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Patently unpatentable: implications of the Myriad court decision on genetic diagnostics

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Abstract

The recent decision in the case *Association for Molecular Pathology et al. v. United States Patent and Trademark Office et al.* shocked the biotechnology industry. Although the case could be overturned on appeal, it will likely change how gene patents are written. The effects of the decision may be most strongly felt in the short-term by clinical laboratories that develop new genetic tests based on single genes. However, evidence suggests that patents are less effective as an incentive to innovate in the field of genetic diagnostics than for pharmaceuticals. In addition, as genomic technologies move towards whole-genome analysis, policy arguments for patent protection for single genes become less compelling. It is clear that the intellectual property model challenged by the Myriad decision will have to be replaced if new genetic technologies are to achieve their full potential in promoting “the progress of science and useful arts.”

Introduction

The recent decision in the case *Association for Molecular Pathology et al. v. United States Patent and Trademark Office et al.*¹ (perhaps better known as the ‘Myriad case’) (Box 1) gave one court’s answer to the question: “Are isolated human genes and the comparison of their sequences patentable?” The short answer, at least for the time being, is ‘no’. In this case, Judge Robert Sweet agreed with Justice Breyer’s assertion in *Labcorp v. Metabolite*² that: “... sometimes too much patent protection can impede rather than ‘promote the progress of science and useful arts’, the constitutional objective of patent and copyright protection.”

Box 1

Myriad case: the arguments

The plaintiffs included medical professional societies, geneticists, cancer patients and health-related advocacy groups. The defendants included the United States Patent and Trademark Office (USPTO), Myriad Genetics, and officials of the University of Utah Research Foundation, who were exclusive licensees and owners of the patents in question.

Plaintiffs’ arguments

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Seven of Myriad's patents (USPTO nos. 5,747,282; 5,693,473; 5,709,999; 5,710,001; 5,753,441; 5,837,392; 6,033,857) were at issue. Myriad's patent portfolio included 16 other patents with claims on genomic DNA sequence of BRCA genes and on BRCA protein sequences that were not challenged. The plaintiffs claimed that they violated the Patent Act 35 USC 101, and were unconstitutional because they did not claim patentable subject matter.

The plaintiffs challenged the USPTO's common practice of granting 'composition of matter claims' on genes if they have been "isolated" from surrounding cellular material. The plaintiffs argued that isolating the gene does not change its function or informational value and cited cases finding that purification of a known material does not result in a patentable product, even if it is novel or useful in its pure form.

The plaintiffs also challenged method claims on the act of analyzing a claimed DNA sequence, or of comparing a DNA sequence to one claimed by a Myriad patent. Their argument was that, without specifying a method of analysis, the patent is on an abstract thought process that amounts to scientific inquiry and thus not patentable.

Lastly, the plaintiffs also argued that the patents violated Article 1, Section 8 of the Constitution because they have impeded rather than promoted "the progress of science and the useful arts" by inhibiting research and clinical practice.

Defendants' arguments

The defendants argued that to invalidate the Myriad patents would be essentially to overrule the famous Chakrabarty case [23], which deemed genetically modified bacteria to be patentable subject matter, and to invalidate many patents granted by the USPTO. They argue that isolated DNA is in a form that does not exist in nature, and thus is patentable. They further argue that DNA is chemical in nature, rather than informational, and thus patentable.

The defendants also argued that the patents provided incentive for Myriad to discover the BRCA genes and to disseminate the BRCA tests to the public, and cited the research of over 18,000 scientists on BRCA genes and the clinical testing of over 400,000 patients as evidence that research and clinical practice had not been impeded.

The Myriad decision potentially has a wide variety of implications for researchers, clinical geneticists, patients and the biotechnology industry. Even to longtime observers of patent law, this decision came as a shock because it questions long-held practices in the writing and granting of gene patents. Although this decision represents a major challenge to the way USPTO has granted patents on genes, its ultimate fate could be decided differently on appeal, and its implications for research, clinical practice and commercialization are mixed, even if the decision is not overturned.

Implication for future gene patents

Is DNA patentable subject matter?

A major impact of this decision is its upending of the USPTO's longstanding practice of granting patents on DNA sequences as long as they were claimed in the form of isolated DNA. Many patents on genes have been granted based on the assumption that DNA is a chemical entity whose purification renders transforms it into a patentable object (Box 2). Judge Sweet's argument is significant because it is the first to treat DNA as "the physical embodiment of biological information" and first to assert that the informational quality of human DNA is not altered by extraction from the cell and by purification of particular segments away from other parts of the chromosome. As a result, future patent claims on nucleic acid sequences where the DNA is used as information (such as in diagnostics) will not be able to rely on the isolation and purification of the gene to make them patentable. Patents on nucleic acid sequences in

which the DNA is used to produce a product or in which the DNA is altered or part of a modified or synthetic genome, however, would not be analogous.

Box 2

Purpose of patents and criteria for patentability

In the United States, patents grant a temporary right (20 years from the time of filing) to exclude others from making, using or selling the patented invention. Research for "purely philosophical" inquiry is not considered infringement, but research for commercial purposes is, with the important exception of research for FDA approval for generic versions of a patented drug.

The purpose of patents, in contrast to copyrights or trade secrets, was to encourage innovation in exchange for disseminating information about inventions, thus spurring further innovation. A patent does not compel the inventor to produce a product based on the invention, it only grants rights to block others from doing so for commercial purposes. This blocking activity can have negative societal consequences and defeat the underlying purpose of patents.

For example, before World War I, the Wright brothers and Glenn Hammond Curtiss were the major holders of patents of critical airplane components¹. Some have suggested that airplane development had been so suppressed in the US by enforcement of patents that American aircraft were unacceptable for wartime use²¹. Therefore, the US government required all aircraft manufacturers to license inventions to each other through a patent pool. More recently, patent pools have been used to encourage wider access to AIDS drugs and the US government threatened compulsory licensing in 2001 to enable production of ciprofloxacin after anthrax attacks.

The five requirements that must be satisfied for an invention to be patented are that it be: (i) patentable subject matter, (ii) useful, (iii) novel, (iv) nonobvious and (v) adequately described in the patent. The first requirement was at-issue in the *Myriad* case. While patentable inventions "include anything under the sun that is made by man"²², consistently excluded by the courts have been laws of nature, natural phenomena and abstract ideas. Patents can be granted by a process, machine, manufacture or composition of matter. Landmark cases, such as *Diamond v. Chakrabarty*²³, have established that living organisms that have been genetically modified are patentable. However, other cases, such as *Bilski v. Kappos*²⁴, have challenged the extent to which algorithms are patentable. In the *Myriad* case, the court relied heavily on the Federal Circuit's decision *In re Bilski*⁶, which held that the patent in question for hedging financial risk was patent-ineligible. The recent Supreme Court ruling affirmed the Federal Circuit's judgement.

Some of the claims in this case were so broad that they should never have been granted, and indicates how the USPTO's treatment of gene patents could be considered careless. For example, in *Myriad*'s patent no. 5,837,492, Claim 6 is for any BRCA2 protein associated with predisposition to breast cancer. Clearly, not all BRCA2 proteins or the DNA or mRNA sequences encoding any BRCA2 protein associated with predisposition to breast cancer had been identified or disclosed, so the claim was invalid on its face. Claims 5 and 6 of patent no. 5,747,282 on the BRCA1 gene were for fragments as short as 15 nucleotides. However, most human genes have some homology to any given 15-mer. Kepler *et al.*³ found that 568 of the 713 entries (80%) for complete coding sequences of human cDNAs in GenBank in 1994 "contain at least one BRCA1-derived 15-mer using [the] restricted codon table", which is an underestimate of the breadth of Claim 5 of the '282 patent. This patent would have

inappropriately rendered any use of an isolated DNA containing one of the claimed 15-mers as infringement.

Two 2005 studies suggested that a large number of human genes and patents could be affected by this decision. Jensen and Murray⁴ found that 20% of human genes were explicitly claimed as US intellectual property at the time. In addition, 38% of 1167 claims examined in 74 patents on human disease-associated genes had problematic claims⁵, including those that claimed all nucleic acid sequences encoding proteins without describing those sequences, and claims for all polymorphisms identified in a 12 Mbp region of the genome (even those not identified by the patent holder). These types of problematic claims were similar to those invalidated by the Myriad case. On the other hand, some of these claims were so broad as to be unenforceable, so the impact of invalidating them could be minimal.

Is “comparison” patentable?

The second part of the decision on patentability invalidated patent claims on comparison of DNA sequences as unpatentable subject matter. In addition, a claim on a method of determining the effectiveness of a potential cancer therapeutic on cells carrying an altered BRCA1 gene by comparing the growth rate of cells in the presence and absence of the test therapeutic (claim 20 of the ‘282 patent) was also invalidated. The decision reaffirmed that, just because something is new, useful and non-obvious does not mean that it is patentable if it does not meet other criteria for patentability. That is, “products of nature” or abstract ideas, such as mathematical formulas or algorithms, are not patentable, even if they are newly discovered.

Perhaps more importantly, the decision articulated that the act of comparison is part of the scientific process, and, in itself, not patentable. This decision relied heavily on the US Court of Appeals for the Federal Circuit in the business methods case *In re Bilski*⁶ and the use of the “machine or transformation test”⁶ - that a process is patent-eligible if it is tied to a particular machine or apparatus or transforms an article into a different state or object. The Supreme Court’s recent decision upholding *Bilski* neither completely undermines nor strongly supports the Sweet decision, because it merely asserted that the machine or transformation test was not the sole criterion for patentability; how common this type of claims language in patents on genetic diagnostics is unknown. However, process patents that claim comparisons of biological characteristics or processes, such as measuring the degree of homology between two DNA sequences, could now be vulnerable to challenge.

Implications for researchers

The impact of this decision on biomedical research will likely be minimal, based on what we know about scientists’ behavior where patents are concerned. Walsh *et al.* found in 2003 that almost no U.S. researchers they interviewed reported their research being inhibited because of intellectual property (IP) barriers⁷. This was apparently because scientists were largely ignoring patents, thus making infringement common. In a 2005 survey of biomedical researchers in the U.S., Walsh *et al.* found that only 5% checked for patents related to their research and 5% said they were made aware of IP relevant to their research through notification by a patent holder⁸. If researchers are not aware of patents relevant to their work or knowingly infringing without consequences, the impact of invalidating even a large number of patents could have limited effect⁹.

Nevertheless, the impact on scientists conducting research on clinical genetic diagnostics or disease-gene associations could be disproportionate. Unlike the biomedical researchers in Walsh’s 2005 survey [8], a survey by Cho *et al.* indicated that 65% of directors of U.S. clinical genetics laboratories had received notification of potential infringement of a patent¹⁰. All of these lab directors reported that they conduct research to develop the tests they perform for

clinical purposes. To the extent that such research is inhibited by perception of a threat of a patent, removing this threat could be significant. The Cho study [¹⁰] also found that 25% of those lab directors discontinued a test and 53% decided not to conduct research to develop a test because of the threat of patent litigation. Sixty-seven percent felt that patents inhibited their ability to conduct genetic research and 85% indicated that patents resulted in less sharing of information among researchers. A study of the ASHG found that 46% of respondents reported that patents delayed or limited their research¹¹. Thus, the subset of researchers for whom gene patents are particularly relevant could be most impacted by the decision.

In the Myriad case, the plaintiffs argued that in prohibiting others from conducting the BRCA1/2 tests, Myriad impeded the understanding of the clinical significance of variants. Opening the field of researchers and allowing unimpeded data sharing about BRCA variants should help clinicians and basic scientists interpret findings about their value in diagnosis and prognosis of hereditary breast and ovarian cancer, the molecular mechanisms involved, and help identify potential therapeutic targets.

As patent holder, Myriad prevented researchers from telling research subjects the results of their BRCA1/2 tests, which went against a growing consensus that there may be an ethical obligation to offer such results^{12, 13}. The court decision would now allow researchers to consider offering individual research results to subjects.

Implications for patients

Because Myriad was the sole provider of the BRCA1/2 tests, the opportunity for others to offer the tests could affect patients in several different ways. One potential change could be lowered costs. Some of the plaintiffs were patients who claimed that they were unable to obtain the test because of the high cost (over \$3,000 USD per test). However, a case study comparing the effects of the tightly-controlled BRCA patents to patents on colon cancer-associated genes, which were subject to non-exclusive licenses, concluded that the main effect of patents is likely to be on volume rather than price¹⁴.

Nevertheless, patients and physicians are likely to gain access to a larger number and variety of clinical laboratories, to their benefit. Cho *et al.* found that after the patent on the gene associated with hereditary hemochromatosis issued, there was a 26% drop in the number of labs offering the test for it¹⁵, suggesting that the opposite will be true for BRCA genes and other genetic diagnostics after this decision. Other labs will offer newer methods of more comprehensive BRCA testing, such as testing for large rearrangements, as follow-ups to a negative test based on full sequencing that previously would have been an infringement of Myriad's patents. The clinical validity of testing could increase because Myriad didn't test for all known mutations, perhaps leading to false negatives. The Myriad opinion cited a study finding that 12% of those from high-risk families and who tested negative with Myriad's test actually had cancer predisposing variants of those genes¹⁶, so more comprehensive testing would have been beneficial. In addition, access to other laboratories would allow patients to obtain a second opinion or an independent confirmatory test. Myriad claimed that other labs at the University of Chicago and Yale had licenses to do BRCA1/2 testing, but confirmatory testing allowed by these licenses was limited to confirming only positive results of specific mutations and prohibited for other positive results and for all negative results; therefore, not all diagnostic test results could be confirmed independently. In the absence of regulation by the FDA or other bodies to ensure the clinical validity of genetic tests, the ability of multiple laboratories to independently validate tests, share data, and compare results becomes critical.

Implications for commercialization

Although in its defense, Myriad and others have asserted that patents are critical to the development of commercialization of biotechnology, citing studies such as the one by the Biotechnology Industry Organization 77% of respondents indicated that they expected to spend 5-15 years and over \$100 million developing a commercial product¹. However, other evidence indicates that for genetic tests in particular, as opposed to therapeutics, this is not the case. Many genetic tests become clinically available before patents issue because the publication of information about the test is sufficient for development, in the absence of extensive testing to meet regulatory requirements. For example, a survey of laboratory directors found that laboratories began offering the hereditary hemochromatosis test immediately upon publication of the location of the gene, and the mean time from the key publication of the isolation of the gene in August 1996 to adoption was 14 months¹⁵. Sixty percent of lab directors surveyed who were performing the test at the time of the survey began testing before the first patent issued in January 1998. These findings suggest that long lead times and vast resources are not necessary to incent researchers to develop, or clinical laboratories to provide, genetic diagnostic tests. Thus, a long period of patent protection and a monopoly on the market are not necessary for genetic tests to be brought to market, which might distinguish genetic tests from pharmaceuticals. Furthermore, a case study of cystic fibrosis testing has suggested that broad, non-exclusive licensing allows for innovation¹⁷.

For genetic tests in particular, the argument that patents are necessary to incent private funding of research leading to patentable discoveries may not hold. Studies have shown that the majority of genetic diagnostic patents (67% in the Cho study¹⁸, 63% in the Leonard Declaration¹) have issued for discoveries that were funded by the US Government (including \$2 million USD to the University of Utah for the identification of BRCA1 sequence). However, if the FDA decides to increase regulation of genetic diagnostic tests or laboratories, as has been hinted by recent activities of the agency¹⁹, one consequence of increased costs to meet regulatory standards after gene discovery could increase time to adoption and incentive for monopoly.

Finally, the diminishing relevance of the model of single-gene tests to diagnostics must be considered²⁰. Given the almost-daily discoveries about multiple genetic contributions to complex conditions, monopolies on single genes will only raise barriers to developing meaningful products and clinical services. The policy arguments about the need for gene patents to stimulate biotechnology were made in the era of discovery of genetic tests for Mendelian diseases - but these reasons are not as compelling in the post-Mendelian era of multiplex testing, genome-wide analysis, whole-genome sequencing, and personalized medicine, where biotechnology developments and business models will increasingly rely on the ability to analyze large numbers of genetic loci at once. It is clear that the intellectual property model challenged by the Myriad decision will have to be replaced if new genetic technologies are to achieve their full potential in promoting “the progress of science and useful arts.”

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