Secretary's Advisory Committee on Genetic Testing

Summary of Panel Session on
Human Gene Patenting and Licensing Practices
and Access to Genetic Tests
June 7, 2000

This session was devoted to an exploration of human gene patenting and licensing issues as they apply to genetic testing. Dr. McCabe, SACGT Chair, introduced the session by noting that while the human genome project and rapid developments in diagnostic technologies are providing many important new tools for enhancing patient care, like any rapid technological change they are also raising new questions. He pointed out that SACGT has heard concerns from members of the public that gene patenting and licensing practices are having an adverse impact on the cost, accessibility, and quality of genetic tests, and we need to learn more about these concerns. At the same time, SACGT is aware that patents are an important part of the commercialization process and that they lead to the development of many beneficial products. The goal of the session was to bring together a wide range of perspectives on the issue to help SACGT members understand how patents and licenses work, how they enhance the public good, what concerns are being raised about them, and whether further study of the issues is warranted. The session was organized into three panels, the first providing a broad overview on the subject, the second focusing on concerns being raised by several constituencies, including representatives of patient groups and ethicists, and the third providing views from several industry representatives on the value of patents in this field. Following the presentations, SACGT engaged in a roundtable discussion with all the presenters.

Panel One: The Basics of Gene Patenting, Licensing, Technology Transfer, and Commercialization

Ms. Lila Feisee, a representative from the U.S. Patent and Trademark Office (PTO), provided SACGT members with an overview of the U.S. patent system, particularly as it applies to developments in biotechnology. She said that the Constitution establishes this system, mandating it to promote the progress of science in the "useful arts" and specifying that inventors are entitled to exclusive commercial rights to their discoveries for limited periods–currently that period extends twenty years from the date an application is filed with PTO–in exchange for disclosing those discoveries to the public. In 1952, Congress specified four requirements to be met for a discovery or invention to qualify for a U.S. patent: it must be useful, novel (not previously discovered), not obvious to someone else familiar with work in the field, and the description of the discovery needs to be complete enough to enable other experts in the field to "practice" or repeat the experiments or work done to make or use the discovery or invention.

As in any area of law, court rulings greatly influence the interpretation and application of patent law. For example, according to Ms. Feisee, a 4th Federal Circuit Court ruling many years ago in "Merck v. Olin Mathieson" specifies that patents may be granted for "products of nature," in that case vitamin B12, so long as those patentable products are "distinct in form or content" from their counterparts found in natural settings. Another court ruling, "in re Bergey," specifies that purified bacterial cultures may be patented because they are not found in such form in nature. Yet another

ruling, this time from the Supreme Court in "Diamond v. Chakrabarti," holds that genetically engineered microorganisms may be patented.

Ms. Feisee said that, once an application is submitted to PTO, the burden is on officials to prove that an invention is not entitled to patent protection—not the other way around. Patent examiners follow carefully developed, from time-to-time modified guidelines when evaluating patent applications and deciding whether proposed inventions meet the congressionally specified and court-interpreted criteria for patentability. For example, the "obviousness" of an invention and the ability of other experts to "practice" the invention whose application is pending represent criteria that change as a particular field develops. Something that seems obvious today may not have been so several months earlier when the inventor was making a series of discoveries. Hence, patent examiners are required to keep abreast of technical developments within the fields in which they evaluate patent applications.

Moreover, PTO sometimes revises its guidelines for evaluating such applications, according to Ms. Feisee. For instance, in December 1999, PTO published draft revisions of its "utility" criteria, specifying what threshold values an invention involving DNA molecules should satisfy to qualify for a patent. The draft guidelines specify three additional tests of utility, namely that an invention be "specific, substantial, and credible" in terms of the utility being claimed for it. For instance, a DNA probe is considered to have specific utility if its target is known and described in the patent application; otherwise, a DNA segment by itself without a specific target will not be considered patentable. Similarly, a therapeutic method for treating a particular disease or a method for diagnosing such a disease could qualify for a patent, whereas uses of a putative invention that entail further research to reach either or both those goals are considered not to have met the "substantial" element of the pending utility criterion. These draft guidelines are themselves subject to revision based on comments from the public.

Ms. Feisee said that PTO recently issued another set of guidelines pertaining to biotechnology inventions, clarifying the criteria that PTO expects inventors to meet when providing written descriptions of their discoveries. The key question is whether the researcher actually accomplished what he or she describes in the patent application—is it credible or merely conjectural and premature–when the description is submitted to PTO.

Mr. Charles Ludlam, a representative from the Biotechnology Industry Organization (BIO) in Washington, DC, said that PTO's current efforts to refine its criteria for issuing gene patents represent a thoroughgoing deliberative process of considerable technical complexity. Once those new draft criteria are revised and put in practice in issuing gene patents, the courts will become involved in arbitrating disputes over specific patents that may come to be contested.

Although BIO does not agree with every detail outlined in the pending PTO draft guidelines for evaluating gene patents, the organization believes that these efforts to develop refined guidelines are fully legitimate and necessary, according to Mr. Ludlam. However, he said that BIO does not believe that it is appropriate for SACGT to become involved in reviewing issues involving gene patents. The principal reason is that the Department of Commerce, rather than the Department of Health and Human Services (DHHS), has specific jurisdiction over patents.

Another more general concern of BIO about other federal entities becoming involved in biotechnology patent-related issues arises from statements made by President Clinton and U.K. Prime Minister Tony Blair in March 2000. Their comments about gene patenting led to a sharp, virtually overnight decline of $55 billion in capital for publicly traded companies within the biotechnology industry, according to Mr. Ludlam. He said that this large-scale loss in resources likely halted life-saving diagnostic and therapeutic research being done by many of these companies within the private sector. Moreover, the entire industry still is losing money in terms of its research and development outlays—for instance, $5 billion in 1999–another sign of its fiscal fragility. He pointed out that President Clinton subsequently clarified his remarks early in April by saying that gene-patenting policy is a matter for PTO and the Department of Commerce to determine.

Mr. Ludlam said that, if DNA patents were discussed in terms of DNA consisting of molecules, the emotional public debate now under way would disappear. Because these molecules may serve in diagnostic or therapeutic purposes, or both, any discussion of them touches on potential therapeutic applications. Hence, he said, discussions about changing patent criteria need to be conducted very carefully, lest contemplated changes undermine efforts to develop products for treating a range of important diseases. Interfering with patent practices in this area of biotechnology could slow progress toward developing such products by taking away commercial incentives that are vital to the private sector pursuit of those products. Although many such human gene-based products are at an early stage of development, other "products of nature," such as recombinant-DNA-based hormones including insulin and growth hormone, are accepted by the public and are serving important medical needs. In such cases, a great deal of research and development effort needs to be invested before those or other therapeutic or diagnostic products can be tested, licensed, and brought into full clinical use.

The biotechnology industry very much depends on patenting its inventions, according to Mr. Ludlam. Those patents ensure that commercial competitors cannot steal a company's products, but the protections conferred by the patent system are not used to interfere with academic researchers conducting studies that are without commercial motives, he said. Any effort to limit the enforcement of patents when they are being used for commercial purposes, even by academic researchers, will be detrimental to the biotechnology industry and to modern medicine and the patients it serves, according to Mr. Ludlam. For example, the Ganske-Frist statute was revised numerous times to make sure that it does not establish such exceptions through precedent, and its final version was designed painstakingly to have no detrimental impact on the biotechnology industry.

Mr. Ludlam pointed out that the biotechnology enterprise arose in large part from funds invested through the National Institutes of Health (NIH) and because of the congressionally mandated technology transfer system intended to move fundamental inventions into practical use by the private sector.

Mr. Ludlam closed by reporting that BIO planned to convene a stakeholders meeting on June 19, 2000, to review gene patenting and licensing issues.

Mr. Stephen Bent, a partner with Foley and Lardner of Washington, DC, agreed with Mr. Ludlam on many issues. He said that, contrary to widely voiced views in the news media, patents do not threaten progress in human genetics research nor do they embody property rights in living

organisms. He also said that the patent system should view DNA molecules in the same way it does inventions involving other chemicals.

Patents provide a mechanism for allocating costs for technology development within a particular sector, such as the biomedical sector, according to Mr. Bent. The intellectual property right acknowledged through patents thus permits market-driven processes to work effectively. Those market forces, in turn, help to ensure that eventually developed diagnostic and therapeutic products remain affordable. In addition, health care providers and government rules about payments further modulate the pricing of such patented products and services.

Mr. Bent said that interesting and sometimes problematic intellectual property issues nonetheless can arise, particularly in the area involving genomics patents. For example, genomics research can foster a good deal of speculative efforts outside the traditional boundaries of the molecular biological laboratory, often conducted through computer-based extrapolations. He said that the extent to which such speculative uses of genomics inventions and patents fosters the treatment of genes as commodities could alter the calculus of technology transfer.

However, court rulings as well as pending adjustments to patent application evaluation criteria (particularly those described by Ms. Feisee from PTO) already seem to be correcting this potential imbalance, according to Mr. Bent. Thus, he said, claims made as part of genomics patent applications increasingly will need to be made on the basis of specific biochemical and molecular biological experimental results rather than on computer-based speculation if those claims within the patent applications are to be upheld by PTO. Moreover, market forces and forces within the legal system tend to exert additional pragmatic, or corrective, effects, according to Mr. Bent.

Mr. Jack Turner, Associate Director of the Technology Licensing Office (TLO) at the Massachusetts Institute of Technology (MIT), said that, with a few notable exceptions, universities derive relatively little revenue from intellectual property-based technology transfer licensing arrangements. For example, royalty revenue to MIT in 1999 was about $14 million, against a research budget of $750 million. For MIT, the main objective of its TLO operations is to license university-developed discoveries to the private sector for commercial development, not to maximize revenues from such licensing agreements. Thus, TLO is viewed as a service rather than a profit center for MIT.

Researchers at MIT are encouraged to file patents through use of outside attorneys, and TLO favors negotiating exclusive, rather than non-exclusive, licensing agreements with single companies in the private sector because this approach typically proves more likely to attract such investments, according to Mr. Turner. MIT also is willing to negotiate equity positions in lieu or partial lieu of royalties, and TLO includes diligence provisions in its licensing agreements specifying that it can reclaim a technology if a licensee decides not to pursue its development.

DISCUSSION

In response to a question from Dr. Reed Tuckson about the degree of control over patenting that PTO exerts, Ms. Feisee said that the agency reviews patent applications purely at the front end and on the basis of their technical merits. PTO exerts no controls over licensing agreements or any other matters involving issued patents.

In response to a question from Dr. Kathy Hudson, NHGRI, about the impact of disclosing human genome consensus sequences on patent applications, Ms. Feisee said that patent examiners are required to consider the "prior art." In this case, such disclosures are considered relevant prior art and would preclude the patenting of human gene fragments. In response to a follow-up question about patenting SNPs (single nucleotide polymorphisms), she said that such entities could be patentable, provided that they satisfy the requisite criteria set out by PTO.

In response to a follow-up question from Dr. Tuckson, Ms Feisee said that PTO considers patent applications for genetic tests or other human-related genetic matters according to the same criteria as other subject matter.

Dr. Tuckson asked Mr. Ludlam whether there is any regulatory mechanism outside the workings of free-market economic forces to prevent monopolistic practices by patent holders. Mr. Ludlam said that the legal system provides means for addressing such issues. In addition, universities that license technologies to companies may retain some influence over how ensuing commercial products are handled. There are additional parties with influence, including HMOs, the federal Medicare system, and of course the overall marketplace.

In response to a follow-up question about BIO's potential role in influencing member companies on such matters, Mr. Ludlam said that it would violate antitrust statutes for BIO to work with member companies on pricing policies. However, BIO is deeply engaged in the national debate over prescription drug pricing and purchasing policies, particularly with regard to Medicare having an enlarged role in providing drug benefits and possibly controlling prescription drug prices, according to Mr. Ludlam. He said that discussions during 1993 and 1994 over imposing price controls on breakthrough drugs led to a collapse in capital markets then supporting the biotechnology industry and scuttled many plans to bring privately held companies to gain public investments in initial public stock offerings. He also noted that NIH offered a blanket "reasonable pricing" clause to technology licensing agreements it made with industry during 1988-1995, but that then-Director Harold Varmus recognized that this clause was not workable and it was dropped.

In response to a question from Dr. McCabe, Mr. Turner said that MIT does not try to influence pricing policies of its licensees, but that it does enforce diligence requirements specifying that companies pursue MIT-licensed technologies through product development and commercialization—in other words, taking steps to ensure that such companies do not stifle those technologies.

Panel Two: Emerging Concerns about the Impact of Gene Patenting and Licensing on Genetic Testing: Clinical, Ethical, and Patient Perspectives

Dr. Michael Watson, a cytogeneticist from Washington University School of Medicine, said that, because of the far-reaching and fundamental implications of human gene patenting, the subject warrants broad public discussion. His particular focus is on how some of those patents are being enforced in diagnostic settings and the impact of that enforcement on health care.

Dr. Watson said that patent-based monopolies restricting specific diagnostic procedures already are having an impact, with some diagnostic laboratories receiving written notices to cease performing certain diagnostic tests and, instead, send materials or specimens to designated test centers or

companies that have exclusive commercial rights to do those tests. Such practices affect competition in diagnostic testing, causing prices for conducting tests to rise.

Another consequence is that subtleties associated with a specific genetic condition may not be explored thoroughly enough. For example, according to Dr. Watson, in the case of cystic fibrosis (CF), patents did not constrain that follow-up research. Thus, after the discovery of several mutations associated with CF, a consortium of researchers in many laboratories identified hundreds of additional, rarer mutations associated with this genetic disease. Such genetic diagnostic testing, particularly in academic settings where much of it is conducted, entails a complex process of analysis and sharing of information among dedicated experts. This process is considerably hampered, if it can continue at all, when diagnostic testing for a particular genetic disease is restricted to a single laboratory or service.

Dr. Watson also reviewed how restrictions on use of a DNA diagnostic test for Canavan's disease have a wider impact on investigations into the nature of this rare condition, including its carrier frequency within specific population groups, as well as on the costs of doing this diagnostic testing. Because of restrictions being imposed through patent enforcement, the cost for this DNA-based test has risen from about $50 to $350, he said. Moreover, the restrictions are interfering with efforts to conduct broad carrier screening studies across Ashkenazi Jewish population groups, those who are principally affected by Canavan's disease. The patent holder also imposes caps on diagnostic laboratories, limiting how many tests for Canavan's disease each of them may conduct, and this in turn is skewing how the population geneticists design population-screening studies, according to Dr. Watson. Similar restrictions are affecting other genetic diseases besides Canavan's disease.

Such restrictive practices also will affect the training of specialists who conduct genetic tests, according to Dr. Watson. If trainees cannot learn firsthand how to conduct specific genetic diagnostic tests, the scope of their education is being reduced, and expertise will be lost, he said. A survey of diagnostic laboratories indicates that many of them are dropping use of tests that are encumbered with patent restrictions and, sometimes, also dropping research into the test-associated genetic diseases as well.

Dr. Ellen Wright Clayton, a geneticist and health policy analyst at Vanderbilt University, said that the committee should consider whether distinctive rules governing the patenting of human disease genes are needed and, if so, how to design those rules. She said that the very way in which information about human genetic disease is collected, with its emphasis on obtaining DNA samples and additional information from individuals and specific population groups, sets this area of research and diagnostic commercial development apart from most others in which patents also come into play. The associated moral and social issues are important matters for SACGT to consider, particularly because they lie outside the province of PTO.

Although several arguments are offered for not allowing patents or providing royalty payments for tests involving human genetic diseases, Dr. Clayton said that the most compelling is that royalty interests do not so much provide incentives for developing such tests or conducting further research as they shift the distribution of funds. Citing the experiences of the National Tuberous Sclerosis Association, she said that a better model might be for population groups who are affected by a specific disease to be given royalty interests in the development of diagnostic tests and other decision-making responsibilities. Thus, for example, instead of following traditional patent practices

by granting exclusive commercial rights to an inventor or company in a particular diagnostic test, those rights could be assigned to the affected population group.

Dr. Clayton said that society can choose to control the assignment of property rights. For example, rules governing human embryos restrict how they are handled or used, reflecting their unusual nature. For example, couples may donate their embryos to other couples or for research, but they are not permitted to sell the embryos. Although this analogy does not correspond exactly for analyzing the patenting of genes associated with human diseases, it raises similar issues about not exploiting those who furnish materials for analyzing those diseases, she said. Moreover, it illustrates that property rights involving sensitive human materials are not absolute but are subject to societal intervention.

Dr. Clayton said that it may be appropriate to revisit the Bayh-Dole Act, which mandates the transfer of technology developed through federal sponsorship to the private sector. That legislation continues to generate enormous private wealth, even while Congress continues to expand the NIH budget. In the aggregate, this process looks like a huge gift to industry at the expense of taxpayers, according to Dr. Clayton.

Dr. Judith Tsipis, a geneticist at Brandeis University, a leader of the National Tay-Sachs and Allied Diseases Association, and a co-chair of the Canavan Foundation, said that experiences with the patenting of the Canavan disease gene show that such patenting runs contrary to the public interest. This autosomal recessive genetic disorder affects mainly Ashkenazi Jewish children, causing a progressive impairment of the central nervous system that typically is fatal by the age of 10 to 15 years.

In 1987, the father of two children with Canavan's disease approached Dr. Reuben Matalon, then at the University of Illinois, to study the biochemical and genetic basis of this disease. With cooperation from other affected families and support mainly from private charitable foundations, Dr. Matalon identified the underlying biochemical basis for the disease and, by 1993, after he moved to the Miami Children's Hospital, also identified the gene and specific mutations associated with it. His results led to the development of diagnostic and carrier tests for the disease. Shortly thereafter, two leading medical organizations recommended that couples with Ashkenazi backgrounds planning families be tested for the Canavan trait.

Throughout these developments, the researchers and affected Canavan families cooperated closely, according to Dr. Tsipis. However, circumstances changed in 1997 when a broad patent covering Canavan diagnostic and therapeutic products was issued to Dr. Matalon and several associates at Miami Children's Hospital. Information about the patent was announced through a letter from the hospital indicating it planned to enforce its patent rights. That letter was distributed in November 1998, a week after the two leading medical organizations recommended population-based screening for the Canavan trait.

Dr. Tsipis said that the patenting of human disease genes can restrict public access to genetic testing and other medical benefits. Although restrictions on patented technology vary, any limits on genetic tests can compromise consumer access to them. In the case of the Canavan's disease test, Miami Children's Hospital sought an exclusive licensing partner, then a market-sector leader, while signing license agreements with university laboratories that, early in the process, specified testing caps but,

more recently, have eased those terms. However, many laboratories that previously conducted a relatively low volume of such tests refuse to sign what they still consider a bad licensing agreement and thus no longer can do the diagnostic testing, she said.

Dr. Tsipis said that royalties charged for genetic tests raise medical costs charged to families and thus limit accessibility to testing for economic reasons. This restriction threatens to grow substantially as more and more genetic tests become available for routine testing. Thus, small royalties associated with single tests could amount to a great deal of money when they are packaged together as a battery. Moreover, health insurance policies do not always cover costs of carrier or prenatal testing for conditions such as Canavan's disease. Gene patents, particularly when assigned exclusively to commercial laboratories, can preclude genetic counseling by academic centers where those tests might otherwise be performed and explained to patients. Restricting access to the patented diagnostic technology also can interfere with efforts to extend research on the underlying genetic disease, as occurred with a couple, one of whom is not Jewish, whose daughter developed Canavan disease, most likely from a novel mutation.

Dr. Jon Merz, an engineer, lawyer, and specialist in bioethics at the University of Pennsylvania, said that patents covering disease genes are not in the public's best interest and are fundamentally incompatible with medical practice. He argues that disease genes should not be considered eligible for patents. Moreover, he said that provisions in the American Medical Association (AMA) code from the middle 19th century deem it unethical for physicians to patent many types of medical discoveries, except devices and various other commercial products.

Dr. Merz and his colleagues have conducted several surveys of patent holders, asking about their licensing efforts with regard to patents covering genetic tests. The survey results indicate that many, but not all, institutions are granting exclusive licenses on disease gene patents, and those licenses are being used in some cases to restrict clinical research and clinical care. He said that NIH should not grant exclusive licenses for such testing.

Dr. Merz said that another survey of labs performing hemochromatosis testing indicates that many of them stopped offering this test after receiving letters from the patent holder indicating that they could no longer do so without a license. One effect of stopping diagnostic testing is that it slows or halts research associated with findings from such tests. He said that policies to prohibit exclusive licensing should be considered.

Panel Three: Importance of Gene Patenting and Licensing: Industry Perspectives

Dr. Thomas Frank, medical director of Myriad Genetics, Inc., said that his company invested the equivalent of 150 person-years of effort and tens of millions of dollars to discovering two genes, BRCA1 and BRCA2, that are responsible for most hereditary breast and ovarian cancers and in developing automated tests for detecting them in human populations.

Myriad holds at least eight patents covering this technology, according to Dr. Frank. By contrast, tests for hereditary non-polyposis colorectal cancer (HNPCC), which is diagnosed on the basis of two genes, designated *h*MLH1 and *h*MSH2, is not covered by comparable patents and exclusive licensing arrangements. He said that patents foster development of high quality tests, provide valuable clinical information, and in turn promote research. Because Myriad has a strong patent

position, it could and did invest in building an advanced automated reference lab that performs full sequence analyses of BRCA1 and BRCA2 genes for each patient sample. The company also is involved in a national collaborative effort to compare and evaluate several different methods for analyzing these mutations. By contrast, there is no comparable effort in terms of quality or scale built around HNPCC testing, according to Dr. Frank.

Dr. Frank said that his company has a strong interest in ensuring that its testing services are widely available. One company program is dedicated to helping individuals receive insurance coverage for such testing, whereas academic centers that conduct HNPCC testing seldom if ever provide such assistance, he said. His company also provides a great deal of information to the medical community and to patients about the subject of its testing programs and its medical significance. He said that the company also encourages investigators to study BRCA1 and BRCA2 genes without restriction for research purposes, and the company has provided funding for several research programs.

The only restrictions the company insists upon are directed to commercial competitors, whereas it has licensed 13 academic laboratories to perform commercial testing for specific mutations within these two genes, according to Dr. Frank. He said that patient needs are best served when complex genetic tests are performed in specialized reference laboratories. He also said that imposing new regulatory burdens on companies such as Myriad will add to the cost of offering genetic testing to patients and health care professionals. Patenting and commercial rights to genetic tests result in enhanced medical care.

Dr. James H. Davis, general counsel of Human Genome Sciences, Inc. (HGS), said that it is important to think beyond diagnosing genetic and other diseases and to consider the development of therapeutic products for controlling those diseases. Although HGS is not seeking to patent human genomic DNA as such, the company is very concerned about patenting human cDNA (complementary DNA or expressed genes) and the proteins that are encoded by such sequences for the purpose of developing therapeutic products.

After considerable effort begun eight years ago, HGS has three such products in clinical testing, including KGF-2 for the treatment of chronic wounds, M-PIF for protecting bone marrow stem cells during chemotherapy, and VEGF-2 as a growth factor for stimulating blood vessel development around the heart and other tissues with insufficient blood supplies, according to Dr. Davis. These developments cost more than $450 million, and it takes more than $500 million typically to take a single therapeutic product through clinical trials to licensure and the market.

Without patent protection, these substantive investments in potentially important therapeutic products would not be feasible, Dr. Davis said. The patents sought by HGS are not directed to genes in the human body but to proteins that are encoded by those genes and that form the basis for therapeutic products. He pointed out that the draft guidelines from PTO clarifying its policies on utility criteria for gene patents are not really a departure from past practices and that patents are vital to the biotechnology industry and its commitment to develop new treatments for patients.

Mr. Lee Bendekgey, general counsel of Incyte Genomics, Inc., said that, because of their utility, the gene discoveries are entitled to patent protection and that patent licensing programs enable research and the broad development of diagnostic and therapeutic products. Accelerated discovery in genomics research will soon make many new diagnostic and therapeutic products available to

patients and health care professionals. He predicted that, within a few years, all potential drug targets will be identified and an increasing fraction of drug research will be done electronically by analyzing genomics and post-genomics databases.

Mr. Bendekgey described the search for the Tangier disease gene, a rare disorder leading to an extreme HDL (high density lipoprotein) deficiency that, in turn, yields a six-fold increased risk for coronary artery disease and early death among those who carry this trait. Working with a corporate collaborator, researchers at the two companies combed through partial genomic databases from patients with this disease and compared that information to data from people without the disease. Within four weeks, they identified a transporter gene on human chromosome 19 that apparently is responsible for this rare disorder. Several other corporate partners are identifying potential therapeutic targets on the basis of the company's databases and analyses, according to Mr. Bendekgey. Hence, he is perplexed that anyone is questioning the utility of patenting and the benefits it provides to health care.

Mr. Bendekgey said that, to benefit the public, gene patent licensing policies should meet several criteria. For one, royalty and transaction costs should be low to encourage the wide availability of diagnostic tests. His company offers non-exclusive licenses for both research and diagnostic uses of its patented technology, and assesses low royalties. Licensees are asked to grant back freedom to operate based on gene discoveries that they make under these agreements. Some 30 corporate clients, including 18 of 20 top pharmaceutical corporations, have agreed to this provision. He said that companies in the private sector do not appear to be using gene patents to inhibit academic research on human diseases.

Mr. Bendekgey said that the patent system should not be used to set national health care policy. However, he endorsed plans calling for increased federal funding for genetic testing and for clinical trials.

Dr. Christopher Palatucci, director of business development at Athena Diagnostics, Inc., a division of Elan Corporation, said that his company is a clinical reference laboratory, with much of its activity devoted to developing and conducting DNA-based testing, including many tests for diagnosing rare neurological disorders.

Dr. Palatucci said the patent system provides important incentives for people to take risks in developing innovative technologies to benefit the public. Various protections, including exclusive licensing arrangements, are critical to the continued success of the system and, without them, many research discoveries would not be brought into clinical use. His company often obtains licenses to use university-discovered diagnostic procedures for rare genetic disorders that larger companies are not interested in pursuing and which the university researchers are typically ill-equipped to pursue in terms of providing broad-based diagnostic services to patients. The company thus benefits researchers by paying royalty fees to universities and by providing information obtained through performing the tests back to the researchers. He said that the current patenting system should be left intact and to do otherwise would lead to fewer diagnostic tests being made available and to poorer quality control over them.

ROUNDTABLE DISCUSSION

In response to a question about arrays of diagnostic tests, several components of which might be separately patented, Dr. Frank said that he was not aware of examples of such tests. Nonetheless, there would be many incentives for the separate patent holders to cooperate over such array-combined testing, he added.

In response to a question from Dr. McCabe about panels of diagnostic tests for Canavan's disease, Dr. Frank pointed out that the initial effort by the patent holder to identify a partner to hold an exclusive license for such testing failed. He said that sometimes such plans do not make good medical sense or good commercial sense.

Dr. Burke said that she disagreed with Dr. Frank's comparisons of BRCA1,2 testing with HNPCC testing, pointing out that the heightened public awareness of breast cancer plays an important role, bringing many more people in for testing than seeking similar gene-based testing for colorectal cancers. Dr. Frank agreed that public awareness can prompt people to seek such tests.

In response to a question from Dr. Francis Collins about patents for DNA-encoded proteins whose initial identification is mainly based on computer analysis, Dr. Davis said that a patent covering a specific claimed use of a chemical may be valid even if that use eventually proves not the most valuable use of that chemical entity. For example, the CCR-5 protein is patented in part on the basis of a claim that it is a mediator of T-cells with the potential use in treating rheumatoid arthritis. Investigators later learned that it also plays a role in HIV infection, but the original patent remains valid. Patents permitted the investigators to share information such as the CCR-5 gene sequence, which otherwise might not have been done before a commercial product came into use many years later, according to Dr. Davis.

Mr. Bendekgey said that obtaining patents does not require having complete knowledge about the patented products. In the case of patenting genes, simply organizing them into particular classes can prove helpful to Incyte's corporate clients. If his company could not do so with the proprietary protection conferred by patents, it would likely keep its human genomics information secret, thereby interfering with the research being done by its large pharmaceutical company clients.

Dr. Collins said that these responses do not address the anti-commons effect of patenting human gene sequences and of the potential for such patents to inhibit other investigators from studying genes whose sequences are patented by others.

In response to a question Dr. Tuckson asked of Mr. Bendekgey about differences between his company and pharmaceutical companies, he said that his company is in the information business, not pharmaceuticals. If his business were to include drug development, it would represent steps toward the vertical integration of the pharmaceutical industry, which he considers a movement toward inefficiency. He said that the patent system now protects early-stage enabling technologies that encourage efficient innovation among companies in different industry sectors.

Mr. Bendekgey also said that the patent system should be applied evenly across all industries, and that other efforts are needed do address specific problems affecting health care policies. In response,

Dr. McCabe said that, because PTO policies affect health care, it is appropriate for SACGT to discuss such matters and advise DHHS on them.

Licensing guidelines. Dr. Burke suggested that the panel consider the development of special guidelines for the licensing of human gene-related patents as a way of promoting research and other benefits while avoiding abuses yet keeping the patent system itself intact.

Dr. Clayton said that there are other models besides patenting for protecting intellectual property—for instance, copyrights—that do not depend on granting exclusive licensing rights. In response, Dr. Frank said that the copyright example is not applicable; moreover, that there are exclusivity elements to it, inasmuch as others cannot exploit the work of a novelist, for example. Dr. Watson said that patenting in genomics raises questions about the ownership of information, and that patents allow one to exclude others using an invention, whereas copyrights do not exclude others from using what is copyrighted.

Dr. Frank also said that it is appropriate for SACGT to develop guidelines for patent licensing in terms of specifying idealized goals, such as free access and high-quality research to gene-based technology, without intervening specifically at the level of patents that cover genes. Dr. Palatucci said that, although NIH issued guidelines regarding material transfer and licensing agreements several years ago, they are rarely followed anymore.

Mr. Ludlam said that any attempt by the government to impose guidelines or standards comes at a cost. He said that companies need incentives, and exclusive licenses are favored as the way of providing some of those incentives. Later, in response to a question from Dr. Tuckson about a technology-driven "land rush," Mr. Ludlam again said that a very large investment is needed in genomics research, to bring the many new potential diagnostic and therapeutic products into use.

Dr. Collins later resumed discussion of patenting gene diagnostic tests, pointing out that claims for such patents generally will meet PTO criteria for patentability, meaning that the concerns about availability and fair costs of gene-based diagnostic tests will need to be addressed subsequently at the level of patent-licensing policies. He said that problems over these issues often are arising not so much in the corporate sector as at universities where those in technology transfer offices may not be familiar with fair pricing standards and also feel some pressure to negotiate lucrative arrangements. Dr. Palatucci agreed that these issues need to be addressed at the level of licensing, not at the patenting level. Dr. Watson said that there is a danger of becoming locked into a particular technology, because of an exclusive licensing agreement, without first more openly exploring alternative technical approaches.

Dr. Merz said that tensions about patenting research that is federally sponsored date back many decades but one consistent conclusion that he draws is that such inventions should not be licensed on an exclusive basis. He said that exclusive licensing should be the exception rather than the rule, perhaps reserved for therapeutic products but not used for diagnostics, which often are more readily adapted for clinical use. In response, Dr. Frank disagreed that genetically based diagnostic tests are relatively easy to bring to use. Dr. Palatucci agreed with him and briefly recounted the technically difficult development of a diagnostic test for Charcot-Marie-Tooth disease.

Ms. Patricia Barr later asked whether the patenting of specific gene sequences could be distinguished, perhaps prohibited, while permitting the patenting of diagnostic tests based on detecting those sequences and whether this would encourage competitive efforts to develop improved tests. In response, Dr. Palatucci said that alternative diagnostic tests may be patented. However, Dr. Merz pointed out that early patent claims often are stated very broadly in an effort to protect all diagnostic tests involving a particular disease gene. In response, Dr. Palatucci said that descriptions that are part of the patent application need to support its specific claims.

Dr. Merz also said that NIH could develop a strong policy on this issue and enforce it, at least through example. In response, Mr. Ludlam said that the Bayh-Dole Act, which underpins NIH policies on technology transfer, is very effective and should not be changed. He said that NIH guidelines for implementing this law already are, in general, anti-patenting and against exclusive licensing arrangements. If NIH or universities amend their policies to become less favorable to commercial development, companies will go to other biomedical discoveries that they find more favorable to develop into diagnostic and therapeutic products.

Canavan disease example. Dr. Tsipis said that it is not the patent itself but the way it is being enforced that has proved damaging in the case of Canavan's disease diagnostic testing. Thus, she said, exclusive licensing is not in the best interest of consumers. Regulating how patents are enforced could help address these problems.

Mr. Ludlam said that this instance represents an example where the license holder took a particular approach to developing a commercial product but, in essence, misjudged market forces. Although the process created discomforts, market forces worked out the problems, and everyone learned a great deal from the experience. Dr. Tsipis said that, although the specific situation involving testing for this disease has improved, it is not in the public interest for similar contests involving other genetic diseases to be fought out with such a heavy toll on public advocacy.

Dr. Clayton said that merely relying on market forces to solve such problems is not satisfactory. Instead, there should be mechanisms permitting stakeholders, particularly affected patients and their families, to influence diagnostic testing that is covered by patents on genes.

Dr. Davis said that lawyers believe that special care is needed in examining cases such as that involving Canavan's disease as it may represent an atypical example, one that forms a bad precedent for developing general policies. Dr. McCabe said that, in medicine, society tends to focus on such examples to develop policies.

In response to a later question from Dr. Tuckson, Dr. Tsipis said that personal moral considerations about her family's genes also come into her analysis of the Canavan's disease situation. Nonetheless, the real concern was for making this disease gene-based test widely available to the families who could benefit from it, but that enforcement of a patent was interfering with accessibility to that testing.

In a later comment, Mr. Ludlam said that Americans typically do not claim a property right in the tissues they donate or in other ways when the participate in clinical trials, and that to begin to do so would be destructive to the current system.

Gene patenting consumer medical issues. Ms. Patricia Barr addressed a series of comments and questions to Dr. Clayton, pointing out that patients often participate in clinical trials risking their lives without claiming a right to financial rewards from therapeutic products that may result from those trials. Thus, she asked whether it is appropriate for patient advocacy groups to have a role in negotiating licensing agreements over patents for specific disease genes. Dr. Clayton said that society may need to step in and say that health care does not involve a free market and that greater social involvement is required in this arena.

Dr. Judy Lewis said that it sometimes is appropriate for government to intervene when it detects imperfections within a market, such as is the case for health care in the United States, largely because of information deficiencies and also because of very uneven coverage of health insurance. She asked whether private sector representatives plan to address such inequities. In response, Mr. Ludlam said that he sees two types of access issues, one involving uneven access to available health care services and the other having to do with everyone's lack of access to treatments (or other products) because they have not yet been developed. He said it would be a mistake merely to redistribute currently available health care products and services if it meant not pursuing the development of new ones.

Dr. Frank said that his company provides diagnostic services for indigent patients. He also said that focusing on gene diagnostic services would not be an appropriate way to solve broader medical care inequities in the U.S. health care system. Dr. Lewis agreed with him.

Orphan diseases and rare mutations. In response to a question from Dr. McCabe about orphan diseases and drugs, Mr. Ludlam said that the exclusivity accorded such drugs by FDA (the system differs from traditional patenting) is very important to the biotechnology industry, which also is exploring ways to develop new incentives for research on vaccines for diseases that are prevalent in the Third world.

Dr. Watson said that there are parallel issues involving rare mutations within relatively common diseases. The patent system does not provide any guarantee that the holder of a patent for a particular gene-based diagnostic test will continue to improve the test so that it can detect all those with rare mutations as well as the more common forms.

Dr. Palatucci said that without incentives embedded in exclusive licenses, companies would not develop diagnostic tests for rare conditions. Mr. Ludlam agreed, saying that without exclusivity incentives, research on orphan drug diseases would stop.

Broader implications. Ms. Mary Davidson said that two days of SACGT discussions, including those about human protections, may represent an opportunity to think about research and research partners in a different light—as providing opportunities to bring the research community together with patient populations in the most productive way possible. In response, Mr. Ludlam said that his organization, BIO, is committed to participating in this dialogue. Dr. Tsipis said that policies are needed to assure consumer groups that their participation in research will serve the common good, not merely commercial interests.