Issue Brief for Congressional Staff

Gene Patents:

What do they do? What policy options have been proposed? What are the implications of the Myriad ruling?

Issue brief prepared by Robert Cook-Deegan, Institute for Genome Sciences & Policy, Duke University[1]

To some, it may seem odd to patent a gene. After all, how can something found in the natural world be patentable? The answer is that it isn't, provided that there is no inventive contribution made by a human being. For example, Banting and Best isolated insulin in 1922 and patented "a substance prepared from fresh pancreatic or related glands" to treat diabetes the next year (US Patent 1,469,994). Louis Pasteur patented regularly and yet was also a true paragon of science; he was spectacularly successful in both science and its practical application. Patenting something biological and useful that is found in nature is not a new idea, and can contribute to "technology transfer" from scientific discovery to commercial availability of useful inventions.

Gene patents were an extension of the legal doctrines that permitted patents on hormones, vaccines, and other "natural products" that had been turned into useful form by human intervention. Patent offices around the world had no great difficulty concluding that genes could be patented in isolated and purified form.

Gene patents appear to have been important in inducing investment to develop some protein therapeutics based on patented genes, analogous to the role of patents in drug development. On the other hand, gene patents (or more precisely, patent claims on molecules or methods for diagnosing genetic diseases) have been controversial in diagnostics. Fears that gene patents could stifle research have not been borne out, for the most part. In diagnostics, there is a vigorous debate, with good arguments on both sides, either that patents might hinder innovation or that they foster it by inducing private R&D that otherwise would not be available.

Commentators are now raising questions about how existing gene patents might be used in the future, particularly with the advent of high-speed low-cost DNA sequencing and methods that detect millions of DNA sequences through sophisticated new technologies.

These technologies are mainly being used in research, but increasingly they are being used in clinical decisions based on individual whole-genome analysis, for ancestry-tracing and other purposes, including "personal genomics," which are offered directly to consumers. If lucrative markets emerge, the incentives to exercise intellectual property

---

[1] This summary is updated and revised from a 2008 policy analysis sponsored by the Hastings Center. Research related to this brief was funded by the National Human Genome Research for the Center for Public Genomics (NIH grant P50 HG003391), the Ewing Marion Kauffman Foundation, and Fondation Brocher (Hermance, Switzerland).

rights in gene patents will also rise, and could influence which technological paths are taken, or at least who makes money in those markets.

What do they do?

The debate about gene patents has some scientists praising the virtues of open science while others point out that patents create commercial incentives to develop the drugs, vaccines, medical devices, and services we want to improve and extend life.

Gene patents have been used for many different purposes, but they generally fit into five categories, patents pertinent to: (1) making therapeutic proteins or enabling gene transfer into cells, (2) diagnostics, (3) research tools, (4) nonmedical uses for identification, forensics, and ancestry-tracing; and (5) regulating DNA expression. A single patent may fit in more than one category. A patent may claim a DNA sequence that is both a research tool and a method to make a protein, for example, or both as a research tool and a diagnostic sequence.

There has been relatively little public controversy about gene patents for therapeutic uses, perhaps because in these cases the disputes were mainly between commercial competitors, with gene patents playing the role of means to produce valuable therapeutic proteins to treat disease. Gene patents have proven more controversial in two other areas: in clinical diagnostic use and as research tools.

Gene patents in research. The second most common cause of litigation over gene patents (six of 31 cases) was in research. One concern is that gene patents could block some lines of research. Making genes in the laboratory is essential for doing many kinds of research, and restrictions on such use would be difficult to work around. In theory, a patent claiming a DNA sequence can cover any use, even in research, not just selling or importing a product or providing a commercial service. In practice, however, research institutions have rarely been sued just for studying a gene or using it in academic research. (But note: rarely does not mean never. There are a few cases of gene patents being asserted against research institutions.) This is partly due to "rational forbearance" by those holding gene patents, because they generally stand to benefit from research that reveals how their patented gene works, and would have difficulty proving damages from research results.

One gray zone is when gene patents are used in clinical research, such as genetic testing in the context of a clinical trial. Here a genetic test may be used as part of a study, and laboratories offering tests allegedly infringing gene patents have been requested to "cease and desist" from such testing without a license from the patent-holder.

The existence of patents owned by different entities could make it difficult to produce collections of DNA sequences necessary to produce diagnostically relevant reagents, such as microarrays. Surveys of scientists in academe and industry have not shown a

powerful blocking effect on research, but the risk is likely to arise in commercial applications of such research, the traditional arena for competing patent rights.

Gene patents for therapeutic proteins—that is, patents to enable production of a protein to treat a disease—are among the most valuable, and most closely resemble the conceptual model of patenting small molecule drugs. Many biotechnology companies sprung up in the heady days of the late 1970s and early 1980s to exploit the new technologies of recombinant DNA and cell fusion (Office of Technology Assessment 1984). Some of these companies, such as Genentech and Amgen, succeeded in cloning genes encoding therapeutic proteins, and patented those genes as a way to make the valuable biological molecule. Several products emerged from this approach. Insulin was the first recombinant product, approved for marketing in 1982. Rat insulin was initially cloned at the University of California, San Francisco, and Genentech licensed cloned human insulin to Eli Lilly (Hall 1987)(Hughes 2011). Insulin was also the subject of a mammoth $30 million patent battle among those three parties. Genentech also became engaged in litigation over growth hormone, tissue plasminogen activator, and other gene patents. Another protein-based hormone, erythropoietin, was the subject of several patent battles that proved crucial to the growth of Amgen.

Gene patents for diagnostics and the controversy over patenting breast cancer genes. The most widely known gene patent controversy arose over the patenting of two genes, *BRCA1* and *BRCA2*, resulting in recent court rulings regarding their patentability that have implications for all patents that claim isolated DNA.

Some mutations in *BRCA1* and *BRCA2* make women who inherit them susceptible to breast cancer, and account for an estimated 5 to 10 percent of breast cancer cases as well as significantly elevated risk for ovarian and other cancers. Following discovery of a genetic linkage to breast cancer susceptibility in 1990, an intense international race began to find the responsible mutations.

That race ended in 1994 with the discovery of *BRCA1* gene (on chromosome 17), followed by *BRCA2* gene (on chromosome 13) in 1995. Myriad Genetics, a Utah-based company, the University of Utah and the US National Institutes of Health were granted patents on the genes, and Myriad in effect now exercises a dominant patent position in the United States. It has enforced those patents to become the main US provider of testing for *BRCA1* and *BRCA2*.

In May 2009, lawyers from the American Civil Liberties Union and the Public Patent Foundation filed a lawsuit on behalf of over 20 plaintiffs against the US Patent and Trademark Office, Myriad Genetics, and officers of the research trust for the University of Utah (*AMP v USPTO*).

On March 29, 2010, Judge Robert Sweet of the US Federal District Court for the Southern District of New York handed down a ruling that all 15 contested claims in 7 patents held by Myriad Genetics were invalid because they did not claim patentable

subject matter. That case was appealed to the Court of Appeals for the Federal Circuit (CAFC), which hears appeals on all patent cases.

A three-judge panel ruled on July 29, 2011. All three judges were in agreement on three points: (1) that five broad method claims are invalid (affirming that part of Judge Sweet's ruling, but on narrower grounds), (2) that one method claim is valid (reversing), and (3) that DNA inventions are not inherently unpatentable (reversing in part).

The ruling was divided 2-1 on whether isolated DNA molecules with sequences corresponding to those that could be found in nature are patentable. Most of the 105 pages of the three judges' analysis focus on this remaining disagreement, and Judge Bryson dissented with the majority over this point. Both sides have requested a rehearing before the 3-judge CAFC panel; future appeals could be directed to the full CAFC (all judges sitting en banc, rather than just the three judges who heard the case in April 2011), or to the US Supreme Court.

What policy options have been proposed?

Various commentators, notably Michael Crichton in his 2006 novel, *Next*, and in a February 13, 2007, *New York Times* OpEd article, have alleged that gene patents could be used "to halt research, prevent medical testing and keep vital information from you and your doctor." Dr. Crichton teamed up with Lori Andrews, a scholar from Kent School of Law, and found resonance with Reps. Xavier Becerra and Dave Weldon, who introduced HR 977, in the 110th Congress to halt future patenting of DNA sequences. Although the Becerra-Weldon bill was never put to a vote, it became the stimulus for ongoing debate.

A 2005 National Research Council report included gene patents in its scope. That report focused on ways Congress, the executive branch and the courts could ensure rapid progress in life sciences and their application. It recommended, for example, an exemption from infringement liability when verifying genetic testing results. Many of its other recommendations dealt with general patent procedures that would have an impact on gene patents and how they are used. Some recommendations have been addressed by decisions of the US Supreme Court since the report came out, but others would require congressional legislation. A subsequent report in 2006 more specifically focused on genomics and proteomics (Merrill and Mazza 2006).

From 2006 until April 2010, a US Department of Health and Human Services advisory committee—the Secretary's Advisory Committee on Genetics, Health and Society (SACGHS)—grappled with evidence about benefits and harms of patents, and how they might be affected clinical access to genetic testing in the United States. The committee produced a report in 2010 that included several recommendations, most notably recommending that there be exemptions from patent infringement liability for uses in research or in diagnostics (SACGHS 2010). SACGHS no longer exists.

Two provisions of the pending patent reform bill are particularly relevant to gene patents. One reform would introduce a procedure for challenging a patent after it is issued similar to the opposition process that narrowed the *BRCA1* patent claims in Europe. Another

contemplated patent reform would shift the US standard for inventorship from a "first to invent" to a "first inventor to file," which would have an effect on some gene patents that result from hotly contested races. (The "interference" proceedings to decide inventorship of the cystic fibrosis gene, for example, took almost ten years.)

All three appeals court judges who ruled in the Myriad case noted that Congress could act to address the specific questions surrounding whether DNA molecules or uses of them can be patented. Two judges argued that any specific provisions about gene patents should be debated by Congress and not decided by the courts. Judge Bryson argued that the Supreme Court quite deliberately decided not to defer to Congress when it decided the landmark *Chakrabarty* case that allowed patenting of a living organism in 1980, a case with even broader implications than the current case over *BRCA* gene patents.

France and Belgium passed national laws that exempt some diagnostic and research uses of patents from infringement liability, and genetic diagnostics were prominent in the legislative debate that produced the statutory change (van Overwalle 2007). Both of those countries and Switzerland have also created statutory authority for government to force patent-owners to license patents (often called compulsory licensing authority) if their management of patents threatens public health; the debate explicitly considered genetic diagnostics as a likely scenario for invoking compulsory licensing (Esther van Zimmeren, Ph.D. Dissertation, University of Leuven Law School, 2011).

Legal scholars have proposed such policy options for US law, either by amending the patent statute itself, which would cover all gene patents, or by amending the Bayh-Dole Act of 1980 that governs patenting and use of inventions arising in research institutions funded by federal grants or contracts, which would cover only inventions arising from those funding streams.

Rep. Lynn Rivers introduced a bill in 2002 (HR 3967) that would have created a diagnostic use exemption from infringement liability and mandated early release of patent-related DNA sequence data. It never came to a vote and redistricting put Rep. Rivers in the same district with John Dingell, who defeated her in the primary so she did not return to the 108th Congress. Both the Becerra-Weldon and Rivers bills were cited by the CAFC judges in their July 29, 2011, ruling (Case docket 2010-1406) as indicators that Congress had considered legislation specific to patenting DNA molecules. In the very recent past, Rep. Wasserman-Schulz proposed an amendment to the patent reform bill that would create an exemption from infringement liability for verification testing (diagnostic testing for a "second opinion" or to confirm another laboratory's test result). That provision was changed to a mandate to the patent office to undertake a study of patenting and genetic diagnostics that is part of the patent reform bill.

When considering statutory changes it would be good to recognize several realities. First, the empirical studies of gene patenting and licensing in diagnostics, including ours, are dated and do not necessarily predict the future, because the complexity of the technologies is increasing and the cost of innovation is rising. Second, patents expire 20

years after their earliest filing date, meaning that most "gene patents" filed as the result of the results of the Human Genome Project and the parallel surge in genomics in general 1990-2003 will expire by around 2020. (There will be no new gene patents *per se*, since the gene sequence information is and has been available on public databases and thus cannot now be patented unless something surprising that goes beyond sequence data is discovered.) Second, the challenge in coming years will be to understand the complex interactions between genes and the environment that result in disease; most diseases are not like *BRCA*-related breast cancer where a single mutation alone can dramatically increase risk of disease. The complexities that can be expected in understanding these interactions make possible alternative forms of intellectual property protection, such as trade secrets, that do not require public disclosure and are not subject to the term limits on patents (i.e., they will not fall into the public domain unless independently discovered). This raises the possibility that weaker patent protection for diagnostic applications could increase incentives for trade secrets and thus harm, rather than foster, efficient sharing of information needed to interpret the coming deluge of genomic data. The proper balance between patenting, public domain sharing, trade secrets, and policies governing the use of intellectual property in genomics will require continual vigilance. Striking that balance will involve the courts, those holding and licensing patents and other intellectual property, civil action groups, and possibly the U.S. Congress.

References

Angrist, M., S. Chandrasekharan, et al. (2010). "Impact of gene patents and licensing practices on access to genetic testing for long QT syndrome." Genetics in medicine : official journal of the American College of Medical Genetics 12(4 Suppl): S111-154.

Caulfield, T., R. M. Cook-Deegan, et al. (2006). "Evidence and anecdotes: an analysis of human gene patenting controversies." Nature biotechnology 24(9): 1091-1094.

Chandrasekharan, S., E. Pitlick, et al. (2010). "Impact of gene patents and licensing practices on access to genetic testing for hereditary hemochromatosis." Genetics in medicine : official journal of the American College of Medical Genetics 12(4 Suppl): S155-170.

Cohen, W. M., C. Cho, et al. (2005). Patents, Material Transfers and Access to Research Inputs in Biomedical Research. Wasington, DC, National Research Council, National Academy of Sciences.

Colaianni, A., S. Chandrasekharan, et al. (2010). "Impact of gene patents and licensing practices on access to genetic testing and carrier screening for Tay-Sachs and Canavan disease." Genetics in medicine : official journal of the American College of Medical Genetics 12(4 Suppl): S5-S14.

Eisenberg, R. S. (2008). "Noncompliance, Nonenforcement, Nonproblem? Rethinking the Anticommons in Biomedical Research." Houston Law Review 45(4): 1059-1099.

Gold, E. R. and J. Carbone (2010). "Myriad Genetics: In the eye of the policy storm." Genetics in medicine : official journal of the American College of Medical Genetics 12(4 Suppl): S39-70.

Hall, S. S. (1987). Invisible Frontiers: The race to synthesize a Human Gene. New York, The Atlantic Monthly Press.

Hayden, E. C. (2011). "Patent Dispute Threatens US Alzheimer's Research." Nature 472(5 April): 20.

Heller, M. A. and R. S. Eisenberg (1998). "Can patents deter innovation? The anticommons in biomedical research." Science 280(5364): 698-701.

Holman, C. M. (2008). "Genetics. Trends in human gene patent litigation." Science 322(5899): 198-199.

Holman, C. M. (2011). "Will Gene Patents Impede Whole Genome Sequencing?: Deconstructing the Myth that Twenty Percent of the Human Genome is Patented." SSRN eLibrary.

Hopkins, M. M., S. Mahdi, et al. (2006). The Patenting of Human DNA: Global Trends in Public and Private Sector Activity (The PATGEN Project). Brussels, Belgium, European Union: 1-57.

Hopkins, M. M. and P. Nightingale (2006). "Strategic risk management using complementary assets: Organizational capabilities and the commercialization of human genetic testing in the UK." Research policy 35(2006): 355–374.

Hughes, S. S. (2001). "Making dollars out of DNA. The first major patent in biotechnology and the commercialization of molecular biology, 1974-1980."

Isis; an international review devoted to the history of science and its cultural influences 92(3): 541-575.
Hughes, S. S. (2011). Genentech: The Beginnings of Biotech. Chicago, IL, University of Chicago Press.
Jensen, K. and F. Murray (2005). "Intellectual property. Enhanced: intellectual property landscape of the human genome." Science 310(5746): 239-240.
Kevles, D. J. (1994). "Ananda Chakrabarty wins a patent: biotechnology, law, and society, 1972-1980." Historical studies in the physical and biological sciences : HSPS / Office of History of Science and Technology, University of California, Berkeley 25(Pt 1): 111-135.
Merrill, S. A., R. C. Levin, et al., Eds. (2005). A Patent System for the 21st Century. Washington, DC, National Academies Press.
Merrill, S. A. and A.-M. Mazza, Eds. (2006). Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation, and Public Health. Washington, DC, National Academies Press.
Merz, J. F., A. G. Kriss, et al. (2002). "Diagnostic testing fails the test." Nature 415(6872): 577-579.
Office of Technology Assessment, U. S. C. (1984). Commercial Biotechnology: An International Analysis. Washington, DC, Government Printing Office.
Parthasarathy, S. (2005). "Architectures of genetic medicine: Comparing genetic testing for breast cancer in the USA and the UK." Social Studies of Science 35(1): 5-40.
Parthasarathy, S. (2007). Building Genetic Medicine: Breast Cancer, Technology, and the Comparative Politics of Health Care. Cambridge, MA, MIT Press.
SACGHS (2010). Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests. Reports of the Secretary's Advisory Committee on Genetics, Health and Society. H. a. S. Secretary's Advisory Committee on Genetics. Washington, DC, US Department of Health and Human Services.
Smith, J. (1990). Patenting the Sun: Polio and the Salk Vaccine. New York, Anchor Books.
UK Human Genetics Commission (2010). Intellectual Property and DNA Diagnostics. London, UK, Human Genetics Commission.
van Overwalle, G., Ed. (2007). Gene Patents and Public Health. Brussels, Bruylant.
Walsh, J. P., C. Cho, et al. (2005). "Science and law. View from the bench: patents and material transfers." Science 309(5743): 2002-2003.