The rapidly growing number of disease gene patents—patents that claim all methods for diagnosis of a particular genetic condition—threatens the ability of physicians to provide medical care to their patients. In the past, patented diagnostic tests were made broadly available to the medical community in the form of test kits or licenses to use the patented test. Disease gene tests, however, are being monopolized by a small number of providers. Monopolization of medical testing services: (a) threatens to restrict research activities; (b) creates unacceptable conflicts of interest; (c) may reduce patient access to testing; (d) may lead to inequitable extensions of patent terms on tests and related discoveries; and (e) grants to patent holders the ability to dictate the standard of care for testing, and to otherwise interfere with the practice of medicine. Because of the risks raised by monopolization, amendment of the patent law to require compulsory licensing of physicians providing medical services is recommended.

Vatican City (Reuters). The Vatican announced today that it has entered into an agreement with Dr. Mark Bogart of Honolulu, Hawaii, which grants to the Vatican exclusive rights to United States Patent no. 4,874,693. That patent, granted to Dr. Bogart in 1989, covers the human chorionic gonadotropin part of the maternal serum triple test for Down syndrome when performed between 18 and 25 weeks of pregnancy. Dr. Bogart, who was collecting royalties of several million dollars per quarter from hospitals, health maintenance organizations, and testing laboratories throughout the US, sold his interests in the patent for an undisclosed sum. The Vatican’s statement made clear that the Church intends to enforce its patent and prevent further use of the test in the US.

The news release above is, in part, fictitious. Dr. Bogart has not licensed his patent to the Vatican, and he continues to receive royalties that his lawyer has said may total $100 million over the term of the patent (1). The good news is that the Church will not prevent prenatal screening for devastating genetic anomalies that often lead to abortion of an affected fetus, a test that is the standard of care throughout the US. The bad news is that there is nothing in law that would prevent the license above from being negotiated, and little to prevent the licensee from preventing others from practicing the patented test.

This case illustrates the fundamental incompatibility of patents that cover procedures that can be practiced by any skilled medical provider and the practice of medicine. Unfortunately, the Bogart patent is not an anomaly. In fact, the number of patents being issued that broadly claim all methods of diagnosis of specific genetic diseases is growing rapidly. So-called disease gene patents claim the observation of an individual’s genetic makeup at a disease-associated locus when done for the purpose of diagnosis. They cover all methods of “looking at” that locus when done for the purpose of diagnosis, based on the basic discovery of a statistical association between genetic variability and disease or risk of disease. In a review of patents claiming gene sequences issued between 1981 and 1994, Thomas et al. (2) found diagnostics to be the fifth most prevalent type of patent. In a follow-up review of patents issued in 1995, diagnostics was first (3).

Disease gene patents are being used in a manner unique to medicine: many of them are being licensed exclusively to large clinical laboratories that then, to varying degrees, are enforcing their patent and preventing clinical molecular pathologists and geneticists from performing the patented tests. Other cases where someone has monopolized a medical service, especially by patent, are hard to imagine.

Essentially, some disease gene patents are being used to prevent physicians from practicing medicine, and there are numerous troubling issues raised by this turn of events. Here I discuss some of the ramifications of creating a monopoly over a medical service, assess the impli-
Some Observations about Disease Gene Patents

Patents promote and reward innovation by granting exclusivity to make, use, or sell an invention for a limited period of time. In exchange, the inventor must teach the world how to practice that invention. Arguably, patenting of the basic discovery of disease genes is unnecessary from the perspective of patent law (4). Gene testing patents are an end in themselves. No further development is generally needed for dissemination among medical practitioners, and broad adoption often follows first publication by only a short time. Moreover, these patents are not necessary to promote downstream development of therapeutics; in fact, they may stifle such development by constraining competition.

Furthermore, most disease genes have been discovered by physician-researchers working with large numbers of high-risk families in which diseases are prevalent. The patents and the licensing fees subsequently earned are windfalls to the doctors and the public institutions in which they work. The dependence on access to patients and the basic nature of this research is reflected in the fact that ~90% of disease gene patents have issued to researchers in universities, medical schools, hospitals, or the National Institutes of Health. In stark contrast, these “public” institutions have received only about one-half of all patents claiming DNA sequences (2).

The concern that without patents, these discoveries would be held as trade secrets is inapposite. Patentee physician-researchers have absolute and irrefutable ethical obligations to disclose and disseminate research findings rapidly and fully. It is difficult to imagine an Institutional Review Board approving any research involving human subjects where the research results would be held secret. Indeed, secrecy is contrary to the mores of all science, and is particularly disgraceful in the health sciences.

Furthermore, basic academic and medical discoveries historically have not been patented. Arguably, biotechnology has blurred the distinction between basic discovery and more applied development (5). Nonetheless, policies promoting the patenting of the fruits of basic discovery may have injurious effects on downstream discovery and development efforts, and the potential impediments on research from patenting are receiving serious attention by the NIH and others (6, 7). The issues raised here will only become more pressing with the heating-up of the race between Incyte Pharmaceuticals, Celera Genomics, and the NIH to rapidly sequence the human genome and particularly to identify—and patent—polymorphisms (8).

Marketing Strategies for Genetic Tests

The process for moving a disease gene from discovery into use is depicted in Fig. 1. Following a discovery, patent application and first publication generally occur relatively quickly and at about the same time (applications must precede publication to retain international rights). Although physicians may adopt the test and it may be accepted within the standard of care, the patent itself will not issue for 2 or more years. When the patent finally issues, laboratories that have adopted the test may be faced with licensing fees, royalty payments, or in the extreme, a prohibition on performing the test.

This raises fundamental questions about how the market will be—or should be—structured for delivering genetic testing services. The market could take three basic forms: monopoly (a single service provider); oligopoly (a limited number of providers in a given market); and “pure” competition (performance by many laboratories). Depending upon various factors, each of these different market structures may best meet the needs of providers and patients.

Several factors that might influence market structure are listed in Fig. 2. First, the number of patents related to a test may strongly influence how many laboratories are permitted to perform the test. One or few patents, particularly when held by an individual provider, will favor monopolization of the service if the patent holder so
chooses. Several patents held by several parties may lead to limited cross-licensing, which can create an oligopoly. Of course, with no patents, or no enforced patents, then pure competition between all laboratories that wish to perform the test may result.

Second, the simplicity of a test may favor pure competition, in that any laboratory can quickly develop and validate a clinically useful test. Thus, we would anticipate that tests for single nucleotide polymorphisms will have much broader adoption than will disease genes having hundreds of mutations [e.g., hereditary hemochromatosis (HFE) vs breast cancer (BRCA1 and BRCA2)]. Similarly, single gene disease tests may be simpler to develop than will tests for diseases having multigene causation [e.g., spinocerebellar ataxia vs spinocerebellar ataxia (SCA)\(^1\)].

Third, the prevalence of a disease or condition may translate to demand for the test. Larger demand will favor broad adoption, whereas a provider may only be willing to spend the resources developing a test for a rare condition if enough testing volume can be generated to make it worthwhile [e.g., cystic fibrosis vs Charcot-Marie-Tooth disease (CMT)]. Of course, the penetrance of the mutation may also determine the medical appropriateness of testing, and may interact with prevalence in influencing how widely genetic testing will be performed.

Supporting the rapid adoption of testing by clinical laboratories is a broad array of biotechnology companies that provide specific test kits for various diseases (e.g., infectious diseases) as well as reagents and probes that enable the development and use of "home brew" tests. Competition in the test market anticipates that laboratories will offer tests that are consistent with their mission to deliver quality medical services at reasonable cost, and those performing the tests will buy test kits as long as those kits are cheaper or better than tests developed in-house. Laboratories may also contract out testing to larger, commercial laboratories, when in-house performance is too expensive or testing volume is too low.

Despite these competing influences in the testing market, it appears that some disease gene patents are being used aggressively to monopolize the testing service market. Athena Diagnostics has secured exclusive licenses to patents for tests for late-onset Alzheimer disease [apolipoprotein E (Apo-E) genotyping], CMT type 1A disease (CMT1A), and, recently, SCA type 1 (SCA1). SmithKline Beecham Clinical Laboratories recently took an exclusive license to a patent covering the test for one HFE mutation. And Myriad Genetics has patented or licensed numerous patents on BRCA1 and BRCA2. Whether and how broadly these patent holders will permit clinical laboratories to perform testing is a currently evolving story.

---

\(^1\) Nonstandard abbreviations: SCA, spinocerebellar ataxia; CMT1A and CMTX, Charcot-Marie-Tooth disease, type 1A and type X; and Apo-E, apolipoprotein E4 genotyping.

**Concerns about Monopolization of Medical Testing Services**

The ability of such exclusive licensees or patent holders to monopolize a medical service raises various concerns:

(a) Potential restrictions on research may arise from: (i) the monopolization of research resources (i.e., blood and other clinical tissue samples); (ii) the inhibition of widespread clinical use and observation so typical and necessary for medical advances; (iii) the inhibition of external study and validation of the patentee’s research and clinical services; (iv) the imposition of stifling reach-through conditions on licensees, if any (e.g., rights of first refusal or compulsory cross-licensing of related discoveries); and (v) the imposition of unethical constraints on the performance of research by others (e.g., limits on clinical uses of research results inconsistent with local Institutional Review Board requirements and accepted medical research practices).

This problem arises in part because there is no statutory “research exception” in the US. Thus, the types of research using patented tests that may be performed without a license are highly uncertain. Largely, infringement may depend on the scope of the research activity. Patent holders may take a relatively hard line, offering royalty-free research licenses but using the licenses to force reach-through clauses on investigators. The problem also stems from the very basic nature of genetic discovery tied up in the patent claims, creating infringement and licensing hurdles for those in the business of developing targeted drug or gene therapies.

(b) Patents clearly raise concerns about conflicts of interest. Laboratories may engage in unwarranted promotion, including direct patient marketing. Individual clinician/researchers may inappropriately (over)use tests in which they have financial or research interests and may be overly aggressive in solicitation of research subjects. In addition, patents clearly raise serious concerns in performing research and publishing findings. Indeed, it is not a patent per se that raises these concerns, but the very filing of a patent application that should raise a warning flag regarding scientific objectivity.

(c) Patents may reduce access to testing services. Single service providers may refuse Medicaid reimbursements, as well as require prepayment by patients. It seems evident that monopoly rents, or excess profits attributable to the patent, will be extracted from those able to pay, to the detriment of those patients effectively priced out of testing by the monopolist.

(d) Disease gene patenting leads to inequitable extensions of the term of the patent monopoly. This is likely a result of the very basic nature of the discoveries underlying these patents. For example, no patent was ever sought for the first and overwhelmingly most prevalent allele of the cystic fibrosis gene, ΔF508. What happens when a subsequent discovery of another mutation of the gene is patented? The subsequent patentee can effectively monopolize the test for the unpatented ΔF508 mutation because it would be extremely inefficient to send samples
to different laboratories for testing for the different mutations, and it may well be malpractice to test for the most prevalent mutation without testing for the patented ones. This situation has occurred: the exclusive provider of CMT1A testing effectively monopolized the market for CMTX testing even before the patent on CMTX was issued. Likewise, at the end of the patent period for the CMT1A test, the patent on CMTX will ensure market exclusivity for CMT1A testing.

This arises when multiple genes are causally implicated in disease (e.g., SCA and BRCA), when there are numerous mutations in the disease genes (e.g., cystic fibrosis and BRCA), and when multiple gene interactions are causal (e.g., Apo-E and ACT/A). 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. This supports the contention that these basic patent grants are too broad.

(e) Exclusive service providers will interfere with the practice of medicine. Direct patient marketing may undermine provider education, and it may well undermine standards calling for adequate patient education and counseling surrounding genetic testing services (9).

In addition, and perhaps most importantly, the point cannot be stressed too strongly that disease gene patentees have the very real ability to prescribe nationwide medical practices and to dictate the medical standard of care. Patents may grant them the ability to dictate what kind of test may be done (e.g., sequencing instead of a less sensitive but substantially less costly methods such as two-dimensional Southern analysis, protein truncation tests, or other of numerous tests available), or limiting the conditions for which testing may be done (such as refusing to perform prenatal testing for late-onset diseases). Simply, this is an unacceptable outcome of medical process patenting and again highlights the fundamental incompatibility between diagnostics process patents and medical care.

Implications for Laboratories
Disease gene patents present unique issues for clinical laboratories. They may cause an increase in test costs for payment of royalties or license fees, and the patents may be used to prevent a laboratory from performing the tests. The knowledge that a patent application has been filed can influence the decision to spend the time and resources to develop a clinical test because of the uncertain risk that a patent holder will later prevent the laboratory from continuing to provide this service.

Laboratories clearly need to be aware of patenting activity. With the publication of a manuscript, unless a patent application is mentioned in the acknowledgments or conflict-of-interest statement, the only prompt means of determining whether a patent is being sought is to contact the investigators and their institutions. Investors should be quite open and honest about patents (although they may not want to discuss specific licensing terms such as royalties). Alternatively, one can gain insights into US patent applications when parallel European patent applications are published, 18 months after the first application is filed.

A laboratory wishing to implement a test on which a patent is pending or has been granted may seek a license to perform the test. This may be easier to secure early after publication, but it is clear that there is growing competition for these patents given the entry of several large commercial laboratory firms with interest in monopolizing testing services. Universities have appeared quite willing to grant such firms exclusive licenses (Athena Diagnostics has secured exclusive licenses from Baylor University for CMT1A, from Duke University for Apo-E genotyping for Alzheimer disease, and from the University of Minnesota for SCA1), which in turn permit this monopolization. From the university's perspective, an exclusive license makes sense because the university and its technology transfer office are not set up to manage the negotiation, collection, and audit of a large number of small licenses. However, universities (and the NIH when it is involved) should consider granting exclusive licenses only for the purpose of sublicensing, and not for the purpose of monopolizing medical services.

Clearly, laboratories need good intellectual property advice. They should have an attorney review their practices, both to check for potential infringement problems and to propose ways to avoid future problems with patents. Such advice usually would include the suggestion of developing a patent portfolio to compel cross-license agreements with primary patentees. Because of the basic nature of disease gene patents, however, it may be difficult to develop patentable inventions important enough to force a gene patent holder to enter a cross-license. New discoveries of mutations or polymorphisms prevalent and penetrant enough to alter the standards for testing could compel licensing. A related invention would be a new method that substantially reduces the cost of testing. The sequencing chips being developed by Affymetrix and others may offer such a tool. However, development of new test methods would not have to be licensed by a gene patent holder, and the new methods could not be used without a license to test for a patented disease gene.

Good legal advice is also a must for negotiation of licenses with patentees. One should never sign an agree-
ment sent by a patent holder without thorough review. Those agreements were written by lawyers for the sole purpose of promoting their client’s interests, and licensees must have adequate counsel to ensure their interests are also represented. Again, conditions that have already been seen in this market include reach-through rights to downstream discoveries and unethical limitations on research.

If laboratories are only performing research with a particular patented test, they must question whether they must have a license at all, and they should be willing to fight any attempts to impose licenses and egregious conditions on their research activities. Again, this is a highly uncertain area because of the lack of a statutory research exemption, but legal counsel may be able to provide bounds on what research activities may be pursued with manageable litigation risk. Infringement may depend on the total volume of testing being performed, whether the results are used clinically or not, whether the research is hypothesis driven or follows some other type of legitimate research design (e.g., familial linkage or studies of prevalence and penetrance in different populations), and whether the laboratory is being compensated (particularly at more than “cost”) to perform the testing. At a minimum, the laboratory should document the purposes for which such testing is done carefully.

Finally, the clinical laboratory community may consider other strategies for responding to these patents, including sanctioning (e.g., ostracizing) physician-researchers who secure patents and seek to enforce them against their colleagues; selectively choosing the laboratory services of competing firms to reward those not using patents in an offensive manner; using contracts or carefully drafted patient consent to restrict research uses of clinical samples (e.g., requiring disposition of excess samples in a culturally sensitive manner and not giving monopolist laboratories any identifying or phenotypic information regarding samples to be tested); preparing samples to be provided for testing to limit subsequent uses; and, finally, attempting to change the patent law.

A Policy Response: Compulsory Licensing

On September 30, 1996, the US Congress enacted a law that holds physicians and institutions free of liability for infringement of “pure process” medical patents (see the Appendix). The law exempts services performed by CLIA-approved laboratories and sweeping exempts process “biotechnology patents” (without definition) (10). Many of the justifications for exceptio
cases (15), and is also quite common in countries other than the US (16). The US is signatory to various treaties that reserve to the government the right to grant such licenses for reasons such as the public health (17). Furthermore, to the extent that some patent holders are monopolizing the testing market, the problems of discovering infringement and enforcing a preventative bar far surmount those of managing licenses and royalty payments. As for determining reasonable royalties, the courts are skilled at this task (18), and the allocation of litigation costs to either party deemed by the court to have been unreasonable in negotiations provides an incentive to both parties to reach mutually agreeable terms. Finally, because this law would still permit a patentee or other equitable owner or licensee to receive adequate compensation for all uses of the patented process and related primers, the law should apply retroactively.

Conclusion

Disease gene patents have spawned a new phenomenon in clinical laboratory medicine: monopolization of testing services. Such monopoly is at fundamental odds with good medical practice, and patents should not be used to limit the practice of medicine in any way. Compulsory licensing is a reasonable compromise aimed at permitting laboratory medicine to proceed subject to payment of royalties, something all laboratories already do for use of methods such as PCR. Compulsory licensing provides patentees with financial reward, thereby preserving the patent system’s incentives while limiting the potential negative effects on delivery of medical services.

I thank Mildred Cho and Debra Leonard for their continued collaboration related to the patenting of genetic tests, and Debra Leonard, Marcie Merz, Sheri Alpert, and Lynn Godmilow for comments on this article. This report was prepared for presentation to the American Association for Clinical Chemistry Forum entitled "Issues in Genetic Testing", November 3–4, 1998, and the Association for Molecular Pathology Annual Meeting, November 5–8, 1998, both held in Crystal City, VA.

Appendix

35 USC §287 (1998)

(c) (1) With respect to a medical practitioner’s performance of a medical activity that constitutes an infringement under section 271(a) or (b) of this title, the provisions of sections 281, 283, 284, and 285 [relating to remedies for infringement of patent] of this title shall not apply against the medical practitioner or against a related healthcare entity with respect to such medical activity.

(2) For the purposes of this subsection:

(A) the term "medical activity” means the performance of a medical or surgical procedure on a body, but shall not include (i) the use of a patented machine, manufacture, or composition of matter in violation of such patent, (ii) the practice of a patented use of a composition of matter in violation of such patent, or (iii) the practice of a process in violation of a biotechnology patent.

(B) the term “medical practitioner” means any natural person who is licensed by a State to provide the medical activity described in subsection (c) (1) or who is acting under the direction of such person in the performance of the medical activity.

(C) the term “related healthcare entity” shall mean an entity with which a medical practitioner has a professional affiliation under which a medical practitioner provides the medical activity on behalf of, or in association with, the healthcare entity.

(D) the term “professional affiliation” shall mean staff privileges, medical staff membership, employment or contractual relationship, partnership or ownership interest, academic appointment, or other affiliation under which a medical practitioner provides the medical activity.

(E) the term “body” shall mean a human body, organ or cadaver, or a nonhuman animal used in medical research or instruction directly relating to the treatment of humans.

(F) the term “patented use of a composition of matter” does not include a claim for a method of performing a medical or surgical procedure on a body that recites the use of a composition of matter where the use of that composition of matter does not directly contribute to achievement of the objective of the claimed method.

(G) the term “State” shall mean any state or territory of the United States, the District of Columbia, and the Commonwealth of Puerto Rico.

(3) This subsection does not apply to the activities of any person, or employee or agent of such person (regardless of whether such person is a tax exempt organization under section 501(c) of the Internal Revenue Code), who is engaged in the commercial development, manufacture, sale, importation, or distribution of a machine, manufacture, or composition of matter or the provision of pharmacy or clinical laboratory services (other than clinical laboratory services provided in a physician’s office), where such activities are:

(A) directly related to the commercial development, manufacture, sale, importation, or dis-
tribution of a machine, manufacture, or composition of matter or the provision of pharmacy or clinical laboratory services (other than clinical laboratory services provided in a physician’s office), and

(B) regulated under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Clinical Laboratories Improvement Act.

(4) This subsection shall not apply to any patent issued before the date of enactment of this subsection.

References

10. USC 35 § 287(c), 1998.