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Invited critical review

# An overview of a recent court challenge to the protection of biomarkers as intellectual property

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ABSTRACT

*Background:* We present an intellectual property case in the United States to demonstrate the recent developments concerning patenting novel biomarker discoveries. A court struck down several patents owned by Myriad Genetics, which were related to breast cancer (BRCA1 and BRCA2). This decision can affect patent eligibility for inventions related to biomarkers, particularly genetic biomarkers.
*Methods:* The court proceedings for the Myriad Genetics case were reviewed by two patent attorneys (SCH and JMT). Relevant discussions applicable to the scientist involved with biomarker discovery were also prepared.
*Results:* In this case, the Plaintiff had argued that the analysis and comparison of various gene mutations merely involved natural phenomena, and, therefore, could not be eligible for patent protection. The patent holder (Myriad) argued that the claimed gene compositions did not exist in nature, and that the claimed methods provided practical utility for science and medicine. The Court held that the patent claims did not meet patent eligibility requirements under United States patent law. It held that the patent claims at issue were merely abstract mental processes of analyzing and comparing gene sequences, and that such abstract mental processes are not patentable. On June 22, 2010, Myriad appealed the ruling.
*Conclusions:* This case provides guidance to inventors in the biomarker field who may be interested in obtaining intellectual property protection for their inventive work, as well as their patent counsel. However, the case also presented unique factors that may not be present in all situations involving biomarker patents.


**Contents**



## 1. Introduction

Scientific discovery is a time-intensive challenge, especially in the biomedical field. Because of many factors, most notably its unpredictable nature, it requires substantial capital to translate important discoveries in the diagnostics field into needed products. For diagnostics and other basic science fields, many investigators rely primarily on governmental funding in the form of grants or awards to offset the cost of their research, but funding can also come from private investment and endowments. In the free marketplace, the primary incentive to invest in biomedical discoveries is directly proportional to the intellectual property attained from the invention

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because intellectual property rights directly affect the ability to realize a return on investment. In fact, the chance for an exclusive use of the product or technology, or stake in the future proceeds derived from such exclusive use, allows for private entities to support such endeavors.

For many scientists, the decision to devote their careers to the discovery of novel technologies to manage, cure or understand various pathological conditions is marked by a servant's attitude. On the other hand, in order to bring inventions to flourish and successfully translate them into practice, the intellectual property associated with their development can be used as leverage to assure continued funding and attention. Simply put, very few investors contemplate allocating their capital to advance a product or a biomarker unless there is good reason to anticipate adequate patent protection. Up to now, numerous patents related to biomarkers and the ability to discern physiologic changes associated with their presence, absence or expression relative to defined disease conditions have been issued. Recently, however, the legal right to exclude others from making, selling, and using such inventions has been the subject of several court proceedings. In this article, we will summarize a major court case which may impact future inventions of biomarkers and their protection.

The Myriad Genetics Inc. ("Myriad") case which will be discussed in detail provides valuable insight into the types of challenges in patent courts as related to biomarkers, their discovery, and their applications in medicine.[1] Discussion of this case can also be beneficial for the scientists thinking about protecting their own intellectual discoveries and inventions. Needless to say, substantial amounts of money are realized or lost solely based on a decision by the Patent and Trademark Office or a federal court regarding patent-related issues. As a result, it behooves the scientists to stay alert and be aware of the consequences of such decisions. Invalidation of patent claims can cost stakeholders the ability to realize a substantial return on their investment. Therefore, it is crucial for those whose work typically leads to intellectual property and inventions to understand this process. Accordingly, before discussion of the Myriad case, we summarize the patent process in the United States.

## 2. The legal and practical considerations of the United States patent system

The United States Constitution authorizes Congress to establish a patent system that encourages and rewards innovation. The Patent Act has existed in various forms for more than two centuries doing just that. During that time, the federal courts have continually interpreted and refined the meaning of the Patent Act to account for changing times and advances in technologies. Accordingly, our patent system is designed to achieve a balance between disclosure of inventions to the public, on one hand, and the right of the inventor to capitalize on his invention and recoup his investment, on the other. The system does so by granting a limited term monopoly (currently set at twenty years from the date of filing the application). During this time, the patent holder owns the exclusive right in the country, or countries, where patent protection is granted to prevent others from making, using, selling, offering to sell, or importing his invention. The patent holder may assign or license all or some of his rights in the patent to others.

To obtain a patent, the invention must be useful (utility), new (novel), and not obvious. Novelty essentially means that the exact same invention must not have been publicly disclosed or used by someone else prior to the inventor's own conception of the invention. Therefore, a rejection of a patent application based on novelty requires the Patent Office to identify a single reference (generally, a prior patent, publication, or product that was disclosed to the public) that contains each and every element and limitation of the claimed invention.

Regarding the non-obviousness requirement, the Patent Office may combine multiple references in order to reject the applicant's patent claims as obvious. In order to properly demonstrate that an invention is obvious, the Patent Office must identify an accepted rationale for combining the references, such as by pointing to a specific teaching, suggestion, or motivation in the prior art for making that combination, or by asserting how several known elements were simply used according to their known functions in order to arrive at the claimed invention. Once the Patent Office has defined what is disclosed by the prior art as a whole, it must then consider the differences between the claimed invention and the prior art. If those differences would have been obvious to a person of ordinary skill in the art, the Patent Office has discretion to reject the patent claims based on obviousness, unless the applicant can show that other factors require issuance of the patent. Such other factors may include unexpected results, a long-felt need in the marketplace which several have tried to meet and failed, or substantial commercial success.

Besides the requirements of utility, novelty, and non-obviousness, the inventor must provide adequate written description of his invention, must set forth the elements (or steps) needed to practice the invention sufficiently to enable a person of ordinary skill in the art to practice the invention, and must disclose the best mode for practicing the invention as he sees it as of the time of filing. These requirements are set forth in 35 U.S.C. § 112. This section of the Patent Act requires the inventor to particularly point out and distinctly claim the invention. This requirement is essential to patent law, because the claims are what establish the right of the patent holder to exclude others from making, using, and selling the patented invention. Accordingly, patents are not issued – *patent claims* are. Likewise, competitors do not infringe patents – but rather *patent claims*.

Just as there are different kinds of technologies, there are also different kinds of patent claims. Many of the biomarker patents state method claims, which are directed to a series of steps. For example, claim 1 of U.S. Patent No. 6 033 857 ("Chromosome 13-linked breast cancer susceptibility gene") was one of the claims the lower court invalidated in the Myriad case:

A method for identifying a mutant BRCA2 nucleotide sequence in a suspected mutant BRCA2 allele which comprises *comparing* the nucleotide sequence of the suspected mutant BRCA2 allele with the wild-type BRCA2 nucleotide sequence, wherein a difference between the suspected mutant and the wild-type sequences identifies a mutant BRCA2 nucleotide sequence.[2] (Emphasis provided.)

This provides an example of a method claim directed to a diagnostic technique. Method claims can also be directed to treatment. For example, Claim 1 of U.S. Patent No. 6 355 623 ("Method of treating IBD/Crohn's disease and related conditions wherein drug metabolite levels in host blood cells determine subsequent dosage") is from a patent involved in the Prometheus case, which is also discussed below in the context of the Myriad case:

A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:

(a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and
(b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder, wherein the level of 6-thioguanine less than about 230 pmol per $8 \times 10^8$ red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and wherein the level of 6-thioguanine greater than about 400 pmol per $8 \times 10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.[3]

In addition to method claims, patents in this area also frequently claim compounds. For example, Claim 6 of U.S. Patent No. 5 837 492 (also titled "Chromosome 13-linked breast cancer susceptibility

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gene") was another of the claims the lower court invalidated in the Myriad case:

An isolated DNA *molecule coding for a mutated form* of the BRCA2 polypeptide set forth in SEQ ID NO:2, wherein said mutated form of the BRCA2 polypeptide is associated with susceptibility to cancer.[4] (Emphasis provided.)

Even with the different kinds of claim protection available, and in spite of the potential incentives for seeking patent claims over the invention, an inventor may decide not to seek a patent. The cost of obtaining a patent is one of a number of factors to consider. Inventors may spend tens of thousands of dollars in legal fees to get a patent, depending on the complexity of the invention and the nature of the prior art. A patent helps recoup that investment, as well as the costs associated with developing the invention.

But other factors besides patentability frequently come into play, as well. These include the scope of the patent claims, market demand, timing, and the perceived value and necessity associated with an invention. In many cases, the infusion of capital necessary to turn inventions into marketable products will come from investors who place their financial and other resources into the enterprise during various rounds of financing. Patentability and other factors like those mentioned above guide these investment decisions.

In order to be attractive to investors, however, a number of criteria must be considered. Awards of peer-reviewed funding (with its attendant rigorous review of scientific merit), the condition of the company's financials compared to "what's needed to finish" and get to market, the likelihood that a company will become cash-flow positive within a finite period of time, the size and makeup of the relevant market, the likelihood of third party reimbursement, the quality and pedigree of the management team, and the positive input of clinicians who would be involved in validating and later using the technology are all essential, not to mention regulatory considerations involving the Food and Drug Administration or other federal agencies. All of these factors need to be carefully weighed in order to "count the costs" of getting to market. At some level, the inventor and his team will weigh the likelihood of success against the investment of time, energy, and money that will be required, and decide whether or not to move forward with patenting. Moreover, even when a decision to move forward has been made, that decision is often reconsidered at various intervals as new developments occur on the path to market.

## 3. The Myriad case

There were seven different patents at issue in this case, each of them referring to a "cancer susceptibility gene" (breast and/or ovarian). In general, some claims were directed to an isolated DNA coding for a BRCA1 polypeptide or a BRCA2 polypeptide. Some claims directed to these compounds provided references to specific nucleotide sequences, while others were directed to a method for detecting the mutation in the gene, or for screening patients to determine if there had been an alteration in the sequence of these genes.

### 3.1. Summary of the patent claims

Claim 1 of U.S. Patent No. 6 033 857, "Chromosome 13-linked breast cancer susceptibility gene" is illustrative of several of the method claims that the court invalidated. Notably, the Plaintiff who challenged this patent argued that the only true step in the claimed method involves a "comparing" step:

A method for identifying a mutant BRCA2 nucleotide sequence in a suspected mutant BRCA2 allele which comprises comparing the nucleotide sequence of the suspected mutant BRCA2 allele with the wild-type BRCA2 nucleotide sequence, wherein a difference between the suspected mutant and the wild-type sequences identifies a mutant BRCA2 nucleotide sequence.

### 3.2. Section 101 of the Patent Act

The lower court relied upon Section 101 of the Patent Act ("Inventions Patentable") when it invalidated the patents. This section of the United States Code, formally known as 35 U.S.C. § 101, states:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Essentially, this means that a scientific principle or law of nature is not, by itself, eligible for patenting, but an invention that *applies* a law of nature in the treatment of a patient could be patent eligible. Stated differently, anything man-made under the sun is probably patent *eligible*, if it is a practical application of science, operating in a physical realm. Eligibility is not the same as having a patentable invention. In many technologies, but not all, courts consider the showing of usefulness needed for patent eligibility to be a fairly low threshold. This is why, frequently when the Patent Office rejects patent claims, the reasons are based upon Sections 102 (the requirement of novelty) and 103 (the requirement that a patentable invention must not be obvious) rather than Section 101. Even though Section 101 sets a lower bar, however, cases in certain technologies are sometimes closely scrutinized to make sure they pass the Section 101 threshold. The Myriad patents presented one of those situations.

### 3.3. Important facts and arguments of the Counsel

The patent claims were applied for in the mid-to-late 1990s, before the completion of the Human Genome Project, while a majority of genes had yet to be identified given the nascent condition of the field. At that time, some companies were attempting to patent DNA sequences, separate and apart from any knowledge of the proteins encoded by a sequence or the clinical relevance of the sequence. According to the transcript of the oral argument before the lower court, the crux of Plaintiff's argument for invalidating the patent is found in this sentence from the oral argument to the Court: "DNA is fundamentally an informational molecule."[5] From that foundation, Plaintiff argued that merely comparing the information contained in DNA after it has been isolated should not be patentable: "Once you patent isolated DNA you have patented the nucleotide sequence that each of us has in our body and people are not allowed to look at that sequence."

Plaintiff went on to assert that the Myriad patents were limited to determining whether or not certain mutations exist, that mutations are caused by nature, and that laws of nature are not patentable. Plaintiff contended that the patented methods merely compare the sequence of letters representing the nucleotides in the individual's sample to what science knows to be the typical sequence, in order to interpret those differences in light of known correlations. Plaintiff also argued that the process of looking at two things and having the thought that they are the same or different and why that matters is not patentable.

As reflected in the transcript of the oral argument to the court, Myriad argued that it not only discovered the two genes, but it also determined the significance of the mutations in terms of a predisposition to cancers. Myriad pointed out that the claimed compositions did not exist in nature, and that only through isolating and processing DNA in a laboratory would it be possible to obtain the claimed compositions. Myriad argued that its patent claims were not merely directed to information, but to chemical information with known practical utility in science and medicine.

Many influential organizations joined in the argument of this case, filing amicus briefs as "friends of the court." For example, the American Medical Association, American Society of Human Genetics, American College of Obstetricians and Gynecologists, and American

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College of Embryology filed briefs asserting that the claims at issue were unpatentable natural phenomena, having no tendency to promote innovation in genetic research, and were, in fact, in violation of medical and scientific ethics. Several other groups filed similar briefs contending that isolated DNA should not be patented and that to do so would stifle innovation and interfere with patient access to medical testing and treatment. Conversely, other organizations filed friend of the court briefs on behalf of Myriad. These organizations asserted that patents directed to isolated DNA should be considered patent eligible, because of the differences between isolated DNA and naturally-occurring DNA. They also asserted that, because patents provide the primary incentives for investment that promotes the advancement of biotechnology and related sciences, a potential for robust patent protection actually fosters innovation. Other organizations and individuals filed friend of the court briefs asserting that to prohibit a patent for isolated human DNA would negatively affect scientific research, in general, and the development of personalized medicine, in particular.

### 3.4. Discussion of the Court's reasoning

According to the lower court, Section 101 requires an invention to do more than merely gather, analyze, and compare data. On that basis, that basis, the lower court held that all the patent claims at issue were invalid, and that any preparatory steps used in obtaining the samples or performing the testing were either not included in the claims, or were not transformative enough to justify issuance of the patent claims.

The lower court also acknowledged the Federal Circuit's 2009 decision in the case of *Prometheus v. Mayo Clinic*.[6] There, the Federal Circuit held that certain biomarker testing methods were valid, because the claimed method for testing a patient for the biomarker required drawing and separating blood and measuring levels of various blood components, each of which amounts to a physical transformation indicative of an actual process. In contrast, the lower court in *Myriad* found that the method claims at issue involved only the abstract mental processes of "analyzing" and "comparing" gene sequences. The *Myriad* court stated that the acts of isolating and sequencing human DNA are merely data gathering steps, which are not central to the purpose of the claimed methods. The *Myriad* court's reasoning is captured well in the following quote from the opinion: "… the plain and ordinary meaning of the terms 'analyzing' or 'comparing' [gene sequences] establish that the method claims in suit are directed only to the abstract mental processes …."

The lower court also accepted the public policy argument that the claimed methods preempted virtually all the knowledge that now exists or could exist in the future as it relates to these genes. The lower court noted that the patent holder appeared to exercise unfettered discretion to prohibit everyone in the country from engaging in any research relating to these genes until the patent claims expired, an event which would not occur for several more years. Thus, public policy – which extends beyond the particular dispute between the litigants and considers what is best for the public as a whole – also factored into the lower court's decision.

Regardless of whether the Federal Circuit upholds this lower court decision, one can look at this opinion and see that courtrooms are similar to laboratories in at least one respect. Just like pH, temperature, and the presence or absence of catalysts can dramatically affect a reaction, sometimes the "environment" of a case may affect perception and influence outcome. In *Myriad*, the "environment" was marked by Plaintiff's successful attempts to create a perception in the Court's eyes that Myriad's patent claims were too encompassing—even to the point where follow-on research could be quenched. Whether justified or not, Plaintiff attempted to bolster the perception by presenting evidence that Myriad had not granted any licenses allowing others to practice these claims, even for the purpose of conducting research.

### 3.5. Practical points

1. For an inventor who seeks patent protection over methods for testing the presence or levels of a biomarker (for example a gene, mRNA, protein, or metabolite), it is important for the claims to include more steps than merely "analyzing" a sample, and "comparing" the data from the sample to other known data. In addition to the "analyzing" and "comparing" steps, it is helpful to identify one or more steps associated with a physical transformation either of the patient or the analyte.
2. The *Prometheus* case provides a good model to follow when defending patent claims against arguments of invalidity under Section 101. Applicants and patent holders (with input from patent counsel) should identify the similarities between their claims and the methods that were involved in the *Prometheus* case. They should also be able to express claim steps that go beyond the gathering and analyzing steps to which the claims in the *Myriad* case were limited.

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## References

[1] Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office, F. Supp. 2d, 2010 WL 1233416 (S.D.N.Y. Mar. 29, 2010), appeal docketed, No. 2010–1406 (Fed. Cir. June 22, 2010).
[2] U.S. Patent No. 6 033 857 (filed Mar. 20, 1998).
[3] U.S. Patent No. 6 355 623 (filed Apr. 8, 1999).
[4] U.S. Patent No. 5 837 492 (filed Apr. 29, 1996).
[5] Transcript of oral argument, Ass'n for Molecular Pathology, F.Supp. 2d, 2010 WL 1233416 (S.D.N.Y. Mar. 29, 2010) (No. 09 Civ. 4515).
[6] Prometheus Labs, Inc. v. Mayo Collaborative Servs., 628 F.3d 1347 (Fed. Cir. 2010).

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