 2008].
[67] *CIGNA HealthCare Coverage Position, Coverage Position Number: 0392.* (Revised date August 15, 2008, effective date July 15, 2005). See http://www.cigna.com/customer_care/healthcare_professional/coverage_positions/medical/mm_0392_coveragepositioncriteria_genetic_testing_alzheimers.pdf [accessed November 14, 2008].
[68] *Frequently Asked Questions for Alzheimer's Mirror.* See http://www.alzmirror.com/alzheimers-common-questions.php#12 [accessed November 14, 2008].
[69] McConnell L, Koenig B, Greely H, Raffin T, Alzheimer Disease Working Group of the Stanford Program in Genomics, Ethics & Society,. Genetic testing and Alzheimer disease: Has the time come? *Nature Medicine* 1998. 4, (7): 757-59.
[70] Post SG, Whitehouse PJ, Binstock RH, Bird TD, Eckert SK, Farrer LA, Fleck LM, Gaines AD, Juengst ET, Karlinsky H, Miles S, Murray TH, Quaid KA, Relkin NR, Roses AD, St George-Hyslop PH, Sachs GA, Steinbock B, Truschke EF, Zinn AB. The clinical introduction of genetic testing for Alzheimer disease. An ethical perspective. *JAMA* 1997. 277, (10): 832-6.
[71] American College of Medical Genetics/American Society of Human Genetics Working Group on ApoE and Alzheimer disease. Statement on Use of Apolipopritein E Testing for Alzheimer Disease Ibid.1995. 274, (20): 1627-29.
Lovestone S. The Genetics of Alzheimer's Disease—New Opportunities and New Challenges *International Journal of Geriatic Psychiatry* 1995. 10: 1-7.
Brodaty H, Conneally M, Gauthier S, Jennings C, Lennox A, Lovestone S. Consensus statement on predictive testing for Alzheimer disease. *Alzheimer disease and associated disorders* 1995. 9, (4): 182 - 87.

stated, "There is general agreement that *APOE* testing has limited value [when] used for predictive testing for AD in asymptomatic persons."[72]

Although APOE genotyping can provide an increase in diagnostic confidence, diagnostic accuracy with current methods can already exceed 90%. Therefore, APOE is used as an adjunct diagnostic test for patients already presenting with symptoms of dementia. One study of LOAD diagnosis pooled pathological confirmation data from more than 2,500 patients from 26 Alzheimer's research centers and concluded that "APOE genotyping does not provide sufficient sensitivity or specificity to be used alone as a diagnostic test, but when used in combination with clinical criteria it improves the specificity of diagnosis" to greater than 97%.[73] This study is a decade old is still one of the largest and most elaborate studies to date.

A series of studies of disclosing APOE genotype to relatives of those with AD has been conducted in a multi-center clinical research consortium based at Boston University (BU).[74] The Risk EValuation and Education for ALzheimer's disease (REVEAL) study began in 2000 at BU, Case Western Reserve University, and Cornell University as a randomized trial of disclosing genotype and risk versus standard counseling and risk evaluation *without* genotype disclosure. The major paper reporting results from REVEAL I has been accepted for publication at the *New England Journal of Medicine*, but is not yet available. REVEAL II expanded to include Howard University, and oversampled African Americans who also received counseling based on ethnicity-specific risk curves. The protocol for disclosure was abbreviated from REVEAL I. REVEAL III is ongoing, with the addition of University of Michigan (replacing Cornell/Weill Medical College) and a further streamlining of protocol and the inclusion of cardiovascular risk assessment. REVEAL did not study *diagnostic* use of APOE testing, but rather *disclosure of risk* information to relatives of those affected with AD. It did, however, extensively use APOE genotyping. Athena Diagnostics performed the tests for the REVEAL trials at a deep discount. REVEAL is the largest clinical study of APOE genotyping, and as its results are reported, they will likely influence clinical use.

Relkin N, Kwon Y, Tsai J, Gandy S. The National Institute on Aging/Alzheimer's Association recommendations on the application of apolipoprotein E genotyping to Alzheimer's disease. *Annals of the New York Academy of Sciences* 1996. 802: 149-76.

Post SG, Whitehouse PJ, Binstock RH, Bird TD, Eckert SK, Farrer LA, Fleck LM, Gaines AD, Juengst ET, Karlinsky H, Miles S, Murray TH, Quaid KA, Relkin NR, Roses AD, St George-Hyslop PH, Sachs GA, Steinbock B, Truschke EF, Zinn AB. The clinical introduction of genetic testing for Alzheimer disease. An ethical perspective. *JAMA* 1997. 277, (10): 832-6.

McConnell L, Koenig B, Greely H, Raffin T, Alzheimer Disease Working Group of the Stanford Program in Genomics, Ethics & Society. Genetic testing and Alzheimer disease: Has the time come? *Nature Medicine* 1998. 4, (7): 757-59.

[72] Bird TD. Genetic Aspects of Alzheimer Disease. *Genetics in Medicine* 2008. 10, (4): 231-39. At 235.

[73] Mayeux R, Saunders A, Shea S, Mirra S, Evans D, Roses A, Hyman B, Crain B, Tang M-X, Phelps CH for the ADCenters Consortium on Apolipoprotein E and AD. Utility of the Apolipoprotein E Genotype in the Diagnoisis of Alzheimer's Disease. *New England Journal of Medicine* 1998. 338: 506-11.

[74] Several members of the original REVEAL team advised Smart Genetics. Robert Green, PI of the overall REVEAL study, is an unpaid consultant for several "personal genomics" firms and also for Smart Genetics.

Non-genetic Screening and Diagnosis Options

Since AD can appear in many ways, it is important that individuals, friends, family members, and family physicians be watchful for changes in an individual's symptoms. A symptom checklist is provided in Appendix 1. Appendix 2 contains criteria for diagnosis of Alzheimer's type dementia. Appendix 3 contains an algorithm for dementia evaluation and diagnosis.

Clinical recognition of progressive memory decline is usually a first step in diagnosing dementia. A physical examination can help determine the specific cause of dementia, for example, those caused by vascular disease or Lewy body disease (although these often occur in combination with AD).[75] Physical examination should include evaluation of aphasia (speech), apraxia (motor memory), agnosia (sensory recognition), and executive functioning (complex behavior sequencing). Laboratory tests may be used to rule out other disorders like hypothyroidism that can cause symptoms of dementia.[76]

EOAD

While not diagnostic, analysis of cerebrospinal fluid for the 42 amino acid form of β-amyloid may be suggestive of early AD.[77] (Tau levels are also measured. This is relevant to all AD, not just early onset.)

Role of Genetic Testing

As noted above, with the exception of EOAD in descendants of affected individuals in high-risk, early-onset families, genetic testing for AD is not recommended at this time. Even for the small percentage of cases of EOAD, detection does not lead to reversal of the disease since there is no known cure for any form of AD. However, diagnosis can aid in increasing a patient's quality of life and facilitating planning for life care and financial needs. In addition, a positive genetic test can end the quest for a specific diagnosis. There is some indication that APOE ε4 is an indicator of poor response, especially in women, to acetylcholinesterase treatments, which has obvious implications for drug prescriptions.[78]

Life Management

Diagnosis, especially in the earlier stages of AD, allows patients to make informed decisions about long-term finances, nursing care options, living wills, etc. Non-medical treatments to improve quality of life such as support groups and increased exposure to music and art can help substantially on the individual level.

"Personalized genomics" and AD testing

Patents and intellectual property concerns could influence the direct-to-consumer "personal genomics" services that are springing up, although we have limited specific information about this. Two examples of how patents might emerge as important can help illustrate the possible future complexities: (1) patents on multiplex genetic testing (or "genomic profiling"), and (2) enforcement of existing patents against multiplex testing. The Perlegen patent application noted above (US 2006/0228728 A1/WO060838354A2) indicates that multi-locus genetic testing is being contemplated commercially. It is also possible that existing patents on genes, mutations, and methods pertinent to genetic tests of many DNA variants associated with AD could be a future legal battleground, if new uses are found to infringe

[75] Santacruz KS, Swagerty D. Early Diagnosis of Dementia. *American Family Physician* 2001. 63, (4): 703-13.
[76] Ibid.
[77] Ibid.
[78] Liddell MB, Lovestone S, Owen MJ. Genetic risk of Azlehimer's disease: advising relatives. *British Journal of Psychiatry* 2001. (178): 7-11.

such patents (or if those wanting to use new methods choose to challenge the validity of claims in existing patents).

It is clear that some risk information about Alzheimer's disease is being disclosed to at least some of those who use "personal genomics" testing services. The April 14, 2008, feature story in the *Los Angeles Times* opens with the author's receipt of APOE risk information about AD from Navigenics in the service that became available that week.[79] The test was based on a DNA base change linked to the APOE ε4 allele.[80] We have asked both Duke and Athena about sublicenses for risk assessment consumer testing but have received no reply. Navigenics has a page on its website with its "Gene Patent Policy," stating its willingness to license patents, with a formula for specifying royalties.[81] If there were a license, then presumably Athena and Duke would receive a royalty stream. If there were no such license, then the Duke patents might be enforced against the testing firms, which would either lead to settlement or litigation. Athena might choose not to enforce its patents against personalized genomics firms, however, if it judged that personal genomics services would drive business to their AD testing service for confirmation in a CLIA-certified laboratory. It is also unclear whether multiplex testing along the lines implied by the Perlegen patent application would require a license for the AD-associated genes and mutations covered by patents.

One interesting sidelight on the personal genomics business models is AD risk assessment by deCODEme. The Duke patent was licensed to Athena with worldwide exclusive rights, but Duke did not secure patent rights in Iceland. DeCODE is therefore not infringing the patent by carrying out the tests there, and courts would have to decide if importation of ***information*** (test results) back to the United States would constitute infringement of patent claims.

Lessons Learned

EOAD is important in those families at risk but such families are rare, and thus the market for such testing is small. During the period when it was not clear whether testing for PSEN2 and APP were even being offered, families faced an access problem, but not one specifically attributable to patent status. Rather,

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[79] Gosline A, "Genome Scans Go Deep into Your DNA," *Los Angeles Times* April 14 2008.

[80] The wording of the relevant claims of the Duke patents is highly convoluted and its interpretation would require legal expertise and might entail disagreement that would be settled definitively only if litigated to completion.

[81] Navigenics, Inc. *Gene Patent Policy*. See http://www.navigenics.com/policies/GenePatents/ [accessed June 6, 2008]. A crucial paragraph in that policy explains:

> "Because our service uses multiple SNPs to assess your genetic risk for a variety of conditions, it requires a new kind of licensing approach for gene patents. For example, if we obtain licenses from third parties to 10 patents, each covering the use of one SNP included in our service, and each subject to a royalty of between 1 percent and 5 percent of our net sales of the service, we would be required to pay between 10 percent and 50 percent of our net sales revenue — just for gene patent licenses! Now consider that the whole genome scanning platform currently utilized in the Navigenics Health Compass service analyzes approximately 900,000 SNPs, and that for certain health conditions included in our service we look at more than 10 SNPs. Also note that this example does not include any up-front or milestone fees or annual minimum royalties, which make the traditional gene patent licensing approach even more untenable for this type of service."

Their royalty model is specified as:

> "We have developed, with input from third parties, a universal royalty model for licensing gene patents for services such as the Navigenics Health Compass. In this model, royalties payable to a hypothetical Party X for a license to patents covering one or more SNPs used by the service to assess risk for hypothetical Condition Y would be calculated as follows:

$$5\% \text{ of Net Sales} \times \frac{\left(\frac{\#\text{ licensed SNPs for Condition Y}}{\text{total \# SNPs for Condition Y}}\right)}{\#\text{ conditions in service}}$$

"

the limitation was absence of a CLIA-approved testing service for genetic testing. We are not aware of enforcement actions for EOAD testing.

The most recent developments in late-onset AD genetic testing are its use in those with mild cognitive impairment and the new availability of direct-to-consumer testing. APOE testing has been considered for use in clinical trials that involve those with mild cognitive impairment, as a way to identify those most at risk of progressing to dementia. APOE genotype is also available direct-to-consumer through some genetic testing services and, as noted, using indirect markers of APOE status, through some "personal genomics" services.

Basic Research

On one hand, an argument can be made that patents were part of the mix of motivations that spurred innovation in Alzheimer's research. Two books, Daniel Pollen's *Hannah's Heirs* and Rudolph E. Tanzi's *Decoding Darkness,* document the hyper-competitive races to trace the genetic origins of Alzheimer's Disease. Some of the major competitors in these races found their way to the patent office with claims covering EOAD, transgenic models of AD, and other inventions related to the research.[82] From various accounts, there was intense animosity among the different research teams, and competition to discover and publish findings motivated the speed of AD research.[83] Both publications and patents were pursued by the various competing laboratories. At least in the initial period of discovery, the patenting landscape encouraged research, or at least did not dramatically hinder it. Dr. Tanzi expressed concern about Athena's patent control of the A-beta protein patents in connection with AD.[84]

Most of the researchers we interviewed expressed ambivalence about patenting, and none attributed the intensity of the races to patent priority. Rather, they stated that the races were driven by wanting priority of scientific discovery, prestige, scientific credit, and the ability to secure funding for additional research based on scientific achievement. If patents added "the fuel of interest to the fire of genius," in Abraham Lincoln's famous phrase, it was here at best a tiny pile of kindling at the outer margin of a large conflagration.

Having not found patents to be a significant impediment to research on AD, are patent benefits any clearer? Here again, it is difficult to argue that patents added much fuel to a fire that was already raging to hypercompetition. Indeed, Dr. Roses corrected us in the interview when we asked if one reason he sought a patent was to verify priority of his discovery associating APOE ε4 with elevated risk of AD. He said it was not ***a*** reason, but it was the ***only*** reason he sought a patent.[85] According to those who were in the race, research would not have slowed without a patent incentive.

Patents did, however, provide a mechanism for academic research institutions to convey rights to Athena Diagnostics, which aggregated patent rights from disparate academic groups to become the main testing service for AD in the United States. Athena Diagnostics' business interests cover the United States, Canada and Japan, and it also does some testing for Europe. In several jurisdictions including the United

[82] Inventors on various patents include Dr. Peter St. George-Hyslop of the Toronto group, Dr. Tanzi of Massachusetts General, Drs. Thomas Bird and Jerry Schellenberg of the University of Washington; Dr. Christine van Broekhoven (then of Antwerp; US 5525714 claiming an APP mutation), Dr. John Hardy (then of Imperial College, London; US 5877015, another APP mutation), and Dr. Allen Roses of Duke University concentrated on APOE for LOAD, as well as co-inventors on their respective teams.
[83] Interview with Dr. Allen Roses, Duke University, July 26, 2007.
Phone interview with Dr. Tom Bird, University of Washington, July 26, 2007
Phone conference with Dr. Rudolph Tanzi, Massachusetts General Hospital, July 3, 2007.
Phone conference with David Galas (formerly of Darwin Molecular, currently at Battelle Memorial Institute; Dr. Galas was chief scientist at Darwin when it collaborated with Drs. Schellenberg and Bird to sequence EOAD-associated genes) July 3, 2007.
[84] Phone interview with Dr. Tanzi, July 3, 2007.
[85] Interview with Dr. Allen Roses, July 5, 2007.

States, Athena has collected rights to genetic tests for many neurological conditions, and it has a sales force that keys to neurologists and other brain disease specialists. Where Athena enforced its exclusively licensed patents against other diagnostic services, it is clear that alternative providers were reduced in number.[86] It is impossible to judge, however, whether this has had an impact on clinical access, or even whether it has affected price (with the exception of APOE testing in Canada, which is listed for considerably less than Athena's price from two providers).

The role of patents in AD testing is thus clear in the sense that it has enabled Athena Diagnostics to consolidate the testing market in the United States. Whether this is optimal for the US health system as a whole is less clear.

Development and Commercialization

Appendix 4 shows a pricing chart of all available AD testing in the U.S. and Canada. With the exception of preimplantation genetic diagnosis, Athena Diagnostics has been the only company offering APOE and PSEN1 screening since it became available, except the 8-month period when Smart Genetics operated with a sublicense. We found no indication that Graceful Earth has a license for APOE genotyping to assess AD risk, and ambiguity about APOE testing for cardiovascular disease (which would not infringe the patents) may enable some AD genetic testing for APOE without a license. Cardiovascular testing would be completely legitimate, while interpreting AD risk assessment or diagnosis from APOE genotyping would be difficult to detect. Within the past year, the Saint Louis center has offered APOE testing for cardiovascular purposes.[87]

It remains to be seen if Duke or Athena will enforce the Duke patents against Graceful Earth or personal genomics firms. Unlike academic centers to which Athena has previously sent cease-and-desist letters, Graceful Earth is not transparent about its process of AD testing, makes no mention of CLIA laboratory certification, and alongside its APOE screening also offers pet hair analysis and herbal supplements.[88] Graceful Earth is not therefore a major clinical service provider, and its direct-to-consumer model raises questions about regulation of direct-to-consumer companies, which are outside this case study's scope.[89]

Compared to prices in the Canadian centers, prices for APOE genetic testing at Athena and at the Saint Louis Center are higher. If the Canadian laboratories' prices accurately reflect production costs, then testing for APOE can be performed at a lower cost. Prices for health goods and services are lower in Canada across the board, however, so APOE testing is not an exception, but conforms to the rule.

Athena is the only available avenue for PSEN1, PSEN2, and APP testing. The $1675 price for PSEN1 is high relative to APOE genotyping, but it entails genomic sequencing, and this price is comparable to other full-sequence tests for BRCA, colon cancer genes, and spinocerebellar ataxias cited in other case studies. The cost of this testing is out of the financial range of many patients, especially when insurers will not cover "experimental" tests. We simply cannot judge the degree to which threat of patent enforcement explains other laboratories not offering testing for the very rare families with APP, PSEN1, and PSEN2 mutations, but it is likely that patent status is just one factor among others such as set-up costs, CLIA certification, ensuring reimbursement, and building a referral network.

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[86] Cho M, Illangasekare S, Weaver M, Leonard D, Merz J. Effects of Patents and Licenses on Provision of Clinical Genetic Testing Services. *Journal of Molecular Diagnostics* 2003. 5, (1): 3-8.
[87] Phone interview with St. Louis University Health Science Center representative, June 19, 2007.
[88] *Graceful Earth, Inc.* See http://www.gracefulearth.com/ [accessed November 14, 2008].
[89] The recent actions by the New York State and California Departments of Health to regulate direct-to-consumer genetic testing are directly relevant. Graceful Earth was not, however, among the 13 laboratories that got letters from California, and we do not know if they got a letter from New York.

Marketing

AD screening in the general population is not recommended at this time. Until recently, *any* testing for either EOAD or LOAD needed to be done by physician referral, so marketing directly to consumers was a nonissue. Patents do appear to have an effect on marketing to physicians, as Athena has a sales force focused on neurologists for its AD tests, which are just a few among many genetic tests it offers for brain, muscle, endocrine, and nervous system disorders.

Patenting also affected health professional marketing indirectly, by using licensing as a tool for constraining clinical use. Dr. Roses said that a major reason Duke University decided to license exclusively to Athena was to ensure that APOE testing was done in compliance with professional standards.[90] While neither Athena nor Duke's Office of Licensing and Ventures has responded to questions about the licensing terms,[91] the end result of the exclusive patenting did ensure that testing complied with professional standards, at a time when concern was high that genetic screening for AD could cause fatalism and commercial incentives would militate to overutilization. This fear of widespread testing does not appear to have materialized, as research suggested that "consumers from our focus groups were not interested in testing that could provide neither predictive data nor a reasonably precise answer about their individual risk of developing AD at a particular age."[92] This suggests that demand would have been low in any event, but Athena's policy of requiring physician corroboration of dementia before genetic testing, as Duke University stipulated, was an additional check on testing outside professional standards.

More recently, companies like Graceful Earth, Inc. and Smart Genetics began to offer testing directly to consumers. Smart Genetics is a unique case, since the firm transiently sublicensed from Athena.[93] Athena has always been a reference lab only available to physicians.[94] Sublicensing to Smart Genetics marked a departure from this policy of ensuring that only individuals with a high likelihood of AD were tested. Both Smart Genetics and Athena received significant press and media coverage from many audiences, including *CBS-3*, *FOX-29*, *Parade* magazine, *USA Today*, and *Science*.[95] Smart Genetics relied on research published in 2005 and conducted by the REVEAL study, which found that "preliminary analyses suggest that risk assessment and genotype disclosure did not adversely affect the psychological well-being of participants."[96]

Adoption by Third-Party Payers

For AD, patents have not detectably helped or hindered the decisions by insurance companies to cover LOAD diagnosis using APOE genotype. Almost all major insurers and payers consider APOE testing experimental. In this situation, patents are irrelevant because the service is not covered as medically necessary.

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[90] Interview with Dr. Allen Roses, July 5, 2007.
[91] Email correspondence with Michael W. Henry, VP of Business Development of Athena Diagnostics, Inc., November 20, 2007. Email correspondence with Rose Ritts and Bob Taber, Office of Licensing & Ventures, Duke University, February 10, 2008.
[92] Post SG, Whitehouse PJ, Binstock RH, Bird TD, Eckert SK, Farrer LA, Fleck LM, Gaines AD, Juengst ET, Karlinsky H, Miles S, Murray TH, Quaid KA, Relkin NR, Roses AD, St George-Hyslop PH, Sachs GA, Steinbock B, Truschke EF, Zinn AB. The clinical introduction of genetic testing for Alzheimer disease. An ethical perspective. *JAMA* 1997. 277, (10): 832-6.
[93] We have sought confirmation that terms of the Duke license precluded sublicensing for risk assessment, and those terms were brought to the attention of Athena as a result of action by Allen Roses, the first inventor on the relevant Duke patents.
[94] *About Athena Diagnostics*. See http://www.athenadiagnostics.com/content/about/ [accessed November 14, 2008].
[95] *Welcome To The Smart Genetics Press Room*. See http://www.smartgenetics.com/index.php/News/Latest/news.html [accessed November 14, 2008].
[96] J. Scott Roberts P, L. Adrienne Cupples, Norman R Relkin, Peter J. Whitehouse, and Robert C. Green,. Genetic Risk Assessment for Adult Children of People With Alzheimer's Disease: The Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study. *Journal of Geriatric Psychiatry and Neurology* 2005. 18, (4): 250-55.

One case where patents might have an impact is with EOAD. Based on its coverage policy for APP and PSEN1, CIGNA Healthcare would likely also cover PSEN2 in "Volga German" family members at risk. Other payers do not have clear policies. Other case studies suggest, however, that so long as prices fall in the range of other genetic tests, patent status would affect access little (and in other cases, pricing has not been clearly associated with patent status).

The main effect of patents is that it enables a sole-provider consolidation of testing, which thereby indirectly links access to coverage and reimbursement (because access is then restricted to the contracts that a sole provider has with payers). If Athena has contracts for payment, then patients would pay a co-payment rather than full cost. If not, patients would bear full costs unless Athena covers them through Athena Access (essentially free or very low cost testing) or its Patient Protection Program (with 20 percent payment up front, but no further direct charges to patients, and refunds if third-party payers later reimburse more than 80 percent). The effect of patents is to block other services from filling in if Athena's own programs do not meet patient needs, precluding alternative laboratories from testing due to fear of patent infringement liability.

Consumer Utilization

In the case of AD genetic testing, consumer utilization is complicated. Athena does not publicly report utilization rates for APOE, PSEN1, PSEN2, or APP testing.[97] Since no academic group is in a position to track those tested, this means Athena is in the best position to inform genetic epidemiology of EOAD and genetic risk of late-onset AD, but unlike Myriad Genetics for BRCA testing, it does not contribute much to the scientific or clinical literature.

The recent rise in direct-to-consumer testing and availability of personal genomics and eventually the broader use of sequencing are likely to increase the number of people who undergo testing, although it will often not be specifically about AD. As *Science* reported, APOE status was "the only genetic information that James Watson, the DNA discoverer who recently had his entire genome sequenced, kept secret."[98] Stanley Lapidus adopted this same stance for his "full genome" analysis as part of the Personal Genome Project,[99] as did Steven Pinker in his January 2009 feature in the New York Times Magazine.[100] It appears that at least for upper income white males past middle age with conspicuous public personae, APOE risk status is a special case.

The extent of testing is highly unpredictable, and will likely depend in part on cost and in part on whether treatments are developed that might reasonably delay the onset of the disease. Patenting could affect access both through price and through single-provider status. And any litigation may also indirectly affect access by limiting the number of providers (but as noted, this does not necessarily imply loss of access). A single provider has strong incentives to advertise and expand market to the point of saturation. A single provider also benefits from establishing an informed network of users (both health professionals and those seeking testing) and securing payment agreements to cover testing with insurers and health plans.

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[97] Email correspondence with Michael W. Henry, VP of Business Development of Athena Diagnostics, Inc., 20 November 2007. Athena does report ApoE genotyping utilization to Duke, and presumably reports PSEN1, PSEN2 and APP testing use to the licnesors as part of its royalty agreements.

[98] Couzin J. Once Shunned, Test for Alzheimer's Risk Headed to Market. *Science* 2008. 319, (5866): 1022-33. Watson's stated purpose was to avoid learning this information himself.

[99] Lapidus SN. Interpreting the genome (video). *Technology Review* 2009 (January/February). See http://www.technologyreview.com/Video/?vid=187 [accessed January 21, 2009].

[100] Pinker S. My genome, my self. *New York Times Magazine* 2009 (January 7). See http://www.nytimes.com/2009/01/11/magazine/11Genome-t.html?_r=1&scp=1&sq=pinker&st=cse [accessed January 21, 2009].

Finally, increased consumer utilization may have an impact on long-term care insurance. In research to find the effect of AD on insurance-purchasing behavior, "Almost 17 percent of those who tested positive subsequently changed their long-term care insurance coverage in the year after APOE disclosure, compared with approximately 2 percent of those who tested negative and 4 percent of those who did not receive APOE disclosure."[101] If more people do decide to screen for APOE with the direct-to-consumer companies, long-term care insurance could be affected. The market may stratify according to APOE genotype (with those having an ε4 allele paying more, especially ε4/ε4 homozygotes). This effect, however, is not attributable to patents, but rather to how many people are tested and informed of their AD risk. Any patent effects would be mediated by price or access constraints.

Acknowledgements

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[101] Cathleen D. Zick , J. Scott Roberts, Robert Cook-Deegan, Robert J. Pokorski, and Robert C. Green. Genetic Testing for Alzhimer's Disease and Its Impact on Insurance Purchasing Behavior. *Health Affairs* 2005. 24, (2): 483-90.

Appendix 1

Symptom Checklist in the Evaluation of Dementia

Impaired cognition	**Impaired function**	**Mood, mental phenomena**		**Behaviors**	**Drives**
Memory	Cooking	Depression	Low energy level	Verbal abuse	Poor appetite
Language	Finances	Self-depreciating	Apathetic	Uncooperative	Weight loss
Orientation	Housekeeping	Somatic complaint	Panic	Physically aggressive	Excessive appetite
Writing, reading	Shopping	Crying spells	Labile	"Sundowning"	Hypersexuality
Calculating	Driving	Diurnal variation	Irritable	Demands interaction	Hyposexuality
Recognizing	Hearing and sight	Withdrawn	Euphoria	Outbursts	Sleeping poorly
Attention	Dressing	Anxiety	Delusions	Catastrophic	Excessive sleep
Concentration	Mobility (falls)	Fatigues easily	Illusions	Noisy	Out of bed at night
Planning, organizing	Bathing, grooming	Death, suicidal	Rapid speech	Wandering	
Personality change	Feeding	Disinterested	Hallucinations	Hoarding, rummaging	
Executing	Continence	Anhedonic	Acute confusion	Sexual aggression	
Social rules				Intrusive	

From Santacruz KS, Swagerty DS. Early diagnosis of dementia. *American Family Physician* 2001. 63(4):705.

Appendix 2: Criteria for clinical diagnosis of Alzheimer's disease

I. The criteria for the clinical diagnosis of PROBABLE Alzheimer's disease
dementia established by clinical examination and documented by the Mini-Mental Test, Blessed Dementia Scale, or some similar examination, and confirmed by neuropsychological tests;
deficits in two or more areas of cognition;
progressive worsening of memory and other cognitive functions;
no disturbance of consciousness;
onset between ages 40 and 60, most often after age 65, and
absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

II. The diagnosis of PROBABLE Alzheimer's disease is supposed by:
progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia);
impaired activities of daily living and altered patterns of behavior;
family history of similar disorders, particularly if confirmed neuropathologically; and
laboratory results of:
normal lumbar puncture as evaluated by standard techniques,
normal pattern or nonspecific changes in EEG, such as increased slow-wave activity, and
evidence of cerebral atrophy on CT with progression documented by serial observation.

III. Other clinical features consistent with the diagnosis of PROBABLE Alzheimer's disease, after exclusion of causes of dementia other than Alzheimer's disease, include:
Plateaus in the course of progression of the illness;
Associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical disorders, sexual disorders, nad weight loss;
Other neulogic abnormalities in patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gain disorder;
Seizures in advanced disease; and
CT normal for age.

IV. Features that make the diagnosis of PROBABLE Alzheimer's disease uncertain or unlikely include:
sudden, apoplectic onset;
focal neurologic findings such as hemiparesis, senory loss, visual field deficits, and incoordination early in the course of the illness; and
seizures or gait disturbances at the onset or very early in the course of the illness.

V. Clinical diagnosis of POSSIBLE Alzheimer's disease:
may be made on the basis of dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course;
may be made in the presence of a second systemic or brain disorder in sufficient to produce dementia, which is not considered to the *cause* of the dementia; and
should be used in research studies when a single, gradually progressive severe cognition deficit is identified in the absence of other identifiable cause.

VI. Criteria for diagnosis of DEFINITE Alzheimer's disease are:
the clinical criteria for probable Alzheimer's disease and
histopathologic evidence obtained from a biopsy or autopsy.

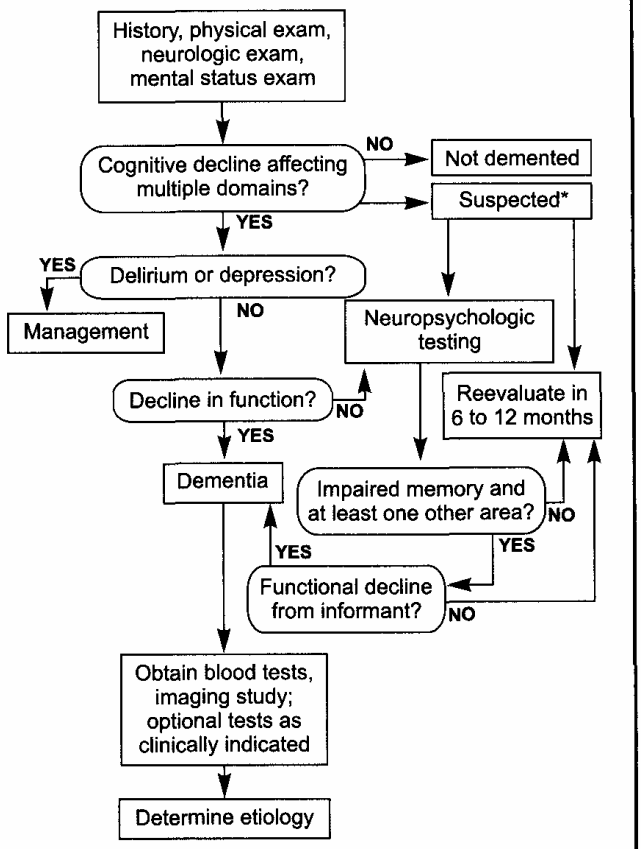
VII. Classification of Alzheimer's disease for research purposes should specific features that may differentiate subtypes of the disorder, such as:

familial occurrence;
onset before age of 65;
presence of trisomy-21; and
coexistence of other relevant conditions such as Parkinson's disease.

From McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's Disease: report of the NINCDS-ADRDA Work Group under the Auspices of Department of Health and Human Services Task Force on Alzheimer's Disease." *Neurology* 1984. 34: 939 – 944.

Appendix 3

FIGURE 3.1 — ALGORITHM FOR DEMENTIA EVALUATION AND DIAGNOSIS



* Worrisome history without obvious mental status deficit or impaired memory only, suggesting mild cognitive impairment (see Chapter 6, *Natural History*).

Modified from: Corey-Bloom J, et al. *Neurology*. 1995;45:211-218.

Reproduced with publisher's permission from Green, RC. *Diagnosis and Management of Alzheimer's Disease and Other Dementias*, 2nd ed. West Islip, NY: Professional Communications, 2005, 24.

Appendix 4

Gene	Institution	Cost**	Type	Patents
APOE	Athena	$475	SISAR	5508167 5716828 6027896
	Smart Genetics*	$399 initially, then $249	SISAR	Sublicensed from Athena*
	Saint Louis University Health Science Center	$365	Targeted Mutation Analysis	
	Graceful Earth, Inc.	$280	NA	
	Sunnybrook Molecular Genetics Laboratory (Canada)	$120 (CD$)***	Targeted Mutation Analysis	
	McGill University Health Center (Canada)	$100	Targeted Mutation Analysis	
APP	Athena		Sequence Analysis	None listed
	Reproductive Genetics Institute	~$5,000	PGD	
PSEN1	Athena	$1,675	Sequence Analysis	6194153
PSEN2	Genesis Genetics Institute	$2,750	PGD	
	Athena		Sequence Analysis	5840540

*Smart Genetics ceased operations October 2008
**All prices in US $ unless otherwise noted
***Price in Canadian dollars, approximately $97 in US dollars at exchange rate of $1 Canadian per $.81 US

SISAR: Serial Invasive Signal Amplification Reaction (a method to detect short, targeted sequence variants)
PGD: Preimplantation Genetic Diagnosis

Compiled by authors.

Appendix 5: Email sent by Dr. Robert Cook-Deegan to Rose Ritts, Director of Duke's Office of Licensing and Ventures, on 10 February 2008 (repeated 18 October 2008)

"Given the potential for confusion here, I think we should resort to formal written questions and answers, so I don't get anything wrong, and so it's all a matter of public record. The federal advisory committee may well want to follow our trail. Feel free to share with your licensee.

I have prepared a list of questions below that will be shared with the Secretary's Advisory Committee on Genetics, Health and Society (SACGHS) on the record. We will share either your reply or we will explain that we got no reply.

The Committee has a task force addressing the impact of patenting and licensing on access to clinical genetic testing, which includes ex officio members from NIH, FDA, CDC, the USPTO and other agencies. You may need to say some information is confidential. That is fine, but being as open as possible would no doubt be welcomed, since this is a federal advisory committee tasked with making recommendations about policy. The more information they have, the more informed their recommendations will be. The responses from Duke and Athena will presumably be interpreted as indicative of how open federal grantees and their licensees are in responding when a researcher requests information pertinent to licensing federally funded inventions, when such research is being carried out on behalf of a federal advisory committee.
Some questions it would be helpful for the task force to answer:

1. Does Athena Diagnostics report the number of ApoE genotyping tests it does each year? [This query was addressed. The answer was 'yes.']

2. Do those data include aggregated (anonymized) results of those tests that might be relevant to gathering data about allele frequencies in populations tested, or other data relevant to public health?

3. Will Duke or Athena share those data with the SACGHS task force?

4. Alan Roses said in his interview that one major reason for licensing exclusively to Athena Diagnostics was to ensure compliance with professional standards emerging at the time, from neurologists' professional organizations and the Stanford group, suggesting ApoE genotyping should only be done in the context of (1) research, or (2) a part of the diagnostic work-up of someone with symptoms of dementia. Was compliance with professional guidelines built into the licensing? How?

5. If so, what diligence provisions were included in the license? How does Duke monitor compliance with such terms?

6. The Duke licenses were negotiated in the mid-1990s. A 2005 National Research Council report recommended licensing of genetic diagnostics to permit verification testing, so that exclusive licensees could not block such verification. Did Duke anticipate such a possibility and include provisions in its license? In the wake of the 2005 recommendation, have Duke and Athena discussed bringing this license into agreement with this NRC recommendation?

7. Now that professional standards are relaxing to use ApoE genotyping for minimal cognitive impairment and for risk profiling without symptoms of dementia, are there mechanisms to adjust the licensing terms to accommodate those changes? Or are the terms of the of the license general enough to permit those changes without renegotiating the license?

8. Smart Genetics announced last week that it will be offering a risk profile service, with a sublicense from Athena. What arrangements has Smart Genetics made with Athena vis a vis the licensing of APOE testing to asymptomatic individuals, if this was stipulated in the Duke-Athena license (see item 4 above)?

9. What is the posture of Athena or Smart Genetics with regard to APOE testing being offered as a stand alone test for AD risk by a company like DNADirect or as part of multi-gene panels by DTC companies such as 23andMe, deCODEme, Navigenics, SeqWright, etc.?

10. If gene panels identify risk markers that are in linkage disequilibrium with ApoE, such as in this article: <http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17474819&ordinalpos=2&itool=EntrezSystem2.PEntrez.Pubmed.Pubmed_ResultsPanel.Pubmed_RVDocSum> is that considered testing for ApoE requiring a license from Duke or sublicense from Athena?"

Dr. Michael Henry of Athena Diagnostics spoke with Dr. Cook-Deegan on February 25, 2008, and several times in October and November 2008 about other matters. Answers to these questions (except the partial answer to question 1) have not been received as of 19 January 2009.

Impact of Gene Patents and Licensing Practices on Access to Genetic Testing for Cystic Fibrosis

Subhashini Chandrasekharan, PhD,[1] Christopher Heaney, BA, [2] Tamara James,[3] Chris Conover, PhD, [4] and Robert Cook-Deegan, MD[5]

Introduction

Approximately 30,000 Americans have cystic fibrosis (CF). It is the most common severe recessive genetic disorder among Caucasians.[6] The disease is caused by mutations in the *CFTR* gene, which encodes a transmembrane chloride ion channel. One mutation, ΔF508, causes approximately 70% of CF cases (~50% of CF patients are homozygous for this mutation) in Caucasian populations. Other mutations are far rarer. Mutation and carrier rates vary by ethnicity. *CFTR* mutations lead to excessively thick and sticky mucus and, as a result, to frequent infections in the lungs. Approximately 90% of CF patients die from obstructive lung disease.[7] As of 2006, half of all CF patients were expected to survive to 36.9 years of age.[8]

Presently there is no cure for CF. Therapies to treat the disease's symptoms include movement and clearing of mucus in the lungs, antibiotic treatment of infections, and diet and pancreatic enzyme replacement to improve nutrition.[9] Lung transplants are an option for adult and pediatric patients, although the procedure's utility for children is unclear.[10] Early detection through newborn screening can reduce CF deaths and alert parents and doctors to the need for disease management.[11] Carrier screening also has implications for reproductive decisions. Hence, the American College of Medical Genetics (ACMG) endorses carrier screening based on testing for *CFTR* mutations and newborn screening that uses DNA testing if high levels of the enzyme immunoreactive trypsinogen (IRT) are detected.[12]

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[1] Center for Public Genomics, Center for Genome Ethics, Law & Policy, Institute for Genome Sciences & Policy, Duke University
[2] Center for Public Genomics, Center for Genome Ethics, Law & Policy, Institute for Genome Sciences & Policy, Duke University
[3] Center for Public Genomics, Center for Genome Ethics, Law & Policy, Institute for Genome Sciences & Policy, Duke University
[4] Center for Health Policy, Terry Sanford Institute of Public Policy, Duke University
[5] Center for Public Genomics, Center for Genome Ethics, Law & Policy, Institute for Genome Sciences & Policy, Duke University
[6] Cutting G. Modifier genetics: cystic fibrosis. *Annual Review of Genomics and Human Genetics* 2005. 6: 237-260.
[7] Welsh MJ et al. Cystic fibrosis. In: Scriver CR et al., eds. *Metabolic and Molecular Bases of Inherited Disease*, 8th ed. New York: McGraw-Hill, 2001, v. 3:5121-88.
American College of Obstetricians and Gynecologists. ACOG committee opinion: update on carrier screening for cystic fibrosis. *Obstetrics and Gynecology* 2005. 6:1465-1468.
[8] Cystic Fibrosis Foundation. *Patient Registry 2006 Annual Report*. Bethesda, Maryland. See http://www.cff.org/UploadedFiles/research/ClinicalResearch/2006%20Patient%20Registry%20Report.pdf [accessed July 21, 2008].
[9] Yankaskas J et al. Cystic fibrosis adult care: consensus conference report. *Chest* 2004. 125: 1S-39S. See http://www.chestjournal.org/cgi/reprint/125/1_suppl/1S [accessed July 21, 2008].
[10] Ventua F et al. Improved results with lung transplantation for cystic fibrosis: a 6-year experience. *Interactive Cardiovascular and Thoracic Surgery* 2004. 3:21-24.
Liou GL et al. Lung transplantation and survival in children with cystic fibrosis. *New England Journal of Medicine* 2007. 357(21): 2143 – 52.
[11] Grosse SD et al. Potential impact of newborn screening for cystic fibrosis on child survival: a systematic review and analysis. *Journal of Pediatrics* 2006. 149(3):362 – 6.
[12] American College of Medical Genetics. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. 2004. See http://www.acmg.net/resources/policies/CF_mutation_8-2004.pdf [accessed April 15, 2007]. American College of Medical Genetics. Immunoreactive Trypsinogen (IRT Elevated). 2006. See http://www.acmg.net/resources/policies/ACT/Visio-IRT(4-17-06).pdf [accessed July 29, 2008].

CF was chosen as a case study specifically because non-exclusive licensing practices for the gene and its mutations allow for a rough comparison to other genes that are exclusively licensed. The University of Michigan, The Hospital for Sick Children in Toronto (HSC), and Johns Hopkins University (JHU) hold patents covering *CFTR* mutations and methods for detecting them. The University of Michigan's patent portfolio includes the important ΔF508 mutation. Currently, 63 labs in the United States test the *CFTR* gene.[13] This is possible in part because the University of Michigan, HSC, and JHU license their respective patents non-exclusively.

A survey of laboratories' prices for CF genetic testing, a review of literature on CF tests' cost effectiveness, and the developing market for testing for CF provide no evidence that patents have significantly hindered access to genetic tests for CF or prevented financially cost-effective screening. Current licensing practices appear to facilitate both academic research and commercialization of products.

Background

Approximately 30,000 Americans have cystic fibrosis (CF), making it the most common severe recessive genetic disorder among Caucasians.[14] Carrier rates vary by ethnicity. According to the American College of Obstetricians and Gynecologists:

- 1/24 Ashkenazi Jews are carriers
- 1/25 Non-Hispanic Caucasians are carriers
- 1/46 Hispanic Americans are carriers
- 1/65 African Americans are carriers
- 1/94 Asian Americans are carriers[15]

The cystic fibrosis transmembrane conductance regulator (*CFTR*) gene encodes a transmembrane chloride ion channel, mutations of which result in defective movements of materials through membranes and excessively thick and sticky mucus throughout the body. CF affects multiple bodily functions including breathing, digestion and reproduction. Symptoms include chronic pulmonary disease, pancreatic exocrine insufficiency, reproductive disorders, and elevated sweat chloride levels. Because CF patients cannot adequately clear their airways of the mucus build-up associated with CF, they wheeze, cough, and suffer from repeated lung infections and other pulmonary pathologies. Approximately 90% of CF patients die because of obstructive lung disease. The thick, sticky mucus found in CF patients also accumulates in the pancreas, thus preventing digestive enzymes from reaching the small intestine and leading to poor digestion, retarded growth, and persistent diarrhea.[16] "Almost all males with CF are infertile due to congenital malformation of the reproductive tract."[17]

According to a consensus panel convened by the Cystic Fibrosis Foundation, "the diagnosis of CF should be based on the presence of one or more characteristic phenotypic features, a history of CF in a sibling, or a positive newborn screening test result plus laboratory evidence of a *CFTR* abnormality as documented by elevated sweat chloride concentration, or identification of mutations in each *CFTR* gene known to

[13] Moskowitz S et al. *CFTR-Related Disorders*. See http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=cf#cf.References [accessed July 21, 2008].
[14] Cutting G. Op. cit.
[15] American College of Obstetricians and Gynecologists. Op. cit.
[16] Cutting G. Op. cit.
Moskowitz S et al. Op. cit.
[17] Welsh et al. Op. cit. at 5121.

cause CF or in vivo demonstration of characteristic abnormalities in ion transport across the nasal epithelium."[18]

Though few children born with cystic fibrosis in the 1950's could expect to survive to attend school, by 2006 half of all CF patients were expected to survive to 36.9 years.[19] 71% of patients are diagnosed within one year of birth; 92% of patients are diagnosed by the time they are ten years old.[20]

Presently there is no cure for CF, although research into normalizing the mutated ΔF508 *CFTR* protein product using small molecule pharmaceuticals continues. Physical therapy and medications can enhance patients' length and quality of life. Current therapies include movement and clearing of mucus in the lungs, pharmaceutical treatment of infections, and diet and pancreatic enzyme replacement to improve nutrition.[21] Lung transplants are an option (but not a cure) for adult patients with damaged lungs.[22] Lung transplants for children are performed, but their clinical utility is unclear.[23] Early detection through newborn screening can reduce deaths due to CF and alert parents and doctors to the need for disease management.[24] Carrier screening also informs prospective parents about their risks of having an affected child. Screening and diagnostic methods, including genetic tests, are discussed in more detail below.

Gene Discovery

Researchers have used a plethora of gene identification methodologies to search for and map the CF gene. The nearly forty-year hunt for the CF gene began in the 1950's. Using linkage analysis, researchers studied whether the CF gene was linked to blood groups but were unsuccessful.[25] A major difficulty in identifying the cystic fibrosis gene was the lack of cytologically detectable chromosome rearrangements or deletions. Such large-scale and DNA changes greatly facilitated the positional cloning of some other human disease genes.

In the 1980's, new technologies were applied to search for the CF gene. Researchers used RFLP's (restriction fragment length polymorphisms, which reflect sequence differences in DNA sites that can be cleaved by restriction enzymes) for linkage analysis to establish the approximate chromosomal location of genes. In 1985, Lap Chee Tsui and colleagues reported that an uncharacterized RFLP marker, DOCRI-917, was linked to the CF gene in 39 families with CF-affected children.[26] It took four years of intensive effort by many laboratories to move from this initial linkage to find the mutated gene. Wainright et al. reported a tight linkage between the CF locus and another chromosome 7 probe, pJ3.11.[27]. Ray White and colleagues independently mapped the gene to chromosome 7.[28] Lap-Chee Tsui and colleagues, using genetic linkage analysis, further localized the DOCRI-917 on human chromosome 7, but additional

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[18] Rosenstein BJ, Cutting GR. The diagnosis of cystic fibrosis: a consensus statement. *Journal of Pediatrics* 1998. 132(4): 589-95, at 590.
[19] Cystic Fibrosis Foundation. Op. cit.
[20] Rosenstein BJ, Cutting GR. Op. cit.
[21] Yankaskas J et al. Op. cit.
[22] Ventua F et al. Op. cit.
[23] Liou GL et al. Op. cit.
[24] Grosse SD et al. Potential impact of newborn screening for cystic fibrosis on child survival: a systematic review and analysis. *Journal of Pediatrics* 2006. 149(3):362 – 6.
[25] Steinberg A et al. Linkage studies with cystic fibrosis of the pancreas. *American Journal of Human Genetics* 1956. 8(3): 162-76.
Steinberg A et al. Sequential test for linkage between cystic fibrosis of the pancreas and the MNS locus. *American Journal of Human Genetics* 1956. 8(3):177-89.
[26] Tsui L et al. Cystic fibrosis locus defined by a genetically linked polymorphic DNA marker. *Science* 1985. 230(4729): 1054-1057.
[27] Wainwright BJ et al. Localization of cystic fibrosis locus to human chromosome 7cen-q22. *Nature* 1985. 318: 384-5.
[28] White R et al. A closely linked genetic marker for cystic fibrosis. *Nature* 1985. 318: 382-384.

studies were needed to determine the exact location of the gene.[29],[30] Zengerling and colleagues in 1987, used human-mouse cell hybrids to narrow the search to a small segment of chromosome 7.[31] Shortly afterward, Estivill et al. reported a potential break-through in disclosing a candidate cDNA for the CF gene,[32] but individuals with CF did not have mutations in that candidate gene. Rommens et al. closed the gap further, mapping two more probes (D78122 and D7S340) to a location between two markers known to flank the CF gene, MET and D7S38.[33] Finally, in 1989, Drs. Tsui and John Riordan and colleagues from The Hospital for Sick Children in Toronto and Dr. Francis Collins and fellow researchers, then at the University of Michigan, identified the gene encoding the cystic fibrosis transmembrane conductance regulator or *CFTR*.[34],[35],[36]

This was the first time a human disease gene had been identified solely on the basis of its chromosomal location, without biochemical clues or the availability of visible cytogenetic rearrangements to guide the search. Although the identification of markers that flanked the gene did not indicate the gene's exact location, the discovery of these markers did provide a starting point for novel DNA-cloning strategies specifically developed to locate the *CFTR* gene. These strategies included chromosome jumping from the flanking markers, cloning of DNA fragments from a defined physical region, a combination of somatic cell hybrid and molecular cloning techniques designed to isolate DNA fragments, chromosome micro-dissection and cloning, and saturation cloning of a large number of DNA markers from the 7q31 region. These techniques were pioneered in the hunt for the CF gene because it was a relatively common disease known to have a single-gene cause, and because the gene's location was approximately known.

The *CFTR* Gene

The *CFTR* gene encodes a protein that regulates the flow of chloride ions through membranes. Mutations in *CFTR* alter protein function, which in turn causes the symptoms of CF in afflicted patients. Because different mutations alter protein function in different ways and to different degrees, there are wide variations in the severity of the clinical syndrome. To date, scientists have found over 1,500 mutations in the *CFTR* gene.[37] ΔF508, a deletion of three nucleotides in DNA causes the protein to lack the amino acid phenylalanine (F) at position 508. That one mutation accounts for 70% of CF chromosomes worldwide, and 90% of CF patients in the United States. Individuals homozygous for ΔF508 (about 50% of patients) have the most severe form of cystic fibrosis.[38]

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[29] Knowlton RG et al. A polymorphic DNA marker linked to cystic fibrosis is located on chromosome 7. *Nature* 1985. 318(6044):380-2

[30] Tsui L et al. Genetic analysis of cystic fibrosis using linked DNA markers. *American Journal of Human Genetics* 1986. 39:720-728.

[31] Zengerling S et al. Mapping of DNA markers linked to the cystic fibrosis locus on the long arm of chromosome 7. *American Journal of Human Genetics* 1987. 40:228-236.

[32] Estivill X et al. A candidate for the cystic fibrosis locus isolated by selection for methylation-free islands. *Nature* 1987. 326:840-845.

[33] Rommens J et al. Identification and regional localization of DNA markers on chromosome 7 for the cloning of the cystic fibrosis gene. *American Journal of Human Genetics* 1988. 43(5):645–663.

[34] Rommens J et al. Identification of the cystic fibrosis gene: chromosome walking and jumping." *Science* 1989. 245(4922): 1059-65.

[35] Riordan JR et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA." *Science* 1989. 245(4922):1066 – 1073

[36] Kerem B et al. Identification of the cystic fibrosis gene: genetic analysis. *Science* 1989. 245(4922):1073–1080.

[37] Cutting G. Op. cit.
Grody W, Cutting GR, Watson MS. The cystic fibrosis mutation 'arms race': when less is more. *Genetics in Medicine* 2007. 9(11):739.

[38] Johansen H et al. Severity of cystic fibrosis in patients homozygous and heterozygous for delta F508 mutation. *Lancet* 1991. 337(8742): 631-4.
Welsh MJ et al. Op. cit.

Differences in the frequency of various mutations among ethnic groups complicate analysis of genetic testing. The Foundation for Blood Research reports: "A different mutation [than ΔF508] is the main cause of cystic fibrosis in Ashkenazi Jews. Half of Ashkenazi Jewish carriers of cystic fibrosis have the W1282X mutation (rarely found in non-Jewish carriers), whereas less than one-third have the [ΔF508] mutation. In other populations, no single mutation accounts for a dominant proportion."[39]

Certain *CFTR* mutations are known to result in a milder clinical syndrome. Some of these spare the pancreatic involvement (and are thus called "pancreatic sufficient"), and even milder mutations may result in just isolated male infertility, due to congenital bilateral absence of the vas deferens. But the severity of lung disease is not entirely predictable on the basis of genotype. As Grody et al. note, "It has been clear since the cloning of the gene that *CFTR* is a very complex genetic element, replete with an ever-growing number of identified mutations and variants and subject to modification in its phenotypic effects by internal polymorphisms and distant gene loci. It has been a major undertaking just to characterize the molecular and functional effects of the more common mutations. When it comes to rare variants… much less is known… The potential for misattribution of effects and for false assumptions is manifest."[40] Thus, there is much to be learned that may affect how tests are licensed or conducted, making the relationship between the intellectual property and clinical data described below subject to continual revision.

Patents

Drs. Francis Collins and colleagues at The University of Michigan, and Drs. Lap-Chee Tsui, John Riordan, and colleagues at The Hospital for Sick Children (HSC) in Toronto, Canada, jointly determined the nucleotide sequence of the *CFTR* gene. Tsui, Collins, and their colleagues were the first to identify the ΔF508 mutation and to then link this mutation with symptomatic CF. According to Dr. Francis Collins, all parties including the CF Foundation and the Howard Hughes Medical Institute,[41] which partially funded their research (along with NIH), agreed that it was important to seek patent protection for the *CFTR* gene and the ΔF508 mutation because of the implications for diagnosis and potential therapies (e.g., gene therapy).[42] Dr. David Ritchie, Senior Technology Licensing Specialist at the University of Michigan's Office of Technology Transfer, recalls that there were extended discussions about whether patents should be applied for in foreign jurisdictions. However, given the possibility of commercial interest in both therapeutic and diagnostic applications, patent applications were eventually filed in the US, the European Patent Office, Japan, Australia, Ireland, and Canada just prior to publication in *Science* on September 8, 1989.[43] This family of US and foreign patent applications covered the sequence of the normal and ΔF508 mutant cDNAs, genetic testing, the normal and mutant *CFTR* proteins, and vectors and cell lines expressing the normal and mutant *CFTR* genes.

The USPTO declared a patent interference after receiving a patent application from Genzyme Corporation, with Richard Gregory as the first inventor. The Genzyme application claimed the sequence of the *CFTR* cDNA, as well as rights to the *CFTR*-containing vector, which overlapped with claims in the Michigan-HSC patent applications. Subsequently, Genzyme argued that Tsui *et al.* failed to provide a written description of the manner and process for their inventions (USPTO interferences 103,882, 103,933, and 104,228). The interference proceedings went on for ten years and were resolved in part in

[39] National Office of Public Health Genomics, CDC, and Foundation for Blood Research. *ACCE Review of CF/Prenatal: Clinical Utility*. 2002. See http://www.cdc.gov/genomics/gtesting/file/print/FBR/CFDisSet.pdf [accessed July 29, 2008 at], at 7.
[40] Grody W et al. The cystic fibrosis mutation 'arms race': when less is more. Op. cit. at 741.
[41] Dr. Francis Collins was a Howard Hughes Medical Institute investigator at the time.
[42] Phone interview with Dr. Francis Collins by Subhashini Chandrasekharan and Christopher Heaney, September 10, 2008.
[43] Priority date of patent application August 22, 1989, versus the acceptance of the manuscript "Identification of the Cystic Fibrosis Gene: Cloning and Characterization of Complementary DNA" on August 18, 1989 (Riordan JR et al. Op. cit.).

Tsui's favor in 2002.[44] The Tsui patents covering both the wild-type *CFTR* cDNA sequence and ΔF508 mutant sequences (US 6,984,487) and the *CFTR* protein sequence (US 6,730,777) were granted. Genzyme was granted patent US 5,876,974, which covers methods for producing the *CFTR* cDNA. In 2006, Genzyme was granted US 7,118,911, which covers vectors for producing the *CFTR* cDNA (See Appendix B). Dr. Ritchie confirmed that the interference was a time consuming and expensive process. However, a licensee that was developing a CF therapeutic funded a majority of the interference costs for the University of Michigan and HSC. Importantly, one of the Tsui patent applications covering genetic testing methods for the ΔF508 mutation was not included in this interference and issued as US Patent No. 5,776,677 on July 7, 1998. Thus, licensing of this particular patent was not affected by the interference.

Licensing

The University of Michigan and HSC choose to license the '677 patent non-exclusively, with University of Michigan managing patent rights in the US and HSC managing patent rights for the rest of the world. Dr. Ritchie indicated that the decision to license non-exclusively was made primarily in keeping with NIH licensing guidelines.[45] According to Dr. Francis Collins, the CF Foundation actively participated in discussions about licensing and provided an important patient advocacy perspective. He recalls that the scientists involved in the discovery of *CFTR* had extensive discussions with technology licensing officers. These highlighted the uncertainty about the number of additional mutations that might be discovered later, the contribution of mutations to disease pathology (ΔF508 accounts for only ~70% of cases worldwide), and which technology platform would be best suited for high-sensitivity carrier detection. The Foundation and scientists were concerned that without complete knowledge of the mutation spectrum, or of future diagnostic testing platforms, an exclusive license to a single provider could impede long-term research and development of diagnostic tools. Dr. Collins stated that the decision made by the University of Michigan and HSC to license the '677 patent non-exclusively grew out of these discussions and concerns.[46] In 1992, the year before the first license for the patent was granted, the NIH's guidelines followed Part 404 of the Code of Federal Regulations, which dealt with licensing of government owned inventions and stated that exclusive licensing is only acceptable if non-exclusive licensing would impede the development of products and not be in the public's best interests.[47] Dr. Ritchie stated that current licensing practices are designed to follow the National Institutes of Health's 1999 Principles and Guidelines, which urge "wide distribution on a nonexclusive basis."[48] Licensing practices are also in accordance with three relevant guidance documents that came out later, the 2004 "Best Practices for Licensing Genomic Inventions" from the National Institutes of Health[49], the 2006 Organisation for Economic Co-Operation and Development's (OECD) "Guidelines for the Licensing of Genetic Inventions,"[50] and the March 2007 "Nine Points" statement later endorsed by the Association of University Technology Managers.[51] Dr. Ritchie shared a template of the non–exclusive license agreement

[44] USPTO Interference Nos 103,882, 103,933 and 104,228 Gregory vs. Tsui, et al. January 4, 2002.
[45] Phone interview with Dr. David Ritchie, Office of Technology Transfer and Corporate Research, University of Michigan, by Subhashini Chandrasekharan and Christopher Heaney, July 3, 2008.
[46] Phone interview with Dr. Francis Collins by Subhashini Chandrasekharan and Christopher Heaney, September 10, 2008.
[47] 37 CFR 404. 1992.
[48] Email from Dr. David Ritchie to Christopher Heaney, July 22, 2008. Email references *Guidance to Campuses on NIH 'Principles and Guidelines for Recipients of NIH Research Grants and Contracts on Obtaining and Disseminating Biomedical Research Resources*. 1999. See http://www.cogr.edu/docs/ResearchTools.htm [accessed July 29, 2008].
[49] Best practices for the licensing of genomic inventions. *Federal Register* 2005 (April 11). 70(68):18413 – 18415. See http://ott.od.nih.gov/pdfs/70FR18413.pdf [accessed November 18, 2008].
[50] Organisation for Economic Co-operation and Development. *Guidelines for the Licensing of Genetic Inventions*. 2006. See http://www.oecd.org/dataoecd/39/38/36198812.pdf [accessed 6 October 2008]. Email from Arlene Yee and Dr. David Ritchie to Yvette Seger, Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) staff.
[51] Association of University Technology Managers. *In the Public Interest: Nine Points to Consider in Licensing University Technology*. March 6, 2007. See http://www.autm.net/aboutTT/Points_to_Consider.pdf [accessed November 18, 2008].

for CF testing "kit" developers (see Appendix A)[52] that enables companies to develop and sell genetic CF testing kits that include the ΔF508 mutation. A second non-exclusive license is also available for companies that wish to develop their own "in-house" CF assays for testing patient samples at a "single site" laboratory.

The initial license fee for kit licenses is $25,000, which has not changed in over 15 years. The annual fees too have remained unchanged since the initial license was granted in 1993. The initial license fee for the in-house commercial test is $15,000.[53] As indicated in section 4.2 of the "Kit" License Agreement (Appendix A), licensees must agree to pay a 6% royalty on their net sales of products. However, as Dr. Ritchie explained, these licenses also take into account "a licensee's need to add additional technologies (i.e., mutations) to a final product by allowing this royalty rate to be reduced by 40%. Thus, the actual royalty percentage generally is agreed to be 3.6%, which does not impede a licensee from entering the marketplace."[54] Revenue obtained from these fees and royalties have gone, in large part, toward covering the costs for international patent protection.

Detailed information about current licensing of the US 5,776,677 patent was initially gathered from The University of Michigan as part of a study of university licensing practices,[55] and then supplemented with their permission. According to Dr. Ritchie, all licenses are non-exclusive. The first license for a therapeutic product was granted in 1993 for gene therapy; the first license for a diagnostic kit was granted in 1996. [56] As of 2008, the University of Michigan and HSC have 21 active licenses covering the ΔF508 mutation. [57] As of 2002, licenses generated between $1 and $10 million in revenue. [58] Currently, 63 American laboratories perform CF testing. The majority of those labs are academic medical centers or hospital-based genetic testing laboratories that use CF test kits developed under these licensees.[59]

Dr. Ritchie recalled only one instance in the past ten years that dealt with potentially infringing activity. A licensee advised the University of Michigan of an unlicensed company advertising CF diagnostic services to consumers. Dr. Ritchie contacted the company and verbally informed it of the '677 patent and asked if the company was interested in taking a license. Because the company in question "dropped it," and presumably ceased offering diagnostic services, the matter was not taken to the level of formal, written communication or legal action. [60]

Licensing practices are especially important because CF tests are essential in newborn screening and population screening for carriers. As Grody et al. state, "Perceiving a large market as CF screening was declared standard of care for the entire population, the first of any commercial consequence in the history of molecular genetics, reagent and equipment vendors quickly developed and began marketing test platforms. Indeed, virtually overnight CF became the flagship test product offered by many established and start-up companies."[61] Currently, the FDA has approved at least two diagnostic "kits" for cystic fibrosis, and other companies are proceeding through the regulatory process for producing and selling diagnostic devices.

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[52] Email from Dr. David Ritchie to Subhashini Chandrasekharan, July 8, 2008.
[53] Phone interview with Dr. David Ritchie, Office of Technology Transfer and Corporate Research, University of Michigan, by Subhashini Chandrasekharan, April 24, 2007, and April 30, 2007.
[54] Email from Dr. David Ritchie to Subhashini Chandrasekharan, July 8, 2008.
[55] Pressman L et al. The licensing of DNA patents by US academic institutions: an empirical survey. *Nature Biotech* 2006. 24(1):31–39.
[56] Email from Dr. David Ritchie to Subhashini Chandrasekharan, July 17, 2008.
[57] Email from Dr. David Ritchie to Subhashini Chandrasekharan, July 17, 2008.
[58] Licensing Revenue Information disclosed with permission of University of Michigan and HSC. Email from Dr. David Ritchie and Lori Pressman to Subhashini Chandrasekharan, October 2007.
[59] *CFTR-Related Disorders*. See www.genetests.org [accessed July 2, 2008].
[60] Phone interview with Dr. David Ritchie by Subhashini Chandrasekharan and Christopher Heaney, July 3, 2008.
[61] Grody W et al. The cystic fibrosis mutation 'arms race': when less is more. Op. cit. at 739.

For example, one FDA-approved diagnostic kit is the Luminex Kit, which includes intellectual property held by HSC and Johns Hopkins.[62] The HSC and Hopkins patents cover mutations other than the ΔF508 mutation (See Appendix B). Two of the four mutations covered by Hopkins patent U.S. Patent No. 5,407,796 are included in the American College of Medical Genetics' (ACMG's) currently recommended list of mutations to test. Laboratories that test for the ΔF508 mutation as well as the mutations patented by HSC and Hopkins presumably must obtain licenses from all three patent-holding institutions (Michigan-HSC, HSC, and Johns Hopkins) since "valuation" of each of the mutations is always a negotiable topic and each institution is best able to defend its valuation philosophy.

Another major player in CF testing is Ambry Genetics, which advertises several proprietary CF tests. The advertisements state that Ambry has "analyzed the complete CF gene for more than 10,000 patient samples."[63] Ambry's most extensive test is CF Amplified, which Ambry promotes as "the most comprehensive CF test available, detecting approximately 99% of mutations in patients of all ethnicities."[64] Unlike Luminex's Tag-It kit that tests for 39 mutations and 4 variants, the CF Amplified test sequences "the full *CFTR* gene as well as surrounding critical introns" and includes rearrangement testing.[65] Presumably Ambry had to license the same patents as Luminex. Johns Hopkins offers non-exclusive licenses to its patent to kit developers, judging from the fact that both Ambry and Luminex offer tests that cover mutations claimed in the Hopkins patent.[66]

Other manufacturers are preparing FDA approved diagnostic tests to compete in the CF testing and screening markets, further increasing the probable number of licensees of the University of Michigan, HSC, and Hopkins patents. In spring 2007, Nanogen announced that "it has submitted the 510(K) [premarket notification] to FDA for its Cystic Fibrosis Kit and NanoChip 400 microarray system."[67] The kit tests for the ACMG-recommended 23 mutations.[68] In January 2007, Third Wave also submitted a 510(K) form for its CF test, which is "intended to provide information to determine CF carrier status in adults, as an aid in newborn screening and in confirmatory diagnostic testing in newborns and children."[69] The FDA has since approved the test for diagnostic use. [70] On June 9, 2008, Third Wave and Hologic announced Hologic's purchase of Third Wave for $580 million cash. In a conference call, Hologic's Chairman said that one reason for the acquisition was that the CF test "will be a natural complement to our full-term preterm birth product which is sold by our OB/Gyn sales force."[71] Although genetic tests for Human Papilloma Virus were described as a more important reason for the acquisition than the CF testing platform, it seems that Third Wave's ability to license and use intellectual property including CF mutations was an asset.

More recently, several nonprofit institutions that fund for-profits doing either CF research or drug development for developing world chronic conditions such as diarrhea have approached the University of Michigan and HSC about licensing rights in order to develop and use screening assays for the discovery

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[62] Luminex licenses cystic fibrosis gene patent from Johns Hopkins. *BIOTECH Patent News* 2007 (March). See http://www.entrepreneur.com/tradejournals/article/164609425.html [accessed July 29, 2008].
[63] Ambry Genetics. *Cystic Fibrosis*. See http://www.ambrygen.com/ts/ts_cf.aspx [accessed July 29, 2008].
[64] Ibid.
[65] Ibid.
[66] JHU confirmed that its cystic fibrosis patent is licensed non-exclusively for commercial *CFTR* testing. Email from Leigh A. Penfield, Associate Director, Johns Hopkins Technology Transfer, Johns Hopkins University to Christopher Heaney, August 4, 2008.
[67] *Nanogen Submits 510 for Cystic Fibrosis Genetic Assay and NanoChip 400 System*. Business Wire 2007 (April 17). See http://findarticles.com/p/articles/mi_m0EIN/is_2007_April_17/ai_n27203429 [accessed July 29, 2008].
[68] Ibid.
[69] *Third Wave Submits 510(k) to FDA for InPlex™ Cystic Fibrosis Molecular Test*. See http://www.medicalnewstoday.com/articles/60125.php [accessed July 29, 2008].
[70] *Transcript of a Conference Call Held by Hologic, Inc on June 9, 2008. Exhibit 99.1.* See http://www.secinfo.com/d14D5a.t3vh8.d.htm [accessed November 18, 2008].
[71] Ibid.

of small molecule drugs useful for treating patients with the ΔF508 mutation, or for drug development to treat diarrhea (which also involves the *CFTR* protein). Because much of the original research leading to the discovery of the *CFTR* gene was funded by two nonprofit organizations, the Cystic Fibrosis Foundation and the Howard Hughes Medical Institute, specific licenses were developed for both The Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT), and for One World Health, whose missions, in part, are to ensure broad access to medical technologies. This is a new type of "research" license for the use of *CFTR*-related patents and grants both CFFT and One World Health rights to sub-license appropriate patents covering research tools such as the *CFTR* gene sequence and cell lines containing either the native gene or ΔF508 mutation to for-profit companies conducting research. Applicable research includes screening small-molecule libraries to produce therapeutic CF or anti-diarrheal drugs.[72] The parties developed this promising licensing strategy to reduce transaction costs and facilitate research on new therapeutic drugs for treating these devastating conditions. Success could be especially beneficial in resource-poor regions of the world where diarrheal diseases are endemic. According to Dr. Ritchie, the University of Michigan and HSC will receive a small sublicense fee whenever a sublicense is granted but will not receive any royalties from sales of the final drug products. In other words, this license does not give the University of Michigan or HSC any "reach through" rights since they have only licensed access to research tools.

The table below shows the test panel currently recommended by the ACMG with annotations describing how the relevant intellectual property is distributed.[73] The clinical importance of the chart is discussed below. The mutation list below is a current standard of care that the test market aims to meet or exceed.

Recommended Core Mutation Panel for Cystic Fibrosis Carrier Screening in the General Population

Standard Mutation Panel	R560T, ΔF508[a], R553X[b], R1162X, ΔI507, 2184delA, G542X, G551D[b], W1282X, N1303K, 621+1GΔT, R117H, 1717-1GΔA, A455E, G85E, R334W, R347P, 711+1GΔT, 1898+1GΔA, 3849+10kbCΔT, 2789+5GΔA, 3659delC, 3120+1GΔA
Additional Testable Mutations	I506V,[c] I507V,[c] F508C[c], 5T/7T/9T[d]

[a]Univ of Michigan/HSC Patent No. U.S. 5,776,677
[b]Johns Hopkins University U.S. Patent No. 5,407,796
[c]Benign variants. This test distinguishes between a CF mutation and these benign variants. I506V, I507V, and F508C are performed only as reflex tests for unexpected homozygosity for ΔF508 and/or ΔI507.
[d]5T in *cis* can modify R117H phenotype or alone can contribute to congenital bilateral absence of vas deferens (CBAVD); 5T analysis is performed only as a reflex test for R117H positives.

Testing Practices for CF

Newborn Screening

Early detection of CF is important to improve disease management. Farrell et al. found that "early diagnosis of CF through neonatal screening combined with aggressive nutritional therapy can result in

[72] Phone interview with Dr. David Ritchie by Subhashini Chandrasekharan, April 24, 2007, and April 30, 2007.
[73] American College of Medical Genetics. *Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel*. 2004. See http://www.acmg.net/resources/policies/CF_mutation_8-2004.pdf [accessed April 15, 2007].

significantly enhanced long-term nutritional status."[74] In 2005 the CDC released recommendations on newborn screening for cystic fibrosis and indicated several benefits from newborn screening both for disease management and improving quality of life.[75] In a review in 2006, Grosse et al. found that newborn screening can reduce childhood mortality from CF.[76]

In May 2006, the ACMG published a report from its Newborn Screening Expert Group, which included academic experts, government officials, professional medical organization representatives, and patient advocates. The report recommended that newborns undergo testing for CF and twenty-eight other conditions in state newborn screening programs. The report considered the model of initial screening for unusually high levels of the enzyme immunoreactive trypsinogen (IRT), followed by a second IRT test and then a DNA test if necessary.[77] In a letter to DHHS Secretary Leavitt, the Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Children (SACHDGDC) "strongly and unanimously recommends that the Secretary initiate appropriate action to facilitate adoption of the ACMG recommended screening panel [which includes CF] by every State newborn screening program."[78]

The ACMG's guidelines for newborn screening call for testing of levels of the IRT enzyme which if unusually high are indicative of CF, followed by a repeat IRT test, or DNA testing, and a sweat test for elevated chloride levels that will confirm indicate a diagnosis of CF. In the screening protocol either a positive repeat of the IRT test or a positive DNA test for one of 23 mutations leads to a sweat chloride test for confirmation.[79]

Although comprehensive data about states' testing practices are not available, some information is available from the National Newborn Screening Information System. According to their 2008 report on cystic fibrosis screening, at least 28 states include cystic fibrosis in their newborn screening programs. All of those states test IRT in the first round of testing; 17 of them use a DNA test if IRT levels indicate a second round of testing is required. At least 7 of those DNA tests are based on testing for 38 to 43 mutations.[80] The Cystic Fibrosis Foundation lists all states but Nevada, Utah, Texas, Tennessee, North Carolina, Pennsylvania, and Connecticut as screening all newborns for CF, and except for North Carolina all of the other state governments are considering or preparing comprehensive state programs.[81] Given the spate of recommendations on CF testing, this situation seems likely to continue evolving rapidly.

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[74] Farrell PM et al. Early diagnosis of cystic fibrosis through neonatal screening prevents severe malnutrition and improves long-term growth. *Pediatrics* 2001. 107(1):1-13, at 2. See http://pediatrics.aappublications.org/cgi/content/abstract/107/1/1 [accessed July 28, 2008].

[75] Neff MJ. CDC releases recommendations for state newborn screening programs for cystic fibrosis. *American Family Physician* 2005 (April 15). See http://www.aafp.org/afp/20050415/practice.html [accessed January 22, 2009].
Grosse SD, Boyle CA, Botkin JR, Comeau AM, Kharrazi M, Rosenfeld M, Wilfond BS. Newborn screening for cystic fibrosis: evaluation of benefits and risks and recommendations for state newborn screening programs. *MMWR Recommendations and Reports* 2004 (October 15). 53(RR-13):1-36.

[76] Grosse SD et al. Potential impact of newborn screening for cystic fibrosis on child survival: a systematic review and analysis. *Journal of Pediatrics* 2006. 149(3):362 – 6.

[77] Watson MS et al. American College of Medical Genetics' Newborn Screening Expert Group. *Newborn Screening: Toward a Uniform Screening Panel and System*. See http://www.acmg.net/resources/policies/NBS/NBS-sections.htm [accessed January 13, 2009].

[78] Howell RR. Chairperson, Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children. Letter to Secretary Michael Leavitt. Undated. See ftp://ftp.hrsa.gov/mchb/genetics/correspondence/ACHDGDNCletterstoSecretary.pdf [accessed July 8, 2008].

[79] American College of Medical Genetics. Immunoreactive Trypsinogen (IRT Elevated). 2006. See http://www.acmg.net/resources/policies/ACT/Visio-IRT(4-17-06).pdf [accessed July 29, 2008].

[80] National Newborn Screening Information System Database. *Cystic Fibrosis (CF) – Laboratory Testing in 2008*. See http://www2.uthscsa.edu/nnsis/ [accessed on July 22, 2008].

[81] Cystic Fibrosis Foundation. *Newborn Screening for Cystic Fibrosis*. http://www.cff.org/GetInvolved/Advocate/WhyAdvocate/NewbornScreening/#What_states_do_newborn_screening_for_CF? [accessed July 29, 2008].

Carrier Testing

ACMG Guidelines and Update (2001 and 2004). Current guidelines for genetic testing for CF mutation carriers were developed in response to a 1997 National Institutes of Health (NIH) report, which stated, "Genetic testing for CF should be offered to adults with a positive family history of CF, to partners of people with CF, to couples currently planning a pregnancy, and to couples seeking prenatal care."[82] In 2001, the ACMG published recommendations on cystic fibrosis carrier screening. In 2001,The American College of Obstetricians and Gynecologists (ACOG), the ACMG and the NIH Steering Committee incorporated those recommendations into a set of clinical guidelines and educational material sent to clinicians. The ACMG called for screening to be offered to a more specific population of "non-Jewish Caucasians and Ashkenazi Jews."[83] The ACMG recommended using a pan-ethnic *CFTR* panel of twenty-five *CFTR* mutations, all of which occurred in at least 0.1% in the general U.S. population. In 2004, additional data on the rarity of two mutations persuaded the ACMG to remove them from the panel.[84] The updated panel will detect mutations in 94% of Ashkenazi Jewish carriers, 88% of non-Hispanic Caucasian carriers, 72% of Hispanic Americans, 65% of African Americans, and 49% of Asian Americans.[85] As of 2006, the ACMG still endorses the updated panel of twenty-three mutations.[86]

In its 2001 recommendations, the ACMG advised providers that they should not routinely offer testing for additional mutations. However, providers could disclose the existence of such extended panels to inquiring patients and use such panels on an *ad hoc* basis. Couples in which one or both partners are positive, those with family history of CF, or males found to have mutations associated with infertility require further genetic counseling or additional testing strategies. In those cases, the ACMG encouraged clinicians to direct patients to visit genetics centers. Also, "patients diagnosed with CF… should be referred [directly] to a genetics center for appropriate testing and counseling."[87] While acknowledging that "testing will often occur in the prenatal setting," the ACMG urged "preconception testing… whenever possible."[88]

The ACMG also recommended that providers make carrier testing available to couples whose ethnic background reduces their risk for CF but also might have CF mutations of lower frequency in existing databases, because current data are based primarily on Caucasian population studies. The ACMG specifically indicated that "Asian-Americans and Native-Americans without significant Caucasian admixture should be informed of the rarity of the disease and the very low yield of the test in their respective populations."[89] Likewise, the ACMG recommend that "testing should be made available [but not offered] to African-Americans, recognizing that only about 50% of at-risk couples will be detected."[90] The corollary is that CF screening and testing in populations outside Europe and North American might require better data about *CFTR* mutations in non-Caucasian populations.

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[82] National Institutes of Health Consensus Development Conference Statement on Genetic Testing for Cystic Fibrosis. Genetic testing for cystic fibrosis. *Archives of Internal Medicine* 1999. 159:1529 –1539, at 1529.
[83] Grody W et al. Laboratory standards and guidelines for population-based cystic fibrosis carrier screening. *Genetics in Medicine* 2001. 3(2):149–154, at 150.
[84] Ibid., 150 – 151.
Watson MS et al. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. *Genetics in Medicine* 2004. 6(5):387–391. See http://www.eurogentest.org/cfnetwork/files/public/doc/artikels/Cystic%20fibrosis%20population%20carrier%20screening%202004.pdf [accessed July 8, 2008].
[85] American College of Obstetricians and Gynecologists. Op. cit.
[86] Amos J et al. American College of Medical Genetics. *Technical Standards and Guidelines for CFTR Mutation Testing 2006 Edition*. See http://www.acmg.net/Pages/ACMG_Activities/stds-2002/cf.htm [accessed July 22, 2008].
[87] Grody W et al. Laboratory standards and guidelines for population-based cystic fibrosis carrier screening. Op. cit. at 149.
[88] Ibid., 150.
[89] Ibid.
[90] Ibid.

For Ashkenazi Jewish and Caucasian couples of Northern European descent, the ACMG recommended couple-based testing. In couple-based testing, or concurrent testing, the lab collects and tests a sample from each partner and fully discloses the results to each partner. In populations in which individuals are less likely to be CF mutation carriers, or in cases where testing both partners simultaneously is difficult, providers can consider testing one person and then only testing the second if the first has a mutation (sequential testing). "In general, the individual provider or center should choose whichever method they feel most appropriate or practical."[91]

ACOG Screening Recommendations (2005). In December 2005, the American College of Obstetricians and Gynecologists (ACOG) updated its recommendations. ACOG expressed concern that "most obstetricians are offering [CF] carrier screening to their pregnant patients… [but] significantly fewer obstetrician-gynecologists offer nonpregnant patients [CF] carrier screening unless a patient requests the information or has a family history."[92] Noting how "difficult [it] is to assign a single ethnicity" to a patient, the ACOG nonetheless recommended increasing the scope of carrier testing. "It is reasonable to offer CF Carrier screening to all couples regardless of race or ethnicity as an alternative to selective screening."[93] This recommendation comes with the caveat that providers should be clear about the impact of ethnicity on carrier risk and test sensitivity. Further, "Cystic fibrosis carrier screening should be offered before conception or early in pregnancy when both partners are of Caucasian, European, or Ashkenazi Jewish ethnicity. Patients may elect to use either sequential or concurrent carrier screening; the latter option may be preferred if there are time constraints for decisions regarding prenatal diagnostic testing or termination of the affected pregnancy. Individuals who have a reproductive partner with cystic fibrosis or congenital bilateral absence of the vas deferens may benefit from screening with an expanded panel of mutations or, in some cases, a complete analysis of the *CFTR* gene by sequencing." [94]

Prenatal Diagnostic Testing

ACMG Guidelines and Update (2002 and 2006). The 2006 updated ACMG Standards and Guidelines for *CFTR* Mutation Testing state that prenatal *CFTR* mutation testing is indicated if there is a "positive family history," "a CF mutation in both partners," or an "echogenic bowel in fetus during second trimester."[95] The test can be performed using "both direct and cultured amniotic fluid cells (AFC) and chorionic villus samples."[96] The parents should both be tested before the fetus. Because of the results' significance, "The laboratory must… provide referring professionals with appropriate instructions. Laboratories must have a prenatal follow-up program in place to verify diagnostic accuracy."[97] The 2006 recommendations also note that prenatal diagnostic testing typically requires a larger mutation panel than carrier screening. "A larger number of mutations (>23) is generally appropriate for diagnostic testing in order to achieve the highest possible clinical sensitivity, but care should be taken to ensure that the penetrance of tested mutations is known."[98] Finally, "A positive prenatal diagnostic test result is considered to be definitive rather than predictive since the penetrances for these 23 mutations are known to be high."[99]

[91] Ibid.
[92] American College of Obstetricians and Gynecologists. Op. cit. at 1465.
[93] Ibid., 1466.
[94] Ibid., 1466 – 1467.
[95] Amos J. et al. Op. cit.
[96] Ibid.
[97] Ibid.
[98] Ibid.
[99] Ibid.

Preimplantation Genetic Diagnosis

ACMG Guidelines and Update (2002 and 2006). In October 2002, the ACMG Laboratory Quality Assurance Committee released *Standards and Guidelines for CFTR Mutation Testing,*[100] intended as an educational resource for clinical laboratory geneticists. Preimplantation testing is indicated for CF in the 2002 guidelines and the 2006 updated version.[101] Despite lingering technical concerns about performing DNA assays using a relatively small sample, preimplantation diagnosis for CF was first reported in 1992 and has continued to occur.[102]

Diagnostic Testing

The updated 2006 ACMG Standards and Guidelines for *CFTR* Mutation Testing note that CF mutation testing is indicated for diagnostic purposes when there is a possible or definite clinical diagnosis of CF, when an infant presents with meconium ileus (excessively thick bowel movements immediately after birth), or when a male presents with congenital bilateral absence of the vas deferens. Because this mutation testing is done for diagnostic rather than screening purposes, laboratories may need to expand the mutation panel beyond the core twenty-three mutations used in carrier testing.[103] The ACOG adds that while gene sequencing "is not appropriate for routine carrier screening," it is acceptable "for patients with cystic fibrosis, a family history of cystic fibrosis, infertile males with congenital bilateral absence of the vas deferens, or a positive newborn screening test result when mutation testing using an expanded panel of mutations has a negative result."[104]

More recently, Grody and others involved in the ACMG statements have expressed personal concern about the use of rapidly increasing number of mutations and gene sequencing options. This trend is not necessarily in patients' best interest because of limited knowledge about the CF's genetic basis. "[A] large number of mutations selected for expanded panels… were chosen because the testing laboratory happened to stumble upon one, or read about it in a research or clinical paper whose researcher or clinician author had likewise stumbled upon it. In other words, these are very rare events, arbitrary almost to the point of randomness."[105] Given the frequency with which guidelines have been released and debated, medical consensus and guidelines for diagnostic testing as well as other testing forms seem likely to evolve.

Cost of CF Genetic Tests

Prices for CF genetic tests were obtained from twelve laboratories. All tests refer to the *CFTR* gene. Prices are those charged to insurance companies, except for Quest Diagnostics and Johns Hopkins University DNA Diagnostic Laboratory, which chose to provide out-of-pocket costs for patients who do not use insurance to cover the test. Sequencing prices are discussed below. The cost of mutation analysis is discussed in "Cost Effectiveness of CF Screening."

Non-Profit Laboratories

ARUP Laboratories[106]

[100] Richards CR et al. Standards and guidelines for *CFTR* mutation testing. *Genetics in Medicine* 2002. 4(5):379-391.
[101] Amos J et al. Op. cit.
[102] Keymolen K et al. Clinical outcome of preimplantation genetic diagnosis for cystic fibrosis: the Brussels' experience. *European Journal of Human Genetics* 2007. 15:752 – 758.
[103] Amos J. et al. Op. cit.
[104] American College of Obstetricians and Gynecologists. Op. cit. at 1466.
[105] Grody et al. The cystic fibrosis mutation 'arms race': when less is more. Op. cit. at 741.
[106] ARUP Laboratories, via phone, Feburary 11, 2008. ARUP Laboratories is a non-profit enterprise owned by the University of Utah.

- Full gene sequencing: $1,200
- Gene deletion/duplication analysis: $525

Baylor College of Medicine[107]:

- Full gene sequencing: $1800
- Full gene sequencing (prenatal): $1500

Boston University Center for Human Genetics[108]

- 40 mutation panel (including ACMG recommended 23 mutations): $195
- 100 mutation panel (including ACMG recommended 23 mutations): $295

City of Hope Molecular Diagnostic Laboratory[109]

- Full gene sequencing: $2,586.96

Harvard[110]

- Gene sequencing: $1,650
- Gene sequencing (prenatal testing): $2,600 ($1,650 + $950 for maternal cell contamination testing)

Johns Hopkins University DNA Diagnostic Laboratory[111]

- Full gene sequencing: $2,298

Mayo Clinic Molecular Genetics Laboratory[112]

- Full gene sequencing: $1,500

For-Profit Laboratories

Ambry Genetics[113]

- CF Amplified (Full gene sequencing and deletion/duplication testing): $3,358
- CF Amplified (Full gene sequencing without deletion/duplication testing): $2,762
- 508 First (ΔF508 mutations only): $84

CytoGenX[114]

- 39 mutation panel (23 ACMG recommended mutations and 16 others): $2,100

Genzyme Genetics[115]

- Full gene sequencing: $2,004

Quest Diagnostics[116]

- Gene deletion/duplication analysis: $420.00
- Full gene sequencing: $2,485.00
- Screen for ACMG 23 recommended mutations: $595.00

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[107] Baylor College of Medicine. Medical Genetics Laboratories. *Prices and CPT Codes.* July 25, 2008. See http://www.bcm.edu/geneticlabs/pricesandCPTcodes.pdf [accessed July 28, 2008].

[108] Boston University Center for Human Genetics. *Direct DNA Tests.* June 9, 2008. See http://www.bumc.bu.edu/Dept/Content.aspx?DepartmentID=118&PageID=2194 [accessed July 28, 2008].
Alison Nicoletti. Boston University Center for Human Genetics, via phone July 28, 2008.

[109] Email from Dr. Juan-Sebastian Saldivar, City of Hope Clinical Molecular Diagnostic Laboratory, to Christopher Heaney, July 8, 2008. Prices are effective as of August 1, 2008.

[110] Harvard Medical School – Partners Healthcare Center for Genetics and Genomics. *CFTR Sequencing Assay for Cystic Fibrosis and CBAVD*. See http://www.hpcgg.org/LMM/comment/Cystic%20Fibrosis%20Info%20Sheet.jsp?name=LMM&subname=genetictests [accessed July 28, 2008].
Samantha Baxter, Harvard Medical School – Partners Healthcare Center for Genetics and Genomics, via phone, July 28, 2008.

[111] Johns Hopkins University DNA Diagnostic Laboratory, via phone February 11, 2008, and 10 September, 2008.

[112] Mayo Clinic Molecular Genetics Laboratory, via phone February 11, 2008.

[113] Lori Ross, Ambry Genetics, via phone, July 28, 2008.
Ambry Genetics. *Cystic Fibrosis Testing.* See http://www.ambrygen.com/ts/ts_cf.aspx [accessed July 28, 2008].

[114] Dr. Dunn, CytoGenX, via phone, July 28, 2008.
CytoGenX. *Cystic Fibrosis Collection*. See http://www.cytogenx.com/cystic_fibrosis.asp [accessed July 28, 2008].

[115] Genzyme Genetics, via phone, February 11, 2008.

[116] Email from Sam Garetano, Quest Diagnostics, to Christopher Heaney, July 28, 2008.

- DNA Analysis, Fetus (23 ACMG recommended mutations and 8 others): $660 ($335 + $325 for maternal cell contamination testing)

Prevention Genetics[117]

- Full gene sequencing: $1,290

Laboratory	Amplicons*	Gene sequencing price	Cost per amplicon**
ARUP Laboratories	30	$1,200	$40
Baylor College of Medicine	29	$1,800	$62.07
City of Hope Molecular Diagnostic Laboratory	30	$2,586.96	$86.23
Harvard	29	$1,650	$56.90
Johns Hopkins University DNA Diagnostic Laboratory	31	$2,298	$74.13
Mayo Clinic	N/A***	$1,500	
Ambry Genetics	50	$2,762	$55.24
Prevention Genetics	29	$1,290	$44.48
Quest Diagnostics	32	$2,485	$77.66

* Number of nucleic acid sequences targeted for amplification (according to number of times CPT billing code 83898 is used)
**Gene sequencing price divided by number of times CPT 83898 billed
***CPT code 83898 is not listed on the Mayo Clinic Molecular Genetics Laboratory's technical specifications (See http://216.245.161.151/TestView.aspx?testID=12286 [accessed January 14, 2009]).

Comparing the prices of CF genetic testing is difficult. First, none of the labs surveyed offered identical mutation panels. Second, although CPT codes provide some standardization, at least for full sequencing analysis tests, they do not necessarily indicate that techniques and procedures are identical. The contribution of different techniques and procedures (usually billed under different CPT codes for each test) is not always known. Even after comparing pricing based on CPT codes, which are not always consistent among labs, the labs surveyed have different overhead costs and ways of accounting for such costs.

With those caveats noted, the price range for *CFTR* gene sequencing among non-profit institutions ($40 to $86.23 for each sequence targeted for amplification or amplicon) is higher than the per amplicon price range for non-profits' sequencing the colorectal cancer gene *APC* ($28.57 to $ 39.88). However the price per amplicon for *CFTR* sequencing is comparable to that of non-profit labs' price ($30.00 to $77.44/amplicon) for sequencing *MLH1*, *MSH2*, and *MSH6* genes.[118] This comparison between the prices of sequencing different genes is only an approximation. The fact that Baylor College of Medicine, City of Hope, and Harvard perform both colorectal cancer and CF testing and that colorectal cancer genes are also licensed non-exclusively by non-profits makes the comparison worth noting. Specifically, the same labs performing these two tests presumably incur similar overhead costs. Also, because JHU has patents on certain *CFTR* mutations as well as *APC* and *MSH2*, there is at least one common actor involved in licensing intellectual property associated with colorectal cancer testing and CF testing. Sequencing the colorectal cancer genes and *CFTR*, on a price per amplicon basis, is comparable to sequencing the *BRCA1* and *BRCA2* genes, for which the sole provider Myriad Genetics charges $38.05

[117] Prevention Genetics, via phone February 11, 2008.
[118] Cook-Deegan R et al. *Impact of Gene Patents on Access to Genetic Testing for Inherited Susceptibility to Cancer: Comparing Breast and Ovarian Cancers to Colon Cancers*. Peer-reviewed case study submitted to the Secretary's Advisory Committee on Genetics, Health, and Society, 2008.

per amplicon.[119] That is, CF and colorectal cancer genes cost slightly more to PCR-amplify and then sequence at non-profit academic institutions than *BRCA1* and *BRCA2* genes at Myriad Genetics, the single for-profit provider.[120]

Cost Effectiveness of CF Screening Tests

Cost effectiveness of CF testing is a concern for payers and consumers. If testing is cost effective at a certain price and CF tests that analyze patented mutations are available at or below that price, then CF licensing practices at least do not preclude cost effective testing. As the CF testing market continues to develop, licensing practices may also have to evolve, although changes are contingent on current licensing terms until they expire or are renegotiated.

The first step in analyzing cost effectiveness for CF testing is to determine the financial cost of treating the disease. According to the 1997 NIH Consensus Development Conference Report:

> Using data from 1989, the Office of Technology Assessment estimated in 1992 that the annual treatment costs for CF were approximately $10,000 per year per individual. Current estimates are over $40,000 per year in direct medical costs and $9,000 per year in other related costs. Using a 3% annual inflation rate, an estimated total of $800,000 [in 1996 dollars] can be assumed for each CF birth. [121]

Other studies give varying U.S. estimates of the lifetime financial cost of medical care for a CF patient, ranging from $220,000 to $844,000 (1996 dollars). [122]

The next step is to compare that cost to the cost of various tests. Evidence is available for carrier and prenatal screening and, to a much lesser extent, preimplantation genetic diagnosis (PGD).

Carrier and Prenatal Screening

When analyzing cost effectiveness of CF carrier testing, costs beyond providing the actual test include obtaining informed consent, providing educational and counseling services, and other administrative costs. To assess the cost effectiveness of universal prenatal screening, a number of additional factors must be considered including the number of participants, the population rate of CF carriers, the number of couples with an affected fetus who would choose to terminate the pregnancy, the number of children couples may desire, and the testing method used.

In one study by Asch et al., the costs and clinical outcomes of sixteen strategies for CF carrier screening were evaluated using a model of 500,000 pregnancies in a population of only European descent.[123] Asch et al. found that a sequential screening approach minimized the cost of averting CF births. With this approach, the first partner was screened with a test for the ΔF508 mutation and five other common mutations known at the time. This panel, covering fewer mutations than the ACMG now recommends, was modeled as identifying 85% of carriers in the population. If the first partner tested positive, the

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[119] Ibid.
[120] Ibid.
[121] NIH Consensus Development Conference Statement. Genetic testing for cystic fibrosis. *Archives of Internal Medicine* 1997. 159: 1529-1539.
[122] Haddow JE et al. *Population-Based Prenatal Screening for Cystic Fibrosis via Carrier Testing: ACCE Review Clinical Utility.* Scarborough, ME: Foundation for Blood Research. June 2002:4-61. See http://www.cdc.gov/genomics/gtesting/file/print/FBR/CFClilUti.pdf [accessed August 17, 2007].
[123] Asch DA et al. Carrier screening for cystic fibrosis: costs and clinical outcomes. *Medical Decision Making* 1998. 18:202–212. Model cohort ethnicity according to email from David Asch to Christopher Heaney, July 24, 2008.

second partner was screened with an expanded test of another twenty to thirty mutations estimated to identify 90% of carriers. In the end, such an approach identified 75% of anticipated CF births at a cost of $367,000 (1995 dollars) per averted birth. However, this estimate only holds true if "all couples who identify a fetus as high risk choose to terminate the pregnancy. If only half of couples will proceed to abortion under these circumstances, the cost per CF birth avoided would increase to $734,000 per CF birth avoided."[124] Also, "for couples planning two pregnancies, the cost effectiveness ratios for CF screening are roughly half those of the single-pregnancy case," meaning that the cost per CF birth avoided is roughly halved.[125]

In 2007, Wei et al. analyzed data collected between 2001 and 2005 on more than 6,000 women screened for CF carrier status at the Henry Ford Health System in Detroit, Michigan.[126] Wei's study complements Asch's work by providing a more ethnically diverse cohort that was 45% African American, 35% non-Jewish Caucasian, 10% Arab American, 5% Hispanic, 5% Asian and 1% Ashkenazi Jewish. The study excluded "patients with a family history of CF, a known/possible diagnosis of CF, males with infertility, and fetuses with echogenic bowels."[127] 98.5% of her cohort received sequential screening that included the 25 ACMG recommended mutations in addition to another seven to seventeen mutations. Over four years and at a total cost of $334,000 (2005 dollars),[128] testing identified six positive couples and one (subsequently aborted) fetus with mutations from both parents. Comparing this to a lifetime care cost of $1 million per CF patient, which is within the range indicated by other studies, Wei et al. concluded that population-based carrier screening is cost-effective even when it includes a high number of non-Caucasians. Wei's cost per CF birth averted is less than Asch et al.'s best-case scenario of $367,000 per averted birth even before the two studies are normalized to same-year dollars.

Rowley et al. used data from a trial of CF carrier screening to analyze cost effectiveness.[129] 4,879 women were tested, 124 of whom were CF carriers but none of whom had pregnancies diagnosed with CF through prenatal testing. Costs (given below) were based on surveys, data from the US Congress's Office of Technology Assessment, and personal communications. Based on those figures and the behaviors observed in the carrier screening trial, Rowley et al. determined the cost effectiveness of screening a hypothetical cohort of a 100,000 women. In their model, at a total cost of $11.1 million, 8.4 CF affected pregnancies were terminated. This translated to $1.322 million to $1.396 million per averted birth, depending on whether parents choose to have another child. Assuming a lifetime care cost of $1.574 million per CF patient, Rowley et al. concluded that "the averted medical-care cost resulting from choices freely made are estimated to offset ~74%-78% of the costs of a screening program."[130] The study added that "the cost of prenatal CF carrier screening could fall to equal the averted costs of CF patient care if the cost of carrier testing were to fall to $100."[131] Assuming that a pregnancy is terminated because of CF and the family does not have another pregnancy, there is no gain in terms of aggregate family quality-adjusted life-years. If the family has another pregnancy, the marginal cost for prenatal CF carrier screening is estimated to be $8,290 per quality-adjusted life-year (QALY). This figure "is comparable to that for newborn screening for phenylketonuria and is more advantageous than the ratios for many widely advocated preventive interventions."[132] Neither Asch et al. nor Wei et al. included QALY in their metrics, precluding a QALY-based comparison.

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[124] Ibid., 209.
[125] Ibid.
[126] Wei S et al. Is cystic fibrosis carrier screening cost effective? *Community Genetics* 2007. 10(2):103-9.
[127] Ibid., 104.
[128] Year for dollars from email from K. Monaghan to Christopher Heaney, July 29, 2008.
[129] Rowley P et al. Prenatal screening for cystic fibrosis carriers: an economic evaluation. *American Journal of Human Genetics* 1998. 63(4):1160-74.
[130] Ibid., 1160.
[131] Ibid.
[132] Ibid., 1168.

Other reports were considered in an extensive review produced by the Foundation for Blood Research in cooperation with the CDC.[133] Although the review's discussion of previous studies is too extensive to describe here, the review did produce a relevant summary of the financial costs of testing. Using 1996 dollars, the review concluded that diagnosing one case of CF by population screening would cost approximately $400,000 for Ashkenazi Jewish descendants, $500,000 among non-Hispanic Caucasians, and $19 million among Asian Americans. The $19 million figure reflects the low rate of detecting CF in Asian Americans.

Boston University's panel of 40 mutations (including the ACMG's recommended mutations) for $195 and Ambry's test for ΔF508 mutations for $85 both show that the market is at least approaching Rowley's threshold cost of $100 for a cost-effective carrier screening test. Although we cannot estimate overall costs from our price survey, the empirical evidence and empirically derived models discussed above suggest that licensing practices for *CFTR* at least do not preclude cost-effective screening for CF.

Summary of Cost Estimates

Study	Asch *et al.* (1995 Dollars)	Wei *et al.* (2005 dollars)	ACCE (1996 Dollars)
Costs	• Testing for 6 mutations: $50 • Testing for approx. 30 mutations: $100 • Genetic counselor's time per hour w/benefits: $26 • Patient time per hour w/ benefits: $15 • Amniocentesis (excluded karotyping): $200 • Microvillar intestinal enzyme analysis (to verify CF diagnosis): $100 • Miscarriage: $260 • Midtrimeseter abortion: $2,800 • Delivery: $3,120 • Travel (per office visit): $5 • Lifetime medical and nonmedical direct costs of CF: $351,278	• DNA mutation testing (including reagents, disposables, technical time, professional interpretation): $50 • 1 hour counseling with genetics counselor and MD or PhD: $175 • Chorionic villus sampling with karotyping: $1,200 • Amniocentesis with karotyping: $900	• Providing education and information to the entire population: $1 to $3 • Obtaining informed consent: $5 to $10 • Collecting and transporting the sample: $10 (blood);$4 (buccal) • Performing the DNA test: $80 to $100 • Reporting negative results: $2 by mail/fax/electronic • Reporting positive results: $20 (individual); $50 (couple) • Performing diagnostic testing: $400 to $600 (w/o karotype) • Accounting for procedure-related fetal losses: $400
Cost per CF affected birth	• $367,000	• $334,000	• $400,000 (Ashkenazi Jewish)

[133] National Office of Public Health Genomics, CDC, and Foundation for Blood Research. *ACCE Review of CF/Prenatal: Clinical Utility*. 2002. See http://www.cdc.gov/genomics/gtesting/file/print/FBR/CFDisSet.pdf [accessed July 29, 2008].

prevented			• $500,000 (non-Hispanic Caucasians) • $4,000,000 (Hispanic Caucasians) • $7,000,000 African Americans • $19,000,000 (Asian Americans)

Preimplantation Genetic Diagnosis (PGD)

Although PGD has been used to detect CF in embryos for more than a decade, there is very limited evidence for its cost effectiveness. In an oral presentation supported by the Reproductive Genetics Institute and reported in *Fertility and Sterility*, the cost of performing PGD on 11,511 embryos ($235 million) was compared to the cost of treating CF patients who have been born had PGD not been used to avoid implanting CF affected embryos (est. total $50 million annually, based on $55,537 annual direct care costs per patient).[134] The presenters concluded, "Offering IVF-PGD to all CF carrier couples… is highly cost effective and will save hundreds of millions of direct health care dollars annually." Working in Taiwan, Tsai performed PGD "without using fluorescent primers and expensive automatic instrumentation," which was an improvement over previous techniques and a reduction in financial cost.[135] Neither of those sources gives as much empirical evidence as the studies discussed above, leaving PGD's cost effectiveness open to further research.

Lessons Learned About the Patent Process

Research

There is no direct evidence that the patent process affected the research that ultimately led to *CFTR* gene discovery. The prospect of patents was not reported as an important incentive to do the research, which was largely funded by government and nonprofit entities hoping to understand the disease. Though linkage analysis of the *CFTR* gene was not successful throughout the 1950's,[136] RFLP (restriction fragment length polymorphism) mapping enabled genetic linkage to chromosome 7 to be established in the 1980's. Researchers identified the first linkage between a marker and the CF phenotype in 1985 and identified the *CFTR* gene and its most common mutation, ΔF508, in 1989.[137]

Multiple individuals and institutions applied for patents at the same time and the discovery of the *CFTR* gene was characterized as a "race."[138] However, academic competition more than the prospect of patents incited the intense hunt for the *CFTR* gene and innovation in techniques for gene mapping and positional cloning of genes, at least among the several academic groups involved. Two primary academic groups

[134] Tur-Kaspa et al. Preimplanation genetic diagnosis (PGD) for all cystic fibrosis (CF) carrier couples: strategy and cost analysis. *Fertility & Sterility* 2006. 86(3):S59.
[135] Tsai YH. Cost-effective one-step PCR amplification of cystic fibrosis delta F508 fragment in a single cell for preimplanation genetic diagnosis." *Prenatal Diagnosis* 1999. 19(11):1048–1051.
[136] Steinberg A et al. Linkage studies with cystic fibrosis of the pancreas. Op. cit.
Steinberg A et al. Sequential test for linkage between cystic fibrosis of the pancreas and the MNS locus. Op. cit.
[137] Tsui L et al. Cystic fibrosis locus defined by a genetically linked polymorphic DNA marker. Op. cit.
Tsui L et al. Genetic analysis of cystic fibrosis using linked DNA markers. Op. cit.
[138] Davies K. The search for the cystic fibrosis gene. *New Scientist* 1989 (21 October). See http://www.newscientist.com/article/mg12416873.900-the-search-for-the-cystic-fibrosis-gene-for-nearly-adecade-several-teams-of-molecular-biologists-h [accessed September 17, 2008].

(Francis Collins and colleagues, University of Michigan and John Riordan, Lap-Chee Tsui and colleagues at The HSC) combined their complementary approaches to advantage and were successful in beating the competition and discovering the *CFTR* gene in June 1989. Collins, Riordan and Tsui published their findings simultaneously in three back to back papers in September 1989 in *Science*. As mentioned earlier, they also jointly filed for patents. We have not found any evidence that CF gene patents impeded subsequent basic or clinical research.

Development

There is no evidence that the patent process affected the speed of genetic test development. The CF patent interferences were ultimately resolved in 2002, largely in the favor of Tsui and Collins. The interference process took several years to resolve at significant expense. However, it does not appear that the interference proceeding added time to the commercial test development process. It did add costs that were largely borne by one of the patent licensees (who had licensed for therapeutic use such as gene therapy) and not the academic research institutions. During patent inference proceedings, the University of Michigan and The Hospital for Sick Children practiced broad, nonexclusive licensing of patents covering mutations including the ΔF508 mutation. The fact that the NIH Consensus Conference (1997) guidelines recommended genetic testing for all "adults with a positive family history of CF, to partners of people with CF, to couples currently planning a pregnancy, and to couples seeking prenatal testing" and that the 2001 ACMG statement made a similarly broad recommendation for carrier screening suggests that CF genetic test was widely available by the time these reports were released.[139]

Commercialization

Development and commercialization of new test techniques and technologies continue for CF genetic testing. Laboratories use several test methods, platforms and kits or analyte specific reagents (ASRs). It is likely that broad and non-exclusive licensing practiced by the University of Michigan, HSC, and Johns Hopkins University has facilitated commercial kit development by lowering IP-related barriers to entry. To date, 64 labs across the country offer CF testing.[140] Patents do not appear to limit overall commercial availability.

Communication/Marketing

Direct-to-consumer marketing has not been practiced for CF testing. Marketing and education for CF testing is provided by health professionals within professional associations, among primary care physicians, and among pediatricians. Most laboratories will not perform tests without a doctor's referral. However, as guidelines have called for widespread use of the test, the number of test providers has risen.[141] Although this may increase access, it also means that companies have an incentive to prepare marketing material for patients. In any case, patents and licensing practices have not prevented marketing and publicizing CF testing to date. Non-exclusive licensing may have facilitated growth of the CF genetic testing market.

Adoption

There is no evidence that patents reduced adoption of CF tests by laboratories, healthcare providers, or third party payers.

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[139] National Institutes of Health Consensus Development Conference Statement on Genetic Testing for Cystic Fibrosis. Op. cit. Grody W et al. Laboratory standards and guidelines for population-based cystic fibrosis carrier screening. Op. cit.
[140] *CFTR-Related Disorders*. See www.genetests.org [accessed July 2, 2008].
[141] Cutting G. Op. cit.
Grody W et al. The cystic fibrosis mutation 'arms race': when less is more. Op. cit.

Consumer Utilization

There is no evidence that *CFTR* gene patents and licensing have limited consumer utilization.

Conclusions

Cystic Fibrosis was selected as a case study for this report to the SACGHS as an example of broad non-exclusive licensing of patented genetic tests. Some providers note that gene patents can limit their practice of medicine and specifically their ability to provide genetic tests. However, Dr. Debra Leonard notes that "[i]f every license or every patent was being licensed like this cystic fibrosis Delta F508 mutation," then such constraints on medical practitioners and the associated controversies would be greatly reduced.[142] Our research shows how patenting and licensing decisions by the University of Michigan, The Hospital for Sick Children and Johns Hopkins University allow for significant research without unduly hindering patient access or commercial markets. These practices also preserve strong patent protection and the accompanying investment incentives for possible therapeutic discoveries arising from the same DNA patents. Our study also suggests that the active participation of the CF Foundation (which funded part of the research)[143] in discussions about intellectual property and licensing allowed patient perspectives to be included and may have significantly influenced decisions about licensing. In addition, scientists' perspectives on uncertainties associated with genetic testing in the long term, especially in light of future discoveries and technological evolution, also helped inform decisions about optimal commercialization strategies. Indeed, the broad, non-exclusive diagnostic licensing practices associated with the patents surrounding CF allow for competition as well as innovation.

Acknowledgements

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[142] Secretary's Advisory Committee on Genetics, Health, and Society (2006). SACGHS Meeting Transcript, June 26-27, 2006. See http://oba.od.nih.gov/oba/SACGHS/meetings/June2006/transcripts/Patents_Licensing-Leonard.pdf [accessed January 14, 2009].
[143] Davies K. Op. cit.

Appendix A: License Agreement

LICENSE AGREEMENT
MICHIGAN FILE 492p2 TECHNOLOGY
DIAGNOSTIC PRODUCT DISTRIBUTION LICENSE

This License Agreement, effective as of the _ day of _____, 2008 (the "Effective Date"), entered into by _____, a corporation incorporated in the State of _____, located at _____ ("LICENSEE"), the Regents of the University of Michigan, a constitutional corporation of the State of Michigan ("MICHIGAN"), and HSC Research and Development Limited Partnership, a partnership organized and subsisting under the laws of the Province of Ontario, Canada ("RDLP"). LICENSEE, MICHIGAN and RDLP agree as follows:

1. BACKGROUND.

1.1 Michigan (in part in the Howard Hughes Medical Institute ("HHMI") laboratories at MICHIGAN) and the Research Institute of The Hospital for Sick Children of Toronto, Ontario, Canada, ("HSC") have conducted research relating to cystic fibrosis. As a result of that research, MICHIGAN and RDLP have developed rights in the "Licensed Patent(s)" defined below.

1.2 LICENSEE desires to obtain, and MICHIGAN and RDLP, consistent with their missions of education and research, desire to grant a license of the "Licensed Patent(s)" on the terms and conditions listed below.

1.3 MICHIGAN and RDLP have entered into a Memorandum of Agreement covering the Licensed Patent(s), consistent with which MICHIGAN and RDLP are entering into this License Agreement jointly as the licensor of the Licensed Patents.

2. DEFINITIONS.

2.1 "TECHNOLOGY", as used in this Agreement, shall mean the information, manufacturing techniques, data, designs or concepts developed by MICHIGAN and HSC, covering the gene for cystic fibrosis and uses thereof as covered by the claims of U.S. Patent No. 5,776,677 entitled "Cystic Fibrosis Gene."

2.2 "Parties", in singular or plural usage as required by the context, shall mean LICENSEE, MICHIGAN and/or RDLP.

2.3 "Affiliate(s)" shall mean any individual, corporation, partnership, proprietorship or other entity controlled by, controlling, or under common control with LICENSEE through equity ownership, ability to elect directors, or by virtue of a majority of overlapping directors, and shall include any individual, corporation, partnership, proprietorship or other entity directly or indirectly owning, owned by or under common ownership with LICENSEE to the extent of thirty percent (30%) or more of the voting shares, including shares owned beneficially by such party.

2.4 "Licensed Patents" shall mean U.S. Patent No. 5,776,677, a divisional of U.S. Patent No. 6,984,487, entitled "Cystic Fibrosis Gene" and all foreign equivalent patent applications and Patent Cooperation Treaty filings, and all patents issuing therefrom in which Michigan and/or RDLP has or acquires a property interest (currently including the applications listed in the Appendix [AI] attached to this Agreement [see below]). "Licensed Patent(s)" shall also include any divisional, continuation (excluding continuations-in-part), reissue, reexamination or

extension of the above-described patent applications and resulting patents, along with any extended or restored term, and any confirmation patent, registration patent, or patent of addition.

2.5 "Valid Claim(s)" means any claim(s) in an unexpired patent or pending in a patent application included within the Licensed Patents which has not been held unenforceable, unpatentable, or invalid by a decision of a court or other governmental agency of competent jurisdiction, unappealable or unappealed within the time allowed for appeal, and which has not been admitted to be invalid or unenforceable through reissue or disclaimer. If in any country there should be two or more such decisions conflicting with respect to the validity of the same claim, the decision of the higher or highest tribunal shall thereafter control; however, should the tribunals be of equal rank, then the decision or decisions upholding the claim shall prevail when the conflicting decisions are equal in number, and the majority of decisions shall prevail when the conflicting decisions are unequal in number.

2.6 "Product(s)" shall mean any product(s) whose manufacture, use or sale in any country would, but for this Agreement, comprise an infringement, including contributory infringement, of one or more Valid Claims.

2.7 "Field of Use" shall refer to the field for which Products may be designed, manufactured, used and/or marketed under this Agreement, and shall mean solely Products to be used for the research of, diagnosis of and screening for the disease cystic fibrosis.

2.8 "Net Sales" shall mean the sum, over the term of this Agreement, of all amounts received and all other consideration received (or, when in a form other than cash or its equivalent, the fair market value thereof when received) by LICENSEE and its Affiliates from persons or entities due to or by reason of the sale or other distribution of Products, or the use of Products, including any use by LICENSEE and Affiliates in the performance of services for their customers; less the following deductions and offsets, but only to the extent such sums are otherwise included in the computation of Net Sales, or are paid by LICENSEE and not otherwise reimbursed: refunds, rebates, replacements or credits actually allowed and taken by purchasers for return of Products; customary trade, quantity and cash discounts actually allowed and taken; excise, value-added, and sales taxes actually paid by LICENSEE for Products; and shipping and handling charges actually paid by LICENSEE for Products.

2.9 "Royalty Quarter(s)" shall mean the three month periods ending on the last day of March, June, September and December of each year.

2.10 "Territory" means all countries of the world.

2.11 "First Diagnostic Sale" shall mean the first sale of any Product (including any sale of a service using a Product in the Field of Use) by LICENSEE or an Affiliate, other than for use in clinical trials being conducted to obtain FDA or other governmental approvals to market Products.

3. GRANT OF LICENSE.

3.1 MICHIGAN and RDLP hereby grant to LICENSEE a non-exclusive license under the Licensed Patents to make, have made, use (including use in the performance of services for its customers), market and sell, in the Territory, Products designed and marketed solely for use in the Field of Use.

3.2 MICHIGAN and RDLP reserve the right to license and use all aspects of the TECHNOLOGY and the Licensed Patents for any use or purpose, including the right to develop and produce Products.

3.3 The license granted to LICENSEE herein shall be without the right to sublicense, except that LICENSEE may sublicense Affiliate(s) who agree to be and are bound in writing to the terms and conditions of this Agreement to the same extent as LICENSEE. LICENSEE agrees to strictly monitor and enforce compliance with the terms and conditions of this Agreement by all Affiliate sublicensees.

4. CONSIDERATION.

4.1 LICENSEE shall pay to MICHIGAN a one-time, non-creditable license issue fee of U.S. $25,000.00, forthwith following the Effective Date. Notwithstanding any other terms of this Agreement, this Agreement and the license granted hereunder shall not become effective until such issue fee is received by MICHIGAN.

4.2 LICENSEE shall also pay MICHIGAN, with respect to each Royalty Quarter, a royalty equal to six percent (6%) of the Net Sales of Products of LICENSEE and Affiliates during such Royalty Quarter.

4.3 The obligation to pay MICHIGAN a royalty under this Article 4 is imposed only once with respect to the same unit of Product regardless of the number of Valid Claims or Licensed Patents covering the same; however, for purposes of determination of payments due hereunder, whenever the term "Product" may apply to a property during various stages of manufacture, use or sale, Net Sales, as otherwise defined, shall be derived from the sale, distribution or use of such Product by LICENSEE or Affiliates at the stage of its highest invoiced value to unrelated third parties.

4.4 LICENSEE shall pay to MICHIGAN an annual license maintenance fee. This annual fee shall accrue in the Royalty Quarter ending in March of the years specified below, and shall be due and payable and included with the report for that quarter.

If LICENSEE defaults in the payment of any annual license maintenance fee, and fails to remedy that default within sixty (60) days after written notice of it by MICHIGAN, then this Agreement and the license rights conveyed herein shall terminate.

The annual license maintenance fees shall be as follows:

(1) In 2005, and in each year thereafter during the term of this Agreement up to and including the year in which LICENSEE first obtains FDA approval or other governmental approval to distribute or use Products in the Field of Use: U.S. $18,000.00;

Also, notwithstanding (1) above (and in place of the amounts therein listed, when applicable):

(2) In the first calendar year following the year in which LICENSEE obtains the approval described in (1) above, and in each year thereafter during the term of this Agreement up to and including the year in which the First Diagnostic Sale occurs: U.S. $20,000.00;

Also, notwithstanding (1-2) above (and in place of the amounts therein listed, when applicable):

(3) In the first calendar year following the First Diagnostic Sale: U.S. $20,000.00;

(4) In the second year following the First Diagnostic Sale: U.S. $22,500.00;

(5) In the third year following the First Diagnostic Sale: U.S. $25,000.00; and

(6) In the fourth year following the First Diagnostic Sale, and in each year thereafter during the term of this Agreement; U.S. $30,000.00.

Each annual fee paid under (3-6) above may be credited by LICENSEE in full against all earned royalties otherwise to be paid to MICHIGAN under Paragraph 4.2 for the calendar year in which the specific annual fee is paid. The year for which such credits against royalties may be taken includes the Royalty Quarter in which the annual fee accrues and the next three Royalty Quarters.

Each annual fee paid under (1-2) above may be credited by LICENSEE in full against all earned royalties otherwise to be paid to MICHIGAN under Paragraph 4.2 after such annual fee is paid.

4.5 If LICENSEE takes any license(s), in a given country, under valid third party patents which would be infringed by the manufacture, use or sale of Products in that country, then LICENSEE can deduct up to forty percent (40%) of the royalties otherwise due and payable in each Royalty Quarter under Paragraph 4.2 above for Net Sales in that country, until such time as LICENSEE has recovered an amount equal to forty percent (40%) of the royalty paid to such third parties; provided that in no event shall such deducted amounts be applied to reduce or require reimbursement of the annual fees required under Paragraph 4.4. This Paragraph is not intended to imply an obligation upon MICHIGAN or RDLP to reimburse LICENSEE's above-described third-party royalties; the rights granted to LICENSEE in this Paragraph shall not exceed the ability of the above-described mechanism (i.e., a deduction of 40% of royalties due upon Net Sales in the country in question) to reimburse such expenses. LICENSEE shall make an accounting to MICHIGAN of all such third-party royalties, and all resulting deductions from royalties otherwise due and payable to MICHIGAN, as part of its reporting obligations under Article 5 below.

4.6 If MICHIGAN and RDLP grant a license under the Licensed Patents and in the Field of Use to any third party which is substantially the same as the license granted to LICENSEE under Article 3 above, for all or any part of the Territory, but which requires a royalty rate or license maintenance fees lower than those required of LICENSEE under this Agreement, then MICHIGAN and RDLP shall offer those terms to LICENSEE for that part of the Territory, to be effective as of the effective date of the license to that third party.

5. REPORTS.

5.1 Within sixty (60) days after the close of (i) any Royalty Quarter in which a fee under Paragraph 4.4 accrues, and (ii) each Royalty Quarter following the First Diagnostic Sale during the term of this Agreement (including the close of any Royalty Quarter immediately following any termination of this Agreement), LICENSEE shall report to MICHIGAN all royalties accruing to MICHIGAN during such Royalty Quarter. Such quarterly reports shall indicate for each Royalty Quarter the gross sales and Net Sales of Products by LICENSEE and Affiliates, and any other revenues with respect to which payments are due, and the amount of such payments, as well as the various calculations used to arrive at said amounts, including the quantity, description (nomenclature and type designation), country of manufacture and country of sale of Products. In case no payment is due for any such period, LICENSEE shall so report.

5.2 LICENSEE covenants that it will promptly establish and consistently employ a system of specific nomenclature and type designations for Products so that various types can be identified and segregated, where necessary; LICENSEE and Affiliates shall consistently employ such system when rendering invoices thereon and henceforth agree to inform MICHIGAN, or its auditors, when requested as to the details concerning such nomenclature system as well as to all additions thereto and changes therein.

5.3 LICENSEE shall keep, and shall require its Affiliates to keep, true and accurate records and books of account containing data reasonably required for the computation and verification of payments to be made as provided by this Agreement, which records and books shall be open for inspection upon reasonable notice during business hours by an independent certified accountant selected by MICHIGAN, for the purpose of verifying the amount of payments due and payable. Said right of inspection will exist for six (6) years from the date of origination of any such record, and this requirement and right of inspection shall survive any termination of this Agreement. MICHIGAN shall be responsible for all expenses of such inspection, except that if such inspection reveals an underpayment of royalties to MICHIGAN in excess of ten percent (10%) for any year, then said inspection shall be at LICENSEE's expense and such underpayment shall become immediately due and payable to MICHIGAN.

5.4 The reports provided for hereunder shall be certified by an authorized representative of LICENSEE to be correct to the best of LICENSEE's knowledge and information.

6. TIMES AND CURRENCIES OF PAYMENTS.

6.1 Payments accrued during each Royalty Quarter shall be due and payable in Ann Arbor, Michigan on the date each quarterly report is due (as provided in Paragraph 5.1), shall be included with such report and shall be paid in United States dollars. LICENSEE agrees to make all payments due hereunder to MICHIGAN by check made payable to "The Regents of The University of Michigan," and sent by prepaid, certified or registered mail, return receipt requested, to the address for notices set forth in Article 19 herein.

6.2 On all amounts outstanding and payable to MICHIGAN, interest shall accrue from the date such amounts are due and payable at two percentage points above the prime lending rate as established by the Chase Manhattan Bank, N.A., in New York City, New York, or at such lower rate as may be required by law.

6.3 Where Net Sales are generated in foreign currency, such foreign currency shall be converted into its equivalent in United States dollars at the exchange rate of such currency as reported (or if erroneously reported, as subsequently corrected) in the Wall Street Journal on the last business day of the Royalty Quarter during which such payments are received by LICENSEE or Affiliates (or if not reported on that date, as quoted by the Chase Manhattan Bank, N.A., in New York City, New York).

6.4 Except as provided in the definition of Net Sales, all royalty payments to MICHIGAN under this Agreement shall be without deduction for sales, use, excise, personal property or other similar taxes or other duties imposed on such payments by the government of any country or any political subdivision thereof; and any and all such taxes or duties shall be assumed by and paid by LICENSEE.

7. COMMERCIALIZATION.

7.1 It is understood that LICENSEE has the responsibility to do all that is necessary for any governmental approvals to manufacture and/or sell Products.

7.2 LICENSEE agrees to use reasonable efforts to develop Products, obtain any government approvals necessary, and manufacture and sell Products at the earliest possible date; and to effectively exploit, market and manufacture in sufficient quantities to meet anticipated customer demand and to make the benefits of the Products reasonably available to the public.

7.3 Within fifteen (15) days of the First Diagnostic Sale, LICENSEE shall report by written letter to MICHIGAN the date and general terms of that sale.

8. PATENT APPLICATIONS AND MAINTENANCE.

8.1 MICHIGAN and RDLP shall control all aspects of filing, prosecuting, and maintaining Licensed Patents, including foreign filings and Patent Cooperation Treaty filings. MICHIGAN and RDLP may in their sole discretion decide to refrain from or to cease prosecuting or maintaining any of the Licensed Patents, including any foreign filing or any Patent Cooperation Treaty filing.

8.2 MICHIGAN shall notify LICENSEE of any issuance of any Licensed Patent(s) and the Valid Claims included therein, and any lapse, revocation, surrender, invalidation or abandonment of any Licensed Patent or Valid Claim.

9. INFRINGEMENT.

9.1 If LICENSEE becomes aware of or reasonably suspects infringement of Licensed Patents by third parties, LICENSEE agrees to promptly notify MICHIGAN of such alleged infringement.

9.2 MICHIGAN and RDLP, at their sole discretion and at their own expense, may initiate proceedings in response to alleged infringement of Licensed Patents, but are under no obligation to do so.

10. NO WARRANTIES; LIMITATION ON MICHIGAN'S and RDLP'S LIABILITY.

10.1 MICHIGAN and RDLP, including their fellows, directors, officers, employees and agents, make no representations or warranties that any Licensed Patent is or will be held valid, or that the manufacture, use, sale or other distribution of any Products will not infringe upon any patent or other rights not vested in MICHIGAN or RDLP.

10.2 **MICHIGAN**, **HSC** AND **RDLP**, INCLUDING THEIR FELLOWS, DIRECTORS, OFFICERS, EMPLOYEES AND AGENTS, MAKE NO REPRESENTATIONS, EXTEND NO WARRANTIES OF ANY KIND, EITHER EXPRESS OR IMPLIED, INCLUDING BUT NOT LIMITED TO THE IMPLIED WARRANTIES OF MERCHANTABILITY OR FITNESS FOR A PARTICULAR PURPOSE, AND ASSUME NO RESPONSIBILITIES WHATEVER WITH RESPECT TO DESIGN, DEVELOPMENT, MANUFACTURE, USE, SALE OR OTHER DISPOSITION BY **LICENSEE** OR **AFFILIATES** OF **PRODUCTS**.

10.3 THE ENTIRE RISK AS TO THE DESIGN, DEVELOPMENT, MANUFACTURE, OFFERING FOR SALE, SALE OR OTHER DISPOSITION, AND PERFORMANCE OF **PRODUCTS** IS ASSUMED BY **LICENSEE** AND **AFFILIATES**. In no event shall MICHIGAN, RDLP or HSC, including their fellows, directors, officers, employees and agents, be responsible or liable for any

direct, indirect, special, incidental, or consequential damages or lost profits to LICENSEE, Affiliates or any other individual or entity regardless of legal theory. The above limitations on liability apply even though MICHIGAN, RDLP, or HSC, including their fellows, directors, officers, employees or agents, may have been advised of the possibility of such damage.

10.4 LICENSEE shall not, and shall require that its Affiliates do not, make any statements, representations or warranties or accept any liabilities or responsibilities whatsoever to or with regard to any person or entity which are inconsistent with any disclaimer or limitation included in this Article 10.

10.5 Regardless of any research or testing that may have been done at HSC or MICHIGAN (including HHMI laboratories), HSC, MICHIGAN, and RDLP make no representations regarding how Products can or should be used in the diagnosis of and screening for the disease cystic fibrosis.

10.6 IT IS UNDERSTOOD THAT THE **TECHNOLOGY** AND THE **LICENSED PATENTS** DO NOT IDENTIFY THE PRESENCE OF THE CYSTIC FIBROSIS DISEASE IN ALL CASES.

11. INDEMNITY; INSURANCE.

11.1 LICENSEE shall defend, indemnify and hold harmless and shall require its Affiliates licensed hereunder to defend, indemnify and hold harmless MICHIGAN, RDLP and HSC, as well as their fellows, officers, trustees, directors, employees and agents, from and against any and all claims, demands, damages, losses, and expenses of any nature (including attorneys' fees and other litigation expenses), resulting from, but not limited to, death, personal injury, illness, property damage, economic loss or products liability arising from or in connection with, any of the following:

(1) Any manufacture, use, sale or other disposition by LICENSEE, Affiliates or transferees of Products;

(2) The direct or indirect use by any person of Products made, used, sold or otherwise distributed by LICENSEE or Affiliates;

(3) The use by LICENSEE or Affiliates of any invention related to the TECHNOLOGY or the Licensed Patents.

11.2 MICHIGAN and RDLP shall be entitled to participate at their option and expense through counsel of their own selection, and may join in any legal actions related to any such claims, demands, damages, losses and expenses under Paragraph 11.1 above.

11.3 HHMI and its trustees, officers, employees, and agents (collectively, “HHMI Indemnitees”), will be indemnified, defended by counsel acceptable to HHMI, and held harmless by the LICENSEE from and against any claim, liability, cost, expense, damage, deficiency, loss, or obligation, of any kind or nature (including, without limitation, reasonable attorneys’ fees and other costs and expenses of defense) (collectively, “Claims”), based upon, arising out of, or otherwise relating to this Agreement, including without limitation any cause of action relating to product liability. The previous sentence will not apply to any Claim that is determined with finality by a court of competent jurisdiction to result solely from the gross negligence or willful misconduct of an HHMI Indemnitee.

11.4 LICENSEE shall purchase and maintain in effect a policy of product liability insurance covering all claims with respect to diagnostic testing for cystic fibrosis using a Product and any Products manufactured, sold, licensed or otherwise distributed by LICENSEE and Affiliates. Such insurance policy must specify MICHIGAN, HHMI, RDLP and HSC, including their fellows, officers, trustees, directors, Regents, agents and employees, as an additional insureds. LICENSEE shall furnish certificate(s) of such insurance to MICHIGAN, upon request.

12. TERM AND TERMINATION.

12.1 Upon any termination of this Agreement, and except as provided herein to the contrary, all rights and obligations of the Parties hereunder shall cease, except as follows:

(1) Obligations to pay royalties and other sums accruing hereunder up to the day of such termination;

(2) MICHIGAN's rights to inspect books and records as described in Article 5, and LICENSEE's obligations to keep such records for the required time;

(3) Obligations of defense and indemnity under Article 11;

(4) Any cause of action or claim of LICENSEE or MICHIGAN or RDLP accrued or to accrue because of any breach or default by another Party hereunder;

(5) The general rights, obligations, and understandings of Articles 2, 10, 15, 17, 26 and 27; and 28;

(6) All other terms, provisions, representations, rights and obligations contained in this Agreement that by their sense and context are intended to survive until performance thereof.

12.2 This Agreement will become effective on its Effective Date and, unless terminated under another, specific provision of this Agreement, will remain in effect until and terminate upon the last to expire of Licensed Patents.

12.3 If LICENSEE shall at any time default in the payment of any royalty or the making of any report hereunder, or shall make any false report, or shall commit any material breach of any covenant or promise herein contained, and shall fail to remedy any such default, breach or report within sixty (60) days after written notice thereof by MICHIGAN specifying such default, then MICHIGAN and RDLP may, at their option, terminate this Agreement and the license rights granted herein by notice in writing to such effect. Any such termination shall be without prejudice to any Party's other legal rights for breach of this Agreement.

12.4 LICENSEE may terminate this Agreement by giving MICHIGAN a notice of termination, which shall include a statement of the reasons, whatever they may be, for such termination and the termination date established by LICENSEE, which date shall not be sooner than ninety (90) days after the date of the notice. Such notice shall be deemed by the Parties to be final.

12.5 In the event LICENSEE shall at any time during the term of this Agreement deal with the TECHNOLOGY or Products in any manner which violates the laws, regulations or similar legal authority of any jurisdiction including, but not limited to, the public health requirements relating to the TECHNOLOGY or Products or the design, development, manufacture, offering for sale, sale or other disposition of Products, the license granted herein shall terminate immediately with respect to such Products within the territory encompassed by such jurisdiction.

13. ASSIGNMENT.

Due to the unique relationship between the Parties, this Agreement shall not be assignable by LICENSEE without the prior written consent of MICHIGAN and RDLP. Any attempt to assign this Agreement without such consent shall be void from the beginning. MICHIGAN and RDLP shall not unreasonably withhold consent for LICENSEE to assign this Agreement to a purchaser of all or substantially all of LICENSEE's business. No assignment shall be effective unless and until the intended assignee agrees in writing with RDLP and MICHIGAN to accept all of the terms and conditions of this Agreement. Further, LICENSEE shall refrain from pledging any of the license rights granted in this Agreement as security for any creditor.

14. REGISTRATION AND RECORDATION.

14.1 If the terms of this Agreement, or any assignment or license under this Agreement are or become such as to require that the Agreement or license or any part thereof be registered with or reported to a national or supranational agency of any area in which LICENSEE or Affiliates would do business, LICENSEE will, at its expense, undertake such registration or report. Prompt notice and appropriate verification of the act of registration or report or any agency ruling resulting from it will be supplied by LICENSEE to MICHIGAN.

14.2 Any formal recordation of this Agreement or any license herein granted which is required by the law of any country, as a prerequisite to enforceability of the Agreement or license in the courts of any such country or for other reasons, shall also be carried out by LICENSEE at its expense, and appropriately verified proof of recordation shall be promptly furnished to MICHIGAN.

15. LAWS AND REGULATIONS OF THE UNITED STATES AND CANADA; EXPORT.

15.1 Activities under this Agreement shall be subject to all appropriate United States and Canadian laws and regulations now or hereafter applicable.

15.2 LICENSEE shall comply, and shall require its Affiliates to comply, with all provisions of any applicable laws, regulations, rules and orders relating to the license herein granted and to the testing, production, transportation, export, packaging, labeling, sale or use of Products, or otherwise applicable to LICENSEE's or its Affiliates' activities hereunder.

15.3 LICENSEE shall obtain, and shall require its Affiliates to obtain, such written assurances regarding export and re-export of technical data (including Products made by use of technical data) as may be required by the United States Office of Export Administration Regulations, and LICENSEE hereby gives such written assurances as may be required under those Regulations to MICHIGAN.

15.4 LICENSEE shall obtain, and shall require its Affiliates to obtain, such authorization regarding export and re-export of technical data (including Products made by use of technical data) as may be required by the Department of External Affairs, Export Controls Division, or any authorization necessary for export from or import into Canada, and LICENSEE hereby gives written assurances as may be required under those regulations to RDLP.

16. BANKRUPTCY.

If during the term of this Agreement, LICENSEE shall make an assignment for the benefit of creditors, or if proceedings in voluntary or involuntary bankruptcy shall be instituted on behalf of

or against LICENSEE, or if a receiver or trustee shall be appointed for the property of LICENSEE, MICHIGAN and RDLP may, at their option, terminate this Agreement and revoke the license herein granted by written notice to LICENSEE.

17. PUBLICITY.

LICENSEE agrees to refrain from using and to require Affiliates to refrain from using the name of MICHIGAN, HHMI, RDLP and HSC in publicity or advertising without the prior written approval of that entity.

18. PRODUCT MARKING.

LICENSEE agrees to mark, and to require Affiliates to mark, Products with the appropriate patent notice as approved by MICHIGAN or RDLP (when appropriate), such approval not to be unreasonably withheld.

19. NOTICES.

Any notice, request, report or payment required or permitted to be given or made under this Agreement by a Party shall be given by sending such notice by certified or registered mail, return receipt requested, to the address set forth below or such other address as such Party shall have specified by written notice given in conformity herewith. Any notice not so given shall not be valid unless and until actually received, and any notice given in accordance with the provisions of this Paragraph shall be effective when mailed.

To LICENSEE:

Attn.:

To MICHIGAN:
The University of Michigan
Technology Management Office
Wolverine Tower, Room 2071
3003 South State Street
Ann Arbor, MI 48109-1280
U.S.A.

Attn.: File No. 492p2

with a copy to:
HSC Research and Development
Limited Partnership
555 University Avenue,
Toronto, Ontario M5G 1X8
CANADA
Attn.: President

20. INVALIDITY.

In the event that any term, provision, or covenant of this Agreement shall be determined by a court of competent jurisdiction to be invalid, illegal or unenforceable, that term will be curtailed, limited or deleted, but only to the extent necessary to remove such invalidity, illegality or unenforceability, and the remaining terms, provisions and covenants shall not in any way be affected or impaired thereby.

21. ENTIRE AGREEMENT AND AMENDMENTS.

This Agreement contains the entire understanding of the Parties with respect to the matter contained herein. The Parties may, from time to time during the continuance of this Agreement, modify, vary or alter any of the provisions of this Agreement, but only by an instrument duly executed by authorized officials of all Parties hereto.

22. WAIVER.

No waiver by a Party of any breach of this Agreement, no matter how long continuing or how often repeated, shall be deemed a waiver of any subsequent breach thereof, nor shall any delay or omission on the part of a Party to exercise any right, power, or privilege hereunder be deemed a waiver of such right, power or privilege.

23. ARTICLE HEADINGS.

The Article headings herein are for purposes of convenient reference only and shall not be used to construe or modify the terms written in the text of this Agreement.

24. NO AGENCY RELATIONSHIP.

The relationship between the Parties is that of independent contractor and contractees. LICENSEE shall not be deemed to be an agent of MICHIGAN or RDLP in connection with the exercise of any rights hereunder, and shall not have any right or authority to assume or create any obligation or responsibility on behalf of MICHIGAN or RDLP.

25. FORCE MAJEURE.

No Party hereto shall be deemed to be in default of any provision of this Agreement, or for any failure in performance, resulting from acts or events beyond the reasonable control of such Party, such as Acts of God, acts of civil or military authority, civil disturbance, war, strikes, fires, power failures, natural catastrophes or other "force majeure" events.

26. GOVERNING LAW.

This Agreement and the relationship of LICENSEE to the other Parties shall be governed in all respects by the law of the State of Michigan or the Province of Ontario (notwithstanding any provisions governing conflict of laws under such law to the contrary), depending upon the jurisdiction in which any action relating to the Agreement is brought; except that questions affecting the construction and effect of any patent shall be determined by the law of the country in which the patent has been granted.

27. JURISDICTION AND FORUM.

LICENSEE hereby consents to the jurisdiction of the courts of the State of Michigan over any dispute concerning this Agreement or the relationship of the Parties. Should LICENSEE bring any claim, demand or other action against MICHIGAN or RDLP, including their fellows, officers, employees or agents, arising out of this Agreement or the relationship between the Parties, LICENSEE agrees to bring said action only in an appropriate court of the State or Province of that Party.

28. HHMI THIRD PARTY BENEFICIARY STATUS

HHMI is not a party to this Agreement and has no liability to any licensee, sublicensee, or user of anything covered by this License Agreement, but HHMI is an intended third-party beneficiary of this License Agreement and certain its provisions are for the benefit of HHMI and are enforceable by HHMI in it own name.

IN WITNESS WHEREOF, the Parties hereto have executed this Agreement in triplicate originals by their duly authorized officers or representatives.

FOR LICENSEE

By_____
(authorized representative)

Typed Name_____

Title_____

Date_____

FOR HSC RESEARCH AND DEVELOPMENT LIMITED PARTNERSHIP

By_____
(authorized representative)

Typed Name_____

Title_____

Date_____

FOR THE REGENTS OF THE UNIVERSITY OF MICHIGAN

By_____
(authorized representative)

Typed Name_____

Title_____

Date_____

492p2-Nonexcl.Diag.Lic.7/9/96

Appendix [AI]: Patents and Pending Patent Applications

July 28, 2005

Title: Cystic Fibrosis Gene

Inventors: Tsui, Riordan, Collins, Rommens, Iannuzzi, Kerem, Drumm, Buchwald,

Abstract: The cystic fibrosis gene and its gene product are described for both the normal and mutant forms. The genetic and protein information is used in developing DNA diagnosis, protein diagnosis, carrier and patient screening, drug and gene therapy, cloning of the gene and manufacture of the protein, and development of cystic fibrosis affected animals.

Patent Applications Pending:

Country	Number	Date Filed
United States	07/396,894	abandoned
United States	07/399,945	abandoned
United States	07/401,609	31/08/89
US Continuation [6]	08/123,864	20/09/93
US Divisional [7]	08/252,778	2/06/94
US Divisional [3]	08/446,866	6/06/95
US Divisional	08/471,654	abandoned
US Divisional	08/466,897	abandoned
US Divisional [5]	08/469,630	6/06/95
US Divisional [4]	08/469,617	6/06/95
Ireland [8]	3024/90	21/08/90
PCT	CA90/00267	20/08/90
	WO 91/02796	7/03/91
EPO [1]	90912428.1	20/08/90
Japan	511424/90	20/08/90
Japan Divisional	029998/04	5/03/04
Canada	2066204-2	20/08/90
Australia [2]	61616/90	20/08/90
		Date Issued
[1] EPO*	0489058	5/11/03
[2] Australia granted	647,408	25/01/94
[3] US issued	5,766,677	7/07/98
[4] US issued	6,201,107	13/03/01
[5] US issued	6,730,777	4/05/04
[6] US allowed on 6/04/05		
[7] US issued	6,902,907	7/06/05
[8] Ireland granted	83911	6/05/05

* Designated States include the following countries: Austria, Belgium, Switzerland, Liechtenstein, Germany, Denmark, Spain, France, United Kingdom, Italy, Luxembourg, Netherlands, Sweden

Appendix B: Patents Related to Discovery of Cystic Fibrosis Gene

Patent No.	Date Filed and Issued	Inventors	Patent Holder	First Independent Claim
W09102796A1 (WIPO)	03/07/1991	Tsui et al.	HSC Research and University of Michigan	(Pending Claim:) A DNA molecule comprising an intronless DNA sequence selected from the group consisting of: (a) DNA sequences which correspond to the DNA sequence of Figure 1 from amino acid residue position 1 to position 1480; (b) DNA sequences encoding normal *CFTR* polypeptide having the sequence according to Figure 1 for amino acid residue positions from 1 to 1480; (c) DNA sequences which correspond to a fragment of the sequence of Figure 1 including at least 16 sequential nucleotides between amino acid residue positions 1 and 1480; (d) DNA sequences which comprise at least 16 nucleotides and encode a fragment of the amino acid sequence of Figure 1; and (e) DNA sequences encoding an epitope encoded by at least 18 sequential nucleotides in the sequence of Figure 1 between amino acid residue positions 1 and 1480.
U.S. 5876974	08/30/1994 03/02/1999	Gregory	Genzyme Corporation	A method of producing a DNA molecule encoding wild type human cystic fibrosis transmembrane conductance regulator protein (*CFTR*), said method comprising: growing E. coli cells comprising a purified and isolated DNA molecule encoding wild type human *CFTR*; and recovering said DNA from said cells
U.S. 5,407,796	01/04/1991 04/18/1995	Cutting et al.	Johns Hopkins University	A nucleic acid probe which is complementary to a mutant allele of the *CFTR* gene said allele being selected from the group consisting of: Asn549, Asp551, Stop553, and Thr559.
U.S. 5776677	06/06/1995 07/07/1998	Tsui et al.	HSC Research and University of	A method for screening a subject to determine if said subject is a CF carrier or a CF patient, comprising: (a) providing a biological sample of the subject to be screened, said sample containing a

			Michigan	mutant or a normal *CFTR* gene; and (b) assaying said biological sample for the mutant or the normal *CFTR* gene, wherein the assay includes: (i) assaying for the presence of a normal *CFTR* gene by hybridization comprising: (A) an oligonucleotide probe which specifically binds to a normal DNA molecule encoding a normal *CFTR* polypeptide, wherein the normal DNA molecule comprises a DNA sequence selected from the group consisting of: (1) a DNA sequence encoding a normal *CFTR* protein having the amino acid sequence depicted in FIG. 1; (2) a DNA sequence which hybridizes under stringent conditions to at least 16 contiguous nucleotides of the DNA sequence of (1); and (3) a DNA sequence complementary to the DNA sequence of (1) or (2), and (B) providing at least one reagent for detecting the hybridization of the oligonucleotide probe to said normal DNA molecule; or (ii) assaying for the presence of a mutant *CFTR* gene by hybridization comprising: (A) an oligonucleotide probe which specifically binds to a mutant DNA molecule encoding a mutant *CFTR* polypeptide, wherein the mutant DNA molecule comprises a DNA sequence selected from the group consisting of: (1) a DNA sequence encoding a mutant *CFTR* protein having the amino acid sequence depicted in FIG. 1 with a .DELTA.F508 CF mutation as a three base pair deletion of the codon encoding phenylalanine at amino acid position 508 in FIG. 1; (2) a DNA sequence which hybridizes under stringent conditions to at least 16 contiguous nucleotides of the DNA sequence of (1), said DNA sequence containing said .DELTA.F508 CF mutation; and (3) a DNA sequence complementary to the DNA sequence of (1) or (2); and (B) providing at least one reagent for detecting the hybridization of the oligonucleotide probe to said mutant DNA molecule, wherein the probe and the reagent in (i) and (ii) are each present in amounts effective to perform the hybridization assay.
U.S. 6001588	07/13/1992 12/14/1999	Tsui et al.	HSC Research	A DNA molecule comprising an intronless DNA sequence encoding a mutant *CFTR* polypeptide, said intronless DNA sequence varying from that of SEQ ID NO:1 in having

				nucleotide sequence variants resulting in a deletion or alteration of an amino acid in the encoded *CFTR* polypeptide, so that the sequence of said encoded *CFTR* polypeptide varies from that of SEQ ID NO:2 in an amino acid residue position selected from the group consisting of amino acid residues 85, 178, 455, 493, 507, 542, 549, 560, and 1092 of SEQ ID NO:2, and wherein an alteration at position 549 is either S549R or S549I.
U.S. 6201107	06/06/1995 03/13/2001	Tsui et al.	HSC Research and University of Michigan	An anti-*CFTR* polyclonal or monoclonal antibody specific for a normal *CFTR* polypeptide (SEQ ID NO:17), wherein said antibody is specific for an epitope of the sequence of SEQ ID NO:17 between amino acid residue positions 1 and 1480.
U.S. 6730777	06/06/1995 05/04/2004	Tsui et al.	HSC Research and University of Michigan	An isolated polypeptide comprising an amino acid sequence (a) according to FIGS. 1A-1H for amino acid residue positions from 1 to 1480 comprising a normal *CFTR* polypeptide.
U.S. 6902907	06/02/1994 06/07/2005	Tsui et al.	HSC Research and University of Michigan	A recombinant vector containing a purified DNA molecule comprising a normal cystic fibrosis transmembrane conductance regulator (*CFTR*) DNA sequence encoding an amino acid sequence depicted in FIGS. 1A-1H selected from the group consisting of amino acid positions: (a) 28 to 45; (b) 58 to 75; (c) 104 to 117; (d) 139 to 153; (e) 204 to 249; (f) 279 to 294; (g) 347 to 698; (h) 500 to 512; (i) 710 to 757; (l) 725 to 739; (k) 758 to 796; (l) 933 to 946; (m) 1066 to 1084; and (n) 1188 to 1480.
U.S. 6984487	09/20/1993 01/10/2006	Tsui et al.	HSC Research and University of Michigan	A purified DNA molecule, comprising a cystic fibrosis transmembrane conductance regulator (*CFTR*) DNA sequence selected from the group consisting of: (a) a DNA sequence encoding a normal *CFTR* protein having the amino acid sequence depicted in FIG. 1; (b) a DNA sequence which hybridizes under stringent conditions to at least 16 contiguous nucleotides of the DNA sequence depicted in FIG. 1; and (c) a DNA sequence complementary to the DNA sequence of (a) or (b), wherein said DNA sequence of (a), (b) or (c), when present as part of a coding sequence of a normal *CFTR* gene,

				is expressed in human epithelial cells as a normal *CFTR* protein which is not characterized as having cystic fibrosis associated activity.

Impact of Patents and Licensing Practices on Access to Genetic Testing for Hearing Loss

Subhashini Chandrasekharan, Ph.D. and Melissa Fiffer

Introduction

Inherited DNA mutations account for over half of all hearing loss cases. Genetic hearing loss can be classified as "syndromic" or "nonsyndromic," depending on whether there are associated clinical features (syndromic) or not (nonsyndromic). Mutations in a multitude of individual genes have been implicated in genetic hearing loss. In some cases, a single mutated gene is associated with hearing loss (dominant) and in others, symptoms occur when both parental genes an individual inherits are mutated (recessive) or a mutation occurs on the X chromosome (X-linked). Mutations in a few genes are the most common: GJB2/Connexin 26, GJB6/Connexin 30, SLC26A4/PDS, MTRNR1, and MTTS1. Those mutations are most commonly tested in the US.

Genetic testing for hearing loss can be controversial. Deafness and acquired hearing loss are disabilities, and whether or not to classify them as medical conditions is contested. Beliefs, lived experiences, and attitudes of individuals, both in the hearing and the Deaf Community differ widely. Whether genetic testing is useful or valuable is not a point of consensus. The complexities of when, whether, and how to classify deafness or hearing loss as a medical condition are beyond the scope of this case study. This case study is about testing for inherited mutations that can cause loss of hearing, but with no particular view about whether such testing is valuable or whether it is a medical service.

The diverse perspectives on whether hearing loss is a disease or a disability influence consumer utilization of tests.[1,2] This complicates the notion of "access," because consumer values and preferences affect utilization. For those who deliberately choose not to use tests, lack of utilization does not indicate lack of access but rather expression of a choice. While this is true in general for all genetic testing, the fact that many in the Deaf Community contest the understanding of deafness as a disability is particularly relevant to this particular case study. Statistics on utilization are always only an indirect measure of access, but for hearing loss utilization rates are particularly suspect. Access is about how many people who want information and could benefit from it can get it; how hearing loss and deafness are regarded directly affects how many people actually want to know the cause, and consequently how many people want testing. Hereafter our analysis will proceed on assumption that we are addressing the use of genetic testing among those who want it and can benefit from it, while recognizing that some would not seek testing even if it were freely available at no cost, and access were not an issue.

Clinical guidelines from the American College of Medical Genetics (ACMG) recommend incorporating genetic testing into the diagnosis of congenital hearing loss.[3] The benefits of genetic testing in diagnostic evaluation of hearing loss include:

(i) Reducing additional time-consuming and expensive testing;

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[1] Burton S, Withrow K, Arnos KS, Kalfoglou AL, Pandya A. A focus group study of consumer attitudes toward genetic testing and newborn screening for deafness. *Genet Med* 2006. 8(12):779-783.

[2] Taneja PR, Pandya A, Foley DL, Nicely LV, Arnos KS. Attitudes of deaf individuals towards genetic testing. *Am J Med Genet* 2004. 130(1):17-21.

[3] American College of Medical Genetics (ACMG). Genetics evaluation guidelines for the etiologic diagnosis of congenital hearing loss. *Genet Med* 2002. 4(3): 162-171.

(ii) Facilitating early interventions such as hearing aids, cochlear implants, or sign language that significantly improve language ability;

(iii) Understanding disease progression;

(iv) Monitoring associated clinical manifestations and complications, particularly for syndromic hearing loss; and

(v) Providing accurate information on the chance of recurrence that some may choose to use in making decisions about having children (and others may not).

Patent Issues Concerning A Multi-Gene, Multi-Mutation Condition

Hearing loss provides an opportunity to investigate how the patenting of different genes, mutations, and methods by multiple parties can affect access to genetic testing. Patents on multiple DNA sequences (both normal genes and mutations) owned by many parties have raised concerns about "patent thickets" or "anticommons." An *anticommons* can occur when it becomes difficult to offer a service because the intellectual property is dispersed, making it difficult to accumulate all the permissions needed to offer genetic tests for the mutations that might cause hearing loss. This problem was characterized most famously in May 1998 by Heller and Eisenberg.[4]

The related notion of a patent *thicket* is that there is so much intellectual property that needs to be accumulated that it becomes difficult to cut through it all. This is a problem of density and profusion. The two concepts are distinct, but travel together in the real world, in areas where many patents have been granted to many players.

Another concern about patents is "*blocking*," where a single patent owner with claims pertaining to common variants (or to a key method) can block others from doing genetic testing. Blocking can happen from just one or a few patents on key sequences, key methods, or other inventions, if they are difficult or impossible to invent around. This is a concern for hearing loss genes because patents on one or a few common variants might enable those who hold the relevant patents to prevent others from testing for other hearing loss genes.

One concept in intellectual property that requires aggregation of many patent rights is the incentive for *hold-out.* This was not highlighted in our case study, but is a possibility in the future, depending on how the tests evolve. The fact that different mutations have different frequencies (and therefore explain different fractions of cases) means that the potential commercial value of a mutation patent varies. Patents covering common variants should, therefore, generally be more valuable for clinical testing than rare ones. This makes patent pooling more complicated, because many pools simply count patents rather than try to weight their value, and this may not work for genetic testing even if all the other issues about setting up patent pools were to get resolved. The hold-out incentive appears when a pool has started to form, but a key patent lies outside the pool, and the patent-holder perceives they have bargaining advantage and get a disproportionate benefit (a "hold-out premium") for joining the pool compared to others already in. This is not distinctive to gene patents, but it could surface as a problem if patent pools begin to emerge.

The blocking effect is related to the somewhat different phenomenon of a "penumbra" effect. We characterize a penumbra as activities effectively controlled by a patent holder that are not strictly speaking infringing activities but that in practice are effectively controlled by having one or a few patents. This phenomenon appears in this case study because having rights to some common variants can in effect

[4] Heller MA, Eisenberg RS. Can patents deter innovation? The anticommons in biomedical research. *Science* 1998 (May 1). 280(5364):698-701.

force those who want genetic testing to go to a particular single provider, even though no one can know in advance whether the mutations for which that provider has exclusive rights are actually the ones that cause symptoms in that individual.

One important purpose of seeking genetic testing for hearing loss is to identify the precise molecular cause of the symptoms. So if one testing service retains exclusive rights to test for a common variant, then everyone will of course need to test for that variant, and therefore will send samples to that service, even though the patient may actually have some other mutation—whether unpatented, discovered by someone else and patented, or that no one has ever before discovered. By having rights to one common variant, therefore, a service can force all who seek genetic testing for an entire clinical syndrome to come to them, even if their intellectual property covers only a fraction of all possible mutations. The owner of the key patent thereby controls not only their own intellectual property, but collateral space. This enables them to accumulate knowledge and expand their intellectual property. All those with hearing loss and seeking genetic testing will come to them, and new mutations will thus be found by them, leading to more patents for mutations for that condition. By this mechanism, a monopoly on the original discovery is leveraged to future discoveries and future patents on new mutations that no one has discovered before, in the clinical penumbra of the originally patented test.

The penumbra effect in effect expands the intellectual property controlled by the initial patent holder, but it can also create some perverse incentives for subsequent inventions falling in the penumbra of the original patent. Those discovering a hearing loss mutation may think about simply leaving the discovery in the public domain. This might even be socially optimal by making the discovery available for both scientific progress and also making it easy for any testing service to incorporate the new discovery into ongoing testing. But if one service is controlling the testing because it has patent rights to common variants, then leaving the discovery unpatented merely fuels that service's advantage. The institution making the new discovery will thus face several choices: (1) patent and license to the dominant provider, getting a piece of the action (and thus increasing costs in general, both transaction costs of getting and licensing the patent, but also the pass-through costs to the provider and even higher pass-through costs to end-users—this is the option taken by many institutions in this case study); (2) patent and nonexclusively license; (3) don't patent and forego royalties (true for several in this case study); or (4) patent and license to an entirely different provider, setting up a mutual-blocking situation among service providers. To our knowledge mutual blocking has not occurred in this case, but it does appear to be developing for Long-QT syndrome in a separate case study. All of these options are socially suboptimal by one criterion or another (fairness, efficiency, or both). The penumbra effect is one of the reasons that diagnostic licensing will be a difficult policy problem to solve.

Finally, when a clinical condition requires testing for mutations or uses methods covered by many patents, this can increase costs due to *royalty stacking* (because payments to many patent owners are required). This is a common problem in technology licensing, and not distinctive to diagnostics. The solutions include having a cap on total royalties, clauses in licenses that permit royalty reduction if further licenses become necessary to practice an invention, patent pools, and renegotiation rules. These solutions are all dependent on licensing terms. Because licensing is largely opaque—those out-licensing in-licensing technologies have no obligation to share terms of licensing with us—we do not know the extent to which these issues have been addressed in patent licenses that affect genetic testing for hearing loss.

In this case study, we assess the patent status of hearing loss genes and go as far as we can in judging whether or not they pose the potential for a patent thicket, or anticommons, and also the possibility of blocking patents and the penumbra effect. To our knowledge, royalty stacking was not identified as a major problem, although some have wondered about it in interviews. Our main findings are:

- Most hearing loss genes identified to date are not patented. It does not follow that testing for mutations in these genes is freely available, because of the penumbra effect.

- Testing for Connexin 26 gene mutations, which account for up to half of all non-syndromic recessive hearing loss cases, is patented.
- Of the five most commonly tested hearing loss genes, three (GJB6, SLC26A4, and MTTS1) are not patented. Clinical testing is offered for each of these genes by several providers listed on the GeneTests.org website.
- Testing for mutations in genes involved in less common forms of hearing loss is predominantly offered on a research basis, if it is available at all. Laboratories doing genetic testing for research purposes are generally not CLIA-certified.
- The Institut Pasteur holds two patents (US 5,998,147 and 6,485,908) for the GJB2/ Connexin 26 gene and for detecting its most common deletion mutation 35delG.
- GJB2 patents have been exclusively licensed, apparently with territory of use restrictions, to the for-profit company Athena Diagnostics for testing in the United States, Canada, and Japan. (The documents that specify terms of licensing, including territorial restrictions, are not public, so we can only infer such terms.)
- Cedars-Sinai Medical Center holds a patent (US 5,506,101) that covers MTRNR1 mutation testing, specifically testing for the most common A1555G mutation. This patent is also exclusively licensed to Athena Diagnostics.

Lessons Learned

Research

Research on both rare and common forms of hearing loss appears to have progressed independently of patenting status. There is no evidence that patents have had any positive or negative impact on hearing loss genetics research.

- Research on microarray and chip-based diagnostics for hearing loss is being performed by multiple groups. These diagnostics include patented genes and mutations and are currently offered on a research-only basis in the U.S.
- Concerns about increased patent enforcement have been raised by some researchers, who worry about both research and clinical access.

Development and Commercialization

- We found no evidence that patents accelerated or inhibited hearing loss test development.
- Diagnostic tests for both patented (GJB2, MTRNR1) and unpatented genes (SLC26A4, GBJ6, and MTTS1) have been developed and are offered as a clinical service by several providers. Demand for testing and the extent of research on hearing loss appear to be the primary factors that determine whether diagnostic testing for a particular hearing loss gene is offered as a clinical service at that institution.
- Several providers offer testing panels that include both patented and unpatented tests, e.g., GJB2/Cx26 and GJB6/Cx 30 and MTRNR1 and MTTS1.
- Testing for GJB2 mutations, which is licensed exclusively to Athena Diagnostics in the U.S., was offered as early as 1998. At least 19 providers offered the test in the U.S in January 2009, a majority of which are academic medical centers. However there have been intermittent

enforcement efforts by Athena Diagnostics and some laboratories have stopped testing. In August 2008 one provider (Boston University's Center for Human Genetics) stopped offering Connexin 26 and MTRNR1 testing following Athena's enforcement actions. The recent discontinuation of ASRs offered by Third Wave Technologies[5] to detect the 35delG mutation has increased concern about inability to circumvent patents covering 35delG mutation detection controlled by Athena. This may change the number of providers offering GJB2 testing. Laboratories previously using a two-tiered approach for GJB2 testing, first detecting the 35delG mutation with the ThirdWave Invader™ assay, followed by full sequencing, especially if the sample is negative for 35delG mutations, may now be prevented from reporting out 35delG mutations. This may limit providers from performing clinically meaningful testing since 35delG is the most common GJB2 mutation and some providers may stop offering the test altogether, especially if Athena steps up enforcement activity.

- The price of genetic tests for hearing loss does not appear to correlate with patent status alone. The most expensive test is for Pendred Syndrome, and involves full sequence analysis of SLC26A4. There are no patents associated with the SLC26A4 gene and average test price is ~$1,700. In contrast, testing for GJB2, which is patented, has a list price ranging from $336 to $818. However the price per amplicon for full sequence analysis of GJB2 ($140.8- $430/per amplicon) appears to be higher than SLC26A4 sequencing prices, which range from $55.00-$125.25/per amplicon. This price differential cannot be attributed to patents or licensing, however, because most providers of GJB2 testing probably do not have sublicenses from Athena. (Athena states it has not issued sublicenses.) Factors such as how labor and fixed costs are distributed in test pricing may contribute to this price difference.
- The cost for GJB2 full sequence analysis offered by Athena Diagnostics ($575) is nearly $100 more than the average price of the same test offered by the other providers. Athena's price is nonetheless in the middle of the price range for full-sequence analysis offered by universities, hospitals and academic medical centers ($290-$816). The price per amplicon for GJB2 sequence analysis offered by several non-profit providers (range $140.8- $430) is comparable to Athena's price ($287.50)
- The cost of the MTRNR1 test offered by Athena Diagnostics ($365) is higher than the price of the test offered by universities and hospitals ($150-$285,average price $210). Athena's higher price is not necessarily due to patents, however, and other factors may also contribute to price difference.
- Testing for the MTTS1gene, which is not patented, is offered at prices comparable (average price $238) to MTRNR1 by universities and hospital-based providers. The test is not offered by any commercial testing providers, including Athena Diagnostics.
- The SoundGene™ diagnostic panel developed by Pediatrix includes testing for the most common mutations associated with hearing loss, including GJB2/Connexin 26. Athena Diagnostics has negotiated a sublicense with Pediatrix for Connexin 26 testing. A guaranteed royalty stream from high volume of testing associated with newborn screening follow-up was a likely motivator of this agreement.

Communication and Marketing

- Patents on hearing loss genes and related genetic tests appear to have little to no impact on dissemination of information about genetic testing or on how tests are marketed.

[5] Third Wave Technologies Inc was acquired by HoloLogics Inc. in June 2008 and has discontinued marketing several ASRs for genetic testing , including Connexin 26 mutation testing, for business reasons.

- Athena Diagnostics does not engage in direct-to-consumer marketing. Athena markets primarily through a sales force keyed to clinical specialists. Athena does not have a sales force dedicated to the marketing of hearing loss tests to pediatricians or hearing loss specialists, rather its sales representatives address many neurological and neuromuscular conditions.

Adoption by Clinical Providers

- To date, exclusive US licenses to patents on Connexin 26 and MTRNR1 testing do not appear to have secured Athena Diagnostics sole provider status. While Athena Diagnostics is the reference provider, a number of additional providers, most of which are academic medical centers, are listed as providers of clinical testing at GeneTests.org. However, Athena has intermittently enforced its patents, and laboratories remain concerned about future enforcement activity.
- Negative effects of patents and licensing practices on adoption of genetic tests for hearing loss by providers are not readily apparent, although concerns were expressed in interviews. As early as 1998, ten providers offered GJB2 testing. The number of providers listed on GeneTests.org has risen to 18 since then. Nine providers for MTRNR1 testing are listed on GeneTests.org. However, there has been intermittent enforcement, and some providers have ceased offering some patented tests. We cannot determine how many laboratories decided against offering tests in the first place due to concerns about patent enforcement.
- Athena Diagnostics has sent at least three "cease and desist" letters to other providers. In one instance, the UCLA Diagnostic Molecular Pathology Laboratory (non-profit) stopped offering a test (Connexin26 GJB2 and GJB6 as part of the panel) and did not negotiate a sublicense, citing substantial up-front payment as an impediment. GeneDx (for-profit) continues to perform full sequence analysis for Connexin 26 to identify mutations associated with a rare skin condition, KID, and agreed not to report hearing loss-associated mutations that are discovered during its full sequence analysis. In August 2008, the Center for Human Genetics of Boston University agreed to stop offering GJB2 testing, along with many other tests for which Athena Diagnostics holds an exclusive license.[6]
- Providers of GJB2 and MTRNR1 testing presumably either collect samples and send them to Athena or offer the service without a sublicense from Athena Diagnostics. Athena states that no sublicenses for hearing loss testing have been negotiated with universities or academic medical centers to date.

Consumer Utilization

- We found no evidence that consumer utilization of these tests is impeded by patents.
- A large number of providers offer these tests with a wide price range.
- Athena Diagnostics does not engage in direct to consumer marketing. There is no evidence that tests may be over utilized by consumers.
- Given the lack of clear correlation between the costs of these tests and patent or license status, there is no evidence that patenting or licensing has hindered consumer utilization in the U.S. because of test price.
- Some consumers (such as those covered by MediCal) may not have tests such as Connexin 26 testing covered by their insurance or health plan, because the reference provider Athena

[6] Biomedicine News. See http://www.bio-medicine.org/medicine-technology-1/Boston-University-and-The-Center-for-Human-Genetics--Inc--Announce-Change-in-Testing-Services-2851-1/ [accessed November 14, 2008].

Diagnostics does not have a contract with that program. Access for these consumers therefore depends on the availability of additional providers who may have contracts with Medicaid or entails direct out-of-pocket payment by consumers. Uncertainty surrounding whether these alternate providers will face enforcement or will stop testing creates an unstable situation.

Adoption by third party payers

- In our informal phone survey, test providers indicated that genetic tests for hearing loss are usually covered by insurance.
- While comprehensive data on the coverage position of all major insurers for all hearing loss tests are not available, it is unlikely that patents have had significant impact on the adoption of tests. CIGNA health care, for example, covers testing for GJB2 (patented) and GJB6 (unpatented).

Clinical and Scientific Background

Hearing loss refers to the permanent, bilateral or unilateral, sensory or conductive, loss of hearing averaging 30 decibels or more in the frequency region important for speech recognition.[7] Hearing loss can present at different stages in life, and therefore can be classified as prelingual (before learning to speak) or postlingual (after having learned a language). Prelingual hearing loss may be congenital or late-onset. Profound congenital hearing loss occurs in 1.8 per 1,000 live births in the U.S. The prevalence increases to 2.7 per 1,000 among those below five years of age. During the teenage years, prevalence increases to 3.5 per 1,000.[8] The lifetime societal costs for childhood hearing loss are estimated at $1.1 million per person, including lost productivity, special education, vocational rehabilitation, medical costs, and assistive devices attributable to deafness. Universal audiological newborn hearing screening programs have been introduced in the U.S. to reduce speech, social and emotional development problems experienced by children through early detection and intervention. At least 37 states have universal newborn hearing screening legislation and every state has early hearing detection and intervention programs, which screen approximately 93% of all infants.

As a heterogeneous trait, hearing loss has many environmental and genetic causes. Its incidence varies over time and across populations (see Figure 1).[9] Environmental causes, such as infections, account for approximately half of hearing loss cases. Congenital cytomegalovirus (CMV) infection, in particular, is responsible for as much as 10 percent of congenital hearing loss.[10] Genetic causes account for the other half of hearing loss cases. Hearing loss typically occurs due to abnormalities in single genes or sometimes gene pairs. A multitude of different genes and gene pairs (at least 65 genes and 110 choromosomal locations) have been implicated. Many others may yet be discovered.[11]

Genetic hearing loss can be further classified as "syndromic" and "non-syndromic," depending on whether it is associated with other clinical features (syndromic) or not (non-syndromic).[12] Syndromic cases represent about 30 percent of genetic hearing loss cases overall and encompass at least 400 syndromes and a similar number of genes. Non-syndromic hearing loss or impairment (NSHL or NSHI) comprises the other 70 percent of genetic hearing loss cases and involves at least 100 loci, which can further be broken down by pattern of inheritance. NSHL loci include 55 autosomal recessive (AR), 41 autosomal dominant (AD), 4 X-linked (XL), and two mitochondrial loci. Different mutations at the same

[7] American College of Medical Genetics (ACMG). Genetics evaluation guidelines for the etiologic diagnosis of congenital hearing loss. Op. cit.
[8] Morton C, Nance WE. Newborn hearing screening - a silent revolution. *NEJM* 2006. 354:2151-2164.
[9] Ibid.
[10] Ibid.
[11] Ibid.
[12] Ibid.

locus (chromosomal location, usually a gene) can present as either non-syndromic or syndromic hearing loss.[13] Mutations in different genes may also result in the similar phenotypes (clinical symptoms and signs).[14] A listing of non-syndromic and syndromic hearing loss disorders and loci, including genes, genetic tests, and associated patents, is presented in the appendix (Appendix I and II).

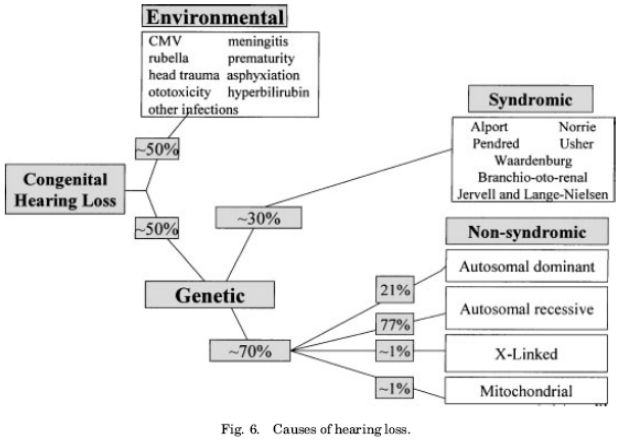

Fig. 6. Causes of hearing loss.

Figure 1. Causes of Hearing Loss (White K. Early hearing detection and intervention programs: opportunities for genetic services. *Am J Med Genet* 2004. 130A(1):29-36.**)**

Five most Common Genetic Tests for Hearing Loss

Given the numerous hearing loss genes, we have chosen to focus on the five genes most commonly tested for, based on population frequency: GJB2/Connexin 26, GJB6/Connexin 30, SLC26A4/PDS, MTRNR1, and MTTS1.[15]

GJB2

Mutations in GJB2, or Gap Junction Protein Beta-2, have by far the highest frequency among genetic causes of deafness and hearing loss, accounting for up to 50 percent of cases of profound deafness caused by DNA mutations (Table 1)[16]. GJB2 encodes Connexin 26 (Cx26), a hexameric gap junction protein widely expressed in the cells and tissues of the cochlea.[17] The link between GJB2 and non-syndromic deafness at the DFNB1 locus[18] was first published in a 1997 *Nature* article by D.P. Kelsell and colleagues at St. Bartholomew's and the Royal London School of Medicine and Dentistry, Queen Mary and Westfield College.[19] That same year at the Institut Pasteur, Christine Petit and colleagues discovered the most prevalent GJB2 mutation, 35delG.[20] The Institut Pasteur holds two patents (US 5,998,147 and

[13] American College of Medical Genetics (ACMG). Genetics evaluation guidelines for the etiologic diagnosis of congenital hearing loss. Op. cit.
[14] Morton C, Nance WE. Op. cit.
[15] The five most common hearing loss genes are also the most frequently tested genes. Authors' email and phone correspondence with Dr. Michael Watson, Director, American College of Medical Genetics, March, 2007.
[16] American College of Medical Genetics (ACMG). (2002). Genetics evaluation guidelines for the etiologic diagnosis of congenital hearing loss. *Genet Med,* 4(3):162-171.
[17] Morton C, Nance WE. Op. cit.
[18] Nonsyndromic hearing loss loci are classified "DFNB" for recessive, "DFNA" for dominant, "DFN" for X-linked, and "DFNM" if they modify the expression of other genetic forms. The loci within each class are then numbered (Morton C, Nance WE. Op. cit.).
[19] Kelsell D, Dunlop J, Stevens HP, Lench NJ, Liang JN, Parry G et al. Connexin 26 mutations in hereditary non-syndromic sensorineural deafness. *Nature* 1997. 387:80-83.
[20] Denoyelle F, Weil D, Maw MA, Wilcox SA, Lench NJ, Allen-Powell DR et al. Prelingual deafness: high prevalence of 30delG mutation in the connexin 26 gene. *Hum Mol Genet* 1997. 6:2173-2177.

6,485,908) for the GJB2/Connexin 26 gene and detection of its common deletion mutation. Patent applications were filed in August 1997 and granted in 1999 and 2002. The Institut Pasteur also holds patents for Connexin 26 in Canada and Japan. We have found no granted patents in Europe, although applications appear to have been filed. Patents have been exclusively licensed to Athena Diagnostics, and we infer these were licensed for use in the U.S., Canada, and Japan. In Europe, the exclusive license for Connexin 26 testing went to Nanogen, a provider of molecular diagnostic services.[21] As of February 2008, "Molecular Diagnostics for Prelingual Hearing" was still listed as a diagnostic technology available for licensing at the Institut Pasteur technology transfer website. This suggests either that existing licenses to Nanogen and Athena do not exhaust all territories worldwide or that provisions for particular fields of use have been retained by Institut Pasteur.[22] We have no direct information about whether Institut Pasteur has granted any additional licenses in Europe or the US.[23]

Based on data gathered through our telephone survey of providers (identified through GeneTests.org), testing for GJB2/Connexin 26 in the United States began as early as 1998. Kenneson et al. surveyed Connexin 26 testing providers in the U.S. in 1999 and 2000 (10 eligible providers in 1999 and 8 providers in 2000).[24] Based on provider information at GeneTests.org, 19 U.S. providers (18 non-profit and 1 for-profit) offered full sequence analysis, which is the most common type of GJB2 testing. PCR-based sequence analysis has been facilitated by the relatively small size of the single GJB2 coding exon.[25] Full sequence analysis is appropriate given that more than 195 GJB2 mutations have been identified,[26] which vary in frequency by race/ethnicity and family history.[27] The average price of the GJB2 full sequence test among non-profit providers is $472.35 compared to the list prices of $575 quoted by Athena Diagnostics, the reference provider (Table 1).

Table 1 Prices of Genetic Tests for the five most commonly tested Hearing Loss Gene

Gene Name	Type of hearing loss	Prevalence in affected	Patent holder	Type of Test	No of providers[a]		Price of Test ($)[b]	
					NonProfit	For Profit	NonProfit	For Profit
GJB2	Non syndromic	>50% [i]	Institut Pasteur US 5998147 US 6485908	Full sequence Analysis	18	1	472.35 [c] (362-818)	Athena 575 Prevention[d] 290 Diagnostics
GJB6	Non syndromic	7-16% [j]	N/A	Deletion Analysis	6	1	300.25 [e] (161-534)	295
SLC26A4	Syndromic	4-10% [k]	N/A	Full sequence Analysis	6	0	1686 [f] (1100-2507)	N/A
MTRNR1	Mitochondrial Non syndromic	<1% [i]	Cedars-Sinai US 5506101	Targeted mutation	8	2	210 [g] (150-285)	248 [h] 365
MTTS1	Mitochondrial	<1% [i]	N/A	Targeted	4	0	238	N/A

[21] Fresh News. Nanogen licenses rights to gene linked to hereditary deafness. 2003. See http://www.freshnews.com/news/biotech-biomedical/article_15724.html?Nanogen [accessed March 10, 2007].
[22] Institut Pasteur Technology Transfer. See http://www.pasteur.fr/ip/easysite/go/03b-000024-0ap/licensing-opportunities/list-of-technologies-available-for-licencing-or-transfer [accessed January 16, 2009]. Currently the technology is listed under Genomics (ID 98.30); however, it is unclear if the technology listed relates to testing for GJB2 specifically. Previous versions of the site accessed in February 2008 indicated that the technology listed was GJB2 testing.
[23] The Institut Pasteur was contacted by email to clarify the status of licenses but has not responded.
[24] Kenneson A, Myers MF, Lubin IM, Boyle C. Genetic laboratory practices related to testing of the GJB2 (connexin 26) gene in the United States in 1999 and 2000. *Genetic Testing* 2003. 7(1):49-56.
[25] Pandya A, Arnos KS, Xia XJ, Welch KO, Blanton SH, Friedman TB et al. Frequency and distribution of GJB2 (connexin 26) and GJB6 (connexin 30) mutations in a large North American repository of deaf probands. *Genet Med* 2003. 5(4):295-303.
[26] Morton C, Nance WE. Op. cit.
University of Cardiff. *Human Gene Mutation Database*. See http://www.hgmd.cf.ac.uk/ac/gene.php?gene=GJB2 [accessed 19 November 2008].
[27] Pandya, A., Arnos KS, Xia XJ, Welch KO, Blanton SH, Friedman TB, et al. Op. cit.

	Non syndromic			mutation		(150-285)

[a] Providers for specific test type identified from Genetests (see http://www.genetests.org) are current as of January 2009.
[b] List prices of tests obtained from phone survey March 2007 or test laboratory web site
[c] Average list price for 14 out of 17 providers offering full sequence analysis
[d] Prices of 2 separate for-profit providers in 2008. Preventions Diagnostics is no longer listed on GeneTests as of January 2009.
[e] Average list price for 4 out of 7 providers
[f] Average list price for 4 out of 6 providers, not including NIH which offers testing free of charge to research participants
[g] Average list price for 6 out of 8 providers
[h] Prices of 2 separate for-profit providers
[i] American College of Medical Genetics (ACMG). Genetics evaluation guidelines for the etiologic diagnosis of congenital hearing loss. *Genet Med* 2002. 4(3): 162-171.
[j] del Castillo et al. Prevalence and evolutionary origins of the del(GJB6-D13S1830) mutation in the DFNB1 locus in hearing-impaired subjects: a multicenter study**.** *Am J of Human Genet* 2003. 73(6):1452-8.
[k] Morton C, Nance WE. Newborn hearing screening - a silent revolution. *NEJM* 2006. 354:2151-2164.

Table 2 Comparison of Prices for Connexin 26 full sequence analysis

Laboratory	**Amplicons***	**Gene sequencing price**	**Cost per amplicon****
Athena Diagnostics (for profit)	2	$575	$287.5
Case Western University	5	$704	$140.8
Emory University	3	$490	$163.33
Univ of Chicago	2	$430	$215.
Cincinnati Childrens Medical Center	2	$533	$266.50
Baylor College	1	$430	$430
Harvard Partners	2	$400	$200
Greenwood Genetics	2	$500	$250
Univ of Washington	2	$362.54	$181.27

* Number of nucleic acid sequences targeted for amplification (according to number of times CPT billing code 83898 is used)
**Gene sequencing price divided by number of times CPT 83898 billed

Prices for full sequence analysis of *Connexin 26,* when normalized for number of amplicons, are also quite variable among providers. The unit price for the test offered by Athena Diagnostics is in the middle of the price range of non-profit providers (Table 2). The average price per amplicon of tests offered by non-profit providers is ~$231 and is comparable to Athena's unit price for full-sequence analysis ($287.5). Although diagnostic billing codes provide some standardization for full-sequence tests, techniques and procedures are not identical among laboratories. Beyond comparing prices based on CPT codes for amplification and the same billing codes are not always used the labs surveyed also likely have different overhead costs.

While it appears that the number of U.S. providers offering Connexin 26 testing has increased to 19 from the 10 identified by Kenneson et al. in 2000 (19 providers listed on Genetests.org offered full sequence analysis in January 2009),[28] it is unclear whether the Institut Pasteur's exclusive license to Athena Diagnostics for Connexin 26 testing has deterred other laboratories from testing. Some listed services may send samples to Athena or to offshore providers. To date, it appears that Athena Diagnostics has not granted sublicenses to any other providers listed on GeneTests.org.[29] It is also not clear whether patents and exclusive licensing have contributed to a pricing differential or monopoly pricing by a sole provider.

[28] Kenneson A, Myers MF, Lubin IM, Boyle C. Op. cit.
[29] Author's personal communications by phone with Dr. Michael Henry, Business Development, Athena Diagnostics, March 2007.

The 14 non-profit institutions we surveyed offer the test at varying prices, some comparable to the price of Athena Diagnostics, as shown in Tables 1 and 2.

GJB6

A significant portion (30-50%) of nonsyndromic genetic hearing loss is attributed to mutations in GJB6, or Gap Junction Protein Beta-6. Like GJB2, GJB6 is expressed in the cochlea and contributes to DFNB1 hearing loss. The GJB6 gene encodes Connexin 30 (Cx 30), a heteromeric gap junction protein that can form channels with Connexin 26, resulting in cases of digenic transmission (that is, the condition results from two different affected genes).[30] The link between the > 300kb GJB6 deletion and nonsyndromic DFNB1 hearing loss was first published in January 2002 in the *New England Journal of Medicine* by Ignacio del Castillo and colleagues at the Unidad de Genética Molecular, Hospital Ramón y Cajal, Madrid, Spain.[31] Genetic testing for GJB6 deletions in patients with hearing loss is linked to the genetic diagnosis of GJB2. GJB6 deletions are found in trans (that is, the genes are located on different chromosomes, suggesting the effect is mediated by a protein produced by the genes, rather than regulation of the genes themselves) with a mutant GJB2 allele and contribute to the same subtype of genetic deafness, DFNB1. The joint contribution of mutations in these two genes to non-syndromic recessive hearing loss is about 30-50%. While prevalence varies across populations, one North American study found a 2.57% prevalence of GJB2/GJB6 digenic cases among deaf individuals, with more severe hearing loss than is typical for GJB2 alone.[32] However a more recent study by Putcha et al. reported that the frequency of a >300Kb deletion in individuals bearing compound GJB2 and GJB6 mutations was only 1% in a large North American cohort. Putcha et al.'s data suggest that this mutation may be quite rare.[33] No U.S. patents or applications associated with the Connexin 30 gene or mutation testing were identified in our patent searches. Dr. Ignacio del Castillo, who first reported the GJB6 deletion mutation, confirmed that he had not applied for patents.[34] To date, seven (six non-profit and one for-profit) providers offer Connexin 30 deletion analysis in the U.S. The test appears to have been offered in the U.S. as early as 2002, based on our telephone survey of providers listed on GeneTests.org. The list price for GJB6/Connexin 30 testing averages $300 at non-profit institutions and is $295 at the one for-profit laboratory.

SLC26A4

In 1997, Eric Green and colleagues at the National Human Genome Research Institute (NHGRI) identified the SLC26A4, or PDS gene, which encodes the protein pendrin, a transporter of chloride, bicarbonate and iodide.[35] Mutations in SLC26A4 are implicated in a form of syndromic deafness (Pendred syndrome), as well as a form of nonysndromic deafness DFNB4. Pendred syndrome is the most common form of syndromic deafness, and accounts for up to 10 percent of deafness. Pendred syndrome has an incidence of 7.15-10 per 100,000 births.[36]

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[30] Morton C, Nance WE. Op. cit.
[31] del Castillo I, Villamar M, Moreno-Pelayo MA, del Castillo FJ, Alvarez A, Telleria D et al. A deletion involving the connexin 30 gene in nonsyndromic hearing impairment. *NEJM* 2002. 346:243-249.
[32] Pandya, A., Arnos KS, Xia XJ, Welch KO, Blanton SH, Friedman TB, et al. Op. cit.
[33] Putcha GV et al. A multicenter study for the frequency and distribution of GJB2 and GJB6 mutations in a large North American cohort. *Gen in Med* 2007. 9:413-426.
[34] Authors' email correspondence with Dr. Ignacio del Castillo, June 2007.
[35] Everett L, Glaser B, Beck JC, Idol JR, Buchs A, Heyman M et al. Pendred syndrome is caused by mutations in a putative sulphate transporter gene (PDS). *Nat Genet* 1997. 17:411-422.
[36] Ibid.

While both Pendred syndrome and DFNB4 involve severe hearing loss and an enlarged vestibular aqueduct, Pendred syndrome is also associated with thyroid goiter.[37] The severity of goiter is variable, and thyroid symptoms may not occur until late childhood or even adolescence. Pendred syndrome typically has a prelingual age of onset (before the critical period for language development), whereas nonsyndromic DFNB4-associated deafness tends to be postlingual.[38] No U.S. patents relating to SLC26A4 were identified.[39]

Based on our informal phone survey of providers, testing for SLC26A4 has been available since at least 2002. The most commonly offered test, full-sequence analysis, can detect disease-causing mutations in about half of multiplex and one-fifth of simplex cases.[40] All six U.S. providers of full sequence analysis SLC26A4 testing are non-profit institutions, and the average price is $1,686. The relatively high price of SLC26A4 full sequence analysis cannot be attributed to the existence of a patent or exclusive licensing. Rather, it appears that the cost of full sequence analysis relates to SLC26A4 being a large gene (~77 Kb) with twenty-one exons encoding a 4.93 Kb transcript. Therefore, testing requires testing methods comparable in complexity and price to testing for inherited susceptibility to colon and breast cancer.[41] The price/per amplicon for sequencing the SLC26A4 gene ranges from $55.00- $125.25 when standardized for the number of PCR amplifications reactions performed.[42] Four providers offer SLC26A4 analysis for specific mutations at lower costs ($635) than the full sequence analysis. Targeted mutation analysis has a sensitivity of 70% for heterozygotes and 91% for those homozygous for a mutation.[43]

MTRNR1 and MTTS1

Mitochondrial forms of moderate to profound nonsyndromic hearing loss result from mutations in either the MTRNR1 or MTTS1 genes in mitochondrial DNA, each of which accounts for fewer than 1% of hearing loss cases. MTRNR1 encodes 12S ribosomal RNA (12S rRNA), while MTTS1 encodes transfer RNA for serine (tRNA Ser[UCN]).[44] The most common MTRNR1 mutation, A1555G, occurs with a 0.3% frequency in the United States.[45] Prezant et al., from Cedars-Sinai Medical Center in Los Angeles, California, first reported the association between A1555G mutations and aminoglycoside-induced and nonsyndromic deafness in *Nature Genetic*s in July 1993.[46,47]

MTRNR1 mutations may contribute to permanent, non-progressive hearing loss either through: (1) susceptibility to aminoglycoside (antibiotic) ototoxicity, irrespective of dose, or (2) late onset hearing loss

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[37] Smith R, Van Camp G. *Pendred Syndrome/DFNB4.* 2008. See http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=pendred [retrieved April 15, 2007]. In the absence of goiter, Pendred syndrome is classified by an abnormal perchlorate discharge test.
[38] Morton C, Nance WE. Op. cit.
[39] Requires independent verification by Dr. Eric Green, the senior author on the publication reporting the discovery of the PDS gene and mutations.
[40] Smith R, Van Camp G. Op. cit.
[41] Morton C, Nance WE. Op. cit.
Cook-Deegan R et al. *Impact of Gene Patents on Access to Genetic Testing for Inherited Susceptibility to Cancer: Comparing Breast and Ovarian Cancers to Colon Cancers.* Peer-reviewed case study submitted to the Secretary's Advisory Committee on Genetics, Health, and Society, 2008.
[42] The number of amplicons for SLC26A4 gene sequencing is 20, the number of nucleic acid sequences targeted for amplification (base on the number of times CPT billing code 83898 is used by the provider).
[43] Ibid.
[44] Pandya A. *Nonsyndromic Hearing Loss and Deafness, Mitochondrial*. 2007. See http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=mt-deafness [accessed January 15, 2008].
[45] Pandya A. *Nonsyndromic Hearing Loss and Deafness, Mitochondrial*. 2007. See http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=mt-deafness [accessed January 15, 2008].
[46] Prezant T, Agapian JV, Bohlman MC, Bu X, Oztas S, Qiu WQ et al. Mitochondrial ribosomal RNA mutation associated with both antibiotic-induced and non-syndromic deafness. *Nat Genet* 1993. 4:289-294.
[47] Estivill X, Govea N, Barcelo A, Perello E, Badenas C, Romero E et al. Familial progressive sensorineural deafness is mainly due to the mtDNA A1555G mutation and is enhanced by treatment with aminoglycosides. *Am J Hum Genet* 1998. 62:27-35.

in the absence of aminoglycoside exposure. MTTS1-related hearing loss, in contrast, has a characteristic progression first appearing during childhood and with penetrance that varies by individual mutational load (more numerous mutations accompany earlier onset and more severe deafness).[48] Higher mutation loads of some MTTS1 mutations also correlate with the manifestation of other clinical signs, such as palmoplantar keratoderma, or ataxia and myoclonus.

The association between mutations in MTTS1 (tRNA –Ser [UCN]) and sensorineural deafness was first reported in 1994 by F.M. Reid and colleagues at the University of Glasgow in Scotland, UK.[49]

Cedars-Sinai Medical Center holds a patent (US 5,506,101) that covers MTRNR1 mutation testing, specifically testing for the A1555G mutation. The patent application was filed in June 1993 and granted in April 1996. Athena Diagnostics acquired an exclusive license for mutation testing for MTRNR1 from Cedars-Sinai Medical Center. Cedars-Sinai Medical Center also holds patents in Japan and Canada for MTRNR1 A1555G mutation and testing. No patents were filed in Europe.

Our searches found no patents covering the MTTS1 sequence or genetic testing for its mutations.

MTRNR1 testing first became available in the U.S in 2000. Targeted mutational analysis is now offered by ten U.S. providers. The two for-profit providers average a higher list price ($355) than the six non-profit (university hospitals and medical center based) providers (average $210) (See Table 1). Information about sublicenses from Athena Diagnostics for MTRNR1 mutation testing is not publicly available. (If SACGHS sends a list of queries to Athena Diagnostics, licensing status of MTRNR1 testing could be included.) In contrast, MTTS1 targeted mutation analysis has been available since 2004 and is offered by four non-profit providers for an average price of $238 (see Table 1). In addition, a subset of non-profit providers also offers testing for a panel of mitochondrial mutations, including both MTRNR1 and MTTS1, for an average price of $438.

Newborn Hearing Screening

Because of the potential for language, social, emotional, and other developmental consequences in children whose hearing loss is detected after six months of age, a 1993 National Institutes of Health (NIH) Consensus Development Conference endorsed universal newborn hearing screening.[50] In 1999, the Health Resources and Services Administration (HRSA) and Centers for Disease Control and Prevention (CDC) began funding state Early Hearing Detection and Intervention (EHDI) programs.[51] At least 37 states have legislation for universal newborn screening for hearing. Today, EHDI programs exist in every state, providing screening for approximately 93% of all infants.[52] The goals of EHDI programs are three-fold: (1) to screen all newborns before one month; (2) to diagnose newborns before three months; and (3) to coordinate intervention before six months[53] (see Appendix III for detailed flowchart). EHDI programs have reduced the average age for confirming hearing loss from 20 to 30 months (before the program), to 2 to 3 months (after implementation).

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[48] Pandya A. Op. cit.
[49] Reid F, Vernham GA, Jacobs HT. A novel mitochondrial point mutation in a maternal pedigree with sensorineural deafness. *Hum Mutat* 1994. 3(3):243-247.
[50] *Early Identification of Hearing Impairment in Infants and Young Children. NIH Consensus Development Conference Statement*. March 1 – 3, 1993. See http://consensus.nih.gov/1993/1993HearingInfantsChildren092html.htm [accessed January 16, 2009].
[51] White KR. The current status of EHDI programs in the United States. *Ment Retard Disabil Res Rev* 2003. 9:79-88.
[52] National Resource Center for Early Hearing Detection and Intervention. See http://www.infanthearing.org/tas/index.html [accessed August 2007].
[53] White KR. The current status of EHDI programs in the United States. Op. cit.

The EHDI programs miss some hearing loss cases, however, because prelingual hearing loss does not always present during infancy. SLC26A4 and A1555G-related hearing loss can appear after infancy, for example. Some cases of GJB2 deafness cannot be detected at birth. With an estimated non-penetrance rate of 3.8%,[54] EHDI programs are seen by some as an opportunity for more genetic testing as part of the evaluation process.[55,56] Practical obstacles remain in screening programs for hearing loss, including uncertainty about the appropriate timing and role of genetic testing in the EHDI process.[57] Survey data show that 20% of professionals who administer EHDI programs lack genetics training, which fuels concern about ordering and interpreting complex genetic tests.[58]

Clinical Guidelines for Genetic Testing

In 2002, the American College of Medical Genetics (ACMG) published clinical guidelines that incorporate genetic testing into the diagnosis of congenital hearing loss.[59] The Cincinnati Children's Hospital Medical Center's testing paradigm exemplifies how hearing loss genetic test providers approach genetic evaluation (see Appendix IV). A pre-test session to explain the causes and types of deafness, along with testing options and modes of inheritance, is important. After the pre-test session, the next step entails getting a family history and an individual patient history and conducting a physical examination to determine whether or not a diagnosis is apparent. If syndromic hearing loss is suspected, the ACMG recommends gene-specific mutation tests. The diagnosis of non-syndromic cases is more complex, and relies on details of family history and individual symptoms. Individuals with hearing-impaired first-degree relatives, or two deaf parents, are also candidates for GJB2 testing. As the most common genetic cause of hearing loss, GJB2 is the first in a series of recommended tests.

If a GJB2 test reveals that an individual is a heterozygote, Cincinnati Children's conducts a follow-up GJB6 deletion screen. If the GJB2 test is negative, the ACMG calls for non-syndromic mitochondrial testing, specifically for the A1555G and A7445G mutations. Cincinnati Children's distinguishes among the types of mitochondrial testing, suggesting MTRNR1 testing only in the presence of aminoglycoside exposure, and a full mitochondrial panel otherwise. Following these initial rounds of genetic testing for GJB2 and mitochondrial mutations, the ACMG recommends post-test counseling and education. Given that 10% of deaf infants have culturally deaf parents, the availability of interpreters and the culturally sensitive interpretation of hearing loss test results are critical.[60]

After parents are informed of their options, follow-up and additional genetic testing may be recommended. Imaging studies may be ordered to consider the possibility of DFNB4 or Pendred syndrome, particularly for progressive hearing loss. Such imaging studies may include temporal bone imaging, to look for an enlarged vestibular aqueduct and/or cochlear dysplasia. If imaging studies have positive findings, mutation screening of SLC26A4 would be recommended.

Clinical Utility of Genetic Testing for Hearing Loss

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[54] Norris V, Arnos KS, Hanks WD, Xia X, Nance WE, Pandya A. Does universal newborn hearing screening identify all children with GJB2 (connexin 26) deafness? Penetrance of GJB2 deafness. *Ear & Hearing* 2006. 27:732-741.
[55] Arnos K. The implications of genetic testing for deafness. *Ear & Hearing* 2003. 24:324-331.
[56] White K. Early hearing detection and intervention programs: opportunities for genetic services. *Am J Med Genet* 2004. 130A(1):29-36.
[57] Schimmenti L, Martinez A, Fox M, Crandall B, Shapiro N, Telatar M et al. Genetic testing as part of the early hearing detection and intervention (EHDI) process. *Genet Med* 2004. 6(6):521-525.
[58] Burton S, Withrow K, Arnos KS, Kalfoglou AL, Pandya A. A focus group study of consumer attitudes toward genetic testing and newborn screening for deafness. *Genet Med* 2006. 8(12):779-783.
[59] American College of Medical Genetics (ACMG). Genetics evaluation guidelines for the etiologic diagnosis of congenital hearing loss. Op. cit.
[60] Ibid.

Genetic tests offer several advantages over conventional hearing loss evaluation without genetic testing. The benefits anticipated from genetic testing include:[61,62,63]

1) Reduction of additional time consuming, invasive, and expensive testing;
2) Choice of early interventions such as hearing aids, cochlear implants , or sign language that significantly improve language ability and quality of life outcomes;
3) Information on the progression of the condition;
4) Ability to monitor associated clinical manifestations and complications, particularly for certain syndromic forms of hearing loss;
5) Information on the chance of recurrence in the family that can inform reproductive decisions; and
6) Information pertinent to risks and health care decisions (e.g., avoiding aminoglycoside antibiotics among those with MTRNR1 mutations).

Genetic testing may be more sensitive and specific than traditional evaluation. A study at Cincinnati Children's Hospital found that 80% of hearing loss patients remained undiagnosed after traditional evaluation. Furthermore, genetic tests may facilitate earlier detection of hearing loss. Despite widespread newborn screening for hearing loss, a recent analysis showed that "current newborn hearing screening does not identify all infants with two GJB2 mutations."[64] The age at which the hearing loss was identified ranged from 12-60 months. A delay in detecting hearing loss has important implications for language acquisition and limits subsequent choices among management strategies. A study about cochlear implants reports, "There seems to be a substantial benefit for both speech and vocabulary outcomes when children receive their implant before the age of 2.5 years."[65] A white paper addressing the societal costs of hearing loss concludes that "early identification of deafness or hearing loss is critical in preventing or ameliorating language delay or disorder in children who are deaf or hard of hearing and allows for appropriate intervention or rehabilitation. Early identification and intervention have lifelong implications for language development."[66] The present value of lifetime societal costs for prelingual hearing loss is estimated as $1.1 million, which includes lost productivity, special education, vocational rehabilitation, medical costs, and assistive devices attributable to deafness.[67]

Cost Effectiveness of Genetic Testing for Hearing Loss

We found no comprehensive cost effectiveness analyses of genetic testing for hearing loss. GJB2 testing may preclude the need for more expensive or invasive tests and provide the emotional benefit of knowing the cause as well as the clinical benefit of predictive information about progression and treatment options.[68] A recent study at the Cincinnati Children's Hospital Medical Center demonstrated that when compared to "simultaneous testing, which comprises a battery of tests including standard laboratory work-up, or diagnostic evaluation by imaging--a diagnostic algorithm with GJB2 genetic testing as the

[61] White K. Early hearing detection and intervention programs: opportunities for genetic services. Op. cit.
[62] Schimmenti, L., Martinez A, Fox M, Crandall B, Shapiro N, Telatar M et al. Op. cit.
[63] Robin N, Prucka SK, Woolley AL, Smith RJH. The use of genetic testing in the evaluation of hearing impairment in a child. *Curr Opin Pediatr* 2005. 17:709-712.
[64] Norris V, Arnos KS, Hanks WD, Xia X, Nance WE, Pandya A. Op. cit.
[65] Connor CM, Craig HK, Raudenbush SW, Heavner K, Zwolan TA. The age at which young deaf children receive cochlear implants and their vocabulary and speech-production growth: is there an added value for early implantation? *Ear Hear* 2006. 27(6):628-44.
[66] *A White Paper Addressing the Societal Costs of Hearing Loss and Issues in Third Party Reimbursement*. 2004. See http://www.audiologyonline.com/articles/article_detail.asp?article_id=1204 [accessed January 16, 2009].
[67] Mohr PE, Feldman JJ, Dunbar JL, McConkey-Robbins A, Niparko JK, Rittenhouse RK, Skinner MW. The societal costs of severe to profound hearing loss in the United States. *Int J Technol Assess Health Care* 2000.16(4):1120-35.
[68] Arnos K. Op. cit.

first step--resulted in a possible savings of $20,180 in imaging costs and $34,000 in laboratory test costs per 100 children screened."[69] The data on test-specific savings are:[70]

Table 2. Cost estimates of alternative SNHL evaluation approaches based on diagnostic yields

Testing yields	Bilateral			Unilateral	Overall
	Mild to moderate	Moderately severe	Severe to profound		
GJB2 screen (N = 161)	15.5% (N= 45)	5.0% (N=20)	37.7% (N= 71)	0.0% (N= 25)	18.0%
Imaging (N = 616)	21.2% (N=144)	24.7% (N=81)	29.9% (N=241)	35.7% (N=150)	27.3%
Laboratory test	0.0%	0.0%	0.3%	0.0%	0.07%
Cost estimates (per 100 children)					
Simultaneous evaluation	$193,200	$193,200	$193,200	$193,200	$193,200
GJB2 paradigm*	$141,096	$152,005	$121,530	n/a	$139,020
Imaging paradigm†	$145,900	$144,034	$144,763	$103,900	$145,766

*Our proposed diagnostic algorithm (*GJB2* paradigm) suggests that children with positive *GJB2* screens do not require further testing. Overall, an 18% yield, as seen in our cohort, would entail savings of up to $20,180 in imaging costs and nearly $34,000 in laboratory costs per 100 children.
†In cases of bilateral SNHL, it could be argued that imaging should be obtained prior to *GJB2* screening (Imaging paradigm). Estimates across SNHL groups, however, generally show cost savings when *GJB2* screening is performed as an initial step.

Another study at Children's Hospital of Alabama assessed the cost of a battery of laboratory tests to evaluate hearing loss, including thyroid function, congenital infection, electrocardiograms, urine analysis, and serum phytanic acid levels, weighed in at more than $1,300, compared to the one-time $425 cost of a GJB2 genetic test.[71]

While the benefits of GJB2 testing have yet to be quantified, researchers note the ability of GJB2 tests to define chance of recurrence, i.e., if a child is GJB2 positive, a hearing couple knows that there is a 25 percent chance they will have a deaf child in each future pregnancy, and a deaf couple (each with GJB2 deafness) can learn that there is a 100% chance they will have deaf children.[72] GJB2 testing may also be important given the success of cochlear implants among GJB2 positive individuals. A GJB2-positive individual may develop the same speech skills as an individual with normal hearing if the hearing loss is diagnosed and the cochlear implants are prescribed at a young enough age.[73]

In the case of non-syndromic mitochondrial testing, quantitative data are scarce. The benefits, however, are significant, considering that a positive A1555G test could prevent an infant from being exposed to aminoglycoside antibiotics, thereby preventing hearing loss. Another consideration associated with testing for these mutations is that aminoglycosides are often given before genetic testing has been performed because the infectious process has to be treated without delay. So in reality, the test is only beneficial if conducted prior to the onset of infection, or if test results can be turned around within a few hours. Due to increased numbers of premature births and widespread use of gentamycin in neonatal intensive care units, neonatologists have been particularly concerned about A1555G mutations and aminoglycoside exposure. However, in the absence of point-of-care testing, it would require screening parents prior to delivery or testing newborns to identify those at high risk of hearing loss from aminoglycoside use. For an individual with an A1555G substitution and no exposure to aminoglycosides, the probability of developing hearing loss by age 30 drops from 100% to 40%.[74] Given the lifetime cost associated with prelingual hearing loss of $1.1 million, that amount could be averted by each case of deafness avoided. Since aminoglycosides

[69] Preciado D, Lim LHY, Cohen AP, Madden C, Myer D, Ngo C et al. A diagnostic paradigm for childhood idiopathic hearing loss. Otolaryngol Head Neck Surg 2004. 131:804-809.
[70] Ibid.
[71] Robin N, Prucka SK, Woolley AL, Smith RJH. Op. cit.
[72] Ibid.
[73] Ibid.
[74] Pandya A, Arnos KS, Xia XJ, Welch KO, Blanton SH, Friedman TB et al. Op. cit.

are only prescribed in the event of severe in-hospital infections, the number of individuals prescribed aminoglycosides and estimates of the increased risk of untreated infection would have to be factored into any cost-effectiveness calculation.[75]

The limitations of genetic testing for hearing loss also have to be taken into account in cost effectiveness analysis. Since genetic deafness is population- and ethnicity-specific, relative frequencies should first be refined to best represent the population being studied. While GJB2 testing may confer large benefits for individuals who test positive, those benefits also have to be measured against the costs for individuals who test negative. Individuals who test negative for GJB2 mutations may have to undergo additional medical and/or genetic testing or may experience emotional difficulty when attempting to comprehend the meaning of the confusing and inconclusive test results.[76]

Molecular Testing for Hearing Loss: New Developments and Technologies

If recommendations to include genetic testing as part of expanded EHDI[77,78] programs and clinical follow up of infants identified by universal newborn hearing loss screening are followed, then the volume of genetic testing for hearing loss could rise dramatically. Testing for mutations associated with the most common forms of syndromic and non-syndromic hearing loss plus congenital CMV infection can determine the cause of hearing loss in most cases of congenital hearing loss. Preciado et al. conclude that introduction of genetic testing (specifically GJB2 testing) for hearing loss in the clinical evaluation paradigm is cost effective.[79]

Recently Pediatrix introduced genetic testing services for hearing loss. Pediatrix is one of the largest providers of newborn metabolic screening and newborn hearing loss screening services in the U.S. Pediatrix's SoundGene™ Screening panel includes mutations associated with the most common forms of nonsyndromic and syndromic hearing loss. It also includes testing for common mutations in the mitochondrial MTTS1 gene, as well as testing for CMV infection (determined by measurement of copies of viral DNA, and therefore also, in essence, another genetic test). CMV infections account for up to 25% of congenital hearing loss caused by pathogenic agents. The SoundGene™ panel includes:

[75] Fischel-Ghodsian N. Mitochondrial mutations and hearing loss: paradigm for mitochondrial genetics. *Am J Hum Genet* 1998. 62:15-19.
[76] Robin N, Prucka SK, Woolley AL, Smith RJH. Op. cit.
[77] White K. Early hearing detection and intervention programs: opportunities for genetic services. Op. cit.
[78] Joint Committee on Infant Hearing (JCIH). Year 2000 position statement: principles and guidelines for early hearing detection and intervention programs. *Pediatrics* 2000. 106(4):798-817.
[79] Preciado D, Lim LHY, Cohen AP, Madden C, Myer D, Ngo C et al. Op. cit.

The SoundGene™ Screening Panel[80]

Connexin 26 (Cx26) GJB2 mutations:
35delG 167delT
235delC M34T

Connexin 30 (Cx30) GJB6 large deletion
309 kb large deletion

Mitochondrial mutations:
7445A>C (A7445C) 961T>C (T961C)
7445A>G (A7445G) 961T>G (T961G)
7444G>A (G7444A) 961 delT + C(n)ins

Pendred SLC26A4 mutations:
L236P 1001+1G>A
E384G T416P

CMV DNA

The SoundGene™ Screening Panel was introduced in December 2006. The list price is $ 95.00.[81] A U.S. patent application for the SoundGene™ Screening Panel is pending (Application U.S. 20040038266A filed in 2003, see Appendix V). SoundGene™ has also been trademarked. The test is described as a "quick and cost-effective alternative" and has an average turnaround time of 48 hours. Genetic counseling services for interpretation of test results and consultation are available through Pediatrix. Pediatrix has acquired a sublicense from Athena Diagnostics for testing of the Connexin 26 35delG mutation, which is included in the SoundGene™ panel. Pediatrix is the only provider to which Athena reports having issued a sublicense for Connexin 26 testing in the U.S. Although we do not have details of the licensing agreement and royalties, it is likely that the anticipation of high testing volume by Pediatrix as part of its newborn hearing loss screening services was an incentive for this agreement. Interestingly, however, the SoundGene™ panel does not include testing for the common A1555G mutation in the mitochondrial MTRNR1 gene (Patent no: US 5,506,101) that is also exclusively licensed to Athena Diagnostics.

High-throughput molecular diagnostics for hearing loss

With over 90 percent of newborns currently being screened for hearing loss and the potential for expanded EHDI programs to include molecular screening, genetic testing may shift to newer platform technologies for high-throughput genetic testing. Microarray-based genetic testing is being actively pursued as an efficient, reliable and potentially cost-effective tool when many mutations in a gene or numerous different genes must be tested. Hearing loss could be such a case. Since hundreds of loci are involved in the biology of hearing loss and additional genes and mutations may yet be discovered, microarray chips that can readily add new genes or mutations might help address both research and clinical needs. Microarray-based diagnostic testing for hearing loss might make it more flexible, less expensive, and more comprehensive while being as sensitive and specific as existing genetic tests.

Several groups report working on microarray-based diagnostic testing for hearing loss. Henrik Dahl and colleagues from the University of Melbourne and Children's Royal Hospital in Australia have developed a hearing loss microarray that detects 15 common mutations in the Connexin 26/GJB2, SLC26A4,

[80] See http://www.pediatrix.com/body.cfm?id=2889 [accessed January 16, 2009].
[81] Information obtained from Pediatrix by phone inquiry, March 2007.

USH2A genes and mitochondrial 12S rRNA.[82] This array-based chip was validated using DNA from 250 patients diagnosed with sensorineural hearing loss. It detected the mutations for which it was designed with 100% accuracy, and Siemering et al. report that no false positives or negatives were detected.[83] Commercial development of the hearing loss biochip is suggested by U.S. patent application US20070009887A1, "Genotyping of deafness by oligonucleotide microarray analysis," which was filed in November 2003, listing Victoria Siemering and Henrik Dahl as the inventors (Appendix V).

Another microarray diagnostic chip was recently reported by Iris Schrijver, Andres Metspalu, and colleagues in September 2006.[84] Their diagnostic panel includes 198 mutations in 8 genes most commonly associated with non-syndromic sensorineural hearing loss. A patent application US20070134691A1 for this diagnostic has been filed by Schrijver and colleagues (Appendix V). The chip uses arrayed primer extension (APEX) technology, first developed by J. M. Shumaker and C.T. Caskey (Baylor College of Medicine, Houston Texas) and A. Metspalu (University of Tartu, Estonia).[85,86] Patents covering this technology, US 6,153,379 and US 7,001,722, were granted in 2000 and 2006.

The hearing loss chip tests for mutations in Connexin 26/GJB2, Connexin 30/GJB6, GJB3, GJA1, SLC26A4, SLC26A5, and mitochondrial 12S rRNA and tRNA Ser[UCN] and includes the commonly tested Connexin 26 35delG and A1555G MTRNR1 mutations, both of which are licensed exclusively to Athena Diagnostics. Currently this diagnostic assay is being offered on a "research only" basis at the Molecular Pathology Laboratory at Stanford University by Dr. Schrijver and colleagues.[87] Genetic testing for hearing loss using this diagnostic chip is being offered by Asper Biotech.[88] Asper Biotech, located in Tartu, Estonia, was founded in 1999 with Dr. Andres Metspalu as its scientific advisor, and has expertise in developing and validating highly customized SNP/mutation screening assays. Asper Biotech also offers genetic testing services for diseases including cystic fibrosis, Usher Syndrome, retinitis pigmentosa, thalassemia, and a panel of genetic disorders common in the Ashkenazi Jewish population.[89] Dr. Andres Metspalu at University of Tartu, Estonia, confirmed that the testing services offered by Asper Biotech are for research. The hearing loss test and other genetic tests offered by Asper Biotech are used by some academic medical centers and hospitals in the U.S in clinical research studies, often as part of collaborative projects.[90] It is not clear that any licenses have been negotiated by Asper Biotech with Institut Pasteur or Nanogen for the use of Connexin 26 mutation testing or with Cedars Sinai Medical Center for MTRNR1 mutation testing, but a license might not be required because they are not patented in Estonia. (Patent applications covering Connexin 26 and MTRNR1 mutations and diagnostic testing were never filed in Estonia.) Dr Metspalu confirmed that there is no patent protection for Connexin 26 and MTRNR1 mutations and testing in Estonia. However, he indicated that if Asper Biotech did decide to market the hearing loss test in the US, it would have to acquire sublicenses for all the relevant intellectual property and would have to factor royalty payments into its business plan. (We are not sure we concur with this judgment if the test itself were conducted in Estonia.)

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[82] Siemering K, Manji SS, Hutchison WM, Du Sart D, Phelan D, Dahl HH. Detection of mutations in genes associated with hearing loss using a microarray-based approach. *J Mol Diagn* 2006. 8(4):483-489.
[83] Ibid.
[84] Gardner P, Oitmaa E, Messner A, Hoefsloot L, Metspalu A, Schrijver I. Simultaneous multigene mutation detection in patients with sensorineural hearing loss through a novel diagnostic microarray: a new approach for newborn screening follow-up. *Pediatrics* 2006. 118(3):985-994.
[85] Shumaker J, Metspalu A, Caskey CT. Mutation detection by solid phase primer extension. *Hum Mutat* 1996. 7(4):346-354.
[86] Kurg A, Tonisson N, Georgiou I, Shumaker J, Tollett J, Metspalu A. Arrayed primer extension: solid-phase four-color DNA resequencing and mutation detection technology. *Genet Test* 2000. 4(1):1-7.
[87] Personal communication, Phone Conversation with Iris Schrijver, March 07
[88] Asper Biotech. *Hereditary Hearing Loss Testing*. See http://www.asperbio.com/HHL.htm [accessed March 10, 2007].
[89] Asper Biotech. *Hereditary Hearing Loss Tests Supplement*. Seewww.asperbio.com/supplement.pdf [accessed March 10, 2007].
[90] Authors' phone conversation with Dr. Andres Metspalu, University of Tartu, Estonia (founder of Asper Biotech), April 14, 2008.

Additional groups in the U.S. (shown in Appendix V) are exploring the use of kits and microarray diagnostics for high-throughput, comprehensive, and cost-effective molecular screening. Dr. John Greinwald and colleagues at the Cincinnati Children's Hospital previously reported that a diagnostic paradigm incorporating genetic testing during clinical evaluation of hearing loss proved more cost effective than standard simultaneous laboratory work-up.[91,92] Dr. Greinwald's group is now testing a microarray-based diagnostic gene chip that includes 13 genes associated with hearing loss. This collaborative project between Cincinnati Children's Hospital Medical Center and the University of Cincinnati Medical Center is being carried out at the Computational Medicine Center and is in an early phase of integrity and validation studies.[93] Dr. Greinwald and colleagues have also filed U.S. patent applications US20050112598A1 and US20040166495A1, "Microarray-based diagnosis of pediatric hearing impairment-construction of a deafness gene chip," based on the development of this gene chip (Appendix V). In a recent paper, Li et al. reported using a multiplex allele-specific PCR-based universal array (ASPUA), which combines Amplification Refractory Mutation System (ARMS) with array technology for clinical diagnostic testing of hearing loss mutations in parallel.[94]

Several groups have thus developed high-throughput diagnostic testing for hearing loss. U.S. patent applications filed by at least two of these groups on microarray-based gene chips suggest the potential for future commercialization of these diagnostic tests. However, we do not know if these tests will be adopted by clinical providers. Factors including test sensitivity, clinical utility and cost of the test are likely to significantly affect their uptake.

We also do not know whether the chip makers and testing service providers have licensed patents for mutations and methods associated with genetic tests for hearing loss. Neither have we studied whether use of short DNA probes on these chips would infringe existing patents, as this would require detailed analysis of claims and deep knowledge of the testing methods.

Finally, we note that full-genome sequencing technologies are progressing apace, and if such analysis became possible, then the basis for genetic testing would be individual genomic sequencing and comparing that sequence to known mutations associated with all genetic forms of hearing loss, rather than tests specifically keyed to hearing loss. The intellectual property implications are unclear, as they are for genetic testing of other clinical conditions.

Lessons Learned about impact of Patents on Access to Hearing Loss Testing

Research

We found no evidence about positive or negative effects of hearing loss gene patents on research in the field of hearing loss genetics. Basic research to determine the associations between candidate genes and their roles in various forms of hereditary hearing loss has steadily progressed. Research appears to be proceeding rapidly on rare forms of deafness that offer the prospect of a small market for diagnostic testing and are therefore unlikely to provide significant monetary incentives for genetic testing. Most genes associated with different forms of syndromic and non-syndromic deafness are not patented (Appendix I and II). Even among the five most commonly tested hearing loss genes, which are

[91] Preciado D, Lim LHY, Cohen AP, Madden C, Myer D, Ngo C et al. Op. cit.
[92] Preciado D, Lawson L, Madden C, Myer D, Ngo C, Bradshaw JK, Choo DI, Greinwald JH Jr. Improved diagnostic effectiveness with a sequential diagnostic paradigm in idiopathic pediatric sensorineural hearing loss. *Otol Neurotol* 2005. 26(4):610-615
[93] Computational Medicine Center. *Gene chip diagnostic test for pediatric hearing impairment*. 2005. See http://www.computationalmedicine.org/project/hearing_loss.htm [March 10, 2007].
[94] Cai-Xia i, Qian P et al. Construction of a multiplex allele-specific PCR-based universal array (ASPUA) and its application to hearing loss screening. *Human Mutation* 2008. 29:306-314.

presumably of greatest commercial interest, three genes are not patented. It is unclear whether patents or the potential for commercialization provided an incentive for the research. At least two research groups at non-profit institutions were engaged in studies to identify Connexin 26 gene mutations. Publications reporting the identification of mutations in Connexin 26 by Kelsell at al (Queen Mary and Westfield College, UK) and Christine Petit et al (Institut Pasteur) were submitted in January (published in May) and August (published in November) of 1997 to *Nature* and *Human Molecular Genetics,* respectively. While the UK group does not appear to have applied for a patent, Christine Petit and Institut Pasteur secured US patents on GJB2/Connexin 26 and its mutations in December 1999. Petit and colleagues applied for a patent in August 1997, the same month they submitted their findings for publication. Dr. Fischel-Ghodsian and colleagues at Cedars-Sinai Medical Center submitted their report on the MTRNR1 A1555G mutation to *Nature Genetics* in February 1993 (published July 1993). The corresponding patent application on detection of A1555G mutation was filed on June 30, 1993, four months after submitting for publication, and granted to Cedars-Sinai in April 1996. While these chronologies suggest that scientific publication and patenting activities proceeded in parallel, we cannot determine if journal submissions were in fact delayed in the first place to prepare patent applications for parallel filing.

Without information on the royalties Institut Pasteur and Cedars-Sinai Medical Center receive from the licenses to Athena Diagnostics for Connexin 26 and MTRNR1 testing, it is also difficult to comment on the impact these patents have had on supporting subsequent basic research at these institutions. Such support would be one of the positive effects of patents.

A substantial amount of clinical research has been performed, for example on the prevalence of Connexin 26 mutations in different populations, and on new methods for diagnostic testing including array-based diagnostics. Such studies include genetic testing for mutations covered by patents and licensed exclusively to Athena Diagnostics (Connexin 26, MTRNR1). However, researchers at academic medical centers remain concerned about the consequences of future enforcement activity by Athena Diagnostics on the clinical testing and clinical research.[95] They warn that uncertainty about whether an academic medical center or reference lab may be required to stop testing and the absence of a clearly stated policy about research use from Athena Diagnostics may have chilling effects on clinical research.

Development and Commercialization

Genetic tests for Connexin 26 and MTRNR1 which are patented, and for GJB6, SLC24A6, and MTTS1, which are not covered by patents, have been developed and are offered by several providers at similar prices. Several providers have in fact developed test panels that include both the patented Connexin 26/MTRNR1 as well as the unpatented Connexin 30/MTTS1 tests. The acquisition of an exclusive license for Connexin 26 diagnostic testing in the US was presumably integral to Athena Diagnostics' plan to commercialize these tests. GJB2 testing was offered by at least 9 providers in the U.S. as early as 1998. The number of providers listed at GeneTests.org has doubled since 1999-2000.[96] Testing for the patented genes GJB2 and MTRNR1 and their most common mutations is offered by more U.S. providers than testing for the unpatented genes SLC26A4, GJB6, and MTTS1. This is not entirely surprising given that GJB2 mutations account for up to 50% of cases of non-syndromic hearing loss. The majority of laboratories listing the tests are academic health centers.

Clinical testing for MTRNR1 in the U.S. may have been delayed. The association of MTRNR1 mitochondrial mutations to hearing loss was published as early as 1993, yet clinical testing appears to have become available only in 2000. In our telephone survey, many laboratories were unable to provide data on when they first made this test available. A more systematic and detailed survey of providers might

[95] Comments provided during external review, August 22, 2008.
[96] Kenneson A, Myers MF, Lubin IM, Boyle C. Op. cit.

help determine if patents impeded or deterred providers from developing these tests, as we did not query providers specifically about this issue.

It is difficult to assess exactly how much of a price premium the exclusive license provides Athena Diagnostics, or what impact the patent licenses have on volume. According to Athena Diagnostics, to date only one sublicense for Connexin 26 testing has been granted (to Pediatrix). Thus, the list price of the other providers must not include royalty or licensing fees. The price range can be attributed to factors such as overhead costs at different institutions. In the case of testing for MTRNR1, the price offered by both for-profit providers is on average $145 more than the price of the test provided by non-profit institutions. The $365 list price of the test offered by Athena Diagnostics is nearly 73 percent higher than the average list price offered by other university and hospital-based providers. In contrast, testing for the unpatented MTTS1 gene is offered by only four non-profit providers and at prices comparable to MTRNR1 testing services offered by these providers. MTTS1 testing is not offered by Athena Diagnostics.

Costs of hearing loss tests do not appear to correlate strongly with patent status. For instance, the price of the most expensive test--SLC26A4 full sequence analysis--can be attributed mostly to the costs of sequencing a large gene. The relatively high cost of the SLC26A4 testing also affects fewer consumers, since Pendred's syndrome accounts for a small fraction of hearing loss cases and testing is recommended only to follow up on positive imaging findings.

Communication/ Marketing

It appears that patents on DNA sequences and platforms for hearing loss genetic testing have had little impact on the dissemination of information about such tests or how they are marketed. We found no evidence of direct-to-consumer marketing. In the course of a phone conversation, Dr. Michael Henry, Vice President of Business Development at Athena Diagnostics, clearly stated the company's commitment to refrain from direct-to-consumer marketing and emphasized that Athena relies primarily on physician-prescribed testing. He also indicated that while Athena Diagnostics does have sales representatives who communicate information about genetic testing for neurological conditions to neurologists and medical practices, there is no sales force specifically committed to marketing hearing loss genetic testing to pediatricians and specialists (e.g., otolaryngologists and audiologists).

Adoption by Clinical Providers and Testing Laboratories

Any effects of patents on adoption of hearing impairment genetic tests by clinical providers are not readily apparent.
The exclusive license procured by Athena Diagnostics for Connexin 26 and MTRNR1 testing does not appear to have established Athena Diagnostics as the sole provider. However, the number of providers currently available may not fully capture the effects of patents on provider adoption. According to Dr. Michael Watson, Director of the ACMG, "Athena aggressively enforced their IP for many years but were increasingly irritating practitioners and made them an example in the press of bad IP behavior. Around 2000, they [Athena] stopped enforcing and tried to develop their 'Academic Partnership Program.' Although the intent was to allow laboratories to retain some volume for research and training of clinical laboratorians, it ultimately failed largely because if a lab did more than 100 cases in a year, the licensing fees made the lab noncompetitive."[97]

[97] Comments provided by Dr Michael Watson, during external review. Email from Dr Watson to SACGHS staff, September 10, 2008.

We have clearly identified three instances of patent enforcement by Athena Diagnostics for Connexin 26 testing against other providers. The first of these proved to be a case of non-infringing use that has been resolved.[98,99] GeneDx currently continues to perform full sequence analysis for Connexin 26 to identify the GJB2 D50N mutation and other mutations associated with a rare skin condition KID, which is not covered by the patents licensed to Athena. We understand the matter reached amicable resolution with GeneDx agreeing not to report hearing loss mutations and referring to Athena if they are found (See Appendix VII). Athena Diagnostics, which holds the exclusive license to GJB2 mutation testing in the U.S., expressed willingness to grant sublicenses. [100] However, according to Dr Sherri Bale, Athena refused to grant a sublicense when GeneDx attempted to acquire one in the context of KID testing.[101] This case also raises concerns about withholding of useful clinical information and increased costs, as another blood draw and test by Athena would be required if GeneDx identified a potential hearing loss mutation in a sample sent to them for KID testing, although this is clinically unlikely.

In another instance, the Diagnostic Molecular Pathology Laboratory at the University of California Los Angeles stopped offering testing for Connexin 26/GJB2 over two years ago, after receiving a "cease and desist letter" from Athena Diagnostics. According to Dr. Wayne Grody,[102] Director of the Laboratory, the terms of the sublicense offered by Athena Diagnostics "were unreasonable, with an upfront fee of $50,000 per year plus a significant per test fee" and not economically viable for the laboratory, given the relatively low volume of testing for hearing loss at UCLA. Attempts to negotiate terms of a sublicense were not successful. It is unclear to what extent cessation of testing at UCLA has affected patient access to hearing loss testing. Dr. Grody indicated that samples are now sent to Athena Diagnostics for clinical testing. His laboratory considered using an alternate test methodology, namely custom ASRs from Third Wave Technologies for Connexin 26 mutation testing. This method reportedly allows laboratories to avoid infringing the Connexin 26 patents licensed to Athena. It is unclear if this is because a sublicense acquired from Athena Diagnostics comes attached to the purchase of the ASRs or because the test methodology (Invader™ assay) offers "workarounds" of the patents (US5998147, 6485908). However, these ASRs are no longer being offered since HoloLogics Inc acquired Third Wave Technologies in June 2008.[103]

Dr. Grody indicated that even if the alternate methodology could help overcome the problem of patent infringement, it is not ideal because ASRs for the 235delC Connexin 26 mutation, found commonly in

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[98] Authors' email communication with Richard Flaherty (BioReference Laboratories, CIO, Director of Technology and Investor Relations) and Sherri Bale, Clinical Director, GeneDx. February 22, 2008.

[99] In testimony before the House Judiciary Subcommittee on Courts, the Internet and Intellectual Property, on October 30, 2007, Marc Grodman, CEO of Bio-Reference Laboratory, Inc., indicated that while GeneDx (a company acquired by BRLI) was performing a genetic test for a rare skin condition by full sequence analysis of the gene in question, it "received a letter from another laboratory claiming that within the sequence being analyzed was another sequence associated with hearing loss." Athena Diagnostics' letter indicated that since testing for this hearing loss gene was patented, performing the test might be an act of infringement. Attempts by GeneDx to perform the test by paying a royalty to the other company were unsuccessful. We have confirmed by personal communication with Dr. Grodman and Dr. Sherri Bale, Clinical Director at GeneDx, that the genetic test in question involved sequencing the Connexin 26 gene for mutations associated with a rare skin condition Keratitis Ichthyosis Deafness (KID). Dr. Bale confirmed that Athena Diagnostics sent a "cease and desist letter" and indicated that the matter has been resolved. "We accepted a letter from Athena that instructed us to not report the 35delG mutation. However, what we've done is: if we find the deletion, we call the referring MD, tell them the results and that we can't report them, and then suggest they redraw the patient and send the sample to Athena for testing." This requires a second visit to the patient's physician, another blood draw, and payment, this time to Athena Diagnostics, to repeat the GJB2 test. (See Appendix VI Letter from Sherri Bale, GeneDx to Athena Diagnostics.)

[100] Authors' phone conversation with Michael Henry, Vice President Business Development, Athena Diagnostics Inc. March 2007.

[101] Authors' email communication with Richard Flaherty (BioReference Laboratories, CIO, Director of Technology and Investor Relations) and Sherri Bale, Clinical Director, GeneDx. February 22, 2008.

[102] Authors' phone conversation with Dr. Wayne Grody, March 21, 2008.

[103] See transcript of HoloLogics press conference about Third Wave Technologies acquisition at http://www.secinfo.com/d14D5a.t3vh8.d.htm [last accessed January 8, 2009].

Asian populations, are not available from Third Wave. Testing for this mutation is particularly relevant at UCLA given the high Asian and Asian American population in California. Dr. Grody also noted that shipping samples to Athena Diagnostics is problematic for indigent patient populations covered by the California MediCaid program (MediCal). MediCal only reimburses laboratories with which it has a contract, which Athena does not have.

We also recently became aware that Athena Diagnostics sent a "cease and desist" letter to the Center for Human Genetics at Boston University regarding testing for a number of genetic conditions including hearing loss.[104] In August 2008, the Center for Human Genetics ceased testing for hearing loss and several other conditions for which Athena has exclusive IP rights.

Athena confirmed that no sublicenses have been given to university and academic or medical centers.[105]

The SoundGene™ panel offered by Pediatrix is performed under a sublicense from Athena Diagnostics for GJB2/Connexin 26 testing. To our knowledge, Pediatrix is the only provider that has received a sublicense from Athena Diagnostics to date. Presumably, this will lead to a steady royalty stream for Athena from genetic testing done by Pediatrix as part of newborn hearing loss screening, and a flow of patients for diagnostic follow up.

Microarray chip-based diagnostics for hearing loss are currently not available as a clinical service in the U.S. However, if chip based diagnostics do become commercialized, and if use of DNA probes on those microarrays infringe the patents that Athena has licensed, Athena Diagnostics could choose to demand a license for testing that includes patented sequences of Connexin 26 and MTRNR1. Simultaneous multi-gene testing also seems to be a departure from the current ACMG clinical guidelines, which call for a systematic utilization of genetic tests based on relative frequencies, family histories, patient symptoms and apparent diagnosis. Those guidelines might change, however, if microarray testing proved equally sensitive, specific, and accurate, while being faster and cheaper and identifying many mutations in different genes in a single test.

Consumer Utilization

This case study finds limited effects on patient access to genetic testing for hearing loss that can be directly attributed to patenting. The availability of genetic testing for hearing loss in California may be limited for MediCal patients because the patent-holder, Athena Diagnostics, lacks a contract with MediCal and is out-of-state. The issue here is not patents per se, but patents preventing other laboratories from offering the test under MediCal contract. The laboratories with MediCal contracts do not have sublicenses from Athena and Athena apparently does not have a contract with MediCal.

We were unable to identify systematic evidence beyond the MediCal situation noted above, that the patents have impeded utilization of hearing loss tests by people who are interested in or require testing. Testing for the genes licensed exclusively to Athena Diagnostics is not marketed directly to consumers by Athena or by other direct-to-consumer providers like DNAdirect. Sixteen providers other than Athena Diagnostics are listed on GeneTests.org as offering Connexin 26 testing. Nine providers in addition to Athena Diagnostics are listed for MTRNR1 testing. Many of these provider websites have detailed information on the availability and cost of both patented and unpatented hearing loss genetic tests.

[104] Authors' phone Communication with Dr. Aubrey Milunsky, Director, Center for Human Genetics, Boston University, May 29, 2008.
[105] Authors' phone conversation with Michael Henry, Vice President Business Development, Athena Diagnostics Inc., March 2007.

Although several providers for these tests have emerged, we found no information about usage of the tests by consumers.

While we did not query test providers about their testing volume or the number of patients requesting each test, a future survey could assess utilization of hearing loss tests by consumers. It would also be valuable to determine how frequently reimbursement for such tests is denied by insurers and payers, as coverage and reimbursement of genetic testing are likely to affect consumer use.

Finally, patient access may be affected, as much or more by factors other than patents, such as the lack of knowledge about the genetics of hearing loss, particularly among primary care physicians, and their low propensity to refer cases for genetic testing as follow-up.[106] A recent survey by Duncan et al. noted that while 86% of pediatric otolaryngologists reported having easy access to genetic testing services for referral, many also identified "discomfort with various aspects of genetic testing" as a reason for not ordering genetic tests.[107] Lack of knowledge about genetic testing or about interpretation of test results may be a more significant barrier to test adoption by healthcare providers than patents.

Coverage and reimbursement by third party payers

We have no evidence that gene patents have directly affected third party payer coverage and reimbursement decisions for hearing loss tests. Laboratories report that insurers have generally adopted genetic testing for some hearing loss genes, as illustrated below by the coverage position from CIGNA HealthCare on "Genetic Testing for Congenital Profound Deafness."[108]

Coverage Position

CIGNA HealthCare covers genetic testing for congenital, nonsyndromic, sensorineural, mild to profound deafness (DFNB1) as medically necessary for ANY of the following indications:

- For diagnostic testing when the clinical examination and conventional studies suggest a diagnosis of congenital, nonsyndromic, sensorineural, mild to profound deafness (DFNB1)
- For carrier testing in EITHER of the following situations:
  - when the patient has a first- or second-degree relative* with a GJB2 or GJB6 gene mutation
  - when the patient is the reproductive partner of a known carrier (deafness-causing mutation of gene GJB2 or GJB6) and the couple has the capacity and intention to reproduce
- For prenatal testing when both parents are known carriers of deafness-causing mutation of gene GJB2 or GJB6 mutation.

CIGNA HealthCare does not cover genetic screening for congenital, nonsyndromic, sensorineural, mild to profound deafness (DFNB1) in the general population because such screening is considered not medically necessary or of unproven benefit.

All individuals undergoing genetic testing for any reason should have both pre- and post-test genetic counseling with a licensed or certified genetic counselor or physician trained in genetics and genetic counseling.

Aetna covers full sequence and targeted mutation analysis of GJB2/Connexin 26 and deletion analysis for GJB6/Connexin 30, but it excludes pre-implantation genetic diagnosis (PGD) for DFNB1, which is deemed an "unproven benefit at this time." We have not verified whether other commercial insurers have

[106] Moeller MP, White KR, Shisler L. Primary care physicians' knowledge, attitudes, and practices related to newborn hearing screening. *Pediatrics* 2006. 118(4):1357-70.
[107] Duncan RD, Prucka S, Wiatrak BJ, Smith RJ, Robin NH. Pediatric otolaryngologists' use of genetic testing. *Arch Otolaryngol Head Neck Surg* 2007. 133(3):231-6.
[108] See http://www.cigna.com/customer_care/healthcare_professional/coverage_positions/medical/mm_0254_coveragepositioncriteria_genetic_test_congenital_profound_deafness.pdf [accessed January 16, 2009].

a similar position, except through the interviews with testing laboratories. Indirect effects that patents may have on price might lead to a higher level of scrutiny by insurance providers if the tests are priced above other genetic tests, but hearing loss genetic test prices are in the same range as other case studies. Decisions about coverage for SLC26A4, MTRNR1 and MTTS1 may be case by case, because these conditions are not common enough to warrant an explicit coverage policy. These tests are likely handled similarly to tests for other rare conditions, covering tests in a routine price range and requiring special justification for expensive testing. During the informal phone survey, most test providers indicated that hearing loss genetic tests were mostly covered by insurance. However, we have no direct evidence about how often consumers are denied coverage for hearing loss testing, pay for them out of pocket, face high co-pay fees because of reimbursement limits, or encounter other factors that affect their choice to get such tests.

Athena Diagnostics has a policy of directly billing insurance providers for services when Athena is the contracted provider for that particular plan. However, when Athena is not a contracted provider and the insurer does not cover the testing in part or full, Athena guarantees as part of its Patient Protection Plan that "an eligible, enrolled patient's liability will be limited to 20% of the cost of the test, even if the patient's insurance plan pays nothing. (These programs are discussed at greater length in the spinocerebellar ataxia case study.) For patients enrolled in the Patient Protection Plan, any amount collected from the insurance company in excess of 80% of the amount billed will be refunded to the patient."[109] The Patient Protection Plan is not, however, available in all states, does not apply to government health programs (Medicare and Medicaid, for example) and does not apply to most insurers and health plans. Florida and Maryland are excluded, for example.

Athena Diagnostics does not participate in Medicaid but it does offer discounts to Medicaid patients through its financial assistance programs. If the test of interest is not covered by Medicare carriers, the patient will be required to pay for the test in advance. In such cases, if the Medicare carrier denies coverage of the test, the patient may have to pay the entire cost out of pocket, since Medicare patients are ineligible for Athena's Patient Protection Plan. Thus insurance coverage, independent of the patenting status of the test, may limit patient access in some cases, specifically Medicaid patients, most Medicare patients, and those covered by health plans with which Athena does not have a contract. However, even in these cases, patients have the option of using other providers who may accept Medicaid, at least as long as those providers continue to offer the service.

Conclusion

Patents do not appear to have significantly impeded patient or clinical access for hearing loss genetic testing. Many institutions provide tests, even those covered by patents exclusively licensed to Athena Diagnostics, presumably without a sublicense. While Athena Diagnostics has sent out some "cease and desist" letters, enforcement is apparently incomplete, as several other testing services are listed on GeneTests.org. It is possible that the volume of testing at most institutions, even for Connexin 26, is not large enough to warrant more aggressive enforcement by Athena Diagnostics.

Given that experts have recommended incorporation of genetic tests into EHDI programs, use of genetic tests for hearing loss is likely to increase. The recent introduction of the SoundGene™ diagnostic panel by Pediatrix Screening is indicative of this trend. However concerns have been raised that a small panel such as SoundGene™ may not be ideal. For example, patients with GJB2 related hearing loss may be missed because they do not carry the mutations represented on the panel. More recent literature suggests it is not sufficient to test only the four common mutations associated with Pendred syndrome included in the panel. This is one reason many labs now sequence the entire SLC26A4 gene because targeted mutation testing misses many mutations. Multi-gene, chip-based tests may help address problems in

[109] See http://www.athenadiagnostics.com/content/ordering/ [accessed August 2007].

diagnosing individuals who develop hearing loss as children or adolescents, and potentially reduce the cost and duration of diagnostic testing. These new diagnostics, although likely to detect a much broader range of mutations and gene variants, may also miss rare and novel mutations, especially for genes like GJB2 and SLC26A4, as patients often have new or private mutations. The clinical utility and analytical validity of such array-based tests also needs to be demonstrated. It remains to be seen whether patents on genes and mutations for hearing loss will impede development of multi-allele methods.

This case study illustrates the complexity of assessing the impact of patents on access to genetic testing. This is in part because of the number of genes and mutations involved, but also depends on patents and their enforcement. Aggressive patent enforcement might reduce the number of outlets for genetic testing, and for those not covered by health plans covering payment to Athena Diagnostics, this would reduce access. It therefore appears that access depends on an unstable intellectual property regime and the vicissitudes of payment contracts between health insurers and health care plans, on one hand, and different testing labs, on the other.

Genetic testing for hearing loss also illustrates several other features of intellectual property and genetic testing. Most of the patents for commonly tested genes are owned by academic institutions and licensed to Athena Diagnostics. The patenting and licensing practices of academic institutions are therefore linked to both the benefits and problems associated with having a single major provider. The case also illustrates the penumbra effect of exclusive rights to some mutations leveraging testing for others, although it is also clear from this case that the effect is incomplete since multiple providers are offering tests.

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Appendix I. ***Nonsyndromic Loci: Known Genes, Genetic Tests, and Patents***

Locus	Pattern of Inheritance	Genes	Age of Onset	Relative Frequency	Test Avalablei	Patent Holder
DFNB61	AR	PRES (SLC26A5)		higher among Caucasians		Northwestern (6602992)
DFNB1	AR	GJB2 (Cx 26), GJB6 (Cx 30)	Prelingual	Up to 50%	GJB2 (Cx 26), GJB6 (Cx 30)	Institut Pasteur (5998147, 6485908)
DFNB2	AR	MYO7A	Prelingual		MY07A	
DFNB3	AR	MYO15A	Prelingual	2% incidence in Benkala, Bali		
DFNB4	AR	SLC26A4	Postlingual	4-10%	SLC26A4	
DFNB6	AR	TMIE	Prelingual			
DFNB7/11	AR	TMC1	Prelingual			
DFNB8/10	AR	TMPRSS3	DFNB8-Prelingual, DFNB10-Postlingual			
DFNB9	AR	OTOF	Prelingual		OTOF	
DFNB112	AR	CDH23				
DFNB16	AR	STRC	Postlingual			
DFNB18	AR	USH1C	Prelingual			
DFNB21	AR	TECTA	Postlingual		TECTA	
DFNB22	AR	OTOA	Prelingual			
DFNB23	AR	PCDH15	Prelingual			
DFNB28	AR	TRIOBP	Prelingual			
DFNB29	AR	CLDN14	Prelingual			
DFNB30	AR	MYO3A	Prelingual			
DFNB31	AR	WHRN	Prelingual			
DFNB36	AR	ESPN	Prelingual			
DFNB37	AR	MYO6	Prelingual			
DFNB67D FNB59	AR	TMHSDFNB59 (pejvakin)				
DFNA1	AD	DIAPH1	Postlingual			
DFNA2	AD	GJB3 (Cx 31), KCNQ4	Postlingual		KQCN4	NeuroSearch A/S (6794161)
DFNA3	AD	GJB2 (Cx 26), GJB6 (Cx 30)	Prelingual	GJB2 >50%	GJB2 (Cx 26), GJB6 (Cx 30)	Institut Pasteur (5998147, 6485908)
DFNA4	AD	MYH14	Varies	1%		
DFNA5	AD	DFNA5	Postlingual			

DFNA6/14/38	AD	WFS1	Prelingual		WFS1	Washington University School of Medicine (WOO18787A1)
DFNA8/12	AD	TECTA	Pre or postlingual		TECTA	
DFNA9	AD	COCH	Postlingual		COCH5B2	Brigham and Women's Hospital (7030235), Brigham and Women's Hospital & U-Antwerp (6730475)
DFNA10	AD	EYA4	Postlingual		EYA4	
DFNA11	AD	MYO7A	Postlingual			
DFNA13	AD	COL11A2	Postlingual		COL11A2	
DFNA15	AD	POU4F3	Postlingual			
DFNA17	AD	MYH9	Postlingual		MYH9	
DFNA20/26	AD	ACTG1	Postlingual			
DFNA22	AD	MY06O	Postlingual			
DFNA28	AD	TFCP2L3	Postlingual			
DFNA36	AD	TMC1	Postlingual			
						Wash U. School of Medicine (WOO18787A1)
DFNA44	AD	CCDC50	Postlingual			
DFNA48	AD	MYO1A	Postlingual			
None Listed	AD	CRYM	Prelingual			
DFN3	XL	POU3F4	Prelingual			
Aminoglycoside Ototoxicity	Mitochondrial	MTRNR-1 (A1555G), MTTS-1	Prelingual	A1555G <1% (1/20-40,000 births)	MTRNR-1, MTTS-1	Cedars-Sinai (5506101) MTRNR1
None Listed		TDC-1, TDC-2			TDC-1, TDC-2	Griffith, Kurima, Wilcox & Friedman (20040249139A1)
Dentinogenesis imperfecta type II (DGI-II)		DSPP			DSPP	Kong, Xiao, Zhao, Yu & Hu (2003018020A1)

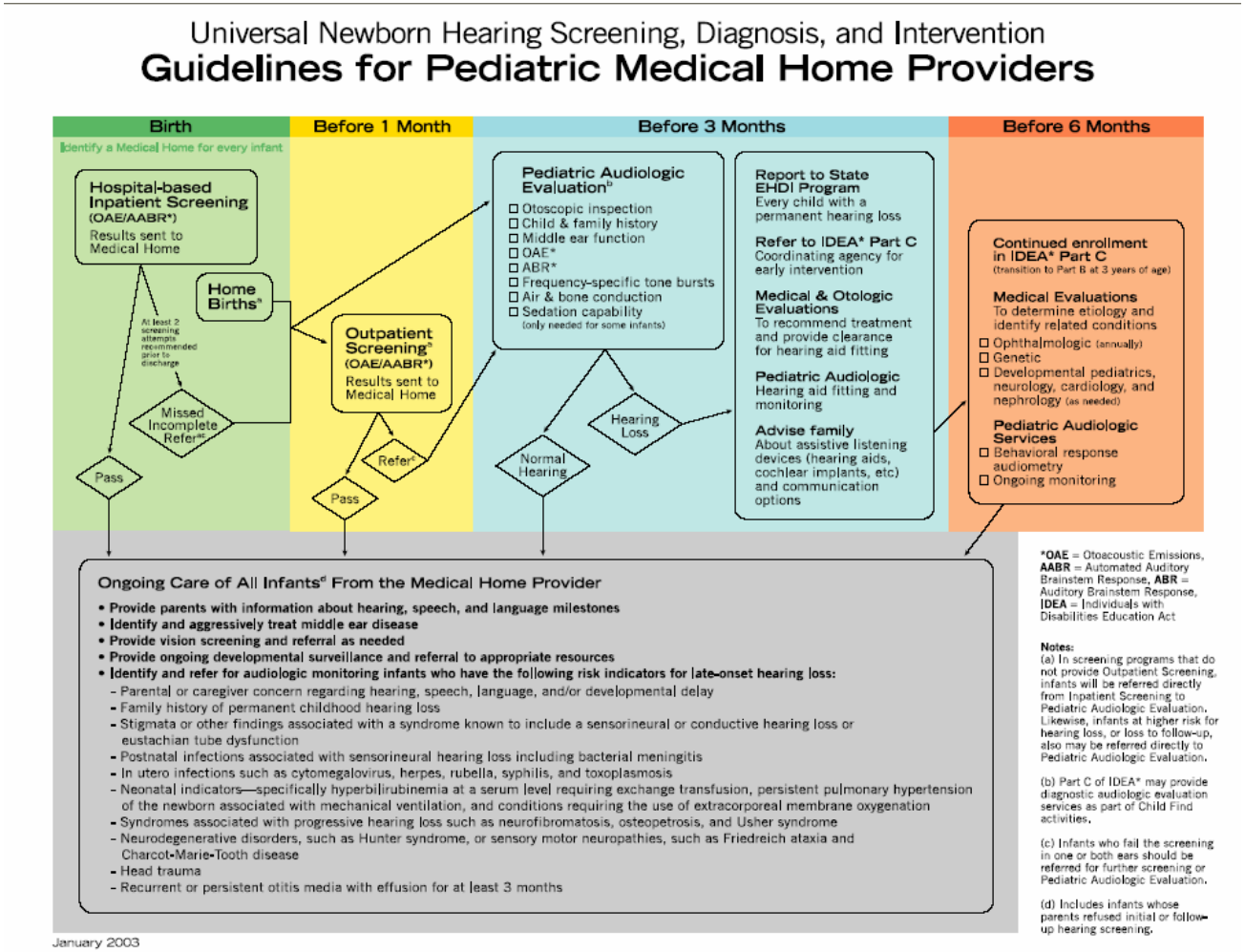
Appendix II. ***Syndromic Disorders: Known Genes, Genetic Tests, and Patents***

Disorder	Type	Pattern of Inheritance	Genes	Age of Onset	Relative Frequency	Prevalence	Test Available?	Patent Holder (Patent Number)
Pendred's Syndrome	Syndromic	AR	SLC26A4	Prelingual	4-10%		SLC26A4	
Type 4 Barter'st Syndrome	Syndromic	AR or digenic	BSND, CLCNKA, CLCNKB		con-sanguineous Middle Easterners			
Branchio-oto-renal (BOR) Syndrome	Syndromic	AD	EYA1, SIX1		1 in 40,000		EYA1, SIX1	
Alport Syndrome	Syndromic	AD	MYH9, COL4A5, COL4A3, COL4A4		Rare		MYH9, COL4A5, COL4A3, COL4A4	
Fechtner's Syndrome	Syndromic	AD	MYH9		Rare			
Sebastian Syndrome	Syndromic	AD	MYH9		Rare			
(DFNA22)	Syndromic	AD	MYO6	Postlingual	Rare			
Renal Tubular Acidosis	Syndromic	AR, consanguinity	ATP6B1, ATP6N1B		con-sanguineous North Africans			
Waardenburg's Syndrome	Syndromic	AD or AR	PAX3, MITF, SOX10, EDN3, EDNRB		1-4%			
Wolfram Syndrome	Syndromic	AD	WFS1	Prelingual			WFS1	Washington University School of Medicine (WOO18787A1)
Meniere's Disease	Syndromic	AD	COCH	Postlingual			COCH5B2	Brigham and Women's Hospital (7030235), Brigham and Women's Hospital & U-Antwerp (6730475)
Cockayne Syndrome Type A	Syndromic		ERCC8	Prelingual			ERCC8	
Cockayne Syndrome Type B	Syndromic		ERCC6	Prelingual			ERCC6	
Diabetes-Deafness Syndrome	Syndromic		MTND5, MTTL1				MTTL1	
Charcot-Marie Tooth Neuropathy Type 1A	Syndromic	AD	PMP22				PMP22	
Charcot-Marie Tooth	Syndromic	AD	MPZ				MPZ	

Neuropathy Type 1B								
Charcot-Marie Tooth Neuropathy Type 1C	Syndromic	AD	LITAF				LITAF	
Charcot-Marie Tooth Neuropathy Type 1D	Syndromic	AD	EGR2				EGR2	
Charcot-Marie Tooth Neuropathy Type 1E	Syndromic	AD	PMP22				PMP22	Athena (5691144), Athena (6001576)
Charcot-Marie Tooth Neuropathy Type 1F/2E	Syndromic	AD	NEFL				NEFL	
Isolated Renal Hypomagnesemia	Syndromic		CLDN16				CLDN16	
Urticaria-Deafness-Amyloidosis (UDA) Syndrome	Syndromic		CIAS1, NLRP3				CIAS1, NLRP3	
Long QT Syndromes and Deafness	Syndromic		KVLQT1, SCN5A				KVLQT1, SCN5A	U-Utah Research Foundation (20020061524 A1), U-Utah Research Foundation and Genzyme, Inc (6582913), U-Utah Research Foundation (6787309)
Jervell and Lange Nielsen (JLN) Syndrome	Syndromic	AR	KLVQT1, KCNQ1 (JLN1), KCNE1 (JLN2)	Prelingual	Rare		KLVQT1, KCNQ1 (JLN1), KCNE1 (JLN2)	U-Utah Research Foundation (6150104)
Stickler Syndrome	Syndromic	AD	COL11A2, COL2A1, COL11A1, COL9A1				COL11A1, COL11A2, COL2A1, COL9A1	
Epstein Syndrome	Syndromic	AD	MYH9				MYH9	
Norrie Disease	Syndromic		NDP				NDP	
Treacher Collins Syndrome	Syndromic		TCOF1				TCOF1	
Usher Syndrome Type I (USH1)	Syndromic	AR	MY07A,O USH1C, CDH23, PCDH15, SANS	Prelingual	all Usher combined 3-6% of child deafness	all Usher combined 4.4/100,000	MY07A, PCDH15	
Usher Syndrome	Syndromic	AR	USH2A, VLGR1,	Prelingual	all Usher combined 3-6% of	all Usher	USH2A	

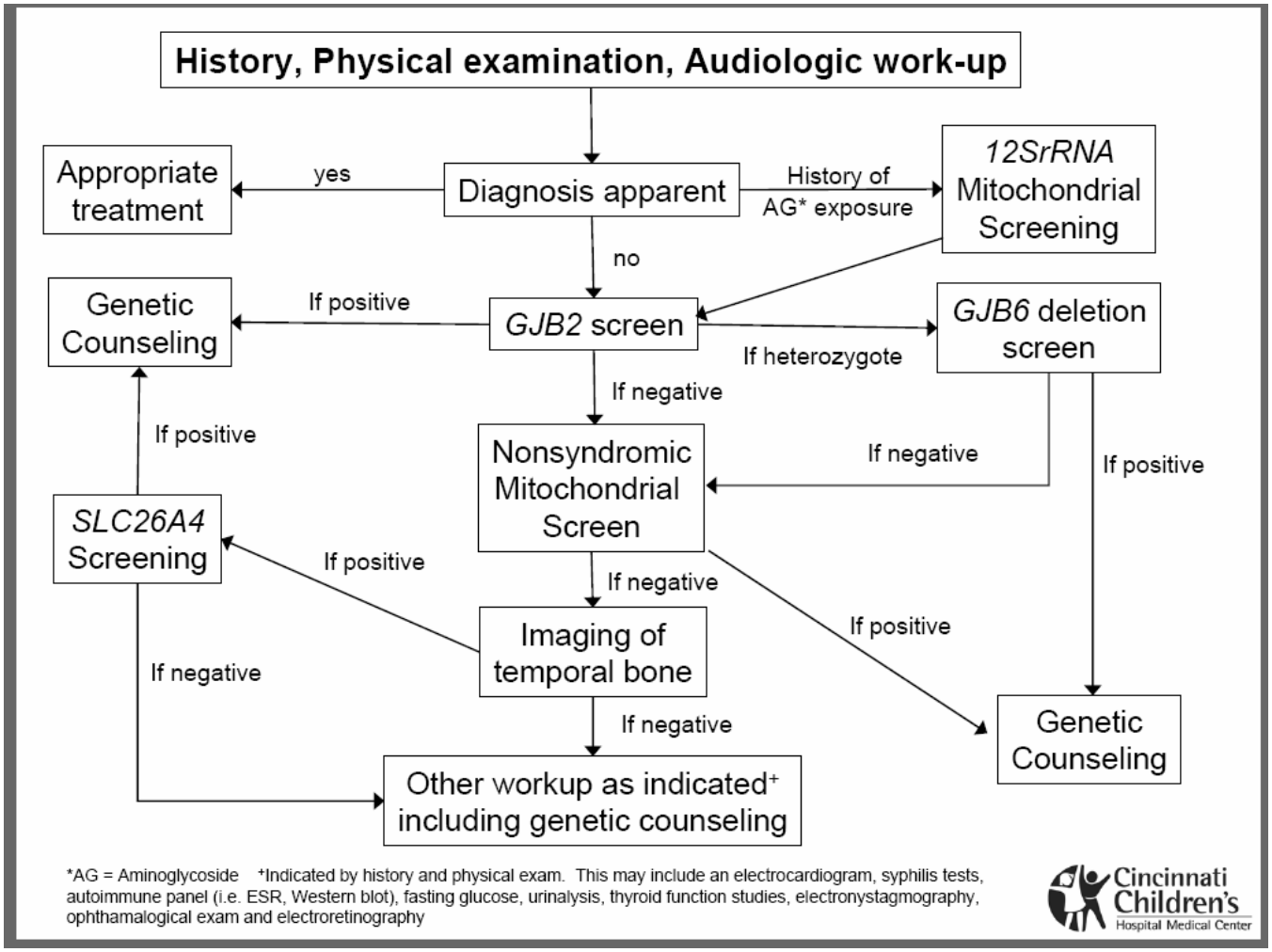
Type II (USH2)			WHRN		child deafness	combined 4.4/100,001		
Usher Syndrome Type III (USH3)	Syndromic	AR	USH3	Postlingual	all Usher combined 3-6% of child deafness	all Usher combined 4.4/100,002	USH3A (CLRN1)	
Kearns-Sayre Syndrome	Syndromic	Mitochondrial					mtDNA deletion syndromes	
Pearson Syndrome	Syndromic	Mitochondrial					mtDNA deletion syndromes	
Progressive External Ophthalmoplegia	Syndromic	Mitochondrial					mtDNA deletion syndromes	
Leigh Syndrome	Syndromic	Mitochondrial	MTATP6, MTTL1, MTTK, MTND1, MTND3, MTND4, MTND5, MTND6, MTCO3, MTTW, and MTTV				MT-ATP6, MT-CO3 , MT-ND1, MT-ND3, MT-ND4 , MT-ND5 , MT-ND6, MT-TK , MT-TL1, MT-TV, MT-TW	
NARP	Syndromic	Mitochondrial	MTATP6				MT-ATP6	
MELAS	Syndromic	Mitochondrial	MTTL1, MTND5, MT-TC, MT-TV, MT-TF, and MT-TS1				MTTL1, MTND5	
MERRF	Syndromic	Mitochondrial	MTTK				MTTK	
Vohwinkel Syndrome	Syndromic		GJB2 (Cx 26)		GJB2 >50%		GJB2 (Cx 26)	Institut Pasteur (5998147, 6485908)
Deafness-Dystonia Syndrome (DDON)	Syndromic	XL	TIMM8A	Varies				
Hypoparathyroidism, Sensorineural Deafness, and Renal (HDR) Disease	Syndromic		GATA3				GATA3	
Ichthyosis, Hystrix-like, with Deafness	Syndromic		GJB2 (Cx 26)				GJB2 (Cx 26)	Institut Pasteur (5998147, 6485908)

Appendix III: Universal Newborn Hearing Screening EHDI Guidelines for Pediatric Medical Home Providers



http://www.infanthearing.org/medicalhome/aap_gpmhp.pdf [accessed January 16, 2009].

Appendix IV: Cincinnati Children's Hospital Hearing Loss Genetic Evaluation Clinical Guidelines



See http://www.cincinnatichildrens.org/assets/0/78/1067/3345/3399/3403/c2eb6159-2c26-43c6-b2cc-0db5785eb0d5.pdf [accessed January 19, 2009].

Appendix V: Patent Applications for high throughput hearing loss diagnostic testing

Patent/ Application No.	Assignee	Inventors	Publication/ File Date	Title
US20070009887A1	None	Victoria Siemering, Henrik Dahl	2007-01-11 / 2003-11-18	Genotyping of deafness by oligonucleotide microarray analysis
US20070134691A1	None	Iris Schrijver et al. (Stanford Univ, CA)	2007-06-14 / 2006-11-14	Methods & compositions for determining whether a subject carries a gene mutation associated with hearing loss.
US20050112598A1 US20040166495A1	None	Greinwald, John H. Wenstrup, Richard J Aronow, Bruce J.	2005-05-26 / 2004-02-24 2004-08-26 / 2003-02-24	Microarray-based diagnosis of pediatric hearing impairment-construction of a deafness gene chip
US20040038266A1[a]	None	Dobrowolski, Steven F Lin, Zhili	2004-02-26 / 2003-05-22	Advancing the detection of hearing loss in newborns through parallel genetic analysis
US20050059041A1	None	Johnson, Robert C. Mohammed, Mansoor Kim, Jae Weon Lu, Xan-Yan	2005-03-17 / 2004-05-17	Nucleic acids arrays and methods of use therefore
US20040203035A1	Third Wave Technologies, Inc.	Mast, Andrea L. Dorn, Erin; Kwiatkowski, Robert J Accola, Molly Wigdal, Susan S	2004-10-14 / 2004-01-09	Connexin allele detection assays

[a] Inventors Steven F.Dobrowolski and Zhili Lin were employees of NeoGen Screening Inc which was acquired by Pediatrix Medical Group and renamed Pediatrix Screening in 2003.

Appendix VI: Letter from GeneDx to Athena Diagnostics regarding Connexin 26 sequencing.

Michael W. Henry
VP, Business Development
Athena Diagnostics, Inc.
Four Biotech Park
377 Plantation Street
Worcester, MA 01605

October 11, 2006

Re: GeneDx testing in GJB2 gene

Dear Mr. Henry:
I am in receipt of your letter dated September 11, 2006 regarding Athena Diagnostics being the exclusive licensee of two US Patents. You noted that a letter had been sent to John Compton on November 11, 2002 regarding this issue. That letter was never received at GeneDx or by John Compton. We had moved to 207 Perry Parkway the previous month and our mail was not being forwarded by the post office.

We have reviewed the two patents to which your letter of September 11, 2006 refer (5,998,147 and 6,485,908). These two patents specifically make claims regarding detecting mutations in the Connexin 26 gene comprising a deletion of a nucleotide from nucleotides 30 to 32 or a deletion of 38 base pairs beginning at position 30 (mutations described as being involved in autosomal recessive prelingual non-syndromic deafness).

GeneDx provides GJB2 (Connexin 26) gene testing for the ectodermal dysplasia known as Keratitis-Ichthyosis-Deafness syndrome, a severe and sometimes lethal autosomal dominant syndromic disorder. KID syndrome is considered an ultra-rare disorder, with only about 100 cases reported in the literature. Nearly 80% of patients with KID syndrome have a mutation, D50N, in the GJB2 gene. The mutation spectrum in KID syndrome and other rare dominant syndromic disorders involving the GJB2 gene have been published by the principals of GeneDx (see below).
You can find the details of the testing we offer on our website (www.genedx.com) and in the information sheet that can be downloaded from the site. Should you have any further questions, please do not hesitate to contact us.

Sincerely,
Sherri J. Bale, Ph.D., FACMG
Clinical Director
GeneDx

Richard G, White TW, Smith LE, Bailey RA, Compton JG, Paul DL, Bale SJ. Functional defects of Cx26 resulting from a heterozygous missense mutation in a family with dominant deaf-mutism and palmoplantar keratoderma. Hum Genet. 1998 Oct;103(4):393-9.
Richard G, Rouan F, Willoughby CE, Brown N, Chung P, Ryynanen M, Jabs EW, Bale SJ, DiGiovanna JJ, Uitto J, Russell L. Missense mutations in GJB2 encoding connexin-26 cause the ectodermal dysplasia keratitis-ichthyosis-deafness syndrome.
Am J Hum Genet. 2002 May;70(5):1341-8. Epub 2002 Mar 22.
Richard G, Brown N, Ishida-Yamamoto A, Krol A. Expanding the phenotypic spectrum of Cx26 disorders: Bart-Pumphrey syndrome is caused by a novel missense mutation in GJB2. J Invest Dermatol. 2004 Nov;123(5):856-63.

Appendix VII: Email response from Athena Diagnostics to Gene Dx shared with permission of Dr. Sherri Bale, Clinical Director, GeneDx

Delivered-To: sherrib@genedx.com
Tue, 31 Oct 2006 15:31:28 -0500

Dear Sherri:
Thank you for your attached letter of October 11 regarding Cx26 (GJB2).
I understand that you test for the GJB2 D50N mutation for Keratitis-Icthyosis-Deafness (KID) syndrome.

Please confirm that GeneDx GJB2 testing does not include testing for the following mutations:
Deletion of nucleotides 27-35
Deletion of 38 base pairs starting at position 30
Deletion at position 30
Deletion of a nucleotide from nucleotide 30 to nucleotide 32

If GeneDx does not test for these GJB2 mutations, then I will consider this matter closed.

Regards,
Mike
Michael W. Henry
Vice President, Business Development
Athena Diagnostics, Inc.
377 Plantation Street
Worcester, MA 01605
(508) 756-2886 x3100
(508) 752-7421 fax
mhenry@athenadiagnostics.com

Impact of Patents and Licensing Practices on Access to Genetic Testing for Hereditary Hemochromatosis

Subhashini Chandrasekharan, Ph.D., Emily Pitlick, J.D., Christopher Heaney and Robert Cook-Deegan, M.D.[1]

Introduction

Hereditary hemochromatosis (HH) is an autosomal recessive disorder that results most often from mutations in the *HFE* gene,[2,3,4] which regulates iron absorption. HH caused by functional mutations in the *HFE* gene is commonly referred to as HH type 1. Mutations in the *HFE* gene place the individual at an increased risk for developing symptomatic HH, an iron metabolism disorder that leads to excess iron absorption from the diet, particularly in males. Since the body lacks a natural way to rid itself of the excess iron, it accumulates over time, resulting in organ damage, particularly in the heart, liver, and pancreas. In extreme cases, hemochromatosis can even lead to death, usually due to heart or liver failure.

Early detection of the disorder, and thus earlier treatment by phlebotomy (repeated blood draws), can greatly mitigate its effects and allow HH patients to live normal, healthy lives.[5] *HFE* testing in combination with a patient's family history and physical health record can provide guidance for clinical interventions or lifestyle changes that a patient would not have without genetic testing. Testing for the presence of *HFE* gene mutations can also help physicians to identify patients experiencing characteristic symptoms of the disorder, clarifying their diagnosis, and sometimes preventing irreversible organ damage.

HH is a candidate for genetic screening for many reasons. First, the mutations associated with HH are present at birth, whereas characteristic symptoms of hemochromatosis as a disease usually do not develop until mid-adulthood, beginning in an individual's 40s and 50s. In addition, the variability and non-specific nature of symptoms can make diagnosis difficult, raising the possibility that patients, especially those with no family history, may be diagnosed too late. Therefore, an early, specific diagnosis allows for an effective treatment plan. Secondly, unlike some hereditary disorders, a limited number of genes are associated with HH that can be tested for mutations to determine a patient's risk. Finally, HH is among the most common recessive genetic traits[6] in some populations of Northern European descent, resulting in a relatively high carrier frequency. Between 1 in 200 and 1 in 400 people of Northern European descent, or 0.5% of this population, is homozygous for the *HFE* mutation and thus at high risk of developing

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[1] Center for Public Genomics, Center for Genome Ethics, Law & Policy, Institute for Genome Sciences and Policy, Duke University (and Duke School of Law, for Emily Pitlick)

[2] *Hemochromatosis.* See http://digestive.niddk.nih.gov/ddiseases/pubs/hemochromatosis/index.htm [accessed November 10, 2008].

[3] Schmitt B, Aronson M, Fitterman N, Snow V, Weiss KV, Owens DK. Screening primary care patients for hereditary hemochromatosis with trasnferrin saturation and serum ferritim level: systematic review for the American College of Physicians. *Ann Intern Med* 2005. 143:522-536.

[4] Olynyk JK, Trinder D, Ramm GA, Britton RS, Bacon BR, Hereditary hemocromatosis in the post-*HFE* era. *Hepatology* 2008. 48(3): 991- 1001.

[5] Crawford DH, Hickman P. Screening for hemochromatosis. *Hepatology* 2000. 31(5):1192-93.

[6] The reason for higher population frequency in Northern Europe is not known. One intriguing, but still speculative, theory posits a survival advantage among those with HH mutations in resisting infections causing plague and other diseases prevalent in Europe. (See, for example, Moalen S, Weinberg ED, Percy ME. Hemochromatosis and the enigma of misplaced iron: implications for infectious disease and survival. *Biometals* 2004. 17(2):135-139.) Another hypothesis, which is not incompatible, is co-selection of hemochromatosis and certain major histocompatibility loci involved in immune function. (See, for example, Cardozo CS, Alves H, Mascarenhas M, Goncalves R, Oliveira P, Rodrigues P, Cruz E, de Sousa M, Porto G. Co-selection of the C64D mutation and HLA-A29 allele: a new paradigm of linkage disequilibrium? *Immunogenetics* 2002. 53:1002-1008.)

clinical hemochromatosis.[7] The estimated carrier frequency of *HFE* mutation is 1 in every 8 to 10 individuals of Northern European ancestry.[8]

Despite this, universal genetic screening has not been recommended for several reasons. First, presence of the mutation does not mean that the individual will develop HH. While testing may assist physicians in diagnosing HH when a patient is presenting characteristic symptoms, presence of the mutation merely indicates one's susceptibility to iron overload and not the certainty of disease for those who are asymptomatic. The symptoms of HH are highly variable among homozygotes (those in whom both chromosomal copies of the HFE gene have hemochromatosis-associated mutations). Some are completely asymptomatic, others are severely affected. Several studies provide evidence that the penetrance of the *HFE* mutations, or the chance that those with the mutations will have HH symptoms, is lower than first estimated and highly variable.[9] The disease is also rarer in non-white populations. Homozygous mutation levels are 0.27 homozygotes per 1,000 Hispanic individuals, less than .0001 homozygotes per 1,000 Asian American individuals, 0.12 homozygotes per 1,000 in Pacific Islanders, and an estimated .14 homozygotes per 1,000 in African–American individuals.[10] The American College of Physicians does not recommend genetic or phenotypic (using biochemical tests) screening for HH in the asymptomatic general population.[11] The U.S. Preventive Services Task Force (USPTF) similarly found insufficient evidence to support broad population genetic screening.[12] Finally, the current price of the genetic diagnostic tests also makes their use as an initial screening procedure for HH prohibitive. Current practice is to identify symptomatic individuals utilizing non-genetic tests that measure iron overload, followed by genetic testing for specific diagnosis and to detect cases in families once an HH proband is identified.

Hereditary hemochromatosis is a natural case study for studying the impact of intellectual property (IP) on patient access to genetic testing. Patents exist on the *HFE* gene, its related protein, genetic screening test methods, and related testing kits.[13] Additional genes linked to rarer forms of HH are also patented.

The impact of these patents and their licensing on access to testing for HH type 1 is complicated by the generally subordinate role of clinical genetic testing in hemochromatosis, but also by the complex history of ownership of these patents. Despite an initial controversy about patenting, *HFE* genetic testing appears to have been adopted in clinical practice and much of the heat may have drained from the public debate. The path to the current state, however, involved transitional periods of turbulence that centered on exclusive licensing of a genetic diagnostic test.

One distinctive feature of this case is how *HFE* testing has evolved over time. *HFE* genetic testing illustrates how patent ownership and use by different patent-holders can affect licensing. *HFE* patent rights were transferred many times, and use and licensing policies changed over time. A 2002 *Nature* article, written when the licensing schema was based on exclusive licensing and a single-provider model, judged that *HFE* genetic testing "failed the test" of socially optimal access. In 2007 and 2008, compared to 2002, we found little controversy surrounding *HFE* genetic testing, and the licensing model has evolved to include several providers and sublicensing for use on different platform technologies. The past

[7] Qaseem A, Aronson M, Fitterman N, Snow V, Weiss KB, Owens DK. Screening for hereditary hemochromatosis: a clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2005. 143:517-521.
[8] *GeneReviews HFE-Associated Hemochromatosis.* See http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=hemochromatosis [accessed November 10, 2008].
[9] Olynyk JK, Trinder D, Ramm GA, Britton RS, Bacon BR. Op. cit.
[10] Whitlock EP, Garlitz BA, Harris EL, Beil TL, Smith PR. Screening for hereditary hemochromatosis: a systematic review for the U.S. Preventative Services Task Force. *Ann Intern Med* 2006. 145:209-223.
[11] Qaseem A, Aronson M, Fitterman N, Snow V, Weiss KB, Owens DK. Op. cit.
[12] Whitlock EP, Garlitz BA, Harris EL, Beil TL, Smith PR. Op. cit.
[13] See Appendix A for a list of patents and their claims.

licensing practices of SmithKline Beecham Clinical Laboratories (SBCL) (exclusive licensing model) were controversial, but the current owner of patent rights, Bio-Rad Ltd., appears to have adopted a broad sub-licensing model that has resulted in broader clinical and patient access and less public conflict.

HFE genetic testing in the context of HH also shows how genetic testing is part of a larger set of diagnostic tools addressing a clinical syndrome. The clinical utility of those tools, including genetic testing, evolves over time. Growing knowledge about the uncertain penetrance of *HFE* mutations required additional research to determine the clinical significance of different *HFE* mutations, and other factors influencing expression of disease. These studies demonstrated a much lower clinical penetrance of *HFE* mutations than first expected, suggesting that the mutations alone were poor predictors of developing clinically significant hemochromatosis. Population screening was more likely to be pursued, if at all, by chemical or protein assays rather than genetic testing—with genetic tests finding more limited use in confirmatory diagnosis and family risk assessment once an index case is found. This most likely had a significant impact on interest in investing in patent enforcement, since the market for HFE genetic testing became much smaller when general population use seemed highly unlikely.

Lessons Learned

Research

- The Mercator Genetics business plan was centered on the identification of candidate genes for a number of complex diseases including asthma, schizophrenia, cardiovascular disease and prostate cancer, all of which presumably had a diagnostic market. The prospects of patents and revenue from diagnostic testing for HH probably stimulated research at Mercator Genetics. However, Dr. Dennis Drayna, co-founder of Mercator Genetics, notes that the company was conceived and initially funded on an agenda much broader than hemochromatosis gene discovery or diagnostic testing alone. Discovery of the *HFE* gene was nonetheless Mercator's signature success.
- The "race" for the HH gene was won by Mercator Genetics with the publication of an August 1996 *Nature Genetics* article. Two additional groups (one in France and another in Australia, which were both in non-profit institutions) were pursuing similar approaches to candidate gene identification and would likely have been successful in their efforts within months. However, the scale and focus of the positional cloning effort at Mercator, enabled by private R&D investment, probably gave their research group a competitive advantage.
- The patent applications filed by Mercator Genetics predated the submission of related manuscripts by nearly a year.[14] It is unclear, however, if this delay resulted from scientific issues, patenting activities, corporate strategy, or commercialization efforts by Mercator. It remains possible that such a delay may be the consequence of factors unrelated to patenting, such as the need for additional research or data prior to submission to peer reviewed journals, journal requests for additional data and experiments, delays in peer review, etc. Dr. Dennis Drayna, a senior author of the *Nature Genetics* paper, indicated that the latter was in fact true, and that Mercator Genetics made every attempt to expedite simultaneous paper submissions and patent filings.
- Concerns regarding inhibition of research due to the *HFE* gene patents do not seem to be supported. Substantial basic research, including identification of genes and mutations associated with other types of hemochromatosis has continued. Similarly, research on improved methods for detection of *HFE* mutations has also progressed. The adoption of broad sublicensing practices by

[14] Merz JF, Kriss AG, Leonard DGB, Cho MK. Diagnostic testing fails the test. *Nature* 2002. 415: 577-79.

Bio-Rad, Ltd., has facilitated commercial research and development efforts focused on alternative methods for *HFE* mutation detection.

Development

- Mercator Genetics announced that it was developing a blood test for *HFE* genotyping within a year of publication of results. It is likely that the prospect of revenues from population wide screening may have served as an incentive for test development. However, no test was marketed before Mercator went out of business and merged with Progenitor.
- Intellectual property ownership alone did not provide incentive for test development. As reported by Merz et al., laboratories were able to develop in-house testing and offer it as clinical service soon after information of the gene sequence and its associated mutation had been made public and well before the patents were granted.

Commercialization

- *HFE* patents were potentially valuable assets for Mercator in facilitating its merger with Progenitor. Exclusive licensing of the *HFE* patents to SmithKline Beecham Clinical Laboratories (SBCL) resulted in significant and guaranteed revenue for Progenitor.
- Until it was sold to Quest Diagnostics, SBCL offered the test as part of its commercial diagnostics services. SBCL also undertook enforcement activities, including sending "cease and desist" letters to clinical laboratories.
- Similarly, the *HFE* patents were perceived as valuable assets when Bio-Rad acquired them subject to the exclusive clinical testing license and all pending patents from Progenitor in 1999. Quest transferred the license to Bio-Rad under undisclosed terms.
- Acquisition of the *HFE* patents was integral to Bio-Rad's business plans to develop and market analyte-specific reagents (ASRs) for *HFE* testing. *HFE* ASRs became available in 2001.
- *HFE* patents do not appear to have blocked commercial development of additional methods of *HFE* testing utilizing different platform technologies. For instance, Bio-Rad Ltd. granted a non-exclusive license to Nanogen Ltd for detection of the C282Y and H63D mutations using the NanoChip™ System. We cannot assess whether alternatives were unimpeded in all cases, but at least some alternatives have developed. The patent-associated fees may have discouraged some laboratories from entering the market,[15] but testing is widely available from multiple sources.
- Several non-profit and for-profit laboratories offer *HFE* testing for a fee. It is unknown how many providers have acquired a sublicense from Bio-Rad for tests developed in-house or use the Bio-Rad analyte specific reagents (ASRs) (in which case a sublicense is built into the purchase).
- It is unclear how much of the price variability among different providers (list price for mutation analysis ranges from approximately $150 to $500) can be attributed to license/royalty fees as opposed to variable overhead costs or costs associated with different testing methodology/platforms.

Communication and Marketing

- Patents have had little to no impact on the communication and marketing of *HFE* testing.

[15] One external reviewer of an early draft of this case study noted he was aware of at least one potential HFE test developer who decided not to develop a test because of the up-front payments to BioRad.

- There is no evidence that *HFE* mutation testing was ever marketed directly to consumers by Mercator Genetics or subsequent holders of *HFE* patent rights.
- Information on promotion of *HFE* testing by Mercator Genetics among clinicians and other medical professionals is also unavailable. Similarly, it is unclear if SBCL and Bio-Rad Ltd. engaged in specific marketing activities to increase utilization of the test by consumers or health care providers.
- Independent campaigns by the Hemochromatosis Foundation, the American Hemochromatosis Society, the American Liver Foundation and the CDC[16] have sought to increase awareness of HH screening and *HFE* genetic testing among patients and medical professionals. The organizations promoting awareness are not the patent-holders, and the motivation appears to be public health awareness.
- Direct-to-consumer testing is also available from DNADirect.

Clinical Adoption

- Adoption of testing was rapid. As reported by Merz et al., adoption began nearly 17 months before the first patent was issued.[17]
- In a survey of testing providers, Merz et al. reported that 5 of 58 clinical laboratories offering the test in January 1998 elected to stop testing after receiving "cease and desist" letters from SBCL. Out of 31 other laboratories that had not developed the test, 22 indicated patents were the primary reason for not doing so. SBCL began patent enforcement ("cease and desist" letters) approximately two years after the patents were issued, by which time there had been significant adoption of the test.
- Although the number of laboratories offering *HFE* testing decreased, the majority of clinical providers (53) continued *HFE* genetic testing services. Therefore, it is unclear if the reduction in laboratories offering the test directly reduced clinical access to *HFE* testing.
- As of May 2007, 37 laboratories were listed as providers of *HFE* testing on the Genetests.org website. In addition, the test is offered directly to consumers by DNADirect.

Adoption by third party payers

- Patents do not appear to have had a direct or significant effect on decisions to cover the test by public or private insurance providers. A number of insurance companies cover genetic testing for HH when "medically necessary."

Consumer utilization

- There is little evidence bearing on the impact of patents on consumer utilization.
- Patent enforcement activities by SBCL led to the discontinuation of testing in some laboratories. Other laboratories reported being deterred from developing an *HFE* test by patent enforcement activities. However, most laboratories did continue offering the test as a

[16] Information about the American Hemochromatosis Society can be found at http://www.americanhs.org/. Efforts by the CDC to improve early detection and promote diagnosis of Hemochromatosis in the US are summarized in McDonnell SM, Witte DL, Cogswell ME, McIntyre R. Strategies to increase detection of hemochromatosis. *Ann Inter Med* 1998. 129:987-992.
[17] Merz JF, Kriss AG, Leonard DGB, Cho MK. Op. cit.

service. The effects that the reduction in number of laboratories had on patient access or consumer utilization cannot be determined.

- *HFE* testing currently appears to be widely available. A large number of clinical laboratories offer the test in the price range of $160- $500. Consumers can also access testing independent of physicians through DNAdirect. The price offered by DNAdirect ($199) is less than that listed by many clinical laboratories and includes genetic counseling services.
- The test is covered by several insurance providers when patients meet the eligibility criteria for testing. In the absence of quantitative data on how many tests are ordered per year and when and how often insurance coverage is denied, it is unclear to what extent third party adoption affects consumer utilization. The effect of patents on such coverage decisions, if any, was not mentioned by those offering tests or seeking reimbursement for them, and was not noted in payer coverage or reimbursement policies.

Background

The clinical syndromes of HH relate to the excessive deposition of iron in various organs. While healthy people usually absorb about 10 percent of the iron contained in their diet to meet their bodies' needs, those with HH absorb more. Chronic iron absorption may lead to a variety of symptoms. The most common symptoms include joint pain, fatigue, lack of energy, abdominal pain, loss of sex drive, and heart problems (including both arrhythmia and cardiomyopathy, or loss of cardiac muscle function). Men are more likely to experience symptoms and experience them earlier in life, between the ages of 30 and 50. Women affected by HH are usually symptomatic after the age of 50. The lower rates of HH in younger women are attributed to the protective effect of physiological blood loss associated with menstruation.[18]

HH begins as mere iron overload, but over time this overload can result in more serious disease through organ failure. Without early detection, the accumulated iron in various tissues may lead to:

- Arthritis (due to joint damage)
- Liver failure and cirrhosis (death of liver cells followed by scarring)
- Pancreatic damage that can possibly include diabetes[19]
- Problems with digestion (due to loss of pancreatic enzymes and paucity of fat-absorbing bile pigments produced by the liver)
- Heart abnormalities such as irregular heart rhythms or congestive heart failure
- Impotence
- Early menopause
- Abnormal pigmentation causing the skin to appear gray or bronze
- Thyroid deficiency

[18] Yen AW, Fancher TL, Bowlus CL. Revisiting hereditary hemochromatosis: current concepts and progress. *Am J Med* 2006. 119(5):391-399.

[19] Dr. Paul Adams cautions "that this area remains controversial since screening studies have not shown an increase in prevalence of diabetes. Several metabolic studies have suggested that the diabetes seen in hemochromatosis is more often insulin resistance of cirrhosis." Email from Paul Adams to SACGHS staff. September 9, 2008.

- Damage to the adrenal gland, and infrequently
- Liver cancer

There are several known types of HH.[20] The most common form, Type 1, affects adults and is usually caused by a defect in the *HFE* gene. Type 2 or juvenile hemochromatosis, which is not associated with the *HFE* gene, leads to severe iron overload and liver and heart disease in young adults between the ages of 15 and 30. Unlike adult-onset HH, juvenile HH affects males and females equally. Similarly, Types 3 and 4 of hereditary hemochromatosis are not associated with *HFE* mutations and they are much rarer.

Since the symptoms of HH can arise from many causes, doctors often focus on treating the individual symptoms and may not identify the underlying HH. Many cases of HH are therefore undiagnosed. This problem of effective diagnosis could be partially solved by genetic screening tests that would easily detect the *HFE* mutation in symptomatic persons and through a systematic screening process that identifies those presymptomatic individuals with iron overload. Individuals with signs of iron overload could then be evaluated with genetic testing and other means for determining causes of iron overload. In most cases, either an environmental source of overwhelming iron intake (e.g., vitamin overdose, dietary practice, water supply, or environmental exposure) or a known genetic mutation would explain the iron overload.

Genes Associated with Hemochromatosis

The gene most commonly associated with Type1 HH is *HFE*, located in the region of the gene *HLA-A* on chromosome 6.[21] There are two known mutations of the *HFE* gene that are most commonly linked to HH. The C282Y mutation is caused by a single base change, resulting in tyrosine replacing the normal cystine at position 282 of the *HFE* protein. C282Y accounts for almost 90 percent of HH cases.[22] Most patients are homozygous for the mutation, which is transmitted in an autosomal recessive manner.[23] Environmental factors and other genotypes also contribute to HH.[24] Another mutation, H63D, is the result of the substitution of an aspartic acid for a histidine at position 63. It is still unclear exactly how the H63D mutation is associated with HH. When H63D is inherited from one parent, it usually causes little increase in iron absorption and rarely leads to the development of hemochromatosis. Although most patients with a clinical diagnosis of HH are homozygous for the C282Y mutation, approximately 10% are compound heterozygotes carrying a single copy each of the C282Y and H63D mutations.[25] S65C is an *HFE* gene mutation tentatively linked to a mild form of iron overload. Other mutations with less frequency and/or low penetrance have also been described, including V53M, V59M, H63H, Q127H, Q283P, P168X, E168Q, E168X, and W168X.[26]

Juvenile hemochromatosis, also called HH type 2, (subtypes 2A and 2B), is an autosomal recessive disorder not caused by a defect in the *HFE* gene. *HJV*, a gene located on chromosome 1q, was recently identified as the cause of HH type 2A. Juvenile HH type 2B is caused by mutation in the *HAMP* gene coding for hepcidin, a peptide hormone that has a key role in human iron metabolism.[27] The hepcidin

[20] Olynyk JK, Trinder D, Ramm GA, Britton RS, Bacon BR. Op. cit.
[21] Whitlock EP, Garlitz BA, Harris EL, Beil TL, Smith PR. Op. cit
[22] Qaseem A, Aronson M, Fitterman N, Snow V, Weiss KB, Owens DK. Op. cit.
[23] Schmitt B, Golub RM, Green R. Op. cit.
[24] Wood M, Powell LW, Ramm GA. Environmental and genetic modifiers of the progression to fibrosis and cirrhosis in hemochromatosis. *Blood* 2008. 111:4456-4462.
[25] Yen AW, Fancher TL, Bowlus CL. Op. cit.
[26] Franchini M, Veneri D. Hereditary hemochromatosis. *Hematology* 2005. 10(2):145-49.
[27] Ibid.

protein hormone was initially called "Liver-Expressed Anti-microbial Protein"[28] because its function appeared to be related to fighting fungal and bacterial infections (iron is essential to the inflammatory response to certain pathogens). HH type 3 is an autosomal recessive disease caused by mutations in the transferrin receptor 2 gene, *TRF2*.[29] HH type 4, which is an autosomal dominant disease, is caused by mutations in the *SLC40A1* gene. *SLC40A1* encodes for a protein implicated in iron intestinal export, ferroportin.[30]

The remainder of this case study focuses on *HFE,* the gene most commonly associated with Type 1 HH, and for which the patenting and licensing stories are best documented.

Genetic Tests for Hemochromatosis

Several genetic tests are currently available for hemochromatosis. Targeted mutation analysis is the most common form of clinical genetic testing. This process tests for the presence of the two most common known disease-causing alleles in the *HFE* gene, C282Y and H63D.[31] Different laboratories use different methods. Several common testing methods for the presence of the C282Y and H63D mutations were used by 90 U.S. laboratories in 2002. These include electrophoresis for restriction fragment length polymorphisms (RFLPs) and size analysis (64% of labs), allele-specific oligonucleotide assay (ASO) (11% of labs), allele-specific polymerase chain reaction and Amplification Refractory Mutation System (PCR/ARMS) (6% of labs), LightCycler (8% of labs), DNA sequencing (3% of labs), and other/unspecified methods (8% of labs).[32] Linked linear amplification (LLA) is another means of amplification of DNA to detect *HFE* mutations.

Some methods are more labor intensive than others, making them suitable only for research rather than diagnostic laboratories. Other methods accommodate the needs of large numbers of specimens requiring short turn-around times. In Canada and Europe, commercial suppliers can provide "kits" to clinical laboratories. However, since such kits used for clinical testing in the United States are regulated by the FDA, increasing the costs associated with development, and analyte specific reagents (ASR) rather than test kits are routinely developed and marketed by biotech companies. Four biotechnology companies, Bio-Rad, Nanogen, LightCycler (a subsidiary of Roche), and Orchid Cellmark, provide reagents for the most commonly used methods of large-scale HH gene testing. A full sequence analysis can also be performed, usually to identify mutant alleles associated with HH that are not C282Y or H63D.

Non-Genetic-Based Means of Diagnosing Hemochromatosis

Currently, diagnosis of HH is often based on first-level biochemical tests, followed by second-level genetic testing. Biochemical methods are simple, fast, and inexpensive. The standard test is transferrin saturation (TS). This test determines how much iron is bound to transferrin, the protein that carries iron in the blood. Measuring a morning fasting TS level eliminates 80 percent of false-positive results. Values of 60% or greater in men and 50% or greater in women have an approximate sensitivity of 92%, specificity of 93%, and positive predictive value of 86% for detecting homozygous individuals with HH.[33] The

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[28] Krausse A et al. LEAP-1 a novel highly disulphide-bonded human peptide, exhibits antimicrobial activity. *FEBS Letters* 2000. 480:147-150. Park CH, Valore EV, Waring AJ, Ganz T. Hepcidin, a urinary antimicrobial peptide synthesized in the liver. *J Biol Chem* 2001. 276:7806-7810.

[29] Ibid.

[30] Ibid.

[31] Roughly 60 – 90% of the persons tested with an *HFE* mutation will have two C282Y alleles. While 3 – 8% will have one C282Y mutation and one H63D mutation, the rarest combination, roughly 1 % of those with *HFE* mutations will have two H63D mutations present. See Appendix D for more information.

[32] *ACC Review of HHC/General Adult Population Analytic Validity.* Centers for Disease Control and Prevention. Version 2003.6 (archived 2002). See http://www.cdc.gov/genomics/gtesting/ACCE/FBR/HH/HHAnaVal_17.htm [accessed January 12, 2009].

[33] Yen AW, Fancher TL, Bowlus CL. Op. cit.

above data are primarily from referral studies in which the TS test is embedded in the clinical diagnosis. In general population screening studies, where there is no referral for testing, the sensitivity of TS is much less. There is also a wide biological variability in the test. Fasting TS has also been shown to be of no increased value over random testing.[34,35] The lack of a uniform cutoff percentage for the optimal detection of disease lowers the specificity and positive predictive value of the TS test. Another limitation of TS is that it is a two-step test and therefore more prone to error.

A second possible test is serum ferritin (SF). This test estimates the total body iron stores. Ferritin values greater than 300 µg/L in men and 200 µg/L in women, suggest iron overload. However, ferritin can be falsely elevated as an acute phase reactant and does not become abnormal until iron loading has advanced due to liver involvement.[36] Therefore, doctors should consider non-HH causes behind a patient's high serum ferritin levels if transferrin saturation is not elevated.

A more recent biochemical method used to test for HH is unbound iron-binding capacity (UIBC). UIBC is a one-step assay that has high sensitivity and has been suggested as a reliable and potentially inexpensive diagnostic test for HH.[37] Prior to the availability of mutation analysis, liver biopsy was the most common second-level diagnostic test for HH. Liver biopsy helps determine the extent of iron accumulation in the liver. However, the biopsy is more often used as a prognostic tool, to review the level of damage in the liver.[38,39] Another non-genetic test used to diagnose HH is quantitative phlebotomy,[40] in which specified amounts of blood are drawn. Removing "4 g or more of mobilizable iron stores (16 phlebotomies, each removing 500 mL of blood [250 mg of iron per 500 mL]) before the development of iron-limited erythropoiesis confirms the presence of primary iron overload due to hemochromatosis."[41] If any of the tests described above suggest iron overload, *HFE* genotype testing is strongly suggested.

Treatment of Hemochromatosis

Unlike many other serious genetic disorders, hemochromatosis may be treated simply, safely, and inexpensively. The most common treatment for HH is phlebotomy, a process used to rid the body of excess iron. In phlebotomy, doctors remove a pint of blood once or twice a week for several months or more, depending on the iron levels. Phlebotomy has been widely adopted because it is inexpensive and safe, and has clear face validity as a common-sense treatment for iron overload. Recent studies have demonstrated a reversal of liver fibrosis with phlebotomy treatment.[42, 43] Treatment for those who already

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[34] Adams PC, Reboussin DM, Press RD, Barton JC, Acton RT, Moses GC, Leiendecker-Foster C, McLaren G, Dawkins F, Gordeuk V, Lovato L, Eckfeldt J. Biological variability of transferrin saturation and unsaturated iron binding capacity. *Am J Med* 2007. 120:999.e1.-e7.

[35] Adams PC, Reboussin DM, Eckfeldt JH, Moses GC, Leiendecker-Foster C, McLaren CE, McLaren GD, Dawkins FW, Kasvosve I, Acton RT, Barton JC, Zaccaro D, Harris EL, Press R, Chang H. A comparison of the unsaturated iron binding capacity to transferrin saturation as a screening test to detect C282Y homozygotes for hemochromatosis in 101,168 participants in the HEIRS study. *Clinical Chemistry* 2005. 51:1048-1052.

[36] Ibid.; Franchini M, Veneri D. Op. cit.

[37] Murtagh LJ, Whiley M, Wilson S, Tran H, Bassett ML. Unsaturated iron binding capacity and transferrin saturation are equally reliable in detection of *HFE* hemochromatosis. *Am J Gastroenterol* 2002. 97(8):2093-9.

[38] Whitlock EP, Garlitz BA, Harris EL, Beil TL, Smith PR. Op. cit.

[39] Adams PC, Kertesz AE, McLaren CE, Barr R, Bamford A, Chakrabarti S. Population screening for hemochromatosis: a comparison of unbound iron-binding capacity, transferrin saturation, and C282Y genotyping in 5,211 voluntary blood donors. *Ann Intern Med* 2000. 31(5):1160-64.

[40] Powell LW, George DK, McDonnell SM, Kowdley KV. Diagnosis of hemochromatosis. *Ann Intern Med* 1998. 129:925-931.

[41] Ibid.

[42] Falize L, Guillygomarch A, Perrin M, Laine F, Guyader D, Brissot P, Turlin B, Deugnier Y. Reversibility of hepatic fibrosis in treated genetic hemochromatosis: a study of 36 cases. *Hepatology* 2006. 44:472-7.

[43] Powell L, Dixon J, Ramm G, Purdie D, Lincoln D, Anderson G, Subramaniam, VN, Hewett DG, Searle JW, Fletcher LM, Crawford DH, Rodgers H, Allen KJ, Cavanaugh JA, Bassett ML. Screening for hemochromatosis in asymptomatic subjects with or without a family history. *Arch Intern Med* 2006. 166:294-301.

have organ damage is more complicated. While phlebotomy may stop the progression of liver disease in its early stages, those with more severe cases may need to seek a specialist. Phlebotomy will not cure other conditions associated with hemochromatosis, but it will help most of them, with the exception of arthritis, for which removal of excess iron has little effect.

Current Guidelines for Genetic Testing

Clinical uses of genetic testing include confirmatory diagnostic testing, predictive testing for at-risk relatives, carrier testing to identify heterozygotes, and prenatal diagnosis (technically available but rarely performed)[44]. The American College of Physicians (ACP) clinical practice guidelines for the screening of HH state evidence is insufficient to recommend for or against screening for HH in the general population.[45] They recognize that the C282Y mutation is the most common predictor of whether the patient will develop HH but note that there is still no way of predicting which homozygous patients will develop HH.[46] For these reasons, the ACP leaves the decision whether or not to perform tests for HH to clinical judgment, based on: whether patients exhibit symptoms of the associated disorders; whether patients exhibit serum ferritin levels of more than 200 µg/L in women and more than 300 µg/L in men combined with transferrin saturation greater than 55%; or whether the individual has a family history of HH. Each factor increases the risk for developing the disease compared to the general population.[47]

The ACP also encourages doctors to discuss the risks and benefits of genetic testing with their patients. This should include a discussion of the available treatment and its efficacy, as well as the social impact of disease labeling, insurability, psychological well-being, and as-yet-unknown genotypes associated with HH.[48] For example, asymptomatic persons found homozygous or not for the C282Y mutation may develop unnecessary stress or false reassurance.[49] The ACP does acknowledge that the lack of information on the natural history of HH makes it difficult to manage patients with the disorder,[50] and considers future technological developments and genetic screening as potential aids in the management of the disease.[51] Finally, the ACP recommends more uniform diagnostic criteria.

The American Association for the Study of Liver Disease recommends genetic testing for all patients in whom there is a strong suspicion for iron overload. Such patients should have C282Y and H63D mutation analysis completed.[52,53]

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[44] See http://www.geneclinics.org/profiles/hemochromatosis/details.html [accessed January 13, 2009].
[45] Qaseem A, Aronson M, Fitterman N, Snow V, Weiss KB, Owens DK. Op. cit.
[46] Ibid.
[47] Ibid.
[48] Ibid. See also Anderson RT, Wenzel L, Walker AP, Ruggiero A, Acton RT, Tucker DC, Thomson E, Harrison B, Howe E, Holup J, Leiendecker-Foster C, Power T, Adams P. Impact of hemochromatosis screening in patients with indeterminate results: the hemochromatosis and iron overload screening study. *Genet Med* 2006. 8(11):681-87. The observational study found that notification of indeterminate results from screening might pose a potential participant risk. Asymptomatic individuals who underwent *HFE* genotype testing, or were tested for HH using the SF or FT methods and were found to have elevated levels of uncertain clinical significance. It found that compared to normal controls, those persons reported diminished general health and mental wellbeing, and more health worries.
[49] Qaseem A, Aronson M, Fitterman N, Snow V, Weiss KB, Owens DK. Op. cit.
[50] Environmental factors often modify the natural expression of iron accumulation and disease. These factors include blood loss from menstruation or donation, alcohol intake, diet, and co-morbid disease including viral hepatitis. Whitlock, E.P.; Garlitz, B.A.; Harris, E.L.; Beil, T.L.; Smith, P.R. Screening for hereditary hemochromatosis: a systematic review for the U.S. Preventative Services Task Force. *Ann Intern Med* 2006. 145:209-223.
[51] Qaseem A, Aronson M, Fitterman N, Snow V, Weiss KB, Owens DK. Op. cit.
[52] See Appendix C.
[53] Yen AW, Fancher TL, Bowlus CL. Op. cit..

Patenting of HH Genes

Bio-Rad Laboratories, Inc., is the owner and licensee of most of the patents relating to HH genetic testing and the *HFE* gene. In 1999, Bio-Rad bought many of those rights from Progenitor, which had retained the rights to HH genetic testing following the Mercator-Progenitor merger. Mercator was the initial patent owner and assignee.

Mercator scientists first identified the *HFE* gene in 1995–96, along with the two mutations, C282Y and H63D, which were present in over 80 percent of people suffering from HH.[54] In 1995 and 1996, Mercator applied for patents related to *HFE* and its mutations. The patents were issued at various times between 1998 and 2000 and covered the whole *HFE* gene sequence, a method for diagnosing the C282Y and H63D mutations within the *HFE* sequence, a method of analyzing C282Y and H63D *HFE* mutations, and a method of analyzing the mutation using a kit. Other patents in the same patent family and with the same group of inventors issued between 2000 and 2006 and were assigned to Bio-Rad. These patents included diagnostic methods for a panel of less prevalent mutations, which did not include C282Y or H63D. They also cover polypeptides related to the *HFE* gene, and the associated proteins. Another patent covers a method of diagnosis for TRF2, another gene related to HH.[55]

Some other patents pertinent to HH are not controlled by Bio-Rad, but they are far fewer in number. Billups-Rothenberg, Inc., (BRI), in San Diego, California owns a gene patent, US 6,355,425 "Mutations Associated with Iron Disorders," which covers a diagnostic method for a panel of *HFE* mutations including S65C, 193T, G93R, 277C, 105T, 314C but does not include C282Y and H63D. BRI has exclusively licensed this patent to Nanogen. The one HH gene patent owned by a non-profit organization is assigned to Erasmus University in Rotterdam, Netherlands. This patent claims a method of diagnosis for SCL11A3, a mutation of the ferroportin 1 gene. We have been unable to determine if this patent was ever licensed. However, these patents may be less relevant to the case study because the predominant tests related to HH genotyping involve the mutations C282Y and H63D that are covered by the Bio-Rad patents.

We know of no litigation over the DNA sequence patents associated with HFE or other genetic forms of hemochromatosis, although given exclusive licenses to Nanogen for several mutations, this is a conceivable prospect.

Licensing of HH Genes

Merz et al. published a report in 2002 highlighting the patenting of the *HFE* gene and the licensing practices of the Mercator/Bio-Rad patents. The authors argued that gene patents had a negative on clinical practice because of the high prices the patent owners commanded.[56] According to the article, in the late 1990s, Progenitor exclusively licensed the patent rights to perform clinical testing of the HH mutations to SmithKline Beecham Clinical Laboratories (SBCL) for an up-front payment and guaranteed continuing fees worth roughly $3 million.[57] The licensing agreement guaranteed that SBCL's exclusive license and payments to Progenitor would continue until a kit became available for use by clinical laboratories.[58] In June 1998, after SBCL obtained the exclusive licensing for the clinical testing component of HH, it began informing laboratories of their possible infringement activities and offering sublicenses for an up-front fee of $25,000 to academic licensees and for 5 to 10 times that amount to commercial laboratories (Appendix

[54] Feder JN et al. A novel MHC class-I like gene is mutated in patients with hereditary hemochromatosis. *Nat Genet* 1996. 13:399-408.
[55] See Appendix A.
[56] Merz JF, Kriss AG, Leonard DGB, Cho MK. Op. cit.
[57] Ibid.
[58] Ibid.

E). It also sought royalties as high as $20 per test.[59] After the sale of SBCL and the patent rights for clinical testing to Quest Diagnostics in 1999, the IP was not enforced again until Bio-Rad began offering analyte-specific reagents (ASRs) in 2001.

When Bio-Rad acquired the portfolio of pending and issued patents covering *HFE* and its mutations from Progenitor in April 1999, it acquired them subject to the exclusive clinical-testing license held by SBCL.[60] Quest transferred the clinical-testing license it acquired from SBCL to Bio-Rad.[61] The terms and conditions of that license agreement were not made public. Bio-Rad obtained other patents related to HH gene products. It began offering analyte-specific reagents (ASR) for testing of the C282Y and H63D alleles in 2001.

Today, Bio-Rad offers two HH test kits, the mDx Hereditary Hemochromatosis ASR kit and mDx Hereditary Hemochromatosis LLA ASR test kit. Both kits provide for 24 tests at a cost of $2,016, or $84 per test. A purchase of the kit includes the purchase of a sublicense from Bio-Rad to perform the test. According to some providers, the sublicenses attached to Bio-Rad's kits are more cost efficient than the licenses it offers to laboratories that develop and offer their own mutation testing or "in-house" assays.[62] However, Dr Michael Watson at the American College of Medical Genetics indicates that, at least initially, the Bio-Rad test kit's inferior performance essentially forced laboratories to develop their own "in-house" tests, which would require paying the higher fee for a sublicense. Such a sub-license includes up-front payments that are inversely proportional to the testing volume of the laboratory plus a per test fee, which was $20 in 2002.[63] It is not known what sublicensing fees are currently paid by laboratories that offer tests they have developed in-house, also known as "home- brews". The CDC review of analytic validity of *HFE* testing [64] noted that since Bio-Rad owned the patent for hereditary hemochromatosis, no other commercially available manufactured reagents were available for this test. However, ASRs for mutation detection using other platform technologies have become available more recently. For example, ASRs are offered by Nanogen Inc,[65] with sublicenses from Bio-Rad and presumably BRI too.

Impact of IP and Licensing on Clinical Genetic Testing for HH

Despite the presence of IP on clinical testing methods, laboratories around the country were performing HH screening on patients before and after the Mercator patents issued.[66] In a study of 128 U.S. laboratories identified as capable of offering the *HFE* test, with 119 of those laboratories responding, 58 laboratories indicated that they were performing *HFE* testing by 1998.[67] Thirty-five of the 58 laboratories were conducting the testing after the *Nature Genetics* paper published in August 1996 identifying the mutation, but before the patent issued in January, 1998.[68] Fifty-four of the 58 laboratories conducting the test received letters from SBCL informing them of the HH IP and offering a sublicense.[69] Ninety-one percent of the interviewed laboratories were aware of the *HFE* patents and 36 revealed that

[59] Ibid.
[60] Ibid.
[61] Ibid.
[62] Merz JF, Kriss AG, Leonard DGB, Cho MK. Op. cit.
[63] Ibid.
[64] *ACC Review of HHC/General Adult Population Analytic Validity.* Op. cit.
[65] Non exclusive license between Nanogen Inc and BioRad for *HFE* C282Y and H63D testing .
See http://sec.edgar-online.com/2003/03/31/0001104659-03-005523/Section8.asp [accessed January 13, 2009]. Third Wave Technologies, which previously marketed custom HFE ASRs, was acquired by HoloLogics in June 2008. Custom ASRs for HFE testing are no longer marketed by HoloLogics.
[66] *ACC Review of HHC/General Adult Population Analytic Validity.* Op. cit.
[67] Cho MK. *Effects of Gene Patents and Licenses on Clinical Genetic Testing*. Presentation to Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS). 27 June 2008. See http://oba.od.nih.gov/oba/SACGHS/meetings/June2006/Cho.pdf [accessed November 12, 2008].
[68] Ibid.
[69] Merz JF, Kriss AG, Leonard DGB, Cho MK. Op. cit.

the patents contributed to their decisions not to offer the test.[70] Five laboratories out of the initial 128 sample, or 4 percent, chose to stop performing the test. Of these 5 labs, 2 stated that the reason to stop testing was patents. One laboratory stated that patents were one of several reasons for abandonment of the HH test. Two additional laboratories stated that patents were not a reason for their decision to abandon the test. Commercial reasons (e.g., lack of adequate volume to cover fixed costs) appeared to be the predominant reason why these laboratories stopped performing the test.[71],[72]

As of May 2007, the GeneTests database (www.genetest.org) listed 37 U.S. laboratories performing targeted mutation analysis for HH. A sampling of 17 of those 37 laboratories revealed a list price for targeted mutation analysis that fell between $125 and $467 [73] indicating a significant range in prices. This may be due to several factors, including variability in methods of mutation testing, reagents costs for each method, and potentially licensing fees to perform HH testing. Some laboratories may perform "home-brew" assays with relatively low reagent costs. In these cases, one must consider the cost of the technical time for reagent preparation and the Quality Control/Quality Assurance (QC/QA) costs. The costs of ASR can be relatively high compared to traditional biochemical assays. At the same time, savings in technical staff time for preparation and QC/QA can offset reagent costs. For screening, the relevant figure is the cost per patient tested, not the cost per mutation tested; a diagnostic test may entail running the test case as well as controls, which also consume reagents covered by the reagent kits.[74] The exact economics of *HFE* mutation testing for HH are therefore not completely transparent. The cost of the IP is a minimum of the $20 per test fee and could be higher, depending on how licensing fees are structured into reagent costs that come with associated patent licenses.

Cost Effectiveness of Screening for *HFE* Mutations

Several studies on the cost-effectiveness and benefits of genotypic screening for the common disease-causing alleles on the *HFE* gene have been performed. As recently reviewed by Phatak et al., these studies provide evidence that screening would improve health status. However, all the studies reviewed support the use of biochemical tests rather than genetic tests as the initial test.[75] In 1999, Adams et al. reported that the genotypic screening of voluntary blood donors and their siblings by genotyping would be less expensive than phenotypic screening with biochemical tests if the genetic test cost less than $28. However, if the genetic test cost $173, then it would cost nearly $110,000 to identify a homozygote with a potentially life-threatening disease. The cost per homozygote identified also increased with decreasing penetrance of the disease. A 10% penetrance (i.e., 10% of those individuals with the relevant mutation actually have HH) resulted in nearly $400,000 in costs per individual identified.[76]

A literature review and synthesis conducted by Whitlock *et al*. for the U.S. Preventive Services Task Force provides some outline of the cost effectiveness of *HFE* screening. However, it could not determine the cost-effectiveness of screening because of uncertainties associated with penetrance of disease in

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[70] Ibid.
[71] Data provided by Jon Merz, September 5, 2008. Data provided during external review process.
[72] Cho MK. Op. cit.
[73] The sample was conducted by informal telephone conversations with laboratory staff on April 6, 2007. The providers were surveyed for their laboratory's "list price" for *HFE* testing. In some situations, staff offered both the individual list price and the insurance list price. See Appendix B. By way of comparison, a study noted that the cost of *HFE*-genotyping in Australia cost less than $28. Adams PC, Kertesz AE, McLaren CE, Barr R, Bamford A, Chakrabarti S. Population screening for hemochromatosis: a comparison of unbound iron-binding capacity, transferrin saturation, and C282Y genotyping in 5,211 voluntary blood donors. *Ann Intern Med* 2000. 31(5): 1160-64.
[74] *ACC Review of HHC/General Adult Population Analytic Validity.* Op. cit.
[75] Phatak PD, Bonkovsky HL, Kowdley KV. Hereditary hemochromatosis: time for targeted screening. *Ann Intern Med* 2008. 149(4):270-2.
[76] Adams PC, Valberg LS. Screening blood donors for hereditary hemochromatosis: decision analysis model comparing genotyping to phenotyping. *Am J Gastroenterology* 1999. 94:1593-1600.

individuals with C282Y mutations, poorly defined natural history of disease progression, and variable prevalence of *HFE* mutations in different ethnic populations.[77] HH testing would not be as effective as the control procedures without evidence establishing that the prevailing symptoms are caused directly by or associated with iron overload. The review outlined several studies suggesting that while members of the general population with symptoms or signs consistent with HH did not have higher levels of C282Y homozygosity, patients in a liver clinic prescreened for higher transferrin saturation levels, hospitalized diabetic patients, and patients referred to specialists for chronic fatigue and arthralgias did.[78] Studies have suggested that most individuals with the genetic abnormality do not have shortened life expectancy or progression of disease when compared with control groups.[79] Morbidity and mortality in HH are related to the presence of iron overload in the blood, tissue, and organ systems, not the *HFE* mutation, per se.[80] End organ damage is related to the severity of iron overload and reduces life expectancy.[81] One study suggests that *HFE* screening is cost effective *if* the proportion of C282Y homozygotes that develop end organ damage when left untreated is over twenty percent.[82] Allen *et al*. recently reported that nearly 28 % of men and 1 % of women with C282Y homozygosity will develop iron overload disease.[83]

To assess the cost-effectiveness of genotype screening for HH, a study would need to address: (1) the prevalence of HH; (2) the probability of developing disease manifestations and cost of managing them; (3) the cost of the screening test; (4) the cost offsets of screening and diagnosis compared to costs avoided by early detection or more effective management; and (5) the discount rate, to accommodate the separation in time from detection to health benefit.

In a recent comprehensive analysis, Gagne et al. evaluated the cost effectiveness of 165 population screening algorithms using biochemical and genetic tests in a simulated virtual population with user defined demographic characteristics including variable *HFE* mutation frequencies and penetrance. Biochemical penetrance was used as an intermediate phenotype in this study. In the 165 algorithms used in 91 virtual populations of a million individuals, biochemical screening tests were more cost effective than genetic tests when used as the initial test. Genetic testing was once again found to be most cost effective when performed as the final confirmatory step.[84]

HFE gene testing for the C282Y mutation is a cost-effective method of screening the siblings and children of patients with HH.[85] The authors incorporated serum iron studies among persons homozygous for C282Y and compared a no-screening strategy with four screening strategies for HH. All the strategies were developed for treating children and siblings of probands, except for one when the spouse was also given a genetic test. This exception strategy was only applied to children. The study recommended a four step clinical intervention: "(1) serum iron studies; (2) gene testing of the proband. If the proband is [without a C282Y mutation], the spouse undergoes gene testing; if he or she is heterozygous [for the C282Y mutation], the children undergo gene testing; (3) Gene testing of the proband; if he or she is homozygous, relatives undergo gene testing; (4) Direct gene testing of relatives."[86] The study concluded

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[77] Whitlock EP, Garlitz BA, Harris EL, Beil TL, Smith PR. Op. cit.
[78] Ibid.
[79] Waalen J, Nordestgaard BG, Beutler E. The penetrance of hereditary hemochromatosis. *Best Pract Res Clin Haematol* 2005. 18(2):203–220. Yen AW, Fancher TL, Bowlus CL. Op. cit.
[80] El-Serag HB, Inadomi JM, Kowdley KV. Screening for hereditary hemochromatosis in siblings and children of affected patients, a cost-effectiveness analysis. *Ann Intern Med* 2000. 132:261–269.
[81] Crawford DH, Hickman P. Op. cit.
[82] Ibid.
[83] Allen KJ et al. Iron-overload-related disease in *HFE* hereditary hemochromatosis. *N Engl J Med* 2008. 358(3):221-30.
[84] Gagne G, Reinharz D, Laflamme N, Adams PC, Rousseau F. Hereditary hemochromatosis: effect of mutation penetrance and prevalence on cost-effectiveness of screening modalities. *Clinical Genetics* 2007. 71: 46-58.
[85] El-Serag HB, Inadomi JM, Kowdley KV. Screening for hereditary hemochromatosis in siblings and children of affected patients, a cost-effectiveness analysis. *Ann Intern Med* 2000. 132:261–269.
[86] Ibid.

that "*HFE* gene testing of the proband was the most cost-effective strategy for screening one child," with an incremental cost-effectiveness ratio of $508 per life-year saved. For screening two or more children, the second most cost effective strategy was "*HFE* gene testing of the proband followed by testing of the spouse." There, the incremental cost-effectiveness ratio was $3665 per life-year saved. The study also concluded that "in siblings, all screening strategies were dominant compared with no screening" and that "strategies using *HFE* [genetic] testing were less costly than serum iron studies."[87] The greater cost-effectiveness of this sequential algorithm, which incorporates genetic testing but does not use genetic testing as the first step, is because the relatively high cost of genetic testing is incurred only in cases where risk is higher than average. The use of clinical genetic testing to confirm a diagnosis of HH among those with iron overload, in this conceptual framework, is an "indicated" preventive intervention targeted at asymptomatic individuals who have evidence of iron overload based on inexpensive biochemical screening tests. Here, we borrow from the terminology of Gordon's classification of preventive strategies, using genetic testing as one step in the prevention strategy.[88]

Phatak et al. recommend selective or "targeted" screening in groups whose risk is elevated such as adult men greater than 25 years of age of Northern European ancestry and first degree relatives of patients with known HH[89].

Lessons Learned About the Patent Process

HH was selected for study to assess the impact of patenting and licensing practices on access to genetic testing. Using the conceptual framework developed for a parallel literature synthesis, we now consider what lessons might be learned from this case.

Research

We considered whether the gene patents in question either accelerated or retarded the original discovery that ultimately led to the development of HH mutation analysis and genetic testing. Initially, the discovery of the HH-related genes was characterized as a "race," which was won by Roger K. Wolff and his colleagues of Mercator Genetics in Mountain View, California. The scientists knew that the gene for HH resided on chromosome 6, but were unable to pinpoint it. They suspected that most people with HH had the same mutations and invested heavily in research to find such mutations. Studying a group of 178 people with iron-overload disease from across the country, the researchers identified a segment of DNA that all patients had in common and used that information to scour that region of chromosome 6 in search of specific mutations. After a long search, they determined that two mutations accounted for 87 percent of iron-overload patients in the study and published their findings in the August 1996 issue of *Nature Genetics*.[90] French and Australian scientists verified these findings a few months later, publishing their findings in the November issue of that same journal.[91] There is no evidence that the patent retarded the original discovery. On the contrary, the potential of revenues from diagnostic testing may have provided added incentive for basic research linking *HFE* mutations to HH by drawing Mercator into the race. Of Mercator's four original patents, the first was filed on May 8, 1995 and the last was filed May 23, 1996.[92]

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[87] Ibid.
[88] Gordon RS. An operational definition of disease prevention. *Public Health Reports* 1983. 98: 107-109.
[89] Phatak PD, Bonkovsky HL, Kowdley KV. Op. cit.
[90] Feder JN et al. Op. cit.
[91] Jazwinska EC et al. Hemochromatosis and HLA-H (Letter). *Nature Genetics* 1996. 14: 249-251.
Jouanolle AM et al. Hemochromatosis and HLA-H (Letter). *Nature Genetics* 1996. 14: 251-252.
Fackelmann K. Rusty origins: researchers identify the gene for iron-overload disease. *Science News* 1997 (January 18). 151(3): 46. See http://findarticles.com/p/articles/mi_m1200/is_n3_v151/ai_19056180/pg_1?tag=artBody;col1 [accessed January 12, 2009].
[92] See Appendix A.

The May 1995 patent application pre-dates the submission of the *Nature Genetics* article by over one year. While some speculated that patenting and commercial positioning might account for the delay, Dr. Dennis Drayna, who was a co-founder of Mercator Genetics and a senior author in the 1996 *Nature Genetics* paper, indicated that "there was no attempt to delay publication for commercial or competitive reasons".[93] He said that delay in publication simply resulted from the time taken for scientific review and subsequent efforts to address reviewers' comments and criticisms before resubmitting the manuscript. In fact he believes that the opposite was true and that it was in Mercator Genetics's best interest to publish their results as early as possible. In Dr. Drayna's opinion, "Early scientific discoveries are essential for raising subsequent rounds of funding from additional investors, and publication of scientific discoveries is paramount to the maintenance of an ongoing enterprise. Laboratory discoveries are trumpeted as loudly and quickly as possible, which is basically what Mercator Genetics did."[94]

Dr. Margit Krikker, medical director of the Hemochromatosis Foundation, opposed Mercator's approach to patenting in a 1996 AP story published in the *New York Times.* "[She] complained about the way Mercator was handling the discovery, saying that by filing a patent for the gene, Mercator had limited other scientists' research opportunities."[95] We found no evidence to corroborate this assertion. Substantial basic and clinical research on the genetics of hemochromatosis has continued since the discovery of *HFE*, including identification of genes and mutations associated with other types of hemochromatosis, suggesting patents have not blocked further research and development. We cannot eliminate the possibility of a "chilling effect" from fear of patent prosecution, but in 2007 and 2008 it did not emerge as a major controversy, as it appears to have been at the time of the patent and again in 2002.

However negotiating licenses for the use of *HFE* patents may have contributed to a several-month delay in initiating research conducted as part of the Hemochromatosis and Iron Overload Screening Study (HEIRS) sponsored by the NHLBI. The purpose of HEIRS is to determine the prevalence, genetic and environmental determinants, and potential clinical, personal, and societal impact of iron overload and hereditary hemochromatosis, in a multi-center, multiethnic, primary care-based sample of 100,000 adults. Dr. Michael Watson, Executive Director of the American College of Medical Genetics, indicated that "the study was delayed by nearly 6 months" because Third wave Technologies needed a sublicense from Bio-Rad Ltd for the use of patents covering *HFE* mutations (C282Y and H63D) for the Invader™ assay ASRs.[96] Dr. Eckfeldt, another prominent researcher in HEIRS, confirmed that the study was indeed delayed between 4-6 months but indicated that start-up logistics also contributed to this delay. A modified Invader™ assay was used for all *HFE* genotyping in the study[97]. NHLBI paid Bio-Rad a license fee to access *HFE* patents for genetic testing performed as part of HEIRS, since the study was designed to return test results to the nearly 100,000 patients enrolled and their physicians. Dr John Eckfeldt stated that the royalty fee per test paid to Bio-Rad was reasonable, although the exact amount is confidential and protected by non-disclosure agreements. He also noted that "considering that 100,000 subjects were screened, the overall cost to NHLBI was quite substantial" despite a nominal fee per test. Bio-Rad subsequently granted a general sublicense to Third Wave Technologies. Until recently, Third Wave

[9393] Email from Dr. Dennis Drayna, Section Chief NIDCD/National Institutes of Health, September 11, 2008. Comments provided during external review process.
[94] Email from Dr. Dennis Drayna, Section Chief NIDCD/National Institutes of Health, September 11, 2008. Comments provided during external review process.
[95] Associated Press. Gene Found For Iron Buildup. *New York Times.* July 31, 1996. See http://query.nytimes.com/gst/fullpage.html?sec=health&res=9800E7DA1439F932A05754C0A960958260 [accessed November 13, 2008].
[96] Meeting with Dr. Michael Watson October 11, 2007.
[97] Adams PC, Reboussin DM, Barton JC, McLaren CE, Eckfeldt JH, McLaren GD, Dawkins FW, Acton RT, Harris EL, Gordeuk VR, Leiendecker-Foster C, Speechley M, Snively BM, Holup JL, Thomson E, Sholinsky P, Hemochromatosis and Iron Overload Screening (HEIRS) Study Research Investigators. Hemochromatosis and iron-overload screening in a racially diverse population. *N Engl J Med* 2005. 352(17):1769-78.

offered *HFE* custom ASRs as a service. Following the acquisition of Third Wave by Hologics Inc., in June 2008, custom ASRs for HFE are no longer being marketed.[98]

Development

Within one year of the *Nature Genetics* publication, Mercator announced that it was developing a blood test for HH genotype testing. The company pointed to the ultimate goal of population-wide screening for HH, whereby all persons, not just those at higher risk for the mutation, would be tested.[99] As demonstrated above, laboratories without IP rights on the *HFE* gene developed genetic tests for the mutations based on the *Nature Genetics* paper before the patent issued. This suggests that information on the gene sequence and its associated mutations was sufficient for other clinical providers to develop and offer genetic testing for HFE.[100]

Commercialization

Mercator Genetics, the company that first patented the *HFE* gene and its corresponding mutations, was founded by a group of doctors and genetic researchers from Stanford Medical School and the Silicon Valley biotechnology sector. Mercator Genetics described itself as a "gene discovery company" that focused on the identification of genes responsible for major diseases. Mercator's business model consisted of positional cloning to discover genes of interest and then capitalizing on the development of diagnostic tools associated with those genes.[101] Financial support was solicited from the pharmaceutical industry and venture capitalists like Robertson Stephens & Co., Interwest Partners, and Oak Investment Partners.[102] Investment was possibly tied to the prospect of patents. According to Dr. Dennis Drayna, "Mercator Genetics was conceived and raised funding on the basis of a far broader agenda. Hemochromatosis was never mentioned in any of the discussions that preceded funding of the company. HH was settled upon as a research and commercial target during later discussions with the Scientific Advisory Board. The choice of a diagnostic as a commercial target, as opposed to our competing genomics companies who mostly worked toward therapeutics as commercial targets, generated some discussion at the time, as the investors had already committed their funds."[103] Mercator was not only "racing" to clone the HH gene but also to search for genes linked with complex diseases like asthma, schizophrenia, prostate cancer, and cardiovascular disease.[104] However, Dr. Drayna said, "While the company did work in a number of other disease areas, these were either small exploratory efforts (such as Werner Syndrome and narcolepsy), or were the subject of primarily business transactions. There was never any work in the laboratory on asthma, schizophrenia, prostate cancer, or cardiovascular disease at Mercator Genetics." Mercator placed second or later and thus lost to Darwin Molecular Corporation in the "race" to patent the gene for the aging disorder Werner's syndrome.[105] Ultimately, the company's only successful entry in a patent race was the search for *HFE* and its mutations. Mercator Genetics's most valuable IP assets were patent rights to *HFE* and its mutations. In 1997, after expending $10 million on developing its method of positional cloning and discovering the association between *HFE* mutations and HH, Mercator went out of business and merged with Progenitor in 1997, which received rights to Mercator's pending and issued patents.[106] Dr. Drayna believes that "Mercator Genetics …. was a clear

[98] Hologics Inc acquired Third Wave technologies in June 2008. See transcript of conference call held by Hologic Inc on 9 June 2008 at http://www.secinfo.com/d14D5a.t3vh8.d.htm [accessed January 13, 2009].
[99] Rusty origins: researchers identify the gene for iron-overload disease – hereditary hemochromatosis. Op. cit.
[100] Cho MK. Op. cit.
[101] Capitalizing on the Genome (Editorial). *Nat Gen* 1996. 13(1):1.
[102] Ibid.
[103] Email from Dr. Dennis Drayna, Section Chief NIDCD/National Institutes of Health, September 11, 2008. Comments provided during external review process.
[104] Rusty origins: Researchers identify the gene for iron-overload disease – hereditary hemochromatosis. Op. cit.
[105] Capitalizing on the genome (Editorial). Op. cit.
[106] Merz JF, Kriss AG, Leonard DGB, Cho MK. Op. cit.

scientific success in the face of exceptionally widespread competition. It was less of a business success largely due to medical, social, and political factors surrounding the adoption of genetic testing on a widespread basis."[107]

Progenitor obtained rights to Mercator's *HFE* patents, and was readying its first initial public offering (IPO) when it was sold to SmithKline Beecham Laboratories, which received assets from both Mercator and Progenitor. Progenitor anticipated an IPO price between $10 and $12 per share and proposed funding its acquisition of Mercator with $22 million of Progenitor Common Stock, based upon an initial public offering price.[108] Again, the value of Progenitor was largely based upon the perceived value of its IP more than tangible assets.

Communication/Marketing

There is no evidence that the patented *HFE* mutation analysis test was ever marketed using direct-to-consumer marketing, although the idea was considered originally. For instance, there has been no ad campaign similar to the one launched by Myriad Genetics during the 2002 Super Bowl and test-marketed in Denver and Atlanta, or Myriad's 2007-2008 BRCA advertising in the Northeast.

Outside of Mercator's promotion activities, organizations committed to HH awareness have led their own marketing campaigns. Following the gene discovery in 1996, Margit Krikker of the Hemochromatosis Foundation bought an advertisement in the New York Times to alert the public to the deadliness of HH. The Foundation was frustrated over the lack of interest in HH displayed by federal officials and wanted to mount an awareness campaign. Another early and active proponent of communicating Mercator's discoveries was the American Liver Foundation.[109] The American Hemochromatosis Society (AHS) designated May 2007 as "National Hereditary Hemochromatosis Genetic Screening & Awareness Month." It asked its membership to contact local newspapers, TV and radio stations with AHS press releases that connected screening to saving lives.[110]

The CDC has also made detailed information available about diagnosis of hemochromatosis for physicians and the use of genetic testing in family based testing for hemochromatosis.[111] However, in the absence of family history, CDC recommends genetic testing for *HFE* mutations only as the confirmatory step of their testing protocol after the appropriate biochemical tests for iron overload (TS and serum ferritin) have been conducted.[112] The HH genetic test is currently also available directly to consumers through DNAdirect. Otherwise, HH testing is primarily offered to consumers by healthcare providers.

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[107] Email from Dr. Dennis Drayna, Section Chief NIDCD/National Institutes of Health, September 11, 2008. Comments provided during external review process.
[108] Progenitor files registration statements for initial public offering of 2,750,000 shares and for acquisition of Mercator Genetics Inc. Business Wire. March 14, 1997.
[109] Email from Dr. Dennis Drayna, Section Chief NIDCD/National Institutes of Health, 11 September 2008. Comments provided during external review process.
[110] The American Hemochromatosis Society's homepage discusses HH awareness. American Hemochromatosis Society. See http://www.americanhs.org [accessed May 3, 2007].
[111] *Hemochromatosis for Health Care Professionals.* Centers for Disease Prevention and Control. November 1, 2007. See http://www.cdc.gov/ncbddd/hemochromatosis/training/family_detection/testing_and_counseling.htm [accessed November 12, 2008]. This program was run by Sharon McDonnell who is now in the Public Health Dept at Dartmouth University Medical School.
[112] *Hemochromatosis for Health Care Professionals: Diagnostic Testing.* Centers for Disease Prevention and Control. November 1, 2007. See http://www.cdc.gov/ncbddd/hemochromatosis/training/diagnostic_testing/testing_protocol.htm [accessed November 12, 2008].

Adoption

Shortly following the *HFE* gene discovery, the CDC considered recommending widespread screening for HH and considered advising doctors to order a gene test for all patients 18 years or older. That recommendation has not been made because of inconclusive evidence on the penetrance of *HFE* mutations and cost-effectiveness of the test. Dr. Dennis Drayna, a Mercator co-founder and NIH molecular geneticist, argued enthusiastically for broad HH genetic screening at a 1997 Ethical, Legal and Social Issues (ELSI) meeting associated with the Human Genome Project.[113] Ethical, legal, and social concerns such as fear of genetic discrimination and questions over whether it made sense to "diagnose people based on genotype and not health" were raised as criticisms.[114] An account of this meeting suggested that the market would determine whether insurance companies and HMOs adopted the test to save money in HH complications like liver transplants.[115] A recent study, which measured the extent of employment and health insurance problems associated with population screening for hereditary hemochromatosis and iron overloads, found that at one year following genotypic and phenotypic screening, only 0.4% of individuals surveyed (3 out of 1154 individuals) reported any problems. Problems primarily involved life insurance and long term care insurance coverage. However, none of the affected individuals reported problems with health insurance coverage or employment. The outcome suggests that genetic discrimination concerns are much lower than originally anticipated.[116] It also suggests, however, that they occur in forms of insurance, long-term care and life insurance, that are not covered by the Genetic Information Nondiscrimination Act passed in 2008 (which begins to take effect in 2009 and 2010).

Insurance companies and at least one Medicare carrier have adopted HH genotype testing but not as the broad screening test initially conceived. Rather, HH genotyping is usually a second-level test conducted after less expensive biochemical tests suggest HH or to test family members of identified HH homozygotes. Insurance policies may cover HH testing if it comports with "medical necessity." To be eligible for testing, the insured individual will likely need to meet defined conditions for testing that in some plans are enforced by preauthorization requirements, such as: (1) prior blood test indicating iron overload; (2) family history of HH; or, (3) member of a family with a known HH mutation. Cost is not cited as an explicit criterion, and patents may not have a direct or significant effect on the decisions to cover the test by insurance providers. However, patents did affect which laboratories offered the test and which laboratories decided to cease testing after patent enforcement by SBCL.[117] Yet the majority of laboratories continued to offer the test either with or without a sublicense. As noted earlier, several providers offer these tests currently and presumably interact with a range of carriers for insurance reimbursement.

Consumer Utilization

The *HFE* test is not available as an initial, universal screening test along the lines originally envisioned. Consumers typically access the tests through clinical laboratories via their physicians. Appendix B provides a sample of some laboratories, their services, and their costs. At least 37 laboratories offered HFE genetic testing as of May 2007. Additional providers not listed on Genetests.org may also offer this test. The test is also easily obtainable without physicians serving as the conduit for HH testing.

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[113] Allen A. Policing the gene machine. *Lingua Franca*. March 1997. See http://linguafranca.mirror.theinfo.org/9703/Policing6.html [accessed May 2, 2007].
[114] Ibid.
[115] Ibid.
[116] Hall M, Barton JC, Adams PC, McLaren CE, Reiss J, Castro O, Ruggiero A, Acton R, Power T, Bent T. Genetic screening for iron overload: no evidence of discrimination at one year. *J Fam Practice* 2007. 56:829-833.
[117] Cho MK. Op. cit.

DNAdirect, a direct-to-consumer genetic testing service, offers HH genetic testing for $199. Consumers using this service can thus choose to avoid involving a doctor or notifying their insurance company.[118] DNAdirect sends consumers a test collection kit in the mail that includes cotton swabs for cheek swabbing and a postage-paid envelope to mail the swabs back to the laboratory for DNA analysis. Unlike most direct-to-consumer testing outlets, DNAdirect offers genetic counseling with the test results. DNAdirect provides forms, CPT Codes, and Letters of Medical Necessity for consumers seeking reimbursement from insurance or health plans. The service also offers anonymity and explains why anonymity might be desirable due to the potential of genetic discrimination. Since the $199 price tag is less than several of the clinical laboratories offering the test,[119] consumers with or without a family history of HH but with some means can easily obtain results, provided that they do not seek insurance reimbursement (insurance coverage would generally be confined to high-risk individuals meeting iron overload or family history criteria). However, DNAdirect and its counterparts are not FDA-regulated, and there is no peer review of the tests' accuracy, although the tests themselves are performed in CLIA-approved laboratories.[120]

Our study does not provide information regarding the impact of patents on under- or over-utilization of the *HFE* genetic test. Test utilization would need to be ascertained more systematically by surveying providers about how frequently the test is ordered and matching clinical indication to test use.

We did not uncover evidence about whether consumers are denied coverage for HH genetic tests. Direct assessment of test utilization and the frequency of inability to receive testing due to insurance coverage problems will help address the issue of patient access more comprehensively.

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Appendix A US Patents related to Hemochromatosis testing.

Patent No. and Title	Date Filed/Issued	Inventors	Assignee	Claims
5705343, Method to Diagnose Hereditary Hemochromatosis	Feb. 9, 1996 / Jan. 6, 1998	Drayna et al.	Mercator Genetics Inc., Menlo Park, CA	Mutation analysis of *HFE* with kit
5712098, Hereditary Hemochromatosis Diagnostic Markers and Diagnostic Methods	Apr. 16, 1996/ Jan. 27, 1998	Tsuchihashi et al.	Mercator Genetics, Menlo Park, CA	Mutation analysis for *HFE*
5753438, Method to Diagnose Hereditary Hemochromatosis	May 8, 1995 / May 19, 1998	Drayna et al.	Mercator Genetics Inc., Menlo Park, CA	Method for diagnosing the mutation of an *HFE*

[118] DNA Direct. See http://www.dnadirect.com/web/article/testing-for-genetic-disorders/hemochromatosis/36/who-should-consider-testing
[accessed January 12, 2009].
[119] See Appendix B.
[120] Shute N. Unraveling your DNA's secret. *US News & World Report*. December 31, 2006.

				sequence; mutation sequences, but not the whole gene.
6025130, Hereditary Hemochromatosis Gene	May 23, 1996 / Feb. 15, 2000	Thomas et al.	Mercator Genetics Inc., Menlo Park, CA	*HFE* gene and a diagnostic method; whole *HFE* gene sequence
6140305, Hereditary Hemochromatosis Gene Products	Apr. 4, 1997 / Oct. 31, 2000	Thomas et al.	Bio-Rad Laboratories, Inc., Hercules, CA	Polypeptides associated with *HFE*
6228594, Method for Determining the Presence or Absence of Hereditary Hemochromatosis Gene Mutation	Feb. 14, 2000 / May 8, 2001	Thomas et al.	Bio-Rab Laboratories, Hercules, CA	Diagnostic method for C282Y and H63D detection using DNA and RNA.
6355425, Mutations Associated With Iron Disorders	Mar. 26, 1999 / Mar. 12, 2002	Rothenberg et al.	Billups-Rothenberg, Inc., San Diego, CA	Diagnostic method for a panel of mutations in *HFE*,including : S65C, 193T, G93R, 277C, 105T, 314C
6762293, Diagnostics and Therapeutics for Autosomal Dominant Hemochromatosis	Oct. 10, 2001 / Jul, 13, 2004	van Duijn et al.	Erasmus University Rotterdam, Rotterdam (NL)	Ferroportin (SLC11A3) sequence and method of diagnosis for SLC11A3
6849399, Methods and Compositions for Diagnosis and Treatment of Iron Misregulation Diseases	Aug. 27, 1997 / Feb. 1, 2005	Feder et al.	Bio-Rab Laboratories, Hercules, CA	Diagnostic method for transferring receptor (TFR2) and mutation A424G
6955875, Mutations associated with iron disorders	Oct. 16, 2001/ Oct. 18, 2005	Rothberg et al.	Billups-othberg Inc.	Methods for diagnosing HFE by detecting mutations in nucleotide position 193
7067255, Hereditary Hemochromatosis Gene	May 2, 2002 / Jun 27, 2006	Thomas et al.	Bio-Rab Laboratories, Hercules, CA	Method for detecting three mutant alleles (24d1, 2 and 7)
7078513, Plasmids Comprising Nucleic Acids from the Hereditary Hemochromatosis Gene	Feb. 4, 2000 / Jul. 18, 2006	Thomas et al.	Bio-Rab Laboratories, Hercules, CA	Plasmid containing HFE mutation 24d1
7026116, Polymorphisms in the Region of the Human Hemochromatosis Gene	May 7, 1997 / Apr. 11, 2006	Ruddy et al.	Bio-Rad Laboratories, Hercules, CA	Isolated polynucleotide of *HFE* gene sequence containing SNP variants, and a kit.

Appendix B Price Comparison for *HFE* testing from a subset of providers.

Laboratory	Genetic Test[121]	List Price[122]		CPT Codes[123]
Arup Laboratory	*HFE* PCR	$225		83890, 83900, 83896 x 4, 83912
Baylor College of Medicine		$200		83914 x 3, 83912, 83898 x 2, 83891
Blood Center of Wisconsin	Allele-specific PCR	$175		83891, 83900, 83896 x 4, 83912
Boston University School of Medicine		$250		
Case Western Reserve Univ.		$275		83890, 83892 x 2, 83894 x 2, 83898 x 2, 83912 x 2
Cincinnati Children's Hosp. Medical Center		$337		83891, 83894, 83898, 83912, 83892
Duke Univ. Health System	ARMS	$467.25		
Greenwood Genetics Center		$250		83894, 83898, 83912
Kimball Genetics, Inc.	PCR analysis for both the C282Y and the H63D mutations	$190		
LabCorp		$297 cost w/o insurance	$229.50 with insurance	
Mayo Clinic	PCR-based assay (using LightCycler technology) used to test for 3 mutations in the *HFE* gene: C282Y, H63D, and S65C. S65C mutation is only reported when it is found with the C282Y mutation. (PCR utilized pursuant to a license agreement with Roche Molecular Systems, Inc.)	$411.20		83890, 83898 x 2, 83912
Michigan State Univ.	Extract DNA from the sample and amplified	$227		83890, 83898 x 2, 83892 x 2, 83894, 83912

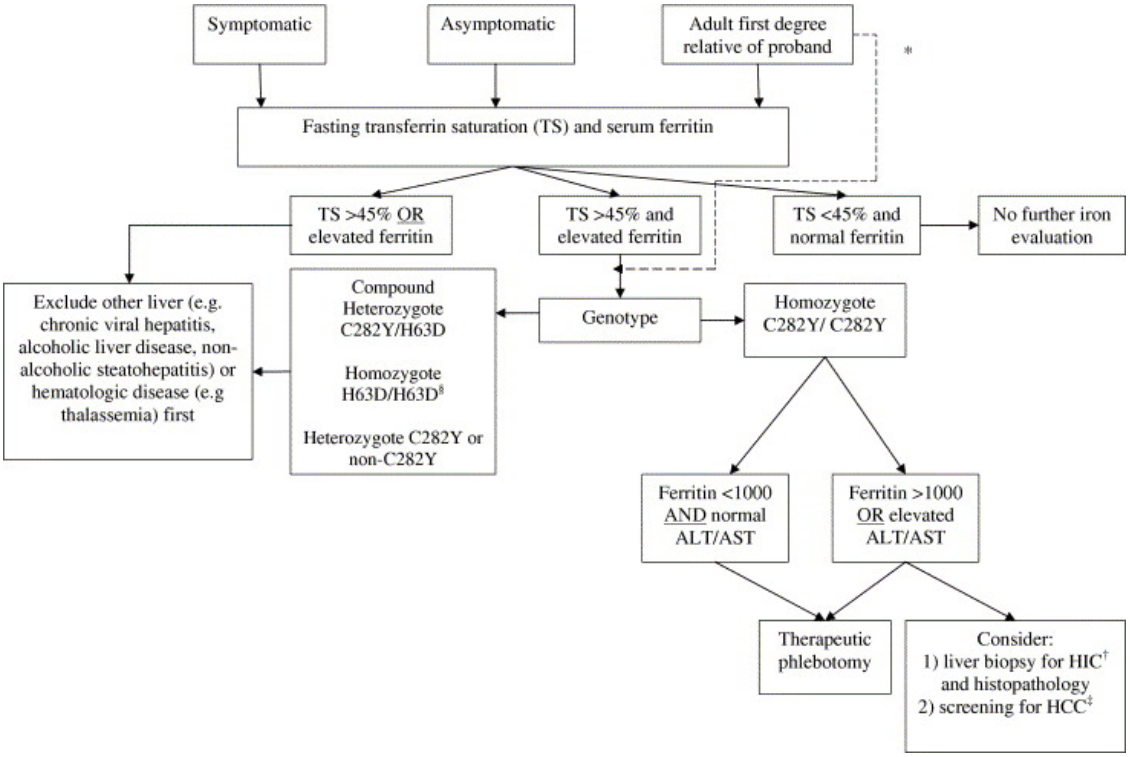
[121] All the tests described are targeted mutation analysis, or allele-specific mutation analysis. The tests are for either (1) a nucleotide repeat expansion, or (2) one or more specific mutations. Some of the labs provided a more specific description of their services. The blank boxes indicate areas for which no information was obtained.

[122] List prices as of May 2007. Prices were obtained either by phone call or from information listed on provider website.

[123] CPT Code Interpretation: 83890 Molecular Isolation and Extraction; 83900 Amplification; 83891 Isolation and extraction of highly purified nucleic acid; 83894; 83896 Nucleic Acid Probes; 38398 Amplification of nucleic acid, each primer pair; 83900 Amplification of nucleic acid, first two sequences; 83912 Interpretation and report; 83914 Mutation identification by enzymatic ligation or primer extension, single segment, each segment (eg, oligonucleotide ligation assay (OLA), single base chain extension (SBCE), or allele-specific primer extension (ASPE)).

	enzymatically then digested with the following restriction enzymes: Rsa I, Dpn II, and Hinf I. After digestion, the fragments are separated by electrophoresis. Testing can detect the C282Y, H63D, and S65C mutations in the *HFE* gene.		
NorDx	Linked Linear Amplification (LLA) with DNA probes	$372.50	83890 83896 x 4 83900 83912
SUNY Upstate Medical Univ.		$158	
Specialty Laboratories	Cleave-based Invader Assay Hemochromatosis GenotypeR	$345	83891, 83892x4, 83896 x 10, 83903 x 2, 83908 x 2, 83912
Spectrum Health		$205.50	8 CPT Codes
University of Alabama @ Birmingham	Detection of C282Y and H63D mutations in the *HFE* gene using multiplex PCR methods.	$200	83890 83898 83892 83894 83912
Univ. of Iowa Hospitals & Clinics		$395	

Appendix C Diagnostic Algorithm for Hereditary Hemochromatosis



Modified from the American Association for the Study of Liver Disease Diagnostic Algorithm, 2001.
*direct testing of first degree probands is an acceptable alternative
†hepatic iron concentration
‡hepatocellular carcinoma

§Although H63D homozygosity is thought to lead to hemochromatosis in some individuals, this is more the exception, rather than the rule. Since the H63D mutation has a higher prevalence than the C282Y mutation, but accounts for a significantly smaller portion of those with clinically relevant hemochromatosis, abnormal iron studies with H63D homozygosity should prompt further evaluation into other disease processes first, with a diagnosis of hereditary hemochromatosis only after other avenues have been explored.

Appendix D Molecular Genetic Testing: Clinical methods and Testing Strategy[124]

There are various ways to detect hemochromatosis:

- Targeted mutation analysis: available on a clinical basis for two known disease-causing alleles in the *HFE* gene (C282Y and H63D). About 87% of individuals of European origin with *HFE*-HH are either homozygotes for the C282Y mutation or compound heterozygotes for the C282Y and H63D mutations. Most clinical laboratories do not routinely test for the S65C allele because it appears to account for only 1% of individuals affected clinically and its clinical significance is unclear.
- Sequence analysis: available in a limited number of clinical and research laboratories to identify other mutant alleles associated with *HFE*-HH laboratories

The table below summarizes molecular genetic testing for this disorder.[125]

Molecular Genetic Testing **Used in *HFE*-HHC**				
Test Method	**Mutations Detected**	**Mutation Detection Rate**		**Test Availability**
		% of Individuals with HHC [1, 2]	**Genotype**	
Targeted mutation analysis	*HFE* mutations: p.C282Y, p.H63D	~60%-90%	p.C282Y/p.C282Y	Clinical Testing
		3%-8%	p.C282Y/p.H63D	
		~1%	p.H63D/p.H63D [3]	
Sequence analysis	*HFE* sequence alterations	Unknown	Unknown [4]	

From Ramrakhiani & Bacon (1998)
1. In populations of European origin
2. Morrison et al 2003
3. There is no evidence that p.H63D/p.H63D is associated with a hemochromatosis phenotype in the absence of another cause of iron overload.
4. A few individuals who are compound heterozygotes for the p.C282Y allele, and one of a small number of rare *HFE* mutations, have the hemochromatosis phenotype.

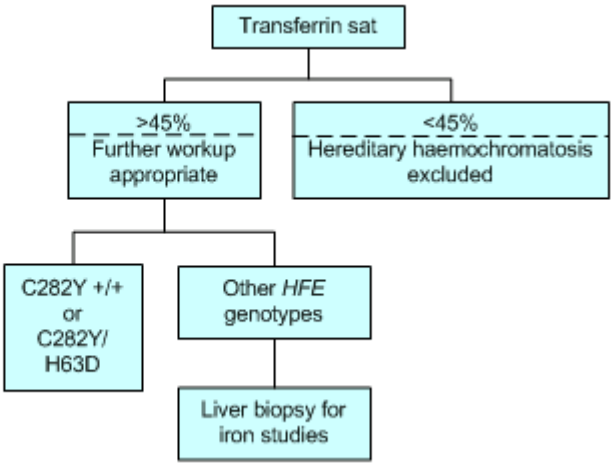
Testing Strategy for a Proband

1. Adults with transferrin-iron saturation higher than 45% warrant targeted mutation analysis. Individuals homozygous for the C282Y mutation or compound heterozygous for the C282Y and H63D mutations can be diagnosed as having the genetic make-up to develop *HFE*-HHC.

2. Individuals who are not C282Y homozygotes generally represent a heterogeneous group who may suffer from liver disease unrelated to *HFE* or have other metabolic syndromes. These individuals should undergo liver biopsy with assessment of histology and measurement of hepatic iron concentration as a next diagnostic step.

[124] Adapted from Genetests.Org. See http://www.geneclinics.org/profiles/hemochromatosis/details.html [accessed May 3, 2007].
[125] Ibid. Copyright University of Washington, Seattle.

The figure below represents the testing strategy to establish the diagnosis of *HFE*-HH for the two groups listed above.[126]



[126] Ibid. Copyright University of Washington, Seattle.

Appendix E Sample letter of patent enforcement for *HFE* testing from SBCL[127]

June 24, 1998

Dr. Debra Leonard
University of Pennsylvania Medical Center
3400 Spruce Street
7103 Founders
Philadelphia, PA 19104-4283

Dear Dr. Leonard:

Hereditary Hemochromatosis Assay

I would like to bring to your attention three U.S. patents, 5,705,343; 5,712,098; and 5,753,438 all relating to an assay for hereditary hemochromatosis. The '098 patent may be of most interest to you and I have taken the liberty of enclosing a copy of it for your convenience. These patents are owned by Progenitor, Inc. and licensed exclusively to SmithKline Beecham Clinical Laboratories, Inc. for use in running a home-brew assay.

If you are offering a genetic test for hereditary hemochromatosis, please provide me with an assurance that the test procedure you are running is not covered by one or more of the three mentioned patents. If your test might be covered by these patents, SBCL is willing to make arrangements to insure that your clients have continued access to this gene-based HHC test discovered by Progenitor within the context of Progenitor's issued patents. I invite you to initiate such arrangements by contacting Rose Tricoski at SmithKline Beecham Clinical Laboratories, 1201 South Collegeville Road, Collegeville, PA 19426. Please feel free to call her at 610.454.6367, by fax at 610.983.2302 or by e-mail at rose.tricoski@sb.com. She and others at SBCL can assist you with making the necessary arrangements to avoid any inconvenience or interruption of services to your clients.

I ask that you follow up with Ms. Tricoski by July 24th. Thank you.

Sincerely,

David O'Bryan

David O'Bryan, Ph.D.
Vice President and Director,
Science and Technology

[127] Sample letter reproduced with permission from Dr. Debra Leonard.

Impact of Patents and Licensing Practices on Access to Genetic Testing for Long QT Syndrome

Misha Angrist, Ph.D., Subhashini Chandrasekharan, Ph.D., Christopher Heaney, B.A., and Robert Cook-Deegan, M.D.

Executive Summary

- Familial Long QT syndrome (LQTS) affects 1 in 3,000 newborns. It is a Mendelian condition in which patients' hearts do not recharge appropriately after heartbeats and can lead to life-threatening arrhythmias. It accounts for a small but significant fraction of sudden death in young people. Beta-blocker drugs and implantable cardioverter-defibrillators are the most common therapies. Patients and those close to them can also endeavor to avoid triggers for arrhythmias such as loud noises or physical or emotional stress.
- Mutations in 12 susceptibility genes account for some 75% of familial LQTS; of that 75%, mutations in three genes account for most cases. Genetic testing for LQTS is important because knowing which gene (and which part of that gene) is mutated can have a direct bearing on decisions regarding preventive measures and pharmacological therapies.
- The major LQTS susceptibility genes were discovered at the University of Utah in the mid-1990s. Their discovery was funded in part by the National Institutes of Health. The first LQTS gene patent was awarded in 1997.
- The University of Utah Research Foundation began licensing patents on LQTS susceptibility genes in the late 1990s. Until recently, at any one time there was never more than a single licensee of the major intellectual property (IP) attached to the three genes that predispose to the majority of familial LQTS. In 2008, Bio-Reference Laboratories (BRLI) obtained an exclusive license for one of those patents as well as two others giving it rights to test for LQT3, which accounts for approximately 10 to 15% of inherited LQTS patients. BRLI has also aggregated IP related to susceptibility genes for LQT1, LQT2, LQT5, LQT6, LQT7, and Jervell and Lange-Nielsen syndrome (JLNS). As a consequence the patent landscape for LQTS testing has become fragmented among different exclusive licensees. It remains to be seen what impact this turn of events will have on the LQTS genetic testing landscape.
- In 2002, before a commercial test of five genes was launched under the name FAMILION®, there were at least two other fee-for-service providers of genetic testing; however, they focused their sequencing on regions previously associated with mutations causing LQTS, which amounted to a minority of the five genes' combined coding sequence. Subsequent enforcement of the gene patents prompted at least one diagnostic provider, GeneDx (subsequently acquired by BRLI), to cease testing in 2002. We suggest, based on incomplete evidence, that this probably had a small but tangible negative effect on patient access to genetic testing for LQTS between 2002 and 2004. We believe this negative effect would likely have been larger had there been greater awareness, understanding and acceptance of genetic testing on the part of cardiologists and electrophysiologists at that time.
- From 2005-2008, most LQTS gene IP relevant to clinical genetic testing was controlled by Clinical Data, Inc., and its subsidiary, PGxHealth LLC. During that period the company did not sublicense its test to any other diagnostic services in the U.S., although it has granted international licenses in Australia, New Zealand and Europe. It has also granted a research license to a company in Utah.

- In general, clinicians we spoke to say that PGxHealth does a very good job of carrying out genetic testing of the five genes that account for ~ 75% of LQTS. Its turnaround time for a complex, sequence-based test is typically less than two months versus what is often a year or more for research-based testing. The company reports that its turnaround time has been substantially reduced since it began offering the test. PGxHealth's FAMILION® testing continues to be widely adopted by cardiologists and electrophysiologists, which the company attributes to its efforts to educate physicians and patients, its customer service, and diligent advocacy for reimbursement policies and payment agreement with insurers and health plans. It can be argued (and has been by PGxHealth parent Clinical Data) that an exclusive license has contributed to the company's skill at performing the test and allowed it to leverage economies of scale. GeneDx parent company BRLI attributes these improvements to the march of technology and the threat of competition.
- PGxHealth has been criticized for occasional laboratory errors (missed mutations and misinterpretations). It is not clear that the lab's error rate is outside acceptable norms, nor worse than its stated analytical accuracy of over 99 percent. PGxHealth says it implements process changes to ensure that any errors are not repeated, thus leading to improved accuracy over time. Misinterpretation, the company says, can be a subjective phenomenon in a complex disease such as LQTS. PGxHealth consults with experts in the field to review variants of questionable interpretation. It also issues amended reports when interpretations change due to new knowledge in the field.
- PGxHealth performs proficiency testing in conjunction with Michael Ackerman, a researcher and physician at the Mayo Clinic who has the sequencing facilities and diverse genetic samples and clinical profiles necessary to conduct such a program in accordance with the relatively nonspecific regulations set forth by the Clinical Laboratory Improvement Amendments (CLIA), the pertinent federal statute. By all accounts Dr. Ackerman is an outstanding clinician and researcher who has greatly advanced the cause and treatment of LQTS patients. His financial arrangements with Clinical Data and PGxHealth have been reported to and vetted by Mayo, and his service as a consultant to PGxHealth has been disclosed in publications.
- In 2005 PGxHealth reported allelic dropout in research laboratory screening of LQTS patients. This phenomenon, a technical issue associated with DNA amplification assays, can result in false negatives (that is, results that report no relevant mutation when in fact a deletion or genomic rearrangement has in fact altered the relevant protein). The company's identification and publication of this problem ultimately increased the sensitivity of LQTS genetic testing.
- The overall yield of FAMILION® testing, as reported by PGxHealth in 2007, was 38 percent, versus 50 percent for the 1995-2004 era of research-based testing. This lower figure is likely due to an increase in surveillance of borderline cases resulting from the availability of large-scale commercial testing. Another possible factor reducing yield might be surveillance of fewer genes in the commercial test than in research laboratories.
- PGxHealth has been criticized by at least one clinician (Wendy Chung, who consults for would-be competitor BRLI) for its difficulty in processing paraffin-embedded samples from deceased individuals. Routine extraction of DNA from such samples remains a challenge. Based on the anecdotal accounts we have received from the company, referring physicians and potential competitors, we have no evidence that PGxHealth is less (or more) adept at performing this procedure than other commercial diagnostic laboratories.
- PGxHealth has thus far decided not to add additional genes to its LQTS testing panel, citing both minimal benefit in light of the rarity of mutations in the seven other genes known to predispose to LQTS, and possible misinterpretation and uncertainty for patients due to decreased clinical specificity resulting from uncharacterized background variants in these genes. Patients who are not found to have a mutation in the five genes included in the panel are referred to research laboratories for additional

testing. Research laboratories, however, may take months or years to return results. While it is possible that sublicensing of the right to test the major genes would have made other providers more willing to assume the burden of testing the rarer loci, we cannot know this.

- The recent acquisition of selected LQTS gene patent licenses by Bio-Reference Laboratories—for testing LQT3, LQT5, LQT6 and LQT7 susceptibility genes, as well as for testing several mutations predisposing to LQT1 and LQT2—may offer a real-world test of how prices respond to competition, and whether testing technology changes with competition, although the nature of the competition may not be head-to-head for the same mutations unless a cross-licensing arrangement is struck between the rival testing services.
- Newer technologies minimize the cost of adding new mutations, but without competition, the commercial incentive to find new platforms is reduced.
- PGxHealth does not offer prenatal genetic diagnosis for LQTS, effectively making it unavailable in the U.S. The company does not have an official policy governing prenatal diagnosis. It claims that there are technical difficulties in distinguishing maternal from fetal DNA; however, other clinicians and would-be LQTS genetic test providers argue that this technical issue is trivial. At least one other former competitor has claimed that the company has denied its request to offer prenatal testing. Given the treatable nature of LQTS and the highly variable phenotype, it is not clear how strong the demand would be for prenatal or preimplantation testing. We do know that at least one provider offered prenatal diagnosis in 2002 prior to patent enforcement actions.
- Since 2004, there have been three publications in peer-reviewed journals that feature PGxHealth scientists as co-authors; most data have been presented at various cardiology meetings. Given the availability of a European mutation database and an international registry containing thousands of LQTS genotypes and phenotypes, PGxHealth's decision seems unlikely to have harmed patient care. Moreover, PGxHealth does not necessarily have access to the detailed phenotypic data that make mutation catalogs useful. One former provider and would-be competitor insisted to us, however, that a knowledge base of certain detailed, clinically useful phenotypic information is likely to come only from high-volume commercial diagnostic labs and not from research labs. In November 2008, PGxHealth announced that, in collaboration with other researchers at multiple institutions, it would make its LQTS mutation database public in 2009.
- FAMILION® LQTS testing costs $5400 per index case (a full-sequence testing to look for mutations) and $900 per confirmatory test in additional family members (for identified mutations). For index cases, this breaks down to $74 per amplicon, nearly twice the $38-per-amplicon cost of hereditary breast cancer testing (albeit at a much lower volume), but significantly less expensive than the $129-per-amplicon partial test that was offered in 2002 and the per-amplicon price of some other tests (see case studies on hearing loss and Tay-Sachs/Canavan). Such a cost comparison does not take into account the more cost-effective technologies that have become available in recent years. Several independent cardiologists, researchers, patient advocates and patients with whom we communicated complained about the cost of the FAMILION® test. The cost will also be compared to the precipitous drop of full genomic sequencing in the foreseeable future. These complaints may have resulted in part from historically incomplete coverage by many payers. To date, the FAMILION LQTS test has received positive coverage decisions from 28 health plans. The company has also established simplified billing codes. Among government payers with favorable coverage policies are TRICARE and Medicaid in 38 states (the company has applied for Medicaid coverage in all 50 states). Insurance coverage of FAMILION® testing increased dramatically in 2007-2008, with the number of covered lives growing from seven million to 155 million lives.
- It's not entirely clear what effect multiple test providers would have had on payer reimbursement in the early years. Multiple providers may have hastened favorable coverage decisions, although all of

the genetic testing providers we spoke with readily admitted that obtaining third-party payer coverage is a lengthy and difficult process. PGxHealth's would-be competitor, BRLI, believes that its own recent aggregation of LQTS gene IP has prompted PGxHealth to more aggressively pursue insurance coverage.

- Having competitors may or may not have led to substantial improvements in quality and coverage, but we believe that a competitive presence could have accelerated the test to market and lowered the cost from its current $5400. BRLI, an admittedly biased party, asserts that competition would have forced providers to differentiate the test in order to survive, by developing newer platforms along with more patient and clinical support and education.
- Our understanding of LQTS genetics remains woefully incomplete. The same mutation in different members of the same family may lead to radically different phenotypes (or to no detectable signs or symptoms). This suggests the existence of yet-to-be discovered modifier genes and environmental factors. Meanwhile, some ten percent of familial LQTS patients are presumptive compound heterozygotes, that is, they carry two distinct variations in LQTS susceptibility genes. This raises difficult clinical questions about which of these variants are pathogenic and which are benign. We believe it is legitimate to ask if the field as a whole might not have made deeper inroads into understanding the clinical significance of those uncertain variants if there were one or more additional commercial entities focused on the same sorts of interpretive questions.
- The results of genetic testing may have profound downstream financial implications. Both cardiologists and manufacturers of implantable cardioverter-defibrillators stand to benefit from the implantation of such devices in actual or suspected LQTS patients.
- Conflicts of interest abound in this case study. These conflicts affect not only officers of PGxHealth and its primary consultant physician-scientist, but also former and would-be providers of LQTS genetic testing who would benefit if they were among the major LQTS gene-patent licensees.

Introduction: What is Long QT Syndrome?

Congenital long QT syndrome (LQTS) is an inherited cardiac disorder affecting about 1 in 3,000 to 1 in 5,000 people. LQTS patients may experience fainting ("syncope"), seizures or sudden death, although the phenotype can vary widely.[1] Most of the 1 in 2,000 people harboring mutations in LQTS susceptibility genes will remain silent carriers throughout their lives.[2] That is, there are more people who have mutations in relevant genes than people who actually have a clinical syndrome. Nevertheless, the disease appears to explain a small but significant fraction of sudden cardiac deaths in young people.[3] Moreover, some five percent of cases of sudden infant death syndrome (SIDS) are thought to be attributable to familial or sporadic LQTS.[4]

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[1] Goldenberg I, Moss AJ. Long QT syndrome. *J Am Coll Cardiol* 2008. 51, (24): 2291-300.
[2] Roden DM. Clinical practice. Long-QT syndrome. *N Engl J Med* 2008. 358, (2): 169-76.
[3] Ibid.
Goldenberg I, Moss AJ, Peterson DR, McNitt S, Zareba W, Andrews ML, Robinson JL, Locati EH, Ackerman MJ, Benhorin J, Kaufman ES, Napolitano C, Priori SG, Qi M, Schwartz PJ, Towbin JA, Vincent GM, Zhang L. Risk factors for aborted cardiac arrest and sudden cardiac death in children with the congenital long-QT syndrome. *Circulation* 2008. 117, (17): 2184-91.
Berul CI. Congenital long-QT syndromes: who's at risk for sudden cardiac death? *Circulation* 2008. 117, (17): 2178-80.
[4] Tester DJ, Ackerman MJ. Sudden infant death syndrome: how significant are the cardiac channelopathies? *Cardiovasc Res* 2005. 67, (3): 388-96.

The "QT" in long QT refers to a telltale measurement seen on an electrocardiogram (ECG). The QT interval is the time it takes for the heart to recharge ("repolarize") after each beat. Depending on age and gender, when the corrected QT interval (QTc) exceeds ~ 440 to 470 milliseconds, it is considered to be prolonged. A prolonged QT interval coupled with a clinical history of fainting and a family history of LQTS or unexplained sudden cardiac death strongly suggests a diagnosis of LQTS.[5]

Clinical manifestations of LQTS are the result of the heart "spinning out of control" into a characteristic tachycardia (speeding of the heart rate) called *torsades de pointes* (TdP). TdP causes an individual to faint; he or she may then wake up, experience seizures, or die. Survival then depends upon whether the heart spontaneously assumes its normal rhythm or an internal or external defibrillator stops the arrhythmia.[6]

High-risk patients are typically treated with beta-blocker drugs, which can reduce the risk of life-threatening cardiac events.[7] Implantable cardioverter-defibrillators (ICDs) may be used as a primary therapy in patients refractory to beta-blocker therapy or as a secondary measure in addition to beta-blockers.[8] Surgical denervation and pacemakers have also been used with some success.[9]

While LQTS with accompanying deafness (Jervell and Lange-Nielsen Syndrome) and the classical form of the disease (LQT1, Romano-Ward Syndrome) were described more than 40 years ago, the exact molecular basis of the disorder eluded investigators until 1995.[10] It was then that Mark Keating's NIH-funded group at the University of Utah isolated genes predisposing to LQT2 and LQT3. With the cloning of these genes and the isolation of the LQT1 gene the next year,[11] it became clear that defects in cellular sodium and potassium ion channels (or related proteins) caused LQTS: the window into the "cardiac channelopathies" was now open.[12] Currently there are 12 known LQTS susceptibility genes,[13] although

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[5] Goldenberg I, Moss AJ. Long QT syndrome. *J Am Coll Cardiol* 2008. 51, (24): 2291-300.

[6] Ackerman MJ. Cardiac channelopathies: it's in the genes. *Nat Med* 2004. 10, (5): 463-4.

[7] Goldenberg I, Moss AJ. Long QT syndrome. *J Am Coll Cardiol* 2008. 51, (24): 2291-300.
Moss AJ, Zareba W, Hall WJ, Schwartz PJ, Crampton RS, Benhorin J, Vincent GM, Locati EH, Priori SG, Napolitano C, Medina A, Zhang L, Robinson JL, Timothy K, Towbin JA, Andrews ML. Effectiveness and limitations of beta-blocker therapy in congenital long-QT syndrome. *Circulation* 2000. 101, (6): 616-23.
Roden DM. Clinical practice. Long-QT syndrome. *N Engl J Med* 2008. 358, (2): 169-76.

[8] Choi GR, Porter CB, Ackerman MJ. Sudden cardiac death and channelopathies: a review of implantable defibrillator therapy. *Pediatr Clin North Am* 2004. 51, (5): 1289-303.
Passman R, Kadish A. Sudden death prevention with implantable devices. *Circulation* 2007. 116, (5): 561-71.
Zareba W, Moss AJ, Daubert JP, Hall WJ, Robinson JL, Andrews M. Implantable cardioverter defibrillator in high-risk long QT syndrome patients. *J Cardiovasc Electrophysiol* 2003. 14, (4): 337-41.

[9] Goldenberg I, Moss AJ. Long QT syndrome. *J Am Coll Cardiol* 2008. 51, (24): 2291-300.
Wang LX. Role of left cardiac sympathetic denervation in the management of congenital long QT syndrome. *J Postgrad Med* 2003. 49, (2): 179-81.

[10] Curran ME, Splawski I, Timothy KW, Vincent GM, Green ED, Keating MT. A molecular basis for cardiac arrhythmia: HERG mutations cause long QT syndrome. *Cell* 1995. 80, (5): 795-803.
Wang Q, Shen J, Li Z, Timothy K, Vincent GM, Priori SG, Schwartz PJ, Keating MT. Cardiac sodium channel mutations in patients with long QT syndrome, an inherited cardiac arrhythmia. *Hum Mol Genet* 1995. 4, (9): 1603-7.
Wang Q, Shen J, Splawski I, Atkinson D, Li Z, Robinson JL, Moss AJ, Towbin JA, Keating MT. SCN5A mutations associated with an inherited cardiac arrhythmia, long QT syndrome. *Cell* 1995. 80, (5): 805-11. Reviewed in
Ackerman MJ. Cardiac channelopathies: it's in the genes. *Nat Med* 2004. 10, (5): 463-4.
Goldenberg I, Moss AJ. Long QT syndrome. *J Am Coll Cardiol* 2008. 51, (24): 2291-300.

[11] Wang Q, Curran ME, Splawski I, Burn TC, Millholland JM, VanRaay TJ, Shen J, Timothy KW, Vincent GM, de Jager T, Schwartz PJ, Toubin JA, Moss AJ, Atkinson DL, Landes GM, Connors TD, Keating MT. Positional cloning of a novel potassium channel gene: KVLQT1 mutations cause cardiac arrhythmias. *Nat Genet* 1996. 12, (1): 17-23.

[12] Marban E. Cardiac channelopathies. *Nature* 2002. 415, (6868): 213-8.

the QTc phenotype can vary and mutations in several have been observed in only a few families. Of the 12 genes, mutations in those predisposing to LQT1 (potassium channel gene KCNQ1), LQT2 (potassium channel gene KCNH2) and LQT3 (sodium channel gene SCN5A) account for some 70% of congenital LQTS.[14]

Intellectual Property and LQTS Testing: Dramatis Personae

The following list (presented alphabetically) is intended to provide capsule descriptions of many of the important stakeholders in and narrators of the LQTS genetic IP story. Some may have a conflict of interest by virtue of past and/or present consultation with genetic diagnostic test providers and/or past, present or future provision of such testing themselves.

Dr. Michael J. Ackerman is Professor of Medicine, Pediatrics and Pharmacology at the Mayo Clinic. He directs the Mayo Clinic Windland Smith Rice Sudden Death Genomics Laboratory. He is Director of the Mayo Clinic's Long QT Syndrome Clinic and is active in clinical translational research efforts devoted to identifying individuals at greatest risk for sudden death. He served on the Genaissance Pharmaceuticals Advisory Board in 2004[15] and is a paid consultant to FAMILION® test provider PGxHealth.[16] He is a strong advocate of exclusive patent licenses for genetic diagnostics. Dr. Ackerman offers a charity waiver and conducts research-based genetic testing for patients unable to pay for FAMILION® testing.[17]

Dr. Charles Antzelevitch is the Executive Director of and Director of Research at the Masonic Medical Research Laboratory (MMRL). He also holds an academic appointment as Professor of Pharmacology at the SUNY Health Science Center at Syracuse and an endowed chair in Experimental Cardiology (Gordon K. Moe Scholar) at the MMRL. Dr. Antzelevitch provides free testing for hardship cases and enrolls patients in genetic research studies at the MMRL.[18] He opposes exclusive patent licenses in the realm of genetic diagnostics.[19]

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[13] Lehnart SE, Ackerman MJ, Benson DW, Jr., Brugada R, Clancy CE, Donahue JK, George AL, Jr., Grant AO, Groft SC, January CT, Lathrop DA, Lederer WJ, Makielski JC, Mohler PJ, Moss A, Nerbonne JM, Olson TM, Przywara DA, Towbin JA, Wang LH, Marks AR. Inherited arrhythmias: a National Heart, Lung, and Blood Institute and Office of Rare Diseases workshop consensus report about the diagnosis, phenotyping, molecular mechanisms, and therapeutic approaches for primary cardiomyopathies of gene mutations affecting ion channel function. *Circulation* 2007. 116, (20): 2325-45.
Ueda K, Valdivia C, Medeiros-Domingo A, Tester DJ, Vatta M, Farrugia G, Ackerman MJ, Makielski JC. Syntrophin mutation associated with long QT syndrome through activation of the nNOS-SCN5A macromolecular complex. *Proc Natl Acad Sci U S A* 2008. 105, (27): 9355-60.

[14] Lehnart SE, Ackerman MJ, Benson DW, Jr., Brugada R, Clancy CE, Donahue JK, George AL, Jr., Grant AO, Groft SC, January CT, Lathrop DA, Lederer WJ, Makielski JC, Mohler PJ, Moss A, Nerbonne JM, Olson TM, Przywara DA, Towbin JA, Wang LH, Marks AR. Inherited arrhythmias: a National Heart, Lung, and Blood Institute and Office of Rare Diseases workshop consensus report about the diagnosis, phenotyping, molecular mechanisms, and therapeutic approaches for primary cardiomyopathies of gene mutations affecting ion channel function. *Circulation* 2007. 116, (20): 2325-45.

[15] Genaissance Pharmaceuticals, *EX-99.1 of 8-K*, 11 May 2004. See: http://www.sec.gov/Archives/edgar/data/1110009/000110465904013687/a04-5741_1ex99d1.htm, [accessed 26 September 2008].

[16] Ackerman MJ, "Interview with Michael J. Ackerman, MD, PhD, director of the Sudden Death Genomics Laboratory at the Mayo Clinic," Rochester, Minnesota: 6 May 2008.

[17] Ibid.

[18] Antzelevitch C. Written comments from Charles Antzelevitch, Ph.D., F.A.C.C., F.A.H.A., Executive Director and Director of Research of the Masonic Medical Research Laboratory (MMRL) 18 November 2008.

[19] Antzelevitch C. Interview with Charles Antzelevitch, Ph.D., F.A.C.C., F.A.H.A., Executive Director and Director of Research of the Masonic Medical Research Laboratory (MMRL) 2 July 2008.

Dr. Sherri J. Bale is co-founder, President and Clinical Director of GeneDx, a firm that specializes in genetic testing for rare hereditary disorders. Dr. Bale is a Board-certified Ph.D. Medical Geneticist and a founding member of the American College of Medical Genetics. GeneDx offered partial genetic testing for LQTS until 2002, when it was sued by then-LQTS-patent-licensee DNA Sciences. The two companies reached an agreement whereby GeneDx would refrain from offering LQTS testing (Appendix 7). In 2006, GeneDx was purchased by BioReference Laboratories, Inc. (BRLI), which has since sought to offer genetic testing for LQTS.[20] Dr. Bale is a strong opponent of exclusive licensing of gene patents for genetic diagnostic purposes, except as a tool to combat other exclusive licensing.

Congressman Howard L. Berman (D-CA) chaired the October 2007 Congressional hearing, "Stifling or Stimulating - The Role of Gene Patents in Research and Genetic Testing," under the auspices of his chairmanship of the House Judiciary Subcommittee on Courts, the Internet, and Intellectual Property.[21]

The Cardiac Arrhythmias Research and Education Foundation, Inc. (C.A.R.E.) is a 501(c)(3) nonprofit corporation based in Washington State. It advocates increased support for comprehensive scientific research and clinical trials; educates patients, the public and health professionals to increase awareness; and advances strategies to identify, protect and support at-risk individuals and their families. Its Board of Directors includes Dr. Arthur J. Moss. Its Scientific Advisory Board includes LQTS experts Dr. Michael J. Ackerman, Dr. Charles Antzelevitch, Dr. Mark T. Keating, Dr. Dan M. Roden, and Dr. Jeffrey A. Towbin, among others.

Dr. Wendy K. Chung is a clinical and molecular geneticist who directs the clinical genetics program at Columbia University and performs human genetic research. She directs research programs in human genetics of complex traits. Clinically, she directs programs in risk assessment for oncogenetics, cardiomyopathy, arrhythmias, and diabetes and develops novel molecular diagnostic methods to improve genetic testing. She was formerly a member of the PGxHealth FAMILION® Advisory Board.[22] She is now a paid consultant to BRLI.[23] She submitted written testimony to the October 2007 Congressional hearing, "Stifling or Stimulating - The Role of Gene Patents in Research and Genetic Testing." Dr. Chung is a strong critic of exclusive patent licenses in genetic diagnostics.[24]

Mr. Drew Fromkin has served as President and Chief Executive Officer of Clinical Data since 2006. Clinical Data is the parent company of PGxHealth, which, from 2005-2008 was—and as of February 2009, is—the exclusive provider of commercial genetic testing for LQTS. In April 2008, Mr. Fromkin submitted a letter to Congressman Berman[25] responding to the 2007 Congressional testimony presented

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[20] "Stifling or stimulating: the role of gene patents in research and genetic testing.," Subcommittee on Courts, the Internet, and Intellectual Property of the Committee on the Judiciary, One Hundred Tenth Congress; First Session ed. Washington, DC: 30 October 2007. Hearing records available online at http://judiciary.house.gov/hearings/hear_103007.html (accessed 24 January 2009).
Grodman M, "Interview with Marc Grodman, MD, CEO of Bio-Reference Laboratories, Inc." 21 August 2008.

[21] "Stifling or stimulating: the role of gene patents in research and genetic testing.," Subcommittee on Courts, the Internet, and Intellectual Property of the Committee on the Judiciary, One Hundred Tenth Congress; First Session ed. Washington, DC: 30 October 2007.

[22] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.

[23] Chung W, "Interview with Wendy Chung, MD, PhD, pediatrician, geneticist and researcher at Columbia University " 7 May 2008.

[24] "Stifling or stimulating: the role of gene patents in research and genetic testing.," Subcommittee on Courts, the Internet, and Intellectual Property of the Committee on the Judiciary, One Hundred Tenth Congress; First Session ed. Washington, DC: 30 October 2007.

[25] Fromkin AJ, "Letter to the Honorable Howard L. Berman from Clinical Data CEO Andrew J. Fromkin." 1 April 2008.

by Clinical Data's competitor BRLI.[26] Mr. Fromkin is a strong advocate of exclusive patent licenses for genetic diagnostics.[27]

Dr. Jorge Goldstein is an attorney at Sterne Kessler Goldstein & Fox. He has prepared and prosecuted patent applications before the U.S. and foreign patent offices in genomics, molecular and cell biology, recombinant DNA technology, immunology, transgenics and therapeutic methods, as well as organic synthesis, pharmaceuticals, and polymers. He has written about patents and genetic diagnostics.[28] He serves as outside counsel to BRLI.

Dr. Marc Grodman founded Bio-Reference Laboratories (BRLI) in 1981 and has remained its Chairman of the Board, President, Chief Executive Officer and a Director. Dr. Grodman is an Assistant Professor of Clinical Medicine at Columbia University's College of Physicians and Surgeons and Assistant Attending Physician at New York Presbyterian Hospital. He gave testimony at the October 2007 Congressional hearing, "Stifling or Stimulating - The Role of Gene Patents in Research and Genetic Testing."[29] BRLI has made inquiries about purchasing Clinical Data's laboratory operations and begun to aggregate LQTS gene IP.[30] Dr. Grodman is a strong critic of exclusive patent licenses in genetic diagnostics, except as a tool to combat other exclusive licensing.[31]

Dr. Richard Judson was Chief Science Officer at Genaissance Pharmaceuticals from 1999-2005 and oversaw the commercial launch of FAMILION® testing in 2004.

Dr. Mark T. Keating elucidated the genetic basis of LQTS in the mid-1990s at the University of Utah and is the principal inventor on several LQTS gene patents, including those covering the most common variants.

Mr. Steven Lehrer was CEO of DNA Sciences, the original licensee of the relevant LQTS gene IP, from 2001-2003. During his tenure as CEO, DNA Sciences filed suit against GeneDx for infringement of LQTS patents. Mr. Lehrer supports exclusive patent rights for genetic diagnostic tests.

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[26] "Stifling or stimulating: the role of gene patents in research and genetic testing.," Subcommittee on Courts, the Internet, and Intellectual Property of the Committee on the Judiciary, One Hundred Tenth Congress; First Session ed. Washington, DC: 30 October 2007.

[27] Fromkin AJ, "Letter to the Honorable Howard L. Berman from Clinical Data CEO Andrew J. Fromkin." 1 April 2008.

[28] Ebersole T, Guthrie M, Goldstein JA. Patent Pools as a Solution to the Licensing Problems of Diagnostic Genetics. *IP and Technology Law Journal* 2005. 17, (1): 6-13.
Ebersole TJ, Guthrie MC, Goldstein JA. Patent pools and standard setting in diagnostic genetics. *Nat Biotechnol* 2005. 23, (8): 937-8.
Goldstein JA and Golod E. Human Gene Patents. *Academic Medicine* 2002. 77 (12, Part 2): 1315-28.

[29] "Stifling or stimulating: the role of gene patents in research and genetic testing.," Subcommittee on Courts, the Internet, and Intellectual Property of the Committee on the Judiciary, One Hundred Tenth Congress; First Session ed. Washington, DC: 30 October 2007.

[30] Fromkin AJ, "Letter to the Honorable Howard L. Berman from Clinical Data CEO Andrew J. Fromkin." 1 April 2008.
Goldstein J, "Email from Jorge Goldstein, JD, patent attorney at Sterne, Kessler, Goldstein & Fox, outside counsel to BioReference Laboratories and GeneDx." 28 October 2008.
Goldstein J, "Interview with Jorge Goldstein, JD, patent attorney at Sterne, Kessler, Goldstein & Fox, outside counsel to Bio-Reference Laboratories and GeneDx." 31 October 2008.

[31] "Stifling or stimulating: the role of gene patents in research and genetic testing.," Subcommittee on Courts, the Internet, and Intellectual Property of the Committee on the Judiciary, One Hundred Tenth Congress; First Session ed. Washington, DC: 30 October 2007.
Grodman M, "Interview with Marc Grodman, MD, CEO of Bio-Reference Laboratories, Inc." 21 August 2008.

Dr. Aubrey Milunsky is Professor of Human Genetics, Pediatrics, Obstetrics and Gynecology, and Pathology, and Founding Director of the Center for Human Genetics at Boston University Medical Center. The Center for Human Genetics is an international referral center for commercial DNA diagnostics and prenatal genetic diagnosis. Dr. Milunsky is board-certified in Internal Medicine, Pediatrics and Clinical Genetics. BU began offering LQTS genetic testing in 2002. Since then Dr. Milunsky has sought to offer prenatal and other commercial genetic testing for LQTS. He is a strong critic of exclusive patent licenses for genetic diagnostics.[32]

Dr. Arthur J. Moss is Professor of Medicine and Professor of Community and Preventive Medicine at the University of Rochester Medical Center. He is Director of the Heart Research Follow-up Program. His clinical research relates to cardiac arrhythmias and heart failure complicating chronic ischemic heart disease due to coronary atherosclerosis. With Dr. Peter Schwartz, he co-founded the International Long QT Registry in 1979.[33] He was a member of the Genaissance Advisory Board[34] and consulted for the company prior to its sale to Clinical Data.[35] At one time he contemplated setting up commercial testing for LQTS at Rochester. He was later asked to consult by BRLI, but declined.[36] BRLI funds LQTS-related research at the University of Rochester. He believes that gene patent licensing exclusivity is not in the best interests of society.[37]

Dr. Silvia G. Priori is Director of Molecular Cardiology and Electrophysiology Laboratories, IRCCS Fondazione Salvatore Maugeri, Pavia, Italy. She is a clinical cardiologist specializing in the field of inherited arrhythmia syndromes. Much of Dr. Priori's research has focused on the genetic component of cardiac defects. She maintains a public database of LQTS mutations. In 2008 she began working at New York University Medical Center part-time. She has met with PGxHealth representatives and encouraged them to solicit input from additional physicians and scientists working in LQTS.[38]

Dr. Carol Reed is Executive Vice President and Chief Medical Officer for Clinical Data Inc. From 2003-2005, she served as Vice President of Medical Affairs for Genaissance Pharmaceuticals. Dr. Reed is a strong advocate for exclusive patent licenses in genetic diagnostics.

Dr. Heidi Rehm is Associate Molecular Geneticist at the Harvard Medical School-Partners Healthcare Center for Genetics and Genomics. She is also Instructor in Pathology (Brigham & Women's Hospital), Director of the Clinical Molecular Genetics Training Program (American Board of Medical Genetics/Harvard Medical School), and Associate Director of the Harvard Medical School Center for Hereditary Deafness. Her clinical role involves daily sign-out of hearing loss and cardiovascular disease testing for the Laboratory for Molecular Medicine in addition to an administrative role in overseeing the

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[32] Milunsky A, "Email from Aubrey Milunsky, MB.B.Ch., D.Sc., F.R.C.P., F.A.C.M.G., D.C.H." 1 October 2008. Milunsky A, "Interview with Aubrey Milunsky, MB.B.Ch., D.Sc., F.R.C.P., F.A.C.M.G., D.C.H., Director of Boston University's Center for Human Genetics." 29 May 2008.

[33] Moss AJ, Schwartz PJ. 25th anniversary of the International Long-QT Syndrome Registry: an ongoing quest to uncover the secrets of long-QT syndrome. *Circulation* 2005. 111, (9): 1199-201.

[34] Genaissance Pharmaceuticals, *EX-99.1 of 8-K*, 11 May 2004. See: http://www.sec.gov/Archives/edgar/data/1110009/000110465904013687/a04-5741_1ex99d1.htm [accessed 26 September 2008].

[35] Moss AJ, "Written comments of Arthur J. Moss, MD, research physician at the University of Rochester, " 28 November 2008.

[36] Moss AJ, "Interview with Arthur J. Moss, MD, research physician at the University of Rochester " 28. August 2008.

[37] Moss AJ, "Written comments of Arthur J. Moss, MD, research physician at the University of Rochester " 28. November 2008.

[38] Priori S, "Interview with Silvia G. Priori, MD, PhD, LQTS researcher and clinician in Pavia, Italy." 29 May 2008.

laboratory. We consulted with her on the evolution of commercial genetic testing for hypertrophic cardiomyopathy (HCM).

Dr. Hugh Y. Rienhoff founded DNA Sciences (originally Kiva Genetics) in 1998, serving as its Chairman and CEO until late 2001. He helped to negotiate the original LQTS gene patent licenses from the University of Utah. He is a clinical geneticist and holds an appointment in the Department of Molecular Biology and Genetics at the Johns Hopkins University School of Medicine. He is also a founder of MyDaughtersDNA.org, an organization dedicated to rare genetic conditions.

Dr. Dan M. Roden is Director of the Institute of Experimental Therapeutics, William Stokes Professor of Experimental Therapeutics, Professor of Medicine, and Professor of Pharmacology at Vanderbilt University. He has treated LQTS patients and carried out research on the disease for many years. He holds a patent on a variant associated with drug-induced LQTS that he and his co-inventor have licensed to Clinical Data Inc. He told us he would be "happy" to give up his royalties if it meant improved patient care.[39]

Dr. Benjamin A. Salisbury is Senior Director of Clinical Genetics for Clinical Data Inc. He previously served as Group Leader for Computational Genomics at Genaissance Pharmaceuticals.

The Sudden Arrhythmia Death Syndromes Foundation (SADS) is a 501(c)(3) nonprofit corporation dedicated to informing the general public (as well as families and medical professionals) about the effects of untreated/undiagnosed cardiac arrhythmias and the methods by which sudden death can be prevented. Initiatives include sponsoring public awareness meetings in local communities, providing educational videos on LQTS, and establishing media relationships to publicize information about arrhythmias. SADS receives financial support from Clinical Data Inc. Its Board of Trustees includes Drs. Michael J. Ackerman and Silvia G. Priori. Its Scientific Advisory Board includes Drs. Charles Antzelevitch, Dan M. Roden, Peter Schwartz, Jeffrey A. Towbin, Arthur Wilde, and Raymond Woosley.

Dr. Jeffrey A. Towbin is Professor in the Departments of Pediatrics (Cardiology), Cardiovascular Sciences, and Molecular and Human Genetics at Baylor College of Medicine. He is Chief of Pediatric Cardiology at Texas Children's Hospital, holds the Texas Children's Hospital Foundation Chair in Pediatric Cardiac Research, and is Director of the Phoebe Willingham Muzzy Pediatric Molecular Cardiology Laboratory. He is Medical Director of the John Welsh Cardiovascular Diagnostic Laboratory and of the Pediatric Heart Failure and Transplantation Service. He is Co-Director of the Cardiovascular Genetics Clinic at Texas Children's Hospital and Director of Research in the BCM Department of Pediatrics (Cardiology). For the last several years, Dr. Towbin's laboratory has offered fee-for-service cardiovascular genetic testing.[40] These services include testing for mutations in KCNJ2 (Andersen syndrome/LQT7 and Short QT syndrome) and Caveolin-3 (LQT9)[41], both of which are rare.[42] Dr. Towbin only offers testing for mutant genes that have been discovered by his laboratory; he has not patented any of these genes.[43]

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[39] Roden DM. "Interview with Dan M. Roden, MDCM, Director of the Institute of Experimental Therapeutics, William Stokes Professor of Experimental Therapeutics, Professor of Medicine, and Professor of Pharmacology, Vanderbilt University School of Medicine." 14 January 2009.

[40] Towbin JA, "Interview with Jeffrey A. Towbin, MD, chief of pediatric cardiology, Baylor College of Medicine." 29 September 2008.

[41] http://www.bcm.edu/pediatrics/index.cfm?Realm=99992426&This_Template=Genetic_Testing [last accessed 19 November 2008]

[42] Goldenberg I, Moss AJ. Long QT syndrome. *J Am Coll Cardiol* 2008. 51, (24): 2291-300.
Roden DM. Clinical practice. Long-QT syndrome. *N Engl J Med* 2008. 358, (2): 169-76.

[43] Towbin JA, "Interview with Jeffrey A. Towbin, MD, chief of pediatric cardiology, Baylor College of Medicine." 29 September 2008.

The University of Utah Technology Commercialization Office owns the patent rights to the major LQTS susceptibility genes. Pursuant to the Bayh-Dole Act,[44] this office licensed rights to diagnostic testing of these genes to DNA Sciences in the late 1990s. Patent licenses were subsequently transferred to Genaissance Pharmaceuticals (circa 2003) and Clinical Data Inc. (circa 2005).[45] During 2006-2008, Utah began licensing patent rights to certain LQTS susceptibility genes to Clinical Data competitor BRLI, thereby creating a potential mutual-blocking situation.[46] Despite repeated requests, the University of Utah Technology Commercialization Office declined to speak with us (for this study or the BRCA case study, in which it is also involved).

Why is Genetic Testing for LQTS Important?

Genetic testing for LQTS is clinically important for several reasons:

- For unequivocal diagnosis of LQTS, it remains the gold standard,[47] although the resting ECG is critical and a negative genetic test cannot rule out the presence of the disease.[48]
- The consequences of relying solely on clinical history and sometimes-imprecise and difficult-to-interpret ECG measurements for diagnosis can be grave. 25 to 50% of genetically proven LQTS

[44] Boettiger S, Bennett AB. Bayh-Dole: if we knew then what we know now. *Nat Biotechnol* 2006. 24, (3): 320-3.
Thursby JG, Thursby MC. Intellectual property. University licensing and the Bayh-Dole Act. *Science* 2003. 301, (5636): 1052.

[45] Genaissance Pharmaceuticals to merge with Clinical Data. *Pharmacogenomics* July 2005. 6, (5): 459.
Clinical Data, *10-K*, 29 June 2006. See: http://www.sec.gov/Archives/edgar/data/716646/000095013506004150/b61410cie10vk.htm [accessed 23 September 2008].
DNA Sciences, *S-1*, 5 January 2001. See: http://www.sec.gov/Archives/edgar/data/1130013/000091205701000445/a2033717zs-1.htm [accessed 22 September 2008].
Genaissance Pharmaceuticals, *10-K*, 30 March 2004. See: http://www.sec.gov/Archives/edgar/data/1110009/000104746904010049/a2131537z10-k.htm [accessed 23 September 2008].
Genaissance Pharmaceuticals, *Genaissance Pharmaceuticals Launches its Proprietary FAMILION™ Test for Genetic Mutations Associated With Sudden Cardiac Death*, 2004. See: http://www.medscape.com/pages/editorial/pressreleases/pr-crm-genaissance2, September 17 2008].
Genaissance Pharmaceuticals, "Event Transcript: GNSC - Q4 2003 Genaissance Pharmaceuticals, Inc. Earnings Conference Call," CCBN Street Events, 2004.

[46] Ebersole T, Guthrie M, Goldstein JA. Patent Pools as a Solution to the Licensing Problems of Diagnostic Genetics. *IP and Technology Law Journal* 2005. 17, (1): 6-13.
Goldstein J, "Email from Jorge Goldstein, JD, patent attorney at Sterne, Kessler, Goldstein & Fox, outside counsel to BioReference Laboratories and GeneDx." 28 October 2008.
Goldstein J, "Interview with Jorge Goldstein, JD, patent attorney at Sterne, Kessler, Goldstein & Fox, outside counsel to Bio-Reference Laboratories and GeneDx." 31 October 2008.

[47] Chung W, "SACGHS Task Force on Gene Patents and Licensing Practices Interview with Wendy Chung, MD, PhD, pediatrician, geneticist and researcher at Columbia University, " 2008.
Napolitano C, Bloise R, Priori SG. Long QT syndrome and short QT syndrome: how to make correct diagnosis and what about eligibility for sports activity. *J Cardiovasc Med (Hagerstown)* 2006. 7, (4): 250-6.
Napolitano C, Priori SG, Schwartz PJ, Bloise R, Ronchetti E, Nastoli J, Bottelli G, Cerrone M, Leonardi S. Genetic testing in the long QT syndrome: development and validation of an efficient approach to genotyping in clinical practice. *JAMA* 2005. 294, (23): 2975-80.

[48] Ackerman MJ. Genetic testing for risk stratification in hypertrophic cardiomyopathy and long QT syndrome: fact or fiction? *Curr Opin Cardiol* 2005. 20, (3): 175-81.
Goldenberg I, Moss AJ. Long QT syndrome. *J Am Coll Cardiol* 2008. 51, (24): 2291-300.

[49] Without treatment, LQTS-mutation carriers not identified by ECG/clinical evaluation have a ten-percent risk of a serious cardiac event by age 40.[50] Conversely, a recent study suggests that LQTS may be overdiagnosed; among a cohort of 176 patients referred to the Mayo Clinic for LQTS, 40 percent left the clinic without such a diagnosis.[51] Such patients who do not truly have LQTS may be given unnecessary beta-blockers or worse, implanted with gratuitous ICDs.

- Management of LQTS can be genotype-dependent.[52] LQT1 mutation carriers are more likely to experience syncope or sudden death in response to emotional or physical stress.[53] For LQT2 patients, cardiac events can be triggered by sudden loud noises.[54] Women with LQT2 mutations are at higher risk for cardiac events during the postpartum period.[55] Thus, genotype-specific management of the environment can be critical. Mutation location within a gene can be an important correlate of severity.[56] Moreover, beta-blocker therapy appears to be more effective in LQT1 patients[57] and may be counterproductive in LQT3, in which the lower heart rate is associated with an increased risk of arrhythmias.[58] In LQT3, the trigger often occurs during rest, while both LQT3 and JLNS are more often associated with fatal outcomes.[59]

Despite these arguments in favor of genetic testing, our understanding of LQTS remains incomplete. First, it must be emphasized again that *a negative genetic test does not rule out a LQTS diagnosis*.

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[49] Priori SG, Napolitano C, Schwartz PJ. Low penetrance in the long-QT syndrome: clinical impact. *Circulation* 1999. 99, (4): 529-33.
[50] Priori SG, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M, Vicentini A, Spazzolini C, Nastoli J, Bottelli G, Folli R, Cappelletti D. Risk stratification in the long-QT syndrome. *N Engl J Med* 2003. 348, (19): 1866-74.
[51] Taggart NW, Haglund CM, Tester DJ, Ackerman MJ. Diagnostic miscues in congenital long-QT syndrome. *Circulation* 2007. 115, (20): 2613-20.
[52] Goldenberg I, Moss AJ. Long QT syndrome. *J Am Coll Cardiol* 2008. 51, (24): 2291-300.
Tan HL, Bardai A, Shimizu W, Moss AJ, Schulze-Bahr E, Noda T, Wilde AA. Genotype-specific onset of arrhythmias in congenital long-QT syndrome: possible therapy implications. *Circulation* 2006. 114, (20): 2096-103.
Ackerman MJ. Genotype-phenotype relationships in congenital long QT syndrome. *J Electrocardiol* 2005. 38, (4 Suppl): 64-8.
[53] Schwartz PJ, Priori SG, Spazzolini C, Moss AJ, Vincent GM, Napolitano C, Denjoy I, Guicheney P, Breithardt G, Keating MT, Towbin JA, Beggs AH, Brink P, Wilde AA, Toivonen L, Zareba W, Robinson JL, Timothy KW, Corfield V, Wattanasirichaigoon D, Corbett C, Haverkamp W, Schulze-Bahr E, Lehmann MH, Schwartz K, Coumel P, Bloise R. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation* 2001. 103, (1): 89-95.
[54] Wilde AA, Jongbloed RJ, Doevendans PA, Duren DR, Hauer RN, van Langen IM, van Tintelen JP, Smeets HJ, Meyer H, Geelen JL. Auditory stimuli as a trigger for arrhythmic events differentiate HERG-related (LQTS2) patients from KVLQT1-related patients (LQTS1). *J Am Coll Cardiol* 1999. 33, (2): 327-32.
[55] Seth R, Moss AJ, McNitt S, Zareba W, Andrews ML, Qi M, Robinson JL, Goldenberg I, Ackerman MJ, Benhorin J, Kaufman ES, Locati EH, Napolitano C, Priori SG, Schwartz PJ, Towbin JA, Vincent GM, Zhang L. Long QT syndrome and pregnancy. *J Am Coll Cardiol.* 2007. 49, (10): 1092-8.
[56] Moss AJ, Shimizu W, Wilde AA, Towbin JA, Zareba W, Robinson JL, Qi M, Vincent GM, Ackerman MJ, Kaufman ES, Hofman N, Seth R, Kamakura S, Miyamoto Y, Goldenberg I, Andrews ML, McNitt S. Clinical aspects of type-1 long-QT syndrome by location, coding type, and biophysical function of mutations involving the KCNQ1 gene. *Circulation* 2007. 115, (19): 2481-9.
[57] Priori SG, Napolitano C, Schwartz PJ, Grillo M, Bloise R, Ronchetti E, Moncalvo C, Tulipani C, Veia A, Bottelli G, Nastoli J. Association of long QT syndrome loci and cardiac events among patients treated with beta-blockers. *JAMA* 2004. 292, (11): 1341-4.
[58] Chung W, "Written comments of Wendy Chung, MD, PhD, pediatrician, geneticist and researcher at Columbia University, " 7 November 2008.
[59] Ching CK, Tan EC. Congenital long QT syndromes: clinical features, molecular genetics and genetic testing. *Expert Rev Mol Diagn* 2006. 6, (3): 365-74.

Second, because it is not always clear that a given variant in a LQTS gene causes disease, the potential for false positive diagnoses remains.[60] Finally, within a family, the same mutation may be associated with radically different severity and type of symptoms.[61] At the moment, genetic testing for LQTS appears to be most useful: (1) when a clinical diagnosis is fairly certain and treatment strategies may depend on the nature of the mutation; or (2) to confirm or rule out the diagnosis in family members of an affected proband with a known mutation.[62] Clinical Data believes that testing may also clarify the clinical status of patients lacking a clear diagnosis,[63] although one clinician told us that the net effect of this approach can "open a can of worms" and leave patients without diagnoses and with variants of uncertain significance.[64]

The major European and American cardiology societies have issued joint guidelines for the care of patients at risk for sudden cardiac death, including those with LQTS.[65] Genetic testing is recommended for diagnosed LQTS patients.

The Sudden Arrhythmia Death Syndromes Foundation (SADS) suggests genetic testing for:

- All patients with a diagnosis of LQTS who have not had a genetic test;
- Anyone tested in a research study with family members yet to be tested; or
- Family members of a LQTS patient known to carry a mutation.[66]

Finally, we note additional incentives for genetic testing. Both cardiologists and makers of ICDs may financially benefit from the implantation of defibrillators in actual or suspected LQTS patients. Data indicate that ICDs are a cost-effective means of preventing sudden cardiac death when clinically indicated.[67] The dollars involved in ICD procedures dwarf those associated with genetic testing. Final

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[60] Taggart NW, Haglund CM, Tester DJ, Ackerman MJ. Diagnostic miscues in congenital long-QT syndrome. *Circulation* 2007. 115, (20): 2613-20.

[61] Oliva A, Bjerregaard P, Hong K, Evans S, Vernooy K, McCormack J, Brugada J, Brugada P, Pascali VL, Brugada R. Clinical heterogeneity in sodium channelopathies. What is the meaning of carrying a genetic mutation? *Cardiology* 2008. 110, (2): 116-22.

[62] Roden DM. Clinical practice. Long-QT syndrome. *N Engl J Med* 2008. 358, (2): 169-76.

[63] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.

[64] Roden DM. "Interview with Dan M. Roden, MDCM, Director of the Institute of Experimental Therapeutics, William Stokes Professor of Experimental Therapeutics, Professor of Medicine, and Professor of Pharmacology, Vanderbilt University School of Medicine." January 14, 2009.

[65] Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C, Smith SC, Jr., Jacobs AK, Adams CD, Antman EM, Anderson JL, Hunt SA, Halperin JL, Nishimura R, Ornato JP, Page RL, Riegel B, Blanc JJ, Budaj A, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL. ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation* 2006. 114, (10): e385-484.

[66] See http://www.sads.org/index.php/Table/Genetic-Testing/ [accessed on September 15, 2008]. Clinical Data has supported SADS financially since the company acquired rights to the major LQTS susceptibility genes in 2005. According to its annual reports available online, SADS received funding from Genaissance Pharmaceuticals, the previous exclusive licensee of the major LQTS gene patents, prior to 2005. (See http://www.sads.org/index.php/Documents/Annual-Reports-Financials.html [accessed September 15, 2008].)

[67] Zareba W, Moss AJ, Daubert JP, Hall WJ, Robinson JL, Andrews M. Implantable cardioverter defibrillator in high-risk long QT syndrome patients. *J Cardiovasc Electrophysiol* 2003. 14, (4): 337-41.

ICD costs in 2007 sometimes approached $40,000.[68] These are strong financial incentives for implanting such devices.

Genetic Testing for LQTS: 1995-2004

Following the identification of the first LQTS susceptibility genes, academic laboratories began offering genetic testing on a research basis. Clinicians we spoke to said that research subjects would often not receive their LQTS genotypes for a year or more,[69] if at all.[70]

In 2001, GeneDx began offering commercial genetic testing for LQT1, LQT2, LQT3, LQT5 and LQT6. Boston University began testing the following year; both labs also offered prenatal testing. As described in Appendix 8, the GeneDx LQTS testing regime was incomplete: it covered about one-third of the combined coding regions of the five most important susceptibility genes.[71] BU's assay was similar but not identical: it covered 26 of 63 exons in the five genes.[72] At the time, there was a tacit assumption that LQTS would resemble cystic fibrosis with respect to mutation distribution, i.e., one or a few major mutations accounting for most of the disease burden plus a fair number of rarer mutations.[73] This turned out not to be the case; the overwhelming majority of LQTS mutations are "private" and not recurring.[74]

In an email, the Mayo Clinic's Dr. Michael J. Ackerman, LQTS expert clinician, researcher and consultant to PGxHealth, emphasized that during this period, there were a substantial number of mis-

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[68] Hlatky MA, Mark DB. The high cost of implantable defibrillators. *Eur Heart J* 2007. 28, (4): 388-91.

[69] Ackerman MJ, "Interview with Michael J. Ackerman, MD, PhD, director of the Sudden Death Genomics Laboratory at the Mayo Clinic," Rochester, Minnesota: 6 May 2008.
Moss AJ, "Interview with Arthur J. Moss, MD, research physician at the University of Rochester " 28 August 2008.

[70] Towbin JA, "Interview with Jeffrey A. Towbin, MD, chief of pediatric cardiology, Baylor College of Medicine." 29 September 2008.

[71] Abbott GW, Sesti F, Splawski I, Buck ME, Lehmann MH, Timothy KW, Keating MT, Goldstein SA. MiRP1 forms IKr potassium channels with HERG and is associated with cardiac arrhythmia. *Cell* 1999. 97, (2): 175-87.
Larsen LA, Andersen PS, Kanters J, Svendsen IH, Jacobsen JR, Vuust J, Wettrell G, Tranebjaerg L, Bathen J, Christiansen M. Screening for mutations and polymorphisms in the genes KCNH2 and KCNE2 encoding the cardiac HERG/MiRP1 ion channel: implications for acquired and congenital long Q-T syndrome. *Clin Chem* 2001. 47, (8): 1390-5.
Neyroud N, Richard P, Vignier N, Donger C, Denjoy I, Demay L, Shkolnikova M, Pesce R, Chevalier P, Hainque B, Coumel P, Schwartz K, Guicheney P. Genomic organization of the KCNQ1 K+ channel gene and identification of C-terminal mutations in the long-QT syndrome. *Circ Res* 1999. 84, (3): 290-7.
Salisbury B, "Email from Ben Salisbury regarding total coding sequence of five LQTS genes." 30 September 2008.
Splawski I, Shen J, Timothy KW, Vincent GM, Lehmann MH, Keating MT. Genomic structure of three long QT syndrome genes: KVLQT1, HERG, and KCNE1. *Genomics* 1998. 51, (1): 86-97.

[72] Milunsky A, "Email from Aubrey Milunsky, MB.B.Ch., D.Sc., F.R.C.P., F.A.C.M.G., D.C.H." 17 November 2008.
Splawski I, Shen J, Timothy KW, Vincent GM, Lehmann MH, Keating MT. Genomic structure of three long QT syndrome genes: KVLQT1, HERG, and KCNE1. *Genomics* 1998. 51, (1): 86-97.
Syrris P, Murray A, Carter ND, McKenna WM, Jeffery S. Mutation detection in long QT syndrome: a comprehensive set of primers and PCR conditions. *J Med Genet* 2001. 38, (10): 705-10.

[73] Tsui LC, Durie P. Genotype and phenotype in cystic fibrosis. *Hosp Pract (Minneap)* 1997. 32, (6): 115-8, 23-9, 34, passim.

[74] Moss AJ, Shimizu W, Wilde AA, Towbin JA, Zareba W, Robinson JL, Qi M, Vincent GM, Ackerman MJ, Kaufman ES, Hofman N, Seth R, Kamakura S, Miyamoto Y, Goldenberg I, Andrews ML, McNitt S. Clinical aspects of type-1 long-QT syndrome by location, coding type, and biophysical function of mutations involving the KCNQ1 gene. *Circulation* 2007. 115, (19): 2481-9.
Roden DM. Clinical practice. Long-QT syndrome. *N Engl J Med* 2008. 358, (2): 169-76.
Towbin JA, "Interview with Jeffrey A. Towbin, MD, chief of pediatric cardiology, Baylor College of Medicine." 29 September 2008.

detections and a high false negative rate (that is, people with mutations causing LQTS but missed by genetic testing methods). He contends that BU, for example, marketed its test as equivalent to his own laboratory's research-based test, despite the former missing more than 30% of the mutations found by the latter. He believes that this confused doctors and patients because they thought the then-commercially available tests were equivalent to the Mayo test.[75] In his view, this period represented the "black hole" era in LQTS genetic diagnostics.[76]

Genetic Testing for LQTS: The Current Protocol

Since its commercial launch by Genaissance Pharmaceuticals[77] under the name FAMILION® in 2004 and through early 2009, the genetic testing protocol for LQTS remained relatively unchanged.[78] As outlined in Appendix 1, a physician or laboratory collects a small blood sample (8 ml) from a LQTS or potential LQTS patient (the index case), and sends it to Clinical Data subsidiary PGxHealth in New Haven, CT. Upon arrival, genomic DNA is extracted from blood and the samples are bar-coded for tracking.

Using primers specific for the five genes, DNA samples are then amplified by polymerase chain reaction (PCR) for direct sequence analysis of the susceptibility genes for LQT1 (the KCNQ1 gene), LQT2 (KCNH2), LQT3 (SCN5A), LQT5 (KCNE1) and LQT6 (KCNE2). This analysis includes comprehensive sequence determination and variant detection in open reading frames and intronic sequences containing splice junction sites for the included exons. FAMILION® testing for LQTS covers approximately 13.4 kilobases of DNA divided among 73 amplicons.[79] Directed sequencing is performed in both directions, except where the DNA sequence constraints preclude this approach (those regions are amplified and sequenced twice in a single direction). The DNA fragments resulting from PCR are electrophoretically separated and sequenced. Sequence traces are analyzed for heterozygous or homozygous variants compared to public reference sequences that have been confirmed by sequencing several hundred healthy individuals of diverse ancestry. Two technologists independently score all traces for variants and a supervisor reconciles any discrepancies.
Mutations in these five genes account for ~75% of clinically verified familial LQTS cases.[80] Actual yield from FAMILION® testing has been substantially lower.[81] This lower yield is likely due to the inclusion of patients with a lower pre-test probability of actually having LQTS.[82] Surveillance of fewer genes by FAMILION® testing versus research laboratories may have also played a role in determining yield.

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[75] Ackerman MJ, "Email from Michael J. Ackerman, MD, PhD; first response to case study." 27 October 2008.
[76] Ackerman MJ, "Interview with Michael J. Ackerman, MD, PhD, director of the Sudden Death Genomics Laboratory at the Mayo Clinic," Rochester, Minnesota: 6 May 2008.
[77] Genaissance was purchased by Clinical Data, Inc. in 2005.
[78] In this report we do not consider other cardiac-related FAMILION tests offered by Clinical Data subsidiary PGxHealth, including tests for Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC), Brugada Syndrome (BrS), Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) and hypertrophic cardiomyopathy (HCM).
[79] Salisbury B, "Email from Ben Salisbury regarding total coding sequence of five LQTS genes." 30 September 2008.
[80] Ackerman MJ. Genetic testing for risk stratification in hypertrophic cardiomyopathy and long QT syndrome: fact or fiction? *Curr Opin Cardiol* 2005. 20, (3): 175-81.
Goldenberg I, Moss AJ. Long QT syndrome. *J Am Coll Cardiol* 2008. 51, (24): 2291-300.
[81] Tester DJ, Salisbury BA, Carr JL, Harris-Kerr C, Reed CR, Ackerman MJ. Clinical phenotype and the yield of the Familion(TM) genetic test for congenital Long QT syndrome. *Abstract presented at Heart Rhythm Society Meeting* 2007.
[82] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.
Tester DJ, Salisbury BA, Carr JL, Harris-Kerr C, Reed CR, Ackerman MJ. The effect of mutation class on QTc in unrelated patients referred for the Familion(TM) genetic test for Long QT syndrome. *Abstract presented at Heart*

As described in the FAMILION® Technical Specifications Sheet (Appendix 1), reported variants are divided into Classes I, II and III:

CLASS I: Deleterious and Probable Deleterious Mutations

1. Evidence of deleteriousness
2. Nonsense variant
3. Missense single-nucleotide variant not seen in the Reference Panel in transmembrane-spanning domain or pore
4. Insertion or deletion
    a. Frameshift variant
    b. In-frame variant in transmembrane-spanning domain or pore

CLASS II: Possible Deleterious Mutations (Variants of Uncertain Significance)

1. Missense single-nucleotide variant not seen in the Reference Panel and not in transmembrane-spanning domain or pore
2. Missense single-nucleotide variant seen in the Reference Panel with allelic frequency < 0.5%, but with published evidence of deleteriousness
3. In-frame insertion or deletion not in transmembrane-spanning domain or pore
4. Predicted splice-site variant

CLASS III: Polymorphisms (Variants Not Generally Expected to be Deleterious)

1. Protein-altering variant seen in the Reference Panel with either
    a. Common frequency (≥ 0.5%) or
    b. Rare frequency (< 0.5%) and without published evidence of deleteriousness

The final report is reviewed and signed by a CLIA-licensed Laboratory Director.[83] Results are returned to the physician, "usually within 6 weeks."[84] When a Class I or Class II mutation is found, a recommendation for clinical evaluation and genetic testing of first-degree blood relatives is included in the report (Appendices 2 and 3). Examples of a negative report and the accompanying letter sent to doctors are shown in Appendices 4 and 5, respectively. If the clinical interpretation of a reported variant changes, an amended test report is generated and provided to the referring physician when possible (Appendix 1).

The test costs $5400 for the index case and $900 to confirm/rule out a previously characterized mutation in each additional family member. PGxHealth maintains a customer service group that works with patients' insurance providers to pre-authorize services. PGxHealth is quoted an estimate of coverage from the insurance carrier but does not guarantee reimbursement.[85]

Rhythm Society Meeting May 2007. Tester DJ, Will ML, Haglund CM, Ackerman MJ. Effect of clinical phenotype on yield of long QT syndrome genetic testing. *J Am Coll Cardiol* 2006. 47, (4): 764-8.

[83] CLIA stands for Clinical Laboratory Improvement Amendments of 1988 (see http://www.cms.hhs.gov/clia/ [accessed November 11, 2008]), which were designed to improve the quality and expand Federal oversight of clinical laboratories in the United States.

[84] See http://www.pgxhealth.com/genetictests/familion/patients/index.cfm [accessed October 7, 2008].

[85] See http://www.pgxhealth.com/genetictests/familion/patients/faq.cfm [accessed October 7, 2008].

LQTS Genes: The Intellectual Property Chain of Custody

Insofar as we can tell, until recently the intellectual property attached to the major LQTS susceptibility genes was exclusively licensed by the University of Utah to a succession of corporate genetic testing firms, but at any given time, exclusive rights were held by a single firm.[86] DNA Sciences Inc. was the sole licensee (1999-2003.)[87] In 2003, most of the assets of DNA Sciences, including patent licenses for the three major LQTS genes, were purchased out of bankruptcy by Genaissance Pharmaceuticals,[88] which, following renegotiation of the patent licenses, launched commercial LQTS testing in 2004 under the name FAMILION®.[89] In 2005, Genaissance was acquired by Clinical Data Inc.[90]

Since that time, Clinical Data subsidiary PGxHealth™ has overseen rapid growth in commercial testing for LQTS and other channelopathies. In fiscal 2008, sales of PGxHealth tests grew 41% year-over-year to $4.6 million. Judging from a recent company presentation,[91] the overwhelming source of this growth was FAMILION® testing (for LQTS, catecholaminergic polymorphic ventricular tachycardia [CPVT], and Brugada syndrome[92]). During the same year, the company launched a provider-focused sales force and customer-service staff to help drive FAMILION® test adoption,[93] to which much of the sales growth can be attributed, along with an increased focus by PGxHealth in working with physicians to convince reluctant insurers to cover genetic testing for LQTS. PGxHealth reported that it has also invested in enhancements in its laboratory operations to handle the increased volume and to reduce turnaround times.[94] According to BRLI CEO Dr. Marc Grodman, the intention of his company to enter the cardiac genetics market became well known by early 2007. He believes this potential competition played an important role in Clinical Data's marketing strategy.[95]

[86] The University of Utah Technology Commercialization Office declined to speak with us on the record, despite repeated requests.
[87] Rienhoff HY, "Interview with Hugh Y. Rienhoff, Jr., MD, founder and former CEO of DNA Sciences." 13 June 2008.
[88] Judson R, "Interview with Richard Judson, PhD, former CSO of Genaissance Pharmaceuticals." 9 July 2008. Company news - DNA sciences declares bankruptcy, sells assets to Genaissance. *Biotechnology Law Report* June 2003. 22, (3): 307.
[89] Genaissance Pharmaceuticals, *Genaissance Pharmaceuticals Launches its Proprietary FAMILION™ Test for Genetic Mutations Associated With Sudden Cardiac Death*, 2004. See: http://www.medscape.com/pages/editorial/pressreleases/pr-crm-genaissance2, September 17 2008].
[90] Genaissance Pharmaceuticals to merge with Clinical Data. *Pharmacogenomics* July 2005. 6, (5): 459.
[91] Clinical Data, *EX-99.1 of 8-K*, 9 July 2008. See: http://www.sec.gov/Archives/edgar/data/716646/000095013508004859/b71062cdexv99w1.htm, [accessed 17 September 2008].
[92] LQTS notwithstanding, Clinical Data has licensed rights to these other cardiac disorders on a non-exclusive basis. In May 2008 the company launched a test for hypertrophic cardiomyopathy.
[93] Clinical Data, *10-K*, 16 June 2008. See: http://www.sec.gov/Archives/edgar/data/716646/000095013508004390/b70423cde10vk.htm, [accessed 17 September 2008].
[94] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.
[95] Grodman M, "Written comments of Marc Grodman, MD, CEO of Bio-Reference Laboratories." 12 November 2008.

Genetic Testing for LQTS: At Issue

Questions about LQTS intellectual property came to the fore and achieved policy significance through the 2007 Congressional testimony of Bio-Reference Laboratories CEO Dr. Marc Grodman and Columbia University clinical geneticist Dr. Wendy Chung.[96] In their testimony they contended that:

- Competition in diagnostic testing is critical to the public health; because of exclusive licensing of the relevant gene patents, in LQTS there is effectively no competition and there has not been since 2002.
- The discovery of the LQTS genes was partly funded by NIH, yet the University of Utah had originally, and at the time of Dr. Grodman's testimony, only seen fit to license the patents to a single private-sector provider.
- By sending cease-and-desist letters to and/or suing the laboratories who were offering LQTS genetic testing prior to commercialization and refusing to sublicense to any other genetic test provider, DNA Sciences Inc (the exclusive patent licensee at the time) created a nearly-two-year period during which only research laboratory-based testing was available to LQTS patients and family members. During that period, DNA Sciences "cleared the market" of potential competitors, including nonprofit testing services, although DNA Sciences did not yet offer a test itself.
- LQTS genetic research has been stifled by Clinical Data's monopoly.
- There have been problems with quality and interpretation of results in Clinical Data's LQTS testing.
- Clinical Data has not developed the ability to reliably perform genetic testing on paraffin-embedded samples from deceased persons.
- Clinical Data's testing regime is incomplete.
- Clinical Data's turnaround time can be as long as six to eight weeks.
- Variants of unknown significance are disproportionately reported in minority populations.
- FAMILION® testing is $5400; a competitive laboratory could offer the test for about "a quarter of the price." The cost of the test is "not routinely covered by most insurance companies without a lengthy preauthorization process that frequently takes 3-12 months to complete." The test would be accessible to many more patients if it were "correctly" priced in a competitive marketplace.[97]

In an April 2008 letter to Howard L. Berman (D-CA), Chairman of the House Judiciary Subcommittee on Courts, the Internet, and Intellectual Property, Clinical Data CEO Drew Fromkin responded to the Grodman/Chung testimony.[98] In his letter Fromkin argued:

- The patent system and the availability of exclusive licensing spurs innovation and provides incentives for product development that can save lives. LQTS is a great example.

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[96] "Stifling or stimulating: the role of gene patents in research and genetic testing.," Subcommittee on Courts, the Internet, and Intellectual Property of the Committee on the Judiciary, One Hundred Tenth Congress; First Session ed. Washington, DC: 31 October 2007.

[97] Ibid...

[98] Fromkin AJ, "Letter to the Honorable Howard L. Berman from Clinical Data CEO Andrew J. Fromkin." 1 April 2008.

- Clinical Data is highly motivated to continually improve FAMILION testing: the company has reduced turnaround time from 6 weeks to 4.5 weeks. With or without competition, poor products stop selling.
- Clinical Data periodically considers adding LQTS mutations to its testing regime. Recently, the susceptibility gene for CPVT was added to the FAMILION® menu.
- In most cases so far, the inclusion of additional genes would add cost to the test with only minimal clinical benefit.
- Research has not been stifled: since the launch of FAMILION® testing, four new LQTS genes have been identified. In the event a FAMILION® test comes back negative, the patient is referred to a research laboratory for further testing.
- Clinical Data is ready to accommodate any common specimen type, including paraffin-embedded tissues.
- Clinical Data holds itself to the highest federal and corporate standards for the quality of its lab work: two clear sequencing reads are required for every sample. All variants are reviewed by three people, including a board-certified medical geneticist.
- Clinical Data responds immediately to reports of inconsistent or erroneous reports.
- Clinical Data regularly presents its LQTS data at national meetings. Additional publications are in preparation.
- Without exclusive patent rights in this and most other fields, competitive pressures would severely limit the disclosure of scientific discovery and harm the public interest.
- Of >1300 non-LQTS individuals tested, mutation information has been published on > 700 with more to come. This testing is done in order to quantify and specify background variation so that the test specificity is understood and so that fewer rare, benign variants are mistaken for pathogenic mutations.[99]
- Half of the healthy subjects who have been tested have come from non-Caucasian populations.
- Health plan coverage of FAMILION® LQTS testing has grown rapidly despite the fact that gaining insurance coverage is "a long and difficult road" that takes years.
- Exclusive licenses lead to higher quality genetic tests that in turn lead to better patient outcomes and a more cost-effective healthcare system. Non-exclusive rights lead to "commodity" and "me-too" tests that place pressures on profit margins that result in mediocrity and can ultimately harm patients and society.
- Dr. Grodman has a financial interest in the non-exclusive licensing of LQTS gene patents. Moreover, he has approached Clinical Data in the past seeking: (1) a license to FAMILION® tests and (2) to acquire Clinical Data's laboratory operations as a whole. Clinical Data is surprised he "would so quickly be transformed from a suitor to a harsh critic."
- Dr. Grodman's words do not match his actions. In early 2008, Dr. Grodman's company acquired an exclusive license to the patent surrounding the LQT7 gene (KCNJ2). [100]

[99] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.

[100] In October 2008, attorney Jorge Goldstein, counsel to BRLI, informed us that, since the time of the testimony of Dr Grodman (October 2007), his client had obtained licenses to several LQTS gene patents relating to LQT1, 2, 3, 5,

Given such highly polarized and seemingly contradictory assertions, LQTS is a natural case study for the effects of IP on access to genetic testing. Beyond the Grodman/Chung testimony and the Fromkin response, there are other reasons to undertake an examination of patenting in LQTS. First, with an incidence of 1 in 3000 to 1 in 5000, [101] it is a relatively common Mendelian disorder. Second, as in hereditary breast cancer testing, from the outset there has been a single exclusive licensee of the major LQTS genes (at least until recently). However, there was a period prior to 2003 when the LQTS gene patent rights were not enforced; thus, we are able to compare the pre- and post-enforcement landscapes, albeit in a highly limited way and with some very serious caveats.[102] Third, genetic testing in LQTS matters: undiagnosed cases may be at high risk for cardiac events,[103] which could potentially be avoided if these individuals were known to carry a mutation in one or more specific genes. Moreover, different mutations in different genes may suggest different therapeutic options.[104]

LQTS Genes and Intellectual Property

Research, Databases, Publications, and Technical Issues

The field of LQTS genetics is young. As with hereditary breast cancer, the molecular basis of the major LQTS genes has only been known since the mid-1990s.[105] The prospect of a Bayh-Dole Act-inspired

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6, and 7. The patent landscape has therefore become divided between the licenses held by PGxHealth and those held by BRLI.

[101] Goldenberg I, Moss AJ. Long QT syndrome. *J Am Coll Cardiol* 2008. 51, (24): 2291-300.
Lehnart SE, Ackerman MJ, Benson DW, Jr., Brugada R, Clancy CE, Donahue JK, George AL, Jr., Grant AO, Groft SC, January CT, Lathrop DA, Lederer WJ, Makielski JC, Mohler PJ, Moss A, Nerbonne JM, Olson TM, Przywara DA, Towbin JA, Wang LH, Marks AR. Inherited arrhythmias: a National Heart, Lung, and Blood Institute and Office of Rare Diseases workshop consensus report about the diagnosis, phenotyping, molecular mechanisms, and therapeutic approaches for primary cardiomyopathies of gene mutations affecting ion channel function. *Circulation* 2007. 116, (20): 2325-45.
Roden DM. Clinical practice. Long-QT syndrome. *N Engl J Med* 2008. 358, (2): 169-76.

[102] BRLI's Dr. Grodman believes that because of advances in technology since the early 2000s, this "then-and-now" comparison unfairly favor current applications. For their part, Clinical Data's Drs. Reed and Salisbury believe that the recent advances in genetic diagnostic technology, the relative completeness of the current commercial test, and the greater awareness of clinicians and patients of genetic testing also casts serious doubt on the validity of this comparison.

[103] Napolitano C, Priori SG, Schwartz PJ, Bloise R, Ronchetti E, Nastoli J, Bottelli G, Cerrone M, Leonardi S. Genetic testing in the long QT syndrome: development and validation of an efficient approach to genotyping in clinical practice. *JAMA* 2005. 294, (23): 2975-80.
Priori SG, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M, Vicentini A, Spazzolini C, Nastoli J, Bottelli G, Folli R, Cappelletti D. Risk stratification in the long-QT syndrome. *N Engl J Med* 2003. 348, (19): 1866-74.

[104] Saenen JB, Vrints CJ. Molecular aspects of the congenital and acquired Long QT Syndrome: clinical implications. *J Mol Cell Cardiol* 2008. 44, (4): 633-46.
Tan HL, Bardai A, Shimizu W, Moss AJ, Schulze-Bahr E, Noda T, Wilde AA. Genotype-specific onset of arrhythmias in congenital long-QT syndrome: possible therapy implications. *Circulation* 2006. 114, (20): 2096-103.
Schwartz PJ. The congenital long QT syndromes from genotype to phenotype: clinical implications. *J Intern Med* 2006. 259, (1): 39-47.

[105] Curran ME, Splawski I, Timothy KW, Vincent GM, Green ED, Keating MT. A molecular basis for cardiac arrhythmia: HERG mutations cause long QT syndrome. *Cell* 1995. 80, (5): 795-803.
Wang Q, Shen J, Li Z, Timothy K, Vincent GM, Priori SG, Schwartz PJ, Keating MT. Cardiac sodium channel mutations in patients with long QT syndrome, an inherited cardiac arrhythmia. *Hum Mol Genet* 1995. 4, (9): 1603-7.
Wang Q, Shen J, Splawski I, Atkinson D, Li Z, Robinson JL, Moss AJ, Towbin JA, Keating MT. SCN5A mutations associated with an inherited cardiac arrhythmia, long QT syndrome. *Cell* 1995. 80, (5): 805-11.
Wang DW, Yazawa K, George AL, Jr., Bennett PB. Characterization of human cardiac Na+ channel mutations in the congenital long QT syndrome. *Proc Natl Acad Sci U S A* 1996. 93, (23): 13200-5.

patent incentive,[106] however, did not appear to stimulate a LQTS gene race akin to the race for the hereditary breast cancer genes,[107] probably because of the relative rarity of LQTS and what was presumed to be a small market for LQTS testing. The principal inventor on the LQTS gene patents, Dr. Mark Keating, a cardiologist then at the University of Utah, was himself skeptical about the commercial value of testing, though his lab was inundated with requests from other physicians to perform genetic tests on their LQTS patients. Dr. Hugh Rienhoff, the founder of DNA Sciences and a friend of Dr. Keating's, thought there would be commercial value beyond diagnosing LQTS mutations, namely, that SIDS might also be a part of the spectrum of LQTS and that variants in certain genes combined with particular drugs might induce LQTS. Consequently DNA Sciences licensed the patents on LQTS genes and mutations with a view toward extending the research to include these new patients: SIDS victims and their families as well as individuals on drug regimens vulnerable to drug-induced LQTS resulting from certain genetic variants. The research into LQTS thus stemmed from Dr. Keating's very successful genetics research. DNA Sciences extended the LQTS paradigm into areas that Dr. Keating thought were likely to be more complicated and scientifically less productive. According to Dr. Rienhoff, Keating was "more or less right about that."[108] Dr. Rienhoff said there was also skepticism on the part of DNA Sciences investors as to whether genetic testing for "infrequent" (in commercial terms) congenital cardiac disorders would be a viable business.[109]

Through 2008, there was no corporate equivalent in LQTS to the extensive Myriad Genetics contributions to the public BRCA mutation database.[110] Dr. Silvia Priori maintains a public, online database in Italy that includes "a couple thousand" LQTS patients; its mutation data are culled mainly from the published literature.[111] Drs. Arthur Moss and Peter Schwartz founded the International Long-QT Syndrome Registry in 1979; today it includes 1276 families and ~3600 affecteds or borderline affecteds, with genetically confirmed diagnoses in ~2000 of those cases.[112] Most of the Registry's genotype information, however, was obtained from research labs and not from FAMILION® testing;[113] Drs. Reed and Salisbury

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Wang Q, Curran ME, Splawski I, Burn TC, Millholland JM, VanRaay TJ, Shen J, Timothy KW, Vincent GM, de Jager T, Schwartz PJ, Toubin JA, Moss AJ, Atkinson DL, Landes GM, Connors TD, Keating MT. Positional cloning of a novel potassium channel gene: KVLQT1 mutations cause cardiac arrhythmias. *Nat Genet* 1996. 12, (1): 17-23.

[106] Thursby JG, Thursby MC. Intellectual property. University licensing and the Bayh-Dole Act. *Science* 2003. 301, (5636): 1052.

Boettiger S, Bennett AB. Bayh-Dole: if we knew then what we know now. *Nat Biotechnol* 2006. 24, (3): 320-3.

[107] Williams-Jones B. History of a gene patent: tracing the development and application of commercial BRCA testing. *Health Law J* 2002. 10: 123-46.

[108] Rienhoff HY, "Written comments of Hugh Y. Rienhoff, Jr., founder and former CEO of DNA Sciences, Inc. ." 1 November 2008.

Tester DJ, Ackerman MJ. Sudden infant death syndrome: how significant are the cardiac channelopathies? *Cardiovasc Res* 2005. 67, (3): 388-96.

[109] Rienhoff HY, "Interview with Hugh Y. Rienhoff, Jr., MD, founder and former CEO of DNA Sciences." 13 June 2008.

[110] Frank TS, Deffenbaugh AM, Reid JE, Hulick M, Ward BE, Lingenfelter B, Gumpper KL, Scholl T, Tavtigian SV, Pruss DR, Critchfield GC. Clinical characteristics of individuals with germline mutations in BRCA1 and BRCA2: analysis of 10,000 individuals. *J Clin Oncol* 2002. 20, (6): 1480-90.

[111] Priori S, "Interview with Silvia G. Priori, MD, PhD, LQTS researcher and clinician in Pavia, Italy." 29 May 2008.

[112] Moss AJ, "Interview with Arthur J. Moss, MD, research physician at the University of Rochester " 28 August 2008.

Goldenberg I, Moss AJ. Long QT syndrome. *J Am Coll Cardiol* 2008. 51, (24): 2291-300.

Moss AJ, Schwartz PJ. 25th anniversary of the International Long-QT Syndrome Registry: an ongoing quest to uncover the secrets of long-QT syndrome. *Circulation* 2005. 111, (9): 1199-201.

[113] Moss AJ, "Interview with Arthur J. Moss, MD, research physician at the University of Rochester. " 28 August 2008.

suggested to us that this is because the Registry was closing around the time of the FAMILION® launch in 2004. According to Baylor's Dr. Towbin, access to the Registry is by application.[114] Prior to the FAMILION® launch, Genaissance and Dr. Michael Ackerman from the Mayo Clinic collaborated to establish an internal database of normal controls and LQTS mutations.[115] Without associated clinical data, it's not clear to us how helpful access to the FAMILION® mutation data would be. Dr. Towbin suggests that it is unreasonable to expect a non-research laboratory to acquire the necessary clinical data.[116] Boston University's Dr. Aubrey Milunsky, however, director of BU's clinical genetics diagnostic service and a former and would-be LQTS testing provider, believes that a knowledge base of certain clinically useful and detailed phenotypic information can come only from a commercial diagnostic lab and not from research labs. Drs. Reed and Salisbury believe such registries should be set up under the auspices of an independent institution with Institutional Review Board approval, as Dr. Moss and Dr. Priori have done. PGxHealth, they say, would support such an initiative.[117] In November 2008, Clinical Data announced that its LQTS mutation data would be made public in spring 2009.[118]

To the best of our knowledge, during the FAMILION® (Genaissance/Clinical Data) testing period from 2004-2008, there have been three full-length LQTS papers published in which scientists employed by the corporate patent licensees shared authorship.[119] The companies have also presented data at national meetings and published their findings in abstract form.[120] PGxHealth representatives informed us in June 2008 that the company had multiple manuscripts in progress.[121]

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[114] Towbin JA, "Interview with Jeffrey A. Towbin, MD, chief of pediatric cardiology, Baylor College of Medicine." 29 September 2008.
[115] Judson R, "Interview with Richard Judson, PhD, former CSO of Genaissance Pharmaceuticals." 9 July 2008.
[116] Towbin JA, "Interview with Jeffrey A. Towbin, MD, chief of pediatric cardiology, Baylor College of Medicine." 29 September 2008.
[117] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.
[118] Clinical Data Launches Genetic Test for Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC); Company to release its genetic databases for inherited cardiac conditions. *Business Wire* 10 November 2008.
[119] Ackerman MJ, Splawski I, Makielski JC, Tester DJ, Will ML, Timothy KW, Keating MT, Jones G, Chadha M, Burrow CR, Stephens JC, Xu C, Judson R, Curran ME. Spectrum and prevalence of cardiac sodium channel variants among black, white, Asian, and Hispanic individuals: implications for arrhythmogenic susceptibility and Brugada/long QT syndrome genetic testing. *Heart Rhythm* 2004. 1, (5): 600-7.
Judson RS, Salisbury BA, Reed CR, Ackerman MJ. Pharmacogenetic issues in thorough QT trials. *Mol Diagn Ther* 2006. 10, (3): 153-62.
Tester DJ, Cronk LB, Carr JL, Schulz V, Salisbury BA, Judson RS, Ackerman MJ. Allelic dropout in long QT syndrome genetic testing: a possible mechanism underlying false-negative results. *Heart Rhythm* 2006. 3, (7): 815-21.
[120] Salisbury BA, Carr JL, Harris-Kerr C, Ackerman MJ. Abstract 2215: Clinical genetic testing for congenital Long QT syndrome: spectrum of mutations discovered in the first two years. *Abstract presented at American Heart Association Meeting* 2006.
Tester DJ, Salisbury BA, Carr JL, Harris-Kerr C, Reed CR, Ackerman MJ. Should a minimum corrected QT interval (QTc) be a prerequisite for Long QT syndrome genetic testing? *Abstract presented at American Heart Association Meeting.* 6 November 2007.
Ackerman MJ, Tester DJ, Valdivia C, Salisbury BA, Wilde AAM, Makielski JC. Is A572-SCN5A a LQT3/sudden death susceptibility mutation or background genetic noise? *Abstract presented at Heart Rhythm Society Meeting* May 2008.
Johnson JN, Haglund CM, Tester DJ, Perry J, Salisbury BA, Reed CR, Ackerman MJ. Prevalence of early onset atrial fibrillation in congenital Long QT syndrome. *Abstract presented at Heart Rhythm Society Meeting* May 2007.
Kapa S, Tester DJ, Salisbury BA, Wilde AA, Ackerman MJ. Distinguishing Long QT Syndrome-causing mutations from "background" genetic noise. *Abstract presented at Heart Rhythm Society Meeting.* 16 May 2008.

As noted in the *Dramatis Personae* section, Dr. Ackerman's group performs LQTS genetic research at the Mayo Clinic, as does Dr. Priori's in Pavia, Dr. Moss's in Rochester, Dr. Towbin's at Baylor, Dr. Roden's at Vanderbilt, and Dr. Chung's at Columbia University, among several others. It is clearly not in PGxHealth's interest to discourage or antagonize these investigators—the LQTS research community is fairly small and these physicians are invaluable liaisons to patients. There has been productive collaboration between PGxHealth and these investigators, including in the interpretation of variants of unknown significance that may or may not cause disease.[122] In a few cases, however, test results and/or their interpretation appear to have differed.[123] This is not surprising: virtually all laboratories make occasional errors,[124] even in cases where they are screening for the same few mutations over and over

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Kapa S, Tester DJ, Salisbury BA, Wilde AA, Ackerman MJ. Amino acid physicochemical differences may serve as an adjunct to frequency analysis to determine mutation pathogenicity in Long QT syndrome. *Abstract presented at Heart Rhythm Society Meeting.* 2008.

Salisbury B, Judson RS, Pungliya M, Carr J, Qi M, Zareba W, Robinson JL, Moss AJ, Will ML, Tester DJ, Ackerman MJ. The single nucleotide polymorphism D85N-KCNE1 is associated with both congenital and drug-induced Long QT. *Abstract presented at Heart Rhythm Society Meeting.* May 2006.

Salisbury BA, Pungliya M, Harris-Kerr C, Judson RS, Tester DJ, Will ML, Ackerman MJ. Distinguishing causative and non-causative mutations in Long QT syndrome. *Abstract presented at Heart Rhythm Society Meeting.* 2006.

Tester DJ, Salisbury BA, Carr JL, Harris-Kerr C, Reed CR, Ackerman MJ. Clinical phenotype and the yield of the Familion(TM) genetic test for congenital Long QT syndrome. *Abstract presented at Heart Rhythm Society Meeting.* 2007.

Tester DJ, Salisbury BA, Carr JL, Harris-Kerr C, Reed CR, Ackerman MJ. The effect of mutation class on QTc in unrelated patients referred for the Familion(TM) genetic test for Long QT syndrome. *Abstract presented at Heart Rhythm Society Meeting.* 2007.

Tester DJ, Will ML, Salisbury BA, Carr JL, Schulz V, Judson RS, Ackerman MJ. Allelic drop-out in long QT syndrome genetic testing: a possible mechanism underlying false negative results. *Abstract presented at Heart Rhythm Society Meeting.* May 2005.

Will ML, Tester DJ, Salisbury BA, Carr JL, Schulz V, Judson RS, Ackerman MJ. Repeat long QT syndrome genetic testing of phenotype positive cases: prevalence and etiology of detection misses. *Abstract presented at Heart Rhythm Society Meeting.* May 2005.

Judson RS, Salisbury BA, Pungliya M, Carr J, Hennessey J, Harris-Kerr C, Qi M, Zareba W, Robinson JL, Moss AJ, Tester DJ, Will ML, Ackerman MJ. A common single nucleotide polymorphism associated with congenital long QT syndrome. *Abstract presented at the American Society of Human Genetics Meeting.* 28 October 2005.

Pungliya M, Salisbury BA, Judson RS, Tester DJ, Will ML, Ackerman MJ. A comparison of mutation patterns in suspected cases of congenital long QT syndrome and controls. *Abstract presented at the American Society of Human Genetics Meeting.* 28 October 2005.

[121] Reed C, Salisbury B, "Interview with Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 12 June 2008.

Ackerman MJ, "Interview with Michael J. Ackerman, MD, director of the Sudden Death Genomics Laboratory at the Mayo Clinic." 2008.

[122] Dr. Ackerman is a paid consultant to Clinical Data. Dr. Chung is a paid consultant to diagnostic firm Bio-Reference Laboratories. Dr. Moss consulted for Genaissance in the past.

[123] Moss AJ, "Interview with Arthur J. Moss, MD, research physician at the University of Rochester. " 28 August 2008.

Chung W, "SACGHS Task Force on Gene Patents and Licensing Practices Interview with Wendy Chung, MD, PhD, pediatrician, geneticist and researcher at Columbia University. " 2008.

Chung W, "Interview with Wendy Chung, MD, PhD, pediatrician, geneticist and researcher at Columbia University" 7 May 2008.

"Stifling or stimulating: the role of gene patents in research and genetic testing.," Subcommittee on Courts, the Internet, and Intellectual Property of the Committee on the Judiciary, One Hundred Tenth Congress; First Session ed. Washington, DC: 31 October 2007.

[124] Ramsden SC, Deans Z, Robinson DO, Mountford R, Sistermans EA, Grody WW, McQuaid S, Patton SJ, Stenhouse SA. Monitoring standards for molecular genetic testing in the United Kingdom, the Netherlands, and Ireland. *Genet Test* 2006. 10, (3): 147-56.

again.[125] But in instances where discrepancies occur, it is conceivable, especially in a disease as challenging to understand as LQTS, that the availability of a second commercial provider held to the same CLIA standards, motivated by the same incentives, and subjected to the same competitive pressures could offer a second source of variant confirmation (and perhaps alternative interpretation).

Clinical Data's Dr. Reed: "We encourage our customers to inform us if there is any question or concern regarding a result or an interpretation. We fully annotate our reports and will work to resolve any concerns. If a mistake on our part is found, we will rectify it and improve any process that might have been faulty. In fact, if we are notified of a discrepancy we are obligated to resolve it."

"Re-interpreting a result would not require a second laboratory, just an expert and/or new information. Research labs are generally headed by exactly the expert individual capable of sorting out discrepancies and/or differences in interpretation."[126]

It is important to note again the existence of conflicts of interest on all sides. Those providing commercial testing (PGxHealth and its consultants) have an interest in maintaining the status quo. Many of those who would like to see other commercial providers and stand to benefit from becoming one of them (former providers, BRLI and its consultants) have an obvious interest in altering the current system.

The most important LQTS patents begin to expire in March 2015.[127] Until then, PGxHealth and recent licensee BRLI may exercise influence over the course of LQTS genetic research in the U.S.

Clinical Data suggested to us that FAMILION® testing might actually be facilitating research by identifying patients with known mutations, allowing research laboratories to focus their resources on those without known mutations. The company also emphasized that it does not prevent research labs from conducting research.[128]

To date, while we cannot know with certainty what might have been had there been multiple providers, we have no evidence that the virtual LQTS monopoly from 2003-2008 has had a stifling effect on research, with the possible exception of interpretation of variants of unknown significance, which is discussed in subsequent sections on test quality.

Development and Commercialization

The University of Utah Research Foundation was granted three patents covering the major genes predisposing to LQT1, LQT2, LQT3 and LQT5 in 1997, 2001 and 2002.[129] DNA Sciences received exclusive licenses to these patents beginning in 1999, under a "fairly standard" royalty agreement with the University of Utah Research Foundation.[130] In 2003, Genaissance purchased most of the assets of DNA

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[125] Hertzberg M, Neville S, McDonald D. External quality assurance of molecular analysis of haemochromatosis gene mutations. *J Clin Pathol* 2006. 59, (7): 744-7.
[126] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.
[127] US Patent No. 5,599,673 (4 February 1997).
[128] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.
[129] US Patent No. 5,599,673 (4 February 1997).
US Patent No. 6,432,644 B1 (13 August 2002).
US Patent No. 6,207,383 B1 (27 March 2001).
[130] Rienhoff HY, "Interview with Hugh Y. Rienhoff, Jr., MD, founder and former CEO of DNA Sciences." 13 June 2008.

Sciences out of bankruptcy.[131] In the first quarter of 2004, Genaissance concluded agreements with the University of Utah and Yale University covering an estate of more than 50 issued and pending patents relating to the five known mutant genes predisposing to cardiac channelopathies.[132] These agreements included an exclusive license to patents pertaining to the three major LQTS susceptibility genes that had been licensed to DNA Sciences.[133] The LQTS patent landscape as we understand it is presented in Appendix 6.

The LQTS gene patents were key assets of both DNA Sciences[134] and then Genaissance.[135] Clearly there was perceived value in LQTS IP. Both Genaissance and Clinical Data appear to have made testing for LQTS a substantive part of their genetic testing business plans.[136] (Nota bene: Clinical Data has declined to share its current or past LQTS-related intellectual property rights with us. We have partially deduced these holdings from interviews with former executives at DNA Sciences and Genaissance, from Securities and Exchange Commission filings, from litigation-related documents and cease-and-desist letters, and from an interview with BRLI's outside legal counsel.)

A patent infringement suit was brought by DNA Sciences against GeneDx[137] in 2002 (Appendix 7). Cease and desist letters were sent to one or more additional labs[138] at around the same time.[139] This suggests an effort by DNA Sciences to "clear the market" in 2002. According to DNA Sciences founder Dr. Rienhoff (who left the company in 2001), one of the stipulations of the company's license agreement with the University of Utah was that the company vigorously defend its IP; to not do so would have been a violation of that agreement.[140] The University of Utah Technology Commercialization Office declined to speak with us for this study.

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[131] Company news - DNA sciences declares bankruptcy, sells assets to Genaissance. *Biotechnology Law Report* June 2003. 22, (3): 307.
Judson R, "Interview with Richard Judson, PhD, former CSO of Genaissance Pharmaceuticals." 9 July 2008.
[132] Genaissance Pharmaceuticals, *EX-99.1 of 8-K*, 11 May 2004. See: http://www.sec.gov/Archives/edgar/data/1110009/000110465904013687/a04-5741_1ex99d1.htm, [accessed 26 September 2008].
[133] Judson R, "Interview with Richard Judson, PhD, former CSO of Genaissance Pharmaceuticals." 9 July 2008.
[134] Rienhoff HY, "Interview with Hugh Y. Rienhoff, Jr., MD, founder and former CEO of DNA Sciences." 13 June 2008.
DNA Sciences, *S-1*, 5 January 2001. See: http://www.sec.gov/Archives/edgar/data/1130013/000091205701000445/a2033717zs-1.htm, [accessed 22 September 2008].
[135] Judson R, "Interview with Richard Judson, PhD, former CSO of Genaissance Pharmaceuticals." 9 July 2008.
Genaissance Pharmaceuticals, "Event Transcript: GNSC - Q4 2003 Genaissance Pharmaceuticals, Inc. Earnings Conference Call," CCBN Street Events, 2004.
[136] Genaissance Pharmaceuticals, *10-K*, 30 March 2004. See: http://www.sec.gov/Archives/edgar/data/1110009/000104746904010049/a2131537z10-k.htm, [accessed 23 September 2008].
Clinical Data, *10-K*, 29 June 2006. See: http://www.sec.gov/Archives/edgar/data/716646/000095013506004150/b61410cie10vk.htm, [accessed 23 September 2008].
[137] GeneDx was acquired by Bio-Reference Laboratories, Inc. for $17 million in 2006 (http://phx.corporate-ir.net/phoenix.zhtml?c=84759&p=irol-newsArticle_Print&ID=900168&highlight=).
[138] Chung W, "SACGHS Task Force on Gene Patents and Licensing Practices Interview with Wendy Chung, MD, PhD, pediatrician, geneticist and researcher at Columbia University. " 2008.
[139] Lehrer S, "Interview with Steve Lehrer, former CEO of DNA Sciences." 27 June 2008.
[140] Rienhoff HY, "Written comments of Hugh Y. Rienhoff, Jr., founder and former CEO of DNA Sciences, Inc. " 1 November 2008.

Because DNA Sciences had not yet developed the test when financial difficulties necessitated the sale of its assets to Genaissance in 2003, commercial testing was not offered until May 2004 with Genaissance's launch of FAMILION®. Thus, it is likely that there was a period of 18 months or so during which genetic testing for LQTS testing was limited mostly to academic labs, whose turnaround time can be a year or more.[141]

Dr. Milunsky at BU reported Clinical Data's more recent efforts to prevent his laboratory from offering genetic testing for LQTS.[142] According to PGxHealth, this was because he had begun to offer the LQTS test more widely, versus only conducting LQTS research.[143]

Genaissance's launch of FAMILION® testing for LQTS in May 2004[144] came nine years after the first patent application was filed.[145] We speculate the delay was likely due to a combination of factors: the bursting of the biotech bubble in 2000,[146] the relative complexity and technical difficulty of the test,[147] and perhaps exclusive IP (which may have created less external competitive pressure on the licensee to launch, although exclusivity also arguably increased investment up front, expediting product launch).

Genaissance (2004-2005) and Clinical Data subsidiary PGxHealth (2005-present) remained essentially the sole commercial providers from 2004-2008. Dr. Milunsky's nonprofit, university-based laboratory offered testing until 2006. From 2006-2008, Bio-Reference Laboratories acquired exclusive licenses from the University of Utah for 13 patents related to composition of matter and/or mutation detection in LQT1, LQT2, LQT3, LQT5, LQT6 and LQT7 (Appendix 6). Thus, the LQTS IP has begun to fragment, with two licensees of different patents covering different genes and mutations. We may be in the early stages of a mutual blocking situation. Those sending samples for testing cannot know in advance which mutations will be found, and yet neither testing service has rights to test for the full range of mutations.[148] As of early 2009, the three interested parties—BRLI, Clinical Data and the University of Utah—were discussing how to proceed.[149] It remains to be seen what impact this turn of events will have on LQTS genetic testing, particularly with respect to pricing and insurer coverage and the prospect of litigation, cross-licensing, or other negotiated legal agreements.

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[141] Moss AJ, "Interview with Arthur J. Moss, MD, research physician at the University of Rochester. " 28 August 2008.

[142] Butkus B. BU Genetics Center Stops Using Athena Dx Tests After Firm Tightens IP Restrictions. *Biotech Transfer Week* 20 August 2008.

[143] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.

[144] "Genaissance Pharmaceuticals Launches its Proprietary FAMILION(TM) Test for Genetic Mutations Associated With Sudden Cardiac Death, *PR Newswire,* 20 May 2004.

[145] US Patent No. 5,599,673 (4 February 1997).

[146] Rienhoff HY, "Interview with Hugh Y. Rienhoff, Jr., MD, founder and former CEO of DNA Sciences." 13 June 2008.

[147] Tester DJ, Cronk LB, Carr JL, Schulz V, Salisbury BA, Judson RS, Ackerman MJ. Allelic dropout in long QT syndrome genetic testing: a possible mechanism underlying false-negative results. *Heart Rhythm* 2006. 3, (7): 815-21.

[148] Ebersole T, Guthrie M, Goldstein JA. Patent Pools as a Solution to the Licensing Problems of Diagnostic Genetics. *IP and Technology Law Journal* 2005. 17, (1): 6-13.
Verbeure B, van Zimmeren E, Matthijs G, Van Overwalle G. Patent pools and diagnostic testing. *Trends Biotechnol* 2006. 24, (3): 115-20.

[149] Goldstein J, "Interview with Jorge Goldstein, JD, patent attorney at Sterne, Kessler, Goldstein & Fox, outside counsel to Bio-Reference Laboratories and GeneDx." 31 October 2008.

The price for complete sequence-based testing of five LQTS genes has remained $5400 since the 2004 Genaissance launch.[150] Payer coverage has increased significantly during these five years.[151] Clinical Data's Dr. Reed says that it is important to note that "…retail price does not directly correlate with revenue generated and cash received by a lab provider, including PGxHealth. Discounting to payers and inability to collect copayments/deductibles from patients leads to a notably lower value to the lab."[152]

In 2002, GeneDx offered partial testing for $2200. GeneDx claimed that it could detect 87% of the mutations present in the genes for LQT1, LQT2, LQT3, LQT5 and LQT6, and that the overall sensitivity of its test was 59% (see Appendix 8). Given what has been learned about LQTS mutations since—namely that most mutations are "private" and not recurring[153]—GeneDx's sensitivity was probably significantly lower than that estimate. By our calculations, GeneDx was screening about 33% of the five genes' approximately 13.4 kilobases of combined coding sequence.[154] PGxHealth charges — and has always charged — $900 to confirm a mutation in additional family members; the same service was reportedly $350 from GeneDx and $250 from Boston University in 2002.[155] The fact that GeneDx and BU both provided fee-for-service testing from ~2001-2002 before the patents were enforced suggests that a patent incentive was not required to develop a test.[156] Clinical Data's Dr. Reed argues that during this period there is no evidence that GeneDx or BU invested in physician education or expanded insurance coverage for their "inferior" tests.[157]

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[150] Reed C, Salisbury B, "Interview with Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 12 June 2008.

[151] Clinical Data Launches Genetic Test for Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC); Company to release its genetic databases for inherited cardiac conditions. *Business Wire* 10 November 2008.

[152] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.

[153] Moss AJ, Shimizu W, Wilde AA, Towbin JA, Zareba W, Robinson JL, Qi M, Vincent GM, Ackerman MJ, Kaufman ES, Hofman N, Seth R, Kamakura S, Miyamoto Y, Goldenberg I, Andrews ML, McNitt S. Clinical aspects of type-1 long-QT syndrome by location, coding type, and biophysical function of mutations involving the KCNQ1 gene. *Circulation* 2007. 115, (19): 2481-9.

Roden DM. Clinical practice. Long-QT syndrome. *N Engl J Med* 2008. 358, (2): 169-76.

[154] Abbott GW, Sesti F, Splawski I, Buck ME, Lehmann MH, Timothy KW, Keating MT, Goldstein SA. MiRP1 forms IKr potassium channels with HERG and is associated with cardiac arrhythmia. *Cell* 1999. 97, (2): 175-87.

Larsen LA, Andersen PS, Kanters J, Svendsen IH, Jacobsen JR, Vuust J, Wettrell G, Tranebjaerg L, Bathen J, Christiansen M. Screening for mutations and polymorphisms in the genes KCNH2 and KCNE2 encoding the cardiac HERG/MiRP1 ion channel: implications for acquired and congenital long Q-T syndrome. *Clin Chem* 2001. 47, (8): 1390-5.

Neyroud N, Richard P, Vignier N, Donger C, Denjoy I, Demay L, Shkolnikova M, Pesce R, Chevalier P, Hainque B, Coumel P, Schwartz K, Guicheney P. Genomic organization of the KCNQ1 K+ channel gene and identification of C-terminal mutations in the long-QT syndrome. *Circ Res* 1999. 84, (3): 290-7.

Salisbury B, "Email from Ben Salisbury regarding total coding sequence of five LQTS genes." 30 September 2008.

Splawski I, Shen J, Timothy KW, Vincent GM, Lehmann MH, Keating MT. Genomic structure of three long QT syndrome genes: KVLQT1, HERG, and KCNE1. *Genomics* 1998. 51, (1): 86-97.

Wang Q, Li Z, Shen J, Keating MT. Genomic organization of the human SCN5A gene encoding the cardiac sodium channel. *Genomics* 1996. 34, (1): 9-16.

[155] Bale S, "Interview with Sherri Bale, PhD, President and Clinical Director of GeneDx." 12 May 2008.

Milunsky A, "Email from Aubrey Milunsky, MB.B.Ch., D.Sc., F.R.C.P., F.A.C.M.G., D.C.H." 17 November 2008.

[156] Milunsky A, "Interview with Aubrey Milunsky, MB.B.Ch., D.Sc., F.R.C.P., F.A.C.M.G., D.C.H., Director of Boston University's Center for Human Genetics." 29 May 2008.

Bale S, "Interview with Sherri Bale, PhD, President and Clinical Director of GeneDx." 12 May 2008.

[157] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.

LQTS testing uptake has grown steadily since 2004. Genaissance reported FAMILION® revenues of $841,000 from the May 2004 launch through June 30, 2005.[158] Subsequently, the test has been a consistent source of growth for Clinical Data. FAMILION® sales grew from ~$2.7 million in fiscal 2007 to ~$4.5 million in fiscal 2008. In the first two quarters of fiscal 2009, FAMILION® generated an estimated $4.1 million.[159] Dr. Reed notes her company's "…significant investment in Clinical Data's sales and marketing efforts, infrastructure and payer contracting. Furthermore, this increase could not have happened without the intensive investment by PGxHealth and collaborations with academia and advocacy groups…"[160]

The fairness of the price of testing ($5400 or ~$74 per amplicon) is difficult to judge definitively given the exclusive license (and therefore no direct competitive comparison). It is worth noting that in 2002, if we assume one amplicon per exon, GeneDx charged ~ $129 per amplicon ($2200) for its partial primary screen of 17 exons selected from the five genes.[161] On the other hand, Myriad Genetics charges $38 per amplicon for its sequence-based testing of the BRCA1 and BRCA2 genes, for which it has exclusive rights (see BRCA case study) and a significantly higher test volume. In the course of preparing this case study, some patients, patient advocates and physicians complained to us about the high cost of the FAMILION® test and less than complete payer coverage, although incomplete coverage is not in Clinical Data's interest, either. Dr. Rienhoff and Mr. Lehrer, both formerly of DNA Sciences, emphasized the complexity of the test that eventually became FAMILION® and said the price should be judged accordingly.[162]

In his rebuttal to the Grodman/Chung testimony, Clinical Data CEO Drew Fromkin pointed out that Grodman's firm had recently secured an exclusive license on KCNJ2, the susceptibility gene for hereditary LQTS7, a rare form of the disease,[163] thereby suggesting that Grodman was being hypocritical. Grodman told us that his licensing of the gene was strategic. "We have exclusive licensing [on KCNJ2 and some others], but we have not exercised it. We were approached by [Clinical Data] to do the [LQT7] test with them and we said we'd be happy to share IP. Part of that is strategic, it's not a belief in the process. It's not what you have, it's what you do with it."[164] Indeed, in the face of a pre-existing exclusive license to a competitor, absence of a patent or a nonexclusive license would not solve the problem, and an exclusive license may be the only legal tool to compel cross-licensing or other negotiated agreement. Securing an exclusive license is therefore not necessarily hypocritical, if it is a strategy to induce negotiation in the face of existing exclusive rights.

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[158] Genaissance Pharmaceuticals, *10-Q*, 9 August 2005. See: http://www.sec.gov/Archives/edgar/data/1110009/000110465905037531/a05-13057_110q.htm, [accessed 24 September 2008].
Genaissance Pharmaceuticals, *10-K*, 15 March 2005. See: http://www.sec.gov/Archives/edgar/data/1110009/000104746905006537/a2152822z10-k.htm, [accessed 24 September 2008].

[159] See http://www.clda.com/uploads/CLDA_Q2-09%2011-3-08FINAL.pdf [accessed November 4, 2008].

[160] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.

[161] In patients and families known to have Jervell and Lange-Nielsen syndrome (JLNS), a rare autosomal recessive variant of LQTS that features profound congenital deafness, GeneDx screened for mutations in all exons of KCNQ1 and KCNE1, the two susceptibility genes known to cause JLNS (see Appendix 8).

[162] Lehrer S, "Interview with Steve Lehrer, former CEO of DNA Sciences." 27 June 2008.
Rienhoff HY, "Written comments of Hugh Y. Rienhoff, Jr., founder and former CEO of DNA Sciences, Inc. ." 1 November 2008.

[163] Fromkin AJ, "Letter to the Honorable Howard L. Berman from Clinical Data CEO Andrew J. Fromkin." 1 April 2008.

[164] Grodman M, "Interview with Marc Grodman, MD, CEO of Bio-Reference Laboratories, Inc." 21 August 2008.

Dr. Reed regards this as "…an incomplete statement and somewhat self-serving. In fact, we approached Dr. Grodman to in-license his 'strategic' IP to run the test for this single gene ourselves, not with [BRLI]. Dr. Grodman would agree only if we cross-licensed the whole of our LQTS IP so [BRLI] could commercialize a directly competitive LQTS test. This was not an appealing proposition to us…[This is] a business dispute where one party simply wants rights to a market the other company has built diligently through entrepreneurial investment of time and resources."[165]

This dispute points up the market constraints of the current situation: given Clinical Data's unwillingness to sublicense to U.S. diagnostic labs, any laboratory interested in non-research-based testing for cardiac channelopathy genes must either restrict itself to genes that have not been patented and licensed exclusively[166] or try to gain leverage by amassing intellectual property on genes outside of Clinical Data's patent estate, but that account for a minority of LQTS.[167] BRLI's recent licensing of multiple LQTS gene patents, including patents for one of the three major genes (SCN5A, mutations in which can predispose to LQT3), will provide a real-time measure of the extent of this leverage.

This case is thus a stark illustration of two features of how exclusive licensing of patent rights can influence diagnostic testing: the potential for mutual blocking situations, and the "penumbra effect" (discussed in the hearing loss case study also) in which exclusive rights to one or a few common genetic variants can in effect drive business for all genetic testing—even for variations that have been discovered but not patented or that have never been discovered before—to the rights holder. That is, rights on one set of mutations can be leveraged to drive business for other mutations not covered by patent claims. This has been the practice until very recently for LQTS testing, and the situation is now unstable because BRLI has obtained countervailing exclusive rights. This cannot be resolved by those seeking genetic test results because they cannot know in advance which mutations will be found.

In at least one instance, Clinical Data has sub-licensed its LQTS IP. In October 2007 the company announced that its PGxHealth subsidiary had entered into a non-exclusive sub-license agreement with the Victorian Clinical Genetics Services, a not-for-profit subsidiary of the Murdoch Children's Research Institute, for the provision of genetic testing for familial LQTS in Australia and New Zealand. [168] According to Dr. Reed, this shows Clinical Data's "…willingness to cede markets to others where we are not equipped to provide services."[169] This has minimal relevance, however, to the U.S. market, since it affects testing in a foreign jurisdiction covered by patent law in that jurisdiction.

PGxHealth has also availed itself of others' nonexclusive licenses. In May 2008 the company launched genetic testing for hypertrophic cardiomyopathy (HCM), which has been licensed by Harvard Medical School to multiple diagnostic providers. [170] Drs. Grodman and Chung contend that HCM is a better model for IP related to genetic testing because it fosters a system of competition and checks and balances.[171] Dr. Ackerman, on the other hand, pointed out that the test continued to lack both Medicare and Medicaid

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[165] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.
[166] Towbin JA, "Interview with Jeffrey A. Towbin, MD, chief of pediatric cardiology, Baylor College of Medicine." 29 September 2008.
[167] Grodman M, "Interview with Marc Grodman, MD, CEO of Bio-Reference Laboratories, Inc." 21 August 2008.
[168] See http://www.clda.com/uploads/LQTaustralia-draft%20press%20release10107FINAL.pdf [accessed October 6, 2008].
[169] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.
[170] See http://www.4hcm.org/WCMS/index.php?id=81,0,0,1,0,0 (accessed October 7, 2008].
[171] Chung W, "Interview with Wendy Chung, MD, PhD, pediatrician, geneticist and researcher at Columbia University. " 7 May 2008.
Grodman M, "Interview with Marc Grodman, MD, CEO of Bio-Reference Laboratories, Inc." 21 August 2008.

coverage in 2008 in most jurisdictions.[172] Dr. Heidi Rehm, Associate Molecular Geneticist at the Harvard Medical School-Partners Healthcare Center for Genetics and Genomics, confirmed this assertion (as did another provider off the record). She said that while Harvard launched the commercial HCM test in 2004, Harvard is proscribed from offering direct third-party billing.[173] The second provider, Correlagen Diagnostics, did not launch until July 2007.[174] Dr. Reed says that by offering HCM testing, Clinical Data is "…[building] on the investment justified by our LQTS test."[175]

Communication and Marketing

In 2004-2005, Dr. Ackerman wrote at least four articles in professional journals that noted the availability of commercial genetic testing for LQTS; his financial interest was disclosed in each case.[176] A 2005 article partially funded by Genaissance concluded that genetic testing for familial LQTS was cost-effective.[177]

Clinical Data has undertaken efforts to market its services to physicians. In 2007, the company established a sales force to promote FAMILION® testing. This sales force makes calls on pediatric electrophysiologists and cardiologists and, increasingly, their adult equivalents. Based on the initial positive results of this effort, the company expanded the size of the sales force in 2008. Clinical Data has also recently added resources to focus on the provider and payer markets[178] and has a dedicated customer service group.[179]

PGxHealth also markets FAMILION® testing via patient advocacy groups and professional organizations that offer patient support and promote research and education. These include the Sudden Arrhythmia Death Syndromes Foundation, or SADS, and "The National Society of Clinical Geneticists."[180]

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[172] Ackerman MJ, "Email from Michael J. Ackerman, MD, PhD; first response to case study." 27 October 2008.
[173] Rehm H, "Interview with Heidi Rehm, PhD, Associate Molecular Geneticist at the Harvard Medical School-Partners Healthcare Center for Genetics and Genomics." 17 November 2008.
[174] See http://www.correlagen.com/about/downloads/Correlagen_CAP_NewsRelease_030507.pdf [accessed November 19, 2008].
[175] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.
[176] Ackerman MJ. Cardiac channelopathies: it's in the genes. *Nat Med* 2004. 10, (5): 463-4.
Ackerman MJ. Genetic testing for risk stratification in hypertrophic cardiomyopathy and long QT syndrome: fact or fiction? *Curr Opin Cardiol* 2005. 20, (3): 175-81.
Ackerman MJ. Genotype-phenotype relationships in congenital long QT syndrome. *J Electrocardiol* 2005. 38, (4 Suppl): 64-8.
Tester DJ, Ackerman MJ. Genetic testing for cardiac channelopathies: ten questions regarding clinical considerations for heart rhythm allied professionals. *Heart Rhythm* 2005. 2, (6): 675-7.
[177] Phillips KA, Ackerman MJ, Sakowski J, Berul CI. Cost-effectiveness analysis of genetic testing for familial long QT syndrome in symptomatic index cases. *Heart Rhythm* 2005. 2, (12): 1294-300.
[178] Clinical Data, *10-K*, 16 June 2008. See: http://www.sec.gov/Archives/edgar/data/716646/000095013508004390/b70423cde10vk.htm, [accessed 17 September 2008].
[179] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.
[180] To our knowledge, there is no "National Society of Clinical Geneticists." It's possible that this could be referring to the National Society of Genetic Counselors or the American College of Medical Genetics. Clinical Data, *10-K*, 16 June 2008. See: http://www.sec.gov/Archives/edgar/data/716646/000095013508004390/b70423cde10vk.htm, [accessed 17 September 2008].

Examining Test Quality

In five cases, Dr. Chung, a paid consultant to BRLI and former consultant to PGxHealth, said she split samples and tried to confirm PGxHealth's results in her own laboratory. In two cases, she said there were discrepancies. In one case, there was a sequencing problem; in the other there was an informatics issue.[181]

In her 2007 statement to Congress and in interviews with us and the SACGHS Task Force on Gene Patents and Licensing Practices, Dr. Chung called PGxHealth's protocol for dealing with variants of unknown significance and other ambiguous results inadequate, especially given that five to ten percent of all results will be difficult to interpret.[182] "…it puts clinicians in a very awkward position [if] the patient has spent $5400 on this test…and [they] don't know how to interpret it…"[183] Dr. Chung has expressed particular concern about the interpretation of so-called "Class II variants," which PGxHealth calls "Variants of Uncertain Significance" and "Possible Deleterious Mutations." These include some missense variants, in-frame deletions/insertions, and predicted splice-site variants (see Appendix 1). Dr. Chung expressed fear that many cardiologists will interpret these as definitive disease-causing variants.[184] Dr. Chung also contended that there has not been robust vetting of these variants because the scientific community has not had access to PGxHealth's database.[185]

Dr. Chung believes that having only a single commercial provider denies clinicians the opportunity to solicit a second opinion. "…when you don't have the ability to get a second opinion, you have no idea where your errors or pitfalls are and [there is] no independent way for clinicians to be able to validate whatever they're seeing or, on the other hand, to be able to come up with [what] at the end is a correct diagnosis."[186] Dr. Milunsky, who is a past and would-be provider of commercial testing, shares this view.[187] Their assumption is that multiple providers would reach consensus interpretations, and alternative providers would be accompanied by more public availability of data and more open discussion of its interpretation.

Dr. Chung also criticizes PGxHealth for the incompleteness of FAMILION® LQTS testing. She takes issue with Clinical Data's contention that the addition of more genes to the FAMILION® panel will not add much value. She says that this cannot be known with certainty.[188]

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[181] Chung W, "Interview with Wendy Chung, MD, PhD, pediatrician, geneticist and researcher at Columbia University " 7 May 2008.

[182] "Stifling or stimulating: the role of gene patents in research and genetic testing.," Subcommittee on Courts, the Internet, and Intellectual Property of the Committee on the Judiciary, One Hundred Tenth Congress; First Session ed. Washington, DC: 31 October 2007.
Chung W, "SACGHS Task Force on Gene Patents and Licensing Practices Interview with Wendy Chung, MD, PhD, pediatrician, geneticist and researcher at Columbia University. " 2008.
Chung W, "Interview with Wendy Chung, MD, PhD, pediatrician, geneticist and researcher at Columbia University." 7 May 2008.

[183] Chung W, "SACGHS Task Force on Gene Patents and Licensing Practices Interview with Wendy Chung, MD, PhD, pediatrician, geneticist and researcher at Columbia University." 2008.

[184] Chung W, "Interview with Wendy Chung, MD, PhD, pediatrician, geneticist and researcher at Columbia University. " 7 May 2008.

[185] Chung W, "SACGHS Task Force on Gene Patents and Licensing Practices Interview with Wendy Chung, MD, PhD, pediatrician, geneticist and researcher at Columbia University. " 2008.

[186] Ibid.

[187] Milunsky A, "Interview with Aubrey Milunsky, MB.B.Ch., D.Sc., F.R.C.P., F.A.C.M.G., D.C.H., Director of Boston University's Center for Human Genetics." 29 May 2008.

[188] Chung W, "Interview with Wendy Chung, MD, PhD, pediatrician, geneticist and researcher at Columbia University." 7 May 2008.

In her 2007 testimony, Dr. Chung stated that PGxHealth is not able to reliably offer genetic testing on paraffin-embedded tissue samples, which is often the only tissue sample available from deceased persons.[189] She told us about a case in which a patient was receiving a heart transplant in which the donor heart had LQTS; she described an "ordeal" in order to get PGxHealth to extract DNA from frozen tissue.[190]

By its own admission, PGxHealth's results have not been perfect. In bi-annual proficiency testing, "there has been an occasional conflict,"[191] although Dr. Reed emphasizes that in every such case, "we have been right."[192]

Responses to Quality Concerns

Dr. Reed takes strong exception to Dr. Chung's claims: "…Dr. Chung [is] a paid consultant to a competitor company that desires access to the patents under discussion."

"…These variants are inherently ambiguous and 'problematic.' This has nothing to do with 'protocols,' rather it is a matter of biomedical science where even experts may disagree. Just because we don't interpret every mutation the way Dr. Chung might, does not make it wrong. We acknowledge that this is a difficult area. Thus, Dr. Chung's concerns are no surprise and are indicative of the state of the art." Dr. Reed also notes that as a former member of a FAMILION® Advisory Board, Dr. Chung has herself engaged in discussions with the company as to the difficulty in interpreting these variants. Dr. Reed also points out PGxHealth uses a reference population of >1300 controls to evaluate all variants (Appendix 1). This reference population, says Dr. Reed, plays a critical role in ensuring that variants are appropriately classified. Finally, with respect to including additional genes, Dr. Reed suggests that the lack of knowledge about these loci makes it "…premature to include these genes in a clinical test…[A]dding them could create more confusion for cardiologists and may decrease the clinical specificity of testing." Furthermore, she notes that Dr. Moss, as quoted in this report (see below), does not think it worthwhile to add genes with non-cardiac syndromic manifestations that can be fairly easily diagnosed by physical exam.[193]

For proficiency testing of the FAMILION® assay, Dr. Ackerman sends blinded, de-identified samples to PGxHealth every six months. According to him, since 2004 there has been only a single discordant result, which was attributable to his lab missing a non-synonymous variant that PGxHealth detected.[194] Dr. Reed notes that these results are available via Clinical Data's periodically audited proficiency testing records.[195]

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[189] "Stifling or stimulating: the role of gene patents in research and genetic testing.," Subcommittee on Courts, the Internet, and Intellectual Property of the Committee on the Judiciary, One Hundred Tenth Congress; First Session ed. Washington, DC: 31 October 2007.
[190] Ibid.
[191] Reed C, Salisbury B, "Interview with Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 12 June 2008.
[192] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.
[193] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.
[194] Ackerman MJ, "Email from Michael J. Ackerman, MD, PhD." 2008.
[195] Reed C, Salisbury B, "Interview with Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 12 June 2008.
Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.

Again, one difficulty in evaluating the quality and proficiency FAMILION® testing is the inherent conflict of interest of a number of the critical stakeholders. Dr. Ackerman, for example, is a paid consultant to Clinical Data. Dr. Chung is a paid consultant to Clinical Data competitor BRLI and former consultant to PGxHealth. Mr. Fromkin and Dr. Grodman are at the helms of the two competing companies, respectively.

Five current and former LQTS genetic researchers/clinicians we spoke to do not have any current and direct financial conflicts of interest related to genetic testing for variants in the five major genes predisposing to congenital LQTS. We asked them specifically to disclose any financial arrangements linked to LQTS patents and licensees. These experts offered their perspectives on the perceived quality of and/or rationale behind FAMILION® testing for LQTS mutations:

- Dr. Silvia Priori: "[M]y interpretation of the situation [is] that the company [PGxHealth] is definitely better than any research laboratory. It has to be better than any research laboratory in handling the samples and quickly performing the sequence analysis. Obviously the difference comes in the interpretation of the mutation…a research laboratory has a lot of time dedicated to studying the individual mutation. So if I have a patient with a new mutation I am also in the position of being the clinician taking care of that patient…I have told [PGxHealth] that I feel quite uncomfortable with the fact that they have been working with very limited input from the scientific community. They seem to be a company consulting with [only] one physician…it is clear that [he] is skilled and competent but it is still only one [physician who] is being consulted."[196],[197]

- Dr. Arthur J. Moss[198]: "[PGxHealth has] more expensive equipment. They do a pretty good job in terms of turnaround [time], but Bio-Reference Laboratories would do the same thing…we have seen a moderate amount of inconsistency and errors. We have had several occasions where PGxHealth was wrong.[199] One occurred—off the top of my head—in a test that was run by Jeff Towbin. The physician sent a blood sample [to him and to] FAMILION® and the results were different. We tracked this down and repeated the test here. We got the same result as Dr. Towbin and reported this to FAMILION® and to the patient. I don't think [the error rate] is large."[200]

  "Complete [genetic] testing of other genes is not really necessary. LQT7 through LQT11 are based on one or two families each, or else based on neurological symptoms where the diagnosis is not very difficult. The Andersen-Tawil syndrome diagnosis is easy to make because of morphological changes in the jaw and face…Timothy syndrome is rare and those people [with the syndrome] have striking skeletal defects. Genetic testing is not critical [in those cases]..."[201]

[196] Dr. Reed notes that Clinical Data held a 19-member advisory board meeting in January 2008 and held a "similarly large" adult electrophysiologist advisory board meeting in the fall of 2008.
[197] Priori S, "Interview with Silvia G. Priori, MD, PhD, LQTS researcher and clinician in Pavia, Italy." 29 May 2008.
[198] Dr. Moss consulted with Genaissance when that firm held the license to LQTS IP. According to Dr. Moss, Dr. Grodman, CEO of BRLI, wanted to establish a consulting relationship; Dr. Moss declined and instead asked that Dr. Grodman direct funds to the University of Rochester, which it did.
[199] Dr. Reed says that she knows of only a single instance. "Again, without specific feedback from our customers, we cannot make test improvements if needed."
[200] Moss AJ, "Interview with Arthur J. Moss, MD, research physician at the University of Rochester " 28 August 2008.
[201] Ibid.

- Dr. Charles Antzelevitch: "We repeated genetic analysis of the same genes screened by FAMILION® in only three patients using CLIA-approved methods and found an error in two of the three; the two were members of the same family. In this case FAMILION® missed detection of a G insertion in exon 12 of KCNH2, causing a frameshift and leading to a stop codon."

  "[M]y personal view is that FAMILION® is filling an important need and is doing a decent job of it, but that it is not in the best interest of science or medicine for any company to a have an absolute monopoly on genetic screening of LQTS. A little friendly competition may improve quality control and reduce prices, thus making it more affordable for all. This would facilitate the acquisition of additional data on genotype-phenotype correlation, thus leading to improved diagnosis, prognosis and a better approach to therapy of LQTS."[202]

- Dr. Jeffrey Towbin: "I think it would be valuable for PGxHealth to publish its data...[But to] make a genotype-phenotype correlation you have to have the [phenotypic information]. FAMILION® can't be expected to have that. I think that while their datasets would be extraordinarily useful if they had the clinical information necessary, I think that's a pipedream the way it's set up now."[203]

  "I have no [real] way of knowing FAMILION's quality. When you send a sample and you get a result you have no way of knowing unless you run parallel samples. Yes there have been discrepancies on occasion that we've seen. But I don't know who's right; I [might] argue that our labs are wrong—we all make mistakes. We don't get the right answer sometimes….On balance, I would say the approach they're taking is reasonable….They've been doing it long enough…. I think their system and their thought process make sense. They've done a good job and for some patients have done a real service. The research labs were never going to do that. I think [commercial testing is] a useful resource and I think [PGxHealth is] doing it pretty well….If you want a CLIA-approved test for LQTS looking at the standard five genes, it's a very good option….I think Art [Moss] is correct that there have been errors, but no one will meet the perfection standard. [PGxHealth is] good or very good….I think they provide a useful service. Could it be better? Yes. [But] I don't look at them as the bad guy. They're in business, they have standards for quality and turnaround time. That is the state of the art at the moment…"

  "[LQTS] is not going to get easier to understand. I don't think we should expect clinicians to understand exactly the meaning of what we're telling people [about their results]…. It's very hard in the early 21st century for the average clinician to know enough about genetics to really utilize a [genetic] test. But it's the sexy thing to do."[204]

- Dr. Hugh Rienhoff: "[Dr. Towbin's comments are] absolutely true and one of the reasons that the inventor, Dr. Keating, was so willing to 'unload' the responsibility of LQTS testing to DNA Sciences. He did not have a CLIA lab, there were no rigorous [standard operating procedures] for testing, no dedicated personnel, [no dedicated] space or devices for the work, and no way to charge for the work. It was regarded as a burden to his lab because it used up valuable technician

[202] Antzelevitch C. Written comments from Charles Antzelevitch, Ph.D., F.A.C.C., F.A.H.A., Executive Director and Director of Research of the Masonic Medical Research Laboratory (MMRL). 18 November 2008.
[203] Towbin JA, "Interview with Jeffrey A. Towbin, MD, chief of pediatric cardiology, Baylor College of Medicine." 29 September 2008.
[204] Ibid.

> [and] student time and resources. This is a very common set of circumstances in an academic lab that has made a discovery and has a unique set of reagents or capabilities."[205]

Dr. Rienhoff, a clinical geneticist and founder of DNA Sciences, elaborated further on the formidable challenge in interpreting the meaning of genetic variants in diseases such as LQTS:

> "This is a problem that is widespread and not specific to the particular parties at hand. New missense mutations will always pose a problem for interpretation. It is a challenge to show that any new variant in a gene has functional consequences [for] either mRNA stability or protein structure and function. It is unrealistic to think anyone could easily resolve the un-interpretability of these findings. Indeed, it simply underscores the fact that we are still early in our description of the human genome and the variants that can be found in it."[206]

In addition to the difficulty of finding experts who do not have a current or past conflict of interest, another impediment to making objective assessments regarding quality is the present inadequacy of CLIA oversight of genetic testing laboratories.[207] The Centers for Medicare & Medicaid Services (CMS) have yet to institute specific requirements for molecular or biochemical genetic testing laboratories. Thus, while CLIA requires laboratories to have quality assurance programs in place, most genetic testing laboratories are not required by CLIA to perform proficiency testing with specific benchmarks.[208] Moreover, petitions to CMS to issue updated standards for genetic testing laboratories, including standards for proficiency testing, have thus far gone unheeded. [209] To its credit, PGxHealth has instituted its own proficiency testing program in conjunction with Dr. Ackerman.[210] When such proficiency testing is in place, however, there is no CLIA guidance about whether such testing under auspices of a paid consultant is an acceptable practice. Clinical Data has opposed more stringent regulation of laboratory-developed tests such as FAMILION®.[211]

Allelic dropout is another issue that pertains to test quality. Allelic dropout is a technical problem in DNA amplification,[212] which likely contributed to the relatively low yield of LQTS mutations in the pre-Genaissance/PGxHealth era. A year after commercial launch, at a national meeting the company presented its experiences with discovery and avoidance of the allelic dropout problems present in assays used by research laboratories.[213] In late 2005, scientists from the Mayo Clinic and what was then still

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[205] Rienhoff HY, "Written comments of Hugh Y. Rienhoff, Jr., founder and former CEO of DNA Sciences, Inc. " 1 November 2008.
[206] Ibid.
[207] Hudson KL. Genetic testing oversight. *Science* 2006. 313, (5795): 1853.
Report of the Secretary's Advisory Committee on Genetics H, and Society, U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services. (Bethesda, MD, 2008).
[208] Report of the Secretary's Advisory Committee on Genetics H, and Society, U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services. (Bethesda, MD, 2008).
[209] See http://www.geneticalliance.org/policy.clia.letter (last accessed on 7 October 2008)
[210] Reed C, "Email from Carol Reed, MD." 2008.
Ackerman MJ, "Email from Michael J. Ackerman, MD, PhD." 2008.
[211] Clinical Data, Inc. Reaffirms Support for Current Regulation of Laboratory-Developed Tests. *Business Wire* 16 December 2008.
[212] Johnson PC, Haydon DT. Maximum-likelihood estimation of allelic dropout and false allele error rates from microsatellite genotypes in the absence of reference data. *Genetics* 2007. 175, (2): 827-42.
[213] Tester DJ, Will ML, Salisbury BA, Carr JL, Schulz V, Judson RS, Ackerman MJ. Allelic drop-out in long QT syndrome genetic testing: a possible mechanism underlying false negative results. *Abstract presented at Heart Rhythm Society Meeting* May 2005.

Genaissance submitted a paper on the allelic dropout phenomenon to a peer-reviewed journal, which appeared in 2006.[214] The recognition of allelic dropout ultimately improved the sensitivity of the test.

As for sample type, PGxHealth Chief Medical Officer Dr. Carol Reed told us via email that, "Our laboratory does and has always accepted paraffin-embedded tissue for testing, so long as it meets quality specifications."[215] Obtaining DNA from paraffin-embedded tissue can be challenging, however, because the DNA tends to be degraded. According to a recent paper from Dr. Ackerman's group, for example, DNA from such tissue should be considered "error prone and unreliable in comprehensive surveillance of sudden unexplained death-associated genes."[216] Some relatively successful protocols appear to exist, however, particularly for subsequent amplification of shorter DNA fragments,[217] although this may not be practical for all exons in LQTS susceptibility genes.[218] Nevertheless, as Dr. Ackerman's group has recommended, given the shortcomings associated with DNA extraction from paraffin-embedded tissue, standard autopsy procedures for sudden unexplained death should include archiving preserved blood or frozen tissue to facilitate postmortem genetic testing.[219]

Adoption by Clinical Providers

We suspect that relatively few LQTS genetic tests were performed before 2004. GeneDx President Sherri Bale told us that over the course of 2001-2002, her firm ran "about 20" tests.[220] In 2002-2003, Dr. Milunsky's lab did 42.[221] After its May 2004 launch, clinical embrace of FAMILION® testing started somewhat slowly but has grown substantially in the last five years. Extrapolating from Genaissance and Clinical Data filings with the Securities and Exchange Commission, FAMILION® LQTS test demand will have increased nearly ten-fold from its launch in 2004 through Clinical Data's fiscal 2009 (ending 31 March, 2009). Genaissance reported FAMILION® revenues of $841,000 from the May 2004 launch through June 30, 2005.[222] If we assume, as Clinical Data has during investor presentations,[223] that

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[214] Tester DJ, Cronk LB, Carr JL, Schulz V, Salisbury BA, Judson RS, Ackerman MJ. Allelic dropout in long QT syndrome genetic testing: a possible mechanism underlying false-negative results. *Heart Rhythm* 2006. 3, (7): 815-21.

[215] Reed C, "Email from Carol Reed, MD." 2008.

[216] Carturan E, Tester DJ, Brost BC, Basso C, Thiene G, Ackerman MJ. Postmortem genetic testing for conventional autopsy-negative sudden unexplained death: an evaluation of different DNA extraction protocols and the feasibility of mutational analysis from archival paraffin-embedded heart tissue. *Am J Clin Pathol* 2008. 129, (3): 391-7.

[217] Dedhia P, Tarale S, Dhongde G, Khadapkar R, Das B. Evaluation of DNA extraction methods and real time PCR optimization on formalin-fixed paraffin-embedded tissues. *Asian Pac J Cancer Prev* 2007. 8, (1): 55-9.
Gillio-Tos A, De Marco L, Fiano V, Garcia-Bragado F, Dikshit R, Boffetta P, Merletti F. Efficient DNA extraction from 25-year-old paraffin-embedded tissues: study of 365 samples. *Pathology* 2007. 39, (3): 345-8.
Santos MC, Saito CP, Line SR. Extraction of genomic DNA from paraffin-embedded tissue sections of human fetuses fixed and stored in formalin for long periods. *Pathol Res Pract* 2008. 204, (9): 633-6.
Santos S, Sa D, Bastos E, Guedes-Pinto H, Gut I, Gartner F, Chaves R. An efficient protocol for genomic DNA extraction from formalin-fixed paraffin-embedded tissues. *Res Vet Sci* 2008.

[218] Reed C, Salisbury B, "Written comments of Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 14 November 2008.

[219] Carturan E, Tester DJ, Brost BC, Basso C, Thiene G, Ackerman MJ. Postmortem genetic testing for conventional autopsy-negative sudden unexplained death: an evaluation of different DNA extraction protocols and the feasibility of mutational analysis from archival paraffin-embedded heart tissue. *Am J Clin Pathol* 2008. 129, (3): 391-7.

[220] Bale S, "Email from Sherri Bale regarding GeneDx's LQTS prenatal diagnosis policy in 2002." 2008.

[221] Milunsky A, "Email from Aubrey Milunsky, MB.B.Ch., D.Sc., F.R.C.P., F.A.C.M.G., D.C.H." 17 November 2008.

[222] Genaissance Pharmaceuticals, *10-Q*, 9 August 2005. See: http://www.sec.gov/Archives/edgar/data/1110009/000110465905037531/a05-13057_110q.htm, [accessed 24 September 2008].

approximately 85.7% of the revenue derived from FAMILION LQTS tests are from initial $5400 tests and the remainder is from $900 confirmatory tests of other family members, then approximately 133 initial and 133 confirmatory tests were run in the first 14 months of FAMILION® availability. More recently, FAMILION® sales grew from ~$2.7 million in fiscal 2007 to ~$4.5 million in fiscal 2008. In the first two quarters of fiscal 2009, FAMILION generated an estimated $4.1 million. [224] Thus, as of early 2009, ignoring what we suspect are modest revenues from non-LQTS FAMILION® testing and no emergence of LQTS testing from any other commercial entity in the near term, our admittedly crude estimate is that the company is on pace to perform 1270 initial tests and approximately the same number of confirmatory tests through 31 March 2009.

In 2006 clinical guidelines published by the American College of Cardiology, the American Heart Association and the European Society of Cardiology,[225] genetic testing for LQTS was deemed "very important" for identifying all affected members within a family. In patients affected by LQTS, genetic analysis was considered "useful for risk stratification and for making therapeutic decisions." In an interview with us, Dr. Towbin thought the 2006 guidelines were somewhat inadequate given how new and poorly understood genetic testing was when those guidelines were written; he noted that the Heart Rhythm Society is preparing new guidelines.[226]

There is ample room for further growth in genetic testing for LQTS. In a January 2007 presentation to investors made by Clinical Data,[227] the company estimated there to be a $94.5-million market for initial LQTS genetic screening ($81 million) and subsequent mutation screening within families ($13.5 million).

Consumer Utilization

We can only speculate about whether the patent enforcement actions of the early 2000s adversely affected consumer access to commercial genetic testing for LQTS. The overall number of LQTS patients affected by the patent enforcement actions was probably small: According to Dr. Towbin, there was minimal awareness of genetic testing and poor understanding of LQTS genetics at the time. "In 2002, nobody took DNA Sciences or anyone else seriously as purveyors of a LQTS diagnostic test, in part because they

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Genaissance Pharmaceuticals, *10-K*, 15 March 2005. See: http://www.sec.gov/Archives/edgar/data/1110009/000104746905006537/a2152822z10-k.htm, [accessed 24 September 2008].

[223] Clinical Data, *EX-99.1 of 8-K*, 18 January 2007. See: http://www.sec.gov/Archives/edgar/data/716646/000095013507000224/b63771cdexv99w1.htm, [accessed 6 June 2008].

[224] See http://www.clda.com/uploads/CLDA_Q2-09%2011-3-08FINAL.pdf [accessed November 4, 2008].

[225] Zipes DP, Camm AJ, Borggrefe M, Buxton AE, Chaitman B, Fromer M, Gregoratos G, Klein G, Moss AJ, Myerburg RJ, Priori SG, Quinones MA, Roden DM, Silka MJ, Tracy C, Smith SC, Jr., Jacobs AK, Adams CD, Antman EM, Anderson JL, Hunt SA, Halperin JL, Nishimura R, Ornato JP, Page RL, Riegel B, Blanc JJ, Budaj A, Dean V, Deckers JW, Despres C, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo JL, Zamorano JL. ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation* 2006. 114, (10): e385-484.

[226] Towbin JA, "Interview with Jeffrey A. Towbin, MD, chief of pediatric cardiology, Baylor College of Medicine." 29 September 2008.

[227] Clinical Data, *EX-99.1 of 8-K*, 18 January 2007. See: http://www.sec.gov/Archives/edgar/data/716646/000095013507000224/b63771cdexv99w1.htm, [accessed 6 June 2008].

themselves didn't: They weren't advertising, they didn't have buy-in, and [they] were talking about testing for *specific* mutations, which didn't make sense."[228]

PGxHealth does not offer prenatal diagnosis, thereby rendering it commercially unavailable in the U.S. When asked about the subject, PGxHealth's Drs. Reed and Salisbury cited "technical concerns" and "very little demand" given the treatable nature of LQTS. They said that while the company does not have an official policy regarding prenatal diagnosis, Drs. Reed and Salisbury's advice to the company would be "not to enforce the patent" for such uses.[229] GeneDx did offer prenatal testing for LQTS in 2002; however, it was offered only in cases where another family member was known to carry a mutation (Appendix 8).[230] In separate interviews, Drs. Moss and Antzelevitch (Masonic Medical Research Laboratory) cautioned us not to overstate the importance of prenatal diagnosis.[231] Both researchers said that prenatal diagnosis would be of limited usefulness given the highly variable phenotype: an infant may harbor a mutation and go on to live a long and healthy life.[232] Dr. Milunsky views the situation differently. He told us that: (1) some families are indeed interested in prenatal diagnosis; (2) distinguishing fetal from maternal DNA is a trivial technical issue that all prenatal diagnostic laboratories must contend with; (3) Clinical Data will not perform prenatal diagnosis; and (4) company representatives made it clear that Clinical Data will not permit his (Milunsky's) laboratory to perform it under any circumstances.[233] Dr. Bale (like Dr. Milunsky, a former and would-be competitor to PGxHealth) agrees with Dr. Milunsky that families are interested in prenatal diagnosis and that distinguishing maternal from fetal DNA is not a major technical barrier.[234]

Consumers pay different prices for FAMILION® testing based on what fraction of the $5400 cost of the test is covered by insurance. Research labs charge nothing; however, it may take many months or even years before patients receive their results from research labs.[235] In some cases, patients may never receive their results and the quality may be sub-standard.[236] Indeed, non-CLIA-certified laboratories are restricted by law from providing results of testing to the patient or referring physician.[237]

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[228] Towbin JA, "Interview with Jeffrey A. Towbin, MD, chief of pediatric cardiology, Baylor College of Medicine." 29 September 2008.
[229] Reed C, Salisbury B, "Interview with Carol Reed, M.D. and Benjamin Salisbury, Ph.D. of Clinical Data subsidiary PGxHealth." 12 June 2008.
[230] Bale S, "Email from Sherri Bale regarding GeneDx's LQTS prenatal diagnosis policy in 2002." 2008.
[231] Antzelevitch C. Interview with Charles Antzelevitch, Ph.D., F.A.C.C., F.A.H.A., Executive Director and Director of Research of the Masonic Medical Research Laboratory (MMRL) 2 July 2008. Moss AJ, "Interview with Arthur J. Moss, MD, research physician at the University of Rochester." 28 August 2008.
[232] Moss AJ, "Interview with Arthur J. Moss, MD, research physician at the University of Rochester." 28 August 2008.
Antzelevitch C. Interview with Charles Antzelevitch, Ph.D., F.A.C.C., F.A.H.A., Executive Director and Director of Research of the Masonic Medical Research Laboratory (MMRL) 2 July 2008.
[233] Milunsky A, "Interview with Aubrey Milunsky, MB.B.Ch., D.Sc., F.R.C.P., F.A.C.M.G., D.C.H., Director of Boston University's Center for Human Genetics." 29 May 2008.
Milunsky A, "Interview with Aubrey Milunsky, MB.B.Ch., D.Sc., F.R.C.P., F.A.C.M.G., D.C.H., Director of Boston University's Center for Human Genetics: Review of case study." 2008.
[234] Bale S, "Written comments of Sherri Bale, PhD, President and co-founder of GeneDx." 12 November 2008.
[235] Priori S, "Interview with Silvia G. Priori, MD, PhD, LQTS researcher and clinician in Pavia, Italy." 29 May 2008.
Moss AJ, "Interview with Arthur J. Moss, MD, research physician at the University of Rochester." 28 August 2008.
[236] Towbin JA, "Interview with Jeffrey A. Towbin, MD, chief of pediatric cardiology, Baylor College of Medicine." 29 September 2008.
[237] Medicare and Medicaid programs; Medicare, Medicaid, and Clinical Laboratories Improvement Act (CLIA) patient confidentiality rules--PHS and HCFA. Final rule. *Fed Regist* 1988. 53, (232): 48645-8.
Schwartz MK. Genetic testing and the clinical laboratory improvement amendments of 1988: present and future. *Clin Chem* 1999. 45, (5): 739-45.

Our own informal collation of consumer views of LQTS testing culled from the online C.A.R.E. Cardiac Arrhythmias Support Community[238] suggests that LQTS patients want information about their condition, including genetic information. Many are understandably frightened by the prospect of sudden cardiac death and are concerned about potential triggers for such events. As far as we can tell, out-of-pocket cost is the most significant deterrent to consumer utilization, although several patients complained about the turnaround time and the time necessary to negotiate insurance coverage. A summary of our very preliminary findings from the C.A.R.E. forum appears below. It is important to note the caveats: all data are self-reported and the sample size is minimal. This is a convenience sample of motivated forum participants, not a representative sample of the general population. We take up the payment issue in the next section on *Adoption by third-party payers.*

C.A.R.E. Cardiac Arrhythmias Support Community LQTS Genetic Testing Data

1. When was your test performed?

Year:	2000	2006	2007	2008	Unknown
Number:	1	1	8	3	5

2. Who performed the test?

Lab:	PGxHealth	Research Lab	Ex-US (PGxHealth)	Unknown
Number:	12	1	2 (Canada)	3

3. How long did it take for you to receive your results?

Lab ▸	PGxHealth	Research Lab	Ex-US (PGxHealth)	Unknown
Time ▾				7
3 weeks*	2			
4 weeks	1			
5 weeks	1			
6 weeks	2		1	
7 weeks	1			
8 weeks	1			
9 weeks	2		1	
2 years		1		

*confirmation testing for additional family members

4. Was a mutation found?

Lab ▸	PGxHealth	Research Lab	Ex-US (PGxHealth)	Unknown
				8
Yes	5			
No	2	1	1	
Class III variant*	1			

Rivers PA, Dobalian A, Germinario FA. A review and analysis of the clinical laboratory improvement amendment of 1988: compliance plans and enforcement policy. *Health Care Manage Rev* 2005. 30, (2): 93-102.
Bookman EB, Langehorne AA, Eckfeldt JH, Glass KC, Jarvik GP, Klag M, Koski G, Motulsky A, Wilfond B, Manolio TA, Fabsitz RR, Luepker RV. Reporting genetic results in research studies: summary and recommendations of an NHLBI working group. *Am J Med Genet A* 2006. 140, (10): 1033-40.
[238] See http://www.inspire.com/groups/care-cardiac-arrhythmias/ [accessed October 6, 2008].

*not expected to be deleterious

5. Who was your insurance carrier and what was your out-of-pocket expense for FAMILION testing*?

Insurer ▸	Blue Cross/Blue Shield	Humana	TriCare (US Military)	Canadian Provincial	Unknown
Percent coverage ▾					
100%	2		1	2	3
90%	1				
80%					1
63%					1
Unknown partial fraction	1	1			
0%	1				1

*FAMILION testing for LQTS costs $5400 for the index case and $900 to confirm the presence of a mutation in each family member.

6. Was cost a factor in your decision to get tested (or not get tested) with FAMILION?

No: 7
Yes: 6
No answer/not clear: 5

The lone study that modeled the cost-effectiveness of genetic testing for LQTS concluded that it is indeed cost-effective when compared to no testing.[239] It should be noted, however, that some funding for this 2005 study was provided by Genaissance through independent consulting contracts to two co-authors, Drs. Phillips and Ackerman.[240] There has been no systematic study of either clinicians' or payers' considerations of cost as part of their LQTS diagnostic heuristics.

The insurance and employment provisions of the Genetic Information Nondiscrimination Act of 2008 will take effect in 2009 and 2010. This may affect utilization of genetic testing.[241]

Adoption by third party payers

According to the PGxHealth website, [242]there were ten commercial payers with coverage policies supportive of FAMILION® testing as of August 2008. These were Aetna, Harvard Pilgrim, BCBS in 16 states (AK, AL, AR, HI, ID, IL, MI, MS, NJ, NM, NY, OK, SD, TN, TX, WA), Cigna, Coventry Health Care, HIP Plan of NY, Health Net, Inc., Humana, Select Health, and Tufts Health. Among government payers with favorable coverage policies, on its website PGxHealth cited: (1) TRICARE[243]; and (2) Medicaid in 37 states (the company has applied for Medicaid coverage in all U.S. state and territorial

[239] Phillips KA, Ackerman MJ, Sakowski J, Berul CI. Cost-effectiveness analysis of genetic testing for familial long QT syndrome in symptomatic index cases. *Heart Rhythm* 2005. 2, (12): 1294-300.
[240] Ibid.
[241] Slaughter LM. The Genetic Information Nondiscrimination Act: why your personal genetics are still vulnerable to discrimination. *Surg Clin North Am* 2008. 88, (4): 723-38, vi.
[242] See http://www.pgxhealth.com/genetictests/familion/patients/insurance.cfm [accessed October 6, 2008].
[243] TRICARE is the Department of Defense's health care program for members of the uniformed services, their families and survivors (see http://www.military.com/benefits/tricare [accessed January 12, 2009]).

Medicaid jurisdictions). FAMILION® testing was not covered by New York State Medicaid until the spring of 2008. Coverage followed a segment on *Good Morning America* highlighting the gap in coverage and its potentially adverse effect on a young LQTS patient of Dr. Chung's. [244]In October 2008, PGxHealth announced that it had become an in-network provider for Aetna's healthcare coverage of FAMILION® tests.[245]

Former Genaissance CSO Dr. Richard Judson told us that, at least initially, "Medicaid's reimbursement rate was so low that it would not begin to cover the cost of the test. It was unfortunate. This is a disease typically diagnosed in childhood and there are lots of children on Medicaid."[246] Dr. Milunsky's lab did accept Medicaid, though he called Medicaid payments "pathetic."[247]

Each of the patent licensees emphasized the difficulty in gaining payer acceptance of the test. At the time of the sale of DNA Sciences' assets to Genaissance, DNA Sciences was negotiating with several private insurers. This process included assembly of a 100- to 150-page package that was meant to justify the cost of the test to potential payers.[248] Dr. Judson said the bar was higher for new, complex tests. "Because there are hundreds of individual insurance companies in the U.S., novel tests can require hundreds of individualized cases to be made for initial acceptance. The more complex a test is (and hence the more expensive), the longer it takes for acceptance."[249] In his letter to Congressman Berman, Clinical Data CEO Drew Fromkin said that anyone providing diagnostic services knows that "…health insurer coverage for lab tests is a long and difficult road and it takes many years for any novel test to gain significant coverage."[250] According to Clinical Data, between January and October 2008 FAMILION® payer coverage increased from 55 million to 155 million lives, including Medicaid coverage increasing from 7 to 37 states during the same period.[251]

The clinicians and researchers we interviewed all said they try to make testing available to those who cannot afford it. Dr. Ackerman described a "gentleman's agreement" with PGxHealth whereby if an insurer denies payment, he will offer a charity waiver.[252] Dr. Priori provides free testing to patients from developing countries.[253] Drs. Moss and Antzelevitch will enroll patients in research studies.[254] Dr. Chung will try multiple strategies, including shopping around for insurance, pooling family resources, and

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[244] See http://abcnews.go.com/GMA/OnCall/story?id=4358619&page=1 [accessed October 22, 2008].
[245] Clinical Data, Inc. Signs Contract with Aetna for In-network Coverage of FAMILION® Genetic Tests for Inherited Cardiac Syndromes. *Business Wire* 27 October 2008.
[246] Judson R, "Interview with Richard Judson, PhD, former CSO of Genaissance Pharmaceuticals." 9 July 2008.
[247] Milunsky A, "Interview with Aubrey Milunsky, MB.B.Ch., D.Sc., F.R.C.P., F.A.C.M.G., D.C.H., Director of Boston University's Center for Human Genetics." 29 May 2008.
[248] Lehrer S, "Interview with Steve Lehrer, former CEO of DNA Sciences." 27 June 2008.
[249] Judson R, "Genetic Diagnostic Notes." 2008.
[250] Fromkin AJ, "Letter to the Honorable Howard L. Berman from Clinical Data CEO Andrew J. Fromkin." 1 April 2008.
[251] Clinical Data, Inc. Signs Contract with Aetna for In-network Coverage of FAMILION® Genetic Tests for Inherited Cardiac Syndromes. *Business Wire* 27 October 2008.
[252] Ackerman MJ, "Interview with Michael J. Ackerman, MD, director of the Sudden Death Genomics Laboratory at the Mayo Clinic." 2008.
[253] Priori S, "Interview with Silvia G. Priori, MD, PhD, LQTS researcher and clinician in Pavia, Italy." 29 May 2008.
[254] Moss AJ, "Interview with Arthur J. Moss, MD, research physician at the University of Rochester " 28 August 2008.
Antzelevitch C. Interview with Charles Antzelevitch, Ph.D., F.A.C.C., F.A.H.A., Executive Director and Director of Research of the Masonic Medical Research Laboratory (MMRL) 2 July 2008.

enrolling patients in research studies.[255] It is important to note again that while the research option is free, it is also very likely to mean a lengthy wait for the patient. And Dr. Towbin worries that in the current fiscal environment, research laboratories will not be able to continue providing complimentary LQTS genetic testing *ad infinitum*.[256]

Summing Up

Genetic testing for LQTS is a complex story that illustrates several features relevant to clinical access to genetic testing in general. Some of the complexity is biological: the clinical syndrome is uncommon but not rare. The mutations causing it are found in a multitude of genes. Sequencing the five genes most commonly mutated accounts for an estimated 75% of cases, but beyond those, there are many variants that truly are rare.

The intellectual property overlay of this biological story is also complex. It started with aggregation of the three initial patents by a single firm that "cleared the market" of testing services offering partial LQTS testing, but went bankrupt before it offered a test itself. Its rights were acquired by a second firm that introduced FAMILION®, which was in turn sold to Clinical Data, Inc., which continues to offer it through its subsidiary, PGxHealth. This was, and for now remains, the main provider of testing in the United States, although some research laboratories do offer testing for indigent patients, for those with rare variants not found by FAMILION®, and perhaps in other circumstances.

BioReference Laboratories, Inc. has quietly accumulated some exclusive patent rights of its own, and is explicit in wanting to use them strategically to change the market dynamics of LQTS testing. This legal situation is unstable, and so the clinical testing situation may change. This case shows both how exclusive licensing can enable a single provider to "own" genetic testing for an entire clinical syndrome by holding rights to the most common patented variants, and leveraging those rights to cover unpatented variants and variants never before discovered. Yet it also illustrates the vulnerability of this strategy to a competitor that acquires countervailing exclusive rights. That is the situation that is unfolding for LQTS testing as this case study was being prepared.

The case also illustrates the fact that coverage decisions by insurers and health plans, and the level of reimbursement payments are arguably larger and more pervasive problems for clinical access to genetic testing than patent status. On the other hand, exclusive patent rights appear also to have contributed to relatively high pricing for LQTS testing (the truth of this statement may become more apparent if more than one provider emerges, although oligopolistic pricing would also reflect a patent premium).

In some ways, this case is simpler than others that could follow. Most of the key patents were licensed by a single institution, the University of Utah, which has now exclusively licensed rights to different mutations to two different firms. If there were multiple patent-holders, then even more parties, with potentially different stakes, would be involved in the negotiations.

Finally, the case illustrates how complex and pervasive the financial connections are. The community of clinical experts is fairly small, and its members respect one anothers' clinical expertise. They disagree about best practices, particularly regarding exclusive licensing of university-based patents involved in genetic testing, and their positions do map to their financial arrangements (although causality could be in both directions—those most trusting of a company's practices are apt to consult for it). Those without

[255] Chung W, "Interview with Wendy Chung, MD, PhD, pediatrician, geneticist and researcher at Columbia University." 7 May 2008.
[256] Towbin JA, "Interview with Jeffrey A. Towbin, MD, chief of pediatric cardiology, Baylor College of Medicine." 29 September 2008.

financial ties acknowledge the value of commercial testing, but also worry about high prices limiting access and the importance of having alternative sources because even high-quality laboratories make mistakes, and the system needs to have checks and balances. We find no consensus among the clinical experts most familiar with the medical consequences of testing, dominated until very recently by a single-provider commercial model, whether the current model is a net social benefit or a problem.

Finally, the case study shows the technological instability of current protocols for genetic testing. If full-genome sequencing becomes feasible in the next few years, and if its price comes into the same range as the $5,400 FAMILION® test, as seems likely, then the intellectual property consequences will become even more complex. The question of patent infringement will turn on the precise language of relevant patents, how courts interpret those claims, and the business decisions of patent holders with claims on DNA sequences and their clinical interpretation. The choice of total genomic sequencing could be either an alternative to testing for a particular syndrome, or full-genome sequencing could become the first step in a clinical decision tree that reduces the role of boutique genetic testing to confirming mutations provisionally detected. This would be a profound perturbation of the current business models.

The current mutually blocking IP of two competing firms has yet to be resolved, and the future promises to add further layers of uncertainty regarding both intellectual property and technological options for genetic testing.

Spinocerebellar Ataxia: Patient and Health Professional Perspectives on Whether and How Patents Affect Access to Clinical Genetic Testing

Ashton Powell, Ph.D.,[1] Subhashini Chandrasekharan, Ph.D.,[2] and Robert Cook-Deegan, M.D.[2]

Abstract

Views of patients and health professionals about the impact of patents on access to genetic testing for spinocerebellar ataxia (SCA) were sampled via a web forum. Questions about access to genetic testing were posted on the website of the National Ataxia Foundation (NAF), which agreed to host the web forum. The web forum was supplemented by interviews with three neurologists and a laboratory director. Both the web forum and interviews focused on perceptions of whether patents impede neurological patients from using diagnostic tests for the most common autosomal dominant forms of spinocerebellar ataxia.

SCA is not a single condition, but a group of progressive neurological genetic disorders with common symptoms and disparate genetic causes. Genetic testing plays a direct role in identifying the molecular defect in some cases.

Patents were generally not perceived to be a major direct impediment in most cases, although they reduced access to the degree they increased the cost of testing borne directly by patients. Most SCA genetic testing in the United States is carried out by Athena Diagnostics, which has in-licensed exclusive patent rights from various holders of SCA patents, mainly universities and nonprofit research institutions. Some genes involved in SCA testing are not patented at all.

Price and concern about genetic discrimination both appear to reduce patient use of genetic tests. The decision not to get tested holds even for those who have progressed far into a diagnostic workup. SCA is a relatively rare syndrome and many genes are involved. The cost of testing can be as high as $7300, and only six out of fourteen patients surveyed who sought testing received reimbursement for testing from their insurance carriers. Yet clinical testing requires CLIA certification and testing for many genes, so patients are generally grateful there is a test provider.

Athena offers a "Patient Protection Program" that caps out-of-pocket payments at 20% of the price for cases where Athena directly bills the patient's insurer. However, this likely covers only a small minority (10-15%) of patients tested by Athena. Some patients who availed themselves of Athena's Patient Protection Program appreciated the out-of-pocket payment caps. Under this program, Athena takes responsibility for seeking reimbursement from payers and insurers for the other 80%. Athena also has an "Athena Access" program for those who cannot afford the 20% copay, which entails case-by-case review by Athena; analysis of SEC filings suggests that this covers relatively few patients. The 20% copay cap for patient outlays under the Patient Protection Program is a standard option, although many patients appear not to know about it, and those in certain health programs are not eligible for it. Athena did not provide statistics on the percentage of patients covered by these two programs, so we are unable to estimate their actual impact. Since the program is discretionary and operated by Athena, independent data about how many people use it, which insurers and health programs are covered, and other details are

[1] Center for Public Genomics, Center for Genome Ethics, Law & Policy, Institute of Genome Sciences & Policy, Duke University, Curriculum in Neurobiology, University of North at Carolina Chapel Hill, Center for Genomics and Society at the University of North Carolina at Chapel Hill.
[2] Center for Public Genomics, Center for Genome Ethics, Law & Policy, Institute of Genome Sciences & Policy, Duke University.

not available. SACGHS might consider requesting details about both the Patient Protection Program and Athena Access from the company, since these details were not shared with us.

We cannot estimate the population prevalence or magnitude of the effects because of the highly selected nature of our sample. The website respondents, however, do indicate the two main reasons that patients with rare genetic conditions may not use genetic tests even when they would like to have the results of them: fear of discrimination and cost.

Background

Spinocerebellar ataxia (SCA) is a designation given to a rare subset of autosomal dominant cerebellar diseases characterized by loss of cerebellar cells. (Spinocerebellar ataxia is also associated with other patterns of inheritance, both autosomal recessive [SCAR] and X-linked (SCAX), but these are even more rare and less well characterized and therefore less relevant for commercial genetic testing.) Symptoms include ataxia, or irregular movement due to loss of neural control, and often also other symptoms attributable to loss of brainstem and spinal cord function.[3] Ataxia is a common symptom found in conditions from chronic alcoholism to stroke. SCA accounts for less than 5% of the ataxic population, an estimated prevalence of 1-5:100,000.[4] While accounting for only one in twenty cases of ataxia, the autosomal dominant SCA syndromes are nonetheless much more common than the other genetic forms, which are quite rare.

The severity and types of symptoms vary among the cerebellar ataxias. Diagnosis often takes years and may entail many visits to a succession of physicians and other health professionals, especially when it is a "proband case," or the first known case in a family cluster. Once a first case is found in a family and confirmed as an inherited condition, genealogical tracing may identify other cases in the family. There are currently more than 30 identified variants of SCA (named SCA1-8, and 10-25 see Table 1), a number that is constantly expanding. Each variant has the symptom of ataxia, however the secondary symptoms can differ greatly. The symptoms associated with variants of SCA have significant overlap, so purely clinical symptom clusters rarely specify a particular mutation without DNA or protein testing. The vagueness with which each variant is described can make purely clinical diagnosis without genetic testing difficult, although there have been many attempts to design clinical scales using symptom correlations to hone in on a diagnosis (Figure 1).[5] There is no known cure for any subtype of SCA, and treatment often involves addressing individual symptoms as they appear.

Before 1982, symptoms that now distinguish the various subtypes of SCA were diagnosed as olivopontine cerebellar atrophy (OPCA), a classification that encompassed a host of cerebellar diseases.[6] Later, a clinical classification was proposed for a subset of these diseases based on mode of inheritance and

[3] Schols L, Bauer P, Schmidt T, Schulte T, Riess O. Autosomal dominant cerebellar ataxias: clinical features, genetics, and pathogenesis. *Lancet Neurol* 2004. 3(5): 291-304.
Taroni F, DiDonato S. Pathways to motor incoordination: the inherited ataxias. *Nat Rev Neurosci* 2004. 5(8): 641-655.
[4] Moseley ML, Benzow KA, Schut LJ, Bird TD, Gomez CM et al. Incidence of dominant spinocerebellar and Friedreich triplet repeats among 361 ataxia families. *Neurology* 1998. 51(6): 1666-1671.
Mori M, Adachi Y, Kusumi M, Nakashima K. A genetic epidemiological study of spinocerebellar ataxias in Tottori prefecture, Japan. *Neuroepidemiology* 2001. 20(2): 144-149.
van de Warrenburg BP, Sinke RJ, Verschuuren-Bemelmans CC, Scheffer H, Brunt ER et al. Spinocerebellar ataxias in the Netherlands: prevalence and age at onset variance analysis. *Neurology* 2002. 58(5): 702-708.
[5] Maschke M, Oehlert G, Xie TD, Perlman S, Subramony SH et al. Clinical feature profile of spinocerebellar ataxia type 1-8 predicts genetically defined subtypes. *Mov Disord* 2005. 20(11): 1405-1412.
Schmitz-Hubsch T, du Montcel ST, Baliko L, Berciano J, Boesch S et al. Scale for the assessment and rating of ataxia: development of a new clinical scale. *Neurology* 2006. 66(11): 1717-1720.
[6] Konigsmark BW, Weiner LP. The olivopontocerebellar atrophies: a review. *Medicine* (Baltimore) 1970. 49(3): 227-241.

secondary neurological symptoms not associated with the cerebellum.[7] These classifications, known as the autosomal dominant cerebellar ataxias (ADCAs), were subdivided into classes I, II, and III. This diagnostic refinement allowed neurologists to distinguish ataxias according to their accompanying symptoms, among those being: peripheral nerve damage and dementia (ADCA I), macular and retinal degeneration (ADCA II), and an especially severe late-onset pure form of ataxia (ADCA III).

Eventually, as genetic research was incorporated into the classification along with symptoms, these conditions were divided further into the more than 30 conditions now known as SCA (Harding 1982; Manto 2005; Maschke et al. 2005).[8] ADCA I was supplanted by SCA1-3, ACDA II was replaced with SCA7, and ACDA III was divided into SCA4-6 and 11. The classification has "gone molecular." It is now based on mutations in genes that encode proteins affecting nerve function. Some mutations are associated with changes in proteins that conduct charged particles through cell membranes ("channel" proteins), receptors, or other surface proteins on nerve cells. Despite the increased specificity in diagnosis, treatment has changed little. Progress in understanding the molecular details has not yet translated to better treatment. The primary benefits of SCA genetic testing for a patient are precision of prognosis, some reassurance from an accurate characterization of the molecular defect, an ability to diagnose those who are affected or presymptomatic among relatives, and the ability to test for a known mutation during preimplantation diagnosis or prenatal diagnosis in the progeny of an affected person.

We focus on the six most common forms, SCA1-3 & SCA 6-8.

Symptoms and Pathology Of SCA Subtypes

SCA1 has pan-cerebellar symptoms that typically begins in a patient's fourth decade, with an average duration of fifteen years (Table 1). Cerebellar symptoms include an atrophy of Purkinje cells, loss of afferent projections into the cerebellar cortex, and atrophy of dentatorubral pathways. Non-cerebellar symptoms include signs associated with damage to the dorsal columns and cranial nerve nuclei. SCA1 maps to chromosome 6p23 in the ataxin-1 gene and is a CAG trinucleotide repeat disorder (i.e., caused by expanded number of those three base pairs inserted as repeats into the gene's DNA). SCA1 is estimated to represent 5.6% of autosomal dominant SCA ataxias.[9]

SCA2, in addition to cerebellar symptoms found with olivopontocerebellar atrophy, is associated with marked loss or slowing of saccadic eye movements, dementia, and other peripheral neuropathy. Patients with SCA2 can show their first symptoms from age 2 to age 65, a huge range in age of onset, with an average duration of 10-15 years from onset to death.[10] SCA2 maps to chromosome 12q24.1 in the ataxin-2 gene and is a CAG trinucleotide repeat disorder. SCA2 is one of the most common of the autosomal dominant cerebellar ataxias accounting for an estimated 15.2% of SCA occurrences.[11]

SCA3, also known as Machado-Joseph disease, is characterized by cerebellar signs including degeneration of the dentate and vestibular nuclei, with no degeneration of the cerebellar cortex. Additional symptoms include extrapyramidal, motor cranial nerve, anterior horn, posterior root ganglion,

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[7] Harding AE. The clinical features and classification of the late onset autosomal dominant cerebellar ataxias. A study of 11 families, including descendants of the 'the Drew family of Walworth'. *Brain* 1982. 105(Pt 1): 1-28.
[8] Ibid.
Manto MU. The wide spectrum of spinocerebellar ataxias (SCAs). *Cerebellum* 2005. 4(1): 2-6.
Maschke M, Oehlert G, Xie TD, Perlman S, Subramony SH et al. Op. cit.
[9] Moseley ML, Benzow KA, Schut LJ, Bird TD, Gomez CM et al. Op. cit.
[10] Auburger G, Orozco Diaz, G, Capote RF, Sanchez SG, Perez MP, Estrada del Cueto M, Meneses MG, Farrall M, Williamson R, Chamberlain S, Baute LH. Autosomal dominant ataxia: genetic evidence for locus heterogeneity from a Cuban founder-effect population. *Am J Hum Genet* 1990. 46: 1163-1177.
[11] Moseley ML, Benzow KA, Schut LJ, Bird TD, Gomez CM et al. Op. cit.

and spinopontine symptoms. SCA3 symptoms begin in the fourth decade with a typical duration of ten to fifteen years. SCA3 maps to chromosome 14q24.3-q32.2 in the ataxin-3 gene and is also a CAG trinucleotide repeat disorder. First described as Machado-Joseph disease, SCA3 accounts for 84% of autosomal dominant ataxias in ethnic Portuguese and 50% in ethnic German populations. In the US, SCA3 accounts for approximately 21% of dominant ataxias. The severity of symptoms correlates with the number of CAG repeats.[12]

SCA6 is an autosomal dominant ataxia that has a variable presentation, classified as three separate syndromes. The SCA6 syndromes are episodic ataxia, cerebellar ataxia plus brainstem or long tract degeneration, or pure cerebellar ataxia. Additional symptoms include a coarse gaze-evoked nystagmus, downbeat nystagmus on lateral gaze, and poor suppression of eye movement by vision.[13] SCA6 is a slowly progressing late-onset version of SCA that begins in the fifth or sixth decade with a typical duration of more than 25 years. The SCA6 mutation has been identified as a CAG expansion located at 19p13, a subunit of the voltage-gated calcium channel CACNL1A4. SCA6 accounts for approximately 15% of autosomal dominant ataxias in the US.

In addition to cerebellar symptoms and ataxia, SCA7 is associated with retinopathy or blindness. Beginning in the third or fourth decade, SCA7 is a slowly progressive ataxia, lasting an average of twenty years. Mapped to 3p21.1-p12, which encodes ataxin-7, SCA7 is a CAG repeat disorder as well. SCA7 accounts for roughly 5% of dominantly inherited ataxias in the United States. It is sometimes associated with genetic anticipation (earlier onset in successive generations, usually indicative of expansions of trinucleotide repeats) and severe childhood onset.

SCA8 is a less severe form of SCA, with symptoms including hyperreflexia, decreased sense of vibration, ataxic dysarthria (lack of control of joints), impaired smooth-pursuit eye movement, horizontal nystagmus, and atrophy of the cerebellar vermis and hemispheres. SCA8 begins in the fourth decade and is not associated with shortened lifespan. SCA8 has been mapped to 13q21, which encodes ataxin-8 and is a CAG/CTG repeat disorder. SCA8 accounts for 2-5% of autosomal dominant ataxias in the US.

Diagnosing Spinocerebellar Ataxia

When first diagnosing or treating an ataxic patient, one of the first lines of evidence is family history. Like many diseases with known genetic causes, a family history that reveals multiple family members afflicted with similar clinical conditions can indicate that diagnosis of SCA should be considered.

While an ataxic patient whose family history includes a genetically confirmed diagnosis of a SCA subtype is an ideal candidate for genetic testing, such cases are unusual. Most family histories contain no results from genetic testing because it is a relatively new technology. If ataxic symptoms exist in a family record, a previous diagnosis is likely to reflect a classification given to the disease at the time of diagnosis. Despite a dated classification, these histories are still valuable for diagnosing hereditary ataxias (Figure 2).

Family history is unavailable in many cases. A patient may be adopted, where heredity is impossible to trace through standard pedigree tracing. A patient may come from a family that has had little exposure to modern medicine and record keeping or adoption. Due to the late onset of some hereditary ataxias (Harding 1982), not all families have had life expectancies long enough for symptoms to be observed.[14]

[12] Onodera O, Idezuka J, Igarashi S, Takiyama Y, Endo K et al. Progressive atrophy of cerebellum and brainstem as a function of age and the size of the expanded CAG repeats in the MJD1 gene in Machado-Joseph disease. *Ann Neurol* 1998. 43(3): 288-296.
[13] Gomez CM, Thompson RM, Gammack JT, Perlman SL, Dobyns WB et al. Spinocerebellar ataxia type 6: gaze-evoked and vertical nystagmus, Purkinje cell degeneration, and variable age of onset. *Ann Neurol* 1997. 42(6): 933-950.
[14] Harding AE. Op. cit.

Many die without a definitive diagnosis, and stigma associated with uncontrollable movement can lead to cases being "hidden" from family discussion and result in incomplete pedigrees.

An initial neurological consultation is also intended to resolve whether the ataxia is acquired (e.g., related to alcohol use, infection, or other known syndromes) or sporadic. Acquired ataxia refers to cases with no known genetic component. These can be highly variable from case to case.[15] Common causes of acquired ataxia include chronic alcoholism, stroke, multiple sclerosis, vitamin deficiency, and metabolic deficiencies.[16] In some cases, identifying the source of an acquired ataxia can lead to a relief or even reversal of symptoms.

Sporadic ataxia is a diagnosis given to a subset of patients who have ataxia with no known hereditary or acquired components. This residual classification is broken into either pure cerebellar or 'cerebellar plus,' depending on whether there are symptoms in addition to ataxia.[17] Regardless of whether the ataxia appears to be hereditary, sporadic or acquired upon an initial evaluation, an ataxic patient will generally undergo a complete neurological evaluation and an MRI scan.

After one or several MRI scans, the neurologist may observe cerebellar atrophy, or loss of cerebellar tissue. In addition to atrophy, the neurologist may observe signs and symptoms of a progressive loss of function in systems associated with the cerebellum. Symptoms can include gait disruption, nystagmus, vertigo, or general lack of coordination. Secondary non-cerebellar symptoms including impaired cognition, memory, and vision can also point to SCA.

Intellectual Property Landscape – Athena Diagnostics

Many genetic tests for SCA are available only from Athena Diagnostics, including the most commonly used SCA genetic tests. There are currently 15 variants of SCA for which genetic testing is available. Athena Diagnostics holds the patent or has exclusive license to 12 patents that identify 6 SCA variants (SCA1-3 & 6-8) and two other hereditary ataxias (Friedreich's Ataxia and Early Onset Ataxia) included in their Complete Ataxia Panel (Table 3). These variants are the most commonly occurring, accounting for roughly 60-80% of known SCA cases, depending on the patient's country of origin (Tang et al. 2000; Lee et al. 2003; Bauer et al. 2005).[18] Athena was also granted a nonexclusive license by Baylor Medical College for US6855497, which covers methods for detecting SCA-10,[19] and Athena also does testing for SCA5, 13, 14 and 17.

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[15] Ibid.
Manto MU. Op. cit.

[16] Gordon N. Cerebellar ataxia and gluten sensitivity: a rare but possible cause of ataxia, even in childhood. *Dev Med Child Neurol* 2000. 42(4): 283-286.
Hadjivassiliou M, Grunewald R, Sharrack B, Sanders D, Lobo A et al. Gluten ataxia in perspective: epidemiology, genetic susceptibility and clinical characteristics. *Brain* 2003. 126(Pt 3): 685-691.
Zumrova A. Problems and possibilities in the differential diagnosis of syndrome spinocerebellar ataxia. *Neuro Endocrinol Lett* 2005. 26(2): 98-108.

[17] Koeppen AH. The pathogenesis of spinocerebellar ataxia. *Cerebellum* 2005. 4(1): 62-73.
Manto MU. Op. cit.
Maschke M, Oehlert G, Xie TD, Perlman S, Subramony SH et al. Op. cit.

[18] Tang B, Liu C, Shen L, Dai H, Pan Q et al. Frequency of SCA1, SCA2, SCA3/MJD, SCA6, SCA7, and DRPLA CAG trinucleotide repeat expansion in patients with hereditary spinocerebellar ataxia from Chinese kindreds. *Arch Neurol* 2000. 57(4): 540-544.
Lee WY, Jin DK, Oh MR, Lee JE, Song SM et al. Frequency analysis and clinical characterization of spinocerebellar ataxia types 1, 2, 3, 6, and 7 in Korean patients. *Arch Neurol* 2003. 60(6): 858-863.
Bauer PO, Zumrova A, Matoska V, Marikova T, Krilova S et al. Absence of spinocerebellar ataxia type 3/Machado-Joseph disease within ataxic patients in the Czech population. *Eur J Neurol* 2005. 12(11): 851-857.

[19] Email and phone correspondence with Teresa L. Rakow, Sr. Licensing Associate Baylor Licensing Group Baylor College of Medicine, April 9 2008.

Of the 12 patents listed by Athena, half are licensed from the University of Minnesota. Three others are from academic institutions (two through Research Foundation, one from Baylor) and only one is assigned to Athena itself. It thus appears that at least 9 of 12 (75%) are licensed from academic institutions and one arose from in-house R&D at Athena.

Athena Diagnostics has enforced its exclusive licenses and is widely assumed to be the sole laboratory for the above tests.[20] Athena's legal department has sent "cease and desist" letters to some laboratories performing SCA genetic tests for which Athena has exclusive patent rights (Figure 3). In another instance, the Diagnostic Molecular Pathology Laboratory at the University of California Los Angeles stopped offering testing for SCA over two years ago, after receiving a "cease and desist" letter from Athena Diagnostics. According to Dr. Wayne Grody,[21] Director of the Laboratory, the terms of the sublicense offered by Athena Diagnostics were not economically viable for the laboratory. Attempts to negotiate terms of a sublicense have not been successful to date. It is unclear to what extent cessation of testing at UCLA has affected patient access to SCA testing. Dr. Grody indicated that samples are now sent to Athena Diagnostics for clinical testing. Several other laboratories are also listed on GeneTests.org for adult SCA diagnoses. Comprehensive Genetics Services offers a complete panel of SCA tests (Table 4) but did not respond to questions about patents or licensing in phone interviews. We recently became aware that Boston University reached a settlement with Athena Diagnostics regarding testing for SCA[22] and several other conditions and no longer offers SCA testing.

Athena Diagnostics does not list prenatal or preimplantation genetic diagnosis. Several labs listed on GeneTests.org perform these tests. We did not verify or otherwise pursue questions about prenatal or pre-implantation genetic testing for SCA.

SCA genetic tests can be performed individually for as little as $400, for the least expensive single-locus test, or as much as $2,335 for full-sequence analysis of the most expensive full-sequence gene test. The lower cost tests are for known mutations in the second or subsequent members of a family, once a proband case in that family is characterized. Athena also offers the Complete Ataxia Panel, a compilation of 18 tests that cover the most commonly identified SCA mutations for the price of $7,300. This cost includes PCR tests and tests requiring sequencing (Table 2 & 4). The Athena price for the five most common SCA's (1, 2, 3, 6 and 7) is $2,300 (if ordered individually, which is the only option). A University genetics laboratory can reportedly perform the same 5 SCA tests for $750 (or $1,500 if ordered individually).[23]

Most of Athena Diagnostic's testing revenue comes from direct billing to hospital and commercial laboratories that send samples to Athena for patients seen or tested within their health-care systems. In a public filing with the Securities and Exchange Commission, Athena indicated that 85% of their revenue comes from this source.[24] This is widely known in the clinical laboratory industry as the most profitable type of billing arrangement: the sending facility is obligated to pay the full contractual price of testing directly to Athena regardless of insurance coverage or patient ability to pay; the sending facility then bills the patient and/or the patient's third party payer for the cost of testing. Since reimbursement for this type

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[20] Schissel A, Merz JF, Cho MK. Survey confirms fears about licensing of genetic tests. *Nature* 1999. 402(6758): 118.
Cho MK, Illangasekare S, Weaver MA, Leonard DG, Merz JF. Effects of patents and licenses on the provision of clinical genetic testing services. *J Mol Diagn* 2003. 5(1): 3-8.
[21] Phone conversation with Dr. Wayne Grody, March 21, 2008
[22] Phone conversation with Dr. Aubrey Milunsky, Director, Center for Human Genetics, Boston University, May 29, 2008.
[23] Laboratory director, name withheld at request.
[24] Athena Diagnostics. *S-1*. October 31, 2001. Table on page 39. See www.secinfo.com/dsvrt.4fD5f.f.htm [accessed 14 January, 2009].

of testing is often low or absent, the financial burden of poorly reimbursed testing is thus transferred from Athena to the sending healthcare facility and thence to the patient.

Athena has a formal policy that limits out-of-pocket expenditures for some patients for whom Athena directly bills the insurer. Athena's Patient Protection Plan (PPP), charges the patient 20% of the test fee (the usual copayment for most insurance programs) up front. After completing the test, if insurance covers the cost of the test, Athena will reimburse the patient for any payment their insurance makes above 80% of the total bill. Such patients must have private insurance. If the patient's insurance does not cover the genetic test, Athena will limit the patient's liability to the 20% already paid. This plan requires preapproval by Athena. There is an additional plan for low-income families, Athena Access. This is for those who may find the 20% co-pay prohibitive. Athena, upon receiving a request for a test, will attempt to contact the patient by mail and phone three times in order to enroll them into the PPP. Athena did not provide specific numbers regarding enrollment percentages into the PPP. It is also not clear whether this program includes persons whose only coverage is Medicare or Medicaid. However, the information in the SEC filing cited above would indicate that this program could apply to no more than 15% of the sources of revenue for testing at Athena in 2001. The PPP will not provide relief to a patient being billed by a health-care facility for testing sent to Athena under the common direct billing arrangement accounting for 85% of Athena's revenues. There is no way from public sources to estimate how much of the remaining 15% of revenue might have been reduced by the company's PPP or Athena Access programs.

Athena also has a repeat customer program that can also reduce costs borne by patients. If a patient has a genetic test performed by Athena and receives a positive result, subsequent family members who request the same test have a greatly reduced price. However, the impact of this program is probably small because of the low rate of positivity for SCA testing (only 6% for patients without a known family history of SCA.)[25]

The benefit of Athena's licensing SCA patents from several different academic institutions and combining them with their own patent is that this enables a single laboratory to test for many variants, and protects the company's investment in CLIA certification, laboratory proficiency testing, a sales force to educate neurologists about the tests, and staff to manage the complex coverage and reimbursement policies of a dizzying array of disparate payers, insurers, and health plans. The syndromes are relatively rare, and it is possible that this full range of tests would not be available without the patent incentive.

The counter-argument is that Athena has consolidated IP into an effective temporary monopoly for genetic testing of the SCA syndromes. It has been vigilant in enforcing its patent rights, and this has led several laboratories to avoid SCA testing who otherwise might have offered a testing alternative. As with all patented inventions, this reduces price competition, means all samples must be sent to an external laboratory, limits alternatives for verification of test results, and reduces the incentive to introduce cheaper and faster tests because the current technology is protected by patents. This could, for example, reduce incentives to develop a chip-based or microarray-bead or sequence-based test using alternative technologies, because the patents apply to any technology for assessing patented mutations or diagnostic methods that entail sequencing or sampling a patented sequence. Sole provider status also means that Athena effectively becomes the only testing service for mutations never yet detected (or patented) because the nature of the mutation is not known when a sample is sent. The means a single private firm becomes the repository for data needed to determine if a discovered DNA change is actually a disease causing pathogenic mutation or a benign polymorphism, information that is critically important to clinical interpretation. Yet Athena does not appear to publish or report such data, leaving reporting to the disparate groups sending samples to their central laboratory.

[25] Edlefsen KL, Tait JF, Wener MH, Astion M. Utilization and diagnostic yield of neurogenetic testing at a tertiary care facility. *Clin Chem* 2007. 53(6): 1016-1022.

Many of these tests were developed through federally funded research and licensed to Athena. The ultimate payer is often the federal government (through Medicare, Medicaid, Federal Employee Health Benefit Plan, Tricare, Veterans Health Administration, military health systems, Indian Health Service, etc.). The patents arising from federally funded research are subject to Bayh-Dole government use rights. Those government use rights are clearly not being interpreted to cover even payments channeled through the same federal Department of Health and Human Services that houses the National Institutes of Health (NIH) that funded the research (such DHHS payers include Medicare and federal components of Medicaid, the Indian Health Service and any genetic services covered by the Health Resources and Services Administration). We do not know if there is a price reduction for NIH-funded clinical trials and clinical research, because none of the respondents in the web forum specifically noted participation in such trials and the physicians interviewed did not mention this. SACGHS could ask Athena if it offers price reduction for genetic testing associated with federally funded research or allows unlicensed testing for clinical and/or basic research.

Physician Utilization and Access (Interviews with Neurologists)

To get clinicians' perspectives on access to genetic testing, we interviewed three neurologists with varying degrees of expertise with SCA, and a laboratory director. The neurologists we interviewed are Dr. Octavio de Marchena from the Neurology Associates of Lynchburg, Dr. James Burke from Duke University Hospital, and Dr. Thomas Bird from the University of Washington. The laboratory director requested that his/her name be withheld, and that interview is protected by a certificate of confidentiality (as are others, except when they were explicitly "on the record") under the IRB-approved interview protocol we followed.

Dr. de Marchena is a general neurologist at a regional hospital; he treats all types of neurological patients and refers cases of ataxia to a subspecialist as needed. Confirmed cases of hereditary ataxia treated by the Dr. de Marchena are rare, but he has had patients for whom he has established a positive diagnosis of SCA using genetic testing.

Dr. James Burke is a neurologist who specializes in neurodegenerative diseases at Duke, a private hospital and clinical outpatient service that is part of a major regional academic medical center. Dr. Burke does not solely treat patients with movement disorders, but does have ataxic patients referred to him from both inside and outside Duke. Cases of SCA are also rare for Dr. Burke, although he orders an estimated 5-10 genetic tests for SCA per year.

Dr. Thomas Bird is a researcher and clinician at the University of Washington and VA Puget Sound Health Care System, an academic health center with a long and distinguished history of medical genetics. His research includes the genetics of neurodegenerative diseases. His patients are often referred to him from all over the country, and many come with the expectation that they will have genetic tests performed as part of their visit. Compared to the other neurologists, Dr. Bird's patients are more often prescreened as candidates for genetic testing. Many patients referred to him have been seeking a specific diagnosis for some time. Many become involved in research studying trinucleotide repeat neurological diseases. Dr. Bird uses genetic tests much more often than most other neurologists. He estimated that in a given year he prescribes genetic testing for 35-45 ataxic patients, most patients receiving testing for multiple variants. When itemized by SCA variant, the number of individual tests that he orders comes to well over 200 per year. He is also a consultant to Athena. That is, he is an international expert on SCA.
We asked all three neurologists to describe their use of genetic testing for SCA and the medical factors most responsible for prescribing tests. We asked them about how they interact with Athena Diagnostics. In addition, we asked them to describe their interactions with insurance companies and how insurance and

health plan factors affect their use of genetic testing for SCA. Finally, we asked whether and how reducing the price of testing to $100 might change their use of genetic testing for SCA.

Clinical Guidelines and Utility of Genetic Testing

Achieving a diagnosis of SCA is more a complex process than a formal algorithm. The primary reasons for this are that ataxia is a common symptom associated with many disorders and because there are numerous forms of SCA. It takes substantial evidence from multiple methodologies (family history, brain imaging and blood tests) over several visits, often documented in medical records from different providers, before a neurologist considers a genetic test for SCA. The only time this is not the case is if the family history contains a specific SCA diagnosis in another family member. (In these cases, while a test will come earlier, there is still no guarantee of a positive result.)

Considering that genetic testing provides the sole confirming diagnosis of SCA, we probed further the rationale for delaying genetic tests until after significant clinical evaluation. The primary reason is low likelihood that genetic testing will be informative in symptomatic ataxia that is not fully characterized (by ruling out alcohol use, stroke, or multiple sclerosis, for example). Even the most common form of SCA in US populations (SCA3)[26] is likely to test negative more than 99% of the time in a patient displaying ataxia without a family history. If a neurologist can follow disease progression long enough, he or she can discern whether it follows any of the identified classifications of SCA, increasing likelihood of a positive genetic test. Clinical heterogeneity even among patients afflicted with the same variant of SCA can make it difficult for a neurologist to identify the SCA genes that should be tested.

Cost and cost-effectiveness enter into decisions about genetic testing for SCA, but not in a simple way. While positive results on genetic tests for SCA subtypes provide definitive diagnosis for ataxia in a patient, the interpretation of a negative result is much less well defined, and yet negative results are common, even among well-screened patients. Many patients with clinical ataxia do not have a mutation in any of the genes known to be associated with SCA. In such cases, the diagnosis will be a clinical, descriptive, or anatomical one, such as olivopontine cerebellar atrophy.

Cost Effectiveness of Genetic Testing

The primary issue associated with genetic testing for SCA is the low rate of positive results. The 30 identified spinocerebellar ataxias only account for an estimated 5% of all diagnosed ataxias.[27] Genetic tests are available for 12 of the genetic subtypes, representing an estimated 65-80% of SCA cases (Table 1). Edlefsen et al. compared the cost effectiveness of genetic tests.[28] In this study, 162 patients were given a total of 282 neurogenetic tests. The patients were referred for genetic testing by a neurologist based upon family history and symptoms. The tests included mutations associated with chorea, neuropathy, muscle weakness, and ataxia. In all, 30.2% of patients received a positive result on a genetic test or panel of tests corresponding to their symptoms. When only looking at probands, patients for whom there is no known family history, the positive rate goes down to 21.5%. For tests related to SCA (SCA1-3, 6-8, 10, 12, 17) the total positive rate for patients was 11% (2/18), and only 5.9% (1/18) for probands without known family history of other SCA cases. This "hit" rate for SCA was the lowest of all genetic tests surveyed.

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[26] Moseley ML, Benzow KA, Schut LJ, Bird TD, Gomez CM et al. Op. cit.
[27] Ibid.
Mori M, Adachi Y, Kusumi M, Nakashima K. Op. cit.
van de Warrenburg BP, Sinke RJ, Verschuuren-Bemelmans CC, Scheffer H, Brunt ER et al. Op. cit.
[28] Edlefsen KL, Tait JF, Wener MH, Astion M. Op. cit.

One way to assess testing cost is to estimate the cost per positive test result. The genetic test for Huntington's disease costs $300. With a positive result in 71.2% of tests the cost per positive is $440. For the HD test, the symptoms, family history of chorea, and need to test only a single locus makes selection of a genetic test straightforward. For the SCA tests, the cost of the test itself varied from $225 for a single-locus test (for a known mutation in a second or subsequent family member) to $2,335 for a test requiring sequencing.[29] Twenty-seven genetic tests for SCA, ordered for 18 patients, were either for single variants (17 of 27; SCA3, 7, 8, 10, 12, 14, 17) or as a panel (10 of 27; SCA1-3, & 6-7). With a positive result rate of 11%, the cost per positive test for SCA was $7,620, the most expensive cost-per-positive-test studied. Edlefsen et al. note that this cost would increase to over $50,000 if all tests were sent to Athena Diagnostics.[30]

Adoption by Clinical Providers

When asked how they obtained SCA genetic testing for a patient, the neurologists said they simply check a box on a requisition form. A blood sample goes with the form to the pathology department of their institution. From there, the in-house laboratory either ships the sample to Athena Diagnostics or performs tests, depending on the test. All three neurologists stated the testing from Athena was generally consistent and reliable. The neurologists all stated their personal preference was that the laboratory of their own institution would perform these tests, especially those that are PCR-based and do not require sequencing.

Neurologists judged that the price of the test was sometimes problematic, mainly because insurance would not always reimburse all costs, and patients were not always able to cover the remaining costs. They considered cost a factor but focused primarily on the clinical value of genetic testing. The patient might decide to forego testing, but while these neurologists considered costs, they saw their main task as explaining the clinical value of a genetic test, and left final determinations about whether a test was worth the cost to their patients.

To probe price sensitivity, the neurologists were asked a question about whether a decrease in test pricing to $100 would increase test prescriptions. All three neurologists reiterated their stance that the limitations of current SCA genetic testing panels place genetic testing for this condition low on the diagnostic tree and late in the process, so such testing is not common and therefore not a major cost driver for diagnosis overall. They indicated that lowering the price to $100 would have little effect on their prescribing pattern. Dr. de Marchena stated that, "any neurologist would call for testing when the symptoms and family history call for it, regardless of price." Price is not the main factor in deciding whether to test, although it is a factor they consider. Dr. Bird noted that any neurologist must take into account "what value is this to a patient and his family, just giving the test without thought will not benefit them." On further reflection, however, Dr. Bird believed he would order more tests if the cost were substantially lower.

Lowering the price of testing would not affect the informational value of the test, as neurologists focus on "benefit to the patient," and indeed it may be appropriate for patients to decide for themselves the value of the genetic test, since there are no clinical treatments that follow from specific genetic diagnosis. The neurologists order the test to provide clinically relevant information; the patients then must decide the personal value of that information to them, compared to their out-of-pocket costs and any other costs (needing to deal with applying for the Patient Protection program, Athena Access, etc.). The benefits of testing are mainly that the diagnostic work-up can end with a definitive result, a genetic diagnosis enables more precise prognosis, and it enables risk evaluation and a much more efficient diagnostic strategy for others related to that person.

[29] Ibid.
[30] Ibid., 1021.

The Edelfsen et al. article notes that testing for ataxia is among the most expensive areas for genetic testing, and that costs would be even higher if patents were enforced rigorously. They conclude:

> For example, the cost per positive result for ataxia testing would increase nearly 7-fold, to >$50 000, if all tests had been obtained from the laboratory [NB: clearly referring to Athena Diagnostics] that claims exclusive patent rights for many of these tests. This increase reflects both higher per-test cost and test packaging that encourages the ordering of larger panels of tests. Thus, policymakers should be aware that many of the costs per positive result found in this study may be greatly increased in the future because of intellectual property restrictions.[31]

Adoption by 3rd Party Payers

While price does not appear to have a strong effect on the number of tests ordered by neurologists, the contribution of insurance may influence whether patients go ahead and get genetic testing. When insurance does cover costs for Athena's Complete Ataxia Panel, generally leaving an estimated 20%, or $1,500 co-pay, almost all patients who were not personally opposed to the test would take it. If insurance refused coverage, and patients were required to pay Athena the full price of $7,300 for the Complete Ataxia Panel, both Dr. Bird and Dr. Burke report that patients were likely to pay for the test less than half the time. Additionally, Dr. Burke stated that, "for individual tests for a specific SCA variant, insurance often covered the request because the evidence of its utility was much greater." Dr Bird noted that $7,300 self-pay is prohibitive for most patients.

The neurologists all concurred about the inconsistency in insurance companies deciding to cover a genetic test. The uncertainty surrounding insurance decisions sometimes led to their postponing genetic testing while awaiting insurer pre-approval and often having to write time-consuming letters of justification. All these factors tend to reinforce a two-tiered health system, with full use of genetic testing by the wealthy and many others foregoing SCA genetic tests.

Patient Perspectives

We solicited direct patient input through a web forum. The mission of the National Ataxia Foundation (NAF, www.ataxia.org) is to improve the lives of those suffering from ataxia by offering information, support, and resources. The NAF maintains a bulletin board forum with over 700 users, many of whom have an ataxia or are family members of someone who does. The forum supplies information about where to go for diagnosis and how to cope with the effects of disease. With the cooperation of the NAF, we established a discussion thread on this forum and asked users to discuss their personal stories regarding genetic testing for ataxia.

We began the discussion with a list of questions about genetic testing, about prices, about the involvement of insurance and health plans, and how the results of the tests affected the patients. The questions are listed below, followed by a discussion of the responses. The participants were fully aware they were participating in a public forum. The entire discussion through 17 October 2007 is Appendix A. One purpose of the web survey and online forum was to convey information about patient perspectives to the SACGHS task force. The survey remains online and may expand due to the patient interest in this topic.

[31] Ibid.

The response was impressive, with 30 responses and 450 views of the website over several weeks. The responses indicated that patients were passionate about the issue of access to genetic testing, and their comments provided insight into complexities of genetic testing that complemented the issues raised by the neurologists, the laboratory director, insurance companies, and policy makers.

Who responded?

Among the 16 forum users who responded to our questionnaire, there were two major groups: those diagnosed with a variant of SCA, and others (many of them caregivers or family members). This is almost surely a highly biased, relatively well-informed and therefore unrepresentative sample. For our purposes of getting knowledgeable and informed patient perspectives, however, it was an excellent convenience sample. Of the 16 respondents, 11 had a SCA genetic test performed. Of the 5 without a test, 1 abstained for fear of genetic discrimination, 1 would have a test performed soon, and the other 3 were not covered by their insurance and could not pay for the testing themselves. Of the 11 responders that took the test, 6 were covered by their insurance carrier, the others paid out of pocket. The users who had a diagnosis achieved it through genetic testing by Athena Diagnostics. Those without an SCA diagnosis either took the test and had negative or inconclusive results, or did not take a genetic test.

Responses regarding insurance deciding on coverage sounded a consistent theme: inconsistency in coverage and reimbursement decisions by payers (insurers and health plans):

> Dancingpoodle wrote "*The insurance company said they wouldn't cover the genetic testing since there was no family history and the cost was so high.*"
>
> Jonab wrote, "*I have called my insurer to see if I am covered, and they have told me that I am covered, if it's 'medically necessary'.*"
>
> Rrose wrote, "*My insurance company did not cover the cost of the test. The cost to me was $2500. They told me at the time it was because Athena was not one of their preferred providers. I was required to pay the entire amount upfront, directly to Athena Labs.*"

Should genetic testing have been prescribed earlier?

Users were generally well informed about the various diseases presenting as ataxia and the limitations surrounding current diagnostic methodology. Most users had ataxia or lived with someone who did. They understood that over two dozen variants of SCA had been identified, 12 of which could be genetically tested. They also understood and agreed that these tests should not be prescribed as a screening test for ataxia because a substantial clinical threshold needed to be crossed before a genetic test was warranted. When asked if their neurologist should have prescribed a genetic test earlier, three patients responded that while they would prefer to have the diagnosis made clear earlier, their neurologist ordered genetic testing at the appropriate time. Two patients stated they went through multiple neurologists to get genetic testing ordered, although both came up negative for a known SCA variant.

How has genetic testing for SCA affected you?

Having an undiagnosed progressive neurological condition is frightening and disheartening, yet the users on the forum seemed patient. Diagnosis was an important uncertainty in the lives of many forum participants. Many had been seeking a diagnosis of their symptoms for years. Many did not have a diagnosis for their ataxia and other symptoms despite having undergone extensive diagnostic evaluation, including genetic testing. Despite this, patients encouraged one another regularly to continue the quest

for precise diagnosis. In their view, a positive or negative result on a diagnostic test helped and also advanced medical practice for future patients. They fully understood the lack of cure or prevention for any type of SCA and viewed their participation as essential to changing this.

For participants who received a positive result on a genetic test for SCA, many described complex emotions. A positive result can give knowledge about the disease and its prognosis, but there is no cure.

> Marjorienye wrote, "*First, when I was diagnosed and then more so as my symptoms have worsened, I've felt more and more helpless to fight what is happening to me. I like to at least be somewhat knowledgeable about the disease that's wringing the freedom out of my life, since there's very little I can do to fight it. There's no surgery I can have, no experimental drugs, and rehabilitative techniques will only slow things down, not cure me. Sometimes it seems like knowledge is all I can depend on.*"

Many of the positive results came from users who had a relative with a specific form of SCA already diagnosed through genetic testing. The result was particularly difficult if the patient was asymptomatic (meaning that the test was presymptomatic) or if they had children of their own.[32]

> Rrose stated, "*Having a definite diagnosis is helpful is some ways, as I tend to focus my research, but troubling in other ways with respect to my children. They know I have the same thing as their grandmother, but the whole question of when to tell them they can be tested is very difficult. How do you tell three young men 20, 18 and 16 with no symptoms, to have testing done that might change the course of their life decisions? I'm not sure I have the answer to that.*"

The benefits of a positive result included certainty of diagnosis, clearer prognosis, and information relevant to family planning decisions. The variable severity of SCA among subtypes meant that knowing which type a patient has could have a significant impact on almost every aspect of their life. For example, a patient with SCA6 can expect slow deterioration with relatively mild secondary symptoms.[33] The SCA6 patient may be able to continue working a job not requiring much physical exertion. A diagnosis of SCA3, however, carries a much worse prognosis. A patient can expect to lose mobility in 5-10 years and face rapid progression of secondary symptoms that often leave the patient unable to work. For a younger or asymptomatic patient, a diagnosis of SCA3 may change long-term life planning. Dr. Burke reflected that some patients reevaluate their lives based upon the expected years of functionality. Some patients ask him, "W*hy should I go to college if I know that in 20 years I'll be in a wheelchair?*"

Do you feel you have access to genetic testing taking into consideration financial constraints?

A majority of the responses from the forum stated that even with genetic tests costing as much as $7,300, genetic testing was accessible. In some cases patients only required a single genetic test for a specific SCA variant. These tests, when performed by Athena, cost the patients from $88 to $440 depending on insurance reimbursement and Patient Protection Program (PPP) enrollment. Four of five patients who had a single test performed felt the price was reasonable even if the out-of-pocket expense was the full $480 cost of the test, that is, without insurance coverage or price reduction through the PPP.

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[32] de Villiers C, Weskamp K, Bryer A. The sword of Damocles: the psychosocial impact of familial spinocerebellar ataxia in South Africa. *Am J Med Genet* 1997. 74(3): 270-274.
Smith CO, Lipe HP, Bird TD. Impact of presymptomatic genetic testing for hereditary ataxia and neuromuscular disorders. *Arch Neurol* 2004. 61(6): 875-880.

[33] Maschke M, Oehlert G, Xie TD, Perlman S, Subramony SH et al. Op. cit.

For a patient who did not have a positive diagnosis in their family history, the Complete Ataxia Panel, with its $7,300 price tag, might be the prescribed diagnostic test. If insurance covered the test or the patient successfully enrolls in the PPP, the patient responsibility was $1,500. There were relatively few complaints about the price on the forum. Some comments, however, implied that $1,500 would inflict hardship on their family, especially considering the likely negative result.

> Dancingpoodle wrote, "*I suppose if I felt the test would help cure me if I knew what I had, I would take out a loan to have it done, but since there are no cures at the moment, I don't see a reason for putting that financial burden on my family.*"

Some paid for a complete ataxia panel without any contribution from insurance or the PPP. Such patients included some who got testing from sources other than Athena. Another group of people appeared to be eligible for Athena's PPP but were unaware of the price reduction available. They assumed that denial by insurance was the end of the story, and both the patient and neurologist were unaware of the possibility of negotiating with Athena. In these cases the price of $7,300 reduced testing, with 5 of 9 patients who were rejected by their insurer deciding to forego it. This indicates that both patients and Athena could benefit from greater coverage and reimbursement, and more knowledge about payment assistance and forgiveness programs.

The perceived risk of genetic discrimination is one unfortunate feature of SCA genetic testing. The survey was done before the Genetic Information Nondiscrimination Act passed in May 2008 (and it will not begin to take effect until mid-2009, in any event).

Some who sought testing and might have been eligible for Athena's PPP abstained from using their insurance because they did not want their insurance company to know they were being tested for SCA. These patients voluntarily decided to pay for testing out of pocket and therefore did not qualify for the PPP and often did not qualify for financial hardship reductions through Athena Access either. While respondents on the forum surely did not reflect the general public, but highly selected individuals, it appeared the number foregoing genetic testing might be a significant number among those who would have found clinical value in the information available from the test. Of patients surveyed who had genetic testing and had insurance coverage for the testing, 4 out of 7 patients chose not to notify their insurer (to avoid genetic discrimination for themselves or others in their family). In such cases, the $7,300 price did appear to result in some people choosing not to get tested. Whether or not genetic discrimination actually occurred, as no one reported an actual case of it, perceptions of the risk clearly did lead to decisions not to seek genetic testing. Several respondents were hopeful that GINA, the Genetic Information Nondiscrimination Act, could alleviate health insurance and employment discrimination based on genetic testing if it became law, as it did in May 2008.

Following are the experiences of two respondents describing their hesitation about getting genetic testing. One patient (poolgirl) had the testing covered by insurance, then wished she had not done so due to the possible repercussions if she had tested positive for a SCA variant.

> Poolgirl wrote, "*I had the genetic tests done at a very vulnerable point in my work-up and thankfully they were negative. Given the implications a positive test could have on my children, had I been thinking clearly, I would not have done the tests or would have considered paying for them myself to avoid having them on record. I will not do any tests that become available in the future unless one of my children specifically requests it be done to help guide them if/when they are thinking of having children and if so, I would probably do it off the record. I have no problems with my medical insurance but my personal interaction with my disability company has made me very cynical about trusting*

any insurance carrier to do the right thing."

Another story shows how one patient did not seek insurance reimbursement for her genetic test out of fear that her family would be labeled as a result. The loss of insurance for future generations was a major concern.[34]

> SunnyKay wrote, "*My mother requested that Athena not bill Medicare because she wanted to keep the results private for numerous reasons. That is why a payment plan was arranged instead. My mother not only did not want the health insurance company/Medicare to know about possible SCA results, she did not want to apply for a handicapped license plate with a diagnosis of some form of ataxia either. This is in addition to other things she did to keep anyone from the government or any other unnecessary place from finding out about my Dad's medical history, which of course becomes our and her children's family medical history for life.*"

Conclusions

- Both neurologists and patients stressed that inconsistency in coverage and reimbursement by payers was as a common problem that has real consequences for patients and their families by reducing access to genetic tests for SCA.
- All three neurologists interviewed agreed that a prescription for SCA genetic testing was based primarily on best medical practice, and the clinical value of information, not price. Despite their belief that Athena's prices are higher than if SCA were available in their home institution's laboratory, they did not describe any reduction in recommending genetic testing, and it was unclear whether lowering the price of testing to $100 would increase the number of tests they ordered. They noted, however, that price did affect their patients, who must decide if the value of the genetic testing information is worth the cost, and so high price reduces utilization (and if this information is deemed clinically useful, then also access).
- The neurologists emphasized the care they must take to ensure they never give a diagnosis of SCA lightly, either positive or negative. An incorrect diagnosis can have devastating consequences. From the neurologists' perspective, one advantage of sending samples to Athena for testing is that the liability risks associated with the tests themselves are then borne by Athena. However, this transfer of liability would apply equally to testing sent to any clinical laboratory facility, and is not unique to Athena.
- When applicable, Athena's "Patient Protection Program" can reduce the financial outlay out-of-pocket, and Athena Access is also available for case-by-case review of hardship. This feature was cited in the patient forum as valuable and may help explain the relative dearth of complaints about Athena's pricing. The actual use of this program is unknown, but statistics from Athena's 2001 stock offering suggest 85% of revenues derive hospital and other facility billing, rather than direct patient or insurance payments. Not all patients know about Athena's Patient Protection Program, which can reduce patient out-of-pocket outlays to 20% of test price. Some who do

[34] We note that in this case, health insurance discrimination from a Medicare carrier is unlikely because Medicare is an entitlement and does not entail medical underwriting. This response may reflect an incomplete understanding of Medicare. It is possible, however, that sunnyKay was worried about how a Medicare reimbursement record might affect insurance status of a younger member of the family not in Medicare. It is unlikely, however, that a specific Medicare genetic testing reimbursement decision would affect underwriting, independent of other information potentially in the medical record and available for any medical underwriting involving another family member. This perception of high risk of genetic discrimination is therefore probably not an accurate assessment or real risk, but it also shows that perception of risk can heavily influence the choice to get a genetic test.

know about it choose not to avail themselves of it for fear of losing health insurance. However, Athena's reported financial data suggest this program is likely applicable to only a small part of Athena's revenue stream (10-15%), and proably a roughly comparable fraction of patients. It is also possible that some patients may not complain about test costs because most of the unreimbursed cost of testing is absorbed by the institutions that are billed directly for testing by Athena.

- From the patient perspective, the main benefit of in-house testing would be any decrease in cost and direct connection between the clinician ordering the tests and the laboratory performing them. Unlike some other case studies, we do not have lists of prices for test providers other than Athena. One published study (Edlefsen et al. 2007) estimated the cost of ataxia testing at an institution would increase nearly seven-fold if all patented tests were referred to Athena rather than being performed by the institution's laboratory. Another estimate of testing price for the five most common SCA mutations was $1,500 for a university laboratory compared to $2,300 for Athena.
- Use of genetic testing is reduced by fear of genetic discrimination by insurers, health plans and employers, which leads some not to seek third-party reimbursement for genetic tests. This was a factor for roughly half those who had insurance coverage, and clearly led to some choices to not get genetic testing despite valuing the clinical information that would result from the tests.
- We cannot discern in most cases whether this fear of genetic discrimination is warranted or merely perceived. Given the long search for a diagnosis in most cases, and thus the accumulation of medical records that would in theory be available to insurers and employers, it could be that the risk attributed to genetic testing specifically is lower than perceived—not necessarily because the risk is not there, but because risks of exclusion from health insurance, disability insurance, employment, or long-term care insurance are present even without the specific action of taking a genetic test. Seeking reimbursement does trigger payer scrutiny, and so the risk of genetic discrimination that some respondents attributed to genetic testing could still be real. Patients expressed a desire for GINA to become law, echoing the calls from the Genetic Alliance and other groups. Passage of the Act, however, will affect employment and health insurance, but not other forms of insurance for disability, life, and long-term care.
- Not all patients know about Athena's Patient Protection Program, which can reduce patient out-of-pocket outlays to 20% of test price. Some who do know about it choose not to avail themselves of it for fear of losing health insurance. GINA's provisions for health insurance may ameliorate this problem when they begin to take effect in 2009.
- The laboratory director believed that exclusive licensing of patented tests created significant barriers to patient access. He believed that academic institutions exclusively licensing patents to single-source providers were short-sighted and did not take into account that a university can achieve an equivalent royalty stream without giving exclusive control of their patents to a single company. He asserted that academic institutions should not accept an exclusive license bid for technologies that can readily enter the market. He believed this was especially true for patents on many diagnostic tests, where the scientific advance may simply be a new combination of nucleotides used as a primer for a previously unidentified gene.

Acknowledgements

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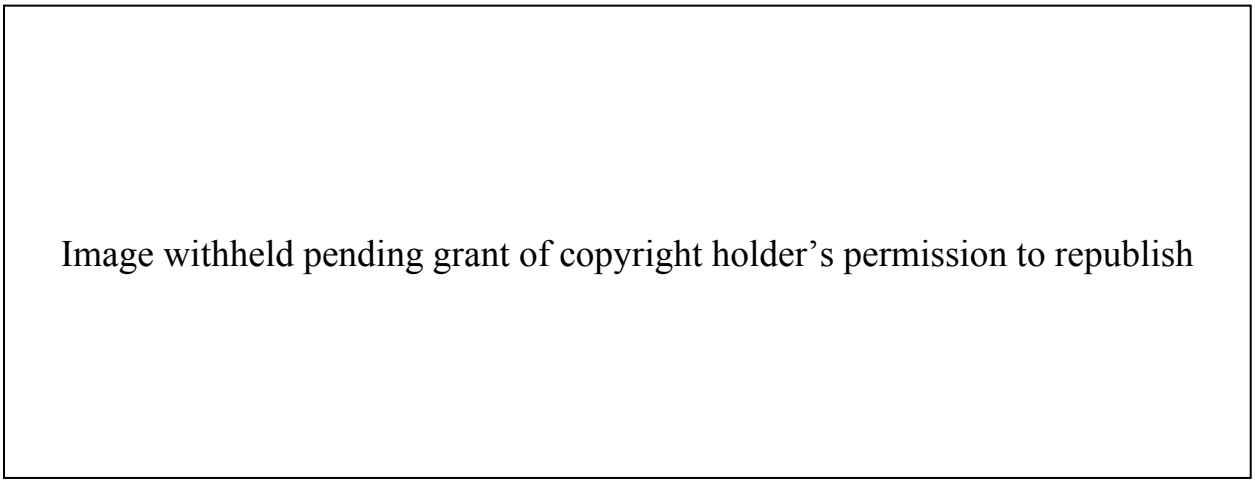
This case study was reviewed by Michael Henry, Athena Diagnostics; Jonathan Tait, University of Washington; Octavio de Marchena, Neurology Associates, Lynchburg, VA; James Burke, Duke University; Michael Hopkins, Sussex University; and Thomas Bird, University of Washington.

Tables & Figures

Table 1. Classification of SCA variants

There are currently 24 genetically distinct forms of SCA. The trinucleotide repeat disorders, SCA1-8, comprise 65-80% of diagnosed patients. The classifications labeled in grey are those tested for in Athena Diagnostic's Complete Ataxia Panel ($7,300). Adapted from Zumrova A. Problems and possibilities in the differential diagnosis of syndrome spinocerebellar ataxia. *Neuro Endocrinol Lett* 2005. 26(2): 98-108.



Genetic Test	Utility	Reference Value	CPT Codes
SCA1	Detects CAG triplet repeat expansion in the SCA1 gene	Normal: < 35 CAG trinucleotide repeats	83891(1), 83898(1), 83904(1), 83909(1), 83912(1)
SCA2	Detects CAG triplet repeat expansion in the SCA2 gene	Normal: < 31 CAG trinucleotide repeats	83891(1), 83898(1), 83909(1), 83912(1)
SCA3	Detects CAG triplet repeat expansion in the SCA3 gene	Normal: < 40 CAG trinucleotide repeats	83891(1), 83898(1), 83909(1), 83912(1)
SCA5	Detects sequence variations in three exons in the Spectrin (SPTBN2) gene known to cause SCA5	No sequence variations detected	83891(1), 83898(3), 83904(3), 83912(1)
SCA6	Detects CAG triplet repeat expansion in the SCA6 gene	Normal: < 18 CAG trinucleotide repeats	83891(1), 83898(1), 83909(1), 83912(1)
SCA7	Detects CAG triplet repeat expansion in the SCA7 gene	Normal: <18 CAG trinucleotide repeats	83891(1), 83898(1), 8909(1), 83912(1)
SCA8	Detects CTA/CTG triplet repeat expansions in the SCA8 gene	Normal: < 50 CTA/CTG trinucleotide repeats	83891(1), 83898(1), 83909(1), 83912(1)
SCA10	Detects ATTCT pentanucleotide expansions in the SCA10 gene	Normal: < 22 ATTCT pentanucleotide repeats detected	83891(1), 83898(1), 83909(1), 83912(1)
SCA13	Detects sequence variations in all of exon 2 and 20 bp of intronic sequence	No sequence variations detected	83891(1), 83898(4), 83904(4), 83909(1), 83912(1)
SCA14	Detects mutations in the SCA14 gene	No sequence alteration detected	83891(1), 83898(15), 83904(16), 83909(1), 83912(1)
SCA17	Detects CAG/CAA triplet repeat expansions in the SCA17 gene	Normal: < 42 CAG/CAA trinucleotide repeats	83891(1), 83898(1), 83909(1), 83912(1)
Frataxin	Detects GAA triplet repeat expansion in the Frataxin gene	Normal: < 33 GAA trinucleotide repeats	83891(1), 83894(1), 83898(1), 83912(1)
Aprataxin	Detects mutations in the aprataxin gene	No sequence alteration detected	83891(1), 83898(7), 83904(7), 83909(1), 83912(1)

Table 2. Description of Genetic Tests on Athena's Complete Ataxia Panel

The Complete Ataxia Panel test for 11 subtypes of SCA, as well as Friedreich's Ataxia and Early Onset Ataxia. Listed are the utility of the test and the reference value of normal for each test. CPT codes are also provided.

Genetic Test	US Patents	**Assignee**
SCA-1	**5741645, 5834183**	Regents of the University of Minnesota, Minneapolis, MN
SCA-2	**6251589**	SRL, Inc., Tachikawa, Japan
SCA-3	**5840491**	Akira Kakizuka, Kyoto, Japan
SCA-6	**5853995**, **6303307, 7329487**	Research Development Foundation, Carson City, NV
SCA-7	**6280938, 6514755**, **7118893**	Regents of the University of Minnesota, Minneapolis, MN
SCA-8	6524791	Regents of the University of Minnesota, Minneapolis, MN
SCA-10	6855497	Baylor College of Medicine, Houston, TX
Friedrichs Ataxia (Frataxin)	6150091	Baylor College of Medicine, Houston, TX, INSERM, Paris, France
Aprataxin	**7119186**	Athena Diagnostics, Inc., Worcester, MA

Table 3. Patents associated with Athena's Complete Ataxia Panel

Athena Diagnostics controls 11 patents (in bold) for 6 tests for hereditary ataxia by exclusive licenses. It also holds a non-exclusive license to US6855497 for SCA-10 testing.
Additional patents for SCA-2 (US6623927, US6673535 and US6844431) were found in our search that Athena does not appear to have licensed.

Provider	Applied Genomics Center at Samaritan	Athena Diagnostics	Baylor College of Medicine	Boston University	Comprehensive Genetic Services, SC	Johns Hopkins University	Reproductive genetics Instutute	US Air Force DNA Diagnostic Laboratory
Lab Name	Genesis Genetics Institute	Reference Lab	Molecular Genetics Laboratories	Center for Human Genetics	Molecular Diagnostic Laboratory	Neurogenetic Testing Laboratory		
Website/ Email	www.genesisgenetics.org	www.athenadiagnostics.com	www.bcm.edu/geneticlabs/	www.bumc.bu.edu	www.compgene.com/	aagarw1@jhmi.edu	www.reproductivegenetics.com/	julie.mcclellan@kirtland.af.mil
Phone	1-313-544-4006	1-800-394-4493	1-800-411-4363	1-617-638-7083	(877) - COMPGENE	(410) 955-1349	773-472-4900	(228) 377-6727
Notes	Prenatal	Adult	Adult and Prenatal	Adult and Prenatal	Adult and Prenatal	Research Only	Prenatal	Military only
Adult Pricing	N/A	PCR=$440 Sequencing=$2,335	$335	SCA1=$310 Others $175	$208	N/A	N/A	N/A
Test Method								
SCA1 Targeted Mutation Analysis (PCR)		X	X	X	X			X
SCA2 Targeted Mutation Analysis (PCR)	X	X		X	X		X	X
SCA3 Targeted Mutation Analysis (PCR)	X	X		X	X		X	X
SCA5 Sequence analysis of entire coding region		X						
SCA6 Targeted Mutation Analysis (PCR)		X		X	X	X	X	X
SCA7 Targeted Mutation Analysis (PCR)	X	X		X	X		X	X
SCA8 Targeted Mutation Analysis (PCR)		X		X	X			
SCA10 Targeted Mutation Analysis (PCR)		X	X	X	X			
SCA12 Targeted Mutation Analysis (PCR)				X		X		
SCA13 Sequence analysis of entire coding region		X						
SCA14 Sequence analysis of entire coding region		X						
SCA17 Targeted Mutation Analysis (PCR)		X		X				
Frataxin Targeted Mutation Analysis (PCR)		X		X	X			
Aprataxin Sequence analysis of entire coding region		X		X				

Table 4. Summary of Genetests.org laboratory directory for SCA testing

Patented tests are labeled in grey. Both tests performed by Johns Hopkins are used for research purposes only.

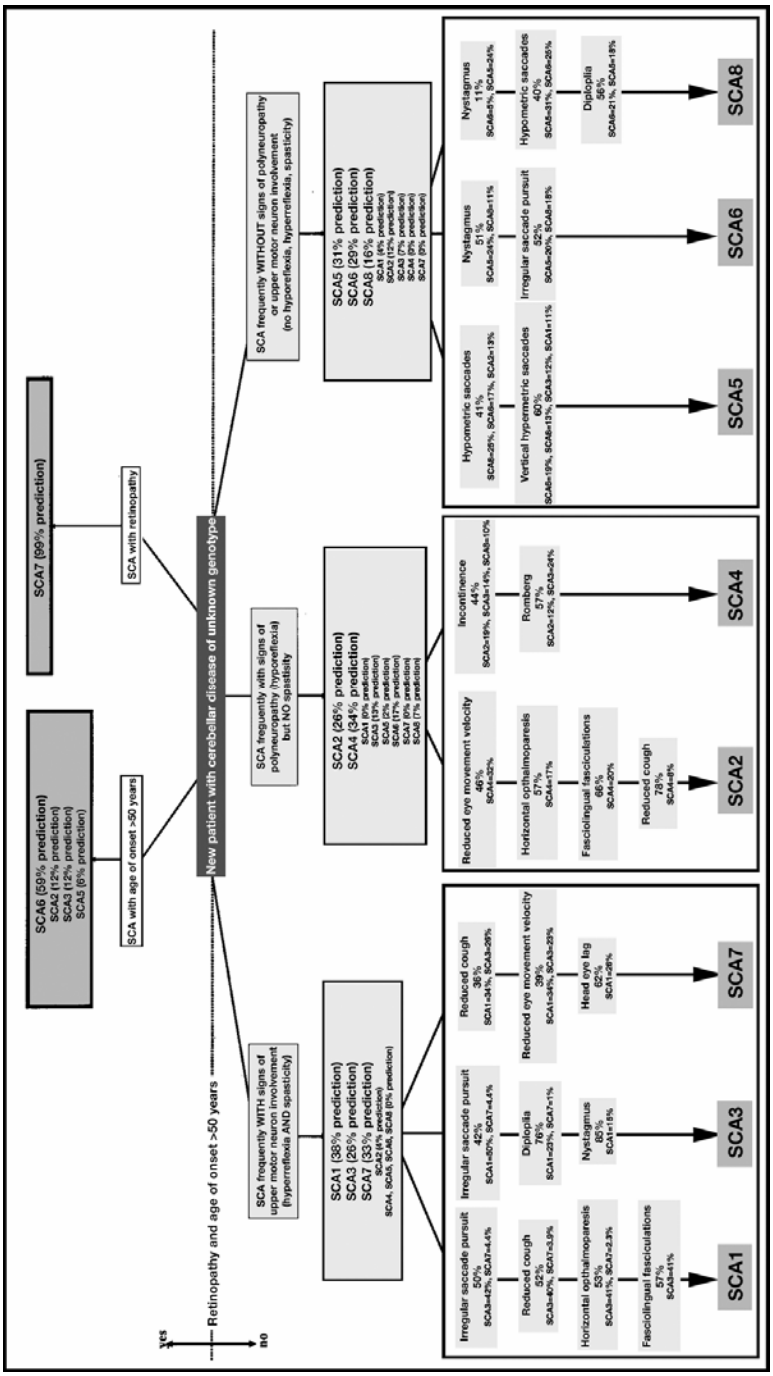


Figure 1. Clinical scales used to determine SCA variants

Many neurologists have attempted to create neurological tests that can increase SCA diagnose accuracy before attempting genetic testing. Adapted from Mashke M et al. Clinical feature profile of spinocerebellar ataxia type 1-8 predicts genetically defined subtypes. *Movement Disorders* 2005. 20(11):1405-1412, at 1410.

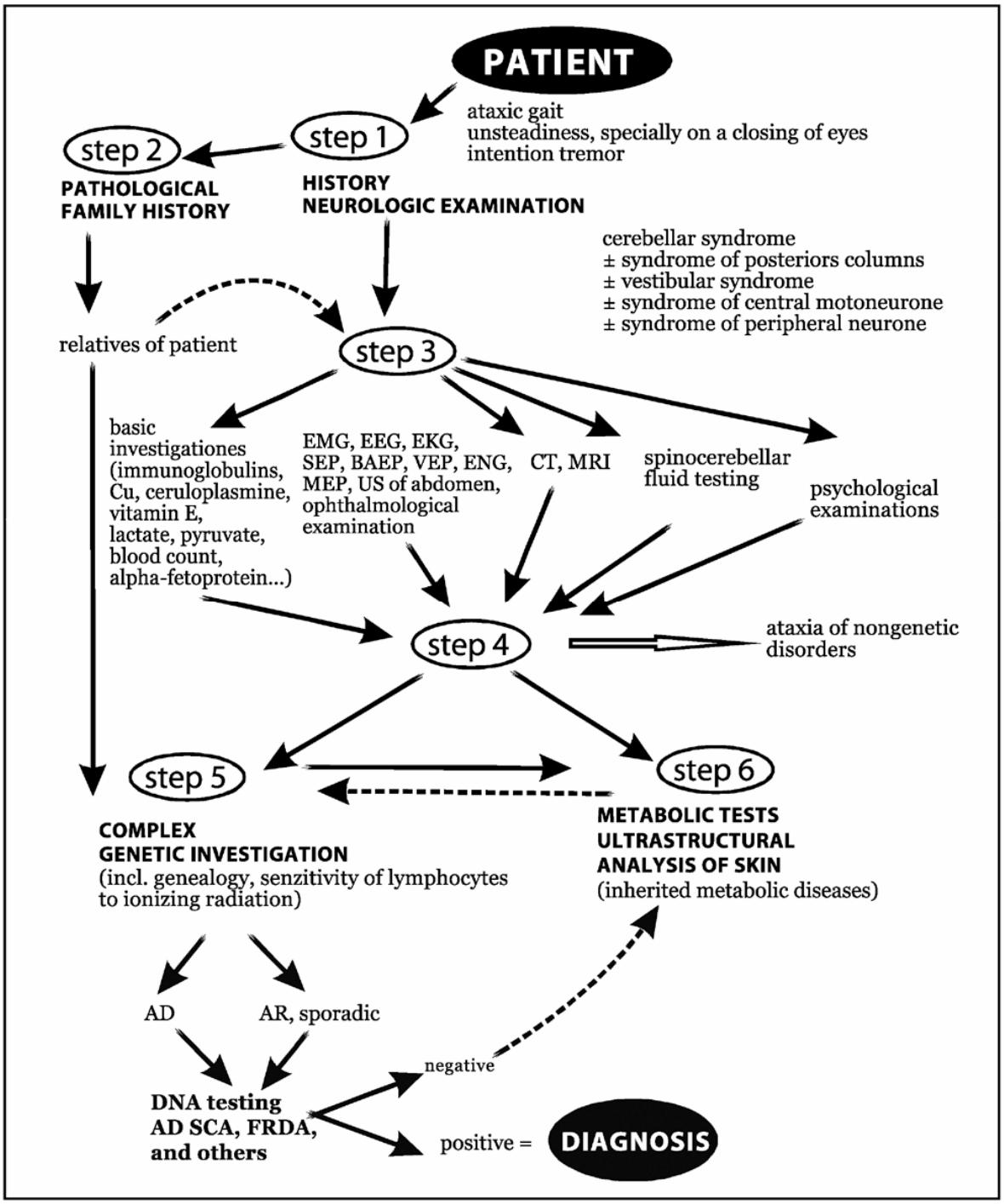
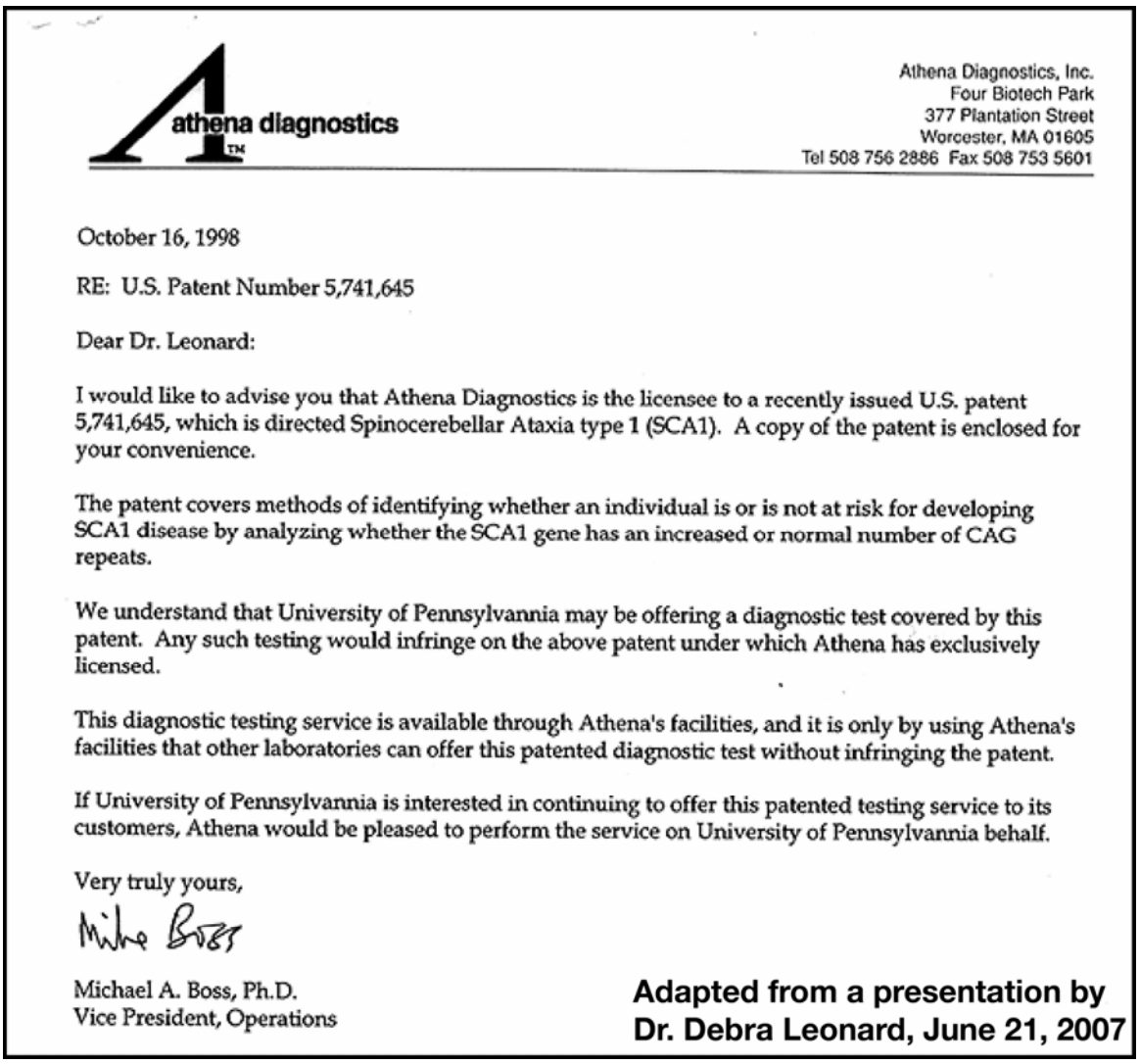


Figure 2. Diagnostic tree for Spinocerebellar Ataxia

The diagnostic tree for SCA relies on many different tools. The most powerful remains family history, as this can quickly bring a patient to genetic testing. Because most ataxias are sporadic (not due to known inheritable factors), genetic testing does not occur early in the tree. Adapted from Adapted from Zumrova A. Problems and possibilities in the differential diagnosis of syndrome spinocerebellar ataxia. *Neuro Endocrinol Lett* 2005. 26(2): 98-108.



athena diagnostics™

Athena Diagnostics, Inc.
Four Biotech Park
377 Plantation Street
Worcester, MA 01605
Tel 508 756 2886 Fax 508 753 5601

October 16, 1998

RE: U.S. Patent Number 5,741,645

Dear Dr. Leonard:

I would like to advise you that Athena Diagnostics is the licensee to a recently issued U.S. patent 5,741,645, which is directed Spinocerebellar Ataxia type 1 (SCA1). A copy of the patent is enclosed for your convenience.

The patent covers methods of identifying whether an individual is or is not at risk for developing SCA1 disease by analyzing whether the SCA1 gene has an increased or normal number of CAG repeats.

We understand that University of Pennsylvannia may be offering a diagnostic test covered by this patent. Any such testing would infringe on the above patent under which Athena has exclusively licensed.

This diagnostic testing service is available through Athena's facilities, and it is only by using Athena's facilities that other laboratories can offer this patented diagnostic test without infringing the patent.

If University of Pennsylvannia is interested in continuing to offer this patented testing service to its customers, Athena would be pleased to perform the service on University of Pennsylvannia behalf.

Very truly yours,

Mike Boss

Michael A. Boss, Ph.D.
Vice President, Operations

Adapted from a presentation by Dr. Debra Leonard, June 21, 2007

Figure 3. Example of a Cease and Desist Letter

Athena Diagnostics has protected their intellectual property rights using letters like the above.

Impact of Patents and Licensing Practices on Access to Genetic Testing and Carrier Screening for Tay-Sachs and Canavan Disease

Alessandra Colaianni, B.A., Subhashini Chandrasekharan, Ph.D., and Robert Cook-Deegan, M.D.*

Introduction

Tay-Sachs and Canavan disease are both neurological conditions that predominantly but not exclusively affect the Ashkenazi Jewish population. Carrier screening and genetic diagnosis for Tay-Sachs are mainly through enzyme assay, with DNA-based testing for ambiguous cases or for diagnostic confirmation. DNA-based analysis is the mainstay for both screening and diagnostic confirmation of Canavan disease. Nonprofit research institutions obtained patents on both relevant genes, first the gene that when mutated cause Tay-Sachs (the HEXA gene encoding the enzyme hexosaminidase A) and later for Canavan disease (the ASPA gene encoding aspartoacylase). The inventor for the HEXA patent worked at the National Institutes of Health, a government laboratory, and her Tay-Sachs patent was never licensed. That discovery is, therefore, effectively in the public domain. The patents relevant to Canavan disease, in contrast, were licensed by Miami Children's Hospital. The patents were eventually nonexclusively licensed at least 20 times. Patenting and licensing were initially highly controversial and led to litigation. Because the two diseases are similar pathologically and affect the same population, this difference in licensing history created a natural experiment to assess the impact of licensing practices on patients' and physicians' clinical access to genetic tests.

Background

Tay-Sachs disease (TSD) is a progressive disease that destroys brain function. TSD is caused by inheriting two mutated copies of the HEXA gene (one from each parent), which produces the hexosaminidase A subunit of an enzyme-protein complex. In an unaffected individual, the enzyme is part of a pathway that degrades Gm2 gangliosides, complex protein-carbohydrate molecules. In an individual affected by TSD, the absence or reduced activity of the enzyme causes the Gm2 gangliosides to build up in the brain—the metabolic pathway is blocked. This causes progressive destruction of the central nervous system. There are three types of TSD, differentiated by age of onset: acute infantile, juvenile, and late-onset. Infantile onset is the most common. In the classic progression of acute infantile TSD, the infant gets progressively weaker and loses motor skills between the ages of six months and three years. The infant has progressively diminished attentiveness and an exaggerated startle response. As TSD continues to destroy the brain, the infant suffers seizures, blindness, and eventually death, which usually occurs before four years of age. Death is painful for its victim and agonizing for parents and family. There is no cure for TSD, and treatment is limited to supportive care.[1]

Canavan disease also causes progressive deterioration of the brain. It is caused by inheriting two mutated copies of the ASPA gene, which encodes the aspartoacylase enzyme. In a normal individual, aspartoacylase breaks down *N*-acetylaspartic acid (NAA). In Canavan disease, the lack of aspartoacylase leads to a buildup of NAA in the brain, which causes demyelination and degeneration. [2] Symptoms of Canavan disease are macrocephaly (larger-than-normal head size), lack of head control, developmental delays by the age of three to five months, and loss of muscle control. As the brain continues to deteriorate,

* Center for Genome Ethics, Law & Policy, Institute for Genome Sciences & Policy, Duke University

[1] Kaback, M. *Hexosaminidase A Deficiency*. See http://www.genetests.org/servlet/access?db=geneclinics&site=gt&id=8888891&key=aMeTZgBKBQcB9&gry=&fcn=y&fw=mD3m&filename=/profiles/tay-sachs/index.html [accessed February 22, 2008].

[2] Matalon R, Michals K, Kaul R. Canavan disease: from spongy degeneration to molecular analysis. *The Journal of Pediatrics*1995. 127(4):511-517, at 511, 512.

the affected child suffers from muscle spasms and seizures. Individuals with Canavan disease are expected to live into their teens.[3] Like TSD, there is no cure for Canavan disease, and treatment is limited to supportive care.

	Tay-Sachs disease	**Canavan disease**
Mode of Inheritance	Autosomal Recessive[4*]	Autosomal Recessive[5]
Cause	Hexosaminidase A deficiency, leading to buildup of Gm2 gangliosides in neuronal cells[6]	Aspartoacylase deficiency leading to buildup of N-acetylaspartic acid, leading to demyelination and spongy degeneration of the brain[7]
Symptoms	Weakness, loss of motor skills, decreased attentiveness, increased startle response, death usually before age four[8]	Macrocephaly (large head), lack of head control, hypotonia (lack of muscle tone), seizures, spasticity, failure to achieve independent sitting, ambulation, or speech, death usually before teenage years[9]
Treatment	Supportive	Supportive
Carrier Rate (Ashkenazim)[10]	1:31	1:41
Natural Incidence[11]	1:3000	1:6400

*In an autosomal recessive inheritance pattern, if both parents are carriers of a mutation that reduces the activity of the resulting enzyme protein, each offspring has a one in four chance of receiving the mutated gene from both parents, and thus being affected by the condition.

Because there is no official disease registry for either TSD or Canavan disease, it is difficult to estimate how many children in the US are affected per year by each disease. However, Kim Crawford, the Director of Member Services at the National Tay-Sachs and Allied Diseases Foundation (NTSAD) estimated, based on the Foundation's best data, that there are 12-15 new infantile diagnoses of Tay-Sachs disease a year, and approximately 50 children currently living in the US with Tay-Sachs.[12] NTSAD is the primary support community for families affected by Tay-Sachs, so their estimates are likely as accurate as can be found. Estimates for Canavan disease are more difficult to find because data for the Canavan community is divided among three major centers: NTSAD, the United Leukodystrophy Foundation, and the Canavan Foundation. However, Drs. Paola Leone (University of Medicine & Dentistry of New Jersey) and Edwin Kolodny (New York University Medical Center) estimate that they see an average of 15-30 new cases a

[3] Matalon R. *Canavan Disease*. See http://www.genetests.org/servlet/access?db=geneclinics&site=gt&id=8888891&key=aMeTZgBKBQcB9&gry=&fcn=y&fw=6vhk&filename=/profiles/canavan/index.html [accessed February 22, 2008].
[4] Kaback M. *Hexosaminidase A Deficiency*. Op. cit.
[5] Matalon R. *Canavan Disease*. Op. cit.
[6] Kabac, M. *Hexosaminidase A Deficiency*. Op. cit.
[7] American College of Obstetricians and Gynecologists Committee on Genetics. Committee opinion number 212: screening for canavan disease. *International Journal of Gynecology & Obstetrics* 1998. 65: 91-92, at 91.
[8] Kaback M. *Hexosaminidase A Deficiency*. Op. cit.
[9] Matalon R. *Canavan Disease*. Op. cit.
[10] Monaghan KG, Feldman GL, Palomaki GE, Spector EB, Ashkenazi Jewish Reproductive Screening Working Group, and Molecular Subcommittee of the ACMG Laboratory Quality Assurance Committee. Technical standards and guidelines for reproductive screening in the Ashkenazi Jewish population. *Genetics in Medicine* 2008. 10(1):57-72, at 69.
[11] Based on a carrier rate of 1:30 and 1:40, respectively, described in: American College of Obstetricians and Gynecologists. Committee opinion 298: prenatal and preconceptional carrier screening for genetic diseases in individuals of Eastern European Jewish descent. *Obstetrics & Gynecology* 2004. 104(2):425-8, at 426.
[12] Ms. Crawford's estimates also include cases of Sandhoff's disease, a clinically similar disorder.

year.[13] Lois Neufeld, past president of the Canavan Foundation, estimated in a phone interview that there are at least 500 children in the US living with Canavan disease.[14]

Genetic Tests for Tay-Sachs and Canavan Disease, and Associated Patents

For a summary, see the timeline in the appendix below.

Tay-Sachs

There are two basic types of tests used to screen people for Tay-Sachs disease: one is an enzyme assay, and the other is a DNA-based test. The enzyme test, which was the basis of many carrier screening campaigns in the US, is still widely used for carrier screening and diagnosis. The DNA-based test can be used to confirm an inconclusive enzyme test, to identify the specific mutation in an individual, to evaluate an individual for a pseudodeficiency[15] allele (a sequence variant that does not alter protein function sufficiently to cause disease), for carrier testing, and for prenatal testing, including pre-implantantation genetic diagnosis (PGD).[16] Some members of the Ashkenazi population use the HEXA DNA test for carrier screening, before an enzyme test.[17] Because the enzyme test will detect all those affected while the DNA test will detect only those affected by known mutations,[18] some carriers may not be identified by the DNA test alone.

Enzyme Test

Drs. John O'Brien and Shintaro Okada developed the first enzyme test in the early 1970's.[19] Dr. Michael Kaback modified O'Brien's enzyme test and used it to spearhead a Tay-Sachs carrier screening campaign in Washington and Baltimore in the 1970's.[20] As a result of the Baltimore/Washington screening campaign, more than 100 cities began their own Tay-Sachs screening campaigns, which resulted in a greater than 90 percent reduction in the disease incidence.[21] The Dor Yeshorim screening program for members of the orthodox Jewish community, led by Rabbi Josef Ekstein, also used this enzymatic test for its carrier screening campaigns.[22] The enzyme test detects enzyme function: carriers (people with one normal and one abnormal allele) have 50 percent normal enzyme function, and those with the disease have less than 10 percent enzymatic function.[23] The enzyme test detects approximately 97-98 percent of

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[13] Author's e-mail communication with Dr. Edwin Kolodny, Bernard A. and Charlotte Marden Professor of Neurology, and Department of Neurology, New York University. August 29, 2007. Author's telephone conversation with Dr. Paola Leone, Associate Professor, Department of Cell Biology, University of Medicine and Dentistry of New Jersey, July 12, 2007.
[14] Phone interview with Lois Neufeld, President, Canavan Foundation, by Catherine Alessandra Colaianni, June 27, 2007.
[15] Individuals with one or two copies of the pseudodeficiency alleles (R247W or R249W) falsely appear to be TSD carriers based on enzyme analysis. This is caused because the hexosaminidase enzyme in these individuals has reduced activity towards the artificial substrate used in the biochemical screening method. Individuals with the pseudodeficiency alleles are not carriers (Monaghan KG et al. Op. cit. at 62.)
[16] Monaghan KG, Feldman GL, Palomaki GE, Spector EB, Ashkenazi Jewish Reproductive Screening Working Group, and Molecular Subcommittee of the ACMG Laboratory Quality Assurance Committee. Op. cit. at 61.
[17] Kaback M. *Hexosaminidase A Deficiency*. Op. cit.
[18] Monaghan et al. put the sensitivity of the enzyme test at 97-98 percent, and the DNA test at 95 percent (op. cit. at 58, 62).
[19] Ross LF. Heterozygote carrier testing in high schools abroad: what are the lessons for the U.S.? *Journal of Law, Medicine & Ethics* 2006. 34(4):753-764.
[20] Kaback MM, Desnick RJ. Tay-Sachs Disease: from clinical description to molecular defect. *Advanced Genetics* 2001. 44:1-9, at 4.
[21] Kaback MM. Screening and prevention in Tay-Sachs Disease: origins, update, and impact. *Advanced Genetics* 2001. 44:253-265, at 257, 259.
[22] Wailoo K, Pemberton S. Eradicating a 'Jewish Gene': promise and pitfalls in the fight against Tay-Sachs Disease. In: *The Troubled Dream of Genetic Medicine: Ethnicity and Innovation in Tay-Sachs, Cystic Fibrosis, and Sickle Cell Disease*. Baltimore: The Johns Hopkins University Press, 2006, 14-61, at 41.
[23] Ross LF. Op. cit.

carriers, no matter their specific mutation.[24] Versions of this enzyme test are still widely used today. According to Dr. Kaback, there was never any effort to patent the original Tay-Sachs enzyme test.[25]

DNA Test

Dr. Rachel Myerowitz was working as a postdoctoral fellow at the NIH under Dr. Elizabeth F. Neufeld when she decided to clone the defective Tay-Sachs gene. She had previously done her biochemistry thesis at the University of Michigan on GM1 gangliosidosis, another rare lysosomal disorder. When she began in Dr. Neufeld's lab, she worked on Hurler syndrome, another lysosomal disorder caused by defective iduronidase enzyme,[26] and decided that she wanted to clone the iduronidase gene. However, material from Tay-Sachs patients was easier to obtain, so she switched to cloning the genes for hexosaminidase.[27] Dr. Myerowitz isolated a cDNA clone of the HEXA gene in 1983 and published these results in 1984.[28] In 1984, Dr. Neufeld, moved from NIH to UCLA. Dr. Myerowitz remained at the NIH and looked for mutations in the HEXA gene that were present in the Ashkenazi Jewish population.

Patenting the gene had never occurred to her, but, as she put it, "… in the late 1980's, NIH was very interested in patenting stuff. They would come around to your lab and say, 'Do you have anything that you think is patentable?'"[29] Myerowitz was approached by a lawyer from NIH who advised her to file a patent application. NIH filed a patent application in 1986[30] and was granted two patents: the first, US 5,217,865 "Screening for Tay-Sachs disease with cloned DNA for beta-hexosaminidase," issued in 1993, which covers diagnostic testing; and the second, US 5,475,095 "Nucleic acid compositions for the alpha chain of beta-hexosaminidase," issued in 1995, which covers the HEXA gene itself.[31]

Myerowitz left the NIH in 1993 for a position at St. Mary's College of Maryland. In 2000, she contacted the NIH legal department to ask about developments with the patents. The legal department told her that although they knew the DNA test based on the patents was widely used, they had never drafted a license because going after infringers was "more trouble than it [was] worth."[32] Thus, although the Tay-Sachs gene was patented, the patents were never licensed, and never enforced.

Canavan Disease

The gene for Canavan disease, called *ASPA*, was discovered and patented by Dr. Reuben Matalon and co-inventors. Dr. Matalon is now at the University of Texas Medical Branch (UTMB) Center for Metabolic Diseases; at the time the gene was discovered and patented, Matalon was affiliated with Miami Children's Hospital (MCH). Matalon had been recruited in May 1987 to search for the cause of Canavan disease while he was a professor at the University of Illinois at Chicago, by Daniel and Deborah Greenberg, a

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[24] Monaghan KG, Feldman GL, Palomaki GE, Spector EB, Ashkenazi Jewish Reproductive Screening Working Group, and Molecular Subcommittee of the ACMG Laboratory Quality Assurance Committee. Op. cit. at 58.
[25] Email from Michael Kaback, Professor of Pediatrics, University of California San Diego, to Catherine Alessandra Colaianni, September 17, 2007.
[26] Clarke LA. *Mucopolysaccharidosis Type 1*. See http://www.genetests.org/servlet/access?db=geneclinics&site=gt&id=8888891&key=pwy2S875SvRNh&gry=&fcn=y&fw=-hHx&filename=/profiles/mps1/index.html [accessed February 22, 2008].
[27] Interview with Dr. Rachel Myerowitz, Professor, Department of Biology, St. Mary's College of Maryland, by Catherine Alessandra Colaianni, July 31, 2007.
[28] Myerowitz R, Proia RL. cDNA clone for the alpha-chain of human beta-hexosaminidase: deficiency of alpha-chain mRNA in Ashkenazi Tay-Sachs fibroblasts. *Proc Natl Acad Sci USA* 1984. 81(17):5394-8.
[29] Interview with Dr. Rachel Myerowitz. Op. cit.
[30] US patent 5,217,865 has a filing date of 10/31/88 and US 5,475,095 has a filing date of 12/7/93; however, both stemmed from one original application 889,502, filed 7/5/86. During the patent prosecution process, the original application's claims were split into two separate patents.
[31] US patents 5,217,865 and 5,475,095.
[32] Interview with Dr. Rachel Myerowitz. Op. cit.

Chicago-based family that had two children, Jonathan and Amy, born with Canavan disease.[33] By 1988, Matalon had discovered and published an article in the *American Journal of Medical Genetics* about the aspartoacylase deficiency that causes Canavan disease.[34] In 1989, Matalon took a position as director of research at the MCH.[35]

In 1990, Matalon published a paper in the *Journal of Inherited Metabolic Diseases* detailing a prenatal enzymatic screening test that could diagnose Canavan disease using amniocytes (cells taken from the amniotic fluid of a gestating pregnancy) or chorionic villus sampling (CVS; cells taken from the placenta).[36] However, the enzymatic testing method proved to be unreliable: it resulted in the births of four babies with Canavan disease, who had been prenatally screened and pronounced free of the disease.[37] At least two lawsuits against MCH resulted, which were settled out of court.[38] It was later determined that Matalon's enzymatic test did not work because the amniocytes and CVS did not have enough enzymatic activity to provide an accurate screen.[39] Matalon's enzymatic test also could not distinguish adult Canavan carriers from non-carriers.[40] Matalon did not receive a patent on this test. In 1993, Bennett et al. published results that suggested that prenatal diagnosis using an enzyme assay of amniotic fluid (rather than amniocytes or CVS) provided more reliable results.[41] However, complications with the amniotic fluid assay were reported: it was only reliable at the extremes, and mid-range levels of enzyme activity were inconclusive.[42] According to the National Tay-Sachs and Allied Diseases Association (NTSAD), only two or three laboratories in the US offer that test.[43] One study recommended that DNA sequencing should accompany amniotic fluid screening wherever possible.[44] The Bennett et al. test was not patented.[45] Unlike Tay-Sachs disease, then, the only way to provide carrier screening for Canavan disease was through DNA-based testing, and DNA-based prenatal diagnosis would be an easier and more reliable method than amniotic fluid analysis.

On October 1, 1993, Matalon and his researchers published exciting results in *Nature Genetics*: they isolated and sequenced the aspartoacylase gene, and found a common mutation that causes Canavan disease.[46] This made a DNA-based Canavan test possible, and the Ashkenazi population leapt into action. Rabbi Josef Ekstein, who had spearheaded the Dor Yeshorim Tay-Sachs screening campaign in the

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[33] Hahn L. Owning a piece of Jonathan. *Chicago Magazine* 2003 (May). Pp. 83-87, 104-106, at 86.
[34] Matalon R, Michals K, Sebasta D, Deanching M, Gashkoff P, Casanova J. Aspartoacylase deficiency and N-acetylaspartic aciduria in patients with Canavan disease. *American Journal of Medical Genetics* 1988. 29: 463-471.
[35] Hahn L. Op. cit. at 87.
[36] Matalon R, Michals K, Gashkoff P, Kaul R. Prenatal diagnosis of Canavan Disease. *Journal of Inherited Metabolic Diseases* 1992. 15:392-394.
[37] Winerip M. Fighting for Jacob. *The New York Times Magazine* 1998 (December 6). Pp. 56-63, 78-82, 112, at 59.
[38] Hahn L. Op. cit. at 87.
[39] Matalon R, Kaul R, Gao GP, Michaels K, Gray GF, Bennett-Briton S, Norman A, Smith M, Jakobs C. Prenatal diagnosis for Canavan disease: the use of DNA markers. *Journal of Inherited Metabolic Diseases* 1995. 18:215-217, at 215.
[40] American College of Obstetricians and Gynecologists Committee on Genetics. Committee opinion number 212: screening for Canavan disease. Op. cit. at 91.
[41] Bennett MJ, Gibson KM, Sherwood WG, Divry P, Rolland MO, Elpeleg ON, Rinaldo P, Jakobs, C. Reliable prenatal diagnosis of Canavan Disease (aspartoacylase deficiency): comparison of enzymatic and metabolite analysis. *Journal of Inherited Metabolic Disease* 1993. 16:831-6.
[42] Besely GNT, Elpeleg ON, Shaag A, Manning NJ, Jakobs C, Walter JH. Prenatal diagnosis of Canavan disease—problems and dilemmas. *Journal of Inherited Metabolic Disease* 1999. 22: 263-266, at 265.
[43] National Tay-Sachs and Allied Diseases Association, Inc. *What is Canavan Disease*? See www.ntsad.org [accessed February 26, 2008].
[44] Besely GNT, Elpeleg ON, Shaag A, Manning NJ, Jakobs C, Walter JH. Op. cit. at 263.
[45] Author's email communication with Dr. Michael J. Bennett, Professor of Pathology and Laboratory Medicine, University of Pennsylvania. February 13, 2008.
[46] Kaul R, Gao GP, Balamurugan K, Matalon R. Cloning of the human aspartoacylase cDNA and a common missense mutation in Canavan disease. *Nature Genetics* 1993. 5: 118-123.

1980's, screened approximately 13,000 people that year for Canavan disease, and in 1996 the Canavan Foundation offered free testing at New York's Mount Sinai Hospital.[47]

Matalon filed a patent application on September 29, 1993,[48] and was granted two US patents, US 5,679,635 in October 1997, and US 7,217,547 in May 2007, both entitled "Aspartoacylase gene, protein, and methods of screening for mutations associated with Canavan disease."[49] The 1997 patent covered the DNA sequence of the gene, mutated sequences associated with Canavan disease, use of the sequence in DNA testing, and test kits for Canavan disease. The 2007 patent claimed mutated versions of the aspartoacylase protein. The patents were assigned to the Miami Children's Hospital Research Institute, Inc.

After the first patent was granted, MCH's chief financial officer, David Carroll, sent letters to laboratories and hospitals, advising them that MCH had received the patent, and that those doing Canavan's tests would have to take out a license or risk an infringement lawsuit. One such letter, received by Debra Leonard in 1999, stated: "We intend to enforce vigorously our intellectual property rights relating to carrier, pregnancy, and patient DNA tests for Canavan Disease mutations."[50] The letter described a $12.50 royalty for each test (the price was marked down from a reported $25. According to one source, MCH had originally set the price at $50[51]).[52] The letter also set volume limitations, or a limit on the number of tests each individual laboratory could perform (100 tests per academic laboratory).[53]

The enforcement of the MCH patent (US 5,679,635) angered many in the Canavan community, including Rabbi Josef Ekstein, members of the Canavan Foundation, and the Greenberg family. In response, the Canavan Disease Screening Consortium was formed. The Consortium consisted of the Canavan Foundation, the National Tay-Sachs and Allied Diseases Association (NTSAD), the National Foundation for Jewish Genetic Diseases, and the Canavan Research Fund. On January 20, 2000, the Canavan Disease Screening Consortium, including Judith Tsipis (NTSAD), Michael Watson (American College of Medical Genetics), Jon Merz (University of Pennsylvania), Orren Alperstein Gelblum, Rosalind Poss Rosen (both of the Canavan Foundation), and Daniel Greenberg (NTSAD) made a presentation to officials from MCH, explaining that they believed the MCH's licensing policies were too restrictive. They wanted the Canavan patent to be dedicated to the public good, as the University of Michigan's patent for the Cystic Fibrosis gene had been. If the patent could not be dedicated to the public good, they requested four actions from MCH:

(1) Remove the volume cap on testing;
(2) Charge a royalty no more than 1-5 percent of the test price;
(3) Develop an educational outreach program to promote carrier screening; and
(4) Set up a fund to assist people unable to pay for screening or prenatal diagnosis.[54]

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[47] Hahn L. Op. cit. at 104.
[48] US 5679635 has a filing date of September 9, 1994 and US 7217547 has a filing date of October 1, 2001. However, both patents' Parent Case Text show that they stemmed from the same application 08/128,020, filed September 29, 1993.
[49] US patents 5,679,635 and 7,217,547.
[50] Leonard D. Presentation to Secretary's Advisory Committee on Genetics, Health, and Society (2006). See http://oba.od.nih.gov/oba/SACGHS/meetings/June2006/Leonard3.pdf [accessed January 14, 2009].
[51] Joshua Greenberg, son of Daniel and Debbie Greenberg, remembers that the price MCH originally intended to charge was $50, not $25. (Author's communication with Joshua Greenberg, January 25, 2008).
[52] Hahn L. Op. cit. at 105.
[53] Author's interview with Dr. Michael Watson, American College of Medical Genetics, Executive Director, October 1, 2007.
[54] Various presentation materials from the Canavan Disease Screening Consortium, provided by Dr. Michael Watson, Executive Director of the American College of Medical Genetics, who was present at the Canavan Disease Screening Consortium meetings and presentations.

According to Dr. Michael Watson, Executive Director of the American College of Medical Genetics, who was present at the meetings, the representatives of MCH offered an undisclosed sum of money to be used for the proposed educational outreach program, but did not agree to the Consortium's other requests.[55] An article by Jon Merz, who was also present at the meetings, says the offered sum was $20,000 per year, with the further condition that the Consortium members not publicly criticize the MCH. [56] The Consortium welcomed the financial help but did not agree to the gag order.[57]

The MCH marketing plan had two phases: first, MCH would offer nonexclusive licenses to a limited number of academic laboratories, allowing them to perform a limited number of tests per year. Then, MCH would identify a "market leader"—a single, high-volume licensee such as Quest or LabCorp—and grant them an exclusive license on the remainder of the testing volume.[58] According to Dr. Michael Watson, MCH originally planned to offer seven unrestricted licenses to the Canavan patents.[59] The effort to find a single large-volume licensee failed, and in April 2000 MCH revised its licensing plan.[60]

In the meantime, Dr. Debra Leonard had been performing Canavan disease testing in her University of Pennsylvania laboratory since before the patent issued. On advice from counsel, she refused to sign the MCH's license agreement with volume limitations and the $12.50 royalty. However, MCH was owed back royalties from the tests that Leonard had previously performed without a license, and Marc Golden, MCH's advisor and consultant, drafted a settlement agreement that prohibited any University of Pennsylvania physician from "perform[ing] or hav[ing] other(s) perform, any Canavan Tests… without first obtaining a license."[61] This would not only prevent Canavan testing at the University of Pennsylvania, but would also prevent University of Pennsylvania physicians from collecting samples and sending them out to licensed laboratories, until the University of Pennsylvania itself obtained a license, which would be at the discretion of MCH. After negotiations, the University agreed to pay MCH past royalties and not infringe the patent in the future.[62]

In the meantime, tensions rose between the MCH, on one hand, and Leonard and the Consortium, on the other. Both Leonard and members of the Consortium tried to learn the names of the dozen or so laboratories that had taken licenses—Leonard, so that she could send samples to licensed laboratories, and the Consortium so that they could direct the community at risk to laboratories at which they could legally get tested. MCH stated that it would release the names of four laboratories, out of approximately twelve that had obtained licenses, to Dr. Leonard, and did not provide any information about licensed services to the Consortium.[63]

In October 2000, the *Greenberg v. Miami Children's Hospital* lawsuit was filed. MCH had alienated the groups that directly contributed clinical data and samples to help discover the gene associated with Canavan disease, and the constituencies most likely to use genetic testing. That is, the licensing scheme offended important and influential users of the Canavan genetic test. Daniel Greenberg, along with the Canavan Foundation, Dor Yeshorim, NTSAD, and three other plaintiffs who had children afflicted with Canavan disease, sued MCH, the Miami Children's Hospital Research Institute and Reuben Matalon. The plaintiffs filed a six-count complaint, alleging a lack of informed consent, breach of fiduciary duty, unjust

[55] Author's interview with Dr. Michael Watson. Op. cit.
[56] Merz JF. Discoveries: are there limits on what may be patented? In: Magnus D, Caplan A, McGee G, eds. *Who Owns Life?* Amherst, New York: Prometheus Press, 2002, 99-116, at 106.
[57] Ibid.
[58] Ibid., 103.
[59] Author's interview with Dr. Michael Watson. Op. cit.
[60] Merz JF. Op. cit. at 106.
[61] Ibid., 105.
[62] Ibid., 105.
[63] Ibid., 106.

enrichment, fraudulent concealment, conversion, and misappropriation of trade secrets.[64] On August 3, 2003, the case settled confidentially out-of-court, and a gag order prevents us from knowing the exact terms of the settlement. A press release from the Canavan Foundation characterized the agreement as follows:

> Canavan Foundation, National Tay-Sachs & Allied Diseases Association, Daniel Greenberg and David Green have agreed not to further challenge Miami Children's Hospital's ownership and licensing of the Canavan gene patent. Miami Children's Hospital will continue to license and collect royalty fees for clinical testing for the Canavan gene mutation. The Agreement also allows license-free use of the Canavan gene in research to cure Canavan disease, including in gene therapy research, genetic testing in pure research, and in mice used to research Canavan disease.[65]

A phone survey conducted in 2001 by Cho, et al., showed that as of September 2001, four Canavan test providers listed on Genetests.org had stopped performing that test, citing the MCH patent as the reason for stopping.[66] The Cho et al. study did not contain information on exactly how many laboratories were performing the Canavan test before 2001, so it is impossible to say what fraction of labs stopped performing the Canavan test due to patent enforcement.

Testing Facilities and Prices

A 2003 newspaper article reported that MCH had licensed the patent to 15 laboratories.[67] Genetests.org currently lists 37 facilities that provide Canavan disease testing, diagnosis, and/or carrier screening. Of these 37 facilities, 23 are listed as providing mutation analysis, full sequencing, carrier testing, and/or prenatal diagnosis. These are all DNA-based tests, so those labs have most likely taken a license with MCH. Fourteen labs are listed as providing analyte testing only, which does not include DNA analysis and would not require a license.

In June 2007, Genetests.org listed 37 U.S. laboratories providing Canavan testing, and 34 for Tay-Sachs testing. Of these, 26 labs were listed as performing both Tay-Sachs and Canavan testing. A telephone survey of all 45 laboratories offering Canavan testing, Tay-Sachs testing, or both was performed between June and August 2007.[68] In the figures that follow, the tests are divided into several different categories, based both on test category information available from Genetests.org, on the website of the testing service, or descriptions of the type of test performed. Tests were divided into categories of Full Sequence Analysis, Targeted Mutation Analysis, and Enzyme Assay/Analyte. Price per Amplicon for Full Sequence Analysis was calculated by dividing the price of the test by the number of amplicons the test sequences; for Tay-Sachs, full sequencing entails 14 amplicons (for the 14 exons in the gene), and for Canavan disease, full sequencing entails 6 amplicons (for the 6 exons in the gene).

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[64] Federico A. Moreno, US District Judge, Opinion. 264 F. Supp 2d 1064; 2003 U.S. Dist LEXIS 8959; 121 A.L.R. 5th 687; 16 Fla. L. Weekly Fed. D 417.

[65] *Canavan Foundation Press Release*. September 29, 2003. See http://canavanfoundation.org/news/09-03_miami.php [accessed February 26, 2008].

[66] Cho M, Illangasekare S, Weaver MA, Leonard DGB, Merz JF. Effects of patents and licenses on the provision of clinical genetic testing services. *Journal of Molecular Diagnostics* 2003. 5(1): 3-8, at 6.

[67] Hahn L. Op. cit. at 105.

[68] Of the 45, six did not respond to repeated telephone calls. Of the 45, two stated that they no longer offered the Tay-Sachs test, and five no longer offered the Canavan test. In addition, 5 labs stated that they only provided the tests as part of a panel including other genetic tests, and these labs were excluded. Laboratory personnel, usually receptionists or billing staff, were asked for the list price of the test in question. When the tests were only available as part of a panel, we did not report the price of the test. Personnel were not asked whether they had a license for the MCH patents, as a negative answer to such a question could have posed a liability to the laboratory. Personnel were not asked whether they had taken a license of the Tay-Sachs patent, as we knew from the NIH OTT staff that it was never licensed.

Full Sequence Analysis

Laboratory	*TS Test Price*	*CD Test Price*
Ambry Genetics[69]	$1,695	$895
Emory University Department of Human Genetics	$1,488[70]	not offered
New York University School of Medicine Neurogenetics Laboratory[71]	$1500	$1500
Average test price:	**$1536**	**$1198**

Full Sequence Analysis, Price per Amplicon

Laboratory	*TS Test Price*	*CD Test Price*
Ambry Genetics[72]	$121.07	$149.17
Emory University Department of Human Genetics	$106.29[73]	not offered
New York University School of Medicine Neurogenetics Laboratory[74]	$107.14	$250
Average test price:	**$111.50**	**$199.58**

Targeted Mutation Analysis

Laboratory	*TS Test Price*	*CD Test Price*
ARUP Laboratories[75]	$300	$300
Baylor College of Medicine[76]	not offered	$125
Boston University Medical Center[77]	$135	$195
Children's Hospital and Regional Medical Center[78]	not offered	$428.40
Genzyme Genetics[79]	$284	$284
Kimball Genetics[80]	$315	not offered
LabCorp[81]	$334	$345
Mayo Clinic Biochemical Genetics Laboratory[82]	$315	$366.80
New Jersey Medical School[83]	$100	$100

[69] Ambry Genetics Corp., via phone June 21, 2007. (866) 262-7943.
[70] See http://www.genetics.emory.edu/egl/test.php?test_id=148 [accessed January 21, 2009].
[71] New York University School of Medicine Neurogenetics Laboratory, via phone June 26, 2007. (212) 263-6628.
[72] 14 amplicons for TS, 6 amplicons for Canavan disease. Ambry Genetics Corp., via phone January 21, 2009. (866) 262-7943.
[73] 14 amplicons for TS. See http://www.genetics.emory.edu/egl/test.php?test_id=148 [accessed January 21, 2009].
[74] 14 amplicons for TS, 6 amplicons for Canavan disease. New York University School of Medicine Neurogenetics Laboratory, via phone January 21, 2009. (212) 263-6628.
[75] ARUP Laboratories, via phone June 21, 2007. (800) 522-2787.
[76] Baylor College of Medicine, via phone June 21, 2007. (800) 411-4363.
[77] Boston University Medical Center, via phone June 21, 2007. (617) 638-7083.
[78] Children's Hospital and Regional Medical Center, via phone June 20, 2007. (206) 987-2289.
[79] Genzyme Genetics, via phone June 22, 2007. (800) 357-5744 ext. 29407.
[80] Kimball Genetics, Inc., via phone June 21, 2007. (800) 320-1807.
[81] LabCorp, via phone June 21, 2007. (919) 361-7700.
[82] Mayo Clinic Biochemical Genetics Laboratory, via phone June 21, 2007. (800) 533-1710.
[83] New Jersey Medical School, via phone June 22, 2007. (973) 972-4480.

New York University School of Medicine Medical Genetics Lab[84]	$252	$128
New York University School of Medicine Neurogenetics Laboratory	$600	$600
ProGene, Inc.[85]	$175	$175
Quest Diagnostics, Inc.[86]	$252	$355
Specialty Laboratories[87]	$440	$440
Wayne State University/Detroit Medical Center University Laboratories[88]	Only offered as part of panel	$325
Average price of test:	**291.84**	**297.66**

Enzyme Assay (Tay-Sachs)/Analyte Test (Canavan)*

Laboratory	*TS Test Price*	*CD Test Price*
Baylor College of Medicine	$128	not offered
Children's National Medical Center[89]	$119 (serum) $172 (white blood cells)	not offered
Duke University[90]	not offered	$260
Emory University Department of Human Genetics	$250[91]	not offered
Emory University Department of Human Genetics	$525[92]	not offered
Genzyme Genetics	$134	not offered
Greenwood Genetics Center[93]	not offered	$200 (analyte)
Kennedy Krieger Institute[94]	not offered	$150 (analyte)
Kimball Genetics, Inc.	$160	not offered
LabCorp	$347 (leukocyte) $175 (serum)	not offered
Mayo Clinic Biochemical Genetics Laboratory	$188.30 (serum) $277.70 (white blood cells)	not offered
New York State Institute of Basic Research in Developmental Disabilities[95]	$280 (leukocytes) $260 (plasma)	$168 (organic acids)
Oregon Health and Science University[96]	$119.44 $223.42 (rush)	not offered

[84] New York University School of Medicine Medical Genetics Laboratory, via phone June 22, 2007. (212) 263-5746.
[85] ProGene, Inc., via phone June 20, 2007. (818) 548-0999.
[86] Quest Diagnostics, Inc., via phone June 20, 2007. (800) 877-2515.
[87] Specialty laboratories, via phone June 26, 2007. (800) 421-7110.
[88] Wayne State University/Detroit Medical Center, via phone June 22, 2007. (3113) 993-0724.
[89] Children's National Medical Center, via phone June 21, 2007. (202) 884-3991.
[90] Duke University Medical Center Pediatric Biochemical Genetics Lab, via phone June 2007. (919) 549-0445.
[91] See http://www.genetics.emory.edu/egl/test.php?test_id=167 [accessed July 24, 2007].
[92] See http://www.genetics.emory.edu/egl/test.php?test_id=20 [accessed July 24, 2007].
[93] Greenwood Genetics Center, via phone June 21, 2007. (800) 473-9411.
[94] Kennedy Krieger Institute, via phone June 21, 2007, (443) 923-2788. Test prices on the order form also available http://www.genetics.kennedykrieger.org/forms/cmsform.pdf [accessed July 24, 2007].
[95] New York State Institute of Basic Research in Developmental Disabilities, via phone June 22, 2007. (718) 494-5369.
[96] Oregon Health and Science University, via phone June 22, 2007. (503) 494-7703.

University of Alabama at Birmingham Metabolic Disease Laboratory[97]	$300	not offered
UCSD Molecular Genetics Laboratory[98]	$116	not offered
University of Maryland Pediatric Biochemical Genetics Laboratory[99]	$90 (serum) $155 (leukocytes)	not offered
Wayne State University/Detroit Medical Center	$63	not offered
Average test price:	**$204**	**$195**

*Analyte tests for Canavan Disease, as discussed previously, are not DNA-based and therefore the MCH patent had no bearing on the price or availability of these tests. These data are included for comparison with the Tay-Sachs enzyme screen.

These data show that, despite the differences in intellectual property, the only significant pricing difference between Canavan and Tay-Sachs laboratory tests occurs in the average price per amplicon. Average test prices of the tests for Tay-Sachs and Canavan Disease were usually less than ten dollars apart. The exception is the Ambry full sequence analysis for Tay-Sachs, which is $800 more than the comparable Canavan test. It is unclear why the Ambry Tay-Sachs test would be so much more expensive than the Ambry Canavan test. One possible reason is that the hexosaminidase gene is longer than the aspartoacylase gene: the ASPA gene is 29kb and the HEXA gene is 35kb.[100] Based on the Ambry prices and the length of the respective genes, the price per base pair for the Ambry Canavan test is $0.031; the price per base pair for the Ambry Tay-Sachs test is $0.048. The average price per amplicon for Tay-Sachs, however, is $111.50 while the price per amplicon for Canavan disease is $199.58: a significant difference that could reflect a patent premium.

There are several confounding factors that may affect these data. First, the number of laboratories offering each test may be inaccurate, because some "labs" are only sample collection points, which then send the samples they collect to other laboratories that perform the test. This would affect both the number of labs offering the test, and the number of labs that have a sub-license of the MCH patents. Also, at least in the case of Tay-Sachs Disease, many schools, universities, and Jewish organizations (such as the Dor Yeshorim) offer free carrier screening throughout the year, which could significantly increase access but does not appear on genetests.org. For example, a branch of NTSAD in the Delaware Valley offered six free Canavan and Tay-Sachs screening dates during the months of May and early June in 2007, and published a list of nine hospitals offering free screening throughout the month of May 2007.[101] Other examples of universities offering free Tay-Sachs screening included the University of Wisconsin-Madison (2003 and 2004),[102] Santa Monica College (2003),[103] University of California at Davis (2005),[104] and San Jose University (2001).[105]

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[97] University of Alabama at Birmingham Metabolic Disease Laboratory, via phone June 26, 2007. (205) 996-4992
[98] UCSD Molecular Genetics Laboratory, via phone June 21, 2007. (858) 534-1353
[99] University of Maryland Pediatric Biochemical Genetics Laboratory, via phone June 25, 2007. (401) 716-4065
[100] Monaghan KG, Feldman GL, Palomaki GE, Spector EB, Ashkenazi Jewish Reproductive Screening Working Group, and Molecular Subcommittee of the ACMG Laboratory Quality Assurance Committee. Op. cit.
[101] National Tay-Sachs and Allied Diseases Association of Delaware Valley. See http://www.tay-sachs.org/centers.php [accessed February 26, 2008].
[102] UW-Madison News: Newslink. University Communications. November 17, 2004. See http://www.news.wisc.edu/newslink/17-Nov-2004 [accessed February 26, 2008].
[103] Santa Monica College Spring 2003 Cover Stories. See http://www.smc.edu/schedules/archives/profiles/2003/031/coverstories_031.htm [accessed February 26, 2008].
[104] Senkevich, K. Free Tay-Sachs screening offered on campus-front page. *The California Aggie.* See http://media.www.californiaaggie.com/media/storage/paper981/news/2005/01/27/FrontPage/Free-TaySachs.Screening.Offered.On.Campus-1319352.shtml [accessed February 26, 2008].

One other confounding factor is the pricing of the tests themselves. Laboratory prices may reflect a change in licensing policy from MCH's original $12.50 royalty; however, because the *Greenberg v MCH* settlement was sealed, any agreed royalty rate may never be publicly available. Overhead costs may also contribute to pricing differences.

Screening for Tay-Sachs and Canavan Disease

In 1995, the American College of Obstetricians and Gynecologists (ACOG) published a committee opinion recommending carrier screening for Tay-Sachs disease before pregnancy if both parents are of Ashkenazi Jewish, French-Canadian, or Cajun descent.[106] That opinion was renewed and re-published in 2005: if both parents were carriers of a mutated HEXA gene, genetic counseling and prenatal diagnosis should be offered.

In 1998, ACOG issued a similar committee opinion for Canavan disease, recommending carrier screening for Canavan disease if both parents were of Ashkenazi Jewish descent.[107] If both parents were carriers of an ASPA functional mutation, prenatal diagnosis would use DNA-based ASPA testing.

Also in 1998, the American College of Medical Genetics (ACMG) issued a position statement that people of Ashkenazi Jewish descent should be offered screening for Canavan disease before becoming pregnant; ACMG also suggested that screening for Canavan disease could be combined with screening for Tay-Sachs, since both disorders were common among Ashkenazi Jewish people.[108]

In 2004, the ACOG issued another committee opinion reiterating recommendations that people of Ashkenazi Jewish descent should be offered carrier screening for Tay-Sachs and Canavan disease, as well as seven other diseases that are common to that group.[109]
These ACOG and ACMG recommendations help set the standard of care for screening for Tay-Sachs and Canavan disease in the U.S.

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[105] Ruf SG. Center to offer free Tay-Sachs Screening. *The Spartan Daily*. See http://media.www.thespartandaily.com/media/storage/paper852/news/2001/11/13/CampusNews/Center.To.Offer.Free.TaySachs.Screening-1494445.shtml [accessed February 26, 2008].
[106] American College of Obstetricians and Gynecologists Committee on Genetics. Committee opinion number 318: screening for Tay-Sachs disease. *Obstetrics & Gynecology* 2005. 106(4):893-894.
[107] American College of Obstetricians and Gynecologists Committee on Genetics. Committee opinion number 212: screening for Canavan disease. Op. cit.
[108] American College of Medical Genetics. *Position Statement on Carrier Testing for Canavan Disease.* January 10, 1998. See http://www.acmg.net/StaticContent/StaticPages/Canavan.pdf [accessed February 26, 2008].
[109] American College of Obstetricians and Gynecologists. Committee opinion 298: prenatal and preconceptional carrier screening for genetic diseases in individuals of eastern European Jewish descent. *Obstetrics & Gynecology* 2004. 104(2):425-8.

Clinical Utility of Genetic Testing for Tay-Sachs and Canavan Disease

Tay-Sachs. The Tay-Sachs Hexosaminidase A enzyme activity assay is very sensitive, with a 97-98% detection rate.[110] DNA testing for three common mutations detects more than 98% of Jewish carriers[111] and 93% of Jewish carriers are identified by the enzyme assay.[112] One study identified DNA-based testing as the preferred carrier screening method in individuals of full Ashkenazi Jewish descent.[113] DNA-based testing is also the only method to do pre-implantation genetic diagnosis (PGD), to confirm which specific mutation an individual has, or to rule out the possibility of pseudodeficiency alleles. In general, the enzyme test is inexpensive, accurate, and easy to do. It is also the best method to detect carrier status in individuals who are not of Ashkenazi Jewish descent (because any mutations might not be known DNA changes detected in current DNA-based tests).

Canavan disease. DNA testing for Canavan disease is based on two common mutations that account for 97-98% of Ashkenazi Jewish carriers.[114] Another mutation accounts for approximately 1 percent of the Ashkenazi Jewish population and about 50 percent of the non-Ashkenazi Jewish population.[115] DNA testing for Canavan Disease is the only way to detect carrier status, because enzymatic screens often fail to distinguish carriers from non-carriers.[116] In addition, prenatal testing using amniotic fluid (not CVS or amniotic *cells*, as previously discussed) is available, but not widespread.[117]

Cost-Effectiveness of Screening for Tay-Sachs and Canavan Disease

We have been unable to find any cost-effective or cost-benefit analysis of genetic screening for Canavan Disease.

We have also been unable to find any cost-effective or cost-benefit analysis of DNA-based testing for Tay-Sachs disease.[118]

This may be because screening for such devastating, incurable diseases as Tay-Sachs and Canavan is considered to be worth whatever the screening program costs. A quote from the National Tay-Sachs and Allied Diseases Association, Inc., illustrates this:

> It is important to note that while the [insurance] appeal process and potential out-of-pocket cost of genetic testing may seem daunting it is a drop in the bucket compared to caring for a child affected by Tay-Sachs, Canavan or another allied disease.[119]

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[110] Monaghan KG, Feldman GL, Palomaki GE, Spector EB, Ashkenazi Jewish Reproductive Screening Working Group, and Molecular Subcommittee of the ACMG Laboratory Quality Assurance Committee. Op. cit. at 58.
[111] An obligate carrier is one who does not show clinical symptoms but who must carry a defective copy of the gene based on family history. For example, if a child is born with Tay-Sachs disease, both parents are obligate carriers.
[112] Monaghan KG, Feldman GL, Palomaki GE, Spector EB, Ashkenazi Jewish Reproductive Screening Working Group, and Molecular Subcommittee of the ACMG Laboratory Quality Assurance Committee. Op. cit. at 58.
[113] Bach G, Tomczak J, Risch N, Ekstein J. Tay Sachs screening in the Jewish Ashkenazi population: DNA testing is the preferred procedure. *American Journal of Medical Genetics* 2001. 99: 70-75.
[114] Monaghan KG, Feldman GL, Palomaki GE, Spector EB, Ashkenazi Jewish Reproductive Screening Working Group, and Molecular Subcommittee of the ACMG Laboratory Quality Assurance Committee. Op. cit. at 58.
[115] Ibid.
[116] American College of Obstetricians and Gynecologists Committee on Genetics. Committee opinion number 212: screening for Canavan disease. Op. cit. at 91.
[117] Monaghan KG, Feldman GL, Palomaki GE, Spector EB, Ashkenazi Jewish Reproductive Screening Working Group, and Molecular Subcommittee of the ACMG Laboratory Quality Assurance Committee. Op. cit. at 60.
[118] There are a few studies that do address the cost-benefit or cost-effectiveness of the Tay-Sachs enzyme test; however, they do not address the economics of the DNA-based test.
[119] *Insurance Coverage.* See http://www.ntsad.org/S06/S06inscoverage.htm [accessed November 5, 2008].

Lessons Learned

Research

It is clear that the Tay-Sachs gene patent did not stifle research as it was never enforced.

The Canavan patent may or may not have stifled basic research until 2003, when the terms of settling *Greenberg v Miami Children's Hospital* were reached. Clinical research labs as well as commercial labs received cease-and-desist letters from MCH in 1998, which could have stopped them from sequencing the ASPA gene and thus have stifled basic research and some clinical research.[120] As discussed previously, one of the terms of the agreement allowed " license-free use of the Canavan gene in research to cure Canavan disease, including in gene therapy research, genetic testing in pure research, and in mice used to research Canavan disease."[121] Thus, though the Canavan patent could in theory have impeded research until 2003, it does not anymore.

Development and Commercialization

The Tay-Sachs patent neither helped nor hindered commercialization of the Tay-Sachs DNA test. One company approached Dr. Rachel Myerowitz before the patent issued to ask whether or not the gene would be patented. According to her, the company did not want to develop a test kit unless the gene was patented. Once the patent issued, however, NIH decided it would be too much trouble to enforce the patent, so it was never licensed. The presence of a reliable enzyme test may have been a deterrent for any commercial interest in a DNA test for Tay-Sachs. The enzyme test for Tay-Sachs was never patented and therefore patents did not help or hinder its development or commercialization.

The impact that the Canavan patent had on commercialization is unclear. The controversy happened at the level of Miami Children's Hospital, not in litigation among competing commercial testing services. The lawsuit was about fair access and distribution of benefits, not commercialization *per se*.

Adoption by Third-Party Payers

Adoption of Tay-Sachs and Canavan disease carrier and prenatal screening by third-party payers is varied. For example, CIGNA covers both carrier and prenatal screening for Tay-Sachs and Canavan if eligibility criteria are met. CIGNA considers carrier testing medically necessary for individuals who have either an affected family member, or a reproductive partner with confirmed adult-onset TSD. Prenatal testing or PGD is considered medically necessary if both parents are heterozygous and do not carry a pseudodeficiency allele; one parent is heterozygous and the other parent's test was inconclusive; the mother is heterozygous and the father's status is unobtainable; or one parent has adult-onset TSD.[122]

CIGNA considers carrier testing for Canavan Disease medically necessary when the ASPA mutation has been identified in a family member, and the patient has the capacity and desire to reproduce. Prenatal testing and PGD are considered necessary when both reproductive partners are of Ashkenazi Jewish

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[120] Flap erupting over royalty for Canavan: Miami Children's Hospital exercises patent for test. Forward staff. *The Jewish Daily Forward* 1999 (August 20). Pp. 15-16.
[121] *Canavan Foundation Press Release*. September 29, 2003. See http://canavanfoundation.org/news/09-03_miami.php [accessed February 26, 2008].
[122] *Cigna Position Statement 0059, Genetic Testing for Tay-Sachs Disease*. See http://cigna.com/customer_care/healthcare_professional/coverage_positions/medical/mm_0059_coveragepositioncriteria_genetic_testing_for_taysachs_disease.pdf [accessed February 26, 2008].

descent, or when both disease-causing alleles have been identified in an affected family member, and one parent is known to be heterozygous.[123]

Aetna does not have a policy on carrier screening, but considers genetic counseling in connection with pregnancy management medically necessary in specific populations, including people of Ashkenazi Jewish descent. Aetna also considers genetic counseling medically necessary in situations where both parents are known carriers of an autosomal recessive disorder, such as Tay-Sachs or Canavan. [124] Aetna's policy on genetic testing does not include carrier screening: their policy position only applies to the establishment of a molecular diagnosis of an inheritable disease in an individual.[125]

For other insurance companies that do not cover genetic testing for people of Ashkenazi Jewish descent, the National Tay-Sachs and Allied Diseases organization offers to send help in the form of a letter to the insurer or health plan.[126]

Reflections

Though the Tay-Sachs and Canavan disease stories have much in common, a few salient differences make a direct comparison difficult. The first such difference is the relative clinical importance of the cloning of the aspartoacylase and hexosaminidase genes. The identification and cloning of the hexosaminidase gene by Dr. Rachel Myerowitz was a scientific and intellectual triumph; the cloning of the aspartoacylase gene by Dr. Reuben Matalon was a medical necessity for a community with very few options. Perhaps Dr. Myerowitz herself put it best:

> …Finding out the mutations [for the HEX genes] was fine… but they have a very fine enzymatic screen which is really far superior, and the reason it's superior is because it's an all-encompassing screen. If you have individual mutation screens, they're okay for ethnic groups, but what if there's an Ashkenazi Jew who has a new mutation, or his mother wasn't really Jewish? You would miss them. So really, my discovery of the mutations was intellectually interesting, but it wasn't like you had a community waiting for prenatal testing like I believe you did in Canavan.[127]

Dr. Myerowitz's modesty understates the importance of Tay-Sachs DNA tests in specific ethnic groups, especially the Ashkenazim. The DNA test for Tay-Sachs also has clinical utility: it is useful for determining the specific mutations in an individual, for confirming an inconclusive enzyme test, for identifying pseudodeficiency alleles, and for preimplantation genetic diagnosis (PGD). It is nonetheless true that DNA testing is much more clinically pervasive for Canavan disease than Tay-Sachs.

Another salient difference is patent status. Both genes were patented, but no attempt was made to commercialize a test based on the Tay-Sachs gene, and that patent was never licensed; in contrast, the Canavan gene was licensed with a relatively high royalty and with volume restrictions. One reason that the Tay-Sachs patent was never licensed is that there was already a working enzyme assay, which may have decreased commercial interest in licensing the DNA-based patent. Because the assay was already

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[123] *Cigna Position Statement 0333, Genetic Testing for Canavan Disease.* See http://www.cigna.com/customer_care/healthcare_professional/coverage_positions/medical/mm_0333_coveragepositioncriteria_genetic_testing_for_canavan_disease.pdf [accessed February 26, 2008].
[124] *Aetna Clinical Policy Bulletin: Genetic Counseling Number 0189.* See http://www.aetna.com/cpb/medical/data/100_199/0189.html [accessed February 26, 2008].
[125] *Aetna Clinical Policy Bulletin: Genetic Testing Number 0140.* See http://www.aetna.com/cpb/medical/data/100_199/0140.html [accessed February 26, 2008].
[126] National Tay-Sachs and Allied Diseases Association, Inc. *Insurance Coverage*. See www.ntsad.org [accessed February 26, 2008].
[127] Interview with Dr. Rachel Myerowitz. Op. cit.

available, there would likely not be a market for an expensive DNA test. With Canavan's, in contrast, the market was open for prenatal screening based on a DNA test, and so the gene patent was more commercially significant.

One interesting fact that has come to light as a result of this study is that the availability and pricing of Tay-Sachs and Canavan Disease screening and DNA testing is similar, despite the difference in the intellectual property scenarios. This may indicate that using such a metric to compare patient access is inaccurate, although this seems unlikely given the similar population and screening scenarios for both conditions. It may also indicate a reduction in royalties as a part of the 2003 settlement of *Greenberg v MCH*.

Had MCH been able to enact the licensing terms they originally intended to pursue—a $25 or $50 royalty, volume limitations, a single high-volume provider, and refusing to name licensed laboratories—it may well have created an access problem for the Canavan community. This case highlights an instance in which members of a community and clinical providers serving that community took legal actions because of their concern over an access problem. The legal actions they pursued may have played a role in mitigating the long-term access problem that might have resulted from the MCH's original licensing scheme.

What has this got to do with patents?

Patents are only a part of any story of health care innovation. This story clearly shows how patent policy is only one feature of a complex set of policies that influence innovation in health care, including introduction of a new genetic screening and testing procedure.

One solution is to eliminate DNA sequence patents, along lines of the Becerra-Weldon bill (HR 110-997). Without patents, the licensing controversy would not have been possible, so patents are part of the story. The implication that eliminating gene patents would resolve all issues, however, introduces other possible consequences. At the time it was discovered, the Canavan gene was considered a possible target for gene therapy; or the gene patent might have been important in producing aspartoacylase protein for therapeutic use, along the lines of treatment for Gaucher's disease, adenosine deaminase deficiency, or other enzyme deficiencies. The absence of a gene patent could have made inducing investment in the therapeutic developments difficult, a socially suboptimal outcome. Such treatments have not developed for Canavan disease, but patents on genes for other therapeutic proteins have proven important in the past and might do so in the future. So the policy option of eliminating DNA sequence patents, while avoiding Canavan-like controversies, also comes with a price.

The main lesson of the Canavan case is that exclusive property rights can be used unwisely. Without the property right, the problems do go away, but so also do any benefits of intellectual property. The Canavan case could easily have been a story similar to cystic fibrosis or Huntington's disease, in which the constituencies that were involved in the discovery were at the table when decisions were made about patenting and licensing. The narrative in those cases is one of scientific success leading to broad availability not only of a genetic test, but also creating new pathways for scientific advance building on the discovery of mutations in a causative gene. Patents were also part of those stories, but patenting did not cause a shift in the CF or Huntington's narrative from heroic scientific discovery to secrecy, betrayal, and greed—the way the Canavan story played out in the public media. The difference was partly about licensing strategy, but more importantly, it was about human and organizational relationships.

One of the emerging frameworks for technology licensing is to see it more as a tool for building a collaborative framework to build relationships and foster innovation and less as a legalistic entitlement to

be used as a weapon to extract revenue and overcome opposition.[128] MCH's patenting and licensing mistakes included failure to inform groups involved in the initial discovery about the decision to apply for a patent and then deciding to engage the organizations that had existing systems of testing Ashkenazi Jewish populations through legalistic "cease and desist" letters rather than involving them early and having them at the table when initial licensing decisions were being made. This is, again, a stark contrast with the much more successful introduction of genetic testing for Huntington's or cystic fibrosis, where analogous constituencies were involved early and directly as partners, rather than late and through legalistic tactics as adversaries.

The main conclusion from this case study is that patents matter, but they are tools, not ends in themselves. How they are used matters, as much or more than whether they exist at all. The story is both a travesty of poor management of intellectual property and a story of tort law and litigation leading to a settlement acceptable to the parties. If managed sensibly, and with involvement of stakeholders, patented technologies can generate revenues for research institutions without hindering research or clinical use and at least in this case ultimately with few discernible impacts on prices of or access to genetic testing; if mismanaged, patent licensing can cause controversy and disrupt systems of genetic testing and screening, and damage the reputations of scientists and research institutions.

Acknowledgements

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Daniel and Debbie Greenberg, Orren Alperstein, Rachel Myerowitz, Michael Hopkins, and Michael Watson kindly reviewed this case study to support the work of the Secretary's Advisory Committee.

[128] International Expert Group in Biotechnology, Innovation and Intellectual Property. *Toward a New Era of Intellectual Property: From Confrontation to Negotiation*. 2008 (October). The Innovation Partnership, McGill Centre for Intellectual Property Policy. See http://www.theinnovationpartnership.org/en/ieg/report/ [accessed January 19, 2009].

Patents and Licensing Events

1997 – US Patent 5,679,635, claiming methods of screening for Canavan disease, issues

1998 – 1999 – Miami Children's Hospital (MCH) sends enforcement letters to hospitals and laboratories testing for Canavan disease

January 20, 2000 – Canavan Disease Screening Consortium and Canavan disease experts meet with MCH to discuss licensing patents

October 2000 – After MCH fails to find single, large-volume licensee for Canavan testing and only discloses information about 4 of 12 licensees to Canavan Disease Screening Consortium, the patient advocacy groups and families with Canavan disease sue MCH, MCH Research Hospital, and Reuben Matalon (Greenberg v. Miami Children's Hospital)

August 3, 2003 – Greenberg v. Miami Children's Hospital settled out of court on confidential terms

Technical and Professional Events

1971 – Drs. John O'Brien and Shintaro Okada develop first enzyme test for Tay-Sachs disease

1990 – Dr. Matalon publishes details of prenatal enzymatic screening test for Canavan Disease

1993 – Dr. Matalon and others publish sequence of normal and mutated aspartoacylase gene, allowing for DNA-based Canavan testing

1995 – American College of Obstetricians and Gynecologists (ACOG) recommend DNA-based carrier screening for Tay-Sachs disease before pregnancy if both parents of Ashkenazi Jewish, French-Canadian, or Cajun descent

1998 – ACOG recommends DNA-based carrier screening for Canavan disease if both parents are of Ashkenazi-Jewish descent and prenatal, DNA-based diagnostic if both parents are carriers

1998 – American College of Medical Genetics (ACMG) recommends that people of Ashkenazi Jewish descent be offered DNA-based carrier screening for Canavan disease prior to pregnancy and that DNA-based screening for Canavan disease and Tay-Sachs disease be combined because both diseases are common among Ashkenazi Jews

Appendix B: Preliminary Findings from a Population Level Study of DNA Patents

Preliminary Findings from a Population Level Study of DNA Patents

By Lori Pressman, Mark Rohrbaugh, and Stephen Finley[1]
February, 2009[2]

Purpose of Commissioning a Population Level Study

To complement the case studies, the SACGHS commissioned a population level analysis of DNA Patents (patents defined by the bioinformatic algorithm described in Ref 1,), licenses to these patents, and products sold under the licenses. Population level studies provide important input into the development of public policy as recommendations are typically directed to populations of patents and licenses, rather than applied on a case by case basis.

The population level study was conducted in two phases. The first phase explored whether and how the bioinformatic algorithm could be used to identify NIH Office of Technology Transfer "OTT" patents, and by implication, patents in general, which cover commercially available clinical diagnostic tests. The second phase compares the licensing practices, policies and commercial outcomes for DNA Patents managed by the National Institutes of Health Office of Technology Transfer (NIH OTT) with those managed by not-for-profit academic institutions (AIs) documented in a prior study.[3] As the AIs and the NIH OTT operate under different policy frameworks, (the Bayh-Dole Act[4] for the AIs, and the Stevenson Wydler Technology Innovation Act[5] and the Federal Technology Transfer Act of 1986[6] for the NIH OTT.) this comparison has the potential to reveal effects of such policies on patent commercialization outcomes, including the commercial availability of clinical genetic diagnostic tests.

Predictive Value of the Bioinformatic Algorithm: The positive and negative predictive values of the i) bioninformatic algorithm and ii) bioinformatic algorithm enhanced by expert curation were explored. The term "marker" means meeting the criteria of the algorithm, and the term "refined marker" means meeting the criteria of the algorithm and *also* further selected by expert curators[7] as a patent with the potential to cover commercial clinical diagnostic tests or services. Approximately one third of patents found by the algorithm were selected by the expert curators.

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[1] Lori Pressman is an independent consultant. Mark Rohrbaugh and Stephen Finley are affiliated with the NIH Office of Technology Transfer. Bob Cook-Deegan, Subhashini Chandrasekharan, and Carla Rydholm, all with the Duke University Center for Genome Ethics, contributed to the study, particularly regarding the expert curation patent taxonomy, but not to the report.

[2] This study is ongoing. Additional licensing data, made available to the first author in January 2009, are still undergoing analysis.

[3] Pressman, L., Burgess, R., Cook-Deegan, R.M., McCormack, S.J., Nami-Wolk, I., Soucy, M., and Walters, L. (2006). The licensing of DNA patents by U.S. academic institutions: an empirical survey. *Nat Biotechnol.* 24:31 – 39.

[4] 35 U.S.C. §§ 200-212

[5] Public Law 96-480

[6] Public Law 99-502

[7] Dr. Subhashini Chandresekharan and Dr. Carla Rydholm.

The precise numbers in this table are expected to change after the new data are integrated. The overall observations are not expected to change.

Table 1: Positive Predictive Value "PPV" and Negative Predictive Value "NPV" of the marker and the refined marker, for predicting i) how the patents will be licensed, ii) whether the patents will be associated with clinical diagnostic tests regardless of analyte, and iii) whether the patents will be associated with clinical diagnostic tests where a nucleic acid sequence is the analyte.

	marker PPV	marker NPV	refined marker PPV *(See note G)*	refined marker NPV *(See note G)*
Ability to predict which patents are in a license with a Diagnostic Sales or Testing Service Field of Use	12-33% 33/273 to 91/273	60-93% 49/81 to 76/81	23-54% 23/102 to 55/102	79-94% 135/171 to 161/171
Ability to predict which patents are associated with a royalty earning clinical diagnostic test or service	23-33% 22/93 to 31/93	66-87% 20/30 to 26/30	23-37% 11/46 to 17/46	70-76% 33/47 to 36/47
Ability to predict which patents are associated with a Nucleic Acid based clinical diagnostic test or service	8-9% 7/93 to 8/93	97-100% 29/30 to 30/30	13-15% 6/46 to 7/46	97% 46/47

Note G: *These calculations ignore the patents not found by the bioinformatic algorithm*

Both markers have incomplete penetrance. DNA patents associated with clinical diagnostic tests are also associated with other products. There are also patents not found by the bioinformatic algorithm, but in the same patent family [8] as a patent found by the bioinformatic algorithm, which are utilized in commercially available clinical diagnostic tests or services. With one exception, these tests are antibody based, rather than nucleic acid based.

The PPV of both markers, the bioinformatic alone, and the refined marker, is poor, both at the license level (predicting which patents are in licenses where the parties contemplated, at the time the license was being negotiated, that the licensee would make a diagnostic product or perform a diagnostic service), and at the product level (a diagnostic product is on the market, or a diagnostic service is commercially available).

The poor PPV of the markers is not surprising, as the search string clearly picks up varied group of biotechnology patents[9] Table 2 below shows the Issued U.S. Patents assigned to companies known to be active in the development of diagnostic tests and platform technologies, and, in the

[8] Patents which derive their support from a shared patent "specification", (the part other than the claims) are said to be in the same patent family. The specification provides the novel and not obvious teaching which entitles the patent holder to their patent.

[9] See Table 1 Reference 1.

case of Illumina and Helicos, patents invented by their University-based founders, David Walt and Stephen Quake, and the number of such patents also detected by the bioinformatic algorithm. The searches were run December 25, 2008. The Delphion U.S. Patent Collection starts in 1971.

Table 2

Company	Number of Issued U.S. Patents	How many are also found by the DPD Algorithm
Roche Is Patent Owner Last 10 years only	10,849 3,579	1258 777
Applied BioSystems is Patent Owner Last 10 years only	186 114	69 43
Illumina is Patent Owner David Walt, (Tufts Professor whose technology formed the basis of Illumina in 1998) is an Inventor	45 36 (30 owned by Tufts University)	27 10 (8 owned by Tufts University, 2 by Illumina)
Helicos is Patent Owner Stephen Quake, (Caltech Professor, whose technology formed the basis of Helicos in 2004) is an inventor	7 57 (all 57 owned by Caltech)	4 12 (all 12 owned by Caltech)

The improved, yet still poor, PPV of the refined marker may be due to the curators intentionally seeking high sensitivity.

The NPV of the simple bioinformatic approach could be useful when restricted to identifying issued patents that are not associated with clinical diagnostic tests which rely primarily on nucleic acids. However, this approach has several limitations. First, many licenses are executed before all patents in a patent family have issued, and some patents in the family have nucleic acid-based claims, others have protein and antibody based claims, and the order in which the claims issue is unpredictable.

More significantly, the approach is limited also because most of the clinical diagnostic tests associated with NIH OTT licensed DNA patents are not nucleic acid based, though they are virtually all are associated with at least one patent, even if through a "patent family" relationship, which has nucleic acid sequences in the claims. Thus, the phrase "clinical genetic diagnostic test" is potentially misleading, as frequently the analyte is not a nucleic acid sequence, but instead a protein product of gene expression, or an antibody to a protein product of gene expression. The phrase "clinical diagnostic test of genetic origin" may be a more accurate description of clinical diagnostic tests informed to some degree by an understanding of the underlying genetics.

Examples of clinical diagnostic tests of genetic origin, grouped by analyte type, from the NIH OTT Licensing Program, from the case studies, and from recent press releases are listed below:

Full Nucleic Acid Sequencing:

BRCA1 and BRCA2 breast/ovarian cancer susceptibility genes, the first case in a family (Myriad Genetics)

Detection of a partial gene sequence via hybridization:

DNA Probe for HER2 gene for predicting response to Herceptin (Invitrogen)

Detection of a protein product of gene expression:

HER2 immunoassay for predicting response to Herceptin
Prezeon® immunoassay for determining PTEN status (Myriad Genetics)
Cerebrospinal fluid tests for Apolipoprotein E or Phosphorylated Tau protein used in Alzheimer's testing. (Athena Diagnostics)

Examination of the function of a protein product of gene expression:

Hexosaminidase assay for Tay-Sachs

Detection of antibodies raised in response to infectious agents:

HIV-1 blood screening tests

The type of test is also to some degree a function of its time in history. If the human immunodeficiency virus (HIV) had been isolated before the tools of genetic engineering and antibody production were readily available, it is possible that a blood screening test could have been developed starting from collecting pooled sera of infected individuals. However, once the virus was isolated, it was easier to start from knowledge of its antigenic surface proteins, as determined precisely by the viral genome, and use that information to develop an antibody based blood screening assay.

Are antibody and protein based tests of equal concern to policymakers as nucleic acid based tests? If not, is this because antibodies are perceived as less biologically fundamental than nucleic acid sequences, even if, from a pure patent point of view, a well written antibody patent could, in theory, obstruct an antibody-based test for a gene expression product? Or, if the antibody has been engineered in some way, perhaps to be make a binding event easier to detect, is such a patent of less concern to policymakers because it appears to capture some more easily recognized technical contribution of the inventors?

If such tests are of equal concern, then the challenge in formulating an objective marker to identify patents claiming amino acid sequences with the potential to obstruct access to protein-based clinical diagnostic tests of genetic origin is greater than that for patents with nucleic acids in the claims, as amino acid sequences have abundant medical and commercial applications apart from clinical diagnostic tests.

The low PPV of patent-level markers, the occurrence of DNA or nucleic acid-based patents in many businesses, including relatively new companies such as Illumina and Helicos, the occurrence of protein and other biomarker based tests in clinical diagnostic tests of genetic origin, the unpredictable order in which patent claims in a patent family issue--including those for nucleic acid sequences and those for protein products of gene expression, or for antibodies to the protein products, --all suggest that public policy recommendations regarding intellectual

property rights should not focus on the patents themselves. One alternative is to consider recommendations for licensing terms, discussed next.

Comparision of Licensing Practices under Two Policy Frameworks

Policy and Practice Differences

In brief, NIH OTT favors nonexclusive licensing,[10] requires a public notice period before granting licenses with exclusivity, and does not grant all field of use exclusive licenses. The NIH OTT maintains more never licensed patents as a percentage of its total, (See table 3 below).

Table 3: Comparison of maintenance status for AI and NIH OTT Never Licensed "DNA Patents"

	Did Not Pay 3.5 Year Patent Maintenance Fee	Did Not Pay 7.5 Year Patent Maintenance Fee	Did Not Pay 11.5 Year Patent Maintenance Fee
AI Never Licensed 771 Unique	57 (about 7%)	36 (about 4.7 %)	8 (about 1%)
NIH Never Licensed 312 Unique	11 (about 3.5%)	8 (about 2.5%)	1 (about .3%)

Based on the results of two studies,[11,12] NIH OTT inventors appear to play a smaller role in invention marketing than AI inventors. AI's have more discretion in the scope of license grants to their patents, are more able to participate in start-up formation, their inventors appear to be more involved in the technology transfer process relative to NIH OTT inventors, and they maintain fewer never licensed patents.

Percentage of Patents Licensed Under the Two Frameworks

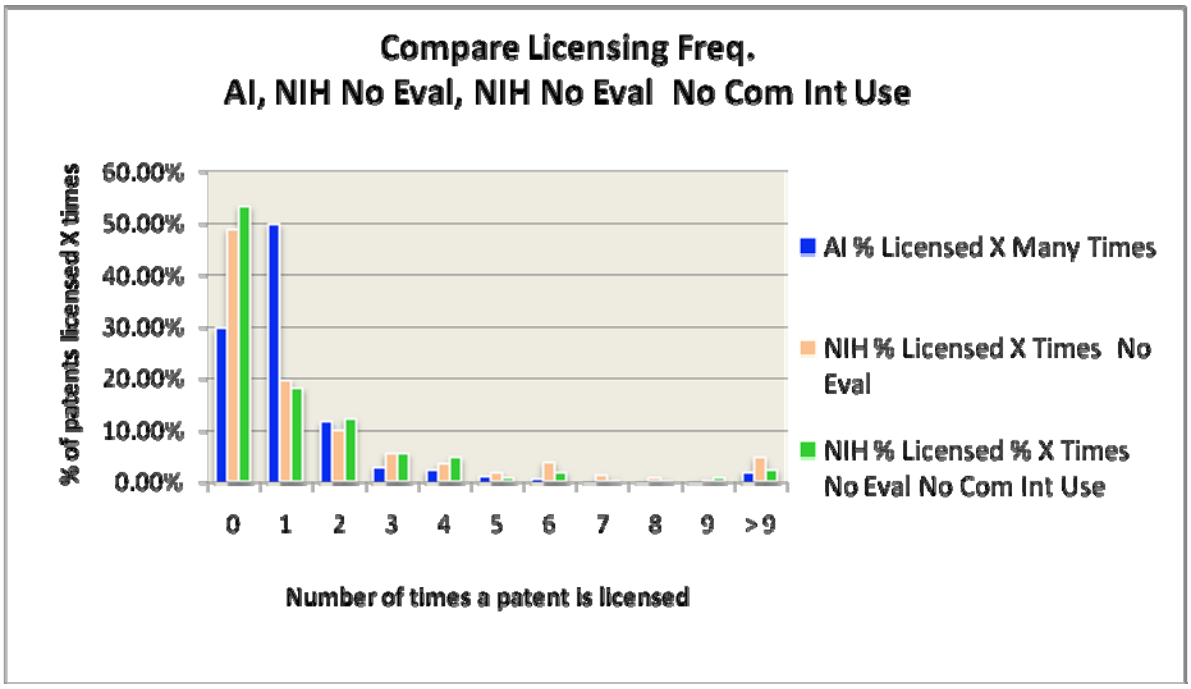
More AI managed DNA Patents are licensed overall relative to NIH OTT managed DNA Patents. This effect remains when controlled for absolute age of the patents, age of the patent at the time the data were gathered, and is not obviously explained by patent classification codes. *The new data which will be integrated may affect these results, but probably not significantly.*

[10] http://www.ott.nih.gov/FAGs/#6 Accessed February 5, 2009

[11] Jansen, Dillon, "Where do the Leads for Licenses Come From" source Data from Six Institutions". Journal of the Association of University Technology Managers, vol XI . p27

[12] Ramakrishnan, Chen, Balakrishnan, "Effective strategies for marketing biomedical inventions: Lessons learnt from NIH license leads" Journal of Medical Marketing Vol 5, 4 342-352.

Figure 1. Licensing Frequency Data for the AI and NIH sets, and accompanying table used to generate the graph. The NIH OTT license agreements which include neither commercial evaluation agreements nor commercial internal use agreements are the most directly comparable to the AI license agreements. Thus, the first and third bars in each group of histograms are the most directly comparable to each other. More than 50% of NIH OTT managed DNA Patents have never been licensed, whereas only 30% of AI managed DNA Patents have never been licensed.



Data Table for Figure 1:

Number of times Licensed	AI Count	AI %	NIH Count no Eval	NIH % No Eval	NIHCount No Eval No Com Int	NIH % No Eval No Com Int
0	771	29.65%	286	48.89%	312	53.33%
1	1297	49.88%	115	19.66%	106	18.12%
2	302	11.62%	58	9.91%	71	12.14%
3	74	2.85%	32	5.47%	32	5.47%
4	58	2.23%	20	3.42%	27	4.62%
5	25	0.96%	10	1.71%	5	0.85%
6	16	0.62%	22	3.76%	10	1.71%
7	3	0.12%	7	1.20%	3	0.51%
8	3	0.12%	5	0.85%	2	0.34%
9	3	0.12%	3	0.51%	4	0.68%
> 9	48	1.85%	27	4.62%	13	2.22%

A preliminary observation is that the percent of patents licensed more than 9 times, sometimes referred to as "broadly" in this report, is similar under the two frameworks. Of course, not all licenses, even nonexclusive ones, are a sign that product is on the market.

Exclusivity Practice: Using the preliminary data, the exclusivity practice is more similar than generally believed, though clearly more NIH OTT licenses are nonexclusive. Generally, licenses with some degree of exclusivity also include considerably more diligence requirements than licenses granted on a non-exclusive basis. "Diligence" refers to the contractual terms which require the licensee to invest in developing and commercializing the invention. License contracts can be drafted so that meeting diligence requirements expands the scope of rights granted therein, and/or so that failure to meet the diligence requirements results in loss of rights under the contract.

Hypothetical Examples of Diligence Terms
Technical and Regulatory Requirements: i) achieve a certain sensitivity or specificity for a clinical diagnostic test, ii) obtain FDA clearance, iii) develop a multivalent monoclonal antibody to the protein product of gene expression
Requirements to Raise or Spend Money, or to support research at the patent owner's institution: i) raise no less than $5M devoted to development of the licensed technology within one year of signing the license, ii) spend [at the licensee] no less than $1M/year until receiving FDA clearance, iii) fund no less than $100,000 per year at the patent owner's institution for a minimum of 3 years after signing the license.
Requirements to demonstrate commercial traction: i) sell a certain dollar volume by a certain date, ii) sell a certain unit volume by a certain date, iii) show increasing sales over a period of years

Hypothetical Examples of Consequences of failing to meet, or meeting Diligence Terms
Negative Consequences: i) failure to meet milestone xyz shall result in termination of the license under paragraph abc, ii) failure to meet milestone xyz shall result in conversion of the license to nonexcljusive, iii) failure to meet milestone xyz shall enable the patent holder to grant one additional license per year to the technology in the licensee's field of use.
Positive Consequences: i) upon meeting milestone xyz, the patent holder will grant no additional licenses in licensee's field of use, ii) upon meeting milestone xyz, the patent holder will grant at most one additional license per year in licensee's field of use, and no more than 2 additional licenses total. iii), upon meeting milestone xyz, the patent holder will expand licensee's Field of Use to include jkl.

Evidence for Incentives Created by Patents: Theoretical Basis for Timeline Analysis

Timeslines[13] are useful tools because they have the potential to shed light on cause and effect,[14] and because timing is itself a potential metric of availability. Product Commercialization timelines provide data on temporality, with the caveat that "home brew" or Laboratory Developed Tests or services not reported to a patent holder are necessarily absent from this analysis. Nonetheless, it is not correct to automatically assume home brew tests are equivalent to commercial tests.

[13] Relative timing of the invention publication, patent filing, license execution, product availability.
[14] Austin Bradford Hill, "The Environment and Disease: Association or Causation?" Proceedings of the Royal Society of Medicine, 58 (1965), 295-300. As a convenience, they are listed here: Strength, Consistency, Specificity, Temporality, Gradient, Plausibility, Coherence, Experiment, Analogy.

Products which appear very quickly after invention publication suggest that little commercial development is required to bring the product to market. Obviously, there was by definition, another incentive. Products which appear years after publication of the invention suggest, though clearly in isolation do not prove, that some additional development was required. In the case of clinical diagnostic tests of genetic origin, additional development could include improving and/or documenting clinical utility or adapting the technology for reproducible use in a commercial manner. Both of these might be needed to obtain FDA approval for a test kit or FDA clearance for marketing claims of a kit or service.

Products which appear on the market soon after the patent license was signed again suggest that the patent itself was not a significant incentive for the company producing the product, particularly when the license is nonexclusive with little diligence required from the licensee. Products which appear years after the patent license was signed are consistent with the patent serving as an incentive for the company to invest in producing a product. The argument that such a license is a development incentive is stronger when the license is at least partially exclusive and supported by the presence of diligence in the license agreements, as there is a clearer and stronger contractual obligation on the part of the licensee and cost to that licensee in advance of the anticipated benefits. The licensee will likely only accept these contractual obligations costs when the license protects them from the risks that others might enter the market later without similar costs of developing the technology.

It is not yet clear how the new data could affect this analysis.

Timeline Data: The available timeline data are presented in tabular form below. The limitations of this data for the AI set include: i) a small number of data points, ii) values distribution, and thus the standard deviations, are quite large, and iii) survey respondents submitted license effective dates and product introduction dates by fiscal year, rather than providing the actual day and year the licenses were executed. There are apparently only a handful of NIH OTT licenses with exclusivity so it is not possible to compare exclusivity types within the NIH OTT set. The AIs did not describe the products in their licenses,only that they existed.

The only set of licenses with an average multi-year delay between signing the license and the appearance of product are the AI Licenses with some exclusivity. One of the NIH OTT licenses with exclusivity has a significant time delay, the others do not. The other NIH OTT Licenses associated with products, all of which are essentially nonexclusive, and the AI nonexclusive licenses tend to be signed close to the time products are introduced, and not, on average, in advance of their introduction.

In isolation, these results do not prove that exclusive licensing creates incentives. However, combined with the documented contractual diligence in the AI licenses with exclusivity the timeline data provide evidence that such licenses create development incentives.

There is also some evidence that NIH OTT Diagnostic Products from commercial providers are on the market later than reagents, possibly showing the effect of a certification or regulatory delay.

Finally, there is some evidence that DNA Patents licensed under an AI practice and policy framework may be associated with commercial products, as indicated by the presence of an earned royalty report, sooner than DNA Patents licensed under the NIH OTT policy framework.

Academic Institution Summary Product Timeline Data

	Number of Data Points	AI Delta 1st pat Priority Date[15] to Product availability years	Standard Deviation	AI Delta License Effective Date to Product Availability years	Standard Deviation
Nonexclusive Mean	11	5.68	4.84	0.00	2.94
Nonexclusive Median	11	4.66		0.00	
Some Exclusivity Mean	20	4.47	3.26	3.10	.90
Some Exclusivity Median	20	4.14		2.75	

NIH OTT Summary Product Timeline Data

NIH Delta 1st pat Priority Date to Product availability	Number of Data Points	NIH Delta 1st pat priority Date to Product Availability years	Standard Deviation	NIH Delta License Effective Date to Product Availability	Standard Deviation
Dx Product Sales Mean	13	8.45	4.15	0.00	3.63
Dx Product Sales Median	13	9.5		0.00	
Reagent Product Sales Mean	42	7.74	4.7	1.13	2.44
Reagent Product Sales Median	42	6.41		.31	

These results suggest that automatic and default nonexclusivity could have a cost, especially given the apparent impossibility of a priori identifying groups of patents "needing" to be licensed nonexclusively because they are certain or likely to be associated with clinical diagnostic tests of genetic origin.

Given the apparent impossibility of identifying patents "needing" to be licensed nonexclusively, and the potential unintended removal of incentives where they could be beneficial, nuanced exclusivity with prudent diligence is an attractive policy option.

[15] Reasonable proxy for invention publication in biotech sector.

Appendix C: Public Commenters

Public Commenters

American Association for Clinical Chemistry

American College of Medical Genetics

American Intellectual Property Law Association

American Medical Association

American Nurses Association

Rebecca Anderson, University of Nebraska Medical Center

Association for Molecular Pathology

Association of American Medical Colleges

Association of Pathology Chairs

Association of Public and Land-Grant Universities

Association of University Technology Managers

Athena Diagnostics

Axial Biotech

Karna Barquist

BayBio

Beyond Batten Disease Foundation

Julie Biggerstaff, Providence Associates Medical Laboratory

Bio-Reference Laboratories

Biotechnology Industry Organization

Boston University Technology Development

Case Western Reserve University Technology Transfer Office

Alyssa Cass

Celera Corporation

Centre for Intellectual Property Rights

Stephen Chambers, Abpro

Claire Altman Heine Foundation

Clinical Data

Rosemary Colantonio

College of American Pathologists

Council on Governmental Relations

Kayla Dean

Emory University School of Medicine

Felix Gaido, Salud Family Health Centers

GeneDx

Eric Hoffman, Children's National Medical Center, George Washington University

Sheryl Hohle, DCG Consulting

Illumina

Donna Immken, 'Specially for Children

John Johnson, Shodair Hospital

Juneau Biosciences

Roger Klein, BloodCenter of Wisconsin

David Koepsell, Delft University of Technology

Life Technologies

Dolores Mackenzie, Rhode Island Hospital

Katherine Matthews, University of Iowa Children's Hospital

Christopher Mazzochi

Mia Movray

MPEG LA

Mueting, Raasch & Gebhardt

NIH Office of Technology Transfer

Navigenics

Danielle Ndi

Oregon Health & Science University

Luigi Palombi, Genetic Sequence Rights Project, The Australian National University

Parent Project Muscular Dystrophy

PHG Foundation

PreventionGenetics

Terese Rakow, Baylor College of Medicine

The Research Foundation of the State University of New York

Sanofi-aventis U.S.

Joshua Sarnoff, Washington College of Law; Jonathan Kahn, Hamline University School of Law; and Lori B. Andrews, Chicago-Kent College of Law

Paul Shelomis

Jill Sorensen, Bilyan

Ruth Kelso Sorrell

Samantha Stone

The Innovation Partnership

Kathleen Thornberry

Tim Trischuk

University of California, Office of the Vice President for Research and Graduate Studies

University of Florida, Office of Technology Licensing

University of Iowa, Office of the Vice President for Research

University of Michigan, Office of Technology Transfer

University of Minnesota, Office for Technology Commercialization

Chad Walker

Wayne State University, Technology Commercialization

Wisconsin Alumni Research Foundation

Yale University, Office of the Vice President and General Counsel

STATEMENT OF DISSENT FROM MS. ASPINALL, DR. BILLINGS, AND MS. WALCOFF

We respectfully disagree with conclusions and recommendations of the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) Gene Patenting report based on our assessment of the evidence available, knowledge of the diagnostics industry and understanding of academic research collaborations. In our current health care system, patients routinely face unequal access to medical care, including diagnostic tests. Consequently, it is our position that statutorily modifying the gene patents system, including the creation of exemptions from liability for infringement upon such patents as defined in this report and proposed in the recommendations, would be more harmful than helpful to patient access and to the quality of innovative genetic diagnostics.

The basis of our position is recognition that there are a variety of financial and scientific decisions made by both government and private stakeholders throughout our health care system that impact patient access to genetic tests. We recognize the importance of supporting and encouraging discovery and, most importantly, translating those genetic discoveries into new tools to improve patient treatment and outcomes.

The patent system, although debatably imperfect, offers those who invest in developing discoveries a value for the investment. We believe that facts and findings cited in this report and in other reliable scientific literature support our view that the recommended change to the patent enforcement statute and the Bayh-Dole Act would have significant negative consequences. Many discoveries, in academic institutions or otherwise, may not be pursued or developed. Notably, the increasing complexity of development and clinical testing for genetic tests and higher evidentiary standards and regulatory hurdles such tests must meet require increasing levels of investment (measured in millions or tens of millions).

Notwithstanding our position that the recommendations regarding the statutory changes to the patent system would not ameliorate the patient access concerns this Committee has identified, we do acknowledge and appreciate the importance of patient access and quality standards with respect to provision of genetic testing. However, while we agree that licensing does play some role in universal access, public health plans such as Medicaid and Medicare, as well as private payers, continue to be free to refuse coverage and payment even if every laboratory in the country offers a test. Moreover, in addition to such reimbursement policy, other factors, including practice patterns and professional talent distribution, also impact what tests are conducted in what regions of the country. Therefore, we do not support the assertion that in most cases gene patents have had a direct and overarching negative impact on the ability of a patient to obtain a test.

In terms of clinical access on behalf of patients, our assessment of the data suggests that clinicians are often significantly limited by contractual and financial barriers placed on them by their organization/institution or cost containment restrictions imposed by public and private payers. The ability for every laboratory to offer every test, in our view, is a commercial objective more than a patient access issue since clinicians can and do order genetic tests for patients every day from laboratories both across the hall and across the county.

Nevertheless, we agree that the inability of certain populations to afford genetic testing is an important and valid concern and should be addressed directly as an integrated component of systemic health care reform. It is important that good intentions do not give way to negative outcomes in other parts of the health system or economy. As such, we would strongly encourage the Department of Health and Human Services ("HHS") to critically evaluate the criteria and requirements of all public health programs, including Medicare and Medicaid, to ensure that every beneficiary of public health funding has reasonable and timely access to genetic tests regardless of income or geographic location. In addition, we strongly encourage HHS to evaluate relevant laws, regulations and policies, such as anti-kickback, health care fraud statutes, and government reimbursement policies, that are overly burdensome or result in practical barriers on diagnostic companies who would otherwise elect to offer tests at little or no cost based on financial need.

We also agree that testing, including quality standards, whether by a single laboratory or multiple laboratories, are an important factor to the public's health. Test quality has been and should continue to be appropriately addressed by the Food and Drug Administration ("FDA") and the Center for Medicare and Medicaid Services ("CMS"). Specifically, those agencies should continue to work together to keep pace with laboratory and diagnostic innovation and identify new ways to evaluate proficiency, reliability, and reproducibility of new and innovative genetic tests. We do not believe, nor has FDA or CMS ever suggested, that there is any credible evidence that the quality of testing performed in sole source laboratories is routinely or demonstrably subpar in any way to that which is done in multiple laboratories. Nor do we believe that data indicate that modifying the gene patent system and protections it offers through exclusive licensee agreements would result in multiple laboratories performing proprietary tests with better quality than generated by current and developing oversight of quality assurance undertaken by these agencies and the laboratories themselves.

Finally, we believe that the determination of patentable subject matter and the protections afforded to such patentable subject matter should remain the primary function of the US Patent and Trademark Office, Congress, and the US courts. The suspension of patent protections such as exemptions from liability for patent infringement for a restricted class of innovation (gene patents), unless they are determined to be non-patentable (for instance, a court determination that they are a "product of nature"), is unwarranted and a risky intrusion in to a process that has delivered many key innovations to needy Americans.