Gene Patents and Personalized Cancer Care: Impact of the *Myriad* Case on Clinical Oncology

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ABSTRACT

Genomic discoveries have transformed the practice of oncology and cancer prevention. Diagnostic and therapeutic advances based on cancer genomics developed during a time when it was possible to patent genes. A case before the Supreme Court, *Association for Molecular Pathology v Myriad Genetics, Inc* seeks to overturn patents on isolated genes. Although the outcomes are uncertain, it is suggested here that the Supreme Court decision will have few immediate effects on oncology practice or research but may have more significant long-term impact. The Federal Circuit court has already rejected Myriad's broad diagnostic methods claims, and this is not affected by the Supreme Court decision. Isolated DNA patents were already becoming obsolete on scientific grounds, in an era when human DNA sequence is public knowledge and because modern methods of next-generation sequencing need not involve isolated DNA. The *Association for Molecular Pathology v Myriad* Supreme Court decision will have limited impact on new drug development, as new drug patents usually involve cellular methods. A nuanced Supreme Court decision acknowledging the scientific distinction between synthetic cDNA and genomic DNA will further mitigate any adverse impact. A Supreme Court decision to include or exclude all types of DNA from patent eligibility could impact future incentives for genomic discovery as well as the future delivery of medical care. Whatever the outcome of this important case, it is important that judicial and legislative actions in this area maximize genomic discovery while also ensuring patients' access to personalized cancer care.

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INTRODUCTION

The translation of genetic and genomic discoveries to clinical care has energized precision or personalized cancer medicine. A case brought before the US Supreme Court, *Association for Molecular Pathology (AMP) v Myriad Genetics, Inc*, has raised questions regarding patent protection for genetic and genomic discoveries.¹ For oncologists, the case is of special interest because the legal challenge is drawn from one company's exclusive claim and restrictive licensing on diagnostic testing of the *BRCA* cancer susceptibility genes, familiar to oncologists providing care to patients with breast cancer and their families.²⁻⁷ As will be discussed, Myriad's broad diagnostic patent claims were rejected by the Court of Appeals for the Federal Circuit in August 2012. The question the Supreme Court agreed to consider was limited to whether human genes are patentable (ie, whether a molecule of isolated DNA is patent-eligible subject matter). This narrow focus has left cancer care providers to wonder to what extent the decisions in this case and prior lower court decisions

will impact them. Here, we will suggest that the outcome of this case will likely not have a large immediate impact for oncologic care of patients. However, the *AMP v Myriad* case may have a larger long-term impact on the role of intellectual property protection in modern genomic and medical science. From the perspective of health care professionals caring for patients and families with cancer, it is important that these legal decisions have a net positive impact on scientific discovery as well as patients' access to new technologies.

LEGAL ASPECTS

Gene Patents

Rooted in the US Constitution, a patent is "the grant of a property right to an inventor, issued by the United States Patent and Trademark Office (USPTO), generally for a period of 20 years from the filing date of the inventor's patent application."⁸ A patent holder may grant permission to others to use the work, such as through licensing. If a patent holder detects infringement by an entity without

permission, the patent holder can choose to enforce the patent through litigation.⁸⁻¹⁰ The Patent Act says that “any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof,” is patent eligible, provided it is novel (ie, not previously known or used in the United States or described anywhere). It also has to be useful and nonobvious to one skilled in the relevant technical, engineering, or science field.⁸ The US Supreme Court has 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. In the Court’s view, “[s]uch discoveries are ‘manifestations of . . . nature, free to all men and reserved exclusively to none.’”^{11,12}

The term gene patents can encompass many different types of patents, including patents on isolated DNA molecules, known as composition of matter patent claims, and patents on processes involving isolated DNA, known as method patent claims. Relevant to *AMP v Myriad*, method patent claims can be further divided into screening method claims and diagnostic patent claims (Table 1). Many thousands of composition of matter and method patent claims involving purified natural substances, including insulin, erythropoietin, and DNA, have been granted by the USPTO and upheld in the courts.⁹ From a legal standpoint, patents are granted on DNA in its isolated or purified form only, not as it exists in the body. Companies can hold multiple types of patents related to the same discovery.

AMP v Myriad Genetics, Inc

In 2009, AMP, the American Civil Liberties Union (ACLU), the Public Patent Foundation, and individual physicians, researchers, and patients questioned the patent eligibility of isolated fragments of DNA. They challenged the range of patents used by Myriad Genetics, a company that had opted to exclusively market its test for the *BRCA1* and *BRCA2* mutations without granting licenses to others.¹ In *AMP v Myriad*, the US District Court (Southern District of New York) held that isolated DNA was not patent-eligible subject matter, invalidating composition of matter claims on sequences of *BRCA* genes held by Myriad, the University of Utah, and the National Institutes of Health. They also invalidated claims for screening and diagnostic methods¹³ (Table 1). Myriad appealed the District Court’s decision to the US Court of Appeals for the Federal Circuit.^{13,14} The Federal Circuit reversed the District Court in part, upholding Myriad’s composition of matter and screening method patent claims. But the Federal Circuit upheld the prior decision invalidating diagnostic method patent claims, in which normal and abnormal *BRCA1* sequences were merely compared to determine breast cancer risk (Table 1). The Federal Circuit rejected the categorical exclusion of isolated DNA (ie, composition of matter claims) from patent-eligible subject matter. The ACLU petitioned the US Supreme Court for review, and the Court vacated the Federal Circuit opinion and remanded the case to the

Federal Circuit for reconsideration in light of its March 2012 decision in *Mayo v Prometheus* (see next section), which rejected patent eligibility for certain diagnostic method patent claims.¹ In August 2012, the Federal Circuit again upheld Myriad’s composition of matter and screening method claims. In September 2012, the ACLU again petitioned the Supreme Court, and the Court granted review in part, agreeing to decide the narrow issue, “Are human genes patentable?”^{15,16} Thus, the court elected not to address the previous lower court decisions regarding the diagnostic and screening method claims.

Relevant Prior Decisions Bearing on AMP v Myriad’s Method Claims

In *Bilski v Kappos* (2010), a patented method for hedging risk in commodities trading was challenged on the basis that it monopolized an abstract thought process. This case yielded the machine or transformation test, which says that a process is not patent eligible unless it is specifically designed to be carried out by machine or transforms an article from one thing or state to another.¹⁷ The Supreme Court upheld the decision that the risk-hedging process was ineligible for patent protection. In *Mayo v Prometheus*, the context of the case was a drug (thioguanine) used by both rheumatologists and oncologists. The Court found that a method for determining the therapeutic dose for individual patients based on metabolite levels in the blood did not add enough inventive, nonroutine elements to the natural relationship between metabolite levels and drug performance to constitute a patent-eligible process.^{15,18} The implications of *Bilski* and *Mayo* are relevant to thought processes or mental steps involved in developing and interpreting the results of single or multiple genetic tests. For example, these decisions bear on companion diagnostics to detect mutations for which there are cancer-targeted therapies, a key component of personalized genomic medicine (eg, *ALK* rearrangements for crizotinib therapy or next-generation sequencing [NGS] to detect therapeutic targets).

As outlined earlier, in earlier stages of the case, *AMP v Myriad* also involved a challenge to two general types of method patent claims held by Myriad—claims on methods for using cells to screen for potential cancer therapeutics and methods for predicting the risk of developing breast cancer in a patient based on detecting mutations in *BRCA1/2*. The Federal Circuit found, and then, considering *Bilski* and *Mayo*, reaffirmed that the screening method patent claim was patent eligible but the diagnostic method patent claims were not¹⁹ (Table 1). The basis for this distinction was that the screening process involved the transformative step of testing a specific therapeutic on non-naturally occurring host cells (cell lines), whereas the diagnostic method claims simply called for the mental step of comparing two sequences of mutant and normal *BRCA1* gene. The Supreme Court chose not to readdress the Federal Circuit decision on diagnostic methods of gene patents, a seemingly decisive blow against Myriad’s claims of use of

Table 1. Summary of Types of Myriad Patent Claims and Legal Decisions to Date

Myriad Patent Claims	District Court	Federal Circuit Appeals Court	Supreme Court
Composition of matter	Invalidated patent claims	Upheld patent claims	2013 decision
Diagnostic method	Invalidated patent claims	Invalidated patent claims	Not addressed
Screening method	Invalidated patent claims	Upheld patent claims	Not addressed

isolated DNA for diagnostic purposes (ie, clinical *BRCA1/2* testing to identify patients at increased risk for cancer). Although this could mean that Myriad no longer has legal standing to bring infringement suits against laboratories offering *BRCA1/2* testing, this question remains legally uncertain. Myriad still holds additional method patents not challenged by the ACLU and could seek to assert other method claims against competing commercial laboratories.

Is Isolated DNA Patent Eligible?

In *AMP v Myriad*, arguments have focused on whether isolated DNA is markedly different from DNA in its natural state. Myriad argued that isolated DNA is different from native DNA because it has different properties, can be used for different purposes, and is isolated through a process that is nonroutine and transformative and because other purified natural substances have been found to be patent eligible by the courts in the past (eg, insulin, paclitaxel [Taxol]).²⁰ To support its claims to invalidate Myriad's patents, ACLU argued that, unlike other purified, natural substances, the utility of isolated DNA sequences is that they code for the same biologic information as native DNA sequences, any differences between isolated and native DNA are incidental to the isolation process, the isolation process is routine scientific practice, and isolated DNA patents allow patent holders to unduly preempt the use of those sequences by others.²¹ The patent eligibility of isolated DNA is the single question addressed by the Supreme Court in 2013.

SCIENTIFIC ASPECTS OF GENE PATENTS

Genes are units of DNA that encode proteins. Isolated DNA can refer to native (genomic) DNA or cDNA. cDNA, a synthetic form of DNA with all of the intervening sequences (introns) removed from it, is commonly produced to clone genes to be used, for example, to make a particular protein of interest. In some cases recombinant DNA has been engineered, combining one gene with regulatory regions of other genes to turn on production of the first gene. The USPTO has granted tens of thousands of patents for genes or genetically engineered substances, modified organisms, or purified cDNAs as tools to manufacture protein products.

The focus of legal argument in *AMP v Myriad Genetics* has been on the chemical properties of DNA (ie, whether the breaking of a covalent bond between base pairs to isolate the DNA transforms the molecule from a natural to a novel state). The breaking of covalent bonds was compared to pulling a leaf from a tree or isolating gold from a streambed. Analogies aside, fragments of human DNA may occur naturally; DNA from an embryo circulates in the mother and can be used diagnostically. Random tumor DNA fragments circulate in patients with cancer.²² Although it may be argued that isolated DNA may be shown to have new properties and uses, the breaking of covalent bonds as the argument that isolated DNA is made by man is questionable. In contrast, cDNA is produced enzymatically in vitro and does not exist in nature. Thus, one of the Federal Circuit judges that heard *AMP v Myriad* viewed cDNA, but not genomic DNA, as patent eligible. This same view of the patent eligibility of cDNA was ultimately taken by the US Department of Justice and a senior scientist of the Human Genome Project.²²⁻²⁴

IMPACT OF GENE PATENTS ON SCIENTIFIC RESEARCH AND PATIENT CARE

Although not to be considered by the Supreme Court in *AMP v Myriad*, the potential broad impact of gene patents was cited by both parties and amici,^{21,25-27} with this debate highly publicized by the lay press. These arguments mirror much of the existing academic literature, where the ethics of gene patents have been frequently considered in terms of beneficence (doing good) and justice (considering the fair distribution of benefits and burdens).^{9,28,29} The ethics of gene patents have also been considered through a framework of benefits and harms or net social benefit, for example relating to scientific progress, quality of care, cost, and access.⁹

The possible benefits of gene patenting have classically been cited as incentivizing commercialization of clinically relevant advances and practice-changing drugs (eg, erythropoietin), as well as more efficient tests for mutations to target cancer therapies (eg, *BRAF***V600E* in melanomas likely to respond to *BRAF* inhibitors). Protection of intellectual property and market exclusivity has incentivized investors in biotechnology. Without patent protection, inventors may withhold their progress as trade secrets, which may still be undermined by independent discoveries.³⁰ Despite these arguments, it also usually acknowledged that the majority of gene discovery efforts originated in academic or federally funded research labs, with commercial investment, when it occurred, occurring relatively late in the process. Another potential benefit of gene patents is the centralization of testing,³¹ leading to improved quality, better reimbursement, wider dissemination of testing, and improved interpretation of genetic variants.

Posited harms of gene patents include potential barriers to and delays in research and translation to clinical care, as a result of license or royalty fees required to work with patented genes or by denying access to such genes completely (referred to as the patent thicket or anticommons).^{32,33} Gene patents could lead, in theory, to diminished development of more effective or efficient tests, increasing costs, limiting second-opinion testing, and potentially exacerbating disparities in health care delivery and outcomes.^{9,34} In addition, holding a gene patent may suppress the development of and increase the cost of new methods of testing. Indeed, Myriad's patents granted by the European Patent Office were successfully opposed, in part based on charges that Myriad missed large rearrangements of *BRCA1*, despite Myriad's documentation of its prior efforts to improve testing sensitivity (*BRCAAnalysis* Rearrangement Test).³⁵⁻³⁷

Despite continued debate over the benefits and harms of gene patents, and particularly Myriad's *BRCA* patents, available analyses and literature evaluating the benefits and harms of gene patents have revealed a mixed picture.³⁸ Contrary to expectations, the cost of genetic testing was not found to be higher when the gene was protected by a patent than when it was not or when patents were exclusively enforced.^{38,39} Centralized *BRCA* testing was accompanied by educational outreach, third-party reimbursement, and quality control. There was little objective evidence that Myriad's *BRCA1* patent dampened basic scientific research, with the possible exception of targeted therapeutics. The company established a lower price for research testing but did take action against plaintiffs Kazazian and Ganguly's university-based laboratory offering commercial *BRCA* testing.³⁵ In contrast to the patented but licensed colon cancer genes, *BRCA1* and *BRCA2* were not licensed in the United States or abroad, leading to

their successful opposition in Europe, although the patents were recently upheld in Australia.^{15,35,36} Although surveys support the perception of the adverse impact of gene patents on diagnostic testing,^{40,41} most patent holders have not aggressively enforced their rights, and few have refused to grant licenses.^{9,42} However, in some cases, exclusive licensing has limited patient access to testing, second opinions, and continued related research.^{29,43-48}

LIKELY IMPACT OF *AMP v MYRIAD* ON CLINICAL ONCOLOGY CARE

The Supreme Court decision in *AMP v Myriad* is not likely to have a substantial immediate impact on the practice of oncology for several reasons. Myriad's broad diagnostic methods claims to detect breast cancer susceptibility were already rejected by the Federal Circuit and will not be revisited by the Supreme Court. However, this new legal standard remains to be tested. There is only one case wherein a patent on isolated DNA was challenged for diagnostic use, and in this case, the patent was not upheld.^{23,49} Thus, the generation of new case law after these decisions will be required to fully assess their impact. Additionally, Myriad's patents on *BRCA1/2* will expire over the next 3 years, and opportunities for other laboratories to offer and researchers to conduct *BRCA1/2* testing will emerge.

Even if the Supreme Court upholds patent eligibility for isolated human DNA, Myriad's patents are vulnerable in other ways. For example, the 15 base-pair short fragments of *BRCA1* patented by Myriad are found elsewhere in the genome, providing fertile soil to contest those patent claims.⁵⁰ For technical reasons, isolated DNA patent claims, even if upheld, would almost certainly not inhibit NGS of entire genomes. Although it remains to be tested, experts have proposed ways to circumvent patent restrictions on NGS capture approaches being used to generate lower cost tests.^{23,51-54} NGS panels of a dozen or more genes can now be offered at a cost comparable to Myriad's price for sequencing just two genes. Myriad will likely soon provide its own panel testing including genes in addition to *BRCA1/2*, mitigating to some extent the current high cost of conventional sequencing of *BRCA1/2* followed by NGS panel testing of the remaining breast cancer genes. Already some genomic testing companies have offered tests for *BRCA1/2* single mutations in seeming defiance of Myriad's patent, whereas others have not included *BRCA1/2* sequencing in gene panels, presumably because of fear of legal challenge.^{44,45,47} In the absence of a legal challenge by one of these companies based on the Circuit Court and Supreme Court rulings, oncologists and patients will be left in limbo. Leaving aside the legal issues of aggregating rights and patent barriers to gene panel testing, the clinician—and patient—will still be faced with barriers as a result of the current payment system, which has historically reimbursed one test at a time. For example, such requirements have led to separate billing for *BRCA* sequencing and *BRCA* rearrangement testing.

With regard to genomically derived therapeutics, there will be little obvious impact of the current case, especially if the Supreme Court, as many expect, follows the path advocated by the US government²⁴ that permits patent claims for isolated cDNA but not genomic DNA or oligonucleotides (small fragments of DNA used for diagnostic applications). This is because these cDNA patents generally are based on cellular and protein applications. For example, Amgen patented recombinant cells transformed or transfected with the claimed

erythropoietin gene, as well as the means to produce the protein product of that gene. Similarly, a nuanced and narrowly crafted decision allowing patent protection for cDNA and not human genomic DNA could ameliorate most of the adverse impact on the biotechnology industry.^{22,35,55,56} Such a decision is also likely to have minimal impact on an industry that also uses genomic technologies to increase plant productivity or livestock resistance to pathogens or to develop novel fragrances and flavorants.

Unfortunately, the outcome of *AMP v Myriad* will also not impact the vital issue of public access to information regarding *BRCA* genetic sequence variants. Myriad's withholding of its mutation database of 300,000 cases from public access compromises clinicians' and researchers' ability to independently characterize missense variants,³¹ despite two reports from the National Academies calling for public depositing of data.^{57,58} Although academic centers have formed consortia to catalogue *BRCA* variants of unknown significance,⁵⁹ and some clinicians have pledged to assemble pooled data sets, this process is still small in scale, may take over a decade to achieve sufficient size, and is hampered by some laboratories withholding deposition of data out of fear of litigation. Despite all of these weaknesses in its legal position, including the decisions of the Federal Circuit, which will not be affected by the Supreme Court decision, Myriad may be able to maintain its current exclusive position by the existence of its remaining patents and the threat of the high cost of litigation. The *Myriad* case is unusual in that one company aggressively acquired patent rights from other domestic as well as international laboratories with the aim of exclusive enforcement on other clinical laboratories. In this regard, the impact of the *Myriad* case on oncology will be profound over the long term. This case brings to light the question of the impact of intellectual property rights enforcement on basic standards of medical practice. Although the clinical impact of the high cost of targeted drugs as a result of pharmaceutical patents is an increasingly recognized concern, the impact of intellectual property barriers on standards of preventive medical care will be much greater in scale. This will require a new convergence of a much broader coalition of stakeholders, as standards of public health policy as well as clinical care may well be impacted by these legal decisions regarding intellectual property.

ADDITIONAL APPROACHES TO PROTECTING INTELLECTUAL PROPERTY FOR GENOMIC DISCOVERY

As previously outlined, Myriad's patent claim on a method for using cells to screen for potential cancer therapeutics was upheld, whereas its method claims for detecting mutations in genes linked to incidence of cancer were invalidated. This screening claim, however, was not based on an actual experiment, but on a hypothetical cell line containing *BRCA1* mutant DNA to be used for the purpose of discovering new drugs. Unlike the case of Amgen's development of erythropoietin based on its genetic sequence, the patenting of the *BRCA* genes has led to no therapeutic use of the protein encoded by the *BRCA* genes. The poly (ADP-ribose) polymerase inhibitors, used to treat *BRCA* mutant cancers, were not discovered by Myriad. Thus, a curious legacy of *AMP v Myriad* seems to be the upholding of a hypothetical nondiscovery (the screening method claim) and the overturning of a patent based on a discovery (rare mutations linked to risk of a common human cancer) claimed by some to be the greatest genetic advance of the past century.

Although such broad patent claims were common in the previous century, to patent a DNA sequence or cDNA, a heightened bar including a test of clinical utility has taken on increasing significance in a scientific landscape in which sequence information for the approximately 20,000 human genes (and intervening sequences) is public knowledge (further discussed in Appendix, online only).

Alternatively, legislative and regulatory changes may be one approach to allow some incentivizing of development of novel genomic diagnostics. Legislation could carve out a safe harbor from infringement for second-opinion testing or for research (as proposed in 2002 in H.R. 3967). Regulatory bodies could also require compulsory licensing to market tests for patented genes.^{60,61} The 2011 America Invents Act (Public Law 112-98) directed the USPTO to analyze how exclusive licensing of genetic testing patents affects the practice of medicine.⁶² Although it undermines the rationale for limited-time monopolies, the notion of mandatory licensure has intuitive appeal to some scientists because it could serve as a legislative protection in the case of an invention that is medically essential. Indeed, it could even be argued that had Myriad's aggressive enforcement of its exclusive patent been tempered by regulation requiring fair licensing arrangements, the uproar that inspired the current litigation about isolated DNA patenting may never have occurred.

CONCLUSION

The Supreme Court decision in *AMP v Myriad* itself is not likely to immediately impact the practice of oncology. Diagnostic methods patents based on DNA sequence have already been weakened by previous decisions that will not be readdressed by the Supreme Court. NGS will most likely not fall under isolated DNA protections, but this may require a legal test case. For most common cancer susceptibility genes other than *BRCA*, genetic testing is not restricted by exclusive patent enforcement. In the therapeutic realm, the outcome of this case will likely have only limited impact on new drug development, because these claims usually involve a methods component based on cellular applications. If, as would seem legally and scientifically sensible, the Court's decision acknowledges the distinction between genomic DNA and cDNA, then a potentially adverse impact of a decision removing patent protection from isolated genomic DNA would be substantially mitigated.

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Appendix

Utility Considerations in Patents on Genomic Discoveries

Although some may argue that diagnostic DNA applications are inherently not patent eligible, there may be concern that it is excessive to exclude from patent protection all discoveries based on DNA sequence. To the oncologist, it is the novel presymptomatic, diagnostic, prognostic, or therapeutic application of a genomic test that is important. One of the threshold standards of 35 USC §101 is that a patentable invention must be useful. In 2001, there was extensive legal guidance for examiners issued by the US Patent and Trademark Office (USPTO) regarding the utility requirement of gene patents, requiring a heightened standard meeting “specific, substantial, and credible” evidence for utility. The USPTO stated that “the courts interpret the statutory term ‘useful’ to require disclosure of at least one available practical benefit to the public” (USPTO: Utility examination guidelines. <http://www.uspto.gov/web/offices/com/sol/og/2001/week05/patutil.htm>). From this perspective, one approach to modernizing patent law in the postgenomic era could be to increase emphasis on the clinical utility requirement for patent eligibility of genomic discoveries.

The thresholds for meeting standards of clinical utility are not obvious and are being addressed by ongoing case-by-case review by federal advisory groups such as the Working Group on the Evaluation of Genomic Applications in Practice and Prevention of the US Centers for Disease Control and Prevention (Calonge N, Fisher NL, Berg AO, et al. *Genet Med* [epub ahead of print on February 21, 2013]), as well other bodies that weigh evidentiary literature. There remains a critical need for legal and scientific scholarship proposing new definitions for thresholds of utility that are appropriate in the postgenomic era. For example, there are now many genomic variants, single nucleotide polymorphisms as well as rare gene variants, whose biologic mechanisms remain unknown and for which disease associations lack clinical utility because of modest increases in cancer risk observed (Offit K. *Hum Genet* 130:3-14, 2011). However, patents for these variants have been issued to many universities as well as for-profit entities. Should one of these entities seek to develop novel diagnostics (or risk algorithms) based on genomic information and to link these diagnostics to medical interventions of proven clinical utility (eg, improved survival), it is unclear whether the current case law summarized here^{1,17,18} (*Myriad*, *Bilski*, and *Mayo* cases) would support incentives for this innovation. Further consideration of strategies to encourage novel diagnostic applications of genomic discoveries constitutes one area of needed policy discussion. Other methods claims relevant to oncologists will likely not be impacted by these cases and will require little immediate action, for example, genomic applications using novel, more rapid, or more effective testing methods, or new therapies involving protein or cellular methods claims. However, even here, courts have been leery to impose on the USPTO clinical utility requirements within the purview of other federal agencies such as the US Food and Drug Administration, which establishes thresholds for clinical trials.