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Do recent US Supreme Court rulings on patenting of genes and genetic diagnostics affect the practice of genetic screening and diagnosis in prenatal and reproductive care?

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Abstract

Thousands of patents have been awarded that claim human gene sequences and their uses, and some have been challenged in court. In a recent high-profile case, Association for Molecular Pathology, et al. vs. Myriad Genetics, Inc., *et al*., the United States Supreme Court ruled that genes are natural occurring substances and therefore not patentable through “composition of matter” claims. The consequences of this ruling will extend well beyond ending Myriad's monopoly over *BRCA* testing, and may affect similar monopolies of other commercial laboratories for tests involving other genes. It could also simplify intellectual property issues surrounding genome-wide clinical sequencing, which can generate results for genes covered by intellectual property. Non-invasive prenatal testing (NIPT) for common aneuploidies using cell-free fetal (cff) DNA in maternal blood is currently offered through commercial laboratories and is also the subject of ongoing patent litigation. The recent Supreme Court decision in the *Myriad* case has already been invoked by a lower district court in NIPT litigation and resulted in invalidation of primary claims in a patent on currently marketed cffDNA-based testing for chromosomal aneuploidies.

Introduction

On June 13, 2013, the nine judges of the Supreme Court of The United States (US) unanimously ruled in the case of the Association for Molecular Pathology (AMP) *et al. vs*. Myriad Genetics, Inc., *et al*.[1], that genes are not patent eligible. The court also stated that

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cDNAs, which do not occur themselves in nature but are created in the laboratory from naturally occurring mRNA as a template, are patentable.[1] In addition to likely ending the Myriad US monopoly on *BRCA1* and *BRCA2* testing to predict hereditary breast and ovarian cancer risk, this ruling in essence may have ended the practice of patenting human genes and related naturally occurring mutations in the US.[2] Thus, the impact of this ruling reaches well beyond the consequences for Myriad Genetics[1] and many aspects of this case and the ruling need to be considered to better understand its full bearing on genetic research, clinical diagnostic development, and patient access to genetic diagnostic tests.[2-7]

The ruling is widely applauded as a victory by those offering genetic diagnostic services, and by academic researchers, clinicians, patient advocacy groups and professional societies that oversee and provide guidance on the practice of clinical and molecular diagnostic genetics.[7] These stakeholders see it as removing barriers for competing commercial and not-for-profit diagnostic laboratories offering *BRCA1* and *BRCA2* testing and believe it could deter other companies from maintaining monopolies on different genetic tests.[4,3] Increased competition may consequently result in wider availability of less expensive genetic tests and may stimulate development of novel expanded test panels that use newer DNA sequencing platforms. In addition, the door for independent validation and second-opinion testing has now been opened.[2] On the opposite side, representatives of the biotechnology industry have voiced concern that the ruling is too broad and open to unpredictable interpretations by the US Patent and Trade Office (USPTO) and by lower courts.[4,6] However, the USPTO has issued guidance documents for use by their examiners.[8]

They also contend that inability to obtain intellectual property protection will result in reduced incentives for biotechnology investment, impede innovation and consequently slow down commercialization and availability of important health products and services.[7]

To provide insight into the potential impact of the Supreme Court's ruling on prenatal genetic testing and screening in the United States, we will first briefly review the history of patent law, patenting of human genes and methods for genetic diagnosis in the US, and the specifics of the Myriad Genetics case. We will further examine consequences of the recent decision on breast cancer susceptibility testing, implications for clinical genetic diagnostic laboratories in general, and in particular for prenatal genetic diagnosis and screening, with specific emphasis on the highly litigious field of Non-Invasive Prenatal Testing (NIPT).

History, purpose and application of US patent law

The constitution of the Unites States contains a clause that “congress shall have the power to promote progress of science and useful arts by securing for limited times to authors and inventors the exclusive rights to their respective writings and discoveries”, which was the foundation for developing patent legislation. Section 101 of the Patent Act defines patentable subject matter and says: “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.”[9] Subsequent revisions of the law included criteria that to be patentable an invention had to be novel, “non-obvious” and useful, a time limitation of 20 years from the original filing, and an improved definition of patentable inventions. Of

relevance to its current decision on genes, the Supreme Court has previously stated that "*anything under the sun that is made by man"* is patent eligible, but that "laws of nature, abstract ideas and physical phenomena" are not because "such discoveries are manifestations of nature, free to all men and reserved exclusively to none".[5] The USPTO is tasked with examining patent applications and awarding patents, and reviews and awards thousands of patents each year.

Patenting human genes

It is estimated that over 60,000 DNA-related patent applications have been filed in the US,[10] and many awarded. Many cover inventions by researchers in academic institutions, alongside patents filed by the biotechnology and pharmaceutical industry. "Gene patents" that claim rights on complete or parts of sequences of human genes are a subset of these DNA-related patents. Several empirical studies in the last decade have used different approaches to quantify the extent of patenting of human genes and human DNA. However, the exact number of patents claiming human DNA sequences or genes still remains an area of uncertainty as empirical studies have used different methods, each with their own limitations. A recent study by Graff *et al*. states that over 15,000 US patents claim at least one "simple nucleic acid" including human gene sequences".[11-14] According to a recent analysis by Schauinger *et al*. over 4,900 gene patents had been awarded in the US as of August 2012 covering about 14% of the human genome.[15] These patents are owned by for-profit and not-for-profit entities that include universities and the US government. Interestingly, more than half are no longer active as they were not maintained through payment of patent maintenance fees. There are two important categories of patent claims involving (human) genes that are relevant to interpreting the implications of current Supreme Court decisions. The first are "*composition of matter*" claims that encompass claims on isolated DNA molecules themselves, including genes, mutations and genetic variants. The second are "*method*" claims that include the processes used to isolate DNA or the use of isolated DNA for diagnostic, screening, therapeutic, or other purposes.[1,5] The only question that the US Supreme Court agreed to consider in the Myriad case was whether human DNA or human genes are patentable products as "compositions of matter".

When patents are awarded, the patent holders can choose to enforce their rights through litigation against those suspected of patent infringement. They can also license specific patent rights broadly to others and thereby derive licensing fees. This approach can offset investments made towards the original invention, but at the same time make the invention available to other entities who can benefit from it, as is illustrated by the broad licensing of patents on genetic testing for cystic fibrosis.[16] Alternatively, patent holders can decide to retain all rights themselves, as was the case with *Myriad Genetics* and *BRCA* patents in the US, or to exclusively license the patent to a single entity. Both approaches essentially create a monopoly on testing.[2] While patents are designed to incentivize investment in innovation, once awarded, exclusive patent rights may impede scientific progress and innovation because others may not be able to access essential patented technologies or may face high costs while circumventing such patents. Monopolies often result in higher prices, and can create unequal access to products.[17]

The case of the Association for Molecular Pathology vs. Myriad Genetics

Myriad Genetics filed the first *BRCA1* gene patents in 1994 and *BRCA2* gene patents in 1995. By 1999 it was the only company performing *BRCA* testing in the US and currently has at least 24 patents covering various aspects of *BRCA* analysis. Several of these patents contain "method" claims related to breast cancer screening and diagnosis, as well as "composition of matter" claims involving the *BRCA1* and *BRCA2* genes.[2,5] Because Myriad did not license the technology to other laboratories in the US, and sued or threatened to sue others offering the test, it became the only provider of *BRCA* testing. Myriad has also kept their database of detected mutations and sequence variants in the *BRCA1* and *BRCA2* genes proprietary since 2004.[2] Although Myriad's BRCA analysis is a high quality test and is reimbursed by many healthcare payers, testing has remained expensive. It is possible that in some cases the absence of other providers has reduced access for some patients whose insurance plans did not have contracts with Myriad. More importantly, it has prevented second-opinion or confirmatory testing by other labs in certain cases with difficult to interpret mutations or sequence variants of unknown clinical significance. While many gene patents have been the subject of patent-infringement disputes, most cases involving genetic diagnostic patents have been settled out of court until recently.[18]

On May 12, 2009 the *American Civil Liberties Union (ACLU)* filed a lawsuit against Myriad Genetics on behalf of the *AMP* and other organizations, including the American College of Medical Genetics and Genomics, patient advocacy groups, as well as individual patients, researchers, clinicians and scientists, some of whom hold prominent positions in the field of medical genetics.[19] These parties challenged that isolated DNA is not patentable subject matter in accordance with US patent law because DNA and genes are naturally occurring substances. They further challenged the patenting of cDNA, method claims related to screening for cancer therapeutics, and method claims for breast cancer risk prediction by mutation analysis of BRCA1/2.[5] The US District Court of the Southern District of New York ruled in favor of the challengers and invalidated certain claims in the patents on *BRCA1* and *BRCA2*. *Myriad* then appealed to the US Court of Appeals for the Federal Circuit (Ct. App.), which in part reversed the District Court's decision by upholding the composition of matter and screening claims, but not the diagnostic method claims. The ACLU subsequently petitioned the US Supreme court to review the ruling, but they sent the case back to the Ct. App. for reconsideration in view of a Supreme Court ruling on March 20, 2012 in another case, *Prometheus vs Mayo*.[20]

In this case, Mayo Collaborative Services and Prometheus Laboratories, *Inc*. were in dispute over Prometheus's patent claims on a diagnostic test that measures thiopurine metabolites to manage the doses of thiopurine immunosuppressant drugs administered to patients with auto-immune diseases. When Mayo began to offer its own test, Prometheus sued them in 2004 for patent infringement. In March 2008, a California District Court ruled that the Prometheus patents were invalid based on section 101 of the patent act. Prometheus appealed and the Ct. App. reversed the decision in September 2009. Mayo then appealed to the Supreme Court, who sent the case back to the Ct. App., which upheld its prior decision. Mayo re-appealed to the Supreme Court, who on March 20, 2012, declared the process claims in Prometheus's patents were invalid on the basis that they effectively claimed

underlying laws of nature and did not contain sufficient innovation.[20] The court ruled that to patent a process that was an application of a natural law, enough inventive steps had to be added so that it was "significantly more than a patent on the natural law itself". The court further added that simply adding routine steps to a natural law did not make it a patentable process.

It was on this basis that the US Supreme court then sent the *Myriad* case back to the Ct. App., but the Ct. App. stood by its prior decision.[5] The *ACLU* once again petitioned the US Supreme court and they agreed to review only the question whether genes isolated from the human genome are patentable. On June 13, 2013, the Court decided unanimously that genes are products of nature and cannot be patented[1] and stated that the act of isolating DNA and the modifications added to DNA simply for the purpose of isolating it do not add sufficient innovation or modification to naturally occurring genes to qualify for patent protection. However, the Supreme Court decided that cDNA, a molecule produced in the laboratory by reverse transcription from naturally occurring mRNA, contains sufficient modification to make it eligible for patenting, because cDNA does not normally reside in the body.[1] Because the Supreme Court chose not to address the lower court rulings on screening and diagnostic method claims, genetic diagnostic patents containing only methods claims are not directly affected by this ruling.[1] Nevertheless, the previous decision of the Supreme Court in *Prometheus vs Mayo* has already influenced court decisions concerning method claims in disputed patents (see below).[21]

The negative effects of this ruling on Myriad's business are predicted to be limited, because some of the patents under question will expire in about three years. Furthermore, Myriad continues to have other potentially enforceable methods-based intellectual property and keeps data for clinical interpretation of genetic variants and mutations proprietary. Nonetheless, after the ruling, challengers claimed victory and several laboratories have either already started or communicated their intention to start offering *BRCA* testing. Myriad then filed suit against such companies, claiming patent infringement and requesting a preliminary injunction to stop other companies from offering BRCA testing. This injunction was recently denied in one case[22] and another was settled out of court.[23] Myriad has also been counter-sued for antitrust violations.[24]

Many scientists, clinicians, and commercial entities in biotechnology and diagnostics, are now wondering how the ruling will impact other domains of biotechnology and the pharmaceutical industry, and whether it will serve the interest of patients and society in general.[2,3] Biotechnology industry representatives have voiced concerns about reduced incentives to innovate in genetic diagnostics, but previous studies suggest that patents are not the main drivers of innovation.[25,18] It has also been argued that many companies will look at other ways to protect their inventions, for example through trade secrets.[6] An important difference between patents and trade secrets is that the latter do not require public disclosure of the invention, which is integral to the process of patent application and they also have no time limit. Thus, if others make the same invention independently, they can still obtain intellectual property rights to an invention protected as a trade secret while public disclosure in patents makes it possible for others to build on that information or find ways to circumvent the patent, leading to new inventions. For example, *Myriad*'s proprietary gene

variant database is held as a trade secret, which may impede competitors and clinicians from being able to access information on genotype-phenotype correlations necessary to provide comparable quality of clinical interpretation.[26] Hence, this proprietary database continues to present a barrier for competitors entering the market even if patents are invalidated or expire.

How does the US Supreme Court decision in the *Myriad* case affect genomic research and genetic diagnosis?

Concerns raised about the *Myriad* ruling surround the definition of cDNA as synthetic DNA that is produced in the lab and is not present in the human body. This definition does not fully clarify the status of *de novo* synthetically produced DNA molecules that are identical to naturally occurring DNA present in the body. One example is oligonucleotides, widely used as primers and probes in research and diagnostic applications. Patent claims on oligomers would be invalid under the Supreme Court's ruling because they exactly match stretches of DNA found widely across the human genome, despite being synthesized entirely *de novo*. Others have also argued that such claims are invalid on the basis of other criteria such as novelty.[27,28]

An important consequence of the ruling that human genes cannot be patented is that it may simplify intellectual property considerations surrounding genome-wide tests, such as array-based copy number analysis or clinical diagnostic sequencing of multiple-gene panels or of an individual's entire exome or genome.[3,29] These technologies have the capacity to reveal diagnostic information on genes for which other entities may hold patents. Until the *Myriad* ruling, it was not clear if incidental diagnostic information about patent-protected genes could be shared with the individual being tested or with that person's healthcare providers without risk of patent-infringement. The inability to report certain results because of possible infringement created the potential ethical conflict that valid diagnostic information related to those genes would be withheld. Diagnostic laboratories worried they would be required to pay multiple licensing fees, covering each patented gene included in a large-scale genomic diagnostic test in order to avoid patent-infringement.[29,30]

While the Supreme Court's decision in *Myriad* should greatly diminish the above concerns as they relate to composition of matter claims, many existing human gene-related patents also contain method claims[31,32]. The Supreme Court did not directly address method claims in the *Myriad* case, but its rulings in. *Prometheus vs Mayo* and other prior cases provide precedent that suggests that genome-wide analyses are not at great risk of patent infringement based on method claims.[20] In addition, after the Supreme Court makes a decision, it is still left to the lower courts to interpret it in litigation surrounding patents involving DNA. Similarly, the USPTO has to interpret and implement the decision in their review of future and pending patent applications. The USPTO very recently issued guidance for examiners on determining “subject matter eligibility of claims reciting or involving laws of nature, natural principles, natural phenomena, and/or natural products”, incorporating the Supreme Court decisions of *Myriad* and *Prometheus*.[8]

Implications for preimplantation and prenatal diagnosis

Implications for prenatal tests covering specific genes—The impact of patents on provision of prenatal testing has not been extensively studied or documented. Concerns have been raised that exclusive licensing of patents may impede availability and quality of prenatal or preconception testing, especially when monopoly providers do not have the incentive to develop these tests or are not experienced with developing them.[29] Anecdotal evidence suggests that preimplantation genetic tests for patented genes are available and that enforcement against test providers has been limited, possibly because of the low volume of testing performed. Nevertheless, the *Myriad* ruling could further reduce intellectual property-related uncertainty for preimplantation and prenatal testing, as well as for applications such as expanded carrier screening panels and chromosomal microarrays, already widely used in preconception and prenatal diagnosis.

Currently, expanded carrier screening panels offered to women and their partners do not include testing for *BRCA1* and *BRCA2* mutations, because these panels are focused on autosomal recessive genetic conditions that can affect children when both parents are carriers and on a few other disorders, such as Fragile X syndrome, that are X-linked. It is uncertain if the Supreme Court ruling on the *Myriad* case will quickly lead to inclusion of *BRCA1* and *BRCA2* testing in such panels considering their focus and purpose. However, *Counsyl*, a company that offers carrier screening in the US, has filed for a declaratory judgment by the Northern District Court of California that it is not infringing *Myriad*'s patents because the relevant claims in those patents are invalid.[33,34] This suggests that some providers may be considering inclusion of *BRCA1* and *BRCA2* in carrier screening panels. Women or men who have been found to be carriers for cancer-predisposing mutations in these genes through family-history based testing or because of a personal history of cancer may request prenatal or preimplantation genetic diagnosis for the mutation they carry. Interestingly, despite the Myriad patents, preimplantation genetic diagnosis for BRCA mutations has already been offered in the US and Europe[35] and experience with PGD for *BRCA1/2* mutations in 717 embryos from 154 cycles on 70 couples was presented at a recent meeting.[36] Hence, we do not anticipate that there will be a significant change in this practice. However, as more patients may now gain access to the initial *BRCA* testing for themselves, it remains possible that the demand for preimplantation genetic diagnosis for *BRCA* mutations may increase.

Intellectual property issues related to non-invasive prenatal testing (NIPT)—NIPT for trisomies 21, 13 and 18, as well as for sex chromosome aneuploidy using cell free fetal (cff) DNA has rapidly entered the US market since late 2011.[37] NIPT is currently offered in the US through four companies who hold many patents covering their respective tests and all four companies have reciprocally sued each other for patent infringement in the US. As recently reported by Agarwal, *et al*.[38], at least 34 awarded and 90 pending US patent applications claim various prenatal testing applications using cffDNA.[37,38] Importantly, most of these patents claim methods on the use of cffDNA for prenatal diagnosis but do not claim composition of matter intellectual property rights for cffDNA itself. Since cff and cell-based fetal DNA naturally occur in the bloodstream of pregnant women, it seems unlikely that, in general, new composition of matter patents will be issued after the *Myriad* ruling.

On July 5, 2012, the US District Court for the Northern District of California denied one company's (Sequenom), request for a preliminary injunction against another company (Ariosa).[14] In response to an appeal by Sequenom, the Ct. App. recently reversed this decision and remanded the case back to the District Court of Northern California with strong guidance about issues the judge should reconsider in decisions about a preliminary injunction. Furthermore the Ct. App.'s opinion stated “because the district court did not have the benefit of Myriad and also in light of this court's disagreement with the district court's claim construction, this court remands for the district court to examine subject matter eligibility in the first instance.” The court clarified that it “offers no opinion as to whether there is or is not a substantial question regarding the subject matter eligibility of the asserted claims”.[39] On October 30, 2013, the Northern District Court of California denied Sequenom summary judgment for preliminary injunction against *Ariosa* for infringing its patents and granted Ariosa summary judgment that it is not infringing on key claims in Sequenom's patents, because they are invalid. The court used as its basis the *Myriad* case, to assert that cffDNA is not patent-eligible because it is natural phenomenon. It further referred to *Mayo vs, Prometheus* and other patent rulings to rule that the method claims in Sequenom's “540 patent” involve methods to detect, isolate, amplify and quantify cffDNA that were well understood and that the only innovation was to apply them to paternally inherited cffDNA, which was not deemed sufficient to make them patent-eligible. *Sequenom* has announced it will appeal this ruling. It therefore remains unclear whether and how the combined *Myriad* and *Prometheus* rulings will affect the outcome of ongoing patent litigation for cffDNA-based NIPT and what impact this will ultimately have on clinical provision of NIPT options. Finally, companies offering NIPT already have proprietary algorithms for data analysis and are undoubtedly accumulating important data about the performance of their tests that they could hold in proprietary databases for competitive advantage. These may also play a role in shaping the future market of NIPT.

Conclusion

The long-awaited ruling by the US Supreme Court that human genes are products of nature and cannot be patented may effectively end the monopoly that companies such as *Myriad Genetics* and others have on genetic testing involving patented genes. While the decision comes relatively late in the history of gene patenting and in fact close to the expiration of some of *Myriad*'s relevant patents, it will have significant effects on molecular genetic diagnostics. It will hopefully result in better access to previously protected tests, in test innovation that can capitalize on recent technological developments in DNA sequencing and in cost reduction of genetic testing. Especially relevant to prenatal genetic diagnosis and screening may be that providers of genome-wide diagnostics, such as chromosomal microarrays and genome-wide sequencing, can be less concerned about intellectual property rights on some of the chromosomal regions and gene sequences included in their tests. However, the *Myriad* case does not resolve all uncertainty related to intellectual property and genetic diagnostics patenting. There remain important questions about the interpretation of rulings related to validity of diagnostic method claims, the scope of cDNA patent claims, and the impact that trade secrets, particularly proprietary variant databases like *Myriad*'s, will continue to have on market competition.

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What is already known?

- Myriad Genetics holds many patents covering *BRCA1* and *BRCA2* gene sequences and methods for testing for hereditary breast and ovarian cancer risk, and has used them to monopolize *BRCA* testing in the United States.
- The US Supreme Court recently ruled that “composition of matter” claims on genes are not patent-eligible because DNA is a naturally occurring substance.
- In 2012 the Supreme Court also ruled in *Prometheus v Mayo* that method claims on natural laws or processes or simply observing natural phenomena are not patent eligible subject matter.

What does this paper contribute?

- We examine how these Supreme Court rulings may affect testing for other patented human genes and prenatal genetic diagnosis and screening.
- We examine if these rulings will lead to broader access to *BRCA* gene testing in prenatal and reproductive care.
- We highlight the consequences of these rulings for ongoing patent litigation for non-invasive prenatal testing “methods” in the US.
- We discuss residual uncertainty surrounding cDNA and method claims, trade secrets, and proprietary mutation databases.