Patent and Licensing Fundamentals and the Nature of the Access Problem

Debra Leonard

SACGHS
June 27, 2006

Overview of Presentation

- Patents and gene patents
- Patent enforcement experiences
- Medical significance of gene patents
- Options for consideration

What are Patents?

- Patents grant right to exclude others from making, using, or selling inventions for a limited time
- An "invention" is anything made by man that is new, nonobvious, and useful
- Purpose of patents in US Constitution: "Promote the progress of science and useful arts, by securing for limited times to…inventors the exclusive right to their…discoveries"
- Cannot patent a product of nature or a basic principle, such as $e=mc^2$ or gravity

Options for the Patent Holder

- Complete restriction of use by anyone
- Monopoly:
  - Patent holder is only user
  - Exclusive licensing to a single user
- Oligopoly: Limited licensing to select users
- “Pure” Competition: Broad licensing and use
- Hold for the public good: Anyone can use

What "DNA" is being patented?

- Chemical compositions
  - DNA, RNA, mRNA and other gene products
  - cDNA
  - Probes or markers (kit or multi-component system)
  - Transgenic organisms
  - Cloning, expression, sequencing, or gene therapy vectors
  - Cell lines and microbial strains
- Methods
  - Genetic diagnostic methods
    - Diagnosis of specific alleles or SNPs
    - Methods of using probes/test kits
  - Production methods
  - Therapeutic processes

Source: DNA Patent Database
http://www.geneticmedicine.org/sp_dpd.htm

Gene Patents

- Small, rapidly growing subset of DNA patents
- Claim the observation of an individual's genetic makeup at a disease-associated locus when done for diagnosis of a specific disease
  - Covers all methods of "looking at" that locus
  - Rests on the basic discovery of a relationship between genetic variability and disease
- Unique type of patent:
  - Permits true monopolization of a medical service
  - Not clear what has been "made by man"
  - Is this patenting of a product of nature?

Sample of Gene Patents

- 5,753,441 BRCA1
- 5,753,438 Hereditary hemochromatosis
- 5,741,645 Spinocerebellar ataxia type 1
- 5,693,470 HNPCC
- 5,691,144 CMT-X
- 5,686,240 Niemann-Pick disease
- 5,681,699 IBD
- 5,679,635 Canavan disease
- 5,670,320 Dystonia, Leber's optic neuro.
- 5,658,729 Premature atherosclerosis
- 5,654,138 Von Hippel-Lindau (VHL)
- 5,650,282 Williams syndrome
- 5,650,281 Colorectal cancer
- 5,645,995 Breast or ovarian cancer
- 5,639,614 Idiopathic dilated cardiomyopathy
- 5,639,607 Lead sensitivity
- 5,565,323 Sporadic Alzheimer disease
- 5,550,021 Compulsive disorder
- 5,541,060 Early-onset diabetes mellitus
- 5,518,880 XSCID
- 5,508,167 Alzheimer disease
- 5,506,101 Ototoxic deafness
- 5,500,343 Compulsive disorder
- 5,498,521 Retinal degenerative diseases
- 5,494,794 Alzheimer, Parkinson
- 5,492,808 Familial colon cancer (FCC)
- 5,429,923 Hypertrophic cardiomyopathy
- 5,387,506 Familial dysautonomia
- 5,374,525 Hypertension
- 5,306,616 CMT-1A
- 5,296,349 Myoclonic epilepsy
- 5,266,459 Gaucher disease
- 5,210,016 Compulsive disorder (alcohol)
- 5,045,449 Vascular aneurysms

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I am a Physician and a Molecular Pathologist

- Medical School training (MD)
- Molecular Biology training (PhD)
- Residency training in Pathology
- Understand use, performance and interpretation of laboratory tests
- Translate genetic/genomic science into diagnostics
- Direct and enhance patient care
- My medical practice, not research
- **Gene patents limit my medical practice**

athena diagnostics
TM formerly Genica Pharmaceuticals Corporation

Athena Diagnostics, Inc.
Four Biotech Park
377 Plantation Street
Worcester, MA 01605
Tel 508 756 2886 Fax 508 753 5601

March 21, 1997

SECOND NOTICE

RE: U.S. Patent Number 5,508,167

As part of our effort to be at the forefront of developments in diagnostic testing, I would like to advise you that Athena Diagnostics has acquired exclusive rights to certain tests in the diagnosis of late onset Alzheimer's disease. These tests are covered under U.S. Patent number 5,508,167 a copy of which is enclosed.

The patent covers methods of diagnosing for increased risk of late onset Alzheimer's disease by testing for the presence of the ApoE 4 allele.

We understand that University of Pennsylvania 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 Pennsylvania is interested in continuing to offer this patented testing service to its customers, Athena would be pleased to perform the services on University of Pennsylvania behalf. Our currently published price is $195 per specimen.

Very truly yours,

Michael A. Boss, Ph.D.
Vice President, Research and Development

MAB/cml

UPenn $100.50

June 24, 1998

SmithKline Beecham
Healthcare Services

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

$25,000 upfront fee or IP rights
+
Fee per test performed

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

SCA1, 2, 3, 6, 7 (1-12)

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

MIAMI CHILDREN'S HOSPITAL
THE MARY ANN KNIGHT INTERNATIONAL INSTITUTE OF PEDIATRICS
FOUNDED AS VARIETY CHILDREN'S HOSPITAL

David W. Carroll
Senior Vice President
and Chief Financial Officer

ACOG recommends screening
for all Jewish women
Part of a "Jewish genetic panel"

November 16, 1999

Re: US Patent Number 5,679,635

Dear Dr. Leonard:

We understand you may be offering an assay employing DNA-based technology to screen for Canavan Disease mutations. As you know, our affiliate, Miami Children's Hospital Research Institute, Inc. ("MCHRI"), has a patent (No. 5,679,635) in this area (the "Canavan Patent"). A copy of the Canavan Patent is attached. The Canavan Patent is available for licensing.

We intend to enforce vigorously our intellectual property rights relating to carrier, pregnancy and patient DNA tests for Canavan Disease mutations.

We are implementing a two-phased licensing program, with the portion relating to academic laboratories (Phase I) just concluded earlier this month. As part of Phase I, MCHRI has signed several binding agreements to provide licenses. MCHRI has been charging a flat rate payment of at least $12.50 per test.

These binding agreements contain volume limitations. **Once MCHRI commences Phase II of its licensing program (likely to occur very soon), it may well be prevented by contract from licensing any latecomers.** In addition, our largest licensee may require the right to enforce the Canavan Patent against non-licensed offerors of Canavan testing.

Myriad Genetics & BRCA1

- BRCA1 mutations increase risk of breast cancer
  - Mutations throughout gene
  - If no common mutation, need full gene screen
  - Myriad Genetics is patent holder
  - Exclusive provider of full BRCA1 screen
  - Also captures BRCA2 testing
  - License laboratories for common mutations only
- Dr. Arupa Ganguly (Dept of Genetics, Penn) stopped providing BRCA1 testing

University of Michigan
Medical School

Office of Technology Transfer and Corporate Research
2715 Furstenberg MSII
1301 Catherine Street
Ann Arbor MI 48109-0619
734.763.6363 FAX: 734.615.0076

October 6, 1999

Dear Dr. Leonard:

RE: Non-Exclusive Cystic Fibrosis Diagnostic Testing License

The University of Michigan (MICHIGAN) and The Hospital for Sick children, through its agent the HSC Research and Development Limited Partnership (RDLP), are co-owners of intellectual property relating to the cystic fibrosis delta F 508 deletion cDNA (United States patent application serial number 401, 609) and U.S. Patent No. 5,776,677 entitled "METHODS OF DETECTING CYSTIC FIBROSIS GENE BY NUCLEIC ACID HYBRIDIZATION" (see enclosure).

Because the '677 patent issued on July 7, 1998, we acknowledge that university diagnostic laboratories currently offering cystic fibrosis diagnostic testing may not be aware of this patent and most certainly are not aware of other related ownership rights held by MICHIGAN and RDLP. It is therefore our intent to inform all cystic fibrosis testing sites that we are offering non-exclusive, worldwide, in-house diagnostic testing licenses for the use of our technologies.

Given University of Pennsylvania Medical Center's active participation in this diagnostic area, we would welcome further discussions with you or some other University representative about obtaining a diagnostic license for use of the delta F 508 deletion in cystic fibrosis testing. In the event that your laboratory is providing diagnostic results to patients at cost, or reagents for the tests are obtained from one of our current product licensees (please contact me for further information), no license will be necessary.

Please feel free to contact me at your earliest convenience.

Sincerely,

David G. Ritchie, Ph.D.
Technology Licensing Specialist

DRAFT

LICENSE AGREEMENT

Between

INVIVOSCRIBE TECHNOLOGIES (IVS)

and

THE UNIVERSITY OF PENNSYLVANIA HEALTH SYSTEM (PENN)

1.02 "***Licensed Patent Rights***" as used herein shall mean to United States Patents Numbered 5,296,351 and 5,418,134.

1.03 "***LICENSEE***" as used herein shall mean LICENSEE and any and all Affiliates of LICENSEE.

1.04 "***Licensed Field***" as used herein shall mean the identification of monoclonality and the diagnosis and monitoring of leukemias, lymphomas and other lymphoproliferative diseases using the Licensed Patent Rights.

- IVS exclusive licensee of patents for clinical detection of B & T cell antigen receptor rearrangements by PCR
  - To determine monoclonality of lymphoid population
  - Diagnosis and monitoring of residual disease
- IVS sells kits for B & T cell antigen receptor testing
- Method has been used widely for clinical testing without use of test kits since 1990

4.0 LICENSE FOR PRIOR ACTS → No Payment for previous tests

Included in the License Issue Fee paid according to Section 5.01 is a retroactive License under Section 3.0 for all of LICENSEE's use of the Licensed Patent Rights prior to the effective date of this Agreement.

5.0 LICENSE ISSUE, CONTINUING ROYALTY FEES License fee Tens of Thousands $$

Payment obligations will accrue during this Agreement as follows:

5.01 Payment for License Issue. In consideration of the issuance of the License granted in Sections 3.0 and 4.0 by IVS under the terms of this Agreement, and as a license issue fee, LICENSEE shall pay IVS the sum of _____ Thousand ($__,000.00) US Dollars, due and payable upon the execution of this Agreement.

Per Test Fee $0 to $60

5.02 Continuing Royalty. In addition to the License Issue Fee paid under Section 5.01, the following continuing Royalty (the "Continuing Royalty") shall be due and owing biannually subject to reduction as outlined in Section 7.03.

$0 for Penn Test using IVS Kit

1. 1. Zero ($0 USD) dollars for each Intramural Test performed using IVS kits using the reaction volumes recommended in the Product Insert or literature accompanying the product(s);

$40 for Penn Test without IVS Kit

2. 2. Forty ($40 USD) dollars for each Intramural Test performed without use of IVS kits;

$40 for Non-Penn Test using IVS Kit

3. 3. Forty ($40 USD) dollars for each Reference Test performed using IVS kits using the reaction volumes recommended in the Product Insert or literature accompanying the product(s);

$60 for Non-Penn Test without IVS Kit

4. 4. Sixty ($60 USD) dollars for each Reference Test performed without use of IVS kits;

Economics of IVS License

- In 2002, 226 IGH and 209 TCR PCR tests
- TCR is lab-developed and IGH uses IVS kit
- Cost to perform each test is ~$300
- No per test fee for UPenn IGH tests
- $40-$60 per test for TCR (15-22% of test cost)
- $8360 to $9540 per year plus license fee
- **Medicare reimburses $55.39 per test**

UPenn Experience

- Stopped testing for:
  - CMT1a
  - ApoE genotyping
  - BRCA1
  - Canavan disease
- Negotiated agreement for:
  - Cystic fibrosis ΔF508
  - B&T cell gene rearrangements
- Notification letters for:
  - Hereditary hemochromatosis
  - Spinocerebellar ataxia, type 1
- Potential of patent enforcement for:
  - Spinal muscular atrophy
  - Myotonic dystrophy
  - Others

Constraints on Medical Practice

- Sole provider of a medical service
  - Eliminates competition for pricing
  - Reduces innovation in testing methods
  - Dictates medical practice
  - Constrains clinical scientific observation and slows new discovery process
  - Limits education of medical students and residents
  - Not in the best interest of the public health
- Unreasonable licensing fees
- Control of one gene controls testing for many genes
- Royalty stacking
- Limitation of test volumes
- Limit use of methods already used in clinical practice

Slide deleted at the request of Dr. Leonard

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Current Medical Genetics

- Diseases caused **entirely** by:
  - Duplication or deletion of entire chromosome, e.g., Down syndrome
  - Alteration of the sequence of a single gene, e.g., cystic fibrosis, Huntington disease, spinal muscular atrophy

Current Medical Genetics

- Focuses on diseases due to mutations in a single gene that are inheritable
- These genetic diseases are very important to affected individuals and their families
- However, these conditions are rare
- Very few people affected
- Small part of medical practice
- Minimal impact on society

Current Medical Genetics

- Healthcare for these genetic diseases provided by medical geneticists and genetic counselors with occasional involvement by other medical specialists, pediatricians and primary care physicians

Future Genetic Medicine

Medical practice based on understanding the role of genetic variations in common diseases

- Diagnosis
- Treatment
- Therapeutic monitoring
- Prognosis
- Prevention
- Prenatal diagnosis
- Preimplantation testing
- Pharmacogenetics

Leading Causes of Death in U.S., 2001

Heart Disease	922,000
Cancer	554,000
Stroke	164,000
Chronic Lung Disease	123,000
Accidents	102,000
Diabetes	71,000
Influenza & Pneumonia	62,000
Alzheimer Disease	54,000
Kidney Failure	39,000
Septicemia	32,000

Source: CDC

≥9 of 10 Leading Causes of Death Are Influenced by Genetics

Heart Disease	922,000
Cancer	554,000
Stroke	164,000
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Accidents	102,000
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Kidney Failure	39,000
Septicemia	32,000

Jim Fixx

5’10”, 150 lbs
Marathon runner
Promoted healthy lifestyle
Died at 52 of MI while running
Father died at 43 of MI

Winston Churchill

5’8”, 270 lbs
Did not exercise
Smoked
Unhealthy lifestyle
Died at 90

The Impact of Genetics!

Future Genetic Medicine

- Common diseases affected by variations in one to many genes
- Germline and somatic variations
- Includes any disease identified now by family history, plus many that are not
- Affects virtually every person
- Practiced by virtually every physician

Gene Patents Limit This Future

- National practice standards set by one provider
- No competition for test cost, quality or method
- Limit advances in scientific knowledge gained through broad clinical practice and observation
- Limit medical education
- Limit medical practice
- Limit broad availability of genetic tests
- **A sole provider of a medical service is not in the best interest of the public health**

Leonard, Acad Med 2002;77:1388-1391.

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Supreme Court Decision LabCorp *v.* Metabolite Laboratories

The writ of certiorari is dismissed as improvidently granted.

The Chief Justice took no part in the consideration or decision of this case.

Quote from Dissenting Opinion of LabCorp *v.* Metabolite Laboratories

From Part I

The relevant principle of law excludes from patent protection… laws of nature, natural phenomena, and abstract ideas…. The justification for the principle does not lie in any claim that "laws of nature" are obvious, or that their discovery is easy, or that they are not useful. To the contrary, research into such matters may be costly and timeconsuming; monetary incentives may matter; and the fruits of those incentives and that research may prove of great benefit to the human race. Rather, the reason for the exclusion is that sometimes *too much* patent protection can impede rather than "promote the Progress of Science and useful Arts," the constitutional objective of patent and copyright protection.

Justices Breyer, Stevens and Souter

Quote from Dissenting Opinion of LabCorp *v.* Metabolite Laboratories

From Part III

…one can reduce *any* process to a series of steps. The question is what those steps embody. And here, aside from the unpatented test, they embody only a correlation between homocysteine and vitamin deficiency that the researchers uncovered. In my view, that correlation is an unpatentable "natural phenomenon," and I can find nothing in claim 13 that adds anything more of significance.

Justices Breyer, Stevens and Souter

Quote from Dissenting Opinion of LabCorp *v.* Metabolite Laboratories

From Part IV

If I am correct in my conclusion … that the patent is invalid, then special public interest considerations reinforce my view that we should decide this case. To fail to do so threatens to leave the medical profession subject to the restrictions imposed by this individual patent and others of its kind. Those restrictions may inhibit doctors from using their best medical judgment; … force doctors to spend unnecessary time and energy to enter into license agreements; … divert resources from the medical task of health care to the legal task of searching patent files …; … raise the cost of healthcare while inhibiting its effective delivery.

Justices Breyer, Stevens and Souter

Philosophical Questions

- Should gene patents be granted?
  - Are gene patents really inventions?
  - Are gene patents claiming a product of nature?
- Do gene patents inhibit or promote the "progress of science and useful arts," in this case medical practice?
- Are patent incentives needed for discovery or clinical implementation of patented genetic information?
- Should exclusive licensing of fundamental medical knowledge be allowed to continue?
- Is sole ownership of a disease in the best interest of the public health?

Options to Consider: Courts, Congress or USPTO

- Exempt medical personnel who perform genetic tests from patent infringement actions
  - Extend 1996 law that protects physicians
  - Lynn Rivers bill introduced 2002 (H.R. 3967)
- Mandate broad licensing at reasonable royalty rates
  - Prevent exclusive licensing for genetic tests

Questions?