

**MAYO, MYRIAD, AND THE FUTURE OF INNOVATION IN
MOLECULAR DIAGNOSTICS AND PERSONALIZED MEDICINE**

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Contrary to popular perception, the Supreme Court's recent decision in Association for Molecular Pathology v. Myriad Genetics, Inc., finding certain patent claims reciting isolated genomic DNA molecules patent ineligible is likely to have a relatively minor impact on the patenting of diagnostics and personalized medicine. Method claims generally play a much more important role than isolated DNA claims in the patenting of innovations in this important technological sector, and the Court's earlier decision in Mayo v. Prometheus Labs that held claims directed towards non-genetic methods of personalized medicine to be patent ineligible will likely prove significantly more problematic in this regard. This article analyzes Myriad and Mayo and discusses their implications, concluding with a critique of Ariosa Diagnostics v. Sequenom, a district court decision applying Mayo to genetic diagnostic method claims in a manner that, if followed by other courts, could substantially threaten the availability of adequate patent protection for molecular diagnostics and personalized medicine.

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I. INTRODUCTION

On June 13, 2013, the U.S. Supreme Court issued a unanimous decision in *Association for Molecular Pathology v. Myriad Genetics, Inc.*¹ invalidating patent claims directed toward isolated DNA molecules derived from the human genome. Some celebrated the decision, calling it a “victory for all those eagerly awaiting more individualized, gene-based approaches to medical care,”² but others, particularly innovators in biotechnology, have expressed concern that the heightened standard for patent eligibility established by *Myriad* will substantially weaken the incentive for

¹ 133 S. Ct. 2107 (2013) [hereinafter *Myriad*].

² See, e.g., Francis S. Collins, *Statement by NIH Director Francis Collins on U.S. Supreme Court Ruling on Gene Patenting*, NAT’L INST. OF HEALTH (June 13, 2013), http://www.nih.gov/about/director/06132013_statement_genepatent.htm.

investment in this important technological sector.³ Particularly troubling is the disruption of investment-backed expectations caused by this reversal of long-standing United States Patent and Trademark Office (“PTO”) policy.⁴

The avowed purpose of the *Myriad* plaintiffs was to invalidate patent claims that they alleged broadly covered clinical and research applications of breast cancer gene (“BRCA”) genetic testing.⁵ Some of the challenged patent claims were in fact explicitly directed towards genetic testing, particularly claims reciting methods of testing for genetic variations in BRCA genes.⁶ Many of the challenged claims, however, were not at all likely to be infringed by genetic testing or research, particularly product claims directed towards isolated DNA molecules.⁷ Nonetheless, the plaintiffs and the courts seem to have assumed that the isolated DNA product claims were highly relevant to genetic testing, and these were the only claims that were actually addressed by the Supreme Court.⁸

Curiously, given that the plaintiffs’ arguments for standing were based on a purported desire for greater access to BRCA genetic diagnostic testing,⁹ one of the challenged claims on its face had absolutely nothing to do with genetic testing. This was Claim 20 of U.S. Patent Number 5,747,282, which is directed towards methods for screening for potential cancer therapeutics.¹⁰ The

³ See, e.g., Roy Zwahlen, *Myriad Supreme Court Decision: BIO’s Statement*, BIOTECHNOW (June 13, 2013), <http://www.biotech-now.org/public-policy/patently-biotech/2013/06/myriad-supreme-court-decision-bios-statement#>.

⁴ Ass’n for Molecular Pathology v. U.S. Patent & Trademark Office, 689 F.3d 1303, 1343–45 (Fed. Cir. 2012).

⁵ Sandra Park, *Today’s the Day: Challenging Human Gene Patents Before the Supreme Court*, AM. CIVIL LIBERTIES UNION (Apr. 15, 2013, 10:16 AM), <https://www.aclu.org/blog/womens-rights-free-speech-technology-and-liberty/todays-day-challenging-human-gene-patents>.

⁶ See, e.g., U.S. Patent No. 5,709,999 col. 161 (filed June 7, 1995).

⁷ See U.S. Patent No. 5,747,282 col. 153 (filed June 7, 1995).

⁸ The diagnostic testing method claims were invalidated by the Federal Circuit and not addressed by the Supreme Court. Ass’n for Molecular Pathology v. U.S. Patent & Trademark Office, 653 F.3d 1329 (Fed. Cir. 2011).

⁹ *Id.* at 1344.

¹⁰ *Id.* at 1343–45.

Myriad plaintiffs' decision to challenge a patent claim solely directed to drug discovery, with no nexus to genetic testing or research,¹¹ raises serious questions regarding their true motives. However, this aspect of the case will not be the subject of this Article.

Instead, this Article will focus on the impact of the Court's two most recent patent eligibility decisions on the availability of effective patent protection for diagnostic tests and personalized medicine. *Myriad* captured public attention, due in large part to the public relations efforts of the lawyers representing the plaintiffs, including their provocative, albeit misleading question for review in the petition for certiorari, i.e., "are human genes patentable?"¹² However, *Mayo Collaborative Services v. Prometheus Laboratories*,¹³ a patent eligibility case decided by the Supreme Court a year before *Myriad*, is likely to be more significant, and indeed more problematic, for those seeking patent protection for innovative diagnostic tests and personalized medicine than the *Myriad* decision.

This Article begins in Part II with a brief introduction to some basic technical aspects of molecular diagnostic testing and personalized medicine. Part III explains why, contrary to popular perception, *Myriad* is likely to have a relatively minimal impact on the patenting of innovations in diagnostics and personalized medicine. Part IV proposes a plausible policy basis for the disparate treatment of isolated genomic DNA and cDNA claims in *Myriad*. Part V explains the importance of method claims in the patenting of diagnostic-based inventions, and Part VI also discusses the potential impact of *Mayo* on patenting in this important area of technology. Finally, Part VII examines *Ariosa Diagnostics*, a recent decision from the Northern District of California that applies *Mayo* to genetic diagnostic method claims

¹¹ Ryan Abbot, *Thoughts on Myriad*, HARVARD L. PETRIE-FLOM CTR. (June 14, 2013), <https://blogs.law.harvard.edu/billofhealth/2013/06/14/thoughts-on-myriad/#more-6517>.

¹² Appellate Petition, *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013) (No. 12-398), 2012 WL 4502947.

¹³ 132 S. Ct. 1289 (2012) [hereinafter *Mayo*].

in a manner that, if followed by other courts, could substantially threaten the availability of adequate patent protection for molecular diagnostics and personalized medicine.

II. MOLECULAR DIAGNOSTIC TESTING AND PERSONALIZED MEDICINE

As a prelude to this Article's discussion of the impact of *Mayo* and *Myriad*, this Part provides a brief introduction to some basic technical aspects of molecular diagnostic testing and personalized medicine. Readers familiar with the technology might choose to skip this Part.

A. *Molecular Diagnostics Testing*

The terms “molecular diagnostics” and “molecular diagnostic testing” refer to methodologies used to assess some medically significant characteristic of a patient based on the detection, and often quantification, of one or more molecular biomarkers.¹⁴ Molecular diagnostic tests are often DNA-based, and are premised on the correlation between a genetic biomarker and some phenotype of clinical significance.¹⁵ The biomarker in a typical DNA-based genetic test is a genetic variation, sometimes referred to as a mutation, or some combination of genetic variations.¹⁶ These genetic biomarkers are typically detected by determining the sequence of nucleotides at a relevant location in a patient's genome in order to test for the presence of the variation.¹⁷

The BRCA tests at issue in *Myriad* fall into this category of DNA-based genetic tests. The BRCA genes code for proteins that play a significant role in warding off cancer.¹⁸ Some individuals have BRCA genes with variations (sometimes referred to as

¹⁴ Linnea M. Baudhuin, Leslie J. Donato & Timothy S. Uphoff, *How Novel Molecular Diagnostic Technologies and Biomarkers are Revolutionizing Genetic Testing and Patient Care*, 12.1 EXPERT REV. OF MOLECULAR DIAGNOSTICS 25 (2012); MOUSUMI DEBNATH ET AL., MOLECULAR DIAGNOSTICS: PROMISES AND POSSIBILITIES v–vii (18th ed. 2010).

¹⁵ DEBNATH ET AL., *supra* note 14, at 106.

¹⁶ *Myriad*, 133 S. Ct. at 2112; DEBNATH ET AL., *supra* note 14, at 106.

¹⁷ *Myriad*, 133 S. Ct. at 2112–13.

¹⁸ *Id.*

mutations) that attenuate the ability of the encoded protein to prevent cancer, thus rendering an individual possessing these variations in her BRCA genes more susceptible to certain forms of cancer.¹⁹ BRCA testing is normally conducted by a clinical laboratory, and involves amplifying portions of the patient's DNA by methodologies such as polymerase chain reaction ("PCR").²⁰ The synthetic copies of the genomic DNA molecules resulting from amplification are then analyzed for the presence of genetic variations associated with an altered susceptibility to cancer.²¹

There are also other types of DNA-based diagnostic tests that look for biomarkers other than genetic sequence variations. For example, many diagnostic tests are based on the level at which a gene (or genes) is (are) expressed in an individual.²² A gene, as it exists in the human genome, is the functional analog of a blueprint, and "expression" refers to processes by which the gene is essentially "turned on," such that the blueprint is actually used as a template for the production of a biologically significant product, typically a protein encoded by that gene.²³ Expression of a gene involves the production of messenger RNA ("mRNA") copies of the gene, which then serve as the intermediary between the gene and protein expression.²⁴ The extent to which a gene is active and "turned on" in a patient can be measured by how many mRNA

¹⁹ *Id.*

²⁰ Robert Cook-Deegan et al., *Impact of Gene Patents and Licensing Practices on Access to Genetic Testing for Inherited Susceptibility to Cancer: Comparing Breast and Ovarian Cancers with Colon Cancers*, 12 *GENETICS IN MED.* 15, S16 (2010).

²¹ *Id.*

²² *Information That Can Help Define Treatment Options and Make Treatment Decisions for Breast (early-stage and DCIS), Colon and Prostate Cancer Patients*, GENOMIC HEALTH, <http://www.genomichealth.com/en-US/OncotypeDX.aspx> (last visited Apr. 4, 2014) (describing a commercially available test); Laura Hoopers, *Genetic Diagnosis: DNA Microarrays and Cancer*, *NATURE* (2008), <http://www.nature.com/scitable/topicpage/genetic-diagnosis-dna-microarrays-and-cancer-1017>.

²³ Andrew W. Torrance, *Gene Concepts, Gene Talk, and Gene Patents*, 11 *MINN. J.L. SCI. & TECH.* 157, 170–72 (2010).

²⁴ *Id.* at 172.

copies of the gene are present in the cells.²⁵ Many diagnostic tests have been developed which correlate some medically significant phenotype with the level of expression of certain genes, as determined by measuring mRNA levels of the genes, typically using a cDNA microarray²⁶ or “gene chip.”²⁷ In many cases it is easier to work with a synthetic DNA copy of mRNA, known as complementary DNA (“cDNA”), which is a form of DNA that garnered much of the Supreme Court’s attention in *Myriad*.²⁸

Molecular diagnostics are not limited to DNA-based tests, because the biomarker could be any other physiologically relevant biomolecule, such as a protein, lipid, carbohydrate, or small-molecule hormone.²⁹ In the first of the five recent patent eligibility grants of certiorari, *LabCorp v. Metabolite*,³⁰ the biomarker was a hormone, and the test was based on the discovery of a correlation between levels of that hormone and a vitamin deficiency in the patient.³¹ In *Mayo*, the biomarker was a drug metabolite, i.e., the physiological breakdown product of a drug in a patient’s blood, and the claimed diagnostic test was based on the discovery of a correlation between the level of biomarker in a patient’s blood and optimal dosage of the drug.³² Although *Mayo* did not involve a genetic diagnostic test, its holding is clearly relevant to molecular diagnostic tests in general, as borne out by the role it played in the

²⁵ Martin Bengtsson et al., *Gene Expression Profiling in Single Cells from the Pancreatic Islets of Langerhans Reveals Lognormal Distribution of mRNA Levels*, 15 GENOME RES. 1388, 1388 (2005).

²⁶ Kai Wang et al., *Monitoring Gene Expression Profile Changes in Ovarian Carcinomas Using cDNA Microarray*, 229 GENE 101, 101–08 (1999).

²⁷ Chris Zanazzi et al., *Gene Expression Profiling and Gene Copy-Number Changes in Malignant Mesothelioma Cell Lines*, 46 GENES, CHROMOSOME & CANCER 895, 900 (2007).

²⁸ Axel Wellmann et al., *Detection of Differentially Expressed Genes in Lymphomas Using cDNA arrays: Identification of Clusterin as a New Diagnostic Marker for Anaplastic Large-cell Lymphomas*, 96 BLOOD 398, 403 (2000).

²⁹ Anupam Talapatra et al., *Protein Microarrays: Challenges and Promises*, 3(4) PHARMACOGENOMICS 527, 527–32 (2002).

³⁰ *Lab Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124 (2006).

³¹ *Id.* at 125.

³² *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, 132 S. Ct. 1289, 1295 (2012).

invalidation of genetic diagnostic testing claims at issue in *Ariosa Diagnostics v. Sequenom*.³³

Diagnostic tests are important for a number of reasons, particularly as tools for enabling patients and their healthcare providers to make more informed medical decisions. For an extreme example of this, we need look no further than the well-publicized decision of Angelina Jolie to undergo double mastectomy based on the results of a BRCA test showing genetic variations associated with a high likelihood of developing breast cancer.³⁴ The tests at issue in *LabCorp*, used to detect vitamin deficiencies, might provide a patient with information that would lead the patient to begin taking vitamin supplements. A genetic test that shows an individual has a heightened likelihood of developing heart disease might lead that individual to stop smoking cigarettes and start exercising more.

B. *Personalized Medicine*

Historically, molecular diagnostic testing has played a relatively minor role in healthcare, but the landscape around diagnostics seems to be changing.³⁵ One particularly significant development in this regard is personalized medicine. Personalized medicine represents a pairing of molecular diagnostics and medical intervention, particularly by means of pharmaceutical therapy.³⁶ Using diagnostic testing, it is becoming increasingly possible to identify a specific drug and treatment regimen for a patient based on that individual patient's own physiological requirements. One example is the use of genetic testing to identify that subset of breast cancer patients who will be amenable to treatment by the biotechnology drug Herceptin. It turns out that Herceptin is highly

³³ No. C 11-06391 SI, 2013 WL 5863022, at *6–11 (N.D. Cal. Oct. 30, 2013); see *infra* Part VII.

³⁴ Angelina Jolie, *My Medical Choice*, N.Y. TIMES (May 14, 2013), available at http://www.nytimes.com/2013/05/14/opinion/my-medical-choice.html?_r=0.

³⁵ George Poste, *Molecular Diagnostics: A Powerful New Component of the Healthcare Value Chain*, 1 EXPERT REV. MOLECULAR DIAGNOSTICS 1, 1 (2001).

³⁶ *Personalized Medicine Today & Tomorrow*, INNOVATION.ORG, http://www.ageofpersonalizedmedicine.org/personalized_medicine/ (last visited Mar. 31, 2014).

effective for some breast cancer patients, but largely ineffective for others, and diagnostic testing plays a critical clinical role in distinguishing between the two.³⁷ The claims at issue in *Mayo* provide another example of personalized medicine, by providing a molecular diagnostic test that informs healthcare providers as to the appropriate dosage of drug for an individual patient.

III. *MYRIAD* WILL LIKELY HAVE A RELATIVELY MINOR IMPACT ON THE PATENTING OF DIAGNOSTICS

Ironically, while the plaintiff's purported motivation in suing *Myriad* was to provide freedom to operate for laboratories engaged in BRCA genetic testing,³⁸ it seems doubtful that the decision will have a major impact on the patenting of innovative genetic tests. Although the PTO recently issued guidance for patent examiners in applying *Myriad* and *Mayo*,³⁹ it is important to bear in mind that it is ultimately up to the courts, not the PTO, to interpret patent law. For example, the PTO issued guidance finding isolated DNA molecules to be patent eligible,⁴⁰ and the Court in *Myriad* showed little if any deference in overruling the PTO's interpretation of the law.⁴¹ As of yet, the courts have not had occasion to apply *Myriad* to DNA product claims, and patent attorneys and biotechnology firms are unsure how broadly the decision will be interpreted. In any event, the impact of *Myriad* will largely be limited to isolated DNA claims that will, in the author's view, not be particularly important for the patenting of new diagnostics. Part of the problem with *Myriad* is that the case was brought as a declaratory judgment action, and the patent owner had never alleged that any of the claims before the Supreme Court were infringed by any form of

³⁷ *What is Personalized Medicine?*, INNOVATION.ORG, http://www.ageofpersonalizedmedicine.org/what_is_personalized_medicine/ (last visited Mar. 31, 2014).

³⁸ *Ass'n of Molecular Biology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2114 (2013).

³⁹ U.S. PATENT & TRADEMARK OFFICE, 2014 PROCEDURE FOR SUBJECT MATTER ELIGIBILITY ANALYSIS OF CLAIMS RECITING OR INVOLVING LAWS OF NATURE/NATURAL PRINCIPLES, NATURAL PHENOMENA, AND/OR NATURAL PRODUCTS, available at <http://www.uspto.gov/patents/law/exam/memoranda.jsp>.

⁴⁰ See U.S. Patent & Trademark Office, Utility Examination Guidelines, 66 Fed. Reg. 1092 (2001).

⁴¹ *Myriad*, 133 S. Ct. at 2115, 2118–19.

genetic testing.⁴² There was no specific product or service alleged to infringe the claims, and perhaps for that reason the district court felt it was unnecessary to hold a *Markman* hearing or to engage in a thorough construction of the claims.⁴³

A. *Native-Source DNA vs. Synthetic DNA*

In particular, the claims at issue in *Myriad* recite “isolated” DNA, and prior to *Myriad* “isolation” had always been understood to play a critical role in distinguishing between patent ineligible naturally occurring DNA and patent eligible isolated DNA.⁴⁴ The Supreme Court ultimately declared “isolated genomic DNA” patent ineligible, but without ever adequately addressing the meaning of the critical term “isolated.” Most significantly, the Supreme Court never clarified whether its holding that isolated genomic DNA is patent ineligible was limited to native source DNA (i.e., DNA that originated in, and has been extracted from, a natural source, such as a naturally occurring human cell), or whether the Court also considered synthetic DNA having the same sequence of nucleotides as a segment of naturally occurring genomic DNA to be patent ineligible. The distinction is of crucial importance, because all conventional forms of genetic testing involve the use of synthetic copies of genomic DNA.⁴⁵ For that matter, essentially any practical application of genomic DNA sequences involves the use of synthetic copies of genomic DNA, including the vast majority of molecular biology research.⁴⁶ If the holding in *Myriad* is limited to native source DNA the decision should have virtually no impact on genetic testing. Ironically, any impact *Myriad* might have will likely be limited to non-DNA biomolecules, which are much more likely to be purified from a

⁴² *Id.* at 2114.

⁴³ See *Markman Hearing*, WIKIPEDIA, http://en.wikipedia.org/wiki/Markman_hearing (last visited Mar. 31, 2014).

⁴⁴ U.S. PATENT & TRADEMARK OFFICE, *supra* note 39.

⁴⁵ Brief for Law Professor Christopher M. Holman as Amicus Curiae Supporting Neither Party, *Myriad*, 133 S. Ct. 2107 (2013) (No. 2010-1406), 2012 WL 2884112.

⁴⁶ *Id.*

native source in usable quantities than DNA, because unlike DNA these molecules cannot be amplified.⁴⁷

In large part, the reason DNA biomarkers make such useful and important targets for molecular diagnostic testing is that DNA is uniquely amenable to amplification, which can be used to create an unlimited number of synthetic copies retaining the nucleotide sequence of a native source DNA molecule.⁴⁸ To illustrate, consider the fact that changes to the BRCA protein are the direct cause of increased risk of cancer, but that we detect these variations indirectly by detecting variations in the DNA that codes for the protein, not directly in a patient's BRCA protein. The reason is that protein does not serve as a template for the production of synthetic copies, and as a result it would be quite difficult, if not impossible, to isolate sufficient protein to analyze for variations. Clearly Myriad's patents would not cover direct testing of BRCA proteins, so plaintiffs' allegations that Myriad's patents provide complete coverage of BRCA testing implies that they considered direct testing of the protein an inadequate substitute for DNA-based testing.

Even when a fragment of genomic DNA (such as a BRCA gene, in whole or in part) is "isolated" for the first time, what is normally "isolated" is not DNA that originated in a naturally occurring human genome, but instead is synthetic DNA produced in a laboratory with the same DNA sequence as native-origin DNA. To better convey this point, it might be useful to provide a brief overview of the methodology typically involved in "isolating" a fragment of genomic DNA for the first time. The process begins with the extraction of naturally occurring chromosomal DNA from a sample of human cells, and then cleaving these long chromosomal DNA strands into shorter

⁴⁷ See *infra* notes 78–85 and accompanying text.

⁴⁸ See *Structural Biochemistry/DNA Amplification Technique: Polymerase Chain Reaction (PCR)*, WIKIBOOKS, [http://en.wikibooks.org/wiki/Structural_Biochemistry/DNA_Amplification_Technique:Polymerase_Chain_Reaction_\(PCR\)](http://en.wikibooks.org/wiki/Structural_Biochemistry/DNA_Amplification_Technique:Polymerase_Chain_Reaction_(PCR)) (last visited Mar. 31, 2014).

fragments.⁴⁹ These fragments of naturally occurring DNA are then inserted into DNA vectors capable of replication in a host cell.⁵⁰ The vectors containing the genomic DNA fragments are subsequently introduced into cells, typically bacterial or yeast, which can be grown in culture.⁵¹ Significantly, these genetically modified cells are not naturally occurring, and like the genetically modified cells at issue in *Diamond v. Chakrabarty*,⁵² they are not products of nature. As these synthetic cells divide and replicate in culture, the genetically modified recombinant vectors also replicate, which results in amplification of the genomic DNA sequence residing in the vector.⁵³ Because the recombinant cell is clearly “made by man” and not a product of nature under *Chakrabarty*, copies of genomic DNA produced by replication of the vectors are also not products of nature, but rather synthetic molecules.

The resulting collection of recombinant cells, which comprises cells containing vectors that harbor synthetic copies of genomic DNA, is referred to as a “genomic DNA library.”⁵⁴ The cells comprising the library contain DNA that retains the primary sequence of genomic DNA, but the DNA molecules themselves did not originate in the human chromosome, but instead were synthesized as copies outside the body. Single cells can be isolated from this mixture, and used to create a culture of cells which all comprise the same fragment of genomic DNA.⁵⁵ To isolate a gene of interest, a biologist screens the library to identify and isolate a pure cell culture that comprises a DNA fragment that includes that gene.⁵⁶

⁴⁹ See generally JOHN J. SAMBROOK ET AL., *MOLECULAR CLONING: A LABORATORY MANUAL*, Ch. 9 (Cold Spring Harbor Laboratory Press, 2nd ed. 1989).

⁵⁰ *Id.*

⁵¹ *Id.*

⁵² 447 U.S. 303 (1980).

⁵³ SAMBROOK ET AL., *supra* note 49.

⁵⁴ *Id.*

⁵⁵ *Id.*

⁵⁶ *Id.*

Once the DNA sequence of a gene has been determined, there is generally little reason to go back and repeat this process, because the sequence information of the DNA can be used to synthesize further copies by more convenient means. For example, as described in a brief the author submitted in the first iteration of this case, conventional BRCA genetic testing involves using techniques such as PCR to amplify DNA molecules representing fragments of a patient's full-length BRCA gene.⁵⁷ Furthermore, once the sequence of a gene has been determined, the technology is available to easily synthesize a DNA molecule corresponding in sequence to the full-length gene.⁵⁸

To give a specific example, the Myriad patents describing the initial "isolation" of the BRCA genes makes clear that what was isolated was actually synthetic DNA having the same sequence of nucleotides as native DNA, not native-origin genomic DNA. U.S. Patent Number 5,747,282 ("the '282 patent"), for example, describes how the inventors "isolated" the BRCA1 gene from synthetic, cloned DNA.⁵⁹ The '282 patent does not describe isolating DNA by extracting it directly from native human chromosome and to do so would make little sense, because that is simply not how DNA was, or is, isolated. It is true that the process of initially isolating the BRCA genes began with the extraction of native chromosomal DNA from human cells, and cleavage of that native DNA into fragments. But these are merely intermediate steps in the preparation of the synthetic genomic DNA library and it is this synthetic library from which the genes were actually isolated.

⁵⁷ See Brief for Christopher M. Holman & Robert Cook-Deegan as Amici Curiae Supporting Neither Party at *16, *Ass'n for Molecular Biology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013) (No. 2010-1406), 2010 WL 4853323; see also Robert Cook-Deegan et al., *supra* note 20, at S16.

⁵⁸ *Home—Gene Design and Synthesis & Bioengineering—DNA 2.0*, DNA TWOPOINTO, INC., <http://www.dna20.com> (last visited Mar. 31, 2014).

⁵⁹ U.S. Patent No. 5,747,282 col. 7, l. 52 – col. 8, l. 5 (filed June 7, 1995) (describing how the inventors "isolated" the BRCA1 gene from cloned DNA residing in yeast artificial chromosomes ("YACs"), bacterial artificial chromosomes ("BACs"), P1 and cosmid clones (i.e., genomic DNA libraries), and explaining that P1 clones were "isolated" using PCR primers).

If *Myriad*'s holding is limited to DNA that has literally been isolated from a natural source, thereby effectively maintaining the status quo with respect to synthetic copies of genomic DNA, i.e., they are patent eligible, *Myriad* should have little if any impact on genetic testing or biotechnology in general.⁶⁰ And although the Supreme Court does not directly address this critical question, there is reason to believe that this is the proper interpretation of the decision. While neither the Supreme Court nor the Federal Circuit explicitly defined the term "isolate," the district court defined isolated DNA as "a segment of DNA nucleotides existing separate from other cellular components normally associated with native DNA, including proteins and other DNA sequences comprising the remainder of the genome, and *includes both DNA originating from a cell* as well as DNA synthesized through chemical or heterologous biological means."⁶¹ The district court's construction of the term was dictated largely by language in *Myriad*'s patent specification that expressly defined "isolated DNA" as a DNA molecule "which is substantially separated from other cellular components which naturally accompany a native human sequence [such as] human genome sequences and proteins' and 'includes recombinant or cloned DNA isolates and chemically synthesized analogs or analogs biologically synthesized by heterologous systems.'"⁶² The most plausible interpretation of these definitions would seem to encompass naturally occurring DNA that originated

⁶⁰ This is not the interpretation of recent PTO Guidance cited above, but as stated, the courts will have the final word in interpreting *Myriad*, not the PTO.

⁶¹ *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office*, 702 F. Supp. 2d 181, 217 (S.D.N.Y. 2010) *aff'd in part, rev'd in part*, 653 F.3d 1329 (Fed. Cir. 2011) *cert. granted, judgment vacated sub nom.* *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 132 S. Ct. 1794 (2012) and *opinion vacated, appeal reinstated*, 467 F. App'x 890 (Fed. Cir. 2012) and *aff'd in part, rev'd in part*, 689 F.3d 1303 (Fed. Cir. 2012) *aff'd in part, rev'd in part sub nom. Myriad*, 133 S. Ct. 2107 (2013) (emphasis added).

⁶² *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office*, 702 F. Supp. 2d 181, 216–17 (S.D.N.Y. 2010) *aff'd in part, rev'd in part*, 653 F.3d 1329 (Fed. Cir. 2011) *cert. granted, judgment vacated sub nom.* *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 132 S. Ct. 1794 (2012) and *opinion vacated, appeal reinstated*, 467 F. App'x 890 (Fed. Cir. 2012) and *aff'd in part, rev'd in part*, 689 F.3d 1303 (Fed. Cir. 2012) *aff'd in part, rev'd in part sub nom. Myriad*, 133 S. Ct. 2107 (2013) (citing patent).

in the genome of a naturally occurring human cell, and which has been “isolated” in the sense of “purified” from other components of a cell.

Neither the Supreme Court nor the Federal Circuit directly address this issue, and this author suspects that the judges and Justices are not sufficiently familiar with molecular biology to recognize the ambiguity, compounded by the manner in which the issue was obfuscated by the parties and amici, as illustrated by the U.S. government’s characterization of isolated DNA.⁶³ But statements made by the Federal Circuit and Supreme Court suggest that in deciding on the patent eligibility of isolated genomic DNA the judges were focusing on native-source genomic DNA, rather than synthetic copies of genomic DNA.⁶⁴ Writing for the Federal Circuit majority, Judge Lourie stated that the term “isolated DNA” refers to two types of DNA: (1) DNA that “has been cleaved (i.e., had covalent bonds in its backbone chemically severed)” from a “larger, natural DNA molecule;” and (2) DNA that has been “synthesized to consist of just a fraction of a naturally occurring DNA molecule.”⁶⁵ Judge Moore’s concurring opinion similarly referred to “the chemical differences between [naturally occurring] and isolated DNA (breaking the covalent bonds).”⁶⁶

Significantly, although the district court and Federal Circuit interpretations of “isolated DNA” appear to encompass both native-origin and synthetic genomic DNA, the Supreme Court appears to be only ruling on the patent eligibility of native-origin genomic DNA. The Supreme Court never addresses or acknowledges the existence of synthetic genomic DNA, but rather focuses on its conclusion that Myriad’s claims “would, if valid, give it the exclusive right to isolate an individual’s BRCA1 and BRCA2 genes (or any strand of 15 or more nucleotides within the genes) by breaking the covalent bonds that connect the DNA to the

⁶³ Brief for the United States as Amicus Curiae Supporting Neither Party, *Myriad*, 133 S. Ct. 2107 (2013) (No. 12-398), 2013 WL 390999.

⁶⁴ See *supra* notes 60 and 62.

⁶⁵ *Ass’n for Molecular Pathology v. U.S. Patent & Trademark Office*, 689 F.3d 1329, 1351 (Fed. Cir. 2012) *cert. granted in part*, 133 S. Ct. 694 (2012) and *aff’d in part, rev’d in part sub nom. Myriad*, 133 S. Ct. 2107 (2013).

⁶⁶ *Myriad*, 133 S. Ct. at 2115.

rest of the individual's genome."⁶⁷ The Court defined the "act of *isolating* DNA [as] separating a specific gene or sequence of nucleotides from the rest of the chromosome."⁶⁸ Consistent with the lower court decisions, the Supreme Court characterizes the claimed isolated molecules as DNA molecules that have been "isolated" from the human genome by "sever[ing] chemical bonds and "separating that gene from its surrounding genetic materials."⁶⁹

Although *Myriad* explicitly holds that synthetic cDNA is patent eligible,⁷⁰ it is silent on the patent eligibility of synthetic DNA in general; and particularly with respect to synthetic genomic DNA. A patent claim that encompasses both patent eligible and patent ineligible subject matter is invalid, so a determination of invalidity naturally flows from the Court's determination that (1) the invalidated claims encompass native genomic DNA and (2) that native genomic DNA is patent ineligible. But this in no way implies that all isolated DNA encompassed by the invalidated claims is patent ineligible. For example, the Supreme Court explicitly upheld the validity of Claim 2 of U.S. Patent Number 5,747,282, directed towards cDNA, and because Claim 2 is dependent upon patent ineligible Claim 1, then Claim 1 by definition must encompass patent eligible subject matter, e.g., the cDNA of claim 2.⁷¹ *Myriad* does not explicitly address the question of whether synthetic genomic DNA is patent eligible, but it certainly appears to leave the door open.

In fact, *Myriad* suggests that synthetic genomic DNA, and synthetic DNA in general, should by and large be treated as patent eligible subject matter.⁷² The Court repeatedly emphasizes that the patent eligible cDNA claims are limited to "synthetic DNA created in the laboratory" rather than native DNA cleaved from a naturally occurring molecule.⁷³ Justice Scalia's concurrence also seems to hinge upon his understanding that cDNA "is a synthetic

⁶⁷ *Id.* at 2113.

⁶⁸ *Id.* at 2114–15.

⁶⁹ *Id.* at 2117–18.

⁷⁰ *Id.* at 2119.

⁷¹ 35 U.S.C. § 112(d) (2013).

⁷² *See supra*, notes 68–70.

⁷³ *Myriad*, 133 S. Ct. at 2112.

creation.”⁷⁴ The Court points out that one distinction between cDNA and the genomic DNA is that while “the natural creation of mRNA involves splicing that removes introns, the synthetic [cDNA] created from mRNA also contains only the exon sequences.”⁷⁵ Significantly, however, the mRNA molecules which are the template for the production cDNA are naturally occurring molecules in their own right, no less than genomic DNA, and the introns are removed from mRNA by natural processes in the cell, not in a synthetic laboratory process.⁷⁶ The nucleotide sequence of cDNA, in other words, is identical to its naturally occurring mRNA cognate.⁷⁷ To better understand how fundamentally similar synthetic cDNA and synthetic genomic DNA are, it is useful to understand what cDNA is and how it is prepared.

As explained in an amicus brief filed with the Federal Circuit filed on behalf of the author, the methodology for producing cDNA is entirely analogous to the methodology for isolating genomic DNA.⁷⁸ As a first step, mRNA is extracted from human cells.⁷⁹ This collection of mRNA molecules will comprise many different sequences, generally representing all of the proteins that are being expressed by the cells.⁸⁰ The extracted mRNA is analogous to the extracted genomic DNA described above. mRNA is structurally very similar to DNA, and contains the sequence information of the gene.⁸¹ However, mRNA is a single-stranded molecule that cannot self-replicate like DNA and is less chemically stable.⁸² To address these issues, scientists use the extracted mRNA molecules as templates to synthesize double-stranded cDNA molecules retaining the sequence information of mRNA, but which are more stable and can serve as a template for their own

⁷⁴ *Id.* at 2120.

⁷⁵ *Id.* at 2112.

⁷⁶ SAMBROOK ET AL., *supra* note 49, Ch. 8.

⁷⁷ *Myriad*, 133 S. Ct. at 2112.

⁷⁸ Brief of Amicus Curiae Law Professor Christopher M. Holman, *supra* note 45.

⁷⁹ *Myriad*, 133 S. Ct. at 2112.

⁸⁰ *Id.*

⁸¹ *See generally* BRUCE ALBERTS ET AL., *MOLECULAR BIOLOGY OF THE CELL* (Garland Science 4th ed. 2002).

⁸² *See supra* note 78.

replication.⁸³ These double-stranded cDNA molecules are inserted into vectors which are then introduced into cells, resulting in a cDNA library entirely analogous to a genomic DNA library as described above.⁸⁴ This library can be screened to isolate a cDNA corresponding to a gene of interest, e.g., a cDNA encoding a BRCA protein.⁸⁵

Significantly, the resulting isolated cDNA is entirely analogous to the claimed isolated genomic DNA. In both cases the DNA did not actually originate in the cell, but it retains the informational content of a native polynucleotide sequence. Specifically, cDNA retains the mRNA nucleotide sequence, while the isolated genomic DNA retains the nucleotide sequence of genomic DNA.

In an amicus brief filed with the Federal Circuit, the United States argued that cDNAs are synthetic molecules “engineered” by scientists to exclude introns and other regulatory regions, but in fact, a cDNA is nothing more than a rote copy of a naturally occurring mRNA molecule.⁸⁶ The “engineer[ing]” to exclude introns and other regulatory regions is accomplished entirely within the cell, by natural processes, in the cellular production of mRNA, without any human intervention.⁸⁷

In her concurring opinion, Judge Moore stated that Claim 2 of the ‘282 patent can be distinguished from Claim 1 in that it is limited to a cDNA molecule (1) having “a completely different nucleotide sequence than the RNA” upon which it is based, and (2) because “DNA has a different chemical structure than RNA, including a different base (T instead of U, respectively) and sugar units (deoxyribose instead of ribose, respectively).”⁸⁸ The first purported distinction is based on a fundamental misunderstanding of the nature of cDNA, perhaps attributable to the inadequate claim

⁸³ *Id.*

⁸⁴ SAMBROOK ET AL., *supra* note 49, at Ch. 8.

⁸⁵ *Id.*

⁸⁶ Brief for the United States, *supra* note 63, at *15.

⁸⁷ Suzanne Clancy, *RNA Splicing: Introns, Exons and Spliceosome*, SCITABLE (2008), <http://www.nature.com/scitable/topicpage/rna-splicing-introns-exons-and-spliceosome-12375>.

⁸⁸ U.S. Patent and Trademark Office v. Myriad Genetics, Inc., 653 F.3d 1329, 1364 (2011).

construction that occurred at the district court. Isolated cDNA is generally a double-stranded molecule, a first strand that is complementary to the RNA in which it is based, and a second strand having the identical sequence.⁸⁹ The '282 patent clearly states that SEQ ID NO: 1 is the coding sequence for the protein, i.e., is the same sequence as the mRNA.⁹⁰

Regarding Judge Moore's second contention, it is true that mRNA bears small chemical differences relative to DNA, but these changes are of the same order as the difference between methylated genomic DNA and its isolated counterpart discussed above. The difference between deoxyribose and ribose is a single oxygen atom; the difference between T and U (thymine and uracil) is a methyl group attached to the ring at the 5 position.⁹¹ This is essentially the same structural modification that occurs in the methylation of genomic DNA, i.e., methylation at the 5 position in the cytosine ring. The structural differences between RNA and DNA are functionally significant, as reflected in the increased stability of cDNA relative to RNA, but methylation of native genomic DNA also performs an important functional role in mediating epigenetic regulation of gene expression.⁹²

Significantly, synthetic copies of genomic DNA have distinct functional and structural characteristics that distinguish the copies from native genomic DNA molecules. It is important to understand that the information content of genomic DNA extends beyond the primary sequence of nucleotides, i.e., the order in which G, A, T, and C appear.⁹³ There are other structural modifications of genomic DNA, referred to as epigenetics, which play an important role in regulating gene expression in the native chromosome.⁹⁴ For

⁸⁹ *Id.* at 1339.

⁹⁰ *Id.* at 1334.

⁹¹ *Structural Biochemistry/Nucleic Acid/Nitrogenous Bases/Pyrimidines/Thymine*, WIKIBOOKS, http://en.wikibooks.org/wiki/Structural_Biochemistry/Nucleic_Acid/Nitrogenous_Bases/Pyrimidines/Thymine (last updated Oct. 30, 2011). Thymine is another name for 5-methyluracil. *Id.*

⁹² *Epigenetics*, WIKIPEDIA, <http://en.wikipedia.org/wiki/Epigenetics> (last updated Mar. 31, 2014).

⁹³ *Id.*

⁹⁴ *Id.*

example, one of the most common epigenetic modifications of human genomic DNA is methylation, a structural modification of certain cytosine bases that occurs at millions of locations throughout the native human genome.⁹⁵ The methylation pattern of genomic DNA plays a critical role in regulating gene expression that not only varies from individual to individual, but also varies from cell to cell in an individual and changes over time. Significantly, the methylation pattern of human genomic DNA is lost when it is amplified in a host cell (e.g., a DNA library) or by laboratory techniques such as PCR.⁹⁶ Thus, the methylation of genomic DNA, along with other epigenetic modifications, is not retained in the isolated DNA.⁹⁷ In short, synthetic isolated DNA not only does not originate from a native source, it is structurally different in a way that significantly affects function.

B. *Full-Length Coding Sequences vs. DNA Fragments*

Even if *Myriad* is interpreted in a manner that renders patent ineligible synthetic copies of genomic DNA, the vast majority of so-called “gene patents” do not include any isolated DNA claim that would be infringed by conventional genetic testing methods.⁹⁸ This is because most isolated DNA claims appear to only cover full-length coding sequences that encode a full-length protein.⁹⁹ Full-length coding sequences can be important in some applications, particularly when the objective is the recombinant production of the encoded protein.¹⁰⁰ These full-length sequences are used to make protein drugs, such as recombinant erythropoietin, or to make recombinant proteins for drug discovery research, which was the subject matter of one of the *Myriad* method claims that was challenged by the plaintiffs but was not at

⁹⁵ Yingying Zhang & Albert Jeltsch, *The Application of Next Generation Sequencing in DNA Methylation Analysis*, 1 GENES 85, 86 (2010).

⁹⁶ *Id.* at 87.

⁹⁷ *Id.*

⁹⁸ Christopher M. Holman, *Will Gene Patents Derail the Next-Generation of Genetic Technologies?: A Reassessment of the Evidence Suggests Not*, 80 UMKC L. REV. 563, 585 (2012).

⁹⁹ *Id.*

¹⁰⁰ *Id.*

issue before the Supreme Court.¹⁰¹ The use of these full-length sequences in drug development and production likely explains why the U.S. government argued for patent eligibility of cDNA, which is typically the form of the DNA used for recombinant protein production.¹⁰² Significantly, however, conventional BRCA mutation testing as it is currently practiced, which involves the amplification and sequencing of relatively short fragments of the full-length gene sequence, would not infringe claims limited to the full-length gene sequence.¹⁰³

Although most of Myriad's isolated DNA claims are limited to full-length coding sequences, Myriad also has a claim that recites shorter DNA fragments of full-length genes.¹⁰⁴ For example, Claim 5 of the '282 patent recites any "isolated DNA having at least 15 nucleotides of the [full length BRCA-encoding DNA sequence]."¹⁰⁵ This claim, on its face, purports to provide much broader coverage than the full-length claims, and arguably encompasses conventional BRCA mutation testing that involves the amplification and analysis of DNA fragments as used in diagnostic testing. If the claim is interpreted this broadly, however, it would raise significant validity issues other than patent eligibility, particularly under Sections 102, 103, and 112 of the patent statute.¹⁰⁶

For example, a recent study found that 80 percent of the cDNA and mRNA sequences that were contributed to GenBank (and hence presumably published) before the effective filing date of the '282 patent contain at least one DNA fragment falling within the scope of Claim 5, and thus would apparently be encompassed by

¹⁰¹ U.S. Patent No. 5,747,282 col. 153 (filed June 7, 1995).

¹⁰² See *infra* Part IV.

¹⁰³ See Brief for Christopher M. Holman & Robert Cook-Deegan, *supra* note 57; Robert Cook-Deegan et al., *Impact of Gene Patents and Licensing Practices on Access to Genetic Testing for Inherited Susceptibility to Cancer: Comparing Breast and Ovarian Cancers with Colon Cancers*, 12 GENETICS MED. S15 (2010).

¹⁰⁴ *Ass'n of Molecular Biology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2113 (2013).

¹⁰⁵ *Id.*

¹⁰⁶ Brief for Christopher M. Holman & Robert Cook-Deegan, *supra* note 57, at *4.

the claim.¹⁰⁷ Follow-up studies have shown many “hits” of 15-mer sequences in GenBank sequences that had already been deposited more than a year before patent application, thus implicating 35 U.S.C. § 102(b).¹⁰⁸ Thus, it appears that either this claim (and by inference other claims directed to fragments of BRCA genes) is invalid because it is not novel, or courts would have to interpret the claim in a narrower sense than suggested by a plain reading of the claim’s language. More generally, enablement and written description are the doctrinal tools conventionally deployed to challenge overly broad patent claims, not patent eligibility.¹⁰⁹

Given the substantial questions regarding whether a court would find fragment claims, such as Claim 5, valid and infringed by conventional genetic diagnostic testing practices, it seems unlikely that *Myriad* has really had much impact. The primary motivation for obtaining DNA claims of this sort is to provide protection against unauthorized use of the gene in the production of recombinant protein, not diagnostic testing for genetic variations in humans.¹¹⁰ As a result, there has never been a case in which the issue of whether a diagnostic testing product or service infringes a claim directed towards isolated human DNA, and in the absence of case law it is difficult to know how a court would rule if actually presented with such an issue. Significantly, extensive research by the author has revealed that the majority of human gene patents do not include short DNA fragment claims of this type, but instead

¹⁰⁷ Thomas B. Kepler, Colin Crossman & Robert Cook-Deegan, *Metastasizing Patent Claims on BRCA1*, 95 GENOMICS 312, 312 (2010) (assuming implicitly that entry in GenBank results in publication).

¹⁰⁸ Thomas B. Kepler, *Notes on the Bioinformatics of Gene Patents*, DUKE U. LIBRS., available at <http://dukespace.lib.duke.edu/dspace/handle/10161/7775>.

¹⁰⁹ *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1203 (Fed. Cir. 1991) (invalidating overly broad gene patent claim invalidated for lack of enablement); *Regents of the Univ. of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1562 (Fed. Cir. 1997) (invalidating overly broad gene patent claim for lack of adequate written description).

¹¹⁰ This is presumably the main reason these claims exist in the patents. At the time of the invention, BRCA was seen not only as a target for genetic diagnostic testing, but also as a target for drug discovery, which would involve using the full-length gene to produce recombinant protein for use in processes such as those described in Claim 20.

only have claims directed towards much longer DNA sequences that generally are not inherently produced in genetic testing.¹¹¹

IV. WHY THE DICHOTOMY BETWEEN ISOLATED GENOMIC DNA AND CDNA?

Given the similarity of cDNA and synthetic genomic DNA, it is difficult to make a case that the two sorts of molecules should be treated differently for purposes of patent eligibility. Nonetheless, the Federal Circuit's Judge Bryson made this distinction and it was adopted as the heart of the Supreme Court's decision.¹¹² The genesis of the disparate treatment appears to have originated, at least in part, from the amicus brief filed by the U.S. government when the Federal Circuit first heard *Myriad*.¹¹³ Although the government's attempt to distinguish the two categories of DNA molecules based on their chemical structure is unconvincing,¹¹⁴ the better explanation for the government's position is that it was attempting to maintain patent incentives for drug discovery while eliminating broad patents in the area of genetic diagnostic testing. As mentioned previously, cDNA is widely used in drug discovery and drug production, and one can suspect that the government used a distinction between cDNA and genomic DNA as a proxy for a distinction between drugs and diagnostic testing, and the Court acquiesced in this policy determination.

In biotechnology, gene patents often serve a function analogous to the role of drug patents in the traditional pharmaceutical industry. For example, most instances of human gene patent infringement litigation have involved an innovator biotechnology company enforcing its patent against a direct competitor in order to maintain market exclusivity for a biologic

¹¹¹ Christopher M. Holman, *Will Gene Patents Derail the Next-Generation of Genetic Technologies?*, *supra* note 98, at 585.

¹¹² *Id.* at 570.

¹¹³ Brief for the United States as Amicus Curiae, *supra* note 63, at *15.

¹¹⁴ Brief of Amicus Curiae Law Professor Christopher M. Holman, *supra* note 45.

drug developed by the patent owner.¹¹⁵ Consistent with this finding, two authoritative reports from the Congressional Office of Technology Assessment, and a 2009 report issued by the Federal Trade Commission, all concluded that gene patents have provided the “fuel” for the “R&D engine” bringing biologic drugs to patients.¹¹⁶

One of the landmark products of biotechnology, for example, is recombinant erythropoietin, a biologic drug first brought to the market in the 1980s by Amgen under the trade name Epogen.¹¹⁷ Recombinant erythropoietin was the product of groundbreaking research conducted by Amgen, and this research required a substantial investment of capital.¹¹⁸ However, erythropoietin is a naturally occurring human protein that was isolated prior to Amgen’s work, and the patent claiming isolated erythropoietin protein per se expired around the time Amgen entered the market with its recombinant product. As a consequence, Amgen has relied primarily on gene patent protection to protect its product.¹¹⁹ For example, when another biotechnology company attempted to bring a competing erythropoietin product to market in the U.S., Amgen successfully sued for infringement of its patent claiming the erythropoietin gene.¹²⁰ It bears noting that Amgen’s core patent

¹¹⁵ Christopher M. Holman, *The Impact of Human Gene Patents on Innovation and Access: A Survey of Human Gene Patent Litigation*, 76 UMKC L. REV. 295, 355 (2007).

¹¹⁶ OFFICE OF TECH. ASSESSMENT, U.S. CONGRESS, COMMERCIAL BIOTECHNOLOGY: AN INTERNATIONAL ANALYSIS, OTA-BA-218 (1984); OFFICE OF TECH. ASSESSMENT, U.S. CONGRESS, BIOTECHNOLOGY IN A GLOBAL ECONOMY, OTA-BA-494 (1991); FED. TRADE COMM., EMERGING HEALTHCARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION (2009). Although the FTC Report does *not* specifically identify “gene patents” as the primary “fuel,” every example cited in the report of a biologic innovator successfully asserting its patent against a competitor involved a gene patent. FED. TRADE COMM., EMERGING HEALTHCARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION 37 (2009).

¹¹⁷ *Amgen, Inc. v. Chugai Pharm. Co.*, 706 F. Supp. 94, 104 (D. Mass. 1989).

¹¹⁸ *Amgen, Inc. v. Chugai Pharm. Co.*, No. 87-2617-Y, 1989 WL 169006, at *7–*18 (Fed. Cir. Dec. 11, 1989).

¹¹⁹ *Id.*

¹²⁰ *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1212–14 (Fed. Cir. 1991).

claim directed toward the gene, which the Federal Circuit held infringed and not invalid in *Amgen v. Chugai*,¹²¹ is almost identical to some of the composition of matter claims invalidated in *Myriad*.¹²²

V. METHOD CLAIMS AND MOLECULAR DIAGNOSTIC TESTING

For reasons discussed earlier, *Myriad* appears unlikely to have much impact on patents in the genetic diagnostic testing and personalized medicine space, to a large extent because most claims directed to isolated genomic DNA molecules are not likely to be infringed by conventional genetic testing.¹²³ Significantly, the publication of the human genome sequence around the turn of the century appears to have rendered patent claims directed towards isolated human DNA largely unavailable for the protection of human diagnostic discoveries, regardless of the patent eligibility of isolated DNA.¹²⁴ But there remains a critical need for investment in the discovery and commercialization of medically significant correlations between biomarkers and medically significant indications.¹²⁵ The availability of methods claims for diagnostics will play a critical role in this regard—without it, incentives for investment in molecular diagnostics and personalized medicine could be severely impacted.

Prior to *Mayo*, the Federal Circuit appeared to have adopted a position such that a method claim reciting nothing more than a step of identifying a biomarker correlated with a clinically significant phenotype is patent ineligible.¹²⁶ However, the inclusion of

¹²¹ *Id.* at 1203.

¹²² Compare Amgen's U.S. Patent No. 4,703,008 Claim 2 (filed Nov. 30, 1984) ("A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin.") with Myriad's U.S. Patent No. 5,747,282 Claims 1 and 2 (filed June 7, 1995).

¹²³ See *supra* Part III.

¹²⁴ Amicus Curiae Supporting Respondent at *5, *Mayo*, 132 S. Ct. 1289 (2012) (No. 10-1150), 2011 WL 5373694.

¹²⁵ *Id.* at *4; see PERSONALIZED MEDICINE COALITION, THE CASE FOR PERSONALIZED MEDICINE (3d ed. 2011), available at http://www.ageofpersonalizedmedicine.org/objects/pdfs/Case_for_PM_3rd_edition.pdf.

¹²⁶ *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, 628 F.3d 1347 (Fed. Cir. 2010) *rev'd*, *Mayo*, 132 S. Ct. 1289 (2012).

physical, transformative steps such as amplifying and/or analyzing DNA, or using detection of the biomarker as the basis for some treatment such as the administration of a drug to a patient, generally appeared to be sufficient to render the claim patent eligible.¹²⁷ This position was grounded in sound innovation policy, and more particularly in recognition that the availability of effective patent protection plays a critical role in incentivizing investment in the development of new molecular diagnostics and personalized medicine. The *Bilski v. Kappos*¹²⁸ machine-or-transformation test played a critical role in the Federal Circuit's distinction between patent eligible and patent ineligible method claims directed towards a medically significant biomarker correlation.¹²⁹ For example, the use of a machine to detect the biomarker, as occurs when DNA is analyzed, would be sufficient to render the claim patent eligible. Similarly, the transformative laboratory steps involved in analyzing DNA could be enough, as would be the transformative step of administering a drug to a patient.

This approach can be seen in the Federal Circuit's initial decisions in *Myriad* and *Mayo*. In particular, when the Federal Circuit first heard *Myriad* it upheld the validity of the isolated DNA claims but struck down as patent ineligible all of the challenged diagnostic method claims.¹³⁰ The case was decided shortly after the Supreme Court issued its decision in *Bilski*,¹³¹ and the Federal Circuit noted that although *Bilski* had rejected the "machine-or-transformation test as the exclusive test for determining whether an invention is a patent-eligible process," the Court had recognized that the test remains "a useful and important clue."¹³² The Federal Circuit then proceeded to declare all of

¹²⁷ *Id.* at *25.

¹²⁸ 130 S. Ct. 3218 (2010).

¹²⁹ *Mayo*, 628 F.3d at 1349; *see infra* Part V.

¹³⁰ *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office*, 653 F.3d 1329, 1358 (Fed. Cir. 2011), *cert. granted, judgment vacated sub nom. Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 132 S. Ct. 1704 (2012) and *opinion vacated, appeal reinstated*, 467 F. App'x 890 (Fed. Cir. 2012).

¹³¹ *Id.*

¹³² *Id.* at 1355.

Myriad's diagnostic method claims patent ineligible for being directed towards abstract mental processes, and for failure to satisfy the machine-or-transformation test.¹³³

In particular, the court found that all of Myriad's diagnostic method claims were broadly directed towards "comparing" or "analyzing" to gene sequences, which the Federal Circuit characterized as an abstract mental process, without the inclusion of steps adequately incorporating a transformation or machine.¹³⁴ The court pointed to claim 1 of the '001 patent, which recites "a 'method for screening a tumor sample' by 'comparing' a first BRCA1 sequence from a tumor sample and a second BRCA1 sequence from a non-tumor sample, wherein a difference in sequence indicates an alteration in the tumor sample."¹³⁵ Myriad argued that the claims implicitly required transformative steps of extracting DNA from a human sample and sequencing the BRCA DNA molecule. The Federal Circuit, however, found that the claims did not recite any such steps, and the mere comparison or analysis of raw sequence information, in the absence of any physically transformative step, was insufficient for patent eligibility.¹³⁶ The Federal Circuit strongly implied that the method claims would have been found patent eligible if they had explicitly included physically transformative steps of DNA analysis and processing.¹³⁷

In contrast, when the Federal Circuit decided *Mayo*, post-*Bilski*, it found the claims patent eligible based on the inclusion of "administering" and "determining" steps, which the Federal Circuit characterized as transformative.¹³⁸ The court acknowledged that under *Bilski* the machine-or-transformation test is not always dispositive, but as the Supreme Court acknowledged, it remains a useful tool for analyzing patent eligibility, and it was the primary doctrinal tool used by the Federal Circuit in upholding the validity

¹³³ *Id.*

¹³⁴ *Id.*

¹³⁵ *Id.*

¹³⁶ *Id.*

¹³⁷ *Id.*

¹³⁸ *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, 628 F.3d 1347, 1352 (Fed. Cir. 2010), *rev'd sub nom. Mayo*, 132 S. Ct. 1289 (2012).

of the diagnostic method claims at issue in *Mayo*.¹³⁹ The Federal Circuit recognized that the claim included a mental step of recognizing a correlation between metabolite level and optimal drug dosage, and that a claim that simply recited the mental step would be patent ineligible.¹⁴⁰ This would be similar to the method claims found patent ineligible by the Federal Circuit in *Myriad*. The Federal Circuit went on to hold that the inclusion of a mental step in a process does not render it patent ineligible, and that a claim can be rendered patent eligible by the inclusion of a transformative step—in this case, the “administering” and “determining” steps recited in the claims were sufficiently transformative to achieve this result.¹⁴¹

With regard to claims including a step of administering drug to a patient, the Federal Circuit held that “when administering a drug . . . the human body necessarily undergoes a transformation . . . In fact, the transformation that occurs, *viz.*, the effect on the body after metabolizing the artificially administered drugs, is the entire purpose of administering these drugs.”¹⁴² The court held that a recited step of determining the level of drug metabolite in a patient necessarily involves a transformation, and that the inclusion of a determining step, thus, was independently sufficient to render the patent claims patent eligible.¹⁴³ The court observed that:

[D]etermining the levels of [drug metabolite] in a subject necessarily involves a transformation. Some form of manipulation, such as the high pressure liquid chromatography method specified in several of the asserted dependent claims or some other modification of the substances to be measured, is necessary to extract the metabolites from a bodily sample and determine their concentration.¹⁴⁴

VI. *MAYO* AND MOLECULAR DIAGNOSTIC TESTING

Although the patent claims at issue in *Mayo* were not directed toward genetic testing *per se*, they did recite methods of

¹³⁹ *Mayo*, 628 F.3d at 1355.

¹⁴⁰ *Id.* at 1358.

¹⁴¹ *Id.* at 1355.

¹⁴² *Id.* at 1356.

¹⁴³ *Id.* at 1357.

¹⁴⁴ *Id.*

non-genetic diagnostic testing as applied in the context of personalized medicine.¹⁴⁵ As a general matter, however, three aspects of *Mayo* in particular could severely limit the availability of effective patent protection for innovations in genetic diagnostics and personalized medicine. The first was the Court's characterization of a correlation between the level of drug metabolite in a patient's blood and the optimal drug dosage for that patient as a "law of nature."¹⁴⁶ The second was its holding that in order for a method claim based on the discovery of a law of nature to be patent eligible it must incorporate an "inventive concept" above and beyond the newly discovered law of nature.¹⁴⁷ Finally, the third was the Court's holding that a method claim is patent ineligible if it "preempts" a newly discovered law of nature.¹⁴⁸

It is important to bear in mind that the "metabolite" referred to in *Mayo* is a non-naturally occurring molecule, essentially the result of a synthetic drug being broken down by the body, and that the Court in *Mayo* characterized the interaction of a non-naturally occurring pharmaceutical compound with the human body as a law of nature.¹⁴⁹ In taking this position, the Supreme Court is adopting the finding of the Federal Circuit and district court. At the district court level, the judge justified his conclusion that the correlation is a natural phenomenon by noting that thiopurine drugs "are converted *naturally* by enzymes within the patient's body to form an agent that is therapeutically active, [and thus] the correlation results from a natural body process."¹⁵⁰ In essence, the court concluded that the mere involvement of a natural process in the interaction between a man-made drug and the human body renders the interaction a "natural phenomenon."¹⁵¹

¹⁴⁵ *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, 132 S. Ct. 1289, 1294 (2012).

¹⁴⁶ *Id.* at 1296.

¹⁴⁷ *Id.* at 1294.

¹⁴⁸ *Id.* at 1296.

¹⁴⁹ *Id.* at 1294.

¹⁵⁰ *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, 2008 WL 878910 at *6 (S.D. Cal. Mar. 28, 2008).

¹⁵¹ *Id.*

In an amicus brief filed with the Federal Circuit this author argued that the district court's expansive definition of "natural phenomena" seemed clearly incorrect, given that virtually every patented invention is based on some discovery involving the interaction of human ingenuity with the natural environment and natural processes.¹⁵² The amicus brief pointed out that an airplane, for example, interacts with the air in a particular manner that results in flight.¹⁵³ The air and its properties are natural phenomena, but surely, that does not render the interaction of an airplane with the air a natural phenomenon.¹⁵⁴ More to the point, what biological or pharmaceutical invention is not based on an interaction with natural biological processes? In particular, drugs operate by means of chemical interactions with naturally occurring proteins and other biomolecules in the body according to the fundamental laws of chemistry and biology. Unfortunately, neither the Federal Circuit nor the Supreme Court adopted this view, and in characterizing the interaction of a non-naturally occurring chemical compound with the human body as a law of nature, the Supreme Court appears to imply that the vast majority of personalized medicine inventions are based on the discovery of a patent ineligible law of nature.

The *Mayo* Court's holding that a patent eligible method must incorporate an "inventive concept" above and beyond the newly discovered law of nature traces its origins back at least as far as the Court's 1978 decision in *Parker v. Flook*,¹⁵⁵ but *Mayo*'s characterization of the "inventive concept" test could be particularly problematic for diagnostic inventions. This is because in applying the "inventive concept" standard, the *Mayo* Court held that the inclusion of method steps consisting of nothing more than "well understood, routine, conventional activity already engaged in by

¹⁵² Brief for Interested Patent Law Professors as Amicus Curiae in Support of Neither Party, *Prometheus Labs. v. Mayo Collaborative Servs. (doing business as Mayo Medical Laboratories) & Mayo Clinic Rochester*, 628 F.3d 1347 (2010) (No. 2008-1403), 2009 WL 462602.

¹⁵³ *Id.* at *12.

¹⁵⁴ *Id.*

¹⁵⁵ 437 U.S. 584, 594 (1978) ("[T]he discovery of such a phenomenon cannot support a patent unless there is some other inventive concept in its application.").

the scientific community[,]” which “when viewed as a whole, add nothing significant beyond the sum of their parts taken separately,” is insufficient to render a claimed method patent eligible.¹⁵⁶

The Supreme Court rejected the Federal Circuit’s conclusion in the decision below that the “administering” step was sufficiently transformative to render the claims patent eligible.¹⁵⁷ To the contrary, the Court characterized the “administering” step as “simply refer[ring] to the relevant audience, namely doctors who treat patients with certain diseases with thiopurine drugs. That audience is a pre-existing audience; doctors used thiopurine drugs to treat patients suffering from autoimmune disorders long before anyone asserted these claims.”¹⁵⁸ The Court went on to explain that, in “any event, ‘the prohibition against patenting abstract ideas cannot be circumvented by attempting to limit the use of the formula to a particular technological environment.’”¹⁵⁹

The Court also rejected the Federal Circuit’s conclusion that the “determining” step conferred patent eligibility on Prometheus’ claims. In the Court’s view, the “determining” step simply “tells the doctor to determine the level of the relevant metabolites in the blood, through whatever process the doctor or the laboratory wishes to use.”¹⁶⁰ The Court found that methods for determining levels of the metabolite in a subject’s body were “well known in the art” and routinely used by scientists, based upon statements appearing in the patents.¹⁶¹ The Court cited *Flook* and *Bilski* for the proposition that “purely ‘conventional or obvious’ ‘[pre]-solution activity’ is normally not sufficient to transform an unpatentable law of nature into a patent eligible application of such a law.”¹⁶²

Turning to the prohibition against preemption of fundamental principles, the Court pointed to earlier precedent, such as

¹⁵⁶ *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, 132 S. Ct. 1289, 1298 (2012).

¹⁵⁷ *Id.* at 1303.

¹⁵⁸ *Id.* at 1297.

¹⁵⁹ *Id.* (citing *Diamond v. Diehr*, 450 U.S. 175, 191 (1981)) (internal quotation marks omitted).

¹⁶⁰ *Id.*

¹⁶¹ *Id.* at 1297–98.

¹⁶² *Id.* at 1298.

Gottschalk v. Benson,¹⁶³ which warns against “upholding patents that claim processes that too broadly preempt[s] the use of a natural law.”¹⁶⁴ According to *Mayo*, the problem with an overly broad claim is that it might “inhibit further [innovation] by improperly tying up the future use of laws of nature.”¹⁶⁵ The Court acknowledged that the laws of nature at issue in the case “are narrow laws that may have limited applications,” but still found that if the claims at issue were found patent eligible there was a danger that the patents would “tie up their use [and] inhibit future innovation premised upon them.”¹⁶⁶ According to the Court, Prometheus’ claims:

[T]ell a treating doctor to measure metabolite levels and to consider the resulting measurements in light of the statistical relationships they describe. In doing so, they tie up the doctor’s subsequent treatment decision whether that treatment does, or does not, change in light of the inference he has drawn using the correlations. And they threaten to inhibit the development of more refined treatment recommendations (like that embodied in Mayo’s test), that combine Prometheus’ correlations with later discovered features of metabolites, human physiology or individual patient characteristics. The “determining” step too is set forth in highly general language covering all processes that make use of the correlations after measuring metabolites, including later discovered processes that measure metabolite levels in new ways.¹⁶⁷

Fortunately, *Mayo* includes passages that offer some hope that some diagnostic testing and personalized medicine method claims might still be found patent eligible post-*Mayo*. In particular, the Court did not overrule *Diamond v. Diehr*,¹⁶⁸ an important 1981 decision finding a computer program patent eligible.¹⁶⁹ In the minds of many, the inventions in *Diehr* and *Flook* are virtually indistinguishable from the perspective of patent eligibility. In seeking to reconcile them, the *Mayo* court suggested that the *Diehr*

¹⁶³ 409 U.S. 63 (1972).

¹⁶⁴ *Mayo*, 132 S. Ct. 1289, 1294 (citing *Gottschalk v. Benson*, 409 U.S. 63 (1972)).

¹⁶⁵ *Id.* at 1301.

¹⁶⁶ *Id.* at 1301–02.

¹⁶⁷ *Id.* at 1302.

¹⁶⁸ 450 U.S. 175 (1981).

¹⁶⁹ *Id.*

claims were patent eligible because the *Diehr* majority never suggested that all the steps, or at least the combination of steps recited in the claims “were in context obvious, already in use, or purely conventional.”¹⁷⁰ *Mayo* concludes that “[t]hese other steps apparently added to the formula something that in terms of patent law’s objectives had significance—they transformed the process into an inventive application of the formula.”¹⁷¹

The Court also made clear that it “need not, and [had] not, now decide[d] whether were the steps at issue here less conventional, these features of the claim would prove sufficient to invalidate them.”¹⁷² The Court took pains to emphasize that it did not intend its decision to eliminate patent protection for new drugs or new uses of existing drugs, opining that unlike patents on drugs, the *Prometheus* claims “do not confine their reach to particular applications.”¹⁷³ Thus, under *Mayo* it still seems possible that an applicant for a diagnostic testing method claim could successfully argue that, unlike the *Prometheus* claims, the applicant’s claims include steps that “in context” introduce something nonobvious or unconventional into the claim, thereby adding something of significance “in terms of patent law’s objectives.”¹⁷⁴ The statement favoring the patenting of drugs might be cited for the proposition that a personalized medicine claim that is perhaps more inventive and/or less preemptive than the *Prometheus* claims might still pass muster post-*Mayo*.

The Federal Circuit’s Chief Judge Rader appears to have adopted a permissive interpretation of *Mayo* that would tend to preserve the patent eligibility of many diagnostic tests and personalized medicine inventions.¹⁷⁵ In an opinion he authored in *CLS Bank Int’l. v. Alice Corp. Pty. Ltd.*,¹⁷⁶ Judge Rader explained that the “inventive concept” language used in *Mayo* “should not be

¹⁷⁰ *Mayo*, 132 S. Ct at 1299.

¹⁷¹ *Id.*

¹⁷² *Id.* at 1302.

¹⁷³ *Id.*

¹⁷⁴ *Id.* at 1299.

¹⁷⁵ See generally *CLS Bank Int’l. v. Alice Corp. Pty. Ltd.*, 717 F.3d 1269 (Fed. Cir. 2013).

¹⁷⁶ 717 F.3d 1269 (Fed. Cir. 2013).

read to conflate principles of patent eligibility with those of validity, [n]or should it be read to instill an ‘inventiveness’ or ‘ingenuity’ component into the inquiry.”¹⁷⁷ Citing to *Diehr*, Judge Rader argued that:

Because a new combination of old steps is patentable, as is a new process using an old machine or composition, subject matter eligibility must exist even if it was obvious to use the old steps with the new machine or composition. Otherwise the eligibility analysis ignores the text of sections 101 and 100(b), and reads Section 103 out of the Patent Act.¹⁷⁸

According to Judge Rader, “[t]he Supreme Court’s reference to ‘inventiveness’ in [*Mayo*] must be read as shorthand for its inquiry into whether implementing the abstract idea in the context of the claimed invention inherently requires the recited steps.”¹⁷⁹

Chief Judge Rader also proffered a relatively narrow interpretation of the preemption test articulated in *Mayo*. In his view, “the question for patent eligibility is whether the claim contains limitations that meaningfully tie that idea to a concrete reality or actual application of that idea.”¹⁸⁰ He acknowledged that “if a claim covers all practical applications of an abstract idea, it is not meaningfully limited,” but he went on to clarify that the question is whether a “claim covers every practical application of [a fundamental principle],”¹⁸¹ such that the claim would necessarily be infringed by anyone wanting to use the principle. In a nod to the *Bilski* machine-or-transformation test, he argued that “a claim is meaningfully limited if it requires a particular machine implementing a process or a particular transformation of matter.”¹⁸²

¹⁷⁷ *Id.* at 1302. (Rader, C.J., concurring in part and dissenting in part).

¹⁷⁸ *Id.* at 1303.

¹⁷⁹ *Id.*

¹⁸⁰ *Id.* at 1299–1300.

¹⁸¹ *Id.* at 1300.

¹⁸² *Id.* at 1301.

VII. *ARIOSIA DIAGNOSTICS* THREATENS INNOVATION IN DIAGNOSTIC-BASED INVENTIONS

A recent decision from the Northern District of California, *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*,¹⁸³ provides a sobering example of an aggressive application of *Mayo* that, if adopted broadly, could severely impact the availability of effective patent protection for future innovations in molecular diagnostic testing and personalized medicine. The patent at issue in *Ariosa Diagnostics*, U.S. Patent Number 6,258,540 (“the ‘540 patent”),¹⁸⁴ was based on the discovery by researchers at Oxford University that the blood of a pregnant woman contains substantial quantities of cell-free fetal DNA (“cffDNA”) and their recognition that cffDNA could be used in pre-natal diagnostic testing of paternally-inherited DNA for purposes such as sex determination, genotyping, and detection of pre-eclampsia in the mother.¹⁸⁵ Oxford University licensed the patent to Sequenom, Inc., a San Diego-based genomics company.¹⁸⁶ Ariosa Diagnostics sued Sequenom in a declaratory judgment action seeking a declaration that its Harmony™ test, a non-invasive cffDNA-based prenatal test, does not infringe the ‘540 patent.¹⁸⁷

On motion for summary judgment, the district court declared a number of the claims in the Sequenom patent invalid for being drawn to patent ineligible subject matter.¹⁸⁸ The court began its analysis by assuming, per agreement of the parties, that “the presence of cffDNA in maternal plasma or serum is a natural phenomenon.”¹⁸⁹ It then proceeded to find the challenged method

¹⁸³ 2013 WL 5863022 (N.D. Cal. Oct. 30, 2013) [hereinafter *Ariosa Diagnostics*].

¹⁸⁴ The original assignee, Isis Innovation Limited, is the technology transfer division for Oxford University. ISIS INNOVATION LTD., <http://www.isis-innovation.com/> (last visited Mar. 30, 2014).

¹⁸⁵ *Ariosa Diagnostics*, 2013 WL 5863022, at *1.

¹⁸⁶ *Id.*; see SEQUENOM, <http://www.sequenom.com/> (last visited Mar. 30, 2014).

¹⁸⁷ *Ariosa Diagnostics*, 2013 WL 5863022, at *1.

¹⁸⁸ *Id.* at *10.

¹⁸⁹ *Id.* at *7.

claims patent ineligible for failure to satisfy the “inventive concept” and “preemption” standards articulated in *Mayo*.¹⁹⁰

In applying the “inventive concept” test, the court essentially treated the natural phenomenon of cffDNA as part of the prior art, holding that “use of a newly discovered natural phenomenon . . . will not render a claim patentable if the use of that natural phenomenon . . . is the only innovation contained in the patent.”¹⁹¹ The claims required steps of amplifying and detecting paternal cffDNA, but the court found that amplification and detection of DNA are conventional techniques “previously engaged in by those in the field,” and thus not sufficiently inventive to render the claims patent eligible.¹⁹² The court concluded that use of a newly discovered natural phenomenon will not render a claim patentable if its use “is the only innovation contained in the patent.”¹⁹³

Turning to the “preemption” test, the district court found the claims patent ineligible based on the patent owner’s failure to present evidence of “commercially viable,” non-infringing methods of testing for paternal cffDNA.¹⁹⁴ The court was not entirely clear as to when the commercially viable, non-infringing alternatives needed to be available, but strongly implied that in order to satisfy the patent eligibility doctrine, the patent owner was required to establish that such methods “existed at the time of the invention or at the time of issuance of the patent.”¹⁹⁵ The “commercially viable” standard applied by the court appears to be substantially more stringent than the preemption test as envisioned by judges on the Federal Circuit. For example, in *CLS Bank v. Alice*, Chief Judge Rader emphasized that preemption only occurs under circumstances such that “the claim covers every practical application of [the fundamental principle].”¹⁹⁶ Sequenom apparently presented evidence of practical non-infringing methods of testing

¹⁹⁰ *Id.* at *7, *11.

¹⁹¹ *Id.* at *9.

¹⁹² *Id.* at *8.

¹⁹³ *Id.* at *9.

¹⁹⁴ *Id.* at *11.

¹⁹⁵ *Id.*

¹⁹⁶ *CLS Bank Int’l. v. Alice Corp. Pty. Ltd.*, 717 F.3d 1269, 1299–1302 (Fed. Cir. 2013) (Rader, C.J., concurring in part and dissenting in part).

for cffDNA, which would seem to satisfy Judge Rader's "practical application" test, but the court disregarded them based on Sequenom's failure to establish commercial viability.¹⁹⁷

The Sequenom patent is not entirely representative of the majority of genetic diagnostic testing patents, it is not based on the discovery of a correlation between a genetic variation (or combination of genetic variations) and some clinically significant phenotype. Still, *Ariosa Diagnostic's* interpretation of *Mayo* does not bode well for a broad swath of diagnostic testing and personalized medicine patents. The Federal Circuit's initial *Myriad* decision invalidated method claims that broadly recited methods of identifying variations in BRCA genes associated with a predisposition to cancer.¹⁹⁸ But *Mayo* was decided in sufficiently vague terms that it seems possible that method claims explicitly reciting physical steps of processing and analyzing the DNA and/or applying the knowledge that variation exists (for example by treating the patient) would remain patent eligible post-*Mayo*. The Supreme Court itself suggested as much in *Myriad*, when it noted with approval an assertion by the Federal Circuit's Judge Bryson that "many of [Myriad's unchallenged patent] claims" are patent eligible.¹⁹⁹ In particular, Judge Bryson explicitly pointed to Claim 21 of U.S. Patent Number 5,753,441 as an example of a patent eligible claim.²⁰⁰ Claims 20 and 21 recite:

A method for detecting a germline alteration in a BRCA1 gene, said alteration selected from the group consisting of the alterations set forth in Tables 11 and 12 which comprises analyzing a sequence of the BRCA1 gene or BRCA1 RNA from a human sample or analyzing the sequence of BRCA1 CDNA made from mRNA from said sample[,] . . . wherein a germline alteration is detected by hybridizing a BRCA1 gene probe which specifically hybridizes to an allele of one of said alterations to RNA isolated from said human sample and detecting the

¹⁹⁷ See *Ariosa Diagnostics*, 2013 WL 5863022, at *11.

¹⁹⁸ *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office*, 653 F.3d 1329, 1355–56 (Fed. Cir. 2011).

¹⁹⁹ *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2120 (2013).

²⁰⁰ *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office*, 689 F.3d 1303, 1349 (Fed. Cir. 2012) (Bryson, J., concurring in part and dissenting in part).

presence of a hybridization product, wherein the presence of said product indicates the presence of said allele in the sample.²⁰¹

The only additional element incorporated into the method of Claim 21 beyond identification of a germline alteration (presumably a law of nature under *Mayo*) is detection by means of a hybridization probe, which has long been a conventional method for analyzing DNA.²⁰² It would seem to be no more of an inventive concept than the hybridization and detection recited in the Sequenom claims. In fact, Sequenom argued that some of its claims must be valid if Judge Bryson is correct with respect to the patent eligibility of Claim 21, but the district court judge rejected this argument in a footnote, noting that, in *Myriad*, Justice Thomas did not specifically identify Claim 21 as one of the claims with regard to which he agreed with Judge Bryson's opinion of validity.²⁰³

With respect to the issue of preemption, *Ariosa Diagnostics'* "commercially viable" standard could also prove problematic, because a patent that fails to encompass a commercially viable means for detecting the genetic variation might very well be of limited value in blocking market entry by competitors. The court's application of the preemption test essentially turns the logic of *Mayo* on its head. While *Mayo* emphasized that the policy behind the preemption test is to prevent an inventor from "improperly tying up the future use of laws of nature,"²⁰⁴ the *Ariosa* court has essentially held that an inventor is not even allowed to tie up currently available and "commercially viable" applications of a law of nature, even if the claim allows for the development of noninfringing future uses.²⁰⁵

One particularly troubling aspect of *Ariosa Diagnostics* is the way that the court used statements by Sequenom management as evidence of preemption. Apparently company management had

²⁰¹ U.S. Patent No. 5,753,441 col.157 (filed May 19, 1998).

²⁰² See generally SAMBROOK ET AL., *supra* note 49 (providing comprehensive protocols and techniques for laboratories working with DNA).

²⁰³ *Ariosa Diagnostics*, 2013 WL 5863022, at *10, n.8.

²⁰⁴ *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, 132 S. Ct. 1289, 1301 (2012).

²⁰⁵ See *Ariosa Diagnostics*, 2013 WL 5863022.

made statements outside the context of the litigation touting the breadth of its claims, and the court used these as evidence of preemption.²⁰⁶ Sequenom presumably made substantial investments in licensing the patent from Oxford and commercializing the technology, and perhaps this would not have occurred if the company did not believe it had reasonably broad coverage. In the same vein, perhaps investors would not have invested in the company in the first place if they had realized they would not be able to preclude other companies from easily tapping into the market.

Ariosa Diagnostics also appears to pose substantial impediments to the patenting of innovations in personalized medicine, an increasingly promising application of diagnostic testing.²⁰⁷ A typical personalized medicine invention is based on the discovery of some genetic variation that is predictive of optimal medical treatment, oftentimes in terms of the best drug for a particular patient, or the optimized dosage for that patient.²⁰⁸ But the *Mayo* Court's interpretation of law of nature suggests that personalized medicine discoveries will be characterized as patent ineligible natural phenomena. Because the techniques used to apply such a discovery in the form of personalized medicine are typically conventional, a court applying the *Ariosa Diagnostics* standard for analyzing "inventive concept" would likely find the typical personal medicine claim invalid for lack of patent ineligibility.

VIII. CONCLUSION

Although many view *Myriad* as a case with important implications for genetic diagnostic testing, it seems more likely that *Mayo* will prove to be the more significant decision in this regard. *Ariosa Diagnostics* provides an example of a stringent application of *Mayo* that, if affirmed by the Federal Circuit and

²⁰⁶ *Id.* at *11.

²⁰⁷ See PERSONALIZED MEDICINE COALITION, THE CASE FOR PERSONALIZED MEDICINE (3d ed. 2011), available at http://www.ageofpersonalizedmedicine.org/objects/pdfs/Case_for_PM_3rd_edition.pdf.

²⁰⁸ *Id.*

broadly adopted, could substantially impact the availability of effective patent protection for molecular diagnostics and personalized medicine. This, in turn, could adversely affect investment in innovation in this critical aspect of healthcare. *Mayo* is amenable to a much more restrained interpretation that would largely preserve patentability for truly innovative diagnostic-based inventions, and one hopes that if the Federal Circuit has an opportunity to review *Ariosa Diagnostics*, it will reverse the decision and recalibrate the standard for patent eligibility in this important area of technology.