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Patent Portfolios After Myriad, How to Fit in Those New Genes?

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ABSTRACT: The recent US Supreme Court decision in Association for Molecular Pathology v. Myriad Genetics, Inc. clarified what is considered patentable subject matter. Patent claims limited to the composition of isolated nucleic acid sequences are now considered a product of nature and not patent eligible, while man-made variants of nucleic acid sequences may still be patentable. The decision is consistent with an earlier ruling in Mayo Collaborative Services v. Prometheus Laboratories., Inc. related to diagnostic methods. In Prometheus, the Court held that a method simply reciting known steps used to observe a natural event is not patentable subject matter. Taken together, the Court's decisions provide guidance as to what constitutes a natural phenomenon outside patent protection and what is considered a man-made creation worthy of protection. Despite misgivings, both decisions will provide impetus for increased genetic research and development of new therapeutics and diagnostics, especially in genomic and personalized medicine.

On June 13, 2013, the US Supreme Court ended 30 years of awarding patents on human genes. In its unanimous decision, the Court decided the case of Association for Molecular Pathology v. Myriad Genetics, Inc. ruling that naturally occurring DNA is a product of nature and not patent eligible merely because it had been isolated.[1] The decision clarified patentable composition of matter in genetic research and paved the way for the future inventive landscape in the biotech industry.

Myriad made a spectacular achievement by discovering the precise location and sequence of the breast cancer susceptibility genes 1 and 2, BRCA1 and BRCA2. Both genes are tumor suppressor genes and encode very large protein products that have little resemblance to one another or to other known proteins. The BRCA proteins are required for maintaining genome integrity at least in part by engaging in DNA repair, cell cycle checkpoint control, and even the regulation of key mitotic or cell division steps in mammalian cells. Mutations in these genes are a bellwether for assessing the risk of breast and ovarian cancer in the general population. A woman who inherited a harmful mutation in BRCA1 or BRCA2 is about five times more likely to develop breast cancer than a woman who does not have such a mutation.[2] Patenting this discovery allowed Myriad to prevent other laboratories from developing tests to identify these mutated genes without obtaining a license, essentially giving Myriad a monopoly on all diagnostic testing in this area.

Patents are awarded, in part, to someone who invents or discovers any new and useful composition of matter, any new and useful method, machine, means of manufacture, or any new improvement thereof.[3] Myriad claimed they used techniques to isolate a previously unknown composition of matter that included the human nucleotide sequence for BRAC1 and BRCA2 and therefore discovered a new composition of matter under 35 U.S.C. §101. While isolating DNA from the human genome may require techniques to cleave the covalent bonds in the DNA backbone and arguably create a different composition than that found naturally, the Court took a less chemical perspective and a more informational approach toward the isolated composition. It is true that isolated DNA has a different composition than that found in nature, but the innovative aspect of the claims did not rely on these chemical changes, which themselves have little novelty. Instead they focused on the genetic information encoded in the BRCA1 and BRCA2 genes as found in nature. Natural phenomena, like laws of nature and abstract ideas, are considered important basic tools in science and technology, but outside the domain of patent protection.

In many ways, this would be like isolating and drying plums found in nature, then claiming discovery of a new fruit, called a prune. The prune may not be found in nature, but the isolation process (e.g., picking and drying) results in a dried plum. It is still a naturally occurring plum, having been dried to preserve and better enjoy the fruit.

Using similar reasoning in a 2012 decision, the Court indicated that simply reciting well-known steps to describe a natural law or abstract idea does not make diagnostic method claims patentable.[4] In a unanimous decision focused this time on a new and useful method under 35 U.S.C. §101, the Court in Prometheus held that claims reciting the relationships between concentrations of certain metabolites in the blood and the likelihood that a drug dosage (thiopurine) will prove ineffective or cause harm are not themselves alone patent-eligible unless they provide additional features. In this case, the claims recited certain laws of nature with any additional steps consisting of well-understood, routine, conventional activity already engaged in by the scientific community. The steps added nothing significant beyond the sum of their parts, which taken separately were to administer a drug to a patient, measure natural metabolites of the drug to compare with a known threshold, and then decide whether to increase or decrease the dosage of the drug. Thus, the Court said that simply observing natural phenomena through routine means is not patentable.

After Prometheus, the biotechnology industry feared that the decision could only hurt the industry, especially the emerging field of personalized medicine.[5,6] Personalized medicine offers

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the physician a more precise means to diagnose and treat individual patients, probing not just the usual suspects, such as a tumor on a mammogram or cells under a microscope, but the very molecular makeup of each patient. Looking at the patient on this level helps the physician get a profile of the patient's genetic distinction. By incorporating this genetic map, individual patients are profiled to plan out a course of treatment that is much more in step with the way their body works. Thus, genomic and personalized medicine incorporates a patient's genetic information in the diagnosis and treatment of diseases. Prometheus, it was feared, would restrict the development of personally tailored treatments and new precision diagnostic tools.

Genotyping to determine which individual patients are likely to benefit from a particular medical regimen for a particular disease has the potential to dramatically improve efficacy, avoid ineffective treatments, and reduce costs in healthcare. The Myriad decision invalidates patents that claim rights to only the isolated DNA necessary to provide a basis for personalized medicine or rights to the isolated DNA associated with a high risk for disease, like breast or ovarian cancer. So like Prometheus, Myriad may be viewed by some as restricting those technical arenas that depend upon the relationship of nucleic acid sequences and disease.

HOW CAN BIOTECH COMPANIES PROTECT THEIR INVENTIONS AFTER PROMETHEUS AND MYRIAD?

While Prometheus and Myriad have certainly limited the scope of diagnostic method and composition claims to isolated nucleic acids, previously believed patentable, the sky is not falling. If the method used to measure the biomarker in a diagnostic method is novel, such as with a novel antibody, then the claim will pass muster under 35 U.S.C. §101. In the plum−prune analogy, simply picking and drying a plum will not pass, but creating a new method of picking plumbs that results in decreased loss of damaged fruit may win the day. Composition of matter claims to non-naturally occurring nucleic acids, such as cDNA or a nucleic acid in which the order of the naturally occurring nucleotides has been altered as in a man-made variant sequence, will also prevail under 35 U.S.C. §101. Using the man-made variant sequence in a therapeutic regimen or diagnostic test will not be affected by the ruling.

First and foremost, companies and their patent attorneys will need to carefully draft patent claims to ensure the broadest coverage, understanding the Court's line in the sand regarding natural law. The critical, man-made concepts in making and using a biotechnology-based invention are still going to be protectable, but the availability now of the basic isolated sequence will allow researchers and competitors to have greater freedom to design around current biotechnology patents. The genetic landscape will not be carved up into licensing fiefdoms that restrict or severely hamper creativity not only related to an individual gene, but discovery involving groups of genes or even the whole-genome.

Patent applicants with pending cases having claims solely to isolated DNA should consider amending to include cDNA or related constructs or examining the isolation process for inventive nuances. For issued patents that are limited to only isolated DNA sequences in the claims, patent holders may look to file for reissue of their patents to ensure protection.

Some of us may be of the opinion that without the ability to patent isolated DNA as a new composition of matter, the likelihood of obtaining funding for companies that are developing new facets of genomic or personalized medicine will be lost or severely hampered. After all, having sole ownership on new technology is very inviting to investors. However, and most likely, the Court's decision could positively impact healthcare and medical research by broadening the participants entering the field, opening the doors to more diverse approaches and ideas when tackling specific diseases. Companies will need to take that extra step (hopefully new and nonobvious) in creating the next diagnostic or therapeutic. Investors will have comfort knowing that the new technology they are funding comes free and clear with no extra baggage or license obligations to the lord of the fiefdom. Moreover, investors will be able to gauge the success of the new technology through the success of multiple participants, rather than gambling on the success of a single player in the field who is focused on untested gene(s).

For researchers, the Court's decision is likely to expand access to discoveries and lead to more diverse genetic testing in areas such as cancer and other diseases.[7] This can only benefit patient care as the ruling will expand access to genetic testing and lower costs for patients.

While it is certainly prudent to review your company's current issued patents and patent applications for enforceability after Myriad, the decision will likely not have an immediate impact on the patent portfolio of most genetic-based therapeutic or diagnostic companies. To protect their piece of technology, these companies typically focus more on patents directed toward multigene products, methods, and cDNAs rather than on claims directed to isolated DNA sequences.

For the few companies that rely solely on patents directed to isolated nucleotide sequences in developing chemical and biological therapeutics, they will need to retool their business model in a manner similar to diagnostic companies after Prometheus. The focus should not be on monopolizing the entire technology, but monopolizing improvements that provide the most effective treatment or most precise diagnostic tool available. Further, the Court's decision may even apply to other types of patents involving the isolation of naturally occurring compounds like proteins, antibodies, and other natural biomolecules. Consequently, patent portfolios will now need to have some type of value-added component, with new and nonobvious characteristics, in addition to the isolated naturally occurring biomolecule since patentability and enforceability will entail a more stringent view of 35 U.S.C. §101.

It is noteworthy that in a world divided by political opinions, especially along party lines, the Justices were unanimous in the Myriad decision and unanimous in Prometheus. It would seem as through the reasoned analysis of each Justice's boundary between natural phenomena and man-made concepts are clear.

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Notes

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REFERENCES

(1) Association for Molecular Pathology v. Myriad Genetics, Inc., No. 12−398 (U.S. June 13, 2013).

(2) O'Donovan, P. J.; Livingston, D. M. BRDA1 and BRCA2: Breast/ovarian cancer susceptibility gene products and participants in DNA double-strand break repair. *Carcinogenesis* **2010**, *31* (6), 961−967.
(3) 35 U.S.C. §101 "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 therefor, subject to the conditions and requirements of this title".
(4) Mayo Collaborative Services v. Prometheus Labs., Inc. 566 U.S. (2012).
(5) Henschel R. F. US Supreme Court Casts Shadow on Personalized Medicine Patents. *Science/Business*, 29 March 2012.
(6) Eisenberg, R. S. Prometheus Rebound, Diagnostics, Nature, and Mathematical Algorithms. *122 Yale L.J. Online* 2013, *341*; see http://yalelawjournal.org/2013/04/01/eisenberg.html.
(7) The Supreme Court's Myriad Decision: Little or No Impact on Basic Research? *The American Society for Cell Biology*, 19 June 2013.