

No. \_\_\_\_\_

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IN THE  
**Supreme Court of the United States**

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THE ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL.,  
*Petitioners,*

—v.—

MYRIAD GENETICS, INC., ET AL.,  
*Respondents.*

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ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES  
COURT OF APPEALS FOR THE FEDERAL CIRCUIT

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**PETITION FOR A WRIT OF CERTIORARI**

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## QUESTIONS PRESENTED

Many patients seek genetic testing to see if they have mutations in their genes that are associated with a significantly increased risk of breast or ovarian cancer. Respondent Myriad Genetics obtained patents on two human genes that correlate to this risk, including any naturally occurring mutations of those genes, on the theory that simply by removing (“isolating”) the genes from the body, they have invented something patentable. Petitioners are primarily medical professionals who routinely use standard genetic testing methods to examine genes, but are prohibited from examining the human genes that Myriad claims to own. This case therefore presents the following questions:

1. Are human genes patentable?
2. Did the court of appeals err in adopting a new and inflexible rule, contrary to normal standing rules and this Court’s decision in *MedImmune, Inc. v. Genentech, Inc.*, 549 U.S. 118 (2007), that petitioners who have been indisputably deterred by Myriad’s “active enforcement” of its patent rights nonetheless lack standing to challenge those patents absent evidence that they have been personally and directly threatened with an infringement action?

## **PARTIES TO THE PROCEEDINGS**

The petitioners are the Association for Molecular Pathology, American College of Medical Genetics, American Society for Clinical Pathology, College of American Pathologists, Haig Kazazian, MD, Arupa Ganguly, PhD, Wendy Chung, MD, PhD, Harry Ostrer, MD, David Ledbetter, PhD, Stephen Warren, PhD, Ellen Matloff, M.S., Elsa Reich M.S., Breast Cancer Action, Boston Women's Health Book Collective, Lisbeth Ceriani, Runi Limary, Genae Girard, Patrice Fortune, Vicky Thomason, and Kathleen Raker. The respondents are Myriad Genetics, Inc., and in their official capacity as directors of the University of Utah Research Foundation, Lorris Betz, Roger Boyer, Jack Brittain, Arnold B. Combe, Raymond Gesteland, James U. Jensen, John Kendall Morris, Thomas Parks, David W. Pershing, and Michael K. Young. The United States Patent and Trademark Office (PTO) was dismissed as a defendant by the district court and that ruling was not appealed. Accordingly, the PTO is not a respondent in this Court.

## **RULE 29.6 CORPORATE DISCLOSURE STATEMENT**

Petitioners do not have any parent corporations, and no publicly held company owns 10 percent or more of the stock of any petitioner.

## TABLE OF CONTENTS

QUESTIONS PRESENTED.....	i
PARTIES TO THE PROCEEDINGS .....	ii
CORPORATE DISCLOSURE STATEMENT .....	ii
TABLE OF CONTENTS.....	iii
TABLE OF AUTHORITIES .....	v
OPINIONS BELOW .....	1
JURISDICTIONAL STATEMENT .....	1
STATUTORY AND CONSTITUTIONAL PROVISIONS.....	1
STATEMENT OF THE CASE.....	2
REASONS FOR GRANTING THE WRIT .....	16
I.    THE QUESTION OF WHETHER HUMAN GENES AND THE INFORMATION THEY CONVEY ARE PATENTABLE IS OF PARAMOUNT IMPORTANCE TO THE FUTURE OF PATENT LAW, THE ADVANCEMENT OF MEDICAL SCIENCE, AND PATIENTS’ HEALTH.....	16
II.   PATENTS ON “ISOLATED” DNA ARE INVALID UNDER THIS COURT’S SECTION 101 JURISPRUDENCE AND THE U.S. CONSTITUTION. ....	25
III.  BY HOLDING THAT PETITIONERS LACKED STANDING UNLESS THEY WERE PERSONALLY THREATENED BY MYRIAD, THE FEDERAL CIRCUIT IMPOSED A RIGID STANDING REQUIREMENT	

CONTRARY TO THIS COURT’S APPROACH IN <i>MEDIMMUNE</i> .....	31
CONCLUSION.....	36
APPENDIX.....	1a
Opinion, United States Court of Appeals for the Federal Circuit, July 29, 2011.....	1a-112a
Amended Opinion, United States District Court for the Southern District of New York, April 5, 2010 .....	113a-238a
Opinion, United States District Court for the Southern District of New York, November 2, 2009.....	239a-306a
Claims.....	307a-308a

## TABLE OF AUTHORITIES

### CASES

<i>Aetna Life Ins. Co. v. Haworth</i> , 300 U.S. 227 (1937) .....	32
<i>American Fruit Growers Inc. v. Brodgex Co.</i> , 283 U.S. 1 (1931) .....	10, 25, 27, 28
<i>Arnold P'ship v. Dudas</i> , 362 F.3d 1338 (Fed. Cir. 2004).....	18
<i>Ashcroft v. Free Speech Coal.</i> , 535 U.S. 234 (2002) .....	30
<i>Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office</i> , 653 F.3d 1329 (Fed. Cir. 2011).....	<i>passim</i>
<i>Bilski v. Kappos</i> , 130 S. Ct. 3218 (2010) .....	16, 25, 29
<i>Biotech. Indus. Org. v. District of Columbia</i> , 496 F.3d 1362 (Fed. Cir. 2007) .....	33
<i>Cf. Great Atl. &amp; Pac. Tea Co. v. Supermarket Equip. Corp.</i> , 340 U.S. 147 (U.S. 1950) .....	23
<i>Diamond v. Chakrabarty</i> , 447 U.S. 303 (1980) .....	<i>passim</i>
<i>Diamond v. Diehr</i> , 450 U.S. 175 (1981) .....	25
<i>Doe v. Bolton</i> , 410 U.S. 179 (1973) .....	33
<i>Funk Bros. Seed Co. v. Kalo Inoculant Co.</i> , 333 U.S. 127 (1948) .....	<i>passim</i>
<i>Gen. Elec. Co. v. De Forest Radio Co.</i> , 28 F.2d 641 (3d Cir. 1928).....	25
<i>Gottschalk v. Benson</i> , 409 U.S. 63 (1972) .....	30

<i>Holder v. Humanitarian Law Project</i> , 130 S. Ct. 2705 (2010) .....	31
<i>In re Marden (Marden I)</i> , 47 F.2d 957 (C.C.P.A. 1931).....	25
<i>In re Marden (Marden II)</i> , 47 F.2d 958 (C.C.P.A. 1931).....	25
<i>Intervet Inc. v. Merial Ltd.</i> , 617 F.3d 1282 (Fed. Cir. 2010) .....	14, 17, 20
<i>J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int’l, Inc.</i> , 534 U.S. 124 (2001) .....	25
<i>Lab. Corp. of Am. Holdings v. Metabolite Labs.</i> , 548 U.S. 124 (U.S. 2006).....	23, 30
<i>Markman v. Westview Instruments, Inc.</i> , 517 U.S. 370 (1996) .....	28
<i>MedImmune, Inc. v. Genentech, Inc.</i> , 549 U.S. 118 (2007) .....	<i>passim</i>
<i>Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings</i> , 370 F.3d 1354 (Fed. Cir. 2004) .....	34
<i>Metabolite v. Laboratory Corp.</i> , cert. dismiss. 548 U.S. 124 (2006) .....	16
<i>Parker v. Flook</i> , 437 U.S. 584 (1978).....	25
<i>Prometheus v. Mayo Collaborative Services</i> , granting, vacating and remanding 130 S. Ct. 3543 (2010), and cert. granted, 131 S. Ct. 3027 (June 20, 2011) .....	16
<i>Virginia v. Am. Booksellers Ass’n, Inc.</i> , 484 U.S. 383 (1988) .....	33
<i>Vt. Right to Life Comm., Inc. v. Sorrell</i> , 221 F.3d 376 (2d Cir. 2000).....	33

<i>Warth v. Seldin</i> , 422 U.S. 490 (1975).....	34
<i>White v. Dunbar</i> , 119 U.S. 47 (1886).....	28

**CONSTITUTION AND STATUTES**

U.S. Const. amend. I.....	1, 6, 30
U.S. Const. art. 1, §8, cl. 8.....	6
Patent Act, 35 U.S.C. § 101.....	<i>passim</i>
28 U.S.C. § 1254(1).....	1

**OTHER AUTHORITIES**

Dep't of Health & Human Serv., Sec'y's Advisory Comm. on Genetics, Health, and Soc'y, <i>Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests</i> (April 2010), available at <a href="http://oba.od.nih.gov/oba/sacghs/reports/SACGHS_patents_report_2010.pdf">http://oba.od.nih.gov/oba/sacghs/reports/SACGHS_patents_report_2010.pdf</a> .....	19
Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).....	18



## OPINIONS BELOW

The opinion of the United States Court of Appeals for the Federal Circuit, App. at 1-112a, is reported at 653 F.3d 1329 (Fed. Cir. 2011). The district court opinion granting summary judgment to plaintiffs/petitioners and denying summary judgment to defendants/respondents, App. at 113-238a, is reported at 702 F. Supp. 2d 181 (S.D.N.Y. 2010). An earlier opinion of the district court, App. at 239-306a, denying the motion to dismiss based, in part, on standing is reported at 669 F. Supp. 2d 365 (S.D.N.Y. 2009).

## JURISDICTIONAL STATEMENT

The Court of Appeals decision in this case was issued on July 29, 2011. Both parties filed petitions for panel rehearing. The court denied the petition by plaintiffs Association for Molecular Pathology *et al.* on September 13, 2011, and the petition of defendants Myriad *et al.* on September 16, 2011. This petition is thus timely. Jurisdiction is conferred by 28 U.S.C. § 1254(1).

## STATUTORY AND CONSTITUTIONAL PROVISIONS

35 U.S.C. § 101 provides: “Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.”

The First Amendment of the United States Constitution provides that:

“Congress shall make no law respecting an establishment of religion, or prohibiting the free exercise thereof; or abridging the freedom of speech, or of the press; or the right of the people peaceably to assemble, and to petition the Government for a redress of grievances.”

### STATEMENT OF THE CASE

1. This case challenges the patenting of human genes. More specifically, it challenges patents awarded to Myriad Genetics<sup>1</sup> on two genes, known as BRCA1 and BRCA2 because mutations of those genes correlate with an increased risk of hereditary breast and ovarian cancer. App. at 19a. Myriad claims exclusive control over the genes once they have been “isolated” – that is, removed from the body and other cellular material. Myriad and other gene patent holders have gained the right to exclude the rest of the scientific community from examining thousands of naturally-occurring human genes and to prevent patients’ access to their own genetic information. The practical consequence of these patents is that Myriad has the authority to stop standard clinical testing of and research on its genes. For those at risk of hereditary cancer, the effect is to prevent second opinions and to block access to alternative and potentially more comprehensive tests and lower cost options.

The BRCA1 and BRCA2 genes exist in the body of every single person. *See* App. at 119a. For

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<sup>1</sup> Myriad obtained the patents at issue with others, including the University of Utah Research Foundation, which is an owner or co-owner of each of the challenged patents. App. at 129a. They have acted jointly throughout this litigation.

many patients, knowing whether their genes contain the harmful mutations is essential to making informed medical decisions. App. at 159-60a. Myriad did not develop the methods by which geneticists look at or “isolate” the BRCA1 and BRCA2 genes. App. at 151-53a. Those methods, which were well-known and are used by geneticists to sequence thousands of other human genes on a daily basis, *id.*, are not the subject of this lawsuit. Myriad’s patents on the genes, however, prevent clinicians from using those methods to examine anyone’s BRCA1 and BRCA2 genes.

Myriad defends its patents on the grounds that those patents cover only “isolated” genes, and that “isolated” genes are distinguishable from genes in the body. Three of the four judges who have issued opinions in this case (the District Court judge and three Court of Appeals judges each writing separate opinions) found that “isolated” genes were functionally identical to genes in the body (the fourth judge did not express an opinion, asserting that this fact was irrelevant). Three of the four judges also found that “isolated” genes were virtually identical structurally to genes in the body (the fourth asserted that an insignificant chemical change was transformative). Notwithstanding these findings, and notwithstanding this Court’s repeated holdings that products and laws of nature are not patentable, a split Federal Circuit ruled that Myriad’s gene patents were valid, reversing the district court.

2. Every human body contains DNA. Genes are segments or fragments of DNA that determine, in part, the structure and functions of the body. App. at 138-44a. They are created naturally. App. at 139-

42a. Through naturally-occurring processes in the body, genes produce proteins (or polypeptides) and those proteins do the work of the body. *Id.* Genes vary from one individual to another. Genetic alterations or variations can be inherited or can occur after birth, but in both instances they come about naturally. App. at 141-42a. Variants can appear to be unimportant, correlate with an increased risk of disease or disorder (“mutations”), or have unknown significance (“variant of unknown significance”). *Id.* The significance of the variant is purely a function of nature. App. at 151a.

In the context of BRCA1 and BRCA2, certain genetic mutations have been correlated with a much higher risk of cancer. “Women with BRCA1 and BRCA2 mutations face up to an 85% cumulative risk of breast cancer as well as an up to 50% cumulative risk of ovarian cancer...The existence of BRCA1 and BRCA2 mutations is therefore an important consideration in the provision of clinical care for breast and/or ovarian cancer.” App. at 159a.

In order to provide effective treatment to patients and to research a wide range of diseases and conditions, including cancer, pathologists, clinical laboratory scientists, and other medical professionals conduct genetic testing for clinically significant alterations. App. at 151-53a. There are a variety of methods by which medical professionals can examine genes. *Id.* Basic methods involve extracting or “isolating” the DNA, which removes the DNA from the cell and associated proteins and randomly fragments it. Second Corrected App. Vol. VI at A7036-39, *Ass’n for Molecular Pathology v. U.S. Patent and Trademark Office*, 653 F.3d 1329 (Fed.

Cir. 2011) (No. 2010-1406). The standard process of isolation does not result in DNA fragments that do not exist naturally in the body. *Id.* It simply makes a person's genetic information more accessible for sequencing by medical professionals. *Id.* Thousands of medical professionals, including many of the plaintiffs, isolate and sequence genes daily, and the processes by which isolation and sequencing are done are not at issue here. App. at 151-53a.

At the end of the process, the medical professional has a long string of four letters (A, C, T, and G) that correspond to the four nucleotides that make up DNA and genes. App. at 138a, 141-42a. The structure, function, and sequence of the nucleotides are created entirely by nature. *Id.* The medical professional looks to see if there are variants, *e.g.*, whether natural processes have caused there to be a C where a T would normally be. App. at 141-42a.

This is what Myriad does when it examines patients' BRCA1 and BRCA2 genes looking for variants. Its process is not unique. What is unique is its exclusive control over people's genetic information as a result of the patents it has been granted for BRCA1 and BRCA2, preventing other clinicians from accessing these genes for testing.

After completing its genetic tests, Myriad issues a report that essentially says: We have examined the genes obtained (or "isolated") from your blood sample. Because they are identical to the genes in your body, we can say with assurance that you do (or do not) have a variant. App. at 151-53a, 160a. The report then informs the patient: Based on the medical literature, this variant does (or does not)

mean you have an increased risk of breast or ovarian cancer (or we do not know what the significance of the variant is). *Id.* If the “isolated” genes patented by Myriad were not identical to the genes in the body, Myriad could not use the “isolated” genes to provide genetic information to patients.

3. This lawsuit began in 2009 with the filing of a complaint in the United States District Court for the Southern District of New York against the United States Patent and Trademark Office (PTO), as well as the patent holders, Myriad Genetics and the directors of the University of Utah Research Foundation. Plaintiffs include four national organizations of physicians, geneticists, researchers, clinicians, and other health professionals with a combined total of over 150,000 members, as well as six of the nation’s leading geneticists, two genetic counselors, two women’s health and breast cancer organizations, and six patients who have been diagnosed with or are at risk of hereditary breast or ovarian cancer. App. at 121-29a.

Plaintiffs alleged in their complaint that the patents are invalid under Section 101 of the Patent Act because they cover products and laws of nature and abstract ideas. They also alleged that the effects of the challenged patents is to preempt scientific inquiry and medical care to the detriment of patients’ health and to scientific advancement, in violation of both Article I, Section 8, Clause 8 and the First Amendment of the U.S. Constitution.

The complaint challenged fifteen claims from seven different patents. App. at 178-84a. The claims relevant to this Petition cover the BRCA1 and

BRCA2 genes.<sup>2</sup> Each of those claims defines the gene according to how it functions in the body. App. at 179-81a. For example, claims in the patent 5,747,282 ('282) include:

1. An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2.
2. The isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID NO:1.
5. An isolated DNA having at least 15 nucleotides of the DNA of claim 1.

App. at 179-80a. The patent specifications define "isolated" DNA as having been removed from the cell and separated from other genetic material. App. at 189-90a. The referenced sequences (*e.g.*, SEQ ID NO.\_\_\_\_) identify the lengthy nucleotide sequences found in a "wild-type" (non-mutated or normal) BRCA1 gene and the amino acid sequence found in a protein created by a wild-type BRCA1 gene. App. at 179a. Other claims<sup>3</sup> cover all variations and mutations in the BRCA1 and BRCA2 genes, both known and unknown. App. at 178-81a.

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<sup>2</sup> The complaint also challenged methods of comparing the "wild-type" or non-mutated genetic sequence to the genetic sequence of a sample obtained from a patient. App. at 181-84a. All but one of the method claims were declared invalid by both the district court and the Court of Appeals. App. at 54-61a, 224-36a. None of the method claims is the subject of this petition.

<sup>3</sup> The other claims at issue in this petition are contained in the Appendix. App. at 307-08a.

According to the patent specifications, each of the claims covers virtually every short fragment of the BRCA1 and BRCA2 genes as well as the full-length genes. *E.g.*, '282 patent at 6:26-30, 25:36-37. Thus, the patents claim any fragments as short as 15 nucleotides (comprised of the A, C, G, and T component bases) of the gene, which consists of many thousands of nucleotides. *Id.*; App. at 179-80a. Additionally, the patents cover cDNA, a form of DNA that can also be found in the body, albeit less frequently, in which some of the inessential (non-coding) nucleotides known as introns have been removed. App. at 148-50a, 218-20a. Myriad has never argued that any of its claims is limited to any one form of DNA, including cDNA. Through its combined patents, Myriad claims ownership of the BRCA1 and BRCA2 genes of every American.

4. In the district court, the defendants moved to dismiss largely on the grounds that the plaintiffs did not have standing. App. at 273a *et seq.* The court denied that motion. App. at 293a. Both plaintiffs and Myriad subsequently moved for summary judgment, and the PTO moved for judgment on the pleadings. App. at 118a. The district court granted the plaintiffs' motion for summary judgment and denied Myriad's motion. *Id.* The court dismissed the constitutional claims against the PTO based on the doctrine of constitutional avoidance. *Id.*; App. at 236-37a.

The district court's finding that each of the plaintiffs had standing was based on an application of this Court's opinion in *MedImmune, Inc. v. Genentech, Inc.*, 549 U.S. 118 (2007), which held that standing in patent cases should be analyzed in the



same manner as standing in non-patent cases. The district court found that Myriad had taken affirmative acts to enforce its patents “through personal communications, cease-and-desist letters, licensing offers, and litigation.” App. at 287a. The court also found that each plaintiff had the capacity, ability, and desire to engage in infringing activity (or activity to contribute to or induce infringement) but was prevented from doing so by the patents. App. at 288-93a. More specifically, each of the physician plaintiffs and at least one physician member of each of the medical association plaintiffs submitted declarations indicating they sequenced genes on a regular basis, would immediately utilize their standard sequencing methods to sequence the BRCA1 and BRCA2 genes if possible, and were prevented from doing so solely as a result of fear of suit by Myriad.<sup>4</sup> App. at 290-91a. The district court found that the remaining plaintiffs (genetic counselors and breast cancer advocacy groups who referred women for testing, and patients who sought to be tested) had standing based on their stated desire to contribute to infringement by referring patients (or themselves) to physicians for testing, a desire frustrated solely by Myriad’s active enforcement of its patents. App. at 291-93a.

The district court granted plaintiffs’ motion for summary judgment in a 153-page, comprehensive opinion that relied heavily on facts presented by both

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<sup>4</sup> Drs. Kazazian and Ganguly had been sequencing BRCA1 and BRCA2 genes until they were forced to stop as a result of letters and lawsuits by Myriad. App. at 20-23a. Their declaration indicated they would consider resuming that activity if the patents were invalidated. App. at 34a.

parties and carefully analyzed the decisions of this Court holding that patents cannot be issued on laws of nature, products of nature, or abstract ideas. App. at 113-238a. The district court began by discussing the standard set by this Court for determining if a patented composition of matter – like the DNA at issue here – has been sufficiently changed such that it is no longer a product of nature. App. at 201-04a (citing *Diamond v. Chakrabarty*, 447 U.S. 303 (1980); *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948); and *American Fruit Growers Inc. v. Brodges Co.*, 283 U.S. 1 (1931)).

The district court considered Myriad’s arguments regarding both structural and functional differences between “isolated” DNA and the DNA inside the human body, ultimately concluding that none caused “isolated” genes to be “markedly different,” *Chakrabarty*, 447 U.S. at 310, from genes in the body. App. at 214-24a. In holding that isolated DNA remains a product of nature, the district court emphasized the unique properties of genes as

[I]nformation ... [that] reflects its primary biological function; directing the synthesis of *other* molecules in the body – namely, proteins, “biological molecules of enormous importance” which “catalyze biochemical reactions” and constitute the “major structural materials of the animal body.”

App. at 216a (emphasis in original; citations omitted). The district court found that in isolating the genes, Myriad did not “alter its essential characteristic – its nucleotide sequence that is

defined by nature and central to both its biological function within the cell and its utility as a research tool in the lab.” App. at 222a. The court also invalidated the patents on cDNA for largely the same reason. App. at 218-20a.

5. Myriad appealed to the Federal Circuit. Plaintiffs did not appeal the dismissal of the PTO, which is therefore no longer a party to the case, although plaintiffs continued to raise their First Amendment claims against the University of Utah defendants. The United States did, however, participate in the appellate proceedings as *amicus curiae*. It was personally represented by the Solicitor General and, as more fully described below, largely supported plaintiffs’ position.

A divided panel of the court of appeals reversed. The court was unanimous, however, in rejecting Myriad’s contention that none of the plaintiffs had standing. Specifically, all three judges agreed that plaintiff Dr. Harry Ostrer had standing to sue because he had received a letter from Myriad proposing a BRCA licensing agreement for which a royalty would need to be paid. The court found:

Myriad’s active enforcement of its patent rights forced [plaintiff] Dr. Ostrer, *as well as every other similarly situated researcher and institution*, to cease performing the challenged BRCA testing services, leaving Myriad as the sole provider of BRCA clinical testing in the United States ... Myriad’s enforcement efforts eliminated all competition...”

App. at 35a (emphasis added). The court further noted that Dr. Ostrer had “not only the resources and expertise to immediately undertake clinical BRCA testing, but also states unequivocally that he will immediately begin such testing.” App. at 34a. While accurate, that statement did not distinguish Dr. Ostrer from the most of the other physician plaintiffs and members of the medical association plaintiffs who submitted similar or identical evidence of their resources, expertise, capability, and desire to begin testing. App. at 288-92a. The court denied the standing of other plaintiffs because, unlike Dr. Ostrer, they had not been individually contacted by Myriad. App. at 39-40a. The court found that although Myriad’s “active enforcement” of its patents had “forced...every other...researcher and institution” to cease testing, Dr. Ostrer alone had standing because there had not been “affirmative acts by the patentee directed at specific Plaintiffs.” App. at 35-39a. The court of appeals discarded the plaintiffs whose standing was based on contributory or inducing infringement essentially without comment.

On the merits, each member of the panel wrote a separate opinion discussing the patentability of human genes, and each opinion analyzed the issue differently. Judge Lourie purported to apply the standard in *Diamond v. Chakrabarty*, 447 U.S. 303, 310 (1980), that a court must analyze whether an “isolated” gene is “markedly different” from what is found in nature.<sup>5</sup> He held that in performing this

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<sup>5</sup> Myriad had argued that the “markedly different” standard had not been established by the Court and should not be applied.

analysis, the functionality of the gene was irrelevant. App. at 49a. Thus, even if “isolated” genes were functionally identical to genes in the body, they would still be patentable. *Id.* He held that “isolated” DNA was structurally different from DNA on the sole basis that in the process of being removed from the body and its surrounding chemicals and tissues, a covalent (electron) bond has been broken. App. at 46-49a. Covalent bonds are naturally-occurring bonds that hold together DNA. Plaintiffs-Appellees’ Petition for Panel Rehearing at 4, *Ass’n for Molecular Pathology v. U.S. Patent and Trademark Office*, 653 F.3d 1329 (Fed. Cir. 2011) (No. 10-01406). They are constantly formed and broken in the body. *Id.*; see Second Corrected App. Vol. VI at A7036-38, *Ass’n for Molecular Pathology v. U.S. Patent and Trademark Office*, 653 F.3d 1329 (Fed. Cir. 2011) (No. 2010-1406).

Judge Moore, by contrast, found that both structure and function were relevant in determining if a composition is “markedly different” from what is found in nature. App. at 77-79a. She found that a full-length “isolated” gene “does not clearly have a new utility and appear to simply serve the same ends devised by nature.” App. at 79a. She said: “If I were deciding this case on a blank canvas, I might conclude that an isolated DNA sequence that includes most or all of a gene is not patentable subject matter.” *Id.* She nevertheless found full-length genes to be patentable because of the “historical background” of the PTO’s past practice of granting gene patents. *Id.* She also held that small fragments of genes were patentable subject matter because removal caused the fragments to have different chemical elements at each end. App. at 75-

77a. Moreover, she noted that small fragments can be used as probes and primers – segments of DNA that are used by laboratories in the process of genetic testing. *Id.*

In his dissenting opinion, Judge Bryson held the genes were not patentable.

Myriad is claiming the genes themselves, which appear in nature on the chromosomes of living human beings. The only material change made to those genes from their natural state is the change that is necessarily incidental to the extraction of the genes.

App. at 98a. Judge Bryson noted that Federal Circuit Judge Dyk had expressed the same view in a separate case, reasoning that “prematurely plucking the leaf [off a tree] would not turn it into a human-made invention. That would remain true if there were minor differences between the plucked leaf and the fallen autumn leaf...” *Intervet Inc. v. Merial Ltd.*, 617 F.3d 1282, 1295 (Fed. Cir. 2010) (Dyk, J., concurring in part). Judge Bryson concluded:

The structural differences between the claimed “isolated” genes and the corresponding portion of the native genes are irrelevant to the claim limitations, to the functioning of the genes, and to their utility in their isolated form. The use to which the genetic material can be put, *i.e.*, determining its sequence in a clinical setting is not a new use; it is only a consequence of possession. In order to

sequence an isolated gene, each gene must function in the same manner in the laboratory as it does in the human body.

App. at 105-06a. He further concluded that the PTO's past practice was not entitled to significant weight because the courts, not the PTO, have ultimate authority to determine what is patentable under the laws enacted by Congress. App. at 110-12a. All three members of the court held that cDNA was patentable subject matter. *E.g.*, App. at 42-43a, 73-74a, 94a. The court ignored the district court's construction of the claims, App. at 189-90a, and found that cDNA did not appear in the body and is simply "inspired by nature." App. at 73a. The majority of the court did not identify which claims in the patents were limited to cDNA. *See* App. at 43a. The court also did not address the constitutional claims raised by plaintiffs.

Plaintiffs petitioned for rehearing by the panel, arguing that certain facts relied on in the opinions of Judge Lourie and Judge Moore were not in the record and were flawed. Specifically, plaintiffs argued that Judge Lourie's reliance on the breaking of covalent bonds that occurs when DNA is "isolated" in concluding that isolated DNA is markedly different from DNA was erroneous. Covalent bonds are indeed broken in the process of "isolation" as the DNA is fragmented. But covalent bonds are also broken inside the body as part of natural processes. Fragments of genes identical to the fragments found after "isolation," with broken covalent bonds and different ends, exist naturally in the body. Plaintiffs-Appellees' Petition for Panel Rehearing at 4, *Ass'n for*

*Molecular Pathology v. U.S. Patent and Trademark Office*, 653 F.3d 1329 (Fed. Cir. 2011) (No. 10-01406); Fed. Cir. App. at A7036-40. Broken covalent bonds simply do not distinguish an “isolated” gene from a product of nature. *Id.* Defendants also petitioned for rehearing on the holding that Dr. Ostrer had standing to challenge the BRCA1 and BRCA2 patents. Both rehearing motions were denied without opinion.

## REASONS FOR GRANTING THE WRIT

### I. THE QUESTION OF WHETHER HUMAN GENES AND THE INFORMATION THEY CONVEY ARE PATENTABLE IS OF PARAMOUNT IMPORTANCE TO THE FUTURE OF PATENT LAW, THE ADVANCEMENT OF MEDICAL SCIENCE, AND PATIENTS’ HEALTH.

In recent years, this Court has granted certiorari on several cases concerning the patentability of methods. *Bilski v. Kappos*, 130 S. Ct. 3218 (2010); *Prometheus v. Mayo Collaborative Services*, granting, vacating and remanding 130 S. Ct. 3543 (2010), and cert. granted, 131 S. Ct. 3027 (June 20, 2011). *See also Metabolite v. Laboratory Corp.*, cert. disp. 548 U.S. 124 (2006). For over thirty years, the Court has not addressed the patentability of compositions of matter under Section 101. There can be little doubt that it is crucial for the Court to address this subject.

The legal community needs guidance from this Court regarding the scope of Section 101 as it applies to compositions of matter and DNA. Four federal judges in this case have written opinions on the



patentability of human genes. Each has adopted a different method of analyzing the issues. The district court judge held that neither DNA nor cDNA is patentable subject matter because the genes that make up DNA function the same whether they are inside or outside the body. App. at 214-24a. He thus rejected the notion that isolated DNA is markedly different than the DNA that exists in nature. Federal Circuit Judge Lourie, by contrast, held that the function of genes inside and outside the body is always irrelevant. App. at 49-50a. In his view, isolated DNA is patentable because removing a gene from the body necessarily alters its chemical structure. App. at 46-47a. Judge Moore thought that the court must examine both function and structure. App. at 75-77a. Although she found that full-length genes were functionally and to a significant degree structurally identical whether isolated or not, she nevertheless found them patentable by deferring to the PTO's past practice. App. at 79a. With respect to small fragments of genes, she found that they could be used outside the body as probes or primers, unlike small identical fragments found inside the body, and were therefore patentable. App. at 75-78a. Finally, Judge Bryson found genes unpatentable because any structural changes were incidental to the isolation process and any functional use was "only a consequence of possession."<sup>6</sup> App. at 105-06a. All three court of appeals judges ignored the district court's factual

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<sup>6</sup> Judge Bryson's analysis was foreshadowed by Federal Circuit Judge Dyk's opinion in an earlier case. See *Intervet v. Merial Ltd.*, 617 F.3d 1282, 1295 (Fed. Cir. 2010) (Dyk, J. concurring in part and dissenting in part).

finding that cDNA appears in the body and found it patentable because it is more often created in a lab. That cDNA and DNA are functionally identical was, they apparently thought, irrelevant. None identified which of the claims, if any, is limited to cDNA.

All of the judges purported to apply this Court's standard in *Chakrabarty* that a patentable composition must be "markedly different" from a product of nature, but each differed in how to apply that standard to full-length genes, gene fragments, and cDNA. Each had divergent views on the relevance of the existence of genes or gene fragments that are identical inside and outside of the body. Each also disagreed on the degree to which minor structural alterations incident to removal render a composition patentable and the relevance of function in assessing patentability. The district court and Judge Bryson found it highly relevant that Myriad's entire business is based on the fact that "isolated" genes have the identical nucleotide sequence as genes in the body – because otherwise any diagnostic conclusions drawn from the "isolated" gene would be impossible. Judges Lourie and Moore found that fact irrelevant.

The executive branch, too, has expressed different opinions in this litigation. The PTO granted the patents at issue in this case and has published guidelines authorizing the patenting of isolated DNA. *See* Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).<sup>7</sup> However, when this case reached the Federal Circuit, the United

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<sup>7</sup> These Guidelines are not entitled to any deference. *Arnold P'ship v. Dudas*, 362 F.3d 1338, 1340 (Fed. Cir. 2004).

States adopted a different position. After consulting with the “Patent and Trademark Office (PTO), the National Institutes of Health (NIH), the Antitrust Division of the Department of Justice, the Centers for Disease Control and Prevention, the Office of Science and Technology Policy, and the National Economic Council, among others,” the United States concluded that DNA and human genes are not patentable, but that cDNA is. Br. for the United States as Amicus Curiae in Supp. of Neither Party at 1, *Ass’n for Molecular Pathology v. U.S. Patent and Trademark Office*, 653 F.3d 1329 (Fed. Cir. 2011) (No. 2010-1406). Contrary to the usual practice, the PTO did not sign the brief that was submitted by the United States. Arguing personally on behalf of the United States, the Solicitor General proposed a new method of analyzing the degree to which a part of the human body is patentable: the “magic microscope.” Because the same DNA molecule could be seen if a magic microscope were to be invented allowing one to zoom in and view the DNA inside a human body, isolated DNA is a product of nature.<sup>8</sup> App. at 83a.

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<sup>8</sup> The Department of Health and Human Services has also weighed in on the question of gene patents. Last year, its Secretary’s Advisory Committee on Genetics, Health, and Society issued a report concluding that gene patents were unnecessary to incentivize research or the development of clinical testing and impeded patient access to genetic testing and quality assurance in testing. Dep’t of Health & Human Serv., Sec’y’s Advisory Comm. on Genetics, Health, and Soc’y, *Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests* (April 2010), available at [http://oba.od.nih.gov/oba/sacghs/reports/SACGHS\\_patents\\_report\\_2010.pdf](http://oba.od.nih.gov/oba/sacghs/reports/SACGHS_patents_report_2010.pdf).

This case is an ideal vehicle to analyze the Section 101 question. Plaintiffs' sole claim under the Patent Act was brought pursuant to Section 101. Unlike other Federal Circuit cases dealing with isolated DNA patents, *see, e.g., Intervet Inc. v. Merial Ltd.*, 617 F.3d 1282, 1293 (Fed. Cir. 2010) (Dyk, J., concurring in part and dissenting in part), this is the first to present and thoroughly litigate the issue of whether isolated DNA falls within the Section 101 exceptions. At the district court, all parties agreed on the fundamental characteristics of isolated DNA and disputed only the application of the law to the facts. App. at 135-60a.

This case is not, however, solely about the pressing need to clarify the legal doctrine governing the patentability of compositions of matter and the scope of the product of nature exception. At its core, it presents a critical question of great concern to this country, especially patients affected by hereditary breast and ovarian cancer and the medical and scientific communities: are patents on genes valid, thus preventing advances in science and medicine that could result in better diagnosis and treatment? There were thirty amicus briefs filed in the court of appeals signed by sixty-seven organizations, corporations, associations, or individuals. Among those who signed briefs supporting plaintiffs were (1) major medical associations (beyond the four associations who are plaintiffs themselves), including the American Medical Association (AMA), the American Society of Human Genetics, the American College of Embryology, and the American College of Obstetricians and Gynecologists, and (2) organizations committed to advocacy on behalf of patients, including the March of Dimes, AARP, the

Canavan Foundation, the Claire Altman Heine Foundation, the National Organization for Rare Disorders, National Tay-Sachs and Allied Diseases Association, Ovarian Cancer National Alliance, and Facing Our Risk of Cancer Empowered, which advocates on behalf of patients and families affected by hereditary breast and ovarian cancer.<sup>9</sup> All of these amici weighed in because of the significant impact of gene patents on patient care. App. at 3-7a, 129-32a. As the Department of Justice said in its brief: “The extent to which basic discoveries in genetics may be patented is a question of great importance to the national economy, to medical science, and to the public health.” Br. for the United States as Amicus Curiae in Supp. of Neither Party at 1, *Ass’n for Molecular Pathology v. U.S. Patent and Trademark Office*, 653 F.3d 1329 (Fed. Cir. 2011) (No. 2010-1406). *See also* Br. for Amicus Curiae Intellectual Prop. Law Ass’n in Supp. of Reversal, but in Supp. of Neither Party at 2, *Ass’n for Molecular Pathology*, 653 F.3d 1329 (Fed. Cir. 2011) (No. 2010-1406) (“Anything but simple, however, are the legal issues raised by those questions and the ramifications of the District Court's decision. At stake are significant medical and economic interests of individuals and industries alike.”).

The patents give Myriad the authority to prevent all research and clinical testing of the BRCA1 and BRCA2 genes. Myriad has vigorously enforced its patents to stop clinical testing by any

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<sup>9</sup> Other amici in support of plaintiffs included the Southern Baptist Convention. Myriad’s amici included associations of biotechnology corporations. They too recognized that this issue is critical.

other lab. App. at 163-66a, 262-65a. Myriad did so even during a period of several years when it failed to look for all known mutations and was thus providing false negative results to some women. App. at 160a. Other labs, which were willing to do more comprehensive and therefore more accurate testing, were barred by Myriad from doing so. App. at 166-67a. Currently, Myriad collects a huge amount of data on the nature and significance of variants in the BRCA1 and BRCA2 genes, but refuses to share that data with the scientific community and has no obligation to fully develop scientific knowledge about the genes. App. at 174a. Many women, upon obtaining results from Myriad, wish to get a second opinion before they submit to life-altering, prophylactic surgery. Myriad refuses to allow any lab to confirm the results through sequencing the genes. App. at 169-70a. The patents preclude others from providing testing, even where they could do so for a lower price or for free. Myriad has contracts with only half of the state Medicaid insurance programs. Only 130 million of America's 308 million people can receive insurance coverage for their testing. Second Corrected App. Vol. VI at A4703, *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 653 F.3d 1329 (Fed. Cir. 2011) (No. 2010-1406).

The usual rationale for granting a patent – the need to create economic incentives to advance science – did not apply in this case and does not apply to products of nature. Researchers besides Myriad's were also looking for the BRCA1 and BRCA2 genes and had indicated that they would share their results with the scientific community. The widespread clinical testing of other, unpatented genes and the

extraordinary importance of breast and ovarian cancers make it clear that diagnostic tests resulting from the discoveries of BRCA1 and BRCA2 would have been made available to the public even without the patent incentive. *See App. at 175-76a.*

Indeed, as this Court has suggested, patenting basic elements of nature has the opposite effect, stifling research and scientific advancement. Where the claimed composition's "qualities are the work of nature," those qualities are not patentable, for "[t]hey are manifestations of laws of nature, free to all men and reserved exclusively to none." *Funk Bros.*, 333 U.S. at 130. To otherwise hold would be "allowing a patent to issue on one of the ancient secrets of nature now disclosed." *Id.* at 132. Accordingly, "[p]atent law seeks to avoid the dangers of overprotection just as surely as it seeks to avoid the diminished incentive to invent that underprotection can threaten," by bringing certain types of invention and discovery within the scope of patentability while excluding others. *Lab. Corp. of Am. Holdings v. Metabolite Labs.*, 548 U.S. 124, 127 (U.S. 2006) (Breyer, J., dissenting); *Cf. Great Atl. & Pac. Tea Co. v. Supermarket Equip. Corp.*, 340 U.S. 147, 155 (U.S. 1950) (Douglas, J., concurring) ("Every patent is the grant of a privilege of exacting tolls from the public. The Framers plainly did not want those monopolies freely granted. The invention, to justify a patent, had to serve the ends of science-to push back the frontiers of chemistry, physics, and the like").

Finally, it is of critical importance to women's health that knowledge about breast and ovarian cancer increase in order to advance diagnosis and

treatment. This case does not question the patentability of new methods of diagnosis or methods of treatment. It does not deal with new drugs or new instruments. Instead, it concerns perhaps the most basic elements of biology, human genes:

Genes are basic units of heredity found in all living organisms and are responsible for the inheritance of a discrete trait . . . . Together, the approximately 25,000 genes in the human body make up the human genome. The genome, and the genes within it, are contained within almost every cell in the human body and define physical traits such as skin tone, eye color, and sex, in addition to influencing the development of conditions such as obesity, diabetes, Alzheimer's disease, and bipolar disorder.

App. at 139-40a. As the district court found, "The widespread use of gene sequence information as the foundation for biomedical research means that resolution of these issues will have far-reaching implications, not only for gene-based health care and the health of millions of women facing the specter of breast cancer, but also for the future course of biomedical research." App. at 243a.

The extraordinary importance of the issues presented by this case combined with the lack of clarity concerning the legal issues it presents merit review by this Court.



## II. PATENTS ON “ISOLATED” DNA ARE INVALID UNDER THIS COURT’S SECTION 101 JURISPRUDENCE AND THE U.S. CONSTITUTION.

The patenting of isolated DNA violates long-established Supreme Court precedent that prohibits the patenting of laws of nature, natural phenomena, products of nature, and abstract ideas. *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980). “[T]he relevant distinction’ for purposes of § 101 is . . . ‘between products of nature, whether living or not, and human-made inventions.” *J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int’l, Inc.*, 534 U.S. 124, 130, 134 (2001) (quoting *Chakrabarty*, 447 U.S. at 313). See also *Gen. Elec. Co. v. De Forest Radio Co.*, 28 F.2d 641, 643 (3d Cir. 1928); *In re Marden (Marden II)*, 47 F.2d 958, 959 (C.C.P.A. 1931); *In re Marden (Marden I)*, 47 F.2d 957 (C.C.P.A. 1931). In *Bilski*, the Court affirmed that subject matter eligibility remains a threshold question, separate and distinct from considerations of utility or novelty. 130 S. Ct. at 3225; see also *Parker v. Flook*, 437 U.S. 584, 593 (1978); *Diamond v. Diehr*, 450 U.S. 175, 189-90 (1981).

In deciding that the patents at issue survive Section 101, the Federal Circuit departed dramatically from *Chakrabarty*, *Funk Brothers*, and *American Fruit Growers*, this Court’s seminal cases on the product of nature doctrine. Those cases held that a claimed composition does not become patentable simply because there has been a change in its structure, as the opinion of Judge Lourie

concluded below. Instead, the Section 101 inquiry involves more: whether the claimed composition has “a distinctive name, character [and] use” and “markedly different characteristics from any found in nature,” *Chakrabarty*, 447 U.S. at 309-10 (citation omitted), and does not cover “nature’s handiwork” or “qualities that are the work of nature.” *Id.*; *Funk Bros.*, 333 U.S. at 130. Unless what is claimed meets these criteria, the patent will encumber “the storehouse of knowledge of all men.” *Funk Bros.*, 333 U.S. at 130.

Thus, the Court has examined the key characteristics, including function, of a claimed composition and determined whether they are the work of nature. Comparing the unpatentable combination of bacteria in *Funk Brothers* with the genetically-engineered and patentable *Chakrabarty* bacterium, the Court in *Chakrabarty* concluded that the latter has “markedly different characteristics from any found in nature,” while the former’s discovery is “nature’s handiwork.”

‘The combination of species [in *Funk Brothers*] produces no new bacteria, no change in the six species of bacteria, and no enlargement of the range of their utility. Each species has the same effect it always had. The bacteria perform in their natural way. Their use in combination does not improve in any way their natural functioning. They serve the ends nature originally provided and act quite independently of any effort of the patentee.’

Here, by contrast, the patentee has produced a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility. His discovery is not nature's handiwork, but his own; accordingly it is patentable subject matter under § 101.

*Chakrabarty*, 447 U.S. at 310 (quoting *Funk Bros.*, 333 U.S. at 131). Because the patent holder of the "isolated" *Funk Brothers* bacteria did "not create [a] state of inhibition or of non-inhibition in the bacteria," he could not patent the product, even though the bacteria did not exist together naturally, and even though their aggregate nitrogen-fixing capability had been newly identified and had commercial utility. 333 U.S. at 130-31. Similarly, in *Am. Fruit Growers, Inc. v. Brogdex Co.*, the Court rejected the patenting of a fruit that had been treated with mold-resistant borax, although the "complete article is not found in nature" and despite its "treatment, labor and manipulation." 283 U.S. 1, 11-12 (1931). The Court held that it did not become an "article of manufacture" unless it "possesses a new or distinctive form, quality, or property" distinct from nature. *Id.*

Just as the fruit and the aggregation of bacteria strains were products of nature, so too are the isolated DNA at issue here. The patent claims themselves define "isolated DNA" according to a naturally-occurring functional characteristic – namely, "coding for" a naturally-occurring polypeptide. Thus, the claims explicitly recognize that DNA stores and conveys specific information –

as dictated by the natural order of nucleotides – that serves as the blueprint for proteins, and ultimately the cells and organs, that make up the human body. Because this blueprint is the essential characteristic of DNA and remains the same before and after isolation, “isolated” DNA has neither a distinctive name, character, or use from naturally-occurring DNA, nor markedly different characteristics. Both are DNA, their structures are not markedly different, the protein coded for by each is the same, and their use in storing and transmitting information about a person’s heredity is identical.

The Federal Circuit failed to properly analyze DNA’s characteristics in light of this Court’s precedents. The opinion of the court by Judge Lourie focused only on the chemical structure of DNA, disregarding its biological characteristics. App. at 50a (“We recognize that biologists may think of molecules in terms of their uses, but genes are in fact materials having a chemical nature and, as such, are best described in patents by their structures rather than their functions.”). That mode of analysis contradicts both the patent claim language – claiming isolated DNA as coding for a specified protein – and this Court’s repeated admonition that patents should be evaluated according to the actual claim language, *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 373 (1996); *White v. Dunbar*, 119 U.S. 47, 52 (1886). It also ignores the Court’s decisions establishing that function is a critical factor for determining whether something is patentable under Section 101. *Chakrabarty*, 447 U.S. at 310. Otherwise, the fruit of *American Fruit Growers* would surely have been patentable, for its structure was quite different from the naturally occurring

fruit, even though its use for human consumption remained the same. *See* 283 U.S. at 11-12. Furthermore, Judge Lourie elevated the importance of chemical bonds such that any cleavage of a covalent bond would render the resulting molecule patentable. App. at 49a. Such a rule has never been endorsed by this Court, or to the best of our knowledge, by any court, and runs counter to the pragmatic approach this Court has taken in applying Section 101. *Bilski*, 130 S. Ct. at 3226-27 (rejecting a rigid “machine-or-transformation” test for method claims). As in *Bilski*, the court of appeals again imposed an inflexible test not rooted in precedent.

Though the concurring opinion by Judge Moore discussed the structure and function of isolated DNA, it failed to take into account whether its qualities are the work of nature. *Chakrabarty*, 447 U.S. at 309-10; *Funk Bros.*, 333 U.S. at 130. In her view, an isolated DNA sequence that includes most or all of a gene might not be patentable because it would not have a clearly new utility or function compared to a naturally-occurring gene; however, a 15 nucleotide segment, as claimed in patent `282 cl. 5, would be patentable, because it could potentially be used as a primer or probe. App. at 75-79a. This holding flatly contradicts the Section 101 case law barring patents on a phenomenon of nature. *Funk Bros.*, 333 U.S. at 130. Because small sequences of DNA are repeated throughout the human genome, a claim on small segments of DNA, like claims 5 or 6 of `282, covers portions of the DNA of nearly all human genes, not just BRCA1. App. at 107-08a. None of the claims at issue here are limited to new uses of DNA fragments as primers or probes. Accordingly, claims like 5 and 6 of patent `282

preempt researchers from working with that segment of DNA, wherever it may appear in the genome, and poses a serious threat to scientific freedom and advancement. See *Bilski*, 130 S. Ct. at 3230-31; *Gottschalk v. Benson*, 409 U.S. 63, 71-72 (1972); *Funk Bros.*, 333 U.S. at 130 (“The qualities of these bacteria, like the heat of the sun, electricity, or the qualities of metals, are part of the storehouse of knowledge of all men . . . . He who discovers a hitherto unknown phenomenon of nature has no claim to a monopoly of it which the law recognizes.”). See also *Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124, 126-27 (2006) (Breyer, J., dissenting) (“[S]ometimes *too much* patent protection can impede rather than ‘promote the Progress of Science and useful Arts.’”).

Patents on isolated DNA, whether small segments or whole genes, also violate the First Amendment because they block scientific inquiry into the patented DNA. These patents prevent access to each person’s individual genetic information and deprive others from examining the BRCA1 and BRCA2 genes and engaging in fundamental scientific work. It is not possible to “invent around” human genes, as it is with a true invention, like a carburetor. Because the patents grant control over a body of knowledge and over pure information, they violate the First Amendment. *Ashcroft v. Free Speech Coal.*, 535 U.S. 234, 253 (2002) (“First Amendment freedoms are most in danger when the government seeks to control thought or to justify its laws for that impermissible end. The right to think is the beginning of freedom . . .”).

**III. BY HOLDING THAT PETITIONERS LACKED STANDING UNLESS THEY WERE PERSONALLY THREATENED BY MYRIAD, THE FEDERAL CIRCUIT IMPOSED A RIGID STANDING REQUIREMENT CONTRARY TO THIS COURT'S APPROACH IN *MEDIMMUNE*.**

In *MedImmune, Inc. v. Genentech, Inc.*, this Court declared that the correct standing analysis in patent cases, as in all other Article III cases, “is whether the facts alleged, under all the circumstances, show that there is a substantial controversy, between parties having adverse legal interests, of sufficient immediacy and reality to warrant the issuance of a declaratory judgment.” 549 U.S. 118, 127 (2007) (citation omitted); *see also Holder v. Humanitarian Law Project*, 130 S. Ct. 2705, 2717 (2010) (citing *MedImmune* in a non-patent case for the proposition that plaintiffs need not await actual enforcement before bringing a lawsuit or to have a credible fear of enforcement). *MedImmune* instructs that bright line rules and steadfast requirements are inappropriate when analyzing a plaintiff’s standing in a declaratory judgment action. 549 U.S. at 127. Yet, the Federal Circuit imposed just such a rule in concluding that plaintiffs lacked standing unless they were personally threatened by Myriad.

The court of appeals found:

Myriad’s active enforcement of its patent rights forced Dr. Ostrer, *as well as every other similarly situated researcher and institution*, to cease performing the challenged *BRCA*

testing services . . . . Myriad's enforcement efforts eliminated all competition . . . . [N]othing in the record suggests that any researcher or institution has successfully attempted to compete with Myriad, or that Myriad has in any way changed its position with regard to its patent rights.

App. at 34-35a (emphasis added). The court then inexplicably held that these facts did not amount to an “injury traceable to Myriad” and amounted to “suffering an attenuated, non-proximate, effect from the existence of a patent,” for all of the plaintiffs other than Dr. Ostrer. App. at 34-39a.

It is difficult to reconcile a holding that all of the plaintiffs have been “forced to cease” their actions as a result of Myriad's actions and that the effect of Myriad's actions was to “eliminate all competition” with a holding that the effect of Myriad's actions was “attenuated, non-proximate,” and insufficient to create standing. Furthermore, the idea that a plaintiff cannot have standing unless a patent holder “directed any letters or other communications regarding its patents at them,” App. at 23a, is contrary to numerous decisions of this Court that parties may bring challenges even if they have not been personally threatened by those who enforce the requirement they seek to challenge.

In *MedImmune*, this Court held that the Federal Circuit's prior standing rules were contrary to precedent including *Aetna Life Ins. Co. v. Haworth*, 300 U.S. 227, 239 (1937), “where jurisdiction obtained even though the very reason the insurer sought declaratory relief was that the



insured had given no indication that he would file suit.” 549 U.S. at 132 n.11. This holding was consistent with many other decisions from this Court. *Doe v. Bolton*, 410 U.S. 179, 188 (1973) (finding that physicians have standing “despite the fact that the record does not disclose that any one of them has been prosecuted, or threatened with prosecution, for violation of the State’s abortion statutes”); *Virginia v. Am. Booksellers Ass’n, Inc.*, 484 U.S. 383, 393 (1988) (“We are not troubled by the pre-enforcement nature of this suit. The State has not suggested that the newly enacted law will not be enforced, and we see no reason to assume otherwise. We conclude that plaintiffs have alleged an actual and well-founded fear that the law will be enforced against them.”). Indeed, as *American Booksellers* suggests, the burden is on the enforcers to say that they will not enforce, a burden Myriad in this case has studiously refused to meet. App. at 286-87a. See also *Vt. Right to Life Comm., Inc. v. Sorrell*, 221 F.3d 376, 382 (2d Cir. 2000) (civil cases); *Biotech. Indus. Org. v. District of Columbia*, 496 F.3d 1362, 1370 (Fed. Cir. 2007).

The Federal Circuit’s newly minted rule that a party does not have declaratory judgment standing unless he or she has been personally threatened by a patent holder is even more restrictive than that court’s prior “reasonable apprehension” test, rejected by this Court in *MedImmune*. If the proper test is applied, based on the findings that all of the plaintiffs have been “forced to cease” activities as a result of Myriad’s actions that “eliminated all

competition” and that “nothing has changed,” each of the plaintiffs has standing.<sup>10</sup>

For the reasons stated above, the Federal Circuit’s new rule is erroneous. The medical organizational plaintiffs and most of the physician plaintiffs would be identical for standing purposes to Dr. Ostrer, because they have the equipment, expertise and desire to engage in testing but have refrained solely as a result of Myriad’s repeated suits and threats. In addition, the Federal Circuit’s inflexible standing requirement led it to wrongly dismiss the plaintiffs whose standing is based on contributory or inducing infringement. *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1365 (Fed. Cir. 2004) (disseminating medical information and a directory of medical service

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<sup>10</sup> This was not the circuit’s only clear error. Although the panel found that plaintiff Dr. Ostrer had standing, the court did not address the standing of the organizational plaintiff American College of Medical Genetics (ACMG), of which Dr. Ostrer is a member. App. at 249a. The undisputed record reflects that gene patenting is germane to ACMG’s purpose. App. at 244-45a. Pursuant to well-established law in this Court, ACMG therefore has organizational standing. *Warth v. Seldin*, 422 U.S. 490, 511 (1975). The panel also asserted that “[n]one of the plaintiffs besides Drs. Kazazian, Ganguly, and Ostrer, allege that Myriad directed any letters or other communications regarding its patents at them.” App. at 23a. That is simply incorrect and contrary to the factual findings of the district court. Plaintiff Ellen Matloff’s declaration makes clear that she personally had conversations with Myriad in which she was told by Myriad that she and geneticists at Yale would violate Myriad’s patents if they performed tests that were not being offered by Myriad, and which she wanted to perform. App. at 264a. The court of appeals held that a plaintiff had standing if Myriad directed “any ... communications regarding its patents at them.” Even under that standard, Ms. Matloff has standing.

providers was sufficient to trigger liability for inducing infringement).

## CONCLUSION

For the reasons stated above, the petition for certiorari should be granted.

Respectfully submitted,

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December 6, 2011

## APPENDIX

**United States Court of Appeals  
for the Federal Circuit**

No. 09-CV-4515

THE ASSOCIATION FOR  
MOLECULAR PATHOLOGY,  
THE AMERICAN COLLEGE  
OF MEDICAL GENETICS,  
THE AMERICAN SOCIETY  
FOR CLINICAL PATHOLOGY,  
THE COLLEGE OF  
AMERICAN PATHOLOGISTS,  
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GANGULY, PHD, WENDY  
CHUNG, MD, PHD, HARRY  
OSTRER, MD, DAVID  
LEDBETTER, PHD, STEPHEN  
WARREN, PHD, ELLEN  
MATLOFF, M.S., ELSA  
REICH, M.S., BREAST  
CANCER ACTION, BOSTON  
WOMEN'S HEALTH BOOK  
COLLECTIVE, LISBETH  
CERIANI, RUNI LIMARY,  
GENAE GIRARD, PATRICE  
FORTUNE, VICKY  
THOMASON, AND  
KATHLEEN RAKER,

*Plaintiffs-Appellees,*

UNITED STATES PATENT  
AND TRADEMARK OFFICE,

*Defendant,*

MYRIAD GENETICS, INC.,

*Defendant-Appellant,*

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PERSHING, AND MICHAEL  
K. YOUNG, IN THEIR  
OFFICIAL CAPACITY AS  
DIRECTORS OF THE  
UNIVERSITY OF UTAH  
RESEARCH FOUNDATION,

*Defendants-Appellants.*

Appeal from the United States District Court  
for the Southern District of New York  
Senior Judge Robert W. Sweet, Presiding.

Decided: July 29, 2011

Before LOURIE, BRYSON, and MOORE,

*Circuit Judges.*

Opinion for the court by *Circuit Judge*  
LOURIE. Opinion concurring in part by *Circuit*  
*Judge* MOORE.

Opinion concurring in part and dissenting in  
part by *Circuit Judge* BRYSON.

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## OPINION

LOURIE, *Circuit Judge*.

Myriad Genetics, Inc. and the Directors of the University of Utah Research Foundation (collectively, “Myriad”) appeal from the decision of the United States District Court for the Southern District of New York holding that an assortment of medical organizations, researchers, genetic counselors, and patients (collectively, “Plaintiffs”) have standing under the Declaratory Judgment Act to challenge Myriad’s patents. *Assoc. for Molecular Pathology v. U.S. Patent & Trademark Office*, 669 F. Supp. 2d 365 (S.D.N.Y. 2009) (“*DJ Op.*”). Myriad also appeals from the district court’s decision granting summary judgment that all of the challenged claims are drawn to non-patentable subject matter under 35 U.S.C. § 101. *Assoc. for Molecular Pathology v. U.S. Patent & Trademark Office*, 702 F. Supp. 2d 181 (S.D.N.Y. 2010) (“*SJ Op.*”). We affirm in part and reverse in part.

On the threshold issue of jurisdiction, we affirm the district court’s decision to exercise declaratory judgment jurisdiction because we conclude that at least one plaintiff, Dr. Harry Ostrer, has standing to challenge the validity of Myriad’s patents. On the merits, we reverse the district court’s decision that Myriad’s composition claims to “isolated” DNA molecules cover patent-ineligible products of nature under § 101 since the molecules as claimed do not exist in nature. We also reverse the district court’s decision that Myriad’s method claim to screening potential cancer therapeutics via changes in cell growth rates is directed to a patent-ineligible scientific principle. We, however, affirm the

court's decision that Myriad's method claims directed to "comparing" or "analyzing" DNA sequences are patent ineligible; such claims include no transformative steps and cover only patent-ineligible abstract, mental steps.

## BACKGROUND

Plaintiffs brought suit against Myriad, challenging the patentability of certain composition and method claims relating to human genetics. *See DJ Op.*, at 369-76. Specifically, Plaintiffs sought a declaration that fifteen claims from seven patents assigned to Myriad are drawn to patent-ineligible subject matter under 35 U.S.C. § 101: claims 1, 2, 5, 6, 7, and 20 of U.S. Patent 5,747,282 ("the '282 patent"); claims 1, 6, and 7 of U.S. Patent 5,837,492 ("the '492 patent"); claim 1 of U.S. Patent 5,693,473 ("the '473 patent"); claim 1 of U.S. Patent 5,709,999 ("the '999 patent"); claim 1 of U.S. Patent 5,710,001 ("the '001 patent"); claim 1 of U.S. Patent 5,753,441 ("the '441 patent"); and claims 1 and 2 of U.S. Patent 6,033,857 ("the '857 patent").

The challenged composition claims cover two "isolated" human genes, *BRCA1* and *BRCA2* (collectively, "*BRCA1/2*" or "*BRCA*"), and certain alterations, or mutations, in these genes associated with a predisposition to breast and ovarian cancers. Representative composition claims include claims 1, 2, and 5 of the '282 patent:

1. An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2.

2. The isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID NO:1.

5. An isolated DNA having at least 15 nucleotides of the DNA of claim 1.

SEQ ID NO:2 depicts the amino acid sequence of the BRCA1 protein, and SEQ ID NO: 1 depicts the nucleotide sequence of the *BRCA1* DNA coding region. '282 patent col.19 ll.48-50.

All but one of the challenged method claims cover methods of “analyzing” or “comparing” a patient’s *BRCA* sequence with the normal, or wild-type, sequence to identify the presence of cancer-predisposing mutations. Representative method claims include claim 1 of the '999 and '001 patents:

1. 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 12A, 14, 18 or 19 in a human which comprises *analyzing* a sequence of a BRCA1 gene or BRCA1 RNA from a human sample or *analyzing* a sequence of BRCA1 cDNA made from mRNA from said human sample with the proviso that said germline alteration is not a deletion of 4 nucleotides corresponding to base numbers 4184-4187 of SEQ ID NO:1.

'999 patent claim 1 (emphases added).

1. A method for screening a tumor sample from a human subject for a somatic alteration in a BRCA1 gene in said tumor which comprises [] *comparing* a first sequence selected from the group consisting of a BRCA1 gene from said tumor sample, BRCA1 RNA from said tumor sample and BRCA1 cDNA made from mRNA from said tumor sample with a second sequence selected from the group consisting of BRCA1 gene from a nontumor sample of said subject, BRCA1 RNA from said nontumor sample and BRCA1 cDNA made from mRNA from said nontumor sample, wherein a difference in the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA from said tumor sample from the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA from said nontumor sample indicates a somatic alteration in the BRCA1 gene in said tumor sample.

'001 patent claim 1 (emphasis added).

The final method claim challenged by Plaintiffs is directed to a method of screening potential cancer therapeutics. Specifically, claim 20 of the '282 patent reads as follows:

20. A method for screening potential cancer therapeutics which comprises: growing a transformed



eukaryotic host cell containing an altered BRCA1 gene causing cancer in the presence of a compound suspected of being a cancer therapeutic, growing said transformed eukaryotic host cell in the absence of said compound, determining the rate of growth of said host cell in the presence of said compound and the rate of growth of said host cell in the absence of said compound and comparing the growth rate of said host cells, wherein a slower rate of growth of said host cell in the presence of said compound is indicative of a cancer therapeutic.

The challenged claims thus relate to isolated gene sequences and diagnostic methods of identifying mutations in these sequences. To place this suit in context, we take a step back to provide background on the science involved, including the identification of the *BRCA* genes, and the Plaintiffs' connections to the invention and to Myriad.

## I.

Human genetics is the study of heredity in human beings.<sup>1</sup> The human genome, the entirety of human genetic information, contains approximately 25,000 genes, which form the basis of human inheritance. The majority of genes act by specifying polypeptide chains that form proteins. Proteins in

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<sup>1</sup> The district court's opinion, *SJ Op.*, at 192-203, contains a detailed and comprehensive discussion of the science involved in this case. We repeat only the basics here.

turn make up living matter and catalyze all cellular processes.

Chemically, the human genome is composed of deoxyribonucleic acid (“DNA”). Each DNA molecule is made up of repeating units of four nucleotide bases—adenine (“A”), thymine (“T”), cytosine (“C”), and guanine (“G”)—which are covalently linked, or bonded,<sup>2</sup> together via a sugar-phosphate, or phosphodiester, backbone. DNA generally exists as two DNA strands intertwined as a double helix in which each base on a strand pairs, or hybridizes, with a complementary base on the other strand: A pairs with T, and C with G. Figure 1 below depicts the structure of a DNA double helix and the complementary pairing of the four nucleotide bases, represented by A, T, C, and G.

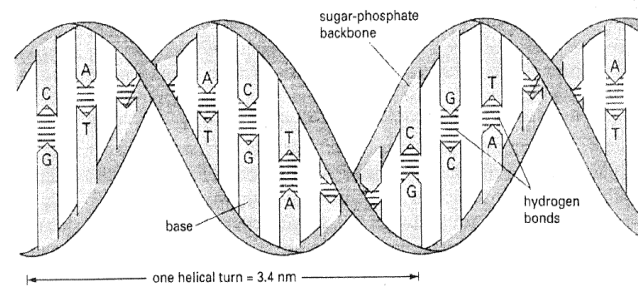


Figure 1

The linear order of nucleotide bases in a DNA molecule is referred to as its “sequence.” The sequence of a gene is thus denoted by a linear sequence of As, Ts, Gs, and Cs. “DNA sequencing” or “gene sequencing” refers to the process by which the

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<sup>2</sup> Covalent bonds are chemical bonds characterized by the sharing of electrons between atoms in a molecule.

precise linear order of nucleotides in a DNA segment or gene is determined. A gene's nucleotide sequence in turn encodes for a linear sequence of amino acids that comprise the protein encoded by the gene, *e.g.*, the *BRCA1* gene encodes for the BRCA1 protein. Most genes have both "exon" and "intron" sequences. Exons are DNA segments that are necessary for the creation of a protein, *i.e.*, that code for a protein. Introns are segments of DNA interspersed between the exons that, unlike exons, do not code for a protein.

The creation of a protein from a gene comprises two steps: transcription and translation. First, the gene sequence is "transcribed" into a different nucleic acid called ribonucleic acid ("RNA"). RNA has a chemically different sugar-phosphate backbone than DNA, and it utilizes the nucleotide base uracil ("U") in place of thymine ("T"). For transcription, the DNA double helix is unwound and each nucleotide on the non-coding, or template, DNA strand is used to make a complementary RNA molecule of the coding DNA strand, *i.e.*, adenine on the template DNA strand results in uracil in the RNA molecule, thymine results in adenine, guanine in cytosine, and cytosine in guanine. The resulting "pre-RNA," like the DNA from which it was generated, contains both exon and intron sequences. Next, the introns are physically excised from the pre-RNA molecule, in a process called "splicing," to produce a messenger RNA ("mRNA"). Figure 2 below shows the steps of transcribing a gene that contains three exons (exon 1-3) and two introns (intron 1 and 2) into a pre-RNA, followed by RNA splicing of the introns to produce an mRNA containing just the exon sequences.

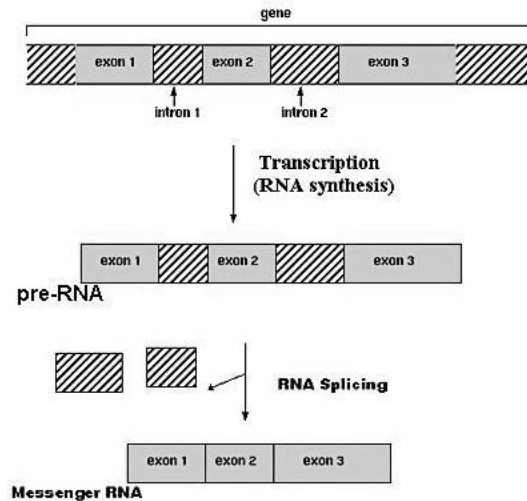


Figure 2

Following transcription, the resulting mRNA is “translated” into the encoded protein. Genes, and their corresponding mRNAs, encode proteins via three-nucleotide combinations called codons. Each codon corresponds to one of the twenty amino acids that make up all proteins or a “stop” signal that terminates protein translation. For example, the codon adenine-thymine-guanine (ATG, or UTG in the corresponding mRNA), encodes the amino acid methionine. The relationship between the sixty-four possible codon sequences and their corresponding amino acids is known as the genetic code. Figure 3 below represents an mRNA molecule that translates into a protein of six amino acids (Codon 1, AUG, methionine; Codon 2, ACG, threonine; Codon 3, GAG, glutamic acid; Codon 4, CUU, leucine; Codon 5, CGG, arginine; Codon 6, AGC, serine), and ends with one of the three stop codons, UAG.

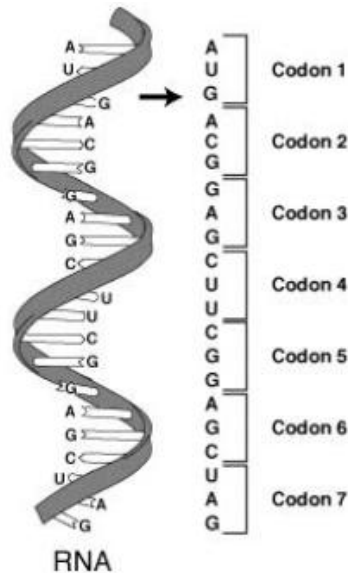


Figure 3

Changes, or mutations, in the sequence of a human gene can alter the structure as well as the function of the resulting protein. Small-scale changes include point mutations in which a change to a single nucleotide alters a single amino acid in the encoded protein. For example, a base change in the codon *GCU* to *CGU* changes an alanine in the encoded protein to an arginine. Larger scale variations include the deletion, rearrangement, or duplication of larger DNA segments, ranging from several hundreds to over a million nucleotides, and result in the elimination, misplacement, or duplication of an entire gene or genes. While some mutations have little or no effect on the body's processes, others result in disease, or an increased risk of developing a particular disease. DNA sequencing is used in clinical diagnostic testing to determine whether a

gene contains mutations associated with a particular disease or risk of a particular disease.

Nearly every cell in the human body contains an individual's entire genome. DNA in the cell, called "native" or "genomic" DNA, is packaged into twenty-three pairs of chromosomes. Chromosomes are complex structures of a single DNA molecule wrapped around proteins called histones, as shown in Figure 4 below.

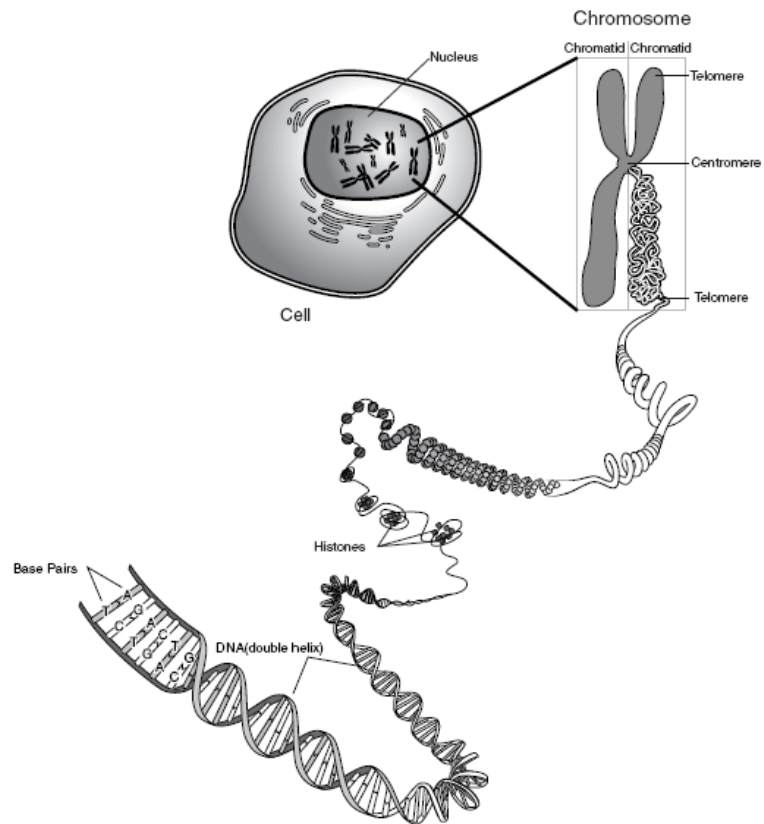


Figure 4

Humans have twenty-two pairs of autosomal chromosomes, numbered one to twenty-two according to size from largest to smallest, and one pair of sex chromosomes, two X chromosomes in females and one X and one Y chromosome in males.

Genomic DNA can be extracted from its cellular environment using a number of well-established laboratory techniques. A particular segment of DNA, such as a gene, can then be excised or amplified from the DNA to obtain the isolated DNA segment of interest. DNA molecules can also be synthesized in the laboratory. One type of synthetic DNA molecule is complementary DNA (“cDNA”). cDNA is synthesized from mRNA using complementary base pairing in a manner analogous to RNA transcription. The process results in a double-stranded DNA molecule with a sequence corresponding to the sequence of an mRNA produced by the body. Because it is synthesized from mRNA, cDNA contains only the exon sequences, and thus none of the intron sequences, from a native gene sequence.

## II.

Mutations in the *BRCA* genes correlate with an increased risk of breast and ovarian cancer. The average woman in the United States has around a twelve to thirteen percent risk of developing breast cancer in her lifetime. Women with *BRCA* mutations, in contrast, face a cumulative risk of between fifty to eighty percent of developing breast cancer and a cumulative risk of ovarian cancer of between twenty to fifty percent. Diagnostic genetic testing for the existence of *BRCA* mutations is therefore an

important consideration in the provision of clinical care for breast or ovarian cancer. This testing provides a patient with information on her risk for hereditary breast and ovarian cancers, and thus aids in the difficult decision regarding whether to undertake preventive options, including prophylactic surgery. Diagnostic results can also be an important factor in structuring an appropriate course of cancer treatment, since certain forms of chemotherapy are more effective in treating cancers related to *BRCA* mutations.

The inventors of the patents in suit identified the genetic basis of *BRCA1* and *BRCA2*-related cancers using an analysis called positional cloning. Relying on a large set of DNA samples from families with inherited breast and ovarian cancers, the inventors correlated the occurrence of cancer in individual family members with the inheritance of certain marker DNA sequences. This allowed the inventors to identify, or “map,” the physical location of the *BRCA* genes within the human genome and to isolate the *BRCA* genes and determine their exact nucleotide sequences. This in turn allowed Myriad to provide *BRCA* diagnostic testing services to women.

Myriad filed the first patent application leading to the patents in suit covering isolated *BRCA1* DNA and associated diagnostic methods in August 1994. The first patent, the '473 patent, issued on December 2, 1997. Myriad filed the first application leading to the patents in suit covering isolated *BRCA2* DNA and associated diagnostic methods in December 1995, and the first patent, the '492 patent, issued on November 17, 1998.



### III.

Myriad, however, was not the only entity to implement clinical *BRCA* testing services. Starting in 1996, the University of Pennsylvania's Genetic Diagnostic Laboratory ("GDL"), co-directed by plaintiffs Haig H. Kazazian, Jr., M.D. and Arupa Ganguly, Ph.D., provided *BRCA1/2* diagnostic services to women. By 1999, however, accusations by Myriad that GDL's *BRCA* testing services infringed its patents forced the lab to stop providing such services.

The first sign of a dispute came in early 1998. At that time, Dr. Kazazian recalls a dinner with Dr. Mark Skolnick, inventor and Chief Science Office at Myriad. At the dinner, Skolnick informed Kazazian that Myriad was planning to stop GDL from providing clinical *BRCA* testing in light of Myriad's patents. A month or two later, in May 1998, Kazazian received a letter from William A. Hockett, Director of Corporate Communications at Myriad. The letter stated that Myriad knew that Kazazian was currently providing *BRCA1* diagnostic testing services, and that Myriad, as patent holder of five patents covering the isolated *BRCA1* gene and diagnostic testing, was making available to select institutions a collaborative license. Attached to the letter was a copy of Myriad's collaborative agreement, which proposed severely limiting GDL's testing services to certain tests for patients of Ashkenazi Jewish descent. Plaintiff Harry Ostrer, M.D, a researcher at New York University ("NYU") School of Medicine, received the same letter and collaborative agreement in May 1998, although his laboratory did not, at the time, provide such testing

services. Rather, Ostrer sent patient samples to GDL for *BRCA* genetic testing.

Months later, in August 1998, Dr. Kazazian received a second letter, this time from George A. Riley of the law firm O'Melveny & Myers LLP. The letter identified by number five Myriad patents "covering, among other things, the *BRCA1* gene sequence . . . and methods for detecting alternations in the *BRCA1* sequence." J.A. 1145. The letter also indicated that it "has come to Myriad's attention that you are engaged in commercial testing activities that infringe Myriad's patents," and that "[u]nless and until a licensing arrangement is completed . . . you should cease all infringing testing activity." *Id.* The letter noted, however, that the cease-and-desist notification did not apply to research testing "for the purpose of furthering non-commercial research programs, the results of which are not provided to the patient and for which no money is received from the patient or the patient's insurance." *Id.*

In June 1999, Robert Terrell, the General Counsel for University of Pennsylvania, received a similar cease-and-desist letter from Christopher Wight, Myriad's General Counsel. The letter stated, "It has come to our attention that Dr. Haig H. Kazazian, Jr. of the University of Pennsylvania is continuing to willfully engage in commercial *BRCA1* and *BRCA2* genetic testing activities, in violation of the University of Pennsylvania's previous assurances that such commercial testing activities would be discontinued." J.A. 2890. Terrell responded to Wight by letter on September 10, 1999, stating that "the University agrees that it will not accept samples for *BRCA1* research testing from third parties." J.A.

2891. Kazazian thus informed Dr. Ostrer that GDL would no longer be accepting patient samples for *BRCA* testing from him or anyone else as a result of the patent infringement assertions made by Myriad. As a result, Ostrer started sending patient samples for *BRCA* genetic testing to Myriad, who became (and remains today) the only provider of such services in the United States.

During this period, Myriad also initiated several patent infringement suits against entities providing clinical *BRCA* testing. Myriad filed suit against Oncormed Inc. in 1997 and again in 1998, *Myriad Genetics v. Oncormed*, Nos. 2:97-cv-922, 2:98-cv-35 (D. Utah), and the University of Pennsylvania in 1998, *Myriad Genetics v. Univ. of Pa.*, No. 2:98-cv-829 (D. Utah). Both lawsuits were later dismissed without prejudice after each defendant agreed to discontinue all allegedly infringing activity.

None of the plaintiffs besides Drs. Kazazian, Ganguly, and Ostrer, allege that Myriad directed any letters or other communications regarding its patents at them. Rather, the other researchers and medical organization members state simply that knowledge of Myriad's vigorous enforcement of its patent rights against others stopped them from engaging in clinical *BRCA* genetic testing, although they have the personnel, expertise, and facilities as well as the desire to provide such testing. The patient plaintiffs state that they have been unable to obtain any *BRCA* genetic testing or their desired *BRCA* testing, either through their insurance or at a price that they can afford, because of Myriad's patent protection.

Like the other researchers, Dr. Kazazian states that if Myriad's patents were held invalid, he

and Dr. Ganguly would be able to resume *BRCA* testing within a matter of a few weeks. He notes, however, that this is only if they “decided to resume *BRCA* testing.” J.A. 2852. Ganguly concurs, stating that if the patents were invalidated, “I would immediately consider resuming *BRCA* testing in my laboratory.” J.A. 2892. Ostrer also indicates that his lab has all the personnel, facilities, and expertise necessary to undertake clinical *BRCA* testing and emphatically states that his lab “would immediately begin to perform *BRCA1/2*-related genetic testing upon invalidation of the Myriad patents.” J.A. 2936-38.

#### IV.

After Plaintiffs filed suit, Myriad moved to have the case dismissed, alleging that the Plaintiffs lacked standing to bring a declaratory judgment suit challenging the validity of its patents. The district court disagreed, however, holding that the Plaintiffs had established Article III standing under the “all the circumstances” test articulated by the Supreme Court in *MedImmune, Inc. v. Genentech, Inc.*, 549 U.S. 118, 127 (2007). *DJ Op.*, at 385-92. The court first found that Myriad had engaged in sufficient “affirmative acts” based on the company’s assertion of its “right to preclude others from engaging in *BRCA1/2* genetic testing through personal communications, cease-and-desist letters, licensing offers, and litigation,” the result of which was “the widespread understanding that one may engage in *BRCA1/2* testing at the risk of being sued for infringement liability by Myriad.” *Id.* at 390. Myriad’s actions, the court concluded, had placed “the Plaintiffs in precisely the situation that the

Declaratory Judgment Act was designed to address: the Plaintiffs have the ability and desire to engage in *BRCA1/2* testing as well as the belief that such testing is within their rights, but cannot do so without risking infringement liability.” *Id.*

In so holding, the court rejected Myriad’s argument that there must be some act directed toward the Plaintiffs, noting that Myriad had, in fact, taken affirmative acts toward plaintiffs Dr. Kazazian and Dr. Ganguly. *Id.* at 387-88. The court also rejected Myriad’s arguments that the cease-and-desist letter sent to plaintiff Kazazian was too old to support declaratory judgment jurisdiction and that the legal actions brought against third parties could not be considered in the jurisdictional analysis. *Id.* at 388-89. The court concluded that rigid adherence to either of these requirements would be inconsistent with *MedImmune’s* mandate that the court assess the facts alleged under all the circumstances. *Id.*

The district court also found that the Plaintiffs had alleged sufficient meaningful preparations for infringement to establish declaratory judgment jurisdiction. *Id.* at 390-92. With respect to the researchers, the court held it was sufficient that they were all “ready, willing, and able” to begin *BRCA1/2* testing within the normal course of their laboratories’ research, rejecting Myriad’s argument that they needed to allege specific preparatory activities. *Id.* at 390-91. The court also rejected Myriad’s argument that plaintiffs Kazazian and Ganguly testified only that they would “consider” engaging in allegedly infringing activities, concluding that the proper focus of the inquiry is whether they are meaningfully prepared, not whether they have made a final,

conclusive decision to engage in such activities. *Id.* at 391 n.18.

The parties then moved for summary judgment on the merits of Plaintiffs' § 101 challenge to Myriad's patent claims. The district court held for Plaintiffs, concluding that the fifteen challenged claims were drawn to non-patentable subject matter and thus invalid under § 101. *SJ Op.*, at 220-37. Regarding the composition claims, the court held that isolated DNA molecules fall within the judicially created "products of nature" exception to § 101 because such isolated DNAs are not "markedly different" from native DNAs. *Id.* at 222, 232 (quoting *Diamond v. Chakrabarty*, 447 U.S. 303 (1980)). The court relied on the fact that, unlike other biological molecules, DNAs are the "physical embodiment of information," and that this information is not only preserved in the claimed isolated DNA molecules, but also essential to their utility as molecular tools. *Id.* at 228-32.

Turning to the method claims, the court held them patent ineligible under this court's then definitive machine-or-transformation test. *Id.* at 233 (citing *In re Bilski*, 545 F.3d 943 (Fed. Cir. 2008), *affirmed on other grounds by Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010)). The court held that the claims covered "analyzing" or "comparing" DNA sequences by any method, and thus covered mental processes independent of any physical transformations. *Id.* at 233-35. In so holding, the court distinguished Myriad's claims from those at issue in *Prometheus* based on the "determining" step in the latter being construed to include the extraction and measurement of metabolite levels from a patient sample. *SJ Op.*, at

234-35 (citing *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, 628 F.3d 1347, 1350 (Fed. Cir. 2010), *cert. granted* 2011 WL 973139 (June 20, 2011)). Alternatively, the court continued, even if the claims could be read to include the transformations associated with isolating and sequencing human DNA, these transformations would constitute no more than preparatory data-gathering steps. *Id.* at 236 (citing *In re Grams*, 888 F.2d 835, 840 (Fed. Cir. 1989)). Finally, the court held that the one method claim to “comparing” the growth rate of cells claimed a basic scientific principle and that the transformative steps amounted to only preparatory data gathering. *Id.* at 237.

Myriad appealed. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

## **DISCUSSION**

### **I. Declaratory Judgment Jurisdiction**

#### **A.**

The first question we must address is whether the district court correctly exercised declaratory judgment jurisdiction over this suit. The Declaratory Judgment Act provides that, “In a case of actual controversy within its jurisdiction . . . any court of the United States . . . may declare the rights and other legal relations of any interested party seeking such declaration, whether or not further relief is or could be sought.” 28 U.S.C. § 2201(a). The phrase “a case of actual controversy” in the Act refers to the types of “cases” and “controversies” that are justiciable under Article III of the U.S. Constitution. *Aetna Life Ins. v. Haworth*, 300 U.S. 227, 239-40 (1937).

Although no bright-line rule exists for determining whether a declaratory judgment action satisfies Article III's case-or-controversy requirement, the Supreme Court has held that the dispute must be "definite and concrete, touching the legal relations of parties having adverse legal interests," "real and substantial," and "admi[t] of specific relief through a decree of a conclusive character, as distinguished from an opinion advising what the law would be upon a hypothetical state of facts." *MedImmune*, 549 U.S. at 127 (quoting *Aetna Life*, 300 U.S. at 240-41). "Basically, the question in each case is whether the facts alleged, under all the circumstances, show that there is a substantial controversy, between parties having adverse legal interests, of sufficient immediacy and reality to warrant the issuance of a declaratory judgment." *Id.* (quoting *Md. Cas. Co. v. P. Coal & Oil Co.*, 312 U.S. 270, 273 (1941)).

In applying *MedImmune's* all-the-circumstances test to a declaratory judgment action, we are guided by the Supreme Court's three-part framework for determining whether an action presents a justiciable Article III controversy: standing, ripeness, and mootness. *See Caraco Pharm. Labs., Ltd. v. Forest Labs., Inc.*, 527 F.3d 1278, 1291 (Fed. Cir. 2008). In this case, the parties have framed the jurisdictional issue as one of standing. *See MedImmune*, 549 U.S. at 128 n.8. ("The justiciability problem that arises, when the party seeking declaratory relief is himself preventing the complained-of injury from occurring, can be described in terms of standing . . . or . . . ripeness." (internal citations omitted)).



“[T]he irreducible constitutional minimum of standing contains three elements.” *Lujan v. Defenders of Wildlife*, 504 U.S. 555, 560 (1992). “First, the plaintiff must have suffered an injury in fact—an invasion of a legally protected interest which is (a) concrete and particularized, and (b) actual or imminent, not conjectural or hypothetical.” *Id.* (internal citations and quotations omitted). “Second, there must be a causal connection between the injury and the conduct complained of—the injury has to be ‘fairly . . . trace[able] to the challenged action of the defendant . . . .’” *Id.* (quoting *Simon v. E. Ky. Welfare Rights Org.*, 426 U.S. 26, 41-42 (1976)). “Third, it must be ‘likely,’ as opposed to merely ‘speculative,’ that the injury will be ‘redressed by a favorable decision.’” *Id.* at 561 (quoting *Simon*, 426 U.S. at 38, 43).

“Whether an actual case or controversy exists so that a district court may entertain an action for a declaratory judgment of non-infringement and/or invalidity is governed by Federal Circuit law.” *MedImmune, Inc. v. Centocor, Inc.*, 409 F.3d 1376, 1378 (Fed. Cir. 2005), *overruled on other grounds*, *MedImmune*, 549 U.S. at 130-31. Following *MedImmune*, this court has held that, to establish an injury in fact traceable to the patentee, a declaratory judgment plaintiff must allege both (1) an affirmative act by the patentee related to the enforcement of his patent rights, *SanDisk Corp. v. STMicroelectronics, Inc.*, 480 F.3d 1372, 1380-81 (Fed. Cir. 2007), and (2) meaningful preparation to conduct potentially infringing activity, *Cat Tech LLC v. TubeMaster, Inc.*, 528 F.3d 871, 880 (Fed. Cir. 2008). We review the exercise of declaratory judgment

jurisdiction upon a particular set of facts *de novo*.  
*SanDisk Corp.*, 480 F.3d at 1377.

**B.**

Myriad challenges the district court's jurisdictional decision on the grounds that Myriad and the Plaintiffs do not have adverse legal interests and that Plaintiffs have failed to allege a controversy of sufficient immediacy and reality to warrant the issuance of a declaratory judgment. Specifically, Myriad argues that Plaintiffs have failed to allege any "affirmative acts" by Myriad within the past ten years relating to the patents in suit or directed at any Plaintiff. According to Myriad, the district court erred by relying on "stale communications" directed at Drs. Kazazian, Ganguly, and Ostrer over a decade ago, as well as ten-year-old licensing and litigation activities directed at third parties, and thus exercised jurisdiction based solely on Plaintiffs' subjective fear of suit, arising from rumor and innuendo in the research community.

Plaintiffs respond that they have standing under *MedImmune's* all-the-circumstances test because, not only are they undisputedly prepared to immediately undertake potentially infringing activities, but also Myriad took sufficient affirmative acts with respect to the patents in suit. Regarding the latter, Plaintiffs assert that Myriad sued, threatened to sue, or demanded license agreements from every known institution offering *BRCA* clinical testing, including university labs directed by plaintiffs Kazazian, Ganguly, and Ostrer, forcing each to cease such testing. And, according to Plaintiffs, the awareness of Myriad's vigorous assertion of its patent rights still continues to

suppress their ability to perform clinical *BRCA* testing, placing Plaintiffs in the very dilemma the Declaratory Judgment Act was intended to address: they must either proceed with *BRCA*-related activities and risk liability for patent infringement, or refrain from such activities despite believing Myriad's patents are invalid.

Under the facts alleged in this case, we conclude that one Plaintiff, Dr. Ostrer, has established standing to maintain this declaratory judgment suit. All Plaintiffs claim standing under the Declaratory Judgment Act based on the same alleged injury: that they cannot undertake the *BRCA*-related activities that they desire because of Myriad's enforcement of its patent rights covering *BRCA1/2*.<sup>3</sup> Only three plaintiffs, however, allege an injury traceable to Myriad; only Drs. Kazazian, Ganguly, and Ostrer allege affirmative patent enforcement actions directed at them by Myriad. Of these three, Dr. Ostrer clearly alleges a sufficiently real and imminent injury because he alleges an intention to actually and immediately engage in allegedly infringing *BRCA*-related activities. We address each in turn.

Although *MedImmune* relaxed this court's more restrictive "reasonable apprehension of suit"

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<sup>3</sup> Certain patients also allege an injury based on their inability to gain access to affordable *BRCA* genetic testing because of Myriad's patent dominance of such services. While denial of health services can, in certain circumstances, state a judicially cognizable injury, *see Simon*, 426 U.S. at 40-41, Plaintiffs have not pressed this as an independent ground for standing. Moreover, we fail to see how the inability to afford a patented invention could establish an invasion of a legally protected interest for purposes of standing.

test for declaratory judgment jurisdiction, *SanDisk*, 480 F.3d at 1380, it did not alter “the bedrock rule that a case or controversy must be based on a *real* and *immediate* injury or threat of future injury that is *caused by the defendants*,” *Prasco, LLC v. Medicis Pharm. Corp.*, 537 F.3d 1329, 1339 (Fed. Cir. 2008). Accordingly, following *MedImmune*, this court has continued to hold that declaratory judgment jurisdiction will not arise merely on the basis that a party learns of the existence of an adversely held patent, or even perceives that such a patent poses a risk of infringement, in the absence of some affirmative act by the patentee. *SanDisk*, 480 F.3d at 1380-81. Thus, without defining the outer boundaries of declaratory judgment jurisdiction, we have held that “where a patentee asserts rights under a patent based on certain identified ongoing or planned activity of another party, and where that party contends that it has the right to engage in the accused activity without license, an Article III case or controversy will arise . . . .” *Id.* at 1381; *see also Prasco*, 537 F.3d at 1338 (“A patentee can cause . . . an injury [sufficient to create an actual controversy] in a variety of ways, for example, by creating a reasonable apprehension of an infringement suit, [or] demanding the right to royalty payments.” (internal citations omitted)).

In this case, Myriad demanded a royalty under its patents from Dr. Ostrer based on his clinical *BRCA*-related activities. In May 1998, Myriad’s Director of Corporate Communications sent Ostrer a letter proposing a collaborative license. The letter stated that Myriad was aware that Ostrer was either currently providing, or was interested in initiating, *BRCA1* diagnostic testing services and that Myriad,

as holder of U.S. patents covering the *BRCA1* gene and diagnostic testing of *BRCA1*, was making available to his institution, NYU Medical Center, a limited collaborative license. The collaborative license required NYU to make a payment to Myriad for each non-research *BRCA* test performed.

At the same time, as Ostrer was aware, Myriad was asserting its patent rights against other similarly situated parties, a fact to be considered in assessing the existence of an actual controversy under the totality of circumstances. *See Micron Tech., Inc. v. Mosaid Techs., Inc.*, 518 F.3d 897, 901 (Fed. Cir. 2008). Soon after Ostrer received Myriad's letter, Dr. Kazazian informed him that, because of Myriad's assertion of its patent rights against him, GDL would no longer be accepting patient samples for *BRCA* genetic testing. Myriad's assertion of its patent rights against Kazazian escalated into a patent infringement suit by Myriad against the University of Pennsylvania, which was later dismissed without prejudice after the University agreed to cease all accused *BRCA* testing services. Myriad also sued Oncormed for patent infringement based on its *BRCA* genetic testing services. As a result of Myriad's patent enforcement actions, Dr. Ostrer was forced to send all patient samples to Myriad, now the sole provider of *BRCA* diagnostic testing services.

Dr. Ostrer, on the other hand, maintains that he could have proceeded with his *BRCA*-related clinical activities without taking a license from Myriad. This assertion is based on his belief that the patents Myriad claims cover such activities are invalid because genes are patent-ineligible products

of nature. Acting on his belief, Ostrer seeks in this lawsuit a declaration of his right to undertake *BRCA*-related clinical activities without a license. Accordingly, Myriad and Dr. Ostrer have taken adverse legal positions regarding whether or not Ostrer can engage in *BRCA* genetic testing without infringing any valid claim to “isolated” *BRCA* DNAs or methods of “analyzing” or “comparing” *BRCA* sequences, as recited in Myriad’s patents. *See Aetna Life*, 300 U.S. at 242 (holding declaratory judgment jurisdiction existed when “the parties had taken adverse positions with respect to their existing obligations” on an insurance contract).

Dr. Ostrer has also alleged a controversy of sufficient reality and immediacy, *MedImmune*, 549 U.S. at 127; he has alleged a concrete and actual injury traceable to Myriad’s assertion of its patent rights, *see Lujan*, 504 U.S. at 560. First, Ostrer seeks to undertake specific *BRCA*-related activities—*BRCA* diagnostic testing—for which Myriad has demanded a license under specific patents—those that cover the isolated *BRCA* genes and *BRCA* diagnostic testing. Thus, Ostrer does not request “an opinion advising what the law would be upon a hypothetical state of facts,” *Aetna Life*, 300 U.S. at 241, but rather whether his proposed *BRCA* testing services are covered by valid patent claims to “isolated” *BRCA* genes and methods of “comparing” the genes’ sequences. Second, Ostrer not only has the resources and expertise to immediately undertake clinical *BRCA* testing, but also states unequivocally that he will immediately begin such testing. In contrast to Ostrer, who alleges an actual and imminent injury for purposes of standing, Drs. Kazazian and Ganguly allege only that they will

“consider” resuming *BRCA* testing. These “some day” intentions” are insufficient to support an “actual or imminent” injury for standing “without . . . any specification of *when* the some day will be.” *Lujan*, 504 U.S. at 564. As a result, Drs. Kazazian and Ganguly do not have standing.

Myriad seeks to escape this result based on the timing of its enforcement actions. Specifically, Myriad argues that time has extinguished the immediacy and reality of any controversy, relying on language that hearkens back to our pre-*MedImmune* reasonable apprehension of suit test. *See, e.g.*, Appellant Br. 26 (“[A] patentee’s ten-year silence presumptively extinguishes any reasonable objective fear of suit.”). We disagree. In many cases a controversy made manifest by a patentee’s affirmative assertion of its patent rights will dissipate as market players and products change. In this case, however, the relevant circumstances surrounding Myriad’s assertion of its patent rights have not changed despite the passage of time.<sup>4</sup>

Myriad’s active enforcement of its patent rights forced Dr. Ostrer, as well as every other similarly situated researcher and institution, to cease performing the challenged *BRCA* testing services, leaving Myriad as the sole provider of *BRCA* clinical testing to patients in the United

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<sup>4</sup> Myriad’s analogy to laches is also unconvincing. Laches bars the recovery of pre-filing damages; it does not preclude a patent action for prospective relief, the type of relief sought here. *See A.C. Aukerman Co. v. R.L. Chaides Const. Co.*, 960 F.2d 1020, 1041 (Fed. Cir. 1992) (*en banc*) (“[L]aches bars relief on a patentee’s claim only with respect to damages accrued prior to suit.”).

States. Since that time, neither the accused activities nor the parties' positions have changed. First, Myriad does not allege that genetic testing technology has changed in any way that renders its past assertions of its patent rights irrelevant to Ostrer's currently proposed *BRCA* testing. Rather, the patents cover, as Myriad asserted in the late 1990s, the basic components of any such test: the isolated *BRCA* genes and the diagnostic step of comparing the genes' sequences.

Second, ever since Myriad's enforcement efforts eliminated all competition, Myriad and Ostrer have not altered their respective positions. Ostrer, still laboring under Myriad's threat of infringement liability, has not attempted to provide *BRCA* testing; yet, as a researcher, he remains in the same position with respect to his ability and his desire to provide *BRCA* testing as in the late 1990s. Furthermore, nothing in the record suggests that any researcher or institution has successfully attempted to compete with Myriad, or that Myriad has in any way changed its position with regard to its patent rights. Just as active enforcement of one's patent rights against others can maintain a real and immediate controversy despite the passage of time, *see Micron*, 518 F.3d at 901, so too can the successful assertion of such rights when the relevant circumstances remain unchanged. Thus, consistent with the purpose of the Declaratory Judgment Act, Ostrer need not risk liability and treble damages for patent infringement before seeking a declaration of his contested legal rights. *See MedImmune*, 549 U.S. at 134.

Myriad also argues that the record refutes Ostrer's claim that he has been restrained from



engaging in *BRCA*-related gene sequencing. Specifically, Myriad argues that since Myriad published its discoveries of the *BRCA1* and *BRCA2* genes in October 1994 and March 1996, respectively, over 18,000 scientists have conducted research on the *BRCA* genes and over 8,600 research papers have been published. Furthermore, according to Myriad, plaintiff Wendy Chung concedes that her lab currently conducts sequencing of *BRCA* genes. Yet, both Drs. Chung and Ostrer state that, although they conduct gene sequencing, they are forbidden from informing their research subjects of the results of their *BRCA* tests without first sending the samples to Myriad. Accordingly, Ostrer is restrained from the *BRCA*-related activity that he desires to undertake: clinical diagnostic testing.

Myriad's communications with Dr. Ostrer confirm this understanding. The licensing letter Myriad sent to Ostrer proposed a collaborative agreement giving NYU the right to perform "Research Tests" without payment to Myriad. J.A. 2967. "Research Tests" are defined as tests that further "non-commercial research programs, the results of which *are not provided to the patient* and for which no money is received." J.A. 2965 (emphasis added). In contrast, the agreement requires payment to Myriad for each "Testing Service" performed, with "Testing Services" defined as "medical laboratory testing . . . for the presence or absence of *BRCA1* mutations for the purpose of determining or predicting predisposition to, or assessing the risk of breast or ovarian cancer in humans." J.A. 2966-67. Thus, Myriad's patent enforcement actions never targeted the non-clinical *BRCA* research now cited by

Myriad, and Ostrer's ability to perform such research does not address the injury asserted here.

Finally, Myriad argued in its reply brief and at oral argument that Plaintiffs' declaratory action will not afford them the relief they want, a requirement for standing. *Lujan*, 504 U.S. at 560-61; *see also MedImmune*, 549 U.S. at 127 n.7 (“[A] litigant may not use a declaratory-judgment action to obtain piecemeal adjudication of defenses that *would not finally and conclusively resolve* the underlying controversy.”). Specifically, Myriad asserts that because Plaintiffs have challenged just fifteen composition and method claims, while admitting that other unchallenged claims to *BRCA* probes and primers will still prevent them from engaging in *BRCA* sequencing, a favorable decision will not redress the Plaintiffs' alleged injury. Again, we disagree.

The Supreme Court has required only that it is “likely,” rather than “merely ‘speculative,’” that the alleged injury will be “redressed by a favorable decision.” *Lujan*, 504 U.S. at 561. The Court has not required certainty. For example, in *Village of Arlington Heights v. Metropolitan Housing Development Corp.*, the Court held that the plaintiffs had standing to challenge a suburb's exclusionary zoning ordinance, as the ordinance stood as “an absolute barrier” to the housing development Metropolitan Housing Development Corp. (“MHDC”) had contracted to provide in the village. 429 U.S. 252, 261 (1977). The Court noted that injunctive relief, while removing the “barrier” of the ordinance, would not “guarantee” that the housing would be built since MHDC still had to secure financing,

qualify for federal subsidies, and carry through with construction. *Id.* The Court nevertheless recognized that “all housing developments are subject to some extent to similar uncertainties,” and concluded that it was sufficient that there was a “substantial probability” that the housing development would be built. *Id.* at 261, 264.

In this case, Myriad’s challenged composition and method claims undisputedly provide “an absolute barrier” to Dr. Ostrer’s ability to undertake *BRCA* diagnostic testing activities, and a declaration of those claims’ invalidity would remove that barrier. *See id.* at 261. Moreover, while there may be other patent claims directed to *BRCA* probes and primers that prevent Ostrer from performing *BRCA* diagnostic testing free of infringement liability, Myriad has failed to direct us to any specific unchallenged claim that will have that effect. And Plaintiffs’ counsel stated at oral argument that his clients can sequence the *BRCA* genes without using *BRCA* probes and primers. Oral Arg. at 34:07-25, 34:53-35:29 available at <http://www.cafc.uscourts.gov/oral-argument-recordings/2010-1406/all>. Accordingly, we decline to construe claims and hold on this record that Dr. Ostrer’s proposed *BRCA*-related activities would infringe unchallenged claims to primers and probes. We thus conclude that it is likely, not merely speculative, that Dr. Ostrer’s injury will be redressed by a favorable decision.

Accordingly, although we affirm the district court’s decision to exercise declaratory judgment jurisdiction, we affirm on much narrower grounds. The district court failed to limit its jurisdictional holding to affirmative acts by the patentee directed

at specific Plaintiffs, *see San-Disk*, 480 F.3d at 1380-81, erroneously holding all the Plaintiffs had standing based on “the widespread understanding that one may engage in *BRCA1/2* testing at the risk of being sued for infringement liability by Myriad,” *DJ Op.*, at 390. We disagree, and thus we reverse the district court’s holding that the various plaintiffs other than Dr. Ostrer have standing to maintain this declaratory judgment action. Simply disagreeing with the existence of a patent or even suffering an attenuated, non-proximate, effect from the existence of a patent does not meet the Supreme Court’s requirement for an adverse legal controversy of sufficient immediacy and reality to warrant the issuance of a declaratory judgment. *See MedImmune*, 549 U.S. at 127.

Having found one plaintiff with standing to maintain this declaratory judgment action, *see Horne v. Flores*, 129 S. Ct. 2579, 2592-93 (2009), we may turn now to the merits of Myriad’s appeal of the district court’s summary judgment decision, which held all fifteen challenged composition and method claims invalid under § 101.

## **II. Patentable Subject Matter**

Under the Patent Act, “Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.” 35 U.S.C. § 101. The Supreme Court has consistently construed § 101 broadly, explaining that “[i]n choosing such expansive terms . . . modified by the comprehensive ‘any,’ Congress plainly

contemplated that the patent laws would be given wide scope.” *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010) (quoting *Chakrabarty*, 447 U.S. at 308).

The Supreme Court, however, has also consistently held that § 101, although broad, is not unlimited. *Id.* The Court’s precedents provide three judicially created exceptions to § 101’s broad patent-eligibility principles: “laws of nature, physical phenomena, and abstract ideas.” *Id.* (quoting *Chakrabarty*, 447 U.S. at 309). The Court has also referred to these exceptions as precluding the patenting of phenomena of nature, mental processes, *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972), and products of nature, *Chakrabarty*, 447 U.S. at 313 (“[T]he relevant distinction for purposes of § 101 is . . . between products of nature . . . and human-made inventions.”). The Court has explained that, although not required by the statutory text, “[t]he concepts covered by these exceptions are ‘part of the storehouse of knowledge of all men . . . free to all men and reserved exclusively to none.’” *Bilski*, 130 S. Ct. at 3225 (quoting *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948))

Plaintiffs challenge under § 101 Myriad’s composition claims directed to “isolated” DNA molecules and method claims directed to “analyzing” or “comparing” DNA sequences. We address each in turn.

#### **A. Composition Claims: Isolated DNA Molecules**

##### **i.**

Myriad argues that its challenged composition claims to “isolated” DNAs cover patent-eligible compositions of matter within the meaning of § 101.

According to Myriad, the district court came to a contrary conclusion by (1) misreading Supreme Court precedent as excluding from patent eligibility all “products of nature” unless “markedly different” from naturally occurring ones; and (2) incorrectly focusing not on the differences between isolated and native DNAs, but on one similarity: their informational content. Rather, Myriad argues, an isolated DNA molecule is patent eligible because it is, as claimed, “a nonnaturally occurring composition of matter” with “a distinctive name, character, and use.” Appellant Br. 41-42 (quoting *Chakrabarty*, 447 U.S. at 309-10). According to Myriad, isolated DNA does not exist in nature, and isolated DNAs, unlike native DNAs, can be used as primers and probes for diagnosing cancer. Moreover, Myriad asserts that a categorical “products of nature” exception not only would be unworkable, as every composition of matter is, at some level, composed of natural materials, but also would be contrary to this court’s precedents, the PTO’s 2001 *Utility Examination Guidelines*, and Congress’s role in enacting the patent laws.

Plaintiffs respond that claims to isolated DNA molecules fail to satisfy § 101 because such claims cover natural phenomena and products of nature. According to Plaintiffs, Supreme Court precedent establishes that a product of nature is not patent eligible even if, as claimed, it has undergone some highly useful change from its natural form. Rather, Plaintiffs assert, to be patent eligible a composition of matter must also have a distinctive name, character, and use, making it “markedly different” from the natural product. In this case, Plaintiffs conclude that because isolated DNAs retain the same nucleotide sequence as native DNAs, they do not

have any “markedly different” characteristics. Furthermore, according to Plaintiffs, the isolated DNA claims also have a preemptive effect, excluding anyone from working with the *BRCA* genes.

The government as amicus curiae does not defend the PTO’s longstanding position that isolated DNA molecules are patent eligible, arguing instead for a middle ground. Specifically, the government argues that DNA molecules engineered by man, including cDNAs,<sup>5</sup> are patent-eligible compositions of matter because, with rare exceptions, they do not occur in nature, either in isolation or as contiguous sequences within a chromosome. In contrast, the government asserts, isolated and unmodified genomic DNAs are *not* patent eligible, but rather patent-ineligible products of nature, since their nucleotide sequences exist because of evolution, not man.

At oral argument, the government illustrated its argument by way of a “magic microscope” test. Oral Arg. at 46:50-47:50. According to the government’s test, if an imaginary microscope could focus in on the claimed DNA molecule as it exists in the human body, the claim covers unpatentable subject matter. The government thus argues that because such a microscope could focus in on the claimed isolated *BRCA1* or *BRCA2* sequences as they exist in the human body, the claims covering those sequences are not patent eligible. In contrast, the government contends, because an imaginary microscope could not focus *in vivo* on a cDNA

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<sup>5</sup> According to the government, several of the composition claims at issue in this suit, including claim 2 of the ’282 patent, are limited to cDNA and thus patent eligible.

sequence, which is engineered by man to splice together non-contiguous coding sequences (*i.e.*, exons), claims covering cDNAs are patent eligible.

In sum, although the parties and the government appear to agree that isolated DNAs are compositions of matter, they disagree on whether and to what degree such molecules fall within the exception for products of nature. As set forth below, we conclude that the challenged claims to isolated DNAs, whether limited to cDNAs or not, are directed to patent-eligible subject matter under § 101.

**ii.**

The Supreme Court's decisions in *Chakrabarty* and *Funk Brothers* set out the framework for deciding the patent eligibility of isolated DNA molecules.<sup>6</sup>

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<sup>6</sup> Other Supreme Court decisions cited by the parties and amici were decided based on lack of novelty, not patentable subject matter. In *American Wood-Paper Co. v. Fibre Disintegrating Co.*, the Court held the challenged patent “void for want of novelty in the manufacture patented,” because the “[p]aper-pulp obtained from various vegetable substances was in common use before the original patent was granted . . . , and whatever may be said of their process for obtaining it, the product was in no sense new.” 90 U.S. 566, 596 (1874). Similarly, in *Cochrane v. Badische Anilin & Soda Fabrik*, the Court held that a claim to artificial alizarine covered an old and well-known substance, the alizarine of madder, which could not be patented although made artificially for the first time. 111 U.S. 293, 311 (1884); see *also id.* at 308-09 (“It is very plain that the specification of the original patent, No. 95,465, states the invention to be a process for preparing alizarine, *not as a new substance prepared for the first time*, but as the substance already known as alizarine, to be prepared, however, by the new process, which process is to be the subject of the patent, and is the process of preparing the *known product* alizarine from anthracine.” (emphases added)).



In *Chakrabarty*, the Court addressed the question whether a man-made, living microorganism is a patentable manufacture or composition of matter within the meaning of § 101. 447 U.S. at 305, 307. The microorganisms were bacteria genetically engineered with four naturally occurring DNA plasmids, each of which enabled the breakdown of a different component of crude oil. *Id.* at 305, 305 n.1. The bacteria, as a result, could break down multiple components of crude oil, a trait possessed by no single naturally occurring bacterium and of significant use in more efficiently treating oil spills. *Id.* at 305, 305 n.2. The Court held that the bacteria qualified as patentable subject matter because the “claim is not to a hitherto unknown natural phenomenon, but to a non-naturally occurring manufacture or composition of matter—a product of human ingenuity ‘having a distinctive name, character [and] use.’” *Id.* at 309-10 (quoting *Hartranft v. Wiegmann*, 121 U.S. 609, 615 (1887)).

To underscore the point, the Court compared Chakrabarty’s engineered bacteria with bacteria inoculants found unpatentable in *Funk Brothers*, again casting this case decided on obviousness in terms of § 101. *See Parker v. Flook*, 437 U.S. 584, 591 (1978); *Benson*, 409 U.S. at 67. In *Funk Brothers*, the patentee discovered that certain strains of nitrogen-fixing bacteria associated with leguminous plants do not mutually inhibit each other. 333 U.S. at 129-30. Based on this discovery, the patentee produced (and claimed) mixed cultures of nitrogen-fixing species capable of inoculating a broader range of leguminous plants than single-species cultures. *Id.* The Court held that the bacteria’s qualities of non-inhibition were, “like the heat of the sun, electricity, or the

qualities of metals,” the “work of nature,” and thus not patentable. *Id.* at 130. The Court also held that application of the newly discovered bacterial trait of non-inhibition to create a mixed bacterial culture was not a patentable advance because no species acquired a different property or use. *Id.* at 131. The *Chakrabarty* Court thus concluded that what distinguished Chakrabarty’s bacteria from those claimed in *Funk Brothers*, and made the former patent eligible, was that Chakrabarty’s bacteria had “markedly different characteristics from any [bacterium] found in nature” based on the efforts of the patentee. *Chakrabarty*, 447 U.S. at 310.

The distinction, therefore, between a product of nature and a human-made invention for purposes of § 101 turns on a change in the claimed composition’s identity compared with what exists in nature. Specifically, the Supreme Court has drawn a line between compositions that, even if combined or altered in a manner not found in nature, have similar characteristics as in nature, and compositions that human intervention has given “markedly different,” or “distinctive,” characteristics. *Id.* *Hartranft*, 121 U.S. at 615; *see also Am. Fruit Growers v. Brogdex Co.*, 283 U.S. 1, 11 (1931). Applying this test to the isolated DNAs in this case, we conclude that the challenged claims are drawn to patentable subject matter because the claims cover molecules that are markedly different—have a distinctive chemical identity and nature—from molecules that exist in nature.

It is undisputed that Myriad’s claimed isolated DNAs exist in a distinctive chemical form—as distinctive chemical molecules—from DNAs in the

human body, *i.e.*, native DNA. Native DNA exists in the body as one of forty-six large, contiguous DNA molecules. Each DNA molecule is itself an integral part of a larger structural complex, a chromosome. In each chromosome, the DNA molecule is packaged around histone proteins into a structure called chromatin, which in turn is packaged into the chromosomal structure. *See supra*, Figure 3.

Isolated DNA, in contrast, is a free-standing portion of a native DNA molecule, frequently a single gene. Isolated DNA has been cleaved (*i.e.*, had covalent bonds in its backbone chemically severed) or synthesized to consist of just a fraction of a naturally occurring DNA molecule. For example, the *BRCA1* gene in its native state resides on chromosome 17, a DNA molecule of around eighty million nucleotides. Similarly, *BRCA2* in its native state is located on chromosome 13, a DNA of approximately 114 million nucleotides. In contrast, isolated *BRCA1* and *BRCA2*, with introns, each consists of just 80,000 or so nucleotides. And without introns, *BRCA2* shrinks to just 10,200 or so nucleotides and *BRCA1* to just around 5,500 nucleotides. Furthermore, claims 5 and 6 of the '282 patent cover isolated DNAs having as few as fifteen nucleotides of a *BRCA* sequence. Accordingly, *BRCA1* and *BRCA2* in their isolated state are not the same molecules as DNA as it exists in the body; human intervention in cleaving or synthesizing a portion of a native chromosomal DNA imparts on that isolated DNA a distinctive chemical identity from that possessed by native DNA.

As the above description indicates, isolated DNA is not purified DNA. Purification makes pure what was the same material, but was previously

impure. Although isolated DNA must be removed from its native cellular and chromosomal environment, it has also been manipulated chemically so as to produce a molecule that is markedly different from that which exists in the body. It has not been purified by being isolated. Accordingly, this is not a situation, as in *Parke-Davis & Co. v. H.K. Mulford Co.*, in which purification of adrenaline resulted in the *identical* molecule being “for every practical purpose a new thing commercially and therapeutically.” 189 F. 95, 103 (C.C.N.Y. 1911). Although, we note, Judge Learned Hand held the claimed purified “Adrenalin” to be patentable subject matter. *Id.* The *In re Marden* cases are similarly inapposite,<sup>7</sup> directed as they are to the patent ineligibility of purified natural

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<sup>7</sup> We note that *Bergy* is no longer binding law. *Bergy* was the companion case to *Charkarbarty*, and was vacated by the Supreme Court and remanded for dismissal as moot. *Diamond v. Chakrabarty*, 444 U.S. 1028 (1980). Other CCPA cases cited by the parties and amici were not decided based on patent eligibility. In *In re Bergstrom*, the court held that pure prostaglandin compounds, PGE(2) and PGE(3), were improperly rejected as lacking novelty. 427 F.2d 1394, 1394 (CCPA 1970); see *Bergy*, 596 F.2d at 961 (recognizing *Bergstrom* as a case decided under § 102). Similarly in *In re Kratz*, the court held non-obviousness claims to synthetically produced, substantially pure 2-methyl-2-pentenoic acid (“2M2PA”), a chemical that gives strawberries their flavor. 592 F.2d 1169, 1170 (CCPA 1979); see also *In re King*, 107 F.2d 618, 619 (CCPA 1939) (holding claims to vitamin C invalid for lack of novelty, as “[a]ppellants were not the first to discover or produce [vitamin C] in its pure form”); *In re Merz*, 97 F.2d 599, 601 (CCPA 1938) (holding claims to artificial ultramarine that contains non-floatable impurities invalid as not “inventive,” and thus as obvious).

elements—ductile uranium, 47 F.2d 957 (CCPA 1931), and vanadium, 47 F.2d 958 (CCPA 1931)—that are inherently ductile in purified form. *Parke-Davis* and *Marden* address a situation in which claimed compound A is purified from a physical mixture that contains compound A. In this case, the claimed isolated DNA molecules do not exist as in nature within a physical mixture to be purified. They have to be chemically cleaved from their chemical combination with other genetic materials. In other words, in nature, isolated DNAs are covalently bonded to such other materials. Thus, when cleaved, an isolated DNA molecule is not a purified form of a natural material, but a distinct chemical entity. In fact, some forms of isolated DNA require no purification at all, because DNAs can be chemically synthesized directly as isolated molecules.

The dissent disparages the significance of a “chemical bond,” presumably meaning a covalent bond, in distinguishing structurally between one molecular species and another. But a covalent bond is the defining boundary between one molecule and another. The dissent’s citation of Linus Pauling’s comment that covalent bonds “make it convenient for the chemist to consider [the aggregate] as an independent molecular species” underlines the point. The covalent bonds in this case separate one chemical species from another.

Plaintiffs argue that because the claimed isolated DNAs retain the same nucleotide sequence as native DNAs, they do not have any “markedly different” characteristics. This approach, however, looks not at whether isolated DNAs are markedly different—have a distinctive characteristic—from

naturally occurring DNAs, as the Supreme Court has directed, but at one similarity: the information content contained in isolated and native DNAs' nucleotide sequence. Adopting this approach, the district court disparaged the patent eligibility of isolated DNA molecules because their genetic function is to transmit information. We disagree, as it is the distinctive nature of DNA molecules as isolated compositions of matter that determines their patent eligibility rather than their physiological use or benefit. Uses of chemical substances may be relevant to the non-obviousness of these substances or to method claims embodying those uses, but the patent eligibility of an isolated DNA is not negated because it has similar informational properties to a different, more complex natural material that embodies it. The claimed isolated DNA molecules are distinct from their natural existence as portions of larger entities, and their informational content is irrelevant to that fact. We recognize that biologists may think of molecules in terms of their uses, but genes are in fact materials having a chemical nature and, as such, are best described in patents by their structures rather than their functions.

The district court in effect created a categorical rule excluding isolated genes from patent eligibility. *See SJ Op.*, at 228-29. But the Supreme Court has "more than once cautioned that courts 'should not read into the patent laws limitations and conditions which the legislature has not expressed,'" *Bilski*, 130 S. Ct. at 3226 (quoting *Diamond v. Diehr*, 450 U.S. 175, 182 (1981)), and has repeatedly rejected new categorical exclusions from § 101's scope, *see id.* at 3227-28 (rejecting the argument that business method patents should be categorically

excluded from § 101); *Chakrabarty*, 447 U.S. at 314-17 (same for living organisms). We therefore reject the district court’s unwarranted categorical exclusion of isolated DNA molecules.

Because isolated DNAs, not just cDNAs, have a markedly different chemical structure compared to native DNAs, we reject the government’s proposed “magic microscope” test, as it misunderstands the difference between science and invention and fails to take into account the existence of molecules as separate chemical entities. The ability to visualize a DNA molecule through a microscope, or by any other means, when it is bonded to other genetic material, is worlds apart from possessing an isolated DNA molecule that is in hand and usable. It is the difference between knowledge of nature and reducing a portion of nature to concrete form, the latter activity being what the patent laws seek to encourage and protect. The government’s microscope could focus in on a claimed portion of any complex molecule, rendering that claimed portion patent ineligible, even though that portion never exists as a separate molecule in the body or anywhere else in nature, and may have an entirely different utility. That would discourage innovation. One cannot visualize a portion of a complex molecule, including a DNA containing a particular gene, and will it into isolation as a unique entity. Visualization does not cleave and isolate the particular DNA; that is the act of human invention.

The parties and amici have provided many thought-provoking hypotheticals, each of which raises a complicated issue of patent eligibility not before the court. Accordingly, we address them only

briefly; courts decide cases, they do not draft legal treatises. It is suggested that holding isolated DNAs patent eligible opens the door to claims covering isolated chemical elements, like lithium; minerals found in the earth, like diamonds; atomic particles, like electrons; and even organs, like a kidney, and a leaf from a tree. None of these examples, however, as far as we can discern, presents the case of a claim to a composition having a distinctive chemical identity from that of the native element, molecule, or structure. Elemental lithium is the same element whether it is in the earth or isolated; the diamond is the same lattice of carbon molecules, just with the earth removed; the kidney is the same kidney, the leaf the same leaf. Some may have a changed form, quality, or use when prepared in isolated or purified form, but we cannot tell on this record whether the changes are sufficiently distinctive to make the composition markedly different from the one that exists in nature. In contrast, a portion of a native DNA molecule—an isolated DNA—has a markedly different chemical nature from the native DNA. It is, therefore, patentable subject matter.

The dissent indicates that we “acknowledge[] that elemental lithium (like other elements) would not be patentable subject matter because it ‘is the same element whether it is in earth or isolated.’” Again, these facts are not before us, so we do not attempt to evaluate the patentability of one form of lithium over another. Suffice it to say, however, that if lithium is found in the earth as other than elemental lithium, such as “in molecular form” “because it reacts with air and water,” it is not the same material as elemental lithium.



It is also important to dispute the dissent's analogy to snapping a leaf from a tree. With respect, no one could contemplate that snapping a leaf from a tree would be worthy of a patent, whereas isolating genes to provide useful diagnostic tools and medicines is surely what the patent laws are intended to encourage and protect. Snapping a leaf from a tree is a physical separation, not one creating a new chemical entity.

The dissent also mentions several times in its opinion the breadth of certain claims as grounds for objecting to their patentability. However, we do not have here any rejection or invalidation on the various grounds relating to breadth, such as in 35 U.S.C. § 112. The issue before us is patent eligibility, not the adequacy of the patents' disclosure to support particular claims.

Finally, our decision that isolated DNA molecules are patent eligible comports with the longstanding practice of the PTO. The Supreme Court has repeatedly stated that changes to longstanding practice should come from Congress, not the courts. In *J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred International, Inc.*, the Court rejected the argument that plants did not fall within the scope of § 101, relying in part on the fact that "the PTO has assigned utility patents for plants for at least 16 years and there has been no indication from either Congress or agencies with expertise that such coverage is inconsistent with [federal law]." 534 U.S. 124, 144-45 (2001); *see also Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 739 (2002) ("[C]ourts must be cautious before adopting changes that disrupt the settled expectations of the

inventing community.” (citing *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 28 (1997)); *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1347 (Fed. Cir. 2010) (upholding a written description requirement separate from enablement based in part on *stare decisis*).

In this case, the PTO has issued patents directed to DNA molecules for almost thirty years. In the early 1980s, the Office granted the first human gene patents. See Eric J. Rogers, *Can You Patent Genes? Yes and No*, 93 J. Pat. & Trademark Off. Soc’y 19 (2010). It is estimated that the PTO has issued 2,645 patents claiming “isolated DNA” over the past twenty-nine years, J.A. 3710, and that by 2005, had granted 40,000 DNA-related patents covering, in non-native form, twenty percent of the genes in the human genome, Rogers, *supra* at 40. In 2001, the PTO issued *Utility Examination Guidelines*, which reaffirmed the agency’s position that isolated DNA molecules are patent eligible, 66 Fed. Reg. 1092-94 (Jan. 5, 2001), and Congress has not indicated that the PTO’s position is inconsistent with § 101. If the law is to be changed, and DNA inventions excluded from the broad scope of § 101 contrary to the settled expectation of the inventing community, the decision must come not from the courts, but from Congress.

## II. Method Claims

We turn next to Myriad’s challenged method claims. The district court’s decision predated the Supreme Court’s decision in *Bilski*, which rejected this court’s machine-or-transformation test as the

exclusive test for determining whether an invention is a patent-eligible process under § 101, although the test remains “a useful and important clue.” 130 S. Ct. at 3227. Both parties, however, had the opportunity to address the Court’s decision in briefing and at oral arguments. Accordingly, we proceed to the merits, and we conclude that all but one of Myriad’s method claims are directed to patent-ineligible, abstract mental processes, and fail the machine-or-transformation test.

#### **A. Methods of “Comparing” or “Analyzing” Sequences**

Myriad argues that its claims to methods of “comparing” or “analyzing” *BRCA* sequences satisfy the machine-or-transformation test as applied by this court in *Prometheus* because each requires a transformation—extracting and sequencing DNA molecules from a human sample—before the sequences can be compared or analyzed. According to Myriad, the district court failed to recognize the transformative nature of the claims by (1) misconstruing the claim term “sequence” as just information, rather than a physical molecule; and (2) erroneously concluding, in the alternative, that Myriad’s proposed transformations were mere data-gathering steps, rather than central to the purpose of the claims.

Plaintiffs respond that these method claims are drawn to the abstract idea of comparing one sequence to a reference sequence and preempt a phenomenon of nature—the correlation of genetic mutations with a predisposition to cancer. And, according to the Plaintiffs, limiting the claims’ application to a specific technological field, *i.e.*, *BRCA*

gene sequences, is insufficient to render the claims patent eligible. Plaintiffs also assert that the claims do not meet the machine-or-transformation test because the claims' plain language includes just the one step of "comparing" or "analyzing" two gene sequences.

We conclude that Myriad's claims to "comparing" or "analyzing" two gene sequences fall outside the scope of § 101 because they claim only abstract mental processes. *See Benson*, 409 U.S. at 67 ("Phenomena of nature, . . . mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work."). The claims recite, for example, 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. '001 patent claim 1. This claim thus recites nothing more than the abstract mental steps necessary to compare two different nucleotide sequences: look at the first position in a first sequence; determine the nucleotide sequence at that first position; look at the first position in a second sequence; determine the nucleotide sequence at that first position; determine if the nucleotide at the first position in the first sequence and the first position in the second sequence are the same or different, wherein the latter indicates an alternation; and repeat for the next position.

Limiting the comparison to just the *BRCA* genes or, as in the case of claim 1 of the '999 patent, to just the identification of particular alterations, fails to render the claimed process patent eligible. As

the Supreme Court has held, “the prohibition against patenting abstract ideas ‘cannot be circumvented by attempting to limit the use of the formula to a particular technological environment.’” *Bilski*, 130 S. Ct. at 3230 (quoting *Diehr*, 450 U.S. at 191-92); see also *id.* at 3231 (“*Flook* established that limiting an abstract idea to one field of use . . . did not make the concept patentable.”). Although the *application* of a formula or abstract idea in a process may describe patentable subject matter, *id.* at 3230, Myriad’s claims do not apply the step of comparing two nucleotide sequences in a process. Rather, the step of comparing two DNA sequences is the entire process claimed.

To escape this result, Myriad attempts to read into its method claims additional, transformative steps. As described above, Myriad reads into its claims the steps of (1) extracting DNA from a human sample, and (2) sequencing the *BRCA* DNA molecule, arguing that both steps necessarily precede the step of comparing nucleotide sequences. The claims themselves, however, do not include either of these steps. The claims do not specify any action prior to the step of “comparing” or “analyzing” two sequences; the claims recite just the one step of “comparing” or “analyzing.” Moreover, those terms’ plain meaning does not include Myriad’s proposed sample-processing steps; neither comparing nor analyzing means or implies “extracting” or “sequencing” DNA or otherwise “processing” a human sample.

Myriad claims that “comparing” and “analyzing” take on this meaning when read in light of the patent specifications. Specifically, Myriad argues that the specifications show that the claim

term “sequence” refers not to information, but rather to a physical DNA molecule, whose sequence must be determined before it can be compared. We disagree. The patent specifications make clear that “sequence” does not exclusively specify a DNA molecule, but refers more broadly to the linear sequence of nucleotide bases of a DNA molecule. For example, Figure 10A-10H is described as showing the “genomic sequence of BRCA1.” ’473 patent col.5 l.66. Figure 10 does not show a physical DNA molecule; the figure lists a series of letters (Gs, As, Ts, and Cs) corresponding to the nucleotides guanine, adenine, thymine, and cytosine of a DNA molecule. Similarly, the patent specifications state that “[t]he nucleotide sequence for BRCA1 exon 4 is shown in SEQ ID NO: 11.” *Id.* col.53 ll.50-53. SEQ ID NO: 11 again lists a series of Gs, As, Ts, and Cs corresponding to the nucleotide sequence of *BRCA1* exon 4.

Accordingly, Myriad’s challenged method claims are distinguishable from the claims upheld under § 101 in *Prometheus*. In *Prometheus*, the patents claimed methods for optimizing the dosage of thiopurine drugs administered to patients with gastrointestinal disorders. 628 F.3d at 1350. As written, the claimed methods included the steps of (a) “administering” a thiopurine drug to a subject, and/or (b) “determining” the drug’s metabolites levels in the subject, wherein the measured metabolite levels are compared with predetermined levels to optimize drug dosage. *Id.* In holding that the claims satisfied § 101, this court concluded that, in addition to the “administering” step being transformative, the “determining” step was both transformative and central to the purpose of the claims. *Id.* at 1357. Specifically, the court held that because the

metabolite levels could not be determined by mere inspection, the determining step necessarily required a transformation: “Some form of manipulation . . . is necessary to extract the metabolites from a bodily sample and determine their concentration.” *Id.* Moreover, we concluded that this transformation was not just insignificant extra-solution activity or necessary data-gathering steps, but was central to the claims, because determining the metabolite levels was what enabled the optimization of drug dosage. *Id.*

Myriad’s claims, in contrast, do not include the step of “determining” the sequence of *BRCA* genes by, *e.g.*, isolating the genes from a blood sample and sequencing them, or any other necessarily transformative step. Rather, the comparison between the two sequences can be accomplished by mere inspection alone. Accordingly, Myriad’s claimed methods of comparing or analyzing nucleotide sequences fail to satisfy the machine-or-transformation test, and are instead directed to the abstract mental process of comparing two nucleotide sequences. The claims thus fail to claim a patent-eligible process under § 101.

## **B. Method of Screening Potential Cancer Therapeutics**

Lastly, we turn to Myriad’s method claim directed to a method for screening potential cancer therapeutics via changes in cell growth rates. ’282 patent claim 20. Plaintiffs challenge this claim as directed to the abstract idea of comparing the growth

rates of two cell populations and as preempting a basic scientific principle—that a slower growth rate in the presence of a potential therapeutic compound suggests that the compound is a cancer therapeutic. We disagree.

Starting with the machine-or-transformation test, we conclude that the claim includes transformative steps, an “important clue” that it is drawn to a patent-eligible process. *Bilski*, 130 S. Ct. at 3227. Specifically, the claim recites a method that comprises the steps of (1) “growing” host cells transformed with an altered *BRCA1* gene in the presence or absence of a potential cancer therapeutic, (2) “determining” the growth rate of the host cells with or without the potential therapeutic, and (3) “comparing” the growth rate of the host cells. The claim thus includes more than the abstract mental step of looking at two numbers and “comparing” two host cells’ growth rates. The claim includes the steps of “growing” transformed cells in the presence or absence of a potential cancer therapeutic, an inherently transformative step involving the manipulation of the cells and their growth medium. The claim also includes the step of “determining” the cells’ growth rates, a step that also necessarily involves physical manipulation of the cells. Furthermore, these steps are central to the purpose of the claimed process. See *Prometheus*, 628 F.3d at 1356-57, 1358 (quoting *In re Bilski*, 545 F.3d at 962). The goal of the claim is to assess a compound’s potential as a cancer therapeutic, and growing the cells and determining their growth rate is what achieves that goal.



Furthermore, the claim is not so “manifestly abstract” as to claim only a scientific principle, and not a patent-eligible process. *See Research Corp. Techs., Inc. v. Microsoft Corp.*, 627 F.3d 859, 869 (Fed. Cir. 2010). The claim does not cover all cells, all compounds, or all methods of determining the therapeutic effect of a compound. Rather, it is tied to specific host cells transformed with specific genes and grown in the presence or absence of a specific type of therapeutic. Moreover, the claim is tied to measuring a therapeutic effect on the cells solely by changes in the cells’ growth rate. The claim thus presents “functional and palpable applications” in the field of biotechnology. *Id.* at 868; *see also Prometheus*, 628 F.3d at 1355 (“[T]he claims do not preempt all uses of the natural correlations; they utilize them in a series of specific steps.”). Accordingly, we hold that claim 20 of the ’282 patent claims patentable subject matter under § 101.

### CONCLUSION

For the foregoing reasons, we affirm the district court’s decision to exercise declaratory judgment jurisdiction over this case, we reverse the district court’s grant of summary judgment with regard to Myriad’s composition claims to isolated DNAs, we affirm the district court’s grant of summary judgment with regard to Myriad’s method claims to comparing or analyzing gene sequences, and we reverse the district court’s grant of summary judgment with regard to Myriad’s method claim to screening potential cancer therapeutics via changes in cell growth rates.

**AFFIRMED IN PART and REVERSED IN PART**

No costs

MOORE, *Circuit Judge*, concurring-in-part.

I join the majority opinion with respect to standing and the patentability of the method claims at issue. I believe, however, that claims directed to isolated DNA sequences present a different set of issues. I join the majority with respect to claims to isolated cDNA sequences, and concur in the judgment with respect to the remaining sequences. I write separately to explain my reasoning.

## I.

The Patent Act, 35 U.S.C. § 101, allows “[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof” to obtain a patent. The plain language of this statute only requires that an invention be “new and useful,” and fall into one of four categories: a “process, machine, manufacture, or composition of matter.” Congress did not impose any additional constraints on the scope of patentable subject matter. In fact, “Congress intended statutory subject matter to ‘include anything under the sun that is made by man.’” *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980) (quoting the statutory history).

While the plain language used by Congress did not limit the scope of patentable subject matter in the statute, the “Court's precedents provide three specific exceptions to § 101's broad patent-eligibility principles: ‘laws of nature, physical phenomena, and abstract ideas.’” *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010) (quoting *Chakrabarty*, 447 U.S. at 309). These exceptions “rest[], not on the notion that natural phenomena are not processes [or other

articulated statutory categories], but rather on the more fundamental understanding that they are not the kind of ‘discoveries’ that the statute was enacted to protect.” *Parker v. Flook*, 437 U.S. 584, 593 (1978).

Applying the judicially created exception to the otherwise broad demarcation of statutory subject matter in section 101 can be difficult. *See Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 134-45 (1948) (Frankfurter, J., concurring) (“[T]erms as ‘the work of nature’ and the ‘laws of nature’ . . . are vague and malleable terms . . . . Arguments drawn from such terms for ascertaining patentability could fairly be employed to challenge almost every patent.”). The analysis is relatively simple if the invention previously existed in nature exactly as claimed. For example, naturally existing minerals, a plant found in the wild, and physical laws such as gravity or  $E=mc^2$  are not patentable subject matter, even if they were “discovered” by an enterprising inventor. *Chakrabarty*, 447 U.S. at 309.

Even though an invention did not previously exist in nature in exactly the claimed state, however, does not automatically mean it is patentable subject matter. For example, in *Funk Brothers*, the Supreme Court held a patent to a combination of multiple naturally occurring bacterial strains was not patentable. Although there was “an advantage in the combination,” which was apparently “new and useful,” none of the bacterial strains “acquire[ed] a different use” in combination. *Id.* at 131-32. The aggregation of the bacterial strains into a single product produced “no new bacteria, no change in the six species of bacteria, and no enlargement of the range of their utility. Each species has the same

effect it always had. The bacteria perform in their natural way. . . . They serve the ends nature originally provided and act quite independently of any effort of the patentee.” *Id.*

In contrast, the Supreme Court held bacteria that included extra genetic material introduced by the inventor were “a nonnaturally occurring manufacture or composition of matter—a product of human ingenuity ‘having a distinctive name, character [and] use’” and therefore patentable. *Chakrabarty*, 447 U.S. at 309-310 (quoting *Hartranft v. Wiegmann*, 121 U.S. 609, 615 (1887)). *Chakrabarty* explained that there is no distinction between inventions based on living and inanimate objects for the purpose of the patent statute; instead, the “relevant distinction” for the section 101 analysis is “between products of nature . . . and human-made inventions.” *Id.* at 312-13. Even if the invention was based on nature, and resulted in a living organism, it may fall within the scope of section 101. For example, “the work of the plant breeder ‘in aid of nature’ was patentable invention” because “a plant discovery resulting from cultivation is unique, isolated, and is not repeated by nature, nor can it be reproduced by nature unaided by man.” *Id.* (quoting S. Rep. No. 315, 71st Cong., 2d Sess., 6-8 (1930)). In *Chakrabarty*, the intervention of man resulted in bacteria with “markedly different characteristics” from nature and “the potential for significant utility,” resulting in patentable subject matter. *Id.* at 310.

*Funk Brothers* and *Chakrabarty* do not stake out the exact bounds of patentable subject matter. Instead, each applies a flexible test to the specific question presented in order to determine whether the

claimed invention falls within one of the judicial exceptions to patentability. *Funk Brothers* indicates that an invention which “serve[s] the ends nature originally provided” is likely unpatentable subject matter, but an invention that is an “enlargement of the range of . . . utility” as compared to nature may be patentable. 333 U.S. at 131. Likewise, *Chakrabarty* illustrates that an invention with a distinctive name, character, and use, e.g., markedly different characteristics with the potential for significant utility, is patentable subject matter. 447 U.S. at 309-310. Although the two cases result in different outcomes, the inquiry itself is similar.

Courts applied an analogous patentability inquiry long before *Funk Brothers* or *Chakrabarty*. In one notable case, Judge Learned Hand held that purified adrenaline, a natural product, was patentable subject matter. Judge Hand explained that even if the claimed purified adrenaline were “merely an extracted product without change, there is no rule that such products are not patentable.” *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F. 95, 103 (S.D.N.Y. 1911). This is because “while it is of course possible logically to call this a purification of the principle” the resulting purified adrenaline was “for every practical purpose a new thing commercially and therapeutically.” *Id.* Similarly, in a case applying the Patent Act of 1952,<sup>1</sup> purified vitamin B-12, another natural product, was also held patentable subject matter within the meaning of

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<sup>1</sup> The Patent Act of 1952 was the first time patentable subject matter (the current section 101) was separated out from novelty (the current section 102). Previously, these two concepts were combined into a single section.

section 101. *Merck & Co. v. Olin Mathieson Chem. Corp.*, 253 F.2d 156 (4th Cir. 1958). The Fourth Circuit explained that purified vitamin B-12 was “far from the premise of the [naturally occurring] principle. . . . The new product, not just the method, had such advantageous characteristics as to replace the [naturally occurring] liver products. What was produced was, in no sense, an old product.” *Id.* at 162-63. These purified pharmaceutical cases are both consistent with Supreme Court precedent: the purified substance was “a new thing . . . therapeutically,” *Parke-Davis*, 189 F. at 103, and had such “advantageous characteristics” that what was produced by purification “was, in no sense, an old product.” *Merck*, 253 F.2d at 162-63. In other words, the purified natural products were held to have “markedly different characteristics,” as compared to the impure products, which resulted in “the potential for significant utility.” *Chakrabarty*, 447 U.S. at 310.

In contrast, mere purification of a naturally occurring element is typically insufficient to make it patentable subject matter. For example, our predecessor court held that claims to purified vanadium and purified uranium were not patentable subject matter since these were naturally occurring elements with inherent physical properties unchanged upon purification. *See In re Marden*, 47 F.2d 958, 959 (CCPA 1931) (“[P]ure vanadium is not new in the inventive sense, and, it being a product of nature, no one is entitled to a monopoly of the same.”); *In re Marden*, 47 F.2d 957 (CCPA 1931) (“ductile uranium” not patentable because uranium is inherently ductile). Likewise, claims to purified ductile tungsten were not patentable subject matter since pure tungsten existed in nature and was

inherently ductile. *Gen. Elec. Co. v. De Forest Radio Co.*, 28 F.2d 641, 643 (3d Cir. 1928). In each of these cases, purification did not result in an element with new properties. Instead, the court held the naturally occurring element inherently had the same characteristics and utility (e.g. ductility) as the claimed invention. Consistent with *Funk Brothers* and *Chakrabarty*, the claims all fell within the laws of nature exception.

As illustrated by these examples, courts have long applied the principles articulated in *Funk Brothers* and *Chakrabarty* to different factual scenarios in order to determine whether an invention, as claimed, falls into the laws of nature exception. I see no reason to deviate from this longstanding flexible approach in this case. Keeping these principles in mind, I analyze the isolated DNA claims below, to determine whether they have markedly different characteristics with the potential for significant utility, e.g., an “enlargement of the range of . . . utility” as compared to nature. *Chakrabarty*, 447 U.S. at 309-310; *Funk Bros.*, 333 U.S. at 131.

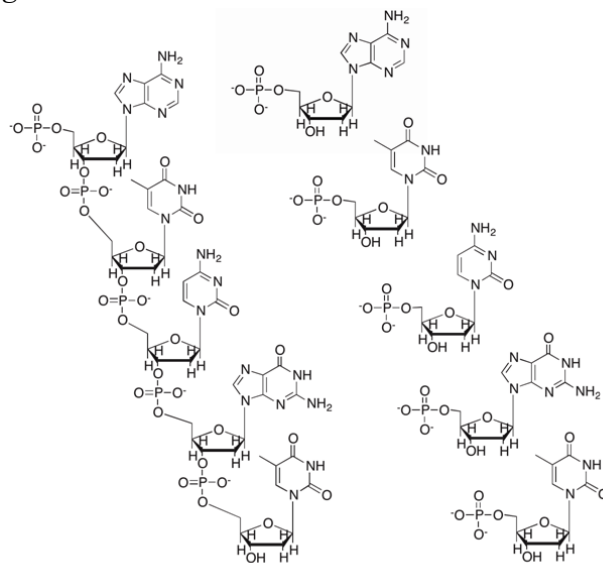
## II.

The majority conducts a thoughtful analysis of the scientific principles associated with the claims at issue in this case. I write separately here to emphasize certain chemical considerations which I believe are particularly important in this case.

DNA is a chemical polymer. In principle, a polymeric DNA sequence is no different than any other well known polymer, for example, nylon. Like any polymer, DNA is made up of repeating monomer

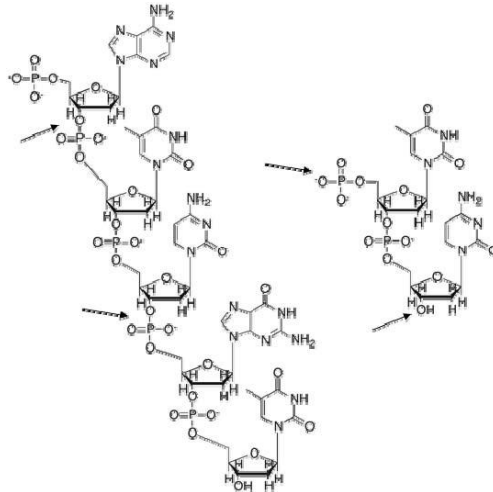


units, connected by chemical bonds to form one larger molecule. In a DNA sequence, the letters A, C, T, and G each represent a different monomer unit; each monomer has a distinct structure, with distinct properties. When they are assembled into a DNA sequence, these monomers are chemically bonded to each other. The process of polymerization of the monomer units—whether carried out by chemical or biological means—results in a new molecule. For example, the sequence A-T-C-G-T represents a single molecule created by polymerizing five monomer units: A, T, C, G, and T again. As illustrated by the figure below, polymerization changes the monomers and results in a molecule with a different ionic charge, different chemical bonds, and a different chemical composition, as compared to the monomers in aggregate.



A-T-C-G-T polymer (left) versus the A, T, C, G, T aggregated monomers (right)

Deconstructing an existing DNA sequence leads to similar results: a fragment of a DNA sequence has different properties than the parent molecule from which it is derived. For example, as shown below, a two nucleotide sequence (T-C), has a different chemical structure, and different chemical connections than the same subunit found within the larger A-T-C-G-T structure. Despite many similarities, it is impossible to find the isolated T-C structure in the A-T-C-G-T molecule. This is because, instead of being connected to a phosphate, the C subunit terminates in a different functional group, a hydroxyl. Likewise, instead of being connected to another sugar via a phosphodiester bond, the T subunit instead terminates in a phosphate. The isolated T-C sequence is a different molecule than the "T-C" sequence appearing as part of the larger A-T-C-G-T polymer. These changes are indicated with arrows below.



A-T-C-G-T polymer (left, with T-C highlighted) versus “isolated” T-C molecule (right)

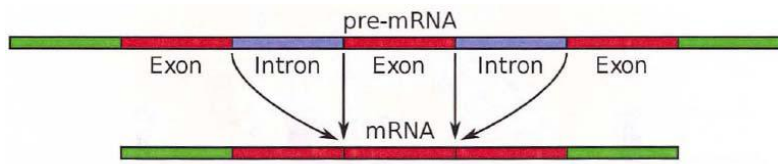
The isolated DNA sequences at issue in this case have the same type of chemical changes, but on a much bigger scale. Instead of a string of five nucleotides, the chromosome is millions of base pairs; instead of a two-monomer molecule, the isolated molecules claimed in this case range from 15 nucleotides to thousands (or tens of thousands) of nucleotides. Nevertheless, like the simple sequences discussed above, just because the same series of letters appears in both the chromosome and an isolated DNA sequence does not mean they are the same molecule. While the isolated DNA molecules claimed in this case are undoubtedly inspired by the corresponding naturally occurring sequence present on the chromosome, man must create these isolated DNA molecules. This can be accomplished by building them de novo using chemical or biological

means, or by chemically altering the larger polymer to cleave off adjacent portions.

Isolation of a DNA sequence is more than separating out impurities: the isolated DNA is a distinct molecule with different physical characteristics than the naturally occurring polymer containing the corresponding sequence in nature. These differences, of course, are directly related to the change in chemical bonds in the isolated DNA. Instead of being connected to many thousands of additional nucleotides at the 3' and 5' ends of the sequence in question, as is the case in the chromosome, the isolated DNA molecules terminate in, for example, a hydroxyl and a phosphate group, respectively.

There are other differences between an isolated DNA sequence and that same DNA sequence as part of the chromosome. The DNA sequence of a gene, as it occurs in nature, is part of a much larger structure, the chromosome. The claims in suit include DNA sequences as short as fifteen nucleotides, and the isolated BRCA1 cDNA sequence has approximately six thousand nucleotides (see, e.g., '282 col.67-80 (SEQ ID NO:1)). Both of these are much smaller than the isolated full length BRCA1 gene sequence, which, as discussed below, includes both exon and intron sequences. Even the isolated BRCA1 gene, however, is substantially smaller than chromosome 17, which includes the unisolated BRCA1 gene as well as many other genes. J.A. 4321. Isolation of a DNA sequence thus results in a substantially smaller molecule compared to the naturally occurring sequence as part of the chromosome.

cDNA, unlike isolated or unisolated DNA, has a unique sequence of DNA bases (A, C, G, T) which is not actually present in nature. While cDNA is derived from RNA, it has a distinctly different sequence of nucleotides, substituting in the complementary nucleotide (swapping G and C, and A and T/U) to form a DNA sequence that is completely different than the corresponding RNA. There is no contiguous sequence on the chromosome that duplicates the cDNA sequence. Moreover, the naturally occurring gene sequence includes both introns (which are removed) and exons (which are included in the mature RNA). The cDNA sequences, which are complementary to the mature RNA, do not include the introns.



Schematic illustrating RNA splicing (J.A. 4331)

Creating isolated DNA allows a scientist, among other things, to remove potentially confounding sequences that are naturally present in the larger chromosomal polymer, and instead focus on just the sequence of interest. This aspect of isolated DNA has important practical consequences and leads to additional utility, particularly for the smaller isolated fragments. For example, a small fragment of isolated DNA can be used as a primer in order to selectively detect the presence of the BRCA1 gene or BRCA1 gene mutation in a patient. Armed with this scientific background, we can now apply the

principles of *Funk Brothers* and *Chakrabarty* to the isolated DNA claims at issue.

### III.

The isolated DNA claims of the patents in suit fall into two categories. The first category of claims is directed to isolated sequences that are identical to naturally occurring gene sequences. These include claims encompassing both the isolated full length gene sequence (e.g. claim 1 of '282 patent), which are thousands of nucleotides, and claims to shorter isolated DNA strands, with as few as fifteen nucleotides, whose nucleotide sequence is found on the chromosome (e.g. claim 5 of '282 patent). The second category of claims is directed to isolated DNA sequences that are different from the naturally occurring gene sequences. These include claims to isolated cDNA molecules (e.g. claim 2 of the '282 patent), which differ from the natural gene sequence in that the introns are removed, and are the opposite (complementary) sequence of the naturally occurring RNA.

The cDNA claims present the easiest analysis. Although the plaintiffs (now plaintiff) in the suit argue, and the district court held, that cDNA falls within the “laws of nature” exception to section 101 patentability, I cannot reconcile this argument with the fact that the claimed cDNA sequences do not exist in nature. Moreover, since cDNA has all of the introns removed, and only contains the coding nucleotides, it can be used to express a protein in a cell which does not normally produce it. Of course, the claimed isolated cDNA is inspired by nature—after all, naturally occurring RNA is the template

upon which cDNA is constructed. Because it is used as a template, however, cDNA has a complementary sequence of nucleotides, and therefore has a completely different nucleotide sequence than the RNA. Moreover, 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). This results in, among other things, greater stability for the DNA sequence as compared to the RNA sequence.

cDNA sequences thus have a distinctive name, character, and use, with markedly different chemical characteristics from either the naturally occurring RNA or any continuous DNA sequence found on the chromosome. The claimed isolated cDNA sequences are the creation of man, made using biological tools and the naturally occurring mRNA as a template. cDNA is therefore not one of the “manifestations of . . . nature, free to all men and reserved exclusively to none” that falls outside of the patent system. *Chakrabarty*, 447 U.S. at 309 (quoting *Funk Bros.*, 333 U.S. at 130). I decline to extend the laws of nature exception to reach entirely manmade sequences of isolated DNA, even if those sequences are inspired by a natural template. I therefore join the majority opinion with respect to the claims to cDNA sequences.<sup>2</sup>

DNA sequences that have the same pattern of DNA bases as a natural gene, in whole or in part,

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<sup>2</sup> To the extent the claims to shorter portions of cDNA include only naturally occurring sequences found in the chromosome, for example claim 6 of the '282 patent, my reasoning is the same as for the isolated sequences of claim 5, discussed below.

present a more difficult issue. Unlike the isolated cDNA molecules, whose sequence is not present in nature, these kinds of isolated DNA claims include nucleotide sequences which are found in the human body, albeit as part of a much larger molecule, the chromosome. The majority analysis focuses on the “markedly different chemical structure” of isolated DNAs, as compared to the corresponding native DNA. Majority at 45. Although the different chemical structure does suggest that claimed DNA is not a product of nature, I do not think this difference alone necessarily makes isolated DNA so “markedly different,” *Chakrabarty*, 447 U.S. at 310, from chromosomal DNA so as to be per se patentable subject matter. *Cf. Funk Bros.*, 333 U.S. at 130-31 (Creation of “a new and different composition” of bacterial strains was nevertheless not patentable subject matter).

Given the chemical differences highlighted by Judge Lourie’s opinion and discussed *supra*, the mere fact that the larger chromosomal polymer includes the same sequence of nucleotides as the smaller isolated DNA is not enough to make it per se a law of nature and remove it from the scope of patentable subject matter. The actual molecules claimed in this case are therefore not squarely analogous to unpatentable minerals, created by nature without the assistance of man. Instead, the claimed isolated DNA molecules, which are truncations (with different ends) of the naturally occurring DNA found as part of the chromosome in nature, are not naturally produced without the intervention of man. *Cf. Chakrabarty*, 447 U.S. at 312-13.



Given the differences, we should, as precedent instructs, consider whether these differences impart a new utility which makes the molecules markedly different from nature. I begin with the short isolated sequences such as those covered by claim 5 which is directed to “an isolated DNA having at least 15 nucleotides of the DNA of claim 1.” This claim covers a sequence as short as 15 nucleotides and arguably as long as the entire gene. For this claim to be patent eligible, all of the sequences ranging from the 15 nucleotide sequence to the full gene must be patentable subject matter. The shorter isolated DNA sequences have a variety of applications and uses in isolation that are new and distinct as compared to the sequence as it occurs in nature. For example, these sequences can be used as primers in a diagnostic screening process to detect gene mutations. These smaller isolated DNA sequences—including isolated radiolabeled sequences mirroring those on the chromosome—can also be used as the basis for probes. Naturally occurring DNA cannot be used to accomplish these same goals. Unlike the isolated DNA, naturally occurring DNA simply does not have the requisite chemical and physical properties needed to perform these functions.

The ability to use isolated DNA molecules as the basis for diagnostic genetic testing is clearly an “enlargement of the range of . . . utility” as compared to nature. *Funk Bros.*, 333 U.S. at 131. Indeed, many of the plaintiffs in this case submitted declarations indicating that they wanted to either offer such testing or receive such testing. These new applications, of course, rely on physical properties devised by nature, namely the ability of a strand of DNA to specifically interact with a complementary

strand. Diagnostic testing, however, is not a natural utility—the body does not naturally engage in this type of testing, and certainly does not do so with the shorter (non-naturally occurring) isolated DNA used by man. As such, the claimed DNA does not “serve the ends nature originally provided.” *Id.* Instead, the isolated DNA sequences have markedly different properties which are directly responsible for their new and significant utility. *Chakrabarty*, 447 U.S. at 309-10. The same sequence, as it appears in nature as part of the chromosome, simply cannot be used in the same way. Because the different chemical structure of the isolated DNA, which is a product of the intervention of man, leads to a different and beneficial utility, I believe small, isolated DNA fragments are patentable subject matter.

In fact, much of the dissent’s analysis with regard to the full gene would seem to support my conclusion that small isolated DNA molecules are directed to patent-eligible subject matter. The dissent explains why the baseball bat is directed to patent eligible subject matter: “man has defined the parts that are to be retained and the parts that are to be discarded. The result of the process of selection is a product with a function that is entirely different from that of the raw material from which it was obtained.” Dissent at 11. The exact same thing is true with regard to primer and probe claims. Man has whittled the chromosomal DNA molecule down to a 15 nucleotide sequence—defining the parts to be retained and discarded. And the result is a product with a function (primer or probe) that is entirely different from the full gene from which it was

obtained.<sup>3</sup> I conclude that the small, isolated DNA molecules, are an alteration of the natural product “with markedly different characteristics from any found in nature and one having the potential for significant utility.” *Chakrabarty*, 447 U.S. at 310.

Longer strands of isolated DNA, in particular isolated strands which include most or all of the entire gene, are a much closer case. Some of the claims at issue, for example '282 patent claim 5, are genus claims, drafted broadly enough to include both short fragments as well as the entire isolated gene sequence. As discussed above, I believe many species within this genus—the shorter isolated DNA fragments—are clearly patentable subject matter based on their new structure and corresponding enlarged range of utility. Yet that still leaves species that include most or all of the isolated gene sequence. While I ultimately conclude that these longer isolated sequences, including the isolated gene sequence as a whole, are also patentable subject matter, I do so for a reason different than for the shorter sequences.

All of the same structural arguments apply to any length of isolated DNA so, like the shorter strands, an isolated DNA coding for a gene does have a literal chemical difference from the gene as it appears on the chromosome. Different ends in a 15 nucleotide sequence have greater significance than different ends in a 6000 nucleotide sequence. Unlike

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<sup>3</sup> The dissent analogizes the full BRCA gene to a slab of marble found in the earth as distinct from the sculpture carved into it, which the dissent indicates would be worthy of intellectual property protection. If the multi-thousand nucleotide BRCA gene is the slab, isn't the 15 nucleotide primer the sculpture?

the shorter strands of isolated DNA, the chemical and structural differences in the isolated gene do not clearly lead to an “enlargement of the range of . . . utility” as compared to nature. *Funk Bros.*, 333 U.S. at 131. For example, the full length gene is too large to be used as a probe. See J.A. 4322 (a probe is a DNA molecule usually 100-1,000 bases long). Likewise, an entire isolated gene appears unsuitable for use as a primer in genetic screening for mutations in that same gene. See J.A. 4323 (Primers “are complementary to an exact location of a *much larger target* DNA molecule.” (emphasis added)). As such, the chemical and structural differences in an isolated DNA sequence which includes most or all of a gene do not clearly lead to significant new utility as compared to nature. Whether an isolated gene is patentable subject matter depends on how much weight is allocated to the different structure as compared to the similarity of the function to nature.

If I were deciding this case on a blank canvas, I might conclude that an isolated DNA sequence that includes most or all of a gene is not patentable subject matter. Despite the literal chemical difference, the isolated full length gene does not clearly have a new utility and appears to simply serve the same ends devised by nature, namely to act as a gene encoding a protein sequence. This case, however, comes to us with a substantial historical background.

Congress has, for centuries, authorized an expansive scope of patentable subject matter. Likewise, the United States Patent Office has allowed patents on isolated DNA sequences for decades, and, more generally, has allowed patents on

purified natural products for centuries. There are now thousands of patents with claims to isolated DNA, and some unknown (but certainly large) number of patents to purified natural products or fragments thereof.<sup>4</sup> As I explain below, I believe we must be particularly wary of expanding the judicial exception to patentable subject matter where both settled expectations and extensive property rights are involved. Combined with my belief that we should defer to Congress, these settled expectations tip the scale in favor of patentability.<sup>5</sup>

#### IV.

For more than a decade the Patent Office's policy has been that "[a]n isolated and purified DNA molecule that has the same sequence as a naturally occurring gene is eligible for a patent because . . .

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<sup>4</sup> See, e.g., U.S. Patent 3,067,099 (claiming vancomycin, an antibiotic produced by bacteria found in soil) and U.S. Patent 4,552,701 (claiming a vancomycin fragment produced by removing a sugar unit). A natural product fragment, for example a naturally occurring antibiotic with a sugar moiety removed, is highly analogous to isolated DNA. In each case, the claimed molecule is a smaller fragment of a naturally occurring molecule, with some naturally occurring functionality removed. See U.S. Patent 4,552,701, col.3-4 (compare entry 2 with entries 10 and 13).

<sup>5</sup> My analysis of the claims at issue assumes that they do not include an isolated, full length chromosome. I do not believe that a claim to an entire chromosome, for example chromosome 17, is patentable subject matter. First, there is no indication that the chromosome in isolation has markedly different characteristics compared to the chromosome in nature. Second, unlike claims to isolated genes, there is no indication of either settled expectations or extensive property rights for claims to isolated chromosomes. This is undoubtedly due to the small number of chromosomes as compared to the number of genes.

that DNA molecule does not occur in that isolated form in nature . . .” 66 Fed. Reg. 1092, 1093 (Jan. 5, 2001). The explicit statement of the Patent Office’s position on isolated DNA, however, is simply a continuation of a longstanding and consistent policy of allowing patents for isolated natural products. *See id.* (noting U.S. Patent 141,072, claiming “[y]east, free from organic germs of disease,” issued to Louis Pasteur in 1873); *cf. In re Bergstrom*, 427 F.2d 1394 (CCPA 1970) (isolated prostaglandins patentable). According to the Patent Office, isolated DNA is no different from the isolated natural products of *Parke-Davis*. *See* 66 Fed. Reg. at 1093 (quoting *Parke-Davis*).

Even before the current guidelines formalized the Patent Office’s position, however, it granted patents to human genes in the early 1980s, and subsequently issued thousands of patents on “isolated DNA.” Majority at 48. In fact, claims similar to the ones at issue in this case have been the focal point of important litigation. For example, *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200 (Fed. Cir. 1991), involved a claim to “[a] purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin.” *Id.* at 1203-04 (quoting U.S. Patent No. 4,703,008, claim 2). We affirmed that this claim was valid and infringed. *Id.* at 1219. Erythropoietin, also known as EPO, went on to become the biggest-selling biotechnology drug developed to that point, resulted in billions of dollars in sales, and accounted for over 50% of Amgen’s revenue in 1997. *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 77 (D. Mass. 2001). Isolated DNA claims, at least

in the case of Amgen, represent crucial and exceedingly valuable property rights.

The settled expectations of the biotechnology industry—not to mention the thousands of issued patents—cannot be taken lightly and deserve deference. This outpouring of scientific creativity, spurred by the patent system, reflects a substantial investment of time and money by the biotechnology industry to obtain property rights related to DNA sequences. The type of fundamental alteration in the scope of patentable subject matter argued in this case “risk[s] destroying the legitimate expectations of inventors in their property.” *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 739 (2002). I believe leaving intact the settled expectations of property owners is particularly important in light of the large number of property rights involved, both to isolated DNA and to purified natural products generally.

The Supreme Court has warned that “courts must be cautious before adopting changes that disrupt the settled expectations of the inventing community.” *Festo*, 535 U.S. at 739. The settled expectations of the inventing community with respect to isolated DNA claims are built upon the broad language of the statute, judicial precedent, such as *Parke-Davis* and *Merck*, and the Patent Office’s long-standing policy and practice. Neither *Funk Brothers* nor *Chakrabarty* purported to overrule either the early cases or the Patent Office’s practice; indeed, as discussed *supra*, these cases weigh the same considerations as *Parke-Davis* and *Merck*. “To change so substantially the rules of the game now,” after more than a century of practice,

“could very well subvert the various balances the PTO sought to strike when issuing the numerous patents which have not yet expired and which would be affected by our decision.” *Festo*, 535 U.S. at 739 (quoting *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 32 n.6 (1997)).

Although the Patent Office has consistently followed the same policy for a decade (and arguably a century or more), the United States, as an amicus represented at argument by the Solicitor General, now argues that the Patent Office’s published guidelines are incorrect and a misstatement of the law. In place of these guidelines, the Solicitor General suggested that we should use a “magic microscope” as part of our section 101 analysis. If we could observe the claimed substance in nature using this microscope, the Solicitor General argues, it is not patentable. The magic microscope test applies equally to portions of a larger, naturally occurring molecule. For example, the optical field of view could be zoomed to see just a sequence of fifteen nucleotides within the chromosome. As long as you could “see” the claimed molecule in nature using the magic microscope, it would fall into the “laws of nature” exception and be unpatentable subject matter.

Certainly the magic microscope has curb appeal—its child-like simplicity an apparent virtue. The magic microscope, however, would not see the claimed DNA molecules at issue in this case. An isolated DNA molecule has different chemical bonds as compared to the “unisolated” sequence in the chromosome (the ends are different). In short, the claimed molecules cannot be seen in nature through



the magic microscope. While you may be able to see the order of DNA nucleotides in the chromosome, the isolated fragment of DNA is a different molecule. It may be that the microscope can also break and form chemical bonds to yield the claimed isolated DNA. Even so, the microscope must make some decisions: should the isolated DNA begin and end in a phosphate? a hydrogen? a hydroxyl? a methyl group? an acyl group? These decisions might be obvious to a person of ordinary skill in the art, but they are not inherent to the unisolated sequence as part of the chromosome. Creating the claimed isolated DNA sequences therefore results in a distinctly unnatural molecule.<sup>6</sup> Even the dissent agrees that the isolated DNA molecules at issue require cleaving chemical bonds, though it disputes the importance of the resulting distinct “molecular species.” Dissent at 7 (quoting Linus Pauling, *The Nature of the Chemical Bond* 6 (3d ed. 1960)). The magic microscope test simply does not work the way the government claims.

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<sup>6</sup> This also illustrates why the government’s analogies to situations dealing with elements, for example lithium, are inapposite. Even assuming the government’s contention that lithium does not exist in isolated form in nature, it is nevertheless clear that elemental lithium, a basic building block provided by nature, at some point must have reacted with, e.g., water to form the naturally occurring lithium salts. In contrast, an isolated DNA sequence did not necessarily exist before reacting further to produce the corresponding naturally occurring chromosomal DNA. Unlike a lithium salt, the chromosome does not imply that an isolated DNA molecule of 15 nucleotides—or even a gene—necessarily previously existed as an isolated molecule in nature.

While the magic microscope creates a bright line rule, it presents a poorly defined question: can we “see” the claimed molecule, or something fairly similar, in nature? Even if the scientific imprecision of the test were excusable, the government also asks us to do away with *Chakrabarty*’s flexible inquiry as to whether the invention, as claimed, has “markedly different characteristics from any found in nature” which result in “the potential for significant utility.” *Id.* at 310. Indeed, the bright line magic microscope test actually appears to be contrary to *Funk Brothers*, since the combination of bacteria in that case was a “new and different composition of non-inhibitive strains,” 333 U.S. at 130-31, and therefore not actually present in nature. There may be additional nuance in the government’s argument that accounts for this inconsistency, but under my understanding of the magic microscope test, the combination in *Funk Brothers* would be patentable subject matter.

Indeed, the government does not apply its own understanding of section 101 consistently. In its brief, the United States explains that “[a] chemical alteration of a bioactive molecule to improve absorption by the body . . . would likely satisfy section 101.” United States Amicus Br. 31 n.8. As discussed *supra*, the isolated DNA molecules at issue in this case are the result of a “chemical alteration of a bioactive molecule” that leads to different properties, including a dramatic reduction in size. Just as the government’s theoretical “chemical alteration” leads to a molecule with improved absorption properties, the isolation of discrete DNA sequences changes the properties of the sequence as compared to the chromosomal DNA. This is not

“[m]erely sorting the proverbial wheat from the chaff,” *id.*, but the creation of new DNA molecules with distinct properties and additional utility, including the ability to be used as a primer in genetic testing.<sup>7</sup>

Also troubling is the apparent lack of awareness about the impact of the proposed test. The government asserts that the magic microscope “is a very limited position”; the government is wrong. This test cannot be limited to DNA by either legal or scientific principles. For example, Louis Pasteur’s 1873 claim to “Yeast, free from organic germs of disease, as an article of manufacture” runs afoul of the magic microscope since the microscope could zoom in to see that yeast free from contaminants. Similarly, isolated naturally occurring molecules long considered patentable subject matter, including adrenaline, vitamin B-12, and prostaglandins, would also fall outside the scope of section 101. Although the powers of the magic microscope are not entirely clear, it appears that patents to smaller fragments of

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<sup>7</sup> The government’s position may be that adding functionality to a naturally occurring molecule, for example adding a lipid chain, is a creation of man while removing functionality, for example truncating a natural DNA sequence or protein to yield smaller molecules with new properties, is not. Scientifically, this distinction makes little sense: in either case, it is the intervention of man that created a new molecule. After all, the hand of man is just as apparent in the David, created by removing stone from a block of marble, as the ceiling of the Sistine Chapel, created by adding layers of paint to an existing structure.

naturally occurring molecules, for example claims to truncated proteins (*see, e.g.*, U.S. Patent No. 4,762,914, entitled “Truncated Protein of Interleukin-1”), would also be unpatentable.

The government’s new test fundamentally changes more than a century of precedent and Patent Office practice in the pharmaceutical and biotechnology arena. The proposed test is a purely mechanical inquiry that fails to account for the possibility that chemical changes to the isolated DNA sequences at issue, as compared to their natural state, could result in markedly different uses. As such, the government’s position in this case calls into question the validity of an unknown number of patents and claims and upsets the settled expectations of some of our most innovative industries. This is not a “very limited position.”

The dissent claims that the Patent Office’s past views are “substantially undermined by the position the government has taken in this case.” Dissent at 18. The Patent Office’s prior practice, however, is particularly important since it resulted in a large number of property rights over the past decades. If the Executive decided to change course in the Patent Office, and decline to issue new patents to isolated genes, it would not impact these existing property rights. This, however, is not what the Executive argues in this case. Instead the Solicitor General argues for an entirely different interpretation of the law that would destroy existing property rights. Although the dissent points out that *Chakrabarty* overturned the Patent Office’s practice of denying patents to microorganisms, there is a clear difference between allowing additional patent

protection where none previously existed, and denying patent protection decades (or centuries) after the fact, thereby eliminating a large number of property rights. Moreover, *Chakrabarty*, consistent with the broad language of the statute, allowed additional patents where none previously existed. Here, the Solicitor General proposes to destroy existing property rights based on a judge made exception to that same broad language. This is a dramatic step that I believe is best left to the legislature.

Nevertheless, the Solicitor General claims that “this is a pure question of law” and that we can therefore feel free to ignore the years of Patent Office practice and the accompanying expectations that practice created within the industry. The Solicitor General argues that we should not defer to the broad language (all but unchanged since 1793) provided by Congress in the patent statute, or allow Congress to decide whether it is necessary to correct the Patent Office’s practice through legislation. It is tempting to use our judicial power in this fashion, especially when the patents in question raise substantial moral and ethical issues related to awarding a property right to isolated portions of human DNA—the very thing that makes us humans, and not chimpanzees.

The Solicitor General’s invitation is tempting, but I must decline the opportunity to act where Congress remains silent. “[O]ur obligation is to take statutes as we find them . . . .” *Chakrabarty*, 447 U.S. at 315. With respect to section 101, “[t]he subject-matter provisions of the patent law have been cast in broad terms to fulfill the constitutional and statutory goal of promoting ‘the Progress of Science and the

useful Arts' . . . ." *Id.* Any judicial exception to the statute's broad language must be applied with care lest the courts usurp Congress's constitutionally mandated authority to promote science and useful arts. Judicial restraint is particularly important here because an entire industry developed in the decades since the Patent Office first granted patents to isolated DNA. Disturbing the biotechnology industry's settled expectations now risks impeding, not promoting, innovation.

Regardless, the judiciary is ill-suited to determine whether the claims at issue promote or inhibit science and useful arts in all but the clearest cases, for example a new mineral discovered in the earth, or a new plant found in the wild, or  $E=mc^2$ , or the law of gravity. Instead, I leave it to Congress, who "has the constitutional authority and the institutional ability to accommodate fully the varied permutations of competing interests that are inevitably implicated by such new technology," *Sony Corp. of America v. Universal City Studios, Inc.*, 464 U.S. 417, 431 (1984), to decide whether it is necessary to change the scope of section 101 to exclude the kind of isolated DNA claims at issue here. "[U]ntil Congress takes such action, this [c]ourt must construe the language of § 101 as it is." *Chakrabarty*, 447 U.S. at 318. Section 101 is, on its face, broad enough to include the claims to isolated DNA at issue here.

The dissent suggests that "this may well be one of those instances in which 'too much patent protection can impede rather than 'promote the Progress of Science and useful Arts.'" Dissent at 17 (quoting *Lab. Corp. of Am. Holdings v. Metabolite*

*Labs., Inc.*, 548 U.S. 124, 126 (2006) (Breyer, J., dissenting from dismissal of writ as improvidently granted)). Yet the biotechnology industry is among our most innovative, and isolated gene patents, including the patents in suit, have existed for decades with no evidence of ill effects on innovation. See David E. Adelman & Kathryn L. DeAngelis, *Patent Metrics: The Mismeasure of Innovation in the Biotech Patent Debate*, 85 Tex. L. Rev. 1677, 1681 (2007) (“The existing empirical studies find few clear signs that the patenting of biotechnology inventions is adversely affecting biomedical innovation.”); *id.* at 1729 (concluding “that overall biotechnology innovation is not being impaired by the growth in patents issued”). Changing course years after the fact will only serve to punish those companies who made the reasonable decision to invest large amounts of time and money into the identification, isolation, and characterization of genes. Unsettling the expectations of the biotechnology industry now, based on nothing more than unsupported supposition, strikes me as far more likely to impede the progress of science and useful arts than advance it. Given the complicated technology and conflicting incentives at issue here, any change must come from Congress. See *Gottschalk v. Benson*, 409 U.S. 63, 72-73 (1972) (A section 101 analysis raises “considerable problems . . . which only committees of Congress can manage, for broad powers of investigation are needed, including hearings which canvass the wide variety of views which those operating in this field entertain. The technological problems tendered [by the parties] . . . indicate to us that considered action by the Congress is needed.”).

In fact, Congress has at least implicitly approved of the Patent Office's policy of awarding patents on genes and DNA sequences. For example, Congress included, as part of the Patent Office's appropriations, language affirming the Patent Office's interpretation of section 101 to prohibit patents on human organisms. Consolidated Appropriations Act, 2004, Pub. L. No. 108-199, § 634, 118 Stat. 3, 101. Although Congress was aware "that there are many institutions . . . that have extensive patents on human genes," 149 Cong. Rec. H7248, H7274, it explicitly declined to implement legislation to "affect any of those current existing patents." *Id.* (statement of Mr. Weldon introducing amendment). To the contrary, it made clear that the language related to "human organisms" was not intended to change the Patent Office's policy with respect to claims to genes, stem cells, or other similar inventions. *Id.*<sup>8</sup> Far from oblivious to the patenting of genes, members of Congress previously introduced bills which would put a moratorium on gene patents,<sup>9</sup> authorize funding for the study of whether

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<sup>8</sup> See also 149 Cong. Rec. E2417-01 ("What I want to point out is that *the U.S. Patent Office has already issued patents on genes, stem cells, animals with human genes, and a host of non-biologic products used by humans, but it has not issued patents on claims directed to human organisms, including human embryos and fetuses. My amendment would not affect the former, but would simply affirm the latter.*") (emphasis added) (statement of Mr. Weldon after amendment approved); see also 157 Cong. Rec. E1177-04 (resubmitting this testimony in the context of the current patent reform legislation).

<sup>9</sup> At least one bill was introduced in Congress to put a moratorium on patents to human genes or gene sequences. See, e.g., The Animal and Gene Patent Moratorium Bill (S.387 1993).



genes ought to be patentable,<sup>10</sup> and exempt from patent infringement anyone who uses patented genes for non-commercial research purposes or medical practitioners who use genetic diagnostic tests.<sup>11</sup> None of these became law. Congress is obviously aware of the issues presented in this case and I believe “[a]ny recalibration of the standard of [patentability] remains in its hands.” *Microsoft Corp. v. i4i Ltd.*, 131 S.Ct. 2238, 2252 (2011).

This case typifies an observation by the late Chief Judge Markey, our first Chief Judge, that “[o]nly God works from nothing. Men must work with old elements.” *Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556 n.3 (Fed. Cir. 1985) (quotation, citations omitted). Human DNA is, for better or worse, one of the old elements bequeathed to men to use in their work. The patents in this case revealed a new molecular understanding about ourselves; “the inventions most benefiting mankind are those that ‘push back the frontiers of chemistry, physics, and the like.’” *Chakrabarty*, 447 U.S. at 316 (quoting *Great A. & P. Tea Co. v. Supermarket Corp.*, 340 U.S. 147, 154 (1950)). We cannot, after decades of patents and judicial precedent, now call human DNA fruit from the poisonous tree, and punish those inquisitive enough to investigate, isolate, and patent it. “Our

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<sup>10</sup> The Genomic Science and Technology Innovation Act of 2002 (H.R. 3966).

<sup>11</sup> The Genomic Research and Diagnostic Accessibility Act of 2002 (H.R. 3967). As the bill’s sponsor explained: “It is important to note that this section would not overturn the commercial rights of patent holders. If a research [organization] utilizing the exemption makes a commercially viable finding, he or she would still have to negotiate any rights to market the new discovery with the patent holder.” 148 Cong. Rec. E353-03.

task . . . is the narrow one of determining what Congress meant by the words it used in the statute; once that is done our powers are exhausted.” *Id.* at 318. This inquiry does not have moral, ethical, or theological components. *Cf. id.* at 316-17 (“[W]e are without competence to entertain” arguments about “the grave risks” generated by genetic research.). The patents in this case might well deserve to be excluded from the patent system, but that is a debate for Congress to resolve. I therefore decline to extend the “laws of nature” exception to include isolated DNA sequences.

BRYSON, *Circuit Judge*, concurring in part and dissenting in part:

I concur with the portions of this court's judgment that are directed to standing, the patentability of the cDNA claims, and the patentability of the method claims. I respectfully dissent, however, from the court's holding that Myriad's BRCA gene claims and its claims to gene fragments are patent-eligible. In my view, those claims are not directed to patentable subject matter, and if sustained the court's decision will likely have broad consequences, such as preempting methods for whole-genome sequencing, even though Myriad's contribution to the field is not remotely consonant with such effects.

In its simplest form, the question in this case is whether an individual can obtain patent rights to a human gene. From a common-sense point of view, most observers would answer, "Of course not. Patents are for inventions. A human gene is not an invention." The essence of Myriad's argument in this case is to say that it has not patented a human gene, but something quite different—an *isolated* human gene, which differs from a native gene because the process of extracting it results in changes in its molecular structure (although not in its genetic code). We are therefore required to decide whether the process of isolating genetic material from a human DNA molecule makes the isolated genetic material a patentable invention. The court concludes that it does; I conclude that it does not.

At the outset, it is important to identify the inventive contribution underlying Myriad's patents. Myriad was not the first to map a BRCA gene to its chromosomal location. That discovery was made by a team of researchers led by Dr. Mary-Claire King. See Jeff M. Hall et al., *Linkage of Early-Onset Familial Breast Cancer to Chromosome 17q21*, 250 *Science* 1684 (1990). And Myriad did not invent a new method of nucleotide sequencing. Instead, it applied known sequencing techniques to identify the nucleotide order of the BRCA genes.<sup>1</sup> Myriad's discovery of those sequences entailed difficult work, and the identified sequences have had important applications in the fight against breast cancer. But the discovery of the sequences is an unprotectable fact, just like Dr. King's discovery of the chromosomal location of the BRCA1 gene.

Of course, Myriad is free to patent applications of its discovery. As the first party with knowledge of the sequences, Myriad was in an excellent position to claim applications of that knowledge. Many of its unchallenged claims are limited to such applications. See, e.g., '441 patent, claim 21; '492 patent, claim 22; '282 patent, claim 9. Yet some of Myriad's challenged composition claims effectively preempt any attempt to sequence the BRCA genes, including whole-genome sequencing. In my view, those claims encompass unpatentable subject matter, and a

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<sup>1</sup> There is some dispute over whether other inventors helped Myriad discover the BRCA sequences or discovered the BRCA2 sequence before Myriad. Because those disputes are irrelevant to the question of patentable subject matter, I refer to the discovery of the BRCA sequences as Myriad's work.

contrary ruling is likely to have substantial adverse effects on research and treatment in this important field.

## I.

As the majority and concurring opinions explain, the claims at issue in this case fall into three categories: claims that cover the isolated BRCA genes (claim 1 of the '282 patent, claim 1 of the '473 patent, and claims 1 and 6 of the '492 patent); claims that cover only the BRCA cDNA (claims 2 and 7 of the '282 patent and claim 7 of the '492 patent); and claims that cover portions of the BRCA genes and cDNA as small as 15 nucleotides long (claims 5 and 6 of the '282 patent). I first address the claims to the BRCA genes.

## A.

In the seminal case of *Diamond v. Chakrabarty*, 447 U.S. 303 (1980), the Supreme Court held that an artificial life form could be patented. In the course of its opinion, and critically for purposes of its reasoning, the Court stated that not all living things or other items found in nature were subject to patenting. The Court explained that although the language of section 101 of the Patent Act is broad, it is not the case that it “has no limits or that it embraces every discovery.” *Id.* at 309. The Court then set forth the general proposition that “laws of nature, physical phenomena, and abstract ideas have been held not patentable.” *Id.* As examples, the Court noted that “a new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter.” Thus, even though a mineral or a plant is a “composition of

matter,” and could be viewed as falling within a broad construction of section 101, the Court explained that those “manifestations of . . . nature” are not patentable subject matter, but are “free to all men and reserved exclusively to none.” *Id.*, quoting *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948); see also *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010).

The Court in *Chakrabarty* held the artificial life form at issue in that case to be patentable because the claim was “not to a hitherto unknown natural phenomenon, but to a nonnaturally occurring manufacture or composition of matter—a product of human ingenuity ‘having a distinctive name, character [and] use.’” *Id.* at 309-10, quoting *Hartranft v. Wiegmann*, 121 U.S. 609, 615 (1887). In distinguishing between naturally occurring substances and nonnaturally occurring manufactures, the Court relied heavily on its earlier decision in *Funk Brothers*, in which the inventor discovered that certain useful bacterial strains did not exert an inhibitive effect on each other. Based on that discovery, the inventor obtained a patent on a mixed culture of those non-inhibitive strains. The Supreme Court held the product unpatentable, however, because the bacteria remained structurally and functionally the same as in their natural state. *Funk Bros.*, 333 U.S. at 131. By contrast, because *Chakrabarty* had produced “a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility,” the Court held *Chakrabarty*’s invention to be patentable. *Chakrabarty*, 447 U.S. at 310.

## B.

Myriad's claims to the isolated BRCA genes seem to me to fall clearly on the "unpatentable" side of the line the Court drew in *Chakrabarty*. Myriad is claiming the genes themselves, which appear in nature on the chromosomes of living human beings. The only material change made to those genes from their natural state is the change that is necessarily incidental to the extraction of the genes from the environment in which they are found in nature. While the process of extraction is no doubt difficult, and may itself be patentable, the isolated genes are not materially different from the native genes. In this respect, the genes are analogous to the "new mineral discovered in the earth," or the "new plant found in the wild" that the Supreme Court referred to in *Chakrabarty*. It may be very difficult to extract the newly found mineral or to find, extract, and propagate the newly discovered plant. But that does not make those naturally occurring items the products of invention.

The same is true for human genes. Like some minerals, they are hard to extract from their natural setting. Also like minerals, they can be used for purposes that would be infeasible if they remained in their natural setting. And the process of extracting minerals, or taking cuttings from wild plants, like the process of isolating genetic material, can result in some physical or chemical changes to the natural substance. But such changes do not make extracted minerals or plant cuttings patentable, and they should not have that effect for isolated genes. In each case, merely isolating the products of nature by extracting them from their natural location and

making those alterations attendant to their extraction does not give the extractor the right to patent the products themselves.

The majority characterizes the isolated genes as “new molecules” and considers them different substances from the corresponding native DNA.<sup>2</sup> Because the native BRCA genes are chemically bonded to other genes and histone proteins, the majority concludes that cleaving those bonds to isolate the BRCA genes turns the isolated genes into “different materials.” Yet there is no magic to a chemical bond that requires us to recognize a new product when a chemical bond is created or broken, but not when other atomic or molecular forces are altered.<sup>3</sup> A chemical bond is merely a force between two atoms or groups of atoms strong enough “to make it convenient for the chemist to consider [the aggregate] as an independent molecular species.”

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<sup>2</sup> Although I recognize that Judge Lourie and Judge Moore, while reaching the same ultimate conclusions, have taken analytical paths that differ in some respects, for convenience I will refer to Judge Lourie’s opinion as the majority opinion and Judge Moore’s opinion as the concurring opinion.

<sup>3</sup> The majority characterizes the question in this case as turning on the breaking of covalent bonds linking the BRCA genes to the rest of the DNA in chromosomes 13 and 17, but its analysis appears to place patentable weight on the breaking of other chemical bonds, such as the hydrogen bonds that are broken when separating DNA from histones or—in an example unrelated to this case—the ionic bonds that are broken when lithium is derived from a salt. It is difficult to see why differences between types of chemical bonds should matter for patentability purposes, and I see little support for such a distinction in the governing precedents.



Linus Pauling, *The Nature of the Chemical Bond* 6 (3d ed. 1960). Weaker interatomic forces will be broken when, for example, a dirty diamond is cleaned with water or another solvent, but that does not make the clean diamond a human-made invention. See *Am. Fruit Growers, Inc. v. Brogdex Co.*, 283 U.S. 1, 12 (1931) (cleaning a shell by acid and then grinding off a layer with an emery wheel did not convert it into a different product). Nor should it make a difference for purposes of patentability if the portion of a wild plant that is collected for purposes of later regeneration is separated from the original plant by chemical means or by scissors.

Although the majority insists that the changes in the DNA molecule that occur as part of the process of isolation render the gene claims patentable, the majority does not appear to take a similar position with respect to chemical elements. The government as amicus curiae argues that patenting the BRCA genes would be like patenting the element lithium. Isolated lithium does not occur naturally because it reacts with air and water and thus is found in nature only as part of a chemical compound, ionically bound to other elements. Robert E. Krebs, *The History and Use of Our Earth's Chemical Elements* 48 (2d ed. 2006). Once isolated, lithium has many industrial applications, and in order to isolate lithium, it is necessary to break ionic bonds in the lithium compounds that are found in nature. But the majority acknowledges that elemental lithium (like other elements) would not be patentable subject matter because it “is the same element whether it is in the earth or isolated.”

The principles underlying that analysis apply to genetic material as well. In order to isolate the BRCA gene, it is necessary to break chemical bonds that hold the gene in its place in the body, but the genetic coding sequence that is the subject of each of the BRCA gene claims remains the same whether the gene is in the body or isolated. The majority, however, does not agree that the cases are analogous, and indeed appears to have adopted the following rule: Isolated atoms are not patent eligible, but isolated molecules are.

Apart from the arbitrariness of such a rule, if we are to apply the conventional nomenclature of any field to determine whether Myriad's isolated DNA claims are "new," it would seem to make more sense to look to genetics, which provides the language of the claims, than to chemistry. Aside from Myriad's cDNA claims, its composition claims are not defined by any particular chemical formula. For example, claim 1 of the '282 patent covers all isolated DNAs coding for the BRCA1 protein, with the protein being defined by the amino acid sequence encoded by the naturally occurring BRCA1 gene. From a molecular perspective, that claim covers a truly immense range of substances from the cDNA that is 5,914 nucleotides long to the isolated gene that contains more than 120,000 nucleotides. And the patent does not define the upper end of that range because the patent does not identify a unique nucleotide sequence for the 120,000-nucleotide-long isolated BRCA1 gene. Instead, the patent contains a sequence that is just 24,000 nucleotides long with numerous gaps denoted "vvvvvvvvvvvvv." '282 patent, fig. 10. An almost incalculably large number of new molecules could be created by filling in those gaps with almost any

nucleotide sequence, and all of those molecules would fall within the scope of claim 1. Included in that set are many important molecular variations to the BRCA1 gene that Myriad had not yet discovered and could not have chemically described. Yet those molecules would share only one unifying characteristic: each codes for the same protein as the naturally occurring BRCA1 gene.

From a genetic perspective, that claim covers one “composition of matter”—the BRCA1 gene. The isolated BRCA genes are identical to the BRCA genes found on chromosomes 13 and 17. They have the same sequence, they code for the same proteins, and they represent the same units of heredity. During the transcription phase of protein synthesis, the BRCA genes are separated from chromosomal proteins. The transcription process then proceeds from a starting point called the promoter to a stopping point often called the terminator. James D. Watson et al., *Molecular Biology of the Gene* 382, 394-96 (6th ed. 2008). The only difference between the naturally occurring BRCA genes during transcription and the claimed isolated DNA is that the claimed genes have been isolated according to nature’s predefined boundaries, i.e., at points that preserve the ability of the gene to express the protein for which it is coded.

In that respect, extracting a gene is akin to snapping a leaf from a tree. Like a gene, a leaf has a natural starting and stopping point. It buds during spring from the same place that it breaks off and falls during autumn. Yet prematurely plucking the leaf would not turn it into a human-made invention. See *Intervet Inc. v. Merial Ltd.*, 617 F.3d 1282, 1295 (Fed. Cir. 2010) (Dyk, J., concurring in part and

dissenting in part). That would remain true if there were minor differences between the plucked leaf and the fallen autumn leaf, unless those differences imparted “markedly different characteristics” to the plucked leaf. *Chakrabarty*, 447 U.S. at 310.

Both the majority and the concurring opinions attach significant weight to the fact that the claimed coding portions of the native BRCA genes are part of a much larger molecule and that the isolated BRCA genes, being smaller molecules extracted from the larger one, are therefore man-made inventions. But to argue that the isolated BRCA gene is patentable because in its native environment it is part of a much larger structure is no more persuasive than arguing that although an atom may not be patentable, a subatomic particle is patentable because it was previously part of a larger structure, or that while a tree is not patentable, a limb of the tree becomes a patentable invention when it is removed from the tree.

Of course, it is an oversimplification to say that something that can be characterized as “isolated” or “extracted” from its natural setting always remains a natural product and is not patentable. One could say, for example, that a baseball bat is “extracted” or “isolated” from an ash tree, but in that case the process of “extracting” the baseball bat necessarily changes the nature, form, and use of the ash tree and thus results in a manmade manufacture, not a naturally occurring product. In that setting, man has defined the parts that are to be retained and the parts that are to be discarded. The result of the process of selection is a product with a function that is entirely different from

that of the raw material from which it was obtained. In the case of the BRCA genes, by contrast, nature has defined the genes as independent entities by virtue of their capacity for protein synthesis and, ultimately, trait inheritance. Biochemists extract the target genes along lines defined by nature so as to preserve the structure and function that the gene possessed in its natural environment. In such a case, the extraction of a product in a manner that retains the character and function of the product as found in nature does not result in the creation of a human invention.<sup>4</sup>

That principle was captured by the Supreme Court's statement in *Chakrabarty* that the invention in that case was not to "a hitherto unknown natural phenomenon, but to a nonnaturally occurring manufacture or composition of matter 'having a distinctive name, character [and] use.'" 447 U.S. at 309-10.

Cases involving the "purification" of a natural substance employ similar analysis. Our predecessor court recognized that merely purifying a naturally occurring substance does not render the substance patentable unless it results in a marked change in functionality. *In re Merz*, 97 F.2d 599, 601 (CCPA 1938) (holding that there was no right to a patent on

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<sup>4</sup> By analogy, extracting a slab of marble from the earth does not give rise to protectable intellectual property rights, but "extracting" a piece of sculpture from that slab of marble does. In the case of the BRCA gene claims, what Myriad has claimed is more akin to the slab of marble found in the earth than to the sculpture carved from it after its extraction.

a purer version of ultramarine, but recognizing that if a claimed article is “of such purity that it differs not only in degree but in kind it may be patentable”); *see also In re King*, 107 F.2d 618, 620 (CCPA 1939) (same, for purified vitamin C); *In re Marden*, 47 F.2d 958, 959 (CCPA 1931) (same, for purified vanadium); *Gen. Elec. Co. v. DeForest Radio Co.*, 28 F.2d 641, 643 (3d Cir. 1928) (same, for purified tungsten). On the other hand, the purified natural substance is patentable if the “purification” results in a product with such distinct characteristics that it becomes “for every practical purpose a new thing commercially and therapeutically.” *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F. 95, 103 (C.C.S.D.N.Y. 1911); *see also Merck & Co. v. Olin Mathieson Chem. Corp.*, 253 F.2d 156, 161-64 (4th Cir. 1958) (holding that a purified composition of vitamin B-12 was patentable because the purification process resulted in a product that was therapeutically effective, whereas the natural form was not).

In sum, the test employed by the Supreme Court in *Chakrabarty* requires us to focus on two things: (1) the similarity in structure between what is claimed and what is found in nature and (2) the similarity in utility between what is claimed and what is found in nature. What is claimed in the BRCA genes is the genetic coding material, and that material is the same, structurally and functionally, in both the native gene and the isolated form of the gene.

The structural differences between the claimed “isolated” genes and the corresponding portion of the native genes are irrelevant to the claim limitations, to the functioning of the genes, and to their utility in

their isolated form. The use to which the genetic material can be put, i.e., determining its sequence in a clinical setting, is not a new use; it is only a consequence of possession. In order to sequence an isolated gene, each gene must function in the same manner in the laboratory as it does in the human body. Indeed, that identity of function in the isolated gene is the key to its value. Moreover, as Judge Moore's concurring opinion explains, Myriad has failed to credibly identify new uses for the isolated BRCA genes as probes or primers. The naturally occurring genetic material thus has not been altered in a way that would matter under the standard set forth in *Chakrabarty*. For that reason, the isolation of the naturally occurring genetic material does not make the claims to the isolated BRCA genes patent-eligible.

## II.

As noted, in addition to the BRCA gene claims discussed above, the claims at issue in this appeal include four claims to BRCA cDNA and two claims to portions of the BRCA genes and cDNA as small as 15 nucleotides long.

I agree with the court that the claims to BRCA cDNA are eligible for patenting. The cDNA cannot be isolated from nature, but instead must be created in the laboratory.<sup>5</sup> Although that process occurs with

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<sup>5</sup> The appellees argue that the BRCA1 cDNA can be isolated from nature, and they refer to a BRCA1 pseudogene called BRCA1P1 that is found in the human genome. However, the appellees have failed to demonstrate that the pseudogene consists of the same sequence as the BRCA1 cDNA.

natural machinery, the end product is a human-made invention with distinct structure because the introns that are found in the native gene are removed from the cDNA segment. Additionally, the cDNA has a utility not present in the naturally occurring BRCA DNA and mRNA because cDNA can be attached to a promoter and inserted into a non-human cell to drive protein expression.

However, I disagree with the court as to the two claims to short segments of DNA having at least 15 nucleotides. Claim 6 of the '282 patent covers any sequence of the BRCA1 cDNA that is at least 15 nucleotides long. That claim encompasses each BRCA1 exon, even though each exon is naturally defined by transcription. Moreover, because small sequences of DNA are repeated throughout the three billion nucleotides of the human genome, the claim covers portions of the cDNA of more than 4% of human genes. It also covers portions of the DNA of nearly all human genes. Accordingly, efforts to sequence almost any gene could infringe claim 6 even though Myriad's specification has contributed nothing to human understanding of other genes.

Myriad could easily have claimed more narrowly to achieve the utility it attaches to segments of cDNA. It contends that those segments can be used as probes and primers. DNA probes must be chemically altered or "tagged" before they can be so used, and Myriad could have claimed the tagged segments to achieve probe functionality. A claim to tagged segments would not encompass the BRCA1 exons. As to primer functionality, many of the cDNA segments will not work. Some will be too long. Some will be too short. Some will be palindromic and fold



in on themselves. Myriad could have identified a subset of the segments that work as primers, and such a claim could be patentable if it were limited to species with “markedly different characteristics from any found in nature and . . . having the potential for significant utility.” *Chakrabarty*, 447 U.S. at 310. The problem with claim 6 is that it is so broad that it includes products of nature (the BRCA1 exons) and portions of other genes; its validity is not salvaged because it includes some species that are not natural. Accordingly, I would hold claim 6 unpatentable.

Myriad’s last claim, claim 5 of the ’282 patent, is breathtakingly broad. That claim covers any segment of the DNA defined by claim 1, provided that the segment is at least 15 nucleotides long. Claim 1, in turn, covers any isolated DNA that codes for the BRCA1 polypeptide. Thus, claim 5 would cover not only the isolated BRCA1 gene in each of its untold molecular variations, but also any subsequence of those molecules, including portions that fall in the undefined range of those molecules denoted “vvvvvvvvvvvvvv.” Claim 5 would therefore be unpatentable for the same reasons as claim 1 and claim 6.

Of course, in light of its breadth, claim 5 of the ’282 patent is likely to be invalid on other grounds, and thus a ruling as to patent-eligibility with respect to that claim may be superfluous. Nonetheless, it is important to consider the effects of such broad patent claims on the biotechnology industry. While Myriad has emphasized the biotechnology industry’s need of patent protection to encourage and reward research in this difficult and important field, there is another side to the coin. Broad claims to genetic material

present a significant obstacle to the next generation of innovation in genetic medicine—multiplex tests and whole-genome sequencing. New technologies are being developed to sequence many genes or even an entire human genome rapidly, but firms developing those technologies are encountering a thicket of patents. Secretary’s Advisory Comm. on Genetics, Health, and Society, Dep’t of Health & Human Servs., *Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests* 49-62 (2010). In order to sequence an entire genome, a firm would have to license thousands of patents from many different licensors. *See id.* at 50-51. Even if many of those patents include claims that are invalid for anticipation or obviousness, the costs involved in determining the scope of all of those patents could be prohibitive. *See id.* at 51-52; Rebecca S. Eisenberg, *Noncompliance, Nonenforcement, Nonproblem? Rethinking the Anticommons in Biomedical Research*, 45 *Hou. L. Rev.* 1059, 1076-1080 (2008) (concluding that existing studies “have focused relatively little attention on downstream product development” and that interviews accompanying those studies suggest that, though smaller than initially feared, the costs associated with the patent thicket are “quite real in the calculations of product-developing firms”). In light of these considerations, this may well be one of those instances in which “*too much* patent protection can impede rather than ‘promote the Progress of Science and useful Arts.’” *Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124, 126 (2006) (Breyer, J., dissenting from dismissal of writ as improvidently granted).

My colleagues assign significant weight to the fact that since 2001 the PTO has had guidelines in

place that have allowed patents on entire human genes. They conclude that those guidelines, and the PTO's earlier practice, are entitled to deference from this court as to the question whether patents to isolated human genes constitute patent-eligible subject matter. I think the PTO's practice and guidelines are not entitled to significant weight, for several reasons.

First, as we have recognized, the PTO lacks substantive rulemaking authority as to issues such as patentability. *Animal Legal Def. Fund v. Quigg*, 932 F.2d 920, 930 (Fed. Cir. 1991). In areas of patent scope, we owe deference only commensurate with the "the thoroughness of its consideration and the validity of its reasoning." *Merck & Co. v. Kessler*, 80 F.3d 1543, 1550 (Fed. Cir. 1996). The comments that the PTO issued at the time of its 2001 guidelines in response to suggestions that isolated human genes were not patentable are, frankly, perfunctory. See John M. Conley & Roberte Makowski, *Back to the Future: Rethinking the Product of Nature Doctrine as a Barrier to Biotechnology Patents*, 85 J. Pat. & Trademark Off. Soc'y 301 (2003). Because those comments, at least on their face, do not reflect thorough consideration and study of the issue, I do not regard them as worthy of much weight in the analysis of this complex question.

Second, whatever force the PTO's views on the issue of patent eligibility may have had in the past has, at the very least, been substantially undermined by the position the government has taken in this case. The Department of Justice filed a brief on behalf of the United States in this court taking the position that Myriad's gene claims (other than the

cDNA claims) are not patent-eligible. Although the PTO did not “sign” the brief and we are left to guess about the status of any possible continuing inter-agency disagreements about the issue, the Department of Justice speaks for the Executive Branch, and the PTO is part of the Executive Branch, so it is fair to assume that the Executive Branch has modified its position from the one taken by the PTO in its 2001 guidelines and, informally, before that.

Finally, prior to the Supreme Court’s decision in *Chakrabarty*, the PTO had determined that microorganisms were not subject to patenting, but the Supreme Court gave no indication that it regarded that view as entitled to deference. Moreover, the Court gave short shrift to the Commissioner’s contention (which was made the lead argument in its brief) that the patentability of life-forms was an issue that should be left to Congress. Citing *Marbury v. Madison*, 5 U.S. (1 Cranch) 137 (1803), the Court explained that “Congress has performed its constitutional role in defining patentable subject matter in § 101; we perform ours in construing the language Congress has employed.” *Chakrabarty*, 477 U.S. at 315. We have the same responsibility and should not shy away from deciding the issues of law that the parties have brought to us. Although my colleagues believe our analysis of the legal question in this case should be influenced by purported expectations of the inventing community based on the PTO’s past practice of issuing patents on human genes, that is in effect to give the PTO lawmaking authority that Congress has not accorded

it.<sup>6</sup> There is no collective right of adverse possession to intellectual property, and we should not create such a right. Our role is to interpret the law that Congress has written in accordance with the governing precedents. I would do so and would affirm the district court's rulings as to the BRCA gene and BRCA gene segment claims.

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<sup>6</sup> Because the asserted reliance interest is based on PTO practice and not on prior judicial decisions, this case is not analogous to *Warner Jenkinson Co. v. Hilton Davis Chemical Co.*, 520 U.S. 17 (1997), or *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722 (2002), where the expectations of the inventing community were based on longstanding Supreme Court precedent.

UNITED STATES DISTRICT COURT  
SOUTHERN DISTRICT OF NEW YORK

ASSOCIATION FOR MOLECULAR PATHOLOGY, ET. AL.,  
*Plaintiffs,*

09 Civ. 4515  
AMENDED  
OPINION

--against--

UNITED STATES PATENT AND  
TRADEMARK OFFICE, ET AL.,  
*Defendants.*

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## TABLE OF CONTENTS

I. PRIOR PROCEEDINGS .....	121a
II. THE PARTIES AND AMICI .....	121a
III. THE FACTS.....	135a
A. The Development of Genetics as a Field of Knowledge.....	136a
B. Molecular Biology and Gene Sequencing.....	138a
1. DNA .....	138a
2. Extracted and purified DNA.....	144a
3. RNA.....	146a
4. cDNA.....	148a
5. DNA sequencing .....	151a
C. The Development of the Patents-in-Suit .....	153a
D. Application of the Patents-in-Suit .....	159a
1. Myriad's <i>BRCA1/2</i> testing .....	160a
2. Funding for Myriad' s <i>BRCA1/2</i> tests .....	160a
E. Disputed Issues.....	166a
1. The impact of Myriad's patents on <i>BRCA1/2</i> testing.....	166a
2. The impact of gene patents on the advancement of science and medical treatment.....	170a



IV. THE PATENTS.....	178a
A. Summary of the Patents.....	178a
B. Construction of the Claims.....	184a
1. Legal standard.....	184a
2. Resolution of the disputed claim terms "DNA" and "isolated DNA" .....	187a
a. "DNA" and "isolated DNA" .....	187a
b. "BRCA1" and "BRCA2" .....	190a
V. CONCLUSIONS OF LAW .....	191a
A. The Summary Judgment Standard .....	191a
B. 35 U.S.C. § 101 and Its Scope.....	192a
C. The Composition Claims Are Invalid Under 35 U.S.C. § 101 .....	197a
1. Consideration of the Merits of Plaintiffs' Challenge is Appropriate .....	198a
2. Patentable subject matter must be a"markedly different" from a product of nature .....	201a
3. The claimed. isolated DNA is not "markedly different" from native DNA .....	214a
D. The Method Claims are Invalid Under 35 U.S.C. § 101.....	224a
1. The claims for "analyzing" and "comparing" DNA sequences are invalid under § 101 ...	226a
2. The Claim for "Comparing" the growth rate of Cells is invalid under § 101 .....	234a

E. The Constitutional Claims Against the USPTO Are Dismissed .....	236a
VIII. CONCLUSION.....	238a

**Sweet, D.J.**

Plaintiffs Association for Molecular Pathology, et al. (collectively "Plaintiffs") have moved for summary judgment pursuant to Rule 56, Fed. R. Civ. P., to declare invalid fifteen claims (the "claims-in-suit") contained in seven patents (the "patents-in-suit") relating to the human *BRCA1* and *BRCA2* genes (Breast Cancer Susceptibility Genes 1 and 2) (collectively, "*BRCA1/2*") under each of (1) the Patent Act, 35 U.S.C. § 101 (1952), (2) Article I, Section 8, Clause 8 of the United States Constitution, and (3) the First and Fourteenth Amendments of the Constitution because the patent claims cover products of nature, laws of nature and/or natural phenomena, and abstract ideas or basic human knowledge or thought. The defendant United States Patent and Trademark *Office* ("USPTO") issued the patents-in-suit which are held by defendants Myriad Genetics and the University of Utah Research Foundation ("UURF") (collectively "Myriad" or the "Myriad Defendants"). Myriad has cross-moved under Rule 56, Fed. R. Civ. P., for summary judgment dismissing Plaintiffs' complaint, and the USPTO has cross-moved under Rule 12(c), Fed. R. Civ. P., for judgment on the pleadings. Based upon the findings and conclusions set forth below, the motion of Plaintiffs to declare the claims-in-suit invalid is granted, the cross-motion of Myriad is denied, and the motion of the USPTO is granted.

As discussed *infra* in greater detail, the challenged patent claims are directed to (1) isolated DNA containing all or portions of the *BRCA1* and *BRCA2* gene sequence and (2) methods for "comparing" or "analyzing" *BRCA1* and *BRCA2* gene

sequences to identify the presence of mutations correlating with a predisposition to breast or ovarian cancer. Plaintiffs' challenge to the validity of these Claims, and the arguments presented by the parties and amici, have presented a unique and challenging question:

Are isolated human genes and the comparison of their sequences patentable?

Two complicated areas of science and law are involved: molecular biology and patent law. The task is to seek the governing principles in each and to determine the essential elements of the claimed biological compositions and processes and their relationship to the laws of nature. The resolution of the issues presented to this Court deeply concerns breast cancer patients, medical professionals, researchers, caregivers, advocacy groups, existing gene patent holders and their investors, and those seeking to advance public health.

The claims-in-suit directed to "isolated DNA" containing human *BRCA1/2* gene sequences reflect the USPTO's practice of granting patents on DNA sequences so long as those sequences are claimed in the form of "isolated DNA." This practice is premised on the view that DNA should be treated no differently from any other chemical compound, and that its purification from the body, using well-known techniques, renders it patentable by transforming it into something distinctly different in character. Many, however, including scientists in the fields of molecular biology and genomics, have considered this

practice a "lawyer's trick"<sup>1</sup> that circumvents the prohibitions on the direct patenting of the DNA in our bodies but which, in practice, reaches the same result. The resolution of these motions is based upon long recognized principles of molecular biology and genetics: DNA represents the physical embodiment of biological information, distinct in its essential characteristics from any other chemical found in nature. It is concluded that DNA's existence in an "isolated" form alters neither this fundamental quality of DNA as it exists in the body nor the information it encodes. Therefore, the patents at issue directed to "isolated DNA" containing sequences found in nature are unsustainable as a matter of law and are deemed unpatentable subject matter under 35 U.S.C. § 101.

Similarly, because the claimed comparisons of DNA sequences are abstract mental processes, they also constitute unpatentable subject matter under § 101.

The facts relating to molecular biology are fundamental to the patents at issue and to the conclusions reached. Consequently, in the findings which follow, the discussion of molecular biology precedes the facts concerning the development, application, and description of the patents. Following those facts are the conclusions which compel the partial grant of summary judgment to the Plaintiffs,

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<sup>1</sup> See, e.g., John M. Conley & Roberte Markowski, Back to the Future: Rethinking the Product of Nature Doctrine as a Barrier to Biotechnology Patents, 65 J. Pat. & Trademark Off. Soc'y 301, 3C5 (2003).

the denial of Myriad's cross-motion, and the grant of the USPTO's motion for judgment on the pleadings.

## **I. PRIOR PROCEEDINGS**

The complaint in this action was filed on May 12, 2009, alleging violations of 35 U.S.C. § 101; Article I, Section 8, Clause 8 of the United States Constitution; and the First and Fourteenth Amendments to the Constitution.

Defendants moved to dismiss the complaint which motion was denied by the opinion of November 1, 2009. See Assoc. for Molecular Pathology v. U.S. Patent and Trademark Office, 669 F. Supp. 2d 365 (S.D.N.Y. 2009). Plaintiffs were found to have the necessary standing to assert their declaratory judgment claims against the Myriad Defendants and the USPTO, and specific personal jurisdiction was found to exist over the Directors of the UURF by virtue of acts performed in their official capacity that were directed to the state of New York. It was also determined that this Court possessed the necessary subject matter jurisdiction to hear Plaintiffs' constitutional claims against the USPTO and that the complaint satisfied the pleading requirements set forth in Ashcroft v. Iqbal, 129 S. Ct. 1937 (2009).

Plaintiffs' motion for summary judgment and the cross-motions for summary judgment and judgment on the pleadings were heard and marked fully submitted on February 4, 2010.

## **II. THE PARTIES AND AMICI**

Plaintiff Association for Molecular Pathology ("AMP") is a not-for-profit scientific society dedicated to the advancement, practice, and science of clinical

molecular laboratory medicine and translational research based on the applications of genomics and proteomics. AMP members participate in basic and translational research aimed at broadening the understanding of gene/protein structure and function, disease processes, and molecular diagnostics, and provide clinical medical services for patients, including diagnosis of breast cancer. Sobel Decl. ¶¶ 2, 4-5.<sup>2</sup>

Plaintiff the American College of Medical Genetics ("ACMG") is a private, non-profit voluntary organization of clinical and laboratory geneticists. The Fellows of the ACMG are doctoral level medical geneticists and other physicians involved in the practice of medical genetics. With more than 1300 members, the ACMG's mission is to improve health through the practice of medical genetics. In order to fulfill this mission, the ACMG strives to define and promote excellence in medical genetics practice and the integration of translational research into practice; promote and provide medical genetics education; increase access to medical genetics services and integrate genetics into patient care; and advocate for and represent providers of medical genetics services and their patients. Watson Decl. ¶¶ 2, 4-5.

Founded in 1922, plaintiff the American Society for Clinical Pathology ("ASCP") is the largest and oldest organization representing the medical specialty of pathology and laboratory medicine.

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<sup>2</sup> For purposes of this opinion, references to the parties' declarations will be in the format [Declarant name] Decl. ¶ [paragraph number].

ASCP is a not-for-profit entity organized for scientific and educational purposes and dedicated to patient safety, public health, and the practice of pathology and laboratory medicine and has 130,000 members working as pathologists and laboratory professionals. ASCP members design and interpret the tests that detect disease, predict outcome, and determine the appropriate therapy for the patient. The ASCP is recognized for its excellence in continuing professional education, certification of laboratory professionals, and advocacy. Ball Decl. ¶¶ 2, 5.

Plaintiff the College of American Pathologists ("CAP") is a national medical society representing more than 17,000 pathologists who practice anatomic pathology and laboratory medicine in laboratories worldwide. The College's Commission on Laboratory Accreditation is responsible for accrediting more than 6,000 laboratories domestically and abroad, and approximately 23,000 laboratories are enrolled in CAP's proficiency testing programs. It is the world's largest association composed exclusively of board-certified pathologists and pathologists in training worldwide and is widely considered the leader in laboratory quality assurance. CAP is an advocate for high quality and cost-effective medical care. Scott Decl. ¶¶ 2, 4-5.

Plaintiff Haig Kazazian, M. D. ("Dr. Kazazian"), is the Seymour Gray Professor of Molecular Medicine in Genetics in the Department of Genetics at the University of Pennsylvania School of Medicine. He is a human genetics researcher and the previous chair of the Department. Dr. Kazazian and plaintiff Arupa Ganguly, Ph.D. ("Dr. Ganguly"), designed tests to screen the *BRCA1* and *BRCA2* genes in their lab and provided screening to



approximately 500 women per year starting in 1996. Drs. Kazazian and Ganguly ceased their *BRCA1/2* testing in response to cease-and-desist letters from Myriad relating to the patents-in-suit. Kazazian Decl. ¶¶ 1-5.

Plaintiff Dr. Ganguly is an Associate Professor in the Department of Genetics at the Hospital of the University of Pennsylvania. Dr. Ganguly's work previously included *BRCA1/2* screening for both research and clinical purposes. She ceased *BRCA1/2* screening following her receipt of cease-and-desist letters from Myriad accusing her lab of violating the patents-in-suit. Ganguly Decl. ¶¶ 1, 3-5.

Plaintiff Wendy Chung, M.D., Ph.D. ("Dr. Chung"), is an Associate Professor of Pediatrics and the Herbert Irving Professor of Pediatrics and Medicine in the Division of Molecular Genetics at Columbia University. Dr. Chung is a human geneticist whose current research includes research on the *BRCA1* and *BRCA2* genes. Because of the patents-in-suit, Dr. Chung currently cannot tell research subjects in her studies the results of their *BRCA1/2* tests and cannot offer clinical *BRCA1/2* testing services. Chung Decl. ¶¶ 1-9, 13, 16.

Plaintiff Harry Ostrer, M.D. ("Dr. Ostrer"), is a Professor of Pediatrics, Pathology and Medicine and Director of the Human Genetics Program in the Department of Pediatrics at New York University School of Medicine. Dr. Ostrer's work has focused on understanding the genetic basis of development and disease, including disorders of sexual differentiation and genetic susceptibility to breast and prostate cancer and malignant melanoma. Dr. Ostrer is actively engaged in identifying genes that convey

risk of breast cancer and that may mitigate the effects of mutations in the *BRCA1* and *BRCA2* genes. Dr. Ostrer is also the Director of the Molecular Genetics Laboratory of NYU Medical Center, one of the largest academic genetic testing laboratories in the United States. Because of the patents-in-suit, Dr. Ostrer currently cannot tell research subjects in his studies the results of their *BRCA1/2* tests and cannot offer clinical *BRCA1/2* testing services. Ostrer ¶¶ 1-4.

Plaintiff David Ledbetter, Ph. D. (“Dr. Ledbetter”), is a Professor of Human Genetics and Director of the Division of Medical Genetics at the Emory University School of Medicine. Research in his laboratory focuses on the molecular characterization of human developmental disorders. Dr. Ledbetter directs the Emory Genetics Laboratory which provides testing services for individuals with or at risk for genetic diseases. Because of the patents-in-suit, Dr. Ledbetter cannot offer comprehensive *BRCA1/2* genetic testing to patients. Ledbetter Decl. ¶¶ 1-8, 16.

Plaintiff Stephen T. Warren, Ph.D. (“Dr. Warren”), is the William Patterson Timmie Professor of Human Genetics, Chairman of the Department of Human Genetics, and Professor of Biochemistry and Professor of Pediatrics at Emory University. He is a past President of the American Society of Human Genetics. Dr. Warren supervises genetic research at Emory and is responsible for the laboratories at the Emory Genetics Laboratory. These laboratories would offer *BRCA1/2* genetic testing but for the patents-in-suit. Ledbetter Decl. ¶¶ 1, 16.

Plaintiff Ellen Matloff, M.S. ("Ms. Matloff"), is Director of the Yale Cancer Genetic Counseling Program. Ms. Matloff advises women on the desirability of obtaining an analysis of their genes to determine if the women have the genetic mutations that correlate with an increased risk of breast and/or ovarian cancer. If she determines that such an analysis is warranted and the individual woman concurs, Ms. Matloff arranges for the analysis and then advises the woman of the significance of the results. Ms. Matloff would like to have the option to send patient samples to laboratories other than Myriad Genetics for *BRCA1/2* sequencing. Matloff Decl. ¶¶ 1-4, 11.

Plaintiff Elsa W. Reich, M.S. ("Ms. Reich"), is a Professor in the Department of Pediatrics at New York University. She is a genetic counselor. She helps women decide whether to be tested for mutations in the *BRC1* and *BRCA2* genes. If they need testing, she sends samples to Myriad and explains the results for the women. Ms. Reich would like to have the option to send patient samples to laboratories other than Myriad for *BRCA1/2* sequencing. Reich Decl. ¶¶ 1-3, 8.

Plaintiff Breast Cancer Action ("BCA") is a national organization of approximately 30,000 members based in San Francisco, California. BCA is dedicated to representing the voices of people affected by breast cancer in order to inspire and compel the changes necessary to end the breast cancer epidemic. Its members include breast cancer survivors, family members of people diagnosed with breast cancer and other people affected by or

concerned about breast cancer. BCA advocates for policy changes directed at achieving prevention, finding better treatments, and reducing the incidence of breast cancer, provides information about breast cancer to anyone who needs it via newsletters, web sites, e-mail and a toll-free number, and organizes people to get involved in advocacy to advance its policy goals. Brenner Decl. ¶¶ 1-3.

Plaintiff Boston Women's Health Book Collective, doing business as Our Bodies Ourselves ("OBOS"), is a nonprofit, public interest women's health education, advocacy, and consulting organization. OBOS provides information about health, sexuality and reproduction from a feminist and consumer perspective. OBOS advocates for women's health and provides information to members of the public about genetic analysis. Norsigian Decl. ¶¶ 1-4.

Plaintiff Lisbeth Ceriani ("Ms. Ceriani") is a 43-year-old single mother who was diagnosed with cancer in both breasts in May 2008. Ms. Ceriani is insured through MassHealth, a Medicaid insurance program for low-income people. Her oncologist and genetic counselor recommended that she obtain *BRCA1* and *BRCA2* genetic testing because she may need to consider further surgery in order to reduce her risk of ovarian cancer. However, Myriad will not accept the MassHealth coverage, and Ms. Ceriani is unable to pay the full cost out-of-pocket. Ceriani Decl. ¶¶ 1-6.

Plaintiff Runi Limary ("Ms. Limary") is a 32-year-old Asian-American woman who was diagnosed with aggressive breast cancer in 2005. Ms. Limary obtained *BRCA1/2* testing through Myriad and

received the following result: "genetic variant of uncertain significance." Because of Myriad's patents, she is unable to pursue alternative testing options. Limary Decl. ¶¶ 1-5.

Plaintiff Genae Girard ("Ms. Girard") is a 39-year-old woman who was diagnosed with breast cancer in 2006. Shortly after her diagnosis, she obtained *BRCA1/2* genetic testing from Myriad and tested positive for a deleterious mutation on the *BRCA2* gene. She sought a second opinion of that test result but learned that Myriad is the only laboratory in the country that can provide full *BRCA1/2* sequencing. Girard Decl. ¶¶ 1-6.

Plaintiff Patrice Fortune ("Ms. Fortune") is a 48-year-old woman who was diagnosed with breast cancer in February 2009. Ms. Fortune is insured through Medi-Cal. Her oncologist and genetic counselor recommended that she obtain *BRCA1/2* genetic testing, including the supplemental testing that is offered by Myriad separate from its standard test, but told her that Myriad would not accept her insurance. Ms. Fortune is unable to pay the full cost out-of-pocket. Fortune Decl. ¶¶ 1-5.

Plaintiff Vicky Thomason ("Ms. Thomason") is a 52-year-old woman who was diagnosed with ovarian cancer in 2006. She obtained *BRCA1/2* genetic testing from Myriad in 2007 and was found to be negative for mutations covered by that test. Her genetic counselor advised her about additional *BRCA1/2* genetic testing offered by Myriad that looks for other large genetic rearrangements that are not included in Myriad's standard full sequencing test, but informed her that her insurance would not cover the full cost of that test. Ms. Thomason is

unable to afford the extra cost. Thomason Decl. ¶¶ 1-8.

Plaintiff Kathleen Raker ("Ms. Raker") is a 41-year-old woman whose mother and maternal grandmother died from breast cancer. She obtained *BRCA1/2* genetic testing from Myriad in 2007 and was found to be negative for mutations covered by that test. Her genetic counselor advised her about additional *BRCA1/2* genetic testing offered by Myriad that looks for other large DNA rearrangements that are not included in Myriad's standard full sequencing test, but informed her that it was unclear whether her insurance would cover the full cost of that test. Ms. Raker is unable to afford the extra cost. Raker Decl. ¶¶ 1-9.

Defendant USPTO is an agency of the Commerce Department of the United States with its principal office in Alexandria, Virginia. USPTO Answer ¶ 27.

Defendant Myriad is a for-profit corporation incorporated in Delaware with its principal place of business in Salt Lake City, Utah. Myriad is the former co-owner of several of the patents-in-suit and the current exclusive licensee of the patents-in-suit. Myriad is the sole provider of full sequencing of *BRCA1* and *BRCA2* genes in the United States on a commercial basis. Myriad Answer ¶ 28.

The University of Utah Research Foundation, whose directors are named as defendants in their official capacity, is an owner or part-owner of each of the patents-in-suit. Myriad Answer ¶ 29.

Amici curiae American Medical Association American Society of Human Genetics, American

College of Obstetricians and Gynecologists, American College of Embryology, and The Medical Society of the State of New York are non-profit organizations representing physicians and medical students throughout the United States, including New York; professionals in the field of human genetics, including researchers, clinicians, academicians, ethicists, genetic counselors and nurses whose work involve genetic testing; women's health care professionals; and embryologists. These amici contend that the patents-in-suit are directed to unpatentable natural phenomena in violation of Article I, Section 8, Clause B of the Constitution, and 35 U.S.C. § 101, are unnecessary to promote innovation in genetic research, and violate medical and scientific ethics.

Amici curiae March of Dimes Foundation, Canavan Foundation, Claire Altman Heine Foundation, Breast Cancer Coalition, Massachusetts Breast Cancer Coalition, National Organization for Rare Disorders, and National Tay-Sachs & Allied Diseases Association are non-profit organizations dedicated to advancing the treatment of a variety of genetic diseases, including breast cancer, Tay-Sachs, Spinal Muscular Dystrophy, Canavan disease, and other rare genetic disorders. These amici contend that Myriad's patents represent patents on natural phenomena and laws of nature, thereby restricting future research and scientific progress.

Amici curiae National Women's Health Network, Asian Communities for Reproductive Justice, Center for Genetics and Society, Generations Ahead, and Pro-Choice Alliance for Responsible Research are non-profit organizations seeking to

improve the health of women; promote reproductive justice; encourage responsible use and governance of genetic, reproductive and biomedical technologies; promote policies on genetic technologies that protect human rights; promote accountability, safety, and social justice in biomedical research from a women's rights perspective. These amici contend that isolated DNA constitutes an unpatentable product of nature whose patenting harms women by stifling innovation and interfering with patient access to medical testing and treatment. These amici also contend that human genes and the information contained therein constitute part of the common heritage of humanity, and patenting human gene sequences is contrary to both international law and treaties as well as the public trust doctrine.

*Amici curiae* The International Center for Technology Assessment, Indigenous People Council on Biocolonialism, Greenpeace, Inc., and Council for Responsible Genetics are non-profit organizations dedicated to assisting the public and policy makers in understanding how technology affects society, protecting the cultural heritage and genetic materials of indigenous peoples; addressing global environmental problems; and protecting the public interest and fostering public debate about the social, ethical, and environmental implications of genetic technologies. These amici contend that the patents-in-suit claim unpatentable products of nature and that gene patents have significant negative consequences, including privatization of genetic heritage in violation of fundamental precepts of common heritage, public domain, and the public trust doctrine; creation of private rights of unknown scope and significance; facilitate the exploitation of



indigenous peoples; and violation of patients' rights to informed consent.

Amicus curiae Biotechnology Industry Organization ("BIO") is the country's largest biotechnology trade association, representing over 1200 companies, academic institutions, and biotechnology centers in all 50 states. BIO members are involved in the research and development of biotechnological healthcare, agricultural, environmental, and industrial products. BIO member companies range from start-up businesses and university spin-offs to large Fortune 500 corporations. BIO contends that patents directed to isolated DNA fall within the categories of patent-eligible subject matter because they differ "in kind" from naturally-occurring DNA. The BIO also contends that patents such as the ones in dispute here provide incentives for investment in biotechnology that promotes the advancement of science.

Amicus curiae Boston Patent Law Association ("BPLA") is a non-profit association of attorneys and other intellectual property professionals. BPLA's members serve a broad range of clients who rely on the patent system, including independent investors, corporations, investors, and non-profit and academic institutions, such as universities and research hospitals. BPLA contends that patents, including patents on gene-related inventions, promote innovation by protecting investments in the innovation process. It further contends that the patents-in-suit satisfy the requirements of 35 U.S.C. § 101 as well as the Constitution.

Amicus curiae Genetic Alliance ("GA") is a not-for-profit, tax-exempt health advocacy organization founded in 1986 (as the Alliance for Genetic Support Groups). It brings together diverse stakeholders that create novel partnerships in advocacy. By integrating individual, family, and community perspectives to improve health systems, Genetic Alliance seeks to revolutionize access to information to enable translation of research into services and individualized decision-making. GA contends that the wholesale abolition of patents on isolated DNA molecules and isolated purified natural substances is legally untenable and undesirable as public policy, because it would diminish the promise of genetic research for patients and negatively affect other areas of medicine.

Amicus curiae Rosetta Genomics, Inc. is a wholly owned subsidiary of amicus curiae Rosetta Genomics, Ltd., a molecular diagnostics company that provides diagnostic tests for cancer and which owns several patents claiming isolated nucleic acid sequences. Amicus curiae George Mason University ("George Mason") is a public university located in Virginia. Research conducted at George Mason has been incorporated into patent applications covering cancer diagnostics. These amici contend that the question of patentability of human gene sequences is appropriately left to Congress; that the patents-in-suit promote, rather than hinder innovation; and that the challenged patents are lawful under 35 U.S.C. § 101 and the Constitution.

Amicus curiae BayBio is an independent, nonprofit 501(c) (6) trade association serving the life sciences industry in Northern California, and

represents more than 330 companies involved in the research and development of treatments, cures, and diagnostics. Amicus curiae Celera Corporation is a manufacturer of diagnostic products that include gene-based products used in genetic testing. Amicus curiae The Coalition for 21st Century Medicine represents some of the world's most innovative diagnostic technology companies, clinical laboratories, researchers, physicians, venture capitalists, and patient advocacy groups that share a common mission to develop advanced diagnostics that improve the quality of healthcare for patients. Amicus curiae Genomic Health, Inc., is a life sciences company committed to improving the quality of cancer treatment decisions through genomics-based clinical laboratory services and currently offers the Oncotype DX breast cancer assay, which predicts the likelihood of the recurrence of specific types of breast cancer and whether a patient will benefit from certain treatment strategies. Amicus curiae Qiagen, N.V. is a leading provider of innovative sample and assay technologies and products which are considered standard for use in molecular diagnostics, applied testing, and academic and pharmaceutical research and development. Amicus curiae Target Discovery, Inc. discovers, validates, and utilizes protein isoforms to improve clinical diagnosis and management of disease. Amicus curiae XDx, Inc., is a molecular diagnostics company focused on the discovery, development and commercialization of non-invasive gene expression testing in the areas of transplant medicine and autoimmunity through the use of modern genomics and bioinformatics technology. These amici contend that patent exclusivity is required for the development of

personalized medicine and that the challenged patents satisfy the requirements of 35 U.S.C. § 101 and the Constitution. In addition, the amici contend that the harm alleged by Plaintiffs can be redressed through traditional judicial remedies and do not require a finding that isolated DNA constitutes unpatentable subject matter.

Amicus curiae Kenneth Chahine, Ph.D. ("Professor Chahine"), is a Visiting Professor of Law at S.J. Quinney College of Law at the University of Utah. Professor Chahine contends that the scope of the claims-in-suit are sufficiently limited to avoid claiming products of nature and that the claims directed to isolated DNA and diagnostic process satisfy the requirements of patentable subject matter under 35 U.S.C. § 101.

Amicus curiae Kevin E. Noonan, Ph.D. ("Dr. Noonan"), is a patent attorney with McDonnell Boehnen Hulbert & Berghoff LLP. Dr. Noonan contends that isolated human DNA constitutes patentable subject matter and that a ban on patenting isolated human DNA would negatively affect the development of human therapeutics, the development of personalized medicine, and the scientific research in general.

### **III. THE FACTS**

The facts as set forth in this section are taken from the parties' respective statements and counterstatements pursuant to Local Civil Rule 56.1 and the affidavits submitted by the parties and amici and are not in dispute except where noted.

## **A. The Development of Genetics as a Field of Knowledge**

The field of genetics - the science of heredity and variation in living organisms - and the concept of units of heredity that could be transmitted from one generation to another originated in the 19th century from experiments with pea plants conducted by Gregor Mendel. Mendel showed that certain traits are passed on from parent to offspring as discrete entities and do not appear blended in the offspring. He hypothesized that it was the plant's genotype, or assortment of hereditary factors, that determined the plant's phenotype, or appearance. Mason Decl. ¶ 8. In 1909, this unit of inheritance was termed a "gene." Yet the gene remained an abstract concept until 1915, when it was shown that genes corresponded to physical spans of chromosomal material. Mason Decl. ¶ 9.

In 1944, scientists determined that the chemical compound known as deoxyribonucleic acid, or DNA,<sup>3</sup> served as the carrier for genetic information by demonstrating that DNA extracted from one strain of bacteria and transferred to another strain could transfer certain characteristics found in the first strain. Oswald Theodore Avery, et al., Studies on the Chemical Nature of the Substance Inducing Transformation of Pneumococcal Types: Induction of Transformation by a Desoxyribonucleic

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<sup>3</sup> Scientists had learned to extract DNA from the body by removing it from the rest of the cellular material since as early as 1869. Ralf Dahm, Discovering DNA: Friedrich Miescher and the Early Years of Nucleic Acid Research, 122 Human Genetics 565-581, 567-68 (2008).

Acid Fraction Isolated from Pneumococcus Type III,  
79 J. Exp. Med. 137- 158 (1944).

On April 25, 1953, James Watson and Francis Crick published their determination of the famous double-helix structure of DNA in the journal *Nature*. James D. Watson & Francis H.C. Crick, A Structure for Deoxyribose Nucleic Acid, 171 *Nature* 737-38 (1953). Dr. Crick subsequently contributed to the decryption of the genetic code and proposed "the central dogma" of molecular biology: (1) information is encoded in a segment of DNA, i.e., a gene; (2) transmitted through a molecule called RNA; and then (3) utilized to direct the creation of a protein, the building block of the body. Mason Decl. ¶ 10.

Our understanding of the DNA contained within our cells has since grown at an exponential rate and has included the landmark completion of the first full-length sequence of a human genome, containing 25,000 genes, as a result of the work performed by the Human Genome Project from 1990 to 2003. Sulston Decl. ¶¶ 11, 22. Access to the information encoded in our DNA has presented expansive new possibilities for future biomedical research and the development of novel diagnostic and therapeutic approaches. How this genomic information is best harnessed for the greater good presents difficult questions touching upon innovation policy, social policy, medical ethics, economic policy, and the ownership of what some view as our common heritage.

## **B. Molecular Biology and Gene Sequencing**

An understanding of the basics of molecular biology is required to resolve the issues presented and to provide the requisite insight into the fundamentals of the genome, that is, the nature which is at the heart of the dispute between the parties. What follows represents the standard undisputed knowledge of those in the field of molecular biology as set forth in the parties' 56.1

Statements and expert declarations. Citations are also made to two established texts in the field: Bruce Alberts, et al, *Molecular Biology of the Cell* (4th ed. 2002) ("*The Cell*") and James Watson, et al, *Molecular Biology of the Gene* (6th ed. 2008) ("*The Gene*").

### **1. DNA**

DNA is a chemical molecule composed of repeating chemical units known as "nucleotides" or "bases." DNA is composed of four standard nucleotides: adenine, thymine, cytosine, and guanine. As shorthand, scientists denote nucleotides by the first letter of the names of their bases: "A" for adenine; "G" for guanine; "T" for thymine; and "c" for cytosine. These nucleotide units are composed of several chemical elements, namely carbon, hydrogen, oxygen, nitrogen, and phosphorus, and are linked together by chemical bonds to form a strand, or polymer, of the DNA molecule. Kay Decl. ¶¶ 14, 125; Linck Decl. ¶ 70.

Although it can exist as a single strand of nucleotides, DNA typically exists as a "double helix,"<sup>4</sup> consisting of two intertwined strands of DNA that are chemically bound to each other. This structure is possible because of a property of DNA known as "base pair complementarity" or "base pairing," in which adenine on one strand of DNA always binds to thymine on the other strand of DNA, and guanine on one strand always bind to cytosine on the other strand. Kay Decl. ¶ 129. For example, if a portion of one strand of DNA has the nucleotide sequence ACTCGT, the corresponding section of DNA on the complementary strand will have the nucleotide sequence TGAGCA.

Genes are basic units of heredity found in all living organisms and are responsible for the inheritance of a discrete trait. Sulston Decl. ¶ 11. In molecular terms, a gene is composed of several, typically contiguous, segments of DNA. Kay Decl. ¶ 142. Each gene is typically thousands of nucleotides long and usually "encodes" one or more proteins, meaning it contains the information used by the body to produce those proteins. Some of the segments of DNA within a gene, known as "exons" or "coding sequences," contain sequences necessary for the creation of a protein, while other segments of DNA, known as "introns," are not necessary for the creation of a protein.<sup>5</sup> See Mason Decl. ¶ 11; Kay Decl. ¶ 151; Schlessinger Decl. ¶ 14. DNA encodes proteins by

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<sup>4</sup> It was the description of this famous "double-helix" structure that earned Watson and Crick the Nobel Prize.

<sup>5</sup> Introns can contain regulatory sequences that affect the body's rate of production of the protein encoded by a gene. Kay Decl. ¶ 151.



way of three nucleotide combinations, termed "codons," that correspond to one of twenty amino acids that constitute the building blocks of proteins. Sulston Decl. ¶¶ 14-15. For example, the codon adenine-thymine-guanine (ATG) encodes the amino acid methionine. Kay Decl. ¶ 158. However, because there are only twenty different amino acids but 64 possible codons that can be derived from combinations of the four DNA nucleotides, most amino acids are encoded by more than one DNA codon. *The Gene* at 37 & Table 2-3.

Together, the approximately 25,000 genes in the human body make up the human genome.<sup>6</sup> The genome, and the genes within it, are contained within almost every cell in the human body and define physical traits such as skin tone, eye color, and sex, in addition to influencing the development of conditions such as obesity, diabetes, Alzheimer's disease, and bipolar disorder. Mason Decl. ¶ 4-5; Sulston Decl. ¶¶ 10-11.

The linear order of DNA nucleotides that make up a polynucleotide, such as a gene, is referred to as the "nucleotide sequence," "DNA sequence," or "gene sequence."<sup>7</sup> Kay Decl. ¶ 126; Schlessinger Decl. ¶ 19; Linck Decl. ¶ 45; Sulston Decl. ¶ 16; Mason Decl. ¶ 13; Chung Decl. ¶ 10. Gene sequences constitute biological information insofar as they describe the structural and chemical properties of a particular

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<sup>6</sup> Genome is defined as [t]he totality of genetic information belonging to a cell or an organism; in particular, the DNA that carries this information." *The Cell* at G:15.

<sup>7</sup> By analogy, if a gene is the equivalent of a word, then the nucleotide sequence is the equivalent of the word's spelling.

DNA molecule and serve as the cellular "blueprint" for the production of proteins. Sulston Decl. ¶ 16; Kay Decl. ¶ 126; Schlessinger Decl. ¶ 19; Linck Decl. ¶¶ 45, 46. Genes and the information represented by human gene sequences are products of nature universally present in each individual, and the information content of a human gene sequence is fixed. While many inventive steps may be necessary to allow scientists to extract and read a gene sequence, it is undisputed that the ordering of the nucleotides is determined by nature. Sulston Decl. ¶ 10, 17; Ostrer Decl. ¶ 14; Chung Decl. ¶ 25; Ledbetter Decl. ¶ 27; Leonard Decl. ¶ 15.

Scientists often use the term "wild-type" to refer to the "normal" human gene sequence, i.e. the sequence of a gene without any variations,<sup>8</sup> against which individuals' gene sequences are compared. Mason Decl. ¶ 17; Grody Decl. ¶ 46. Variations in the human genome are very common; aside from identical twins, the genomes of any two individuals are estimated to have one to five nucleotide differences for every 1000 nucleotides. Mason Decl. ¶ 14; Sulston Decl. ¶ 12.

Variations in the human genome, also known as "mutations," can occur at different scales. Small scale variations can be manifested as slight sequence differences between the same genes in different individuals. Thus, for example, if the wild-type

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<sup>8</sup> At the same time there is an increasing recognition that the notion of a single "normal" gene sequence may not be entirely accurate in light of the high frequency of variations in a gene's sequence between individuals. Mason Decl. ¶ 17. For purposes of this opinion, however, genes are treated as having a single "normal" DNA sequence.

sequence of a portion of a gene is represented by GACTCG, a variation of that sequence might omit the first C (resulting in GATCG) or contain an extra C at that point (resulting in GACCTCG) or reverse the order of two of the letters (e.g., GCATCG). Mason Decl. ¶ 16. Alternatively, there can be large scale variations, such as the addition or deletion of substantial chromosomal regions. Thus, a particular gene may omit several hundred letters at one point or may add several hundred letters where they do not normally exist in the wild-type gene sequence. Even larger variations, known as structural variants, also can occur, involving the deletion or duplication of up to millions of nucleotides. Extra copies or missing copies of the genome that are larger than 1000 nucleotides are called "copy number variants" ("CNVs"). Mason Decl. ¶ 15, 18.

Some of these mutations have little or no effect on the body's processes, while other mutations, including those that appear to correlate with an increased risk of particular diseases, do interfere with the body's processes.<sup>9</sup> There are also variants of uncertain significance ("VUS"): variants whose effect on the body's processes, if any, is currently unknown. Mason Decl. ¶ 19; Sulston Decl. ¶ 18; Kay Decl. ¶ 76.

DNA as it is found in the human body - "native DNA" or "genomic DNA" - is packaged, along with

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<sup>9</sup> The correlation between a particular mutation and disease susceptibility is not self-evident from the mutation itself; rather, extensive statistical analysis is required to identify which alterations in the nucleotide sequence correlate with a particular medical condition, a process which may take many years. Kay Decl. ¶ 190.

proteins, into complex structures known as chromosomes, which contain the vast majority of the genes located in the cells of the human body. Kay Decl. ¶ 131; Schlessinger Decl. ¶ 12. This mixture of DNA and proteins that makes up chromosomes is also referred to as chromatin. See *The Gene* at 135. Genes are organized on forty-six chromosomes (twenty-three of which are inherited from the mother, and twenty-three of which are inherited from the father) which together constitute the vast majority of the human genome.<sup>10</sup> Mason Decl. ¶ 5. The proteins within the chromosomes are bound<sup>11</sup> to the DNA molecules and modulate the structure and function of the DNA molecules to which they are associated. Kay Decl. ¶ 131; Schlessinger Decl. ¶ 12; *The Cell* at 198, 208, Fig. 4-24. This interaction between chromosomal proteins and native DNA is one method by which the body establishes which genes are inactive, which genes are active, and the level of activity. Kay Decl. ¶ 132. Some DNA in the body also undergoes chemical modifications, such as

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<sup>10</sup> A very small fraction of human genes are located in a cellular organelle known as the mitochondria. Kay Decl. ¶ 144; Schlessinger Decl. ¶ 23. Neither party appears to believe that a discussion of mitochondrial DNA bears much relevance to the legal issues presented.

<sup>11</sup> The ionic chemical bonds that exists between proteins and DNA molecules differ from the covalent chemical bonds which hold DNA itself together. See *The Cell* at 198 (describing DNA in the cell as "associated with proteins that fold and pack the fine DNA thread into a more compact structure."); id. at 208 Fig. 4-24 (demonstrating dissociation of histone proteins from DNA by high salt solution, indicating lack of covalent bond between DNA and histones).

methylation,<sup>12</sup> which can affect the level of activity of a gene, but does not affect the nucleotide sequence of the gene. Kay Decl. ¶ 132; Mason Supp. Decl. ¶ 22.

## **2. Extracted and purified DNA**

Native DNA may be extracted from its cellular environment, including the associated chromosomal proteins, using any number of well-established laboratory techniques. Grody Decl. ¶ 13; Leonard Decl. ¶ 33. A particular segment of DNA, such as a gene, contained in the extracted DNA may then be excised from the genomic DNA in which it is embedded to obtain the purified DNA of interest. Kay Decl. ¶¶ 133, 137. DNA molecules may also be chemically synthesized in the laboratory. Kay Decl. ¶¶ 17, 133, 137.

Although the parties use the term "isolated DNA" to describe DNA that is separated from proteins and other DNA sequences, the term "isolated DNA" possesses a specific legal definition reflecting its use in the patents-in-suit. To avoid any confusion for purposes of this fact recitation, the term "extracted DNA" will be used to refer to DNA that has been removed from the cell and separated from other non-DNA materials in the cell (e.g., proteins); "purified DNA" will be used to refer to extracted DNA which has been further processed to separate the particular segment of DNA of interest from the other DNA in the genome; and "synthesized

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<sup>12</sup> Methylation refers to the addition of a small chemical group composed of one carbon atom and three hydrogen atoms (CH<sub>3</sub>), known as a "methyl group," to the nucleotides of a segment of DNA. See *The Cell* at 430.

DNA" will be used to refer to DNA which has been synthesized in the laboratory.

As noted above, native DNA, unlike purified or synthesized DNA, is not typically found floating freely in cells of the body, but is packaged into chromosomes. Kay Decl. ¶¶ 131, 148. However, when DNA is copied, or replicated, in preparation for cell division, short segments of DNA are dissociated from the chromosomal proteins, although they are still contained within the cell. Similarly, when a particular portion of DNA is transcribed into RNA, segments of DNA exist dissociated from the proteins normally bound to it. Mason Supp. Decl. ¶ 23.

Purified or synthesized DNA may be used as tools for biotechnological applications for which native DNA cannot be used. Kay Decl. ¶¶ 134, 138; Schlessinger Decl. ¶ 27. For example, unlike native DNA, purified or synthesized DNA may be used as a "probe,"<sup>13</sup> which is a diagnostic tool that a molecular biologist uses to target and bind to a particular segment of DNA, thus allowing the target DNA sequence to be detectable using standard laboratory machinery. Kay Decl. ¶ 135; Schlessinger Decl. ¶ 29. Purified or synthesized DNA can also be used as a "primer,"<sup>14</sup> to sequence a target DNA, a process used by molecular biologists to determine the order of nucleotides in a DNA molecule, or to perform polymerase chain reaction ("PCR") amplification, a

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<sup>13</sup> A probe is a DNA fragment that is usually between 100-1000 nucleotides long. Kay Decl. ¶ 135.

<sup>14</sup> A primer is a DNA fragment, usually between 15 and 30 nucleotides long, that binds specifically to a target DNA sequence. Kay Decl. ¶ 183.

process which utilizes target-DNA specific primers to duplicate the quantity of target DNA exponentially. Critchfield Decl. ¶ 40; Kay Decl. ¶ 184.

During this process, the DNA molecule being used as a probe or a primer binds, or "hybridizes," to a specific nucleotide sequence of a DNA target molecule, such as the *BRCA1* or *BRCA2* gene. This sequence-specific binding of two strands of DNA results from the same base-pairing phenomenon which allows two complementary strands of DNA to form the double helix structure. As a result, a strand of isolated DNA being used as a primer with the sequence ATGTCG, for example, will bind specifically to the portion of the target DNA molecule containing the nucleotide sequence TACAGC. The hybridization of a primer or probe to a DNA target, such as *BRCA1* or *BRCA2*, results in the formation of a "hybridization product" that either acts as a substrate for the enzymes used in the sequencing or amplification reaction or permits the detection of the target DNA. See Kay Decl. ¶¶ 138, 183; Schlessinger Decl. ¶ 30; *The Gene* at 105-06; 113-15.

The utility of purified *BRCA1/2* DNA molecules as biotechnological tools therefore relies on their ability to selectively bind to native or isolated *BRCA1/2* DNA molecules, which ability is a function of the isolated DNA's nucleotide sequence. Kay Decl. ¶ 138.

### **3. RNA**

Ribonucleic acid ("RNA") is another nucleic acid found in cells. Like DNA, an RNA molecule is composed of a combination of four different nucleotides, three of which are the same bases

incorporated into DNA: adenine, cytosine, and guanine. Unlike DNA, however, RNA utilizes uracil as the fourth nucleotide base, rather than thymine. In addition, the sugar-phosphate backbone in RNA is chemically different from the sugar-phosphate backbone of DNA. Kay Decl. ¶ 170.

The creation of proteins, which do the work of the body, comprises two steps: transcription and translation. Transcription is the process by which a temporary copy of a particular DNA sequence, in the form of an RNA molecule, is generated. Mason Decl. ¶¶ 11-12; Kay Decl. ¶¶ 149, 150. During transcription, a discrete segment of DNA unwinds itself inside the cell and the bases of the DNA molecule act as "clamps" that hold the bases of the newly forming RNA molecule in place while the chemical bonds of its sugar-phosphate backbone are formed. Kay Decl. ¶ 150. Each nucleotide in the DNA strand corresponds to a nucleotide to be incorporated into the newly forming RNA molecule: adenine on the DNA molecule binds to and thereby acts as a clamp for RNA nucleotide uracil, thymine for adenine, guanine for cytosine, and cytosine for guanine. Kay Decl. ¶ 150. This newly generated RNA is termed "pre-messenger RNA" or "pre-mRNA" and, like the DNA from which it was generated, contains both introns and exons. In a process known as "splicing," the introns are physically cut out of the pre-mRNA by the cell and the remaining RNA segments containing the exons are rejoined, or "ligated," together in consecutive order to form the final "messenger RNA," or "mRNA." Mason Decl. ¶ 11; Kay Decl. ¶ 151; Schlessinger Decl. ¶ 14. Pre-mRNAs can also undergo a process known as "alternative splicing," in



which different combinations of exons from the same pre-mRNA molecule are ligated together to yield different final mRNA products.<sup>15</sup> Kay Decl. ¶ 152; Schlessinger Decl. ¶ 14.

During translation, an mRNA molecule serves as a template for the assembly of a protein. Kay Decl. ¶ 157. In a process that parallels the transcription of DNA, the mRNA bases, along with other proteins in the cell, serve as clamps to hold the corresponding amino acids in place while the chemical bonds between the individual amino acids are formed. Kay Decl. ¶ 157. The three-nucleotide codons originally found in DNA and copied into mRNA determine which amino acids are incorporated into the protein and the order in which they are incorporated. Kay Decl. ¶ 157.

#### 4. cDNA

Complementary DNA, or "cDNA," is a type of DNA molecule generated from mRNA during a process known as "reverse transcription" which is catalyzed by a protein known as "reverse transcriptase." cDNA derives its name from the fact that it is "complementary" to the mRNA from which it is produced - that is, each base in the cDNA can

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<sup>15</sup> For example, a pre-mRNA molecule containing exons ("E") numbered 1-6, with introns ("I") between each axon whose structure is represented as follows: E1+I1+E2+I2+E3+I3+E4+I4+E5+I5+E6. After splicing, the introns would be removed to form an mRNA composed only of exons: E1+E2+E3+E4+E5+E6. On the other hand, the same pre-mRNA molecule might undergo alternative splicing to form final mRNAs with a variety of different exon compositions: for example, E1+E2+E5; E1+E3+E6; and E1+E4+E6.

bind to the corresponding base in the mRNA from which it is generated. Kay Decl. ¶ 161. Because it is derived from mRNA, a cDNA molecule represents an exact copy of one of the protein coding sequences encoded by the original genomic DNA. Leonard Decl. ¶ 75. In this respect, cDNA contains the identical protein coding informational content as the DNA in the body, even though differences exist in its physical form. Mason Decl. ¶ 32.

During reverse transcription, each base of the mRNA serves as a clamp for its complementary nucleotide to be incorporated into the new cDNA molecule while the chemical bonds between the nucleotides of the cDNA strand are formed. Much like transcription, uracil on the mRNA binds to and thereby acts as a clamp for the nucleotide adenine, adenine for thymine, guanine for cytosine, and cytosine for guanine. Kay Decl. ¶ 165. The synthesis of cDNA from very long mRNA molecules, such as *BRCA1* and *BRCA2*, often does not result in a cDNA strand that is as long as the mRNA chain. Kay Decl. ¶ 166.

cDNA is typically generated by scientists in a laboratory. Kay Decl. ¶ 164, Linck Decl. ¶ 48. However, naturally occurring cDNAs, known as "pseudogenes," exist in the human genome and are structurally, functionally, and chemically identical to cDNAs made in the laboratory. Mason Supp. Decl. ¶¶ 18-21; Nussbaum Decl. ¶¶ 41-42.

cDNA possesses certain structural and functional differences from native DNA. In contrast to most forms of native DNA, cDNA does not contain non-coding intronic sequences because it *is* derived from mRNA *in* which the introns have been removed.

As a result, the production of proteins from cDNA does not require RNA splicing, in contrast to the production of proteins from native DNA as described above. Some cDNAs cannot be used to produce proteins without the addition of certain regulatory sequences, although other cDNAs possess some of the necessary regulatory sequences. cDNAs also usually contain nucleotides corresponding to the so-called "poly A tail" sequence found in mRNA, which native DNA does not possess. In addition, as mentioned above, native DNA is often (although not always) chemically modified in the body, e.g., by methylation, while cDNA generated in the laboratory is not so modified. Kay Decl. ¶¶ 168, 169; Mason Supp. Decl. ¶¶ 18-22; Nussbaum Decl. ¶¶ 41-42. cDNA also differs from mRNA in that it is a more stable compound and requires both transcription and translation to produce protein, rather than simply translation, as is the case with mRNA. Kay Decl. ¶ 171.

Much like purified DNA, cDNA can be used as a tool for biotechnological and diagnostic applications for which native DNA cannot be used. Kay Decl. ¶ 162. In addition, a scientist seeking to learn more about a protein of interest may transfer a cDNA encoding the protein into a recipient cell that does not normally express that protein. If the cDNA is operatively linked to particular "promoter" sequences that initiate transcription from the cDNA, the recipient cell will then express the protein of interest. Kay Decl. ¶ 163.

## 5. DNA sequencing

DNA sequencing is the process by which one "reads," or determines the ordering of the nucleotides within a DNA molecule. Sulston Decl. ¶ 20; Kay Decl. ¶ 138. In the context of a gene or a portion of the genome, sequencing is designed to illuminate the information that nature has dictated in that person's genome, and the sequencing process, by design, does not alter the information content of the native DNA sequence. Sulston Decl. ¶ 27; Mason Decl. ¶ 32. In that respect, sequencing is analogous to examining something through a microscope insofar as it makes visible something that exists in nature but is too small to be seen otherwise. Mason Decl. ¶ 23. Gene sequencing is used in diagnostic testing, such as Myriad's tests, to determine whether a gene contains mutations that have been associated with a particular condition. Sulston Decl. ¶ 24; Chung Decl. ¶ 10; Swisher Decl. ¶¶ 23-26; Mason Decl. ¶ 21. These mutations, along with any association with a propensity to develop a particular disease, are caused by nature. Chung Decl. ¶ 10; Mason Decl. ¶ 20; Sulston Decl. ¶¶ 19, 27; Ledbetter Decl. ¶ 26. Therefore, the significance of any person's gene sequence, including its relationship to any disease, is dictated by nature. Mason Decl. ¶ 32.

Sequencing is often used to identify single nucleotide substitutions or the insertion or deletion of a small number of nucleotides in a gene. Swisher Decl. ¶ 23; Kay Decl. ¶ 180. However, even full sequencing of an entire gene can miss large genomic rearrangements in which whole sections of the gene have been deleted or moved to a different

part of the genome. Other tests have been developed that better detect these large rearrangements. Swisher Decl. ¶ 24; Ledbetter Decl. ¶¶ 16-17.

Sequencing native DNA first requires that cells of a tissue sample<sup>16</sup> be broken open to permit extraction of the DNA contained within the cells. Sulston Decl. ¶ 25. The extracted DNA of the entire genome contains over three billion nucleotides, of which the gene of interest comprises a very small portion. Kay Decl. ¶ 178. *BRCA1/2* sequencing by Myriad follows the typical process for sequencing extracted genomic DNA, which begins with obtaining a sufficient quantity of the *BRCA1/2* genomic DNA to permit its sequencing. Critchfield Decl. ¶ 40.

Under the current state of the art, the only practical way to obtain a sufficient amount of *BRCA1/2* genomic DNA for mutation detection purposes is to PCR amplify the genomic DNA in segments. Critchfield Decl. ¶ 40. In order to design the necessary primers to PCR amplify the correct region of the genome, at least a portion of the sequence of the target DNA molecule must be known. Kay Decl. ¶ 184. Typically, each exon of the *BRCA1/2* genes, including a small adjacent portion of the flanking introns, is separately amplified by PCR into one or more amplified DNA fragments, also called "amplicons." The *BRCA1* and *BRCA2* genes have a total of 48 coding exons containing over 15,700 nucleotide base pairs. More than 50 amplicons are typically produced as part of Myriad's *BRCA1/2* testing. Critchfield Decl. ¶ 40.

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<sup>16</sup> Various types of patient samples can be used, e.g., blood, tumor tissue, or non-tumor tissue. Kay Decl. ¶ 186.

Following PCR amplification of the target DNA, a sequencing reaction is performed to determine the nucleotide sequence of the amplicon. Kay Decl. ¶ 183. As with PCR, at least some of the target sequence must be known in order to design a primer specific to the target DNA to be sequenced. Kay Decl. ¶¶ 177, 179, 183. For this reason, primers that bind only to specific DNA sequences in the *BRCA1* and *BRCA2* genes permit the analysis of a patient's native DNA sequence to determine *if* the nucleotide composition is the same or different from the nucleotide composition of the normal *BRCA1* and *BRCA2* gene. Kay Decl. ¶ 187. Gene sequencing also sometimes utilizes cDNA as the DNA template. Leonard Decl. ¶ 75.

The techniques required for gene sequencing are well-known and understood by scientists skilled in molecular biology, and scientists and clinicians sequence and analyze genes literally every day. Chung Decl. ¶¶ 10-11; Mason Decl. ¶ 22; Hegde Decl. ¶¶ 6-7. However, because sequencing requires knowledge of the sequence of a portion of the target sequence, some ingenuity and effort is required for the initial sequencing of a target DNA. See Kay Decl. ¶ 183; Klein Decl. ¶ 32-34.

### **C. The Development of the Patents-in-Suit**

Breast cancer is the most frequently diagnosed cancer worldwide and is the leading cause of cancer death for women in Britain and the second leading cause of cancer death for women in the United States. Parthasarathy Decl. ¶ 8.<sup>17</sup> Ovarian cancer is

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<sup>17</sup> Dr. Parthasarathy has researched the development of genetic testing for breast and ovarian cancer in the United States and

the eighth most common cancer in women and causes more deaths in the Western world than any other gynecologic cancer. Swisher Decl. ¶ 10.

Throughout the 1980s, organizations dedicated to breast cancer awareness began efforts to increase public and governmental awareness of the breast cancer epidemic. In 1991, the U.S. Department of Defense created a research program devoted to breast cancer research. Over the years this funding has grown from less than \$90 million during the fiscal year 1990 to more than \$2.1 billion during the fiscal year 2008. Parthasarathy Decl. ¶ 10.

Throughout the 1980s, scientists from the United States, England, France, Germany, Japan, and other countries sought to be the first to identify DNA nucleotide sequences associated with breast cancer. Parthasarathy Decl. ¶ 11. In 1989, various European and American research laboratories participated in the International Breast Cancer Linkage Consortium (the "Consortium"), and in 1990, a group of researchers led by Mary-Claire King ("Dr. King") at the University of California, Berkeley, published a landmark paper demonstrating for the first time that a gene linked to breast cancer, whose sequence was unknown but which was later designated Breast Cancer Susceptibility Gene 1 (*BRCA1*), was located on a region of chromosome 17. See Jeff M. Hall, et al., Linkage of Early-Onset Familial Breast Cancer to Chromosome 17q21, 250 *Science* 1684-89 (1990); Parthasarathy Decl. ¶ 11.

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Britain and has interviewed over 100 individuals involved in the process, including research scientists, officials at research institutions, health care professionals, patent office officials, bioethicists, and journalists. Parthasarathy Decl. ¶ 6.

Soon afterwards, research intensified as teams around the world, including groups led by Dr. King, Dr. Mark Skolnick ("Dr. Skolnick") (co-founder of Myriad), and Dr. Michael Stratton ("Dr. Stratton") (Institute for Cancer Research, London ("ICR")), focused in on this region of the genome in an attempt to be the first to determine the DNA sequence of *BRCA1*. Parthasarathy Decl. ¶ 11.

Dr. Skolnick, a 1968 economics graduate of the University of California, Berkeley, had become interested in the application of demography to the study of genetics while doing research for his Ph.D. in genetics, which he received from Stanford University in 1975. While reconstructing genealogies in Italy, he met three Mormons who were microfilming parish records and from whom he learned of the resources of the Utah Genealogical Society in Salt Lake City. Thereafter, in 1973, after an inquiry from the organizers of a cancer center at the University of Utah, Dr. Skolnick suggested linking the Utah Mormon Genealogy with the Utah Cancer Registry. To further this effort, a familial cancer screening clinic was established and a program for mapping genes was developed. Skolnick Decl. ¶¶ 7, 11, 12.

Following publication of the King group's study relating to *BRCA1* in the fall of 1990, Dr. Skolnick and his collaborators concluded that additional resources would be required to compete with the team of Dr. Francis Collins, which had received a substantial grant from the National Institutes of Health ("NIH"), Skolnick Decl. ¶¶ 11 13, 14, and in 1991 Myriad was founded by Dr. Skolnick and a local venture capital group interested in



genetics. Myriad received \$5 million in funding in 1992, \$8 million in 1993, and \$9 million in 1994. Skolnick Decl. ¶ 16.

Locating the *BRCA1* gene relied on the use of linkage analysis, in which correlations between the occurrence of cancer and the inheritance of certain DNA markers among family members were used to identify, or "map," the physical location of, the *BRCA1* gene within the human genome. See '282 patent, col. 7:39-52. Once the physical location had been narrowed down to a sufficiently small region of the genome, Myriad was able to directly analyze the sequence of the DNA in this region and identify the nucleotides comprising the *BRCA1* gene. See '282 patent, col. 7:53-8:7. Successful linkage analysis requires large and genetically informative families, or kindreds, and detailed family information, such as detailed genealogical records, are an important component to this analysis. Shattuck Decl. ¶¶ 10, 13; '282 patent, col. 8:16-29.

In September 1994, the group at Myriad, along with researchers from the National Institute for Environmental Health Sciences ("NIEHS") (a subdivision of the NIH), the University of Utah, McGill University, and Eli Lilly and Company announced that they had sequenced the *BRCA1* gene. See Yoshio Miki, et al., A Strong Candidate for the Breast and Ovarian Cancer Susceptibility Gene *BRCA1*, 266 *Science* 66-71 (1994). In addition to funding the six NIEHS researchers who participated in the identification of *BRCA1*, the NIH had also provided approximately \$2 million in funding to the

University of Utah.<sup>18</sup> See id. at 71 n.52; Parthasarathy Decl. ¶ 18. According to one analysis, the NIH contributed one-third of the funding for the identification of *BRCA1*. Parthasarathy Decl. ¶ 18.

A dispute subsequently arose between Myriad and the NIH over the NIEHS scientists' exclusion as co-inventors on the *BRCA1* patents. Parthasarathy Decl. ¶ 19. The NIH maintained that its scientists had conducted some of the most important work leading up to the sequencing of the gene, including identifying the sequences of two of the *BRCA1* gene fragments and assembling the complete *BRCA1* sequence. Id. Myriad agreed to include the names of the NIEHS researchers as inventors on its patent application and pay inventors' royalties, although no payments appear to have been made as of 2005. Id.

Following the isolation of *BRCA1*, scientists continued to search for a second gene also believed to be linked with breast and ovarian cancer.<sup>19</sup> Parthasarathy Decl. ¶ 12. Myriad collaborated with several research groups, including scientists at the University of Laval in Quebec, Canada, the Hospital for Sick Children in Toronto, Canada, and the University of Pennsylvania in their search for this second gene. It also collaborated with a team of researchers led by Dr. Stratton at the ICR which, in

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<sup>18</sup> According to the description of author associations, the first and second authors of the paper were associated with the University of Utah.

<sup>19</sup> The same positional cloning approach utilized to isolate the *BRCA1* gene was relied on to isolate the *BRCA2* gene. Tavtigian Decl. ¶ 4.

November 1995, identified a mutation in breast cancer patients that appeared to be located in the as-yet unpublished *BRCA2* gene. Dr. Stratton ended the collaboration with Myriad upon learning of Myriad's plans to patent the *BRCA2* gene sequence. Sulston Decl. ¶ 30.

On December 21, 1995, Myriad filed for patents on the *BRCA2* gene in both the U.S. and Europe. Tavgigian Decl. ¶ 5. The next day, the Stratton group published its identification of the *BRCA2* gene in the journal *Nature*, and Myriad submitted the sequence of *BRCA2* to GenBank, an international depository of gene sequence information. Parthasarathy Decl. ¶ 12; Tavgigian Decl. ¶ 9; Richard Wooster, et al., Identification of the Breast Cancer Susceptibility Gene *BRCA2*, 378 *Nature* 789-92 (1995). Subsequent analysis of the *BRCA2* sequence from the Stratton group indicated that while they had correctly sequenced the primary portion of the *BRCA2* gene, their published sequence had errors in both ends of the *BRCA2* gene. Tavgigian Decl. ¶¶ 7-10. Nonetheless, the consensus among the scientific community is that the Stratton group, rather than Myriad, was the first to sequence the *BRCA2* gene. Parthasarathy Decl. ¶ 13.

The isolation of the *BRCA1/2* genes required considerable effort on the part of Myriad and its collaborators as well as ingenuity in overcoming technical obstacles associated with the isolation process. However, the process and techniques used were well understood, widely used, and fairly uniform insofar as any scientist engaged in the search for a gene would likely have utilized a similar

approach. Parthasarathy Decl. ¶ 19; Tavigian Decl. ¶ 13.

#### **D. Application of the Patents-in-Suit**

Mutations in the *BRCA1/2* genes correlate with an increased risk of breast and ovarian cancer. Women with *BRCA1* and *BRCA2* mutations face up to an 85% cumulative risk of breast cancer, as well as up to a 50% cumulative risk of ovarian cancer. Love Decl. ¶ 10; Parthasarathy Decl. ¶ 9. In addition, among the 10-15% of ovarian cancer cases that are inherited genetically, 80% of women diagnosed under the age of 50 carry mutations in their *BRCA1* genes and 20% carry mutations in their *BRCA2* genes. The women with inherited *BRCA1* mutations have a 40-52% cumulative risk of ovarian cancer by the time they reach 70 years old. For women with inherited *BRCA2* mutations, the risk is approximately 15-25%. Swisher Decl. ¶ 11. Male carriers of mutations are also at an increased risk for breast and prostate cancer. Love Decl. ¶ 10.

The existence of *BRCA1/2* mutations is therefore an important consideration in the provision of clinical care for breast and/or ovarian cancer. A patient will not only learn of her risk for hereditary breast and ovarian cancer, but also can gain information that may be useful in determining prevention and treatment options. This information is useful for women who are facing difficult decisions regarding whether or not to undergo prophylactic surgery, hormonal therapy, chemotherapy, and other measures. Swisher Decl. ¶ 12; Love Decl. ¶ 11. Testing results for the *BRCA1/2* genes can be an important factor in structuring an appropriate course of cancer treatment, since certain forms of

chemotherapy can be more effective in treating cancers related to *BRCA1/2* mutations. Swisher Decl. ¶ 13; Love Decl. ¶ 18.

### **1. Myriad's BRCA1/2 testing**

Myriad offers multiple forms of *BRCA1/2* testing to the general public. Its standard test, called Comprehensive BRACAnalysis, originally only consisted of the full sequencing of the *BRCA1/2* genes. Swisher Decl. ¶ 29-30; Reich Decl. ¶ 10; Parthasarathy Decl. ¶ 26; Critchfield Decl. ¶ 49. In 2002, Myriad supplemented its full sequencing analysis with a large rearrangement panel ("LRP") for detecting five common large rearrangement mutations which is now included in the Comprehensive BRACAnalysis. Critchfield Decl. ¶¶ 49, 51. In 2006, Myriad began offering a supplemental test to Comprehensive BRACAnalysis called the BRACAnalysis Rearrangement Test ("BART"), which, according to Myriad, can detect virtually all large rearrangement mutations in the *BRCA1* and *BRCA2* genes.<sup>20</sup> Swisher Decl. ¶¶ 29-30; Reich Decl. ¶ 10; Parthasarathy Decl. ¶ 26; Critchfield Decl. ¶ 51.

### **2. Funding for Myriad's BRCA1/2 tests**

The Myriad tests are available to clinicians and patients at a cost of over \$3000 per test. In 2006, the total cost to Myriad of providing these tests was

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<sup>20</sup> Myriad also offers other more limited forms of *BRCA1/2* genetic testing. Swisher Decl. ¶¶ 29-30; Reich Decl. ¶ 10; Parthasarathy Decl. ¶ 26.

\$32 million with resulting revenues of \$222 million. See Myriad Genetics, Inc., Annual Report (Form 10-K), at 27 (Aug. 28, 2008). In Ontario, where the regional public healthcare plan is ignoring Myriad's patent, the testing for breast cancer is performed for a third of Myriad's cost. See CBC News, Ontario to Offer New Genetic Test for Breast, Ovarian Cancer (Jan. 8, 2003), available at [http://www.cbc.ca/health/story/2003/01/06/test\\_genetic030106.html](http://www.cbc.ca/health/story/2003/01/06/test_genetic030106.html).

Plaintiffs have noted several instances where women have been unable to obtain funding for all of Myriad's testing services. For example, Myriad refused to process Ms. Ceriani's sample because it did not accept coverage by Ms. Ceriani's insurance carrier. Unable to pay for Myriad's tests, and unable to find scholarship programs to fund her testing, Ms. Ceriani has not been tested. Ceriani Decl. ¶¶ 5-7. Ms. Fortune's insurance carrier is not accepted by Myriad, and Ms. Fortune is also unable to pay the full out-of-pocket cost of Myriad's test. Fortune Decl. ¶ 5.

Myriad's BART test is not covered by a number of insurers, and unless a patient is one of a limited number of "high risk patients" who meet certain clinical criteria established by Myriad, a patient must pay an extra fee for BART testing. Swisher Decl. ¶¶ 29-30; Reich Decl. ¶ 10; Parthasarathy Decl. ¶ 26; Critchfield Decl. ¶ 52. As a result of the cost of BART testing, the test is unavailable to women who would otherwise choose to utilize the test. Swisher Decl. ¶¶ 30-31; Reich Decl. ¶ 10. For example, Ms. Raker is unable to afford the extra cost for BART testing and has not

been tested for large genomic rearrangements, despite the advice of her genetic counselor. Raker Decl. ¶¶ 7-11. Similarly, Ms. Thomason has been unable afford the BART testing recommended by her genetic counselor. Thomason Decl. ¶¶ 6-9.

Myriad has pursued Medicaid coverage for years, but has been unable to secure "participating provider" status in 25 states which would allow it to offer testing to that state's Medicaid patients. Myriad also has a financial assistance program which provides free testing to low-income and uninsured patients who meet certain economic and clinical requirements. In addition, Myriad provides free testing to independent non-profit institutions. In particular, Ms. Ceriani may be eligible to receive BRCAanalysis testing at no charge through the non-profit organization Cancer Resource Foundation, for which Myriad has provided free testing since 2009. Rusconi Decl. ¶¶ 4-6; Critchfield Decl. ¶ 33; Ogaard Decl. ¶¶ 4-6. Currently, 90% of the tests Myriad performs are covered by insurance at over 90% of the test cost. Critchfield Decl. ¶ 1 32, 33, 52, 53.

A number of researchers, clinicians, and molecular pathologists have the personnel, equipment, and expertise to sequence and analyze genes, including the *BRCA1* and *BRCA2* genes, at a lower cost than Myriad's testing. Kazazian Decl. ¶¶ 8, 11; Matloff Decl. ¶ 12; Ostrer Decl. ¶¶ 8-9; Ledbetter Decl. ¶¶ 16-18. For example, the *BRCA1/2* testing previously conducted by the Yale DNA Diagnostics Laboratory and the University of Pennsylvania Genetic Diagnostic Laboratory ("GDL") cost less than what Myriad

charges, and testing by OncorMed, a one-time competitor, was cheaper than Myriad's testing. Matloff Decl. ¶ 7; Kazazian Decl. ¶ 8; Parthasarathy Decl. ¶ 24. However, on a "cost per exon" basis, Myriad's BRACAnalysis test costs less than testing for other genes performed by the GDL at the University of Pennsylvania and Drs. Ledbetter and Warren at Emory University. See *infra*; Critchfield Decl. ¶ 35.

### **3. Myriad's enforcement of the Patents-in-suit**

During the mid-to-late-1990s, Drs. Kazazian and Ganguly offered, for a fee, screening services for *BRCA1* mutations through the GDL at the University of Pennsylvania. Kazazian Decl. ¶ 4; Ganguly Decl. ¶ 3. The screening methodology utilized by Drs. Kazazian and Ganguly differed from the testing method used by Myriad, but involved using isolated DNA encoding *BRCA1* or *BRCA2*. Kazazian Decl. ¶ 9; Parthasarathy Decl. ¶ 23. At some point during this period, Dr. Skolnick advised Dr. Kazazian that Myriad planned to stop the *BRCA1/2* testing being conducted at the GDL. Kazazian Decl. ¶ 6. On May 29, 1998, Myriad offered Dr. Kazazian a collaborative license in connection with the '473, '999, '001, '282, and '441 patents. Ganguly Decl. Ex. 2. However, the license covered only single mutation tests and multiple mutation panels of up to four mutations to allow for testing of patients of Ashkenazi Jewish descent. Ganguly Decl. ¶ 5. Myriad subsequently sent cease and desist letters to Dr. Kazazian and the University of Pennsylvania. On August 26, 1998, O'Melveny & Myers LLP gave notice to Dr. Kazazian of



infringement in the absence of a license. Ganguly Decl. Ex. 3. Myriad subsequently sued the University of Pennsylvania in November 1998 for infringement of the patents-in-suit. See Myriad Genetics v. Univ. of Pennsylvania, 2: 98-cv-00829 (D. Utah) (filed November 19, 1998). On June 10, 1999, Myriad's general counsel, Christopher Wright, sent a letter to the University of Pennsylvania seeking written assurances that Dr. Kazazian and the University of Pennsylvania had ceased *BRCA1/2* clinical testing. Ganguly Decl. Ex. 4. This demand was repeated in a September 22, 1999 letter from Myriad to the University of Pennsylvania. Ganguly Decl. Ex. 6.

As a result of Myriad's efforts to enforce its patents against the University of Pennsylvania, the GDL no longer conducts *BRCA1/2* screening for research or as part of its clinical practice. Kazazian Decl. ¶ 5; Ganguly Decl. ¶¶ 8-9; Parthasarathy Decl. ¶ 28. However, sometime between 1999 and 2000, Dr. Critchfield, on behalf of Myriad, informed Dr. Kazazian that he is free to conduct academic research on the *BRCA1/2* genes, including sequencing the genes and detecting mutations in the genes. Critchfield Decl. ¶ 22.

In May 1998, Myriad offered Dr. Ostrer a license agreement to conduct diagnostic *BRCA1/2* genetic testing. The proposed license would permit Dr. Ostrer to conduct single mutation tests and multiple mutation panels (up to four mutations) for patients of Ashkenazi Jewish descent only. Dr. Ostrer declined the offer as too narrow to allow him to perform any meaningful *BRCA1/2* testing. Ostrer Decl. ¶ 7.

On September 15, 1998, Myriad also notified Dr. Barbara Weber ("Dr. Weber"), a principal investigator on the Cancer Genetics Network Project ("CGNP") sponsored by the National Cancer Institute ("NCI"), that Myriad's patent position might impact research sponsored by NCI. As a result of that letter, the GDL at the University of Pennsylvania ceased conducting *BRCA1/2* analysis for Dr. Weber. Ganguly Decl. ¶ 12, Ex. 7. According to Myriad, the GDL's involvement in CGNP was to provide DNA testing on *BRCA1/2* genes for a fee, similar to the activity of any commercial core lab. Critchfield Decl. ¶ 21. In September 1999, Myriad also requested that Georgetown University, one of the other cancer centers participating in the CGNP, to cease sending genetic samples to the GDL for *BRCA1/2* analysis. Ganguly Decl. ¶ 13.

In December 2000, the director of the Yale DNA Diagnostics Lab received a cease and desist letter concerning *BRCA1/2* genetic testing being conducted by the lab. As a result of the letter, the lab ceased *BRCA1/2* genetic testing. Matloff Decl. ¶ 7. In 2005, Dr. Matloff sought permission from Myriad for the Yale DNA Diagnostics Lab to conduct screening for mutations caused by large rearrangements, which Myriad was not conducting at the time. Her request was denied. Matloff Decl. ¶ 8.

Myriad was also involved in a series of lawsuits in the late 1990s against Oncormed, another company undertaking BRCA-related testing, regarding patents that covered various aspects of the *BRCA1* gene sequence. Parthasarathy Decl. ¶ 27.

Myriad eventually purchased Oncormed's patents and testing services in 1998. Id.

## **E. Disputed Issues**

### **1. The impact of Myriad's patents on BRCA1/2 testing**

According to Plaintiffs, Myriad's patents and its position as the sole provider of *BRCA1/2* testing has hindered the ability of patients to receive the highest quality breast cancer genetic testing and has impeded the development of improvements to *BRCA1/2* genetic testing. Plaintiffs first note deficiencies in the genetic testing services offered by Myriad, alleging that in the several years prior to the addition of the LRP, the testing done by Myriad did not reveal all known mutations in the *BRCA1/2* genes or utilize known methodologies that would have revealed these additional mutations.<sup>21</sup> Chung Decl. ¶ 19; Matloff Decl. ¶ 8; Swisher Decl. ¶ 26; Ledbetter Decl. ¶ 16; Parthasarathy Decl. ¶ 29. As a result, Myriad's test may have reported false negative results during this period. Plaintiffs also cite a study published in 2006 in the Journal of the American Medical Association that concluded that 12% of those from high risk families with breast cancer and with negative test results from Myriad carried cancer-predisposing genomic deletions or duplications in one of those genes. Swisher Decl. ¶¶ 25-26. Plaintiffs also note that the sensitivity and specificity of the BART test has not been validated by

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<sup>21</sup> For example, the Myriad test received by Ms. Thomason, Ms. Raker, and Ms. Limary did not look for all known large rearrangements in the *BRCA* genes. Thomason Decl. ¶ 6; Raker Decl. ¶¶ 7-8; Limary Decl. ¶ 7.

comparing the results of BART testing with Multiplex Ligation Dependent Probe Amplification ("MLPA") testing commonly used by researchers. Swisher Decl. ¶¶ 32, 33.

According to Plaintiffs, other labs are in a position to offer more comprehensive testing than Myriad's standard testing services and would use newer testing methods with improved testing quality and efficiency. These labs would also include large rearrangement testing after a negative test result is received from full sequencing. Ledbetter Decl. ¶¶ 17-18; Chung Decl. ¶ 18; Ostrer Decl. ¶ 9. In addition, labs would perform genetic testing on tumor specimens preserved in paraffin from deceased family members, which Myriad does not regularly perform even though, according to Plaintiffs, such testing can often provide valuable genetic information for living relatives and is often necessary for accurate test interpretation. Chung Decl. ¶ 24.

According to Myriad, however, its full sequencing test has been recognized as the "gold standard" for *BRCA1/2* mutation testing, and it continues to improve its testing process. Critchfield Decl. ¶ 37. Myriad contends that it researched and developed a commercially viable high quality test for detecting large rearrangements as soon as it and the research community recognized the need for such testing, and continues work towards a test capable of detecting all large rearrangement mutations, including extremely rare ones. Critchfield Decl. ¶¶ 49, 50. According to Myriad, *BRCA1/2* studies conducted by outside researchers confirmed that the BART test exhibited superior performance over other methods for

mutation detection, including the MLPA kit often used by academic researchers.<sup>22</sup> Critchfield Decl. ¶ 51.

According to Plaintiffs, the lack of independent *BRCA1/2* analysis also undermines the ability of the scientific community to determine the meaning of VUS results, which are reported disproportionately for members of minority groups, and whose significance would be more extensively analyzed by other labs. Chung Decl. ¶ 20-21; Ostrer Decl. ¶ 12; Matloff Decl. ¶ 9. Myriad, however, asserts that it has undertaken significant efforts to determine the clinical importance of VUSs by establishing an in-house review committee for variant classification and developing a systematic approach to providing clinical interpretations for detected sequence variants based on generally accepted scientific data and analysis of its own database. In addition, clarification of any VUS previously reported to a patient is immediately provided to the patient and her doctor. According to Myriad, the VUS reporting rate has decreased markedly, with a 50% decrease in major ethnic groups between 2002 and 2006, and a total of 850 VUSs for about 21,000 patients have been clarified, including 502 VUSs for 13,127 patients since the beginning of 2008. Myriad also asserts that it has made critical data available to researchers to assist in the analysis of VUSs and

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<sup>22</sup> In addition, Myriad states that the MLPA kit is for research use only, is not approved for clinical testing by the FDA, and is incapable of detecting certain smaller rearrangements. Critchfield Decl. ¶¶ 49, 50.

which have the potential of improving the diagnostic testing for other genes. Critchfield Decl. ¶¶ 57-59.

Plaintiffs contend that as a result of the patents-in-suit, *BRCA1/2* genetic testing is one of the very few tests performed as part of breast cancer care and prevention for which a doctor or patient cannot get a second confirmatory test done through another laboratory. Love Decl. ¶ 12. In particular, women who receive a positive result cannot confirm the lab's findings or seek a second opinion on the interpretation of those results.<sup>23</sup> Ledbetter Decl. ¶ 23; Ostrer Decl. ¶ 11. According to Myriad, absent any doubts regarding the accuracy of the original test, re-sequencing the patient's genes by another laboratory would be an unnecessary waste of resources, and Myriad has never prohibited a second interpretation of the results of its diagnostic tests. Critchfield Decl. ¶ 64; Reilly Decl. ¶¶ 54, 55. In addition, there are multiple laboratories available to conduct confirmatory *BRCA1/2* testing pursuant to patent licenses granted by Myriad, including both the University of Chicago Genetic Services Laboratories and Yale DNA Diagnostic Laboratories. Critchfield Decl. ¶ 62. That confirmatory testing, however, is limited to the confirmation of certain, specific positive test results; the remaining types of

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<sup>23</sup> For example, Ms. Girard sought but was unable to obtain confirmatory testing of her Myriad test results that indicated the presence of a deleterious mutation in her *BRCA2* gene. A second opinion would also be important for her immediate family's screening options. Girard Decl. ¶¶ 4-9. Similarly, Ms. Ceriani and Ms. Fortune would both want a second opinion concerning their *BRCA1/2* status before taking major surgical steps. Ceriani Decl. ¶¶ 9, 11; Fortune Decl. ¶ 7.

positive test results as well as all negative test results are excluded from such testing services. Matloff Decl. ¶¶ 9, 10.

Whether the patents at issue impact the testing for *BRCA1/2* mutations favorably or unfavorably is an issue of factual dispute not resolvable in the context of the instant motions.

## **2. The impact of gene patents on the advancement of science and medical treatment**

There exists a deep disagreement between the parties concerning the effects of gene patents on the progression of scientific knowledge.

According to Plaintiffs, data sharing is the key to the future of genetic discoveries and bioinformatics, and gene patents impede research aimed at identifying the role of genes in medical conditions. Sulston Decl. ¶¶ 36, 38. Plaintiffs assert that this understanding has wide acceptance, noting that from the beginning of the Human Genome project,<sup>24</sup> most scientists and even some private companies recognized the importance of keeping the genome freely available to all. For example, in 1994, the pharmaceutical company Merck funded a massive drive to generate gene sequences and place them into public databases, thereby making them difficult to patent. Sulston Decl. ¶¶ 22, 29. In 1996, a group of 50 of the most prominent geneticists who

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<sup>24</sup> The Human Genome Project was an international project initiated in 1990 with the aim of sequencing an entire human genome and in which Sir John Sulston, a Nobel laureate, actively participated. Sulston Decl. ¶¶, 22.

were involved with the sequencing of the human genome adopted the Bermuda principles which included the mandate that all "human genome sequence information should be freely available and in the public domain in order to encourage research and development and to maximize its benefit to society." Sulston Decl. ¶ 33. The proliferation of intellectual property rights directed to genetic material has also been postulated to contribute to a phenomenon dubbed "the tragedy of the anti-commons," in which numerous competing patent rights held by independent parties prevents anyone party from engaging in productive innovation. See, e.g., Michael A. Heller & Rebecca S. Eisenberg, Can Patents Deter Innovation? The Anticommons in Biomedical Research, 280 *Science* 698 (1998) (citing Michael A. Heller, The Tragedy of the Anticommons: Property in the Transaction from Marx to Markets, 111 *Harv. L. Rev.* 621 (1998)).

According to Dr. Fiona Murray ("Dr. Murray"), who received a grant to research the impact of gene patenting on scientific research and commercialization, 4382 of the 23,688 genes listed in the database of the National Center for Biotechnology Information ("NCBI") nearly 20% of human genes - are explicitly claimed as United States intellectual property. Murray Decl. ¶ 6. After devising a study to gauge the impact of gene patenting on public knowledge that utilized the time lag between publication of papers on a gene sequence and the issuance of a patent claiming that gene sequence, Dr. Murray concluded that the Myriad patents have negatively impacted the public knowledge of the *BRCA1* and *BRCA2* genes by 5-10%. Murray Decl. ¶¶ 7-15, 20.



Plaintiffs have cited other studies to demonstrate the chilling effect of gene patents on the advancement of both genetic research and clinical testing. A survey of laboratory directors in the United States conducted by Dr. Mildred Cho (the "Cho study") found that 53% decided not to develop a new clinical test because of a gene patent or license, and 67% believed that gene patents decreased their ability to conduct research. Cho Decl. ¶ 10. This correlated with a study conducted by the American Society of Human Genetics that reported that 46% of respondents felt that patents had delayed or limited their research. Cho Decl. ¶ 11. The Cho study also revealed that of those who stopped performing a clinical test because of a gene patent or license, the largest number stopped doing *BRCA1* and *BRCA2* testing (with the same number having stopped Apolipoprotein E testing). Cho Decl. ¶ 16. Specifically, the survey found that nine labs had ceased performing *BRCA1/2* genetic testing as a result of the patents-in-suit. In addition to labs that have ceased performing *BRCA1/2* genetic testing, labs have avoided or refrained from developing tests for *BRCA1* and *BRCA2* as a result of the patents held by Myriad. Ostrer Decl. ¶ 6; Ledbetter Decl. ¶¶ 14-16. Studies of other gene patents have also revealed that labs frequently stop developing or offering clinical tests for disease as a result of gene patents. For example, a purportedly valid scientific survey of labs in the United States found a 26% drop in the number of labs performing testing for hemochromatosis as a result of gene patents. Cho Decl. ¶¶ 18-20.

Researchers, clinicians, and pathologists are aware that Myriad has sent cease and desist letters

in connection with the patents-in-suit and that Myriad prohibits clinical testing of the *BRCA1/2* genes. Kazazian Decl. ¶¶ 5-11; Ganguly Decl. ¶¶ 4-14; Chung Decl. ¶ 15; Hegde Decl. ¶ 10; Matloff Decl. ¶¶ 5-7; Ostrer Decl. ¶¶ 4-7; Swisher Decl. ¶ 28; Hubbard Decl. ¶¶ 7-8; Kant Decl. ¶ 4; Ledbetter Decl. ¶ 13; Reich Decl. ¶¶ 3, 5; Parthasarathy Decl. ¶¶ 28-31. Myriad also does not permit researchers to tell patients involved in research the results of their *BRCA1/2* testing, leading physicians involved in breast cancer care and research unable to meet their ethical obligations to provide genetic test results to research subjects, when requested. Ostrer Decl. ¶ 10; Chung Decl. ¶ 13, 14. In addition to the direct benefits to the patient of knowing the results of their testing, such disclosure would also provide valuable insights into patient behavior that would enhance patient care. Ostrer Decl. ¶ 10. The AMA has also expressed its belief that the "[t]he use of patents . . . or other means to limit the availability of medical procedures places significant limitation on the dissemination of medical knowledge, and is therefore unethical." American Medical Association, Opinion 9.095 - The Use of Patents and Other Means to Limit Availability of Medical Procedures, (adopted June 1995), available at <http://www.ama-assn.org/ama/pub/physician-resources/medical-ethics/code-medical-ethics/opinion9095.html>. In addition, others have argued that human genes are the common heritage of mankind whose use should not be restricted by patent grants. See, e.g., Pilar A. Ossorio, The Human Genome as Common Heritage: Common Sense or Legal Nonsense?, 35 J.L. Med. & Ethics 425, 426 (2007); Melissa L. Sturges, Who Should Hold Property Rights to the Human Genome?

An Application of the Common Heritage of Humankind, 13 Am. U. Int'l L. Rev. 219, 245 (1997); Barbara Looney, Should Genes Be Patented? The Gene Patenting Controversy: Ethical and Policy Foundations of an International Agreement, 26 Law & Pol'y Int'l Bus. 231 (1994); Hubert Curien, The Human Genome Project and Patents, 254 Science 1710, 1710-12 (1991).

According to Plaintiffs, Myriad has withheld critical data concerning genetic predisposition to breast cancer from the Breast Cancer Information Core ("BIC"), an international, open access online database that is a central repository for information about the *BRCA1/2* genes and their genetic variants. The BIC facilitates the identification of deleterious mutations (i.e. those associated with a higher risk of cancer), provides a mechanism to collect and distribute data about genetic variants, and plays an important role in helping to elucidate the significance of those variants through its collection of data. Swisher Decl. ¶¶ 15, 17, 18; Chung Decl. ¶ 22; Ostrer Decl. ¶ 13. Although the value of the BIC comes from the amount and quality of data provided by the scientific community, Myriad, according to Plaintiffs, has not contributed any data to BIC in the past two years. Sulston Decl. ¶ 36; Swisher Decl. ¶¶ 19-21; Ostrer Decl. ¶¶ 12-13; Chung Decl. ¶¶ 21-22; Ledbetter Decl. ¶ 20.

Plaintiffs also assert that gene patents impede the development of improved genetic testing. For example, as new sequencing technologies offer the possibility of faster and less expensive sequencing of a patient's genes, patents on one or more genes may impede scientists' ability to develop a

comprehensive test for complex diseases or provide a person with an analysis of his or her entire genome. Sulston Decl. ¶ 38; Ledbetter Decl. ¶ 24. In addition, Plaintiffs assert that gene patents interfere with the ability of physicians and researchers to investigate complex diseases. For example, *BRCA1/2* may be associated with cancers other than breast and ovarian cancer, but so long as the patents on these genes remain, no one will be able to include these genes in tests for other disease predispositions. Ledbetter Decl. ¶¶ 24-25. Gene patents similarly impede the development and improvement of tests for diseases by geneticists. Ledbetter Decl. ¶¶ 14-15. Plaintiffs also assert that allowing only a single lab to offer testing means that the one lab dictates the standards for patient care in testing for that disease; in contrast, patient care is promoted when more than one lab offers a particular genetic test, utilizing different methodologies, since this can ensure the quality of the testing and accuracy of the test results. Chung Decl. ¶ 23; Ledbetter Decl. ¶ 23; Reich Decl. ¶¶ 9, 11; Ostrer Decl. ¶¶ 11; Parthasarathy Decl. ¶ 31.

Plaintiffs further assert that gene patents are not necessary to create incentives for initial discoveries or the development of commercial applications, including diagnostic tests. Cho Decl. ¶ 25; Leonard Decl. ¶¶ 20-21. Patents have not been necessary for the rapid introduction of genetic testing, as evidenced by genetic testing that has been offered prior to the issuance of a patent. Cho Decl. ¶ 21. In support of this assertion, Plaintiffs cite a study of gene patents issued in the United States for genetic diagnostics that showed that 67% of these patents were issued for discoveries funded by

the U.S. government. Cho Decl. ¶ 22. Similarly, another study showed that 63% of patents on gene sequences resulted from federally supported research. Leonard Decl. ¶ 22. As previously noted, the NIH provided \$2 million in research grants to the University of Utah, or approximately one-third of the total funding, for the identification of the *BRCA1* sequence. Parthasarathy Decl. ¶ 18.

Myriad has contested these assertions and disputes the idea that patenting of isolated human DNA conflicts with the advancement of science. According to Myriad, the quid pro quo of the patent system is that inventors, in exchange for a limited period of patent exclusivity, must provide a sufficient description of the patented invention so that others may improve upon it. Reilly Decl. ¶ 24; Doll Decl. ¶ 44. Furthermore, according to Myriad, its policy and practice has been and still is to allow scientists to conduct research studies on *BRCA1* and *BRCA2* freely, the result of which has been the publication of over 5,600 research papers on *BRCA1* and over 3,000 research papers on *BRCA2*, representing the work of over 18,000 scientists. Critchfield Decl. ¶¶ 3, 13; Li Decl. ¶¶ 3-6; Baer Decl. ¶¶ 3-6; Parvin Decl. ¶¶ 3-6; Sandbach Decl. ¶¶ 3-7.

According to Myriad, patents on isolated DNA, including the patents-in-suit, actually promote research and advance clinical development to the benefit of patients. Reilly Decl. ¶¶ 38, 43; Critchfield Decl. ¶¶ 2-18, 65, 68; Linck Decl. ¶¶ 27-28, 71, 73; Tavtigian Decl. ¶¶ 14-17; Doll Decl. ¶¶ 45-46; Schlessinger Decl. ¶¶ 31-32. Myriad has contended that gene patents are essential for obtaining capital

investment in the development and commercialization of technological breakthroughs. Linck Decl. ¶¶ 27, 28; Reilly Decl. ¶¶ 16; Doll Decl. ¶ 46. In support, Myriad has cited a survey published in 2009 by the BIO of 150 biotechnology member companies in the therapeutic and diagnostic healthcare industry stating that the majority of companies (61%) generally in-licensed projects that are in the pre-clinical or Phase I stage of development, and thus still require substantial R&D investment and commercialization risk by the licensee. A substantial majority (77%) of the respondents without approved products indicated that they expect to spend 5-15 years and over \$100 million developing a commercial product. Myriad asserts that these expenditures dwarf any initial research funding by the federal government. Reilly Decl. ¶ 22. In particular, Myriad notes that a significant amount of private investment led to its identification of the *BRCA1* and *BRCA2* sequences, with the expectation of patent protection providing an incentive to fund the research into the determination of the gene sequences. Skolnick Decl. ¶¶ 14-16. Therefore, Myriad asserts that absent the promise of a period of market exclusivity provided by patents and the infusion of venture and risk capital derived therefrom, companies such as Myriad that capitalize on innovation simply would not be created and their products would not be brought to market or the clinic. Reilly Decl. ¶¶ 18, 34, 51, 52, 62; Critchfield Decl. ¶¶ 67, 68; Linck Decl. ¶ 73.

Myriad also notes that it has made over 20,000 submissions to the BIC database, making it the largest contributor to the database. It has also

published the largest clinical series of mutation risk in the *BRCA1/2* genes based on its testing data and has tabulated and posted the data on Myriad's website, where it is freely available to researchers throughout the world. Critchfield Decl. ¶¶ II, 12.

According to Myriad, the majority of academic researchers operating laboratories (as opposed to Clinical Laboratory Improvement Amendments ("CLIA")-certified laboratories) do not believe that they should share test results with subjects outside of the standard clinical setting. Reilly Decl. ¶ 57-59. As the declarations submitted by the parties make clear, there exists a sharp dispute concerning the impact of patents directed to isolated DNA on genetic research and consequently the health of society. As with the dispute concerning the effect of the patents-in-suit on *BRCA1/2* genetic testing, the resolution of these disputes of fact and policy are not possible within the context of these motions.

#### **IV. THE PATENTS**

##### **A. Summary of the Patents**

The subjects of this declaratory judgment action are fifteen claims contained in seven patents issued by the USPTO: <sup>25</sup> claims 1, 2, 5, 6, 7, and 20 of U.S. patent 5,747,282 (the "282 patent"); claims 1, 6, and 7 of U.S. patent 5,837,492 (the "492 patent") ;

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<sup>25</sup> The USPTO granted these patents pursuant to a formal written policy that permits the patenting of "isolated and purified" DNA encoding human genes and pursuant to a practice that permits such DNA patents and the patenting of correlations created by nature between natural elements of the body and a predisposition to disease. See Utility Examination Guidelines, 66 Fed. Reg. 1,093 (Jan. 5, 2001).

claim 1 of U.S. patent 5,693,473 (the "'473 patent"); claim 1 of U.S. patent 5,709,999 (the "'999 patent"); claim 1 of U.S. patent 5,710,001 (the "'001 patent"); claim 1 of U.S. patent 5,753,441 (the "'441 patent"); and claims 1 and 2 of U.S. patent 6,033,857 (the "'857 patent").<sup>26</sup>

The claims-in-suit may be divided into two types of claims: composition claims and method, or process, claims. Independent claim 1 of the '282 patent representative of the group of composition claims and claims:

An isolated DNA coding for a *BRCA1* polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO: 2.

This claim is therefore directed to an isolated DNA molecule possessing a nucleotide sequence that translates into the *BRCA1* protein. Because most amino acids can result from the translation of more than one DNA codon, multiple DNA sequences correspond to the nucleotide sequence claimed by this claim. Claim 2 of the '282 patent is dependent on claim 1 but contains an additional limitation that identifies the specific *BRCA1* nucleotide sequence of the claimed DNA.<sup>27</sup> Claims 5 and 6 of the '282 patent are directed to fragments as short as 15 nucleotides

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<sup>26</sup> For purposes of understanding what the claim terms would have meant to a person of ordinary skill in the art at the time of the application for the patents, an application date of August 1994 is presumed for the '282, '473, '999, '001, and '441 patents and December 1995 for the '492 and '857 patents.

<sup>27</sup> Claim 2 of the '282 patent reads: "The isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID NO: 1."



of the DNA molecules claimed in claims land 2 of the '282 patent.<sup>28</sup> Finally, claim 7 of the '282 patent and claim 1 of the '473 patent are directed to isolated DNA possessing one of the specified mutant *BRCA1* gene sequences.<sup>29</sup>

Claims 1, 6, and 7 of the '492 patent are also composition claims covering isolated DNA molecules containing certain specified nucleotide sequences relating to the *BRCA2* gene. Claim 1 is directed to an isolated DNA molecule encoding the BRCA2 protein.<sup>30</sup> Like claim 1 of the '282 patent, claim 1 of the '492 patent is directed to multiple possible DNA sequences as a result of the redundancy of the DNA codons. Claim 6 of the '492 patent, however, is considerably broader than claim 1 and is directed to

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<sup>28</sup> Claim 5 of the '282 patent claims: "An isolated DNA having at least 15 nucleotides of the DNA of claim 1." Claim 6 of the '282 patent reads: "An isolated DNA having at least 15 nucleotides of the DNA of claim 2."

<sup>29</sup> Claim 7 of the '282 patent reads: "An isolated DNA selected from the group consisting of: (a) a DNA having the nucleotide sequence set forth in SEQ ID NO: 1 having T at nucleotide position 4056; (b) a DNA having the nucleotide sequence set forth in SEQ ID NO: 1 having an extra C at nucleotide position 5385; (c) a DNA having the nucleotide sequence set forth in SEQ ID NO: 1 having G at nucleotide position 5443; and (d) a DNA having the nucleotide sequence set forth in SEQ ID NO: 1 having 11 base pairs at nucleotide positions 189-199 deleted." Claim 1 of the '473 patent reads: "An isolated DNA comprising an altered BRCA1 DNA having at least one of the alterations set forth in Tables 12A, 14, 18 or 19 with the proviso that the alteration is not a deletion of four nucleotides corresponding to base numbers 4184-4187 in SEQ. ID. NO: 1."

<sup>30</sup> Claim 1 of the '492 patent reads: "An isolated DNA molecule coding for a BRCA2 polypeptide, said DNA molecule comprising a nucleic acid sequence encoding the amino acid sequence set forth in SEQ ID NO: 2."

any DNA nucleotide encoding any mutant *BRCA2* protein that is associated with a predisposition to breast cancer.<sup>31</sup> Claim 7 of the '492 patent depends on claim 6, but is restricted to the mutated forms of the *BRCA2* nucleotide sequence set forth in the specification.<sup>32</sup> As a result of the breadth of these composition claims, they reach isolated *BRCA1/2* DNA obtained from any human being.

Claim 1 of the '999 patent is representative of the group of method claims. It claims:

A method for detecting a germline alteration in a *BRCA1* gene, said alteration selected from a group consisting of the alterations set forth in Tables 12A, 14, 18, or 19 in a human which comprises analyzing a sequence of a *BRCA1* gene or *BRCA1* RNA from a human sample or analyzing a sequence of *BRCA1* cDNA made from mRNA from said human sample with the proviso that said germline alteration is not a deletion of 4 nucleotides corresponding to base numbers 4184-4187 of SEQ ID NO: 1.

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<sup>31</sup> Claim 6 of the '492 patent reads: "An isolated DNA molecule coding for a mutated form of the *BRCA2* polypeptide set forth in SEQ ID NO: 2, wherein said mutated form of the *BRCA2* polypeptide is associated with susceptibility to cancer."

<sup>32</sup> Claim 7 of the '492 patent reads: "The isolated DNA molecule of claim 6, wherein the DNA molecule comprises a mutated nucleotide sequence set forth in SEQ ID cNO: 1. "

Thus, claim 1 of the '999 patent covers the process of identifying the existence of certain specific mutations in the *BRCA1* gene by "analyzing" the sequence of the *BRCA1* DNA, RNA, or cDNA made from *BRCA1* RNA obtained from a human sample.

Most of the remaining method claims-in-suit are similarly structured and directed to the comparison of gene sequences. Claim 1 of the '001 patent claims a method for determining whether a human tumor sample contains a mutation in the *BRCA1* gene by "comparing" the sequence of the *BRCA1* gene from the tumor with the sequence of the *BRCA1* gene from a non-tumor sample from the same person.<sup>33</sup> Claim 1 of the '441 patent and claim 1 of the '857 are both directed to the same process, differing only as to whether the claimed method is directed to *BRCA1* ('441) or *BRCA2* ('857). Both of these independent claims are directed to the process of determining whether an individual has inherited an altered *BRCA1* or *BRCA2* gene by "comparing" the individual's *BRCA1* or *BRCA2* gene

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<sup>33</sup> Claim 1 of the '001 patent reads "A method for screening a tumor sample from a human subject for a somatic alteration in a *BRCA1* gene in said tumor which comprises gene comparing a first sequence selected from [sic] the group consisting of a *BRCA1* gene from said tumor sample, *BRCA1* RNA from said tumor sample and *BRCA1* cDNA made from mRNA from said tumor sample with a second sequence selected from the group consisting of *BRCA1* gene from a nontumor sample of said subject, *BRCA1* RNA from said nontumor sample and *BRCA1* cDNA made from mRNA from said nontumor sample, wherein a difference in the sequence of the *BRCA1* gene, *BRCA1* RNA or *BRCA1* cDNA from said tumor sample from the sequence of the *BRCA1* gene, *BRCA1* RNA or *BRCA1* eDNA from said nontumor sample indicates a somatic alteration in the *BRCA1* gene in said tumor sample."

sequence with the wild-type *BRCA1* or *BRCA2* gene sequence.<sup>34</sup> 34 Claim 2 of the '857 patent covers a method for determining whether an individual has a predisposition for breast cancer by "comparing" the individual's *BRCA2* gene sequence with the known wild-type *BRCA2* gene sequence.<sup>35</sup>

Finally, claim 20 of the '282 patent claims a method for determining the effectiveness of a potential cancer therapeutic comprising growing cells carrying an altered *BRCA1* gene known to cause cancer in the presence and absence of a potential cancer therapeutic, comparing the growth rates of the cells, and concluding that a slower growth rate in

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<sup>34</sup> Claim 1 of the '441 patent reads: "A method for screening germline of a human subject for an alteration of a *BRCA1* gene which comprises comparing germline sequence of a *BRCA1* gene or *BRCA1* RNA from a tissue sample from said subject or a sequence of *BRCA1* cDNA made from mRNA from said sample with germline sequences of wild-type *BRCA1* gene, wild-type *BRCA1* RNA or wild-type *BRCA1* cDNA, wherein a difference in the sequence of the *BRCA1* gene, *BRCA1* RNA or *BRCA1* cDNA of the subject from wild-type indicates an alteration in the *BRCA1* gene in said subject." Claim I of the '857 patent claims: "A method for identifying a mutant *BRCA2* nucleotide sequence in a suspected mutant *BRCA2* allele which comprises comparing the nucleotide sequence of the suspected mutant *BRCA2* allele with the wild-type *BRCA2* nucleotide sequence, wherein a difference between the suspected mutant and the wild-type sequences identifies a mutant *BRCA2* nucleotide sequence."

<sup>35</sup> Claim 2 of the '857 patent reads: "A method for diagnosing a predisposition for breast cancer in a human subject which comprises comparing the germline sequence of the *BRCA2* gene or the sequence of its mRNA in a tissue sample from said subject with the germline sequence of the wild-type *BRCA2* gene or the sequence of its mRNA, wherein an alteration in the germline sequence of the *BRCA2* gene or the sequence of its mRNA of the subject indicates a predisposition to said cancer."

the presence of the potential therapeutic indicates that it is indeed a cancer therapeutic.<sup>36</sup>

## **B. Construction of the Claims<sup>37</sup>**

### **1. Legal standard**

Before considering the patent-eligibility of a patent claim, the disputed terms in the claims must be construed in order ensure the scope of the claims is accurately assessed. See, e.g., Datamize, LLC v. Plumtree Software, Inc., 417 F.3d 1342, 1354 (Fed. Cir. 2005) ("[A] utility patent protects 'any new and useful process, machine, manufacture, or composition of matter, or any new or useful improvement thereof,' 35 U.S.C. § 101 (2000), the scope of which is defined by the patent's written claims."). Courts are charged with interpreting disputed claim terms as a matter of law. Markman v. Westview Instruments, Inc., 517 U.S. 370, 384-85 (1996).

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<sup>36</sup> Claim 20 of the '282 patent reads: "A method for screening potential cancer therapeutics which comprises: growing a transformed eukaryotic host cell containing an altered BRCA1 gene causing cancer in the presence of a compound suspected of being a cancer therapeutic, growing said transformed eukaryotic host cell in the absence of said compound, determining the rate of growth of said host cell in the presence of said compound and the rate of growth of said host cell in the absence of said compound and comparing the growth rate of said host cells, wherein a slower rate of growth of said host cell in the presence of said compound is indicative of a cancer therapeutic."

<sup>37</sup> In addition to the claim terms discussed below, the parties also dispute the proper interpretation of the method claims - i.e., whether they may be construed to encompass certain transformative steps. Because this issue is broader in scope than simple claim term definition, it is addressed *infra* in Section VII.D.

In interpreting the meaning of claim terms, "words of a claim are generally given their ordinary and customary meaning" to a person of ordinary skill in the art at the time of invention (i.e., the effective filing date of the patent application). Philips v. AWH Corp., 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (internal citations and quotation marks omitted). "Importantly, the person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification." Id. at 1313. Thus, the Federal Circuit has emphasized the importance of "intrinsic" evidence in claim construction: the words of the claim themselves, the written description in the patent's specification, and, when necessary, the history of the patent application's prosecution before the USPTO. Id. at 1314-17.

The process of claim construction begins with the language of the claims themselves. The language of the claim is what the patentee chose to use to "particularly point [ ] out and distinctly claim [ ] the subject matter which the applicant regards as his invention." Id. at 1311-12 (quoting 35 U.S.C. § 112, ¶ 2). Thus, "the claims themselves provide substantial guidance as to the meaning of particular claim terms." Id. at 1314. In addition to the particular claim being examined, the context provided by other claims may be helpful as well. "For example, the presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim." Id. at 1314-15.

Claim language must also be read in the context of the specification. Id. at 1315. As the Federal Circuit has made clear, "claims, of course, do not stand alone. Rather, they are part of 'a fully integrated written instrument,' consisting principally of a specification that concludes with the claims." Id. (quoting Markman v. Westview Instruments, Inc., 52 F.3d 967, 978 (Fed. Cir. 1995)). "For that reason, claims 'must be read in view of the specification, of which they are a part.'" Id. (quoting Markman, 52 F.3d at 979). The specification "is always highly relevant to the claim construction analysis. Usually it is dispositive; it is the single best guide to the meaning of a disputed term." Id. (quoting Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed. Cir. 1996)). Moreover, when the patentee "act[s] as his or her own lexicographer" and includes an explicit definition of a claim term in the specification, that definition is dispositive over any ordinary meaning. Id. at 1319 (internal citation and quotation marks omitted); see also Digital Biometrics, Inc. v. Identix, Inc., 149 F.3d 1335, 1344 (Fed. Cir. 1998).

In relying on the specification to interpret claim terms, the Federal Circuit has also "repeatedly warned against confining the claims" to the embodiments described in the specification. Phillips, 415 F.3d at 1323. The mistake of "reading a limitation from the written description into the claims" is one of the cardinal sins of patent law." Id. at 1320 (quoting SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc., 242 F.3d 1337, 1340 (Fed. Cir. 2001)).

Courts may also utilize the prosecution history which "consists of the complete record of the proceedings before the PTO and includes the prior

art cited during the examination of the patent . . . . [T]he prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be." Id. at 1317 (internal citations omitted). However, the prosecution history "often lacks the clarity of the specification and thus is less useful claim construction purposes." Id.

Lastly, courts may rely on extrinsic evidence such as dictionaries, treatises, and expert testimony, which may serve to provide a source of "accepted meaning of terms used in various fields of science and technology," or by providing "background on the technology at issue." Id. at 1317-18. However, such "extrinsic" evidence is "less significant than the intrinsic record in determining the legally operative meaning of the claim language." Id. At 1317 (internal citations and quotation marks omitted). The use of extrinsic evidence may not be used to contradict the meaning of the claim terms as evidenced by the intrinsic evidence. Id. at 1317-19; Biagro W. Sales, Inc. v. Grow More, Inc., 423 F.3d 1296, 1302 (Fed. Cir. 2005).

## **2. Resolution of the disputed claim terms**

### **a. "DNA" and "isolated DNA"**

The parties approach the terms "DNA" and "isolated DNA" from opposing perspectives.<sup>38</sup>

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<sup>38</sup> The degree to which the parties actually disagree on the meaning of the discussed claim terms is unclear; however, to



Plaintiffs contend that the term "DNA" means "a sequence of nucleic acids, also referred to as nucleotides" and therefore constitutes a "nucleotide sequence" or a "polynucleotide," Pl. Br. at 10.<sup>39</sup> Myriad disputes Plaintiffs' definition of "DNA" insofar as Plaintiffs' definition suggests that the term "DNA" refers merely to information, that is, "a description of the linear order of nucleotide units that make up the polynucleotide." Myriad Br. at 15. Myriad instead argues that "DNA" refers to "a real and tangible molecule, a chemical composition made up of deoxyribonucleotides linked by a phosphodiester backbone." Myriad Br. at 14.

As its name implies, DNA, or deoxyribonucleic acid, is an acid - a tangible, chemical compound. As Myriad correctly notes, the specifications make clear

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the extent some disagreement has been noted by the parties, this section seeks to resolve them.

<sup>39</sup> For purposes of this opinion, "Pl. Br." refers to Plaintiffs' Memorandum of Law in Support of Motion for Summary Judgment; "Myriad Br." refers to Myriad Defendants' Memorandum of Law (1) in Support of Their Motion for Summary Judgment and (2) in Opposition to Plaintiffs' Motion for Summary Judgment; "Pl. Reply" refers to the Memorandum of Law (1) in Further Support of Plaintiffs' Motion for Summary Judgment Against All Defendants and (2) in Opposition to the Myriad Defendants' Motion for Summary Judgment and (3) in Opposition to Defendant United States Patent and Trademark Office's Motion for Judgment on the Pleadings; "Myriad Reply" refers to Myriad Defendants' Memorandum in Reply to Plaintiffs' Opposition to Myriad Defendants' Motion for Summary Judgment; and "USPTO Reply" refers to the Reply Memorandum of Law in Further Support of Defendant United States Patent and Trademark Office's Motion for Judgment on the Pleadings and in opposition to Plaintiffs' Motion for Summary Judgment.

that "DNA," as used in the patents, refers to the physical manifestation of the acid, one that may be "substantially separated from other cellular components which naturally accompany a gene." '473 patent, col. 19: 8-9; '282 patent, col. 19: 10-11; '492 patent, col. 17: 64-65. Despite the description of the term "DNA" set forth in the briefs, this understanding of the meaning of "DNA" is shared by both Plaintiffs' and Myriad's declarants. Kay ¶ 125; Linck ¶ 45; Schlessinger ¶ 12; Grody ¶ 10; Leonard ¶ 30.

The term "isolated DNA" is defined by Plaintiffs as "a fragment of DNA substantially separated from other cellular components and other DNA." PI. Br. at 10. Myriad disputes Plaintiffs' definition insofar as it implies that fragments of DNA exist free-floating in the cell, separate from other cellular components, such as proteins and the other DNA in the chromosome. Myriad Br. at 16. The patent specifications expressly define "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." '473 patent, col. 19: 6-15; '282 patent, col. 19: 8-18; '492 patent, col. 17: 62-18:5.

"Isolated DNA" is therefore construed to refer to 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.

**b. "BRCA1" and "BRCA2 "**

Plaintiffs define the term "BRCA1" as "a particular fragment of DNA found on chromosome 17 that relates to a person's predisposition to develop breast and ovarian cancer." Pl. Br. at 11. Similarly, Plaintiffs define the term "BRCA2" as "a particular fragment of DNA found on chromosome 13 that relates) to a person's predisposition to develop breast and ovarian cancer." Pl. Br. at 14. As with Plaintiffs' proposed definition of "isolated DNA," Myriad argues that these definitions are inconsistent with the patents' definition of "BRCA1" and "BRCA2" as "cancer-predisposing gene[s]. some alleles of which cause susceptibility to breast and ovarian cancers" because they suggest that the *BRCA1* and *BRCA2* genes are not integrated into a chromosome, but are broken, detached, or otherwise easily removed from their respective chromosomes. Myriad Br. at 16.

The specifications of the patents-in-suit define the terms "BRCA1" and "BRCA2" as "a human breast cancer predisposing gene . . . some alleles of which cause susceptibility to cancer, in particular breast and ovarian cancer." '282 patent, col. 4:33-36; see also '282 patent, col. 1: 22-23; '492 patent, col. 1: 20-21, 4:28-29. Further, neither party disputes that "genes" refer to segments of DNA incorporated into chromosomes.

"BRCA1" is therefore construed to refer to a human gene, normally integrated into chromosome 17, some alleles of which cause susceptibility to

breast and ovarian cancer. Similarly, "BRCA2" is construed to refer to a human gene, normally integrated into chromosome 13, some alleles of which cause susceptibility to breast and ovarian cancer.

## V. CONCLUSIONS OF LAW

### A. The Summary Judgment Standard

Summary judgment is granted only where there exists no genuine issue of material fact and the moving party is entitled to judgment as a matter of law. Fed. R. Civ. P. 56(c); see Celotex Corp. v. Catrett, 477 U.S. 317, 322-3 (1986); SCS Commc'ns, Inc. v. Herrick Co., 360 F.3d 329, 338 (2d Cir. 2004). The courts do not try issues of fact on a motion for summary judgment, but, rather, determine "whether the evidence presents a sufficient disagreement to require submission to a jury or whether it is so one-sided that one party must prevail as a matter of law." Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 251-52 (1986).

"The party seeking summary judgment bears the burden of establishing that no genuine issue of material fact exists and that the undisputed facts establish [its] right to judgment as a matter of law." Rodriguez v. City of New York, 72 F.3d 1051, 1060-61 (2d Cir. 1995). In determining whether a genuine issue of material fact exists, a court must resolve all ambiguities and draw all reasonable inferences against the moving party. See Matsushita Elec. Indus. CO. V. Zenith Radio Corp., 475 U.S. 574, 587-88 (1986); Gibbs-Alfano v. Burton, 281 F.3d 12, 18 (2d Cir. 2002). However, "the non-moving party may not rely simply on conclusory allegations or speculation to avoid summary judgment, but instead

must offer evidence to show that its version of the events is not wholly fanciful." Morris v. Lindau, 196 F.3d 102, 109 (2d Cir. 1999) (internal quotation marks omitted).

Summary judgment is appropriate where the moving party has shown that "little or no evidence may be found in support of the nonmoving party's case. When no rational jury could find in favor of the nonmoving party because the evidence to support its case is so slight, there is no genuine issue of material fact and a grant of summary judgment is proper." Gallo v. Prudential Residential Servs., L.P., 22 F.3d 1219, 1223-24 (2d Cir. 1994) (internal citations omitted).

#### **B. 35 U.S.C. § 101 and Its Scope**

Section 101 of Title 35, United States Code, provides:

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

In interpreting this language, the Supreme Court has observed that "Congress plainly contemplated that the patent laws would be given wide scope." Diamond v. Chakrabarty, 447 U.S. 303, 308 (1980); see also J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc., 534 U.S. 124, 131 (2001) ("[W]e are mindful that this Court has already

spoken clearly concerning the broad scope and applicability of § 101.”)

However, this broad reading of § 101 and statutory patent eligibility is not without limits. "The Supreme Court has recognized that scientific principles and laws of nature, even when for the first time discovered, have existed throughout time, define the relationship of man to his environment, and, as a consequence, ought not to be the subject of exclusive rights to anyone person." In re Meyer, 688 F.2d 789, 795 (C.C.P.A. 1982) (citing Leroy v. Tatham, 55 U.S. 155, 175 (1852)). Specifically, the Supreme Court has recognized three categories of subject matter that fall outside the scope of § 101: "The laws of nature, physical phenomena, and abstract ideas have been held not patentable." Chakrabarty, 447 U.S. at 309; see also Diamond v. Diehr, 450 U.S. 175, 185 (1981). "The rule that the discovery of a law of nature cannot be patented rests, not on the notion that natural phenomena are not processes, but rather on the more fundamental understanding that they are not the kind of 'discovery' that the statute was enacted to protect." Parker v. Flook, 437 U.S. 584, 593 (1978).

The exclusion of products of nature<sup>40</sup> as patentable subject matter under § 101 also reflects

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<sup>40</sup> Myriad distinguishes between "laws of nature," "natural phenomena," and "abstract ideas." which it concedes are not patentable, and "products of nature," for which it appears to argue no prohibition to patentability exists. Although the distinction between these two categories is unclear, it is well established that "products of nature" are not patentable. See, e.g., Chakrabarty, 447 U.S. at 13 (stating that relevant distinction for § 101 patentability is "between products of nature, whether living or not, and human-made inventions"); Gen. Elec. Co. v. De Forest Radio Co., 28 F.2d 641, 642 (3d Cir.

the Supreme Court's recognition that “[p]henomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work.” Gottschalk v. Benson, 409 U.S. 63, 67 (1972). Thus, as Justice Breyer has observed, “the reason for this exclusion is that sometimes *too much* patent protection can impede rather than ‘promote the Progress of Science and useful Arts,’ the constitutional objective of patent and copyright protection.” Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc., 548 U.S. 124, 126-27 (2006) (Breyer, *J.*, dissenting) (quoting U. S. Const., Art. I, § 8, cl. 8.) (emphasis in original). For these reasons, “manifestations of laws of nature [are] free to all men and reserved exclusively to none.” Funk Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 130 (1948).

The inquiry into an invention's patent eligibility is a fundamental one, and as such, “[t]he obligation to determine what type of discovery is sought to be patented must precede the determination of whether that discovery is, in fact, new or obvious.” Flook, 437 U.S. at 593; see also In re Bilski, 545 F.3d 943, 950 (Fed. Cir. 2008) (en

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1928) (noting that “a patent cannot be awarded for a discovery or for a product of nature, or for a chemical element”); In re Marden, 47 F.2d 957, 957 (C.C.P.A. 1931) (concluding that “[u]ranium is a product of nature, and the appellant is not entitled to a patent on the same, or upon any of the inherent natural qualities of that metal”); In re Marden, 47 F.2d 958, 959 (C.C.P.A. 1931) (stating that “pure vanadium is not new in the inventive sense, and, it being a product of nature, no one is entitled to a monopoly of the same”).

banc), cert. granted, 129 S. Ct. 2735 (2009) ("Whether a claim is drawn to patent-eligible subject matter under § 101 is a threshold inquiry, and any claim of an application failing the requirements of § 101 must be rejected even if it meets all of the other legal requirements of patentability." (citing In re Comiskey, 499 F.3d 1365, 1372 (Fed. Cir. 2007)); Prometheus Labs. v. Mayo Collaborative Servs., 581 F.3d 1336, 1343 (Fed. Cir. 2009) (noting that in determining patent eligibility, "it is improper to consider whether a claimed element or step in a process is novel or nonobvious, since such considerations are separate requirements set forth in 35 U.S.C. §§ 102, and 103, respectively." (citing Bilski, 545 F.3d at 958)). Consistent with this approach, the courts have rejected patent claims even when the purported invention was highly beneficial or novel, or the research and work that went into identifying it was costly or time-consuming. See, e.g., Funk Bros., 333 U.S. at 130; Am. Fruit Growers, Inc. v. Brodget Co., 283 U.S. 1, 11-13 (1931); Gen. Elec. Co. v. De Forest Radio Co., 28 F.2d 641, 642-43 (3d Cir. 1928).

The distinction between the § 101 inquiry into patentable subject matter and the other requirements for patentability set forth in Title 35 is of particular importance in evaluating the authorities cited by the parties and the arguments presented. The discussion of § 101 in In re Bergy, 596 F.2d 952 (C.C.P.A. 1979) by the late Honorable Giles S. Rich, one of the authors of the 1952 Patent Act, is particularly informative in clarifying the proper scope of a § 101 analysis. There, Judge Rich stated what considerations were salient - and



importantly, what considerations were not - in a § 101 analysis:

Section 101 states three requirements: novelty, utility, and statutory subject matter. The understanding that these three requirements are separate and distinct is long-standing and has been universally accepted. . . . Thus, the questions of whether a particular invention is novel or useful are questions wholly apart from whether the invention falls into a category of statutory subject matter. *Of the three requirements stated in § 101, only two, utility and statutory subject matter, are applied under § 101.* As we shall show, in 1952 Congress voiced its intent to consider the novelty of an invention under § 102 where it is first made clear what the statute means by "new," notwithstanding the fact that this requirement is first named in § 101.

Id. at 960-61 (emphasis added). Judge Rich further cautioned that "statements in the older cases must be handled with care lest the terms used in their reasoning clash with the reformed terminology of the present statute; lack of meticulous care may lead to distorted legal conclusions." Id. at 959. The Supreme Court subsequently affirmed this understanding of the § 101 analysis in Diehr, noting that while it had been argued that "novelty is an appropriate consideration under § 101," "[t]he question . . . of

whether a particular invention is novel is 'wholly a part from whether from whether the invention falls into a category of statutory subject matter.'" 450 U.S. at 189-90 (quoting Bergy, 596 F.2d at 961); see also Bilski, 545 F.3d at 958 ("So here, it is irrelevant to the § 101 analysis whether Applicants' claimed process is novel or nonobvious.")

Accordingly, in considering whether the patents-in-suit comply with § 101, the proper analysis requires determining (1) whether the claimed invention possesses utility; and (2) whether the claimed invention constitutes statutory subject matter, that is, whether it is a "process, machine, manufacture, or composition of matter, or any new and useful improvement thereof," 35 U.S.C. § 101, or whether the claimed invention instead falls within the judicially created "products of nature" exception to patentable subject matter, i.e., "laws of nature, natural phenomenon, and abstract ideas," Chakrabarty, 447 U.S. at 309. In contrast, the question of whether an invention is "new" or "novel" over the prior art is a question addressed by § 102 and falls outside of the scope of the present § 101 analysis. Because it is undisputed that the claimed compositions and methods possess utility, the sole task of this Court is to resolve whether the claimed compositions and methods constitute statutory subject matter or fall within the judicially created products of nature exception to patentable subject matter.

### **C. The Composition Claims Are Invalid Under 35 U.S.C. § 101**

As noted, the issue presented by the instant motions with respect to the composition claims is

whether or not claims directed to isolated DNA containing naturally-occurring sequences fall within the products of nature exception to § 101. Based upon the reasons set forth below, it is concluded that the composition claims-in-suit are excepted.

### **1. Consideration of the Merits of Plaintiffs' Challenge is Appropriate**

Myriad offers several arguments for why this Court should not engage the substance of Plaintiffs' claims, but should instead dismiss them out of hand. Foremost among them is Myriad's assertion that Plaintiffs' claims should be dismissed in light of the "carefully considered policy of the USPTO," which is "entitled to great respect from the courts." Myriad Br. at 26. In so arguing, Myriad notes the presumption of validity afforded to patents, see 35 U.S.C. § 282, and the USPTO's prior consideration of the eligibility of gene-related patents, see Utility Examination Guidelines 66 Fed. Reg. 1092, 1092-99 (Jan. 5, 2001), as well as the Supreme Court's statements in J.E.M. Ag Supply, 534 U.S. 124.

The Federal Circuit has previously held that it owes no deference to USPTO legal determinations. See, e.g., Arnold P'ship v. Dudas, 362 F.3d 1338, 1340 (Fed. Cir. 2004) ("This court reviews statutory interpretation, the central issue in this case, without deference."). While Congress has created a presumption of validity for issued patents, approximately 40% of patents challenged in the courts have been found invalid, demonstrating that this presumption is far from absolute. See Institute for Intellectual Property & Information Law, University of Houston Law Center, Patstats.org, Full Calendar Year 2008 Report, <http://www.patstats.org/>

2008\_Full\_Year\_Posting.rev3.htm (indicating that 40% of all validity determinations in federal court in 2008 found the challenged patent invalid); Paul F. Morgan & Bruce Stoner, *Reexamination v. Litigation - Making Intelligent Decisions in Challenging Patent Validity*, 86 J. Pat. & Trademark Off. Soc'y 441-461 (2004) (citing USPTO statistics showing that 74% of patents previously issued by the Patent Office and later challenged through the reexamination process were either canceled or changed by the USPTO). Moreover, the lack of Congressional action to specifically prohibit gene patents in response to the USPTO's prior grant of such patents does not preclude their review by the courts. For example, in Bilski, 545 F.3d 943, the Federal Circuit set out a test for the patentability of method claims that potentially will invalidate thousands of patents on business method patents, despite Congress' silence concerning the patentability of such methods. Finally, while the Supreme Court in J.E.M. Ag Supply noted the USPTO's practice of issuing patents on sexually reproducing plants in concluding that such plants represented patentable subject matter under § 101, that passing observation was neither dispositive nor central to the Court's holding and does not establish a rule of judicial deference to the USPTO's practices. See J.E.M. Ag Supply, 534 U.S. at 144-45. Indeed, the judicial deference urged by *Myriad* is difficult to reconcile with the courts' consideration of the substantive issues presented in cases such as Chakrabarty and indeed, J.E.M. Ag Supply itself.

Moreover, in the absence of a § 101 challenge to patent validity, the fact that courts have previously upheld the validity of patents directed to

biological products in response to § 102 and/or § 103 challenges has no bearing on the present inquiry. See, e.g., In re Kubin, 561 F.3d 1351 (Fed. Cir. 2009) (considering obviousness of claims); In re O'Farrell, 853 F.2d 894 (Fed. Cir. 1988) (same). The Patent Act sets out patent invalidity as an issue to be raised by the parties, see 35 U.S.C. § 282, and it would be erroneous to treat a case involving DNA-related patents as holding that isolated human genes constitute patentable subject matter under § 101. Were that the case, the Supreme Court could have proceeded with its consideration of Metabolite Labs., after it granted certiorari and the parties and amici had fully briefed the issue of patentable subject matter eligibility, rather than dismissing certiorari as improvidently granted based on the parties' failure to raise the § 101 issue below. 548 U.S. 124.

Finally, Myriad's suggestion that invalidating the patents-in-suit would constitute an unconstitutional taking in violation of the Fifth Amendment of the Constitution or a violation of the United States' obligations under the Agreement on Trade-Related Aspects of Intellectual Property Rights ("TRIPS") is unpersuasive. Myriad's novel takings argument runs counter to a long history of invalidation of patent claims by the courts and is unsupported by legal precedent. Similarly, Articles 8.1 and 27.3 of TRIPS permit governments to incorporate public health concerns into their intellectual property laws and to exclude from patentability diagnostic, therapeutic, or surgical methods as well as particular inventions on the grounds of public interest. As a result, invalidation of

the patents-in-suit would constitute neither a constitutional violation nor a conflict with the United States' treaty obligations.

**2. Patentable subject matter must be "markedly different" from a product of nature**

Supreme Court precedent has established that products of nature do not constitute patentable subject matter absent a change that results in the creation of a fundamentally new product. In American Fruit Growers, the Supreme Court rejected patent claims covering fruit whose skin had been treated with mold-resistant borax. Acknowledging that the "complete article is not found in nature," and "treatment, labor and manipulation" went into producing the fruit, the Court nonetheless held that the fruit did not become an "article of manufacture" unless it "possesses a new or distinctive form, quality, or property" compared to the naturally-occurring article.<sup>41</sup> 283 U.S. at 11. The Court went on to observe:

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<sup>41</sup> Myriad argues that American Fruit Growers was decided on novelty grounds, rather than subject matter patentability. See Myriad Br. at 26. However, the Court's novelty discussion was restricted to its analysis of the process claims. Am. Fruit Growers, 263 U.S. at 13-14 ("If it be assumed that the process claims under consideration cover an invention, we think this lacked novelty when application was made for the patent August 13, 1923"). In contrast, its rejection of the composition claims was based on an analysis of subject matter patentability. See id. at 11 ("Is an orange, the rind of which has become impregnated with borax, through immersion in a solution, and thereby resistant to blue mold decay, a 'manufacture,' or

Manufacture implies a change, but every change is not manufacture, and yet every change in an article is the result of treatment, labor, and manipulation. But something more is necessary . . . There must be transformation; a new and different article must emerge having a distinctive name, character, or use.

Id. at 12-13 (quoting Anheuser-Busch Brewing Ass'n v. United States, 207 U.S. 556, 562 (1908)) (internal citation and quotation marks omitted).

Similarly, in Funk Brothers, the Supreme Court considered whether a mixture of several naturally-occurring species of bacteria was patentable.<sup>42</sup> 333 U.S. at 128-31. Each species of bacteria in the mixture could extract nitrogen from the air for plant usage. While the patent holder had created a mixture by selecting and testing for strains of bacteria that did not mutually inhibit one another, the Court concluded that the patent holder "did not create a state of inhibition or of non-inhibition in the bacteria. Their qualities are the work of nature. Those qualities are of course not patentable." Id. at 130.

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manufactured article, within the meaning of section 31, title 35, U.S. Code?").

<sup>42</sup> Myriad suggests that the Supreme Court's holding in Funk Brothers was premised on an obviousness determination, rather than patentable subject matter. Subsequent Supreme Court opinions, however, have treated the holding in Funk Brothers as a statement of patentable subject matter. See Chakrabarty, 447 U.S. at 309-10; Flook, 437 U.S. at 591-92; Benson, 409 U.S. at 67-68.

Most recently, the Supreme Court addressed the application of § 101 to product claims in Diamond v. Chakrabarty, 447 U.S. 303. In Chakrabarty, the Court considered whether a "live, human-made micro-organism is patentable subject matter under 35 U.S.C. I 101." Id. At 305. The microorganism in question was a bacterium that had been genetically engineered to break down multiple components of crude oil and possessed considerable utility in the treatment of oil spills. Id. In concluding that the man-made bacterial strain was patentable, the Court observed that the claim "is not to a hitherto unknown natural phenomenon, but to a nonnaturally occurring manufacture or composition of matter - a product of human ingenuity 'having a distinctive name, character [and] use.'" Id. at 309-10 (quoting Hartranft v. Wiegmann, 121 U.S. 609, 615 (1887)). The Court went on to contrast the Chakrabarty bacterium with the bacterial mixture at issue in Funk Brothers, stating that in Chakrabarty's case, "the patentee has produced a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility. His discovery is not nature's handiwork, but his own . . . ." Id. at 310.<sup>43</sup> This requirement that an invention

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<sup>43</sup> Although Chakrabarty is often cited for the proposition that "anything under the sun that is made by man" is patentable, id. at 309, that phrase is a misleading quotation from the legislative history of the Patent Act of 1952. The full quote clearly acknowledges the statutory limitations to patentable subject matter: "A person may have 'invented' a machine or a manufacture, which may include anything under the sun made by man, but it is not necessarily patentable under section 101 unless the conditions of the title are fulfilled." H.R. Rep. No. 1923. 82d Cong., 2d Sess. 6 (1952).



possess "markedly different characteristics" for purposes of § 101 reflects the oft-repeated requirement that an invention have "a new or distinctive form, quality, or property" from a product of nature. Am. Fruit Growers, 283 U.S. at 11; In re Merz, 97 F.2d 599,601 (C.C.P.A. 1935) ("[M]ere purification of known materials does not result in a patentable product," unless "the product obtained in such a case had properties and characteristics which were different in kind from those of the known product rather than in degree.").

Courts have also specifically held that "purification" of a natural compound, without more, is insufficient to render a product of nature patentable. In The American Wood-Paper Co. v. The Fibre Disintegrating Co., 90 U.S. (23 Wall.) 566 (1874), the Supreme Court held that refined cellulose, consisting of purified pulp derived from wood and vegetable, was unpatentable because it was "an extract obtained by the decomposition or disintegration of material substance." Id. at 593. As the Court observed:

There are many things well known and valuable in medicine or in the arts which may be extracted from divers[e] substances. But the extract is the same, no matter from what it has been taken. A process to obtain it from a subject from which it has never been taken may be the creature of invention, but the thing

itself when obtained cannot be called  
a new manufacture.

Id. at 593-94.<sup>44</sup> Similarly, in Cochrane v. Badische Anilin & Soda Fabrik, 111 U.S. 293 (1884), the Court rejected a patent on an artificial version of a natural red dye called alizarine that was produced by manipulating another compound through acid, heat, water or distillation. See generally, id. Although the artificial version of the dye was of a brighter hue than the naturally occurring dye, the Court concluded that "[c]alling it artificial alizarine did not make it a new composition of matter, and patentable as such . . . ." Id. at 311 (citing Am. Wood-Paper, 90 U.S. (23 Wall.) at 593).

In General Electric, 28 F.2d at 642, the Third Circuit Court of Appeals considered the patentability of purified tungsten, which possessed superior characteristics and utility over its brittle, naturally-occurring form. The court first noted that "[i]f it is a natural thing then clearly, even if [the patentee] was the first to uncover it and bring it into view, he cannot have a patent for it because a patent cannot be awarded for a discovery or for a product of nature, or for a chemical element." Id. The court went on to state:

Naturally we inquire who created  
pure tungsten. Coolidge? No. It  
existed in nature and doubtless has  
existed there for centuries. The fact

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<sup>44</sup> Given the posture of the challenge to the patent's validity, the Court rested its holding on the fact that the patent in question was invalid as non-novel. Id.

that no one before Coolidge found it there does not negative its origin or existence.

The second part of the claim reads: "Having ductility and high tensile strength." Did Coolidge give those qualities to "substantially pure tungsten"? We think not for it is now conceded that tungsten pure is ductile cold. If it possess that quality now it is certain that it possessed it always.

Id. at 643. The Court of Customs and Patent Appeals ("C.C.P.A."), the precursor to the Federal Circuit Court of Appeals,<sup>45</sup> subsequently relied on General Electric in rejecting patents claiming purified uranium and vanadium. See In re Marden, 47 F.2d 957, 957-58 (C.C.P.A. 1931) ("Marden I"); In re Marden, 47 F.2d 958, 1059 (C.C.P.A. 1931) ("Marden II") ("The quality of purity of vanadium or its ductility is a quality of a natural product and as such is not patentable."). Similarly, in Ex Parte Latimer, the Patent Commissioner refused to allow a patent on pine needle fibers that were better suited for textile production, even though it was necessary to remove the needle from its sheath

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<sup>45</sup> The decisions of the C.C.P.A. remain binding precedent in patent cases. See South Corp. v. United States, 690 F.2d 1368, 1370-71 (Fed. Cir. 1982) (en banc) (adopting "[t]hat body of law represented by the holdings of . . . the Court of Customs and Patent Appeals" as "precedent" for the then-new Federal Circuit so as to "continu[e] the stability in those areas of the law previously within the jurisdiction of our predecessor courts").

and other resinous material. 1889 Dec. Comm'r Pat. 123, 125 (1889) ("Nature made them so and not the process by which they are taken from the leaf or needle.").

Myriad argues that purification of "'naturally occurring' compounds that 'do not exist in nature in pure form' renders such compounds patent-eligible." Myriad Br. at 21 (quoting In re Bergstrom, 427 F.2d 1394, 1401 (C.C.P.A. 1970)). However, Myriad cites no Supreme Court authority that would rebut the authorities presented by Plaintiffs, nor do the cited cases support Myriad's position.

Myriad has relied heavily on the holding of the Honorable Learned Hand in Parke-Davis & Co. v. H.K. Mulford Co., 189 F.2d 95 (S.D.N.Y. 1911).<sup>46</sup> In

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<sup>46</sup> The invocation of Judge Hand is frequently practiced in this Circuit. See, e.g., United States v. Rigas, 583 F.3d 108, 121 n.3 (2d Cir. 2009) (quoting Learned Hand for the proposition that appellate courts may not *find facts*); United States v. Parker, 554 F.3d 230 (2d Cir. 2009) (quoting Learned Hand for his formulation of the requirements of conspiracy); In re City of New York, 522 F.3d 279, 284 (2d Cir. 2008) (citing Learned Hand for his formulation of negligence); In re Hyman, 501 F.3d 61, 67 (2d Cir. 2007) (quoting at length Learned Hand's inconclusive discussion of the meaning of the word "defalcation" in 11 U.S.C. § 523 (a) (4)); United States v. Brand, 467 F.3d 179, 190 (2d Cir. 2006) (quoting Learned Hand's definition of inducement by the government); In re Enron Corp., 419 F.3d 115, 123 (2d Cir. 2005) (quoting Learned Hand's critique of statutes of limitations); Shannon v. Jacobowitz, 394 F.3d 90, 95 (2d Cir. 2005) (quoting Learned Hand's instruction that "[w]ords are not pebbles in alien juxtaposition . . ."); Danahy v. Buscaglia, 134 F.3d 1185, 1189 (2d Cir. 1998) (quoting Learned Hand on the rationale for qualified immunity). See also, Remarks of the Honorable John M. Walker, Jr. Upon Receiving the Learned Hand Medal for Excellence in Federal Jurisprudence, 76 St. John's L. Rev. 595, 596 (2002) ("Judge

Parke-Davis, Judge Hand considered a challenge to the validity of a patent claiming an adrenaline compound that had been isolated and purified from animal suprarenal glands. Id. at 97. It had been known that suprarenal glands in powdered form had hemostatic, blood-pressure-raising and astringent properties, but could not be used for those purposes in gross form. The isolated adrenaline, however, possessed the desired therapeutic properties and could be administered to humans.

Although Myriad argues that the holding in Parke-Davis establishes that the purification of a natural product necessarily renders it patentable, the opinion, read closely, fails to support such a conclusion. The question before the court in Parke-Davis was one of novelty (a modern-day § 102 question), not of patentable subject matter

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Hand is widely considered to have been one of the four greatest judges of the first half of the twentieth century.”); James L. Oakes, Personal Reflections on Learned Hand and the Second Circuit, 47 Stan. L. Rev. 387 (1995); Gerald Gunther, Learned Hand: the Man and the Judge (1994); Kathryn Griffin, Judge Learned Hand and the Role of the Federal Judiciary (1973); Marvin Schick, Learned Hand's Court (1970); Marcia Nelson, ed., The Remarkable Hands: An Affectionate Portrait (1983); Hershel Shanks, ed., The Art and Craft of Judging: The Decisions of Judge Learned Hand (1968). Although Judge Hand once turned his back on the author of this opinion arguing before him on behalf of the Government, his opinion in Parke-Davis deserves careful review but brings to mind that oft repeated adage "*Quote Learned, but follow Gus.*" See Oakes, 47 Stan. L. Rev. at 389 n.175. This author, confronted by genomics and molecular biology, also emphatically empathizes with Judge Hand's complaint in Parke-Davis about his lack of knowledge of the rudiments of chemistry. See Parke-Davis, 189 F. at 114.

(the § 101 question before this Court). In framing the issue, Judge Hand observed that, "[the validity of the claims] is attacked, first, because they are *anticipated* in the art; and second, for a number of technical grounds which I shall take up in turn." *Id.* at 101 (emphasis added). He went on to conclude that the patented purified extract was not, in fact, different from the prior art "only for a degree of purity," but rather was a different chemical substance from that found in the prior art. *Id.* at 103 (observing that "no one had ever isolated a substance [adrenaline] which was not in salt form" and that "the [claimed] base [form of adrenaline] was an original production of [the patentee's]"). Thus, Judge Hand held that the purified adrenaline was not anticipated by the prior art, namely, the ground paradrenal gland that was known to possess certain beneficial properties. See Merck & Co. v. Olin Mathieson Chem. Corp., 253 F.2d 156, 162 (4<sup>th</sup> Cir. 1958) ("It was further held [in Parke-Davis] that the invention was not anticipated, though the principle was known to exist in the suprarenal glands.").

Only after concluding that the claimed purified adrenaline was novel over the prior art did Judge Hand offer, as dicta, the statement to which Myriad cites: "But, even if it were merely an extracted product without change, there is no rule that such products are not patentable." *Id.* at 103. While the accuracy of this statement at the time was written is dubious in light of American Wood-Paper (to which Judge Hand did not cite) it is certainly no longer good law in light of subsequent Supreme Court cases, which, as noted above, require that a claimed invention possess "markedly different characteristics" over products existing in nature in

order for it to constitute patentable subject matter.<sup>47</sup> Chakrabarty, 447 U.S. at 310; see also Funk Bros., 333 U.S. at 130-32. By the same token, Judge Hand's suggestion that a claimed invention was patentable since it was a "new thing commercially and therapeutically," Parke-Davis, 189 F.2d at 103, is firmly contradicted by subsequent case law establishing that "it is improper to consider whether a claimed element or step in a process is novel or nonobvious, since such considerations are separate requirements" when evaluating whether a claim is patent-eligible subject matter. Prometheus, 581 F.3d at 1343; see also Bergy, 596 F.2d at 960-61. Such an approach would also be inconsistent with the Supreme Court's rejection of the patentability the commercially useful mixture of bacteria in Funk Brothers, the refined cellulose in American Wood-Paper, and the electromagnetic communication devices in O'Reilly v. Morse, 56 U.S. (15 How.) 62 (1853).

The distinction between considerations of novelty and patentable subject matter similarly undermines Myriad's reliance on Bergstrom and In re Kratz, 592 F.2d 1169 (C.C.P.A. 1979), both of which presented issues of novelty and anticipation rather than the question of patentable subject matter. In Bergstrom, the C.C.P.A. considered an appeal from a rejection by the Board of Patent and Interferences ("BPAI") of a patent claiming the purified prostaglandins PGE<sub>2</sub> and PGE<sub>3</sub> that had

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<sup>47</sup> Notwithstanding Judge Hand's reputation, see supra note 46, his opinion in Parke-Davis was one of a district court judge and does not supersede contrary statements of the law by the C.C.P.A. or the Supreme Court.

been extracted from human or animal prostate glands. 427 F.2d at 1398. Although the BPAI cited § 101 in its rejection, the C.C.P.A. recognized the issue as a § 102 question of novelty. Id. at 1400 (“Tested by the conventional evidentiary criteria or 'conditions for patentability' relevant to the present factual situation which Congress has expressed in the various provisions of 35 U.S.C. § 102, appellants are undoubtedly correct, for the Patent Office has not been able to . . . establish that the claimed subject matter lacks ‘novelty.’”); see also id. at 1401 (“[T]he fundamental error in the board's position, as we see it, is the analysis and answer it gave to the sole issue it accurately posed - whether the claimed pure materials are novel as compared with the less pure materials of the reference.” (internal citation and quotation marks omitted)). Indeed, the C.C.P.A. itself has subsequently recognized that Bergstrom is properly viewed as a case concerning novelty. Bergy, 596 F.2d at 961 (“Our research has disclosed only two instances in which rejections for lack of novelty were made by the PTO under § 101 . . . In In re Bergstrom we in effect treated the rejection as if it had been made under § 102, observing in the process that “The word “new” in § 101 is defined and to be construed in accordance with the provisions of § 102.” (internal citation omitted)).

Kratz examined the rejection of a patent claiming a substantially purified chemical compound naturally occurring in strawberries, called 2-methyl-2-pentenoic acid (“2M2PA”). 592 F.2d at 1170. The patentee had appealed from the BPAI's determination that the purified compound was obvious over the prior art under § 103. See id. Although there was some discussion about whether



the composition claimed was a naturally-occurring compound, the C.C.P.A. did not view the question before it as a § 101 inquiry. Instead, the court treated the appeal as a question of novelty and anticipation pursuant to § 102.<sup>48</sup> See, e.g., id. at 1174 (“It should be clear that an anticipation rejection in such a case is necessarily based on a dual footing.”).<sup>49</sup>

Finally, Merck & Co., Inc.v. Olin Mathieson Chern. Corp., 253 F.2d 156, cited by Myriad, is entirely consistent with the principle set forth in Funk Brothers and American Fruit Growers that something derived from a product of nature must “possess a new or distinctive form, quality, or property” in order to become patentable subject matter. Am. Fruit Growers, 283 U.S. at 11. In Merck, the Fourth Circuit considered the validity of a patent claiming a Vitamin B12 composition useful for

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<sup>48</sup> The differences between the test applied in Kratz and the “markedly different” requirement set forth in Chakrabarty and other Supreme Court precedent further demonstrates that the Kratz court was engaged in a § 102 anticipation analysis and not a § 101 statutory subject matter analysis. See id. at 1174 (requiring, for a finding of anticipation, that “the natural composition must inherently contain the naturally occurring compound” and that “the claim must be of sufficient breadth to encompass both the known natural composition and the naturally occurring compound.”).

<sup>49</sup> Bergy also cited by Myriad, considered the question of whether microorganisms constituted patentable subject matter, an issue subsequently addressed by the Supreme Court in Chakrabarty. It *did* not address the patentability of purified natural products, and its citation to Merck and Parke-Davis was only for the purpose of noting that courts had upheld patents on pharmaceutical compounds such as vitamin B12” and adrenaline. See Bergy, 596 F.2d at 974-75 & n.13.

treating pernicious anemia. Id. at 157. Although naturally occurring Vitamin B12 produced in cows had known therapeutic properties and was commercially available, the court found the purified B12 composition, which was obtained from a microorganism, patentable. In upholding the validity of the patent, the court held:

Every slight step in purification does not produce a new product. What is gained may be the old product, but with a greater degree of purity. Alpha alumina purified is still alpha alumina, In re Ridgway, 76 F.2d 602, [ ] and ultramarine from-which floatable impurities have been removed is still ultramarine, In re Merz, 97 F.2d 599 . . .

Id. at 163. Because the court concluded that the purified B12 was more than a "mere advance in the degree of purity of a known product," it determined that the claimed invention was entitled to patent protection. Id. at 164.

In sum, the clear line of Supreme Court precedent and accompanying lower court authorities, stretching from American Wood-Paper through to Chakrabarty, establishes that purification of a product of nature, without more, cannot transform it into patentable subject matter. Rather, the purified product must possess "markedly different characteristics" in order to satisfy the requirements of § 101.

### **3. The claimed isolated DNA is not "markedly different" from native DNA**

The question thus presented by Plaintiffs' challenge to the composition claims is whether the isolated DNA claimed by Myriad possesses "markedly different characteristics" from a product of nature.<sup>50</sup> Chakrabarty, 447 U.S. at 310. In support of its position, Myriad cites several differences between the isolated DNA claimed in the patents and the native DNA found within human cells. None, however, establish the subject matter patentability of isolated *BRCA1/2* DNA.

The central premise of Myriad's argument that the claimed DNA is "markedly different" from DNA found in nature is the assertion that "[i]solated DNA molecules should be treated no differently than other chemical compounds for patent eligibility," Myriad Br. at 26, and that the alleged "difference in the structural and functional properties of isolated DNA" render the claimed DNA patentable subject matter, Myriad Sr. at 31.

Myriad's focus on the chemical nature of DNA, however, fails to acknowledge the unique characteristics of DNA that differentiate it from other chemical compounds. As Myriad's expert Dr. Joseph Straus observed: "Genes are of double nature: On the one hand, they are chemical substances or molecules. On the other hand, they are physical carriers of information, i.e., where the actual biological function of this information is coding for

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<sup>50</sup> The parties do not appear to dispute that isolated DNA claimed in the patents-in-suit are "useful" for purposes of § 101.

proteins. Thus, inherently genes are multifunctional." Straus Decl. ¶ 20; see also *The Cell* at 98, 104 ("Today the idea that DNA carries genetic information in its long chain of nucleotides is 50 fundamental to biological thought that it is sometimes difficult to realize the enormous intellectual gap that it filled . . . DNA is relatively inert chemically."); Kevin Davies & Michael White, *Breakthrough: The Race to Find the Breast Cancer Gene 166* (1996) (noting that Myriad Genetics' April 1994 press release described itself as a "genetic information business"). This informational quality is unique among the chemical compounds found in our bodies, and it would be erroneous to view DNA as "no different [ ]" than other chemicals previously the subject of patents.<sup>51</sup>

Myriad's argument that all chemical compounds, such as the adrenaline at issue in Parke-Davis, necessarily conveys some information ignores the biological realities of DNA in comparison to other chemical compounds in the body. The information encoded in DNA is not information about

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<sup>51</sup> Myriad and many of the amici suggest that the invalidation of the patents-in-suit will result in the decimation of the biotechnology industry. See, e.g., Myriad Br. at 28-29 (suggesting that a finding that DNA is unpatentable subject matter will invalidate patents to important chemical compounds such as the anticancer drug Taxol (paclitaxel) and leave "little to nothing" of the United States biotechnology industry). The conclusions reached in this opinion concerning the subject matter patentability of isolated DNA, however, are based on the unique properties of DNA that distinguish it from all other chemicals and biological molecules found in nature. As a result, Myriad's predictions for the future of the U.S. biotechnology industry are unfounded.

its *own* molecular structure incidental to its biological function, as is the case with adrenaline or other chemicals found in the body. Rather, the information encoded by DNA reflects its primary biological function: directing the synthesis of *other* molecules in the body - namely, proteins, "biological molecules of enormous importance" which "catalyze biochemical reactions" and constitute the "major structural materials of the animal body." O'Farrell, 854 F.2d at 895-96. DNA, and in particular the ordering of its nucleotides, therefore serves as the physical embodiment of laws of nature – those that define the construction of the human body. Any "information" that may be embodied by adrenaline and similar molecules serves no comparable function, and none of the declarations submitted by Myriad support such a conclusion. Consequently, the use of simple analogies comparing DNA with chemical compounds previously the subject of patents cannot replace consideration of the distinctive characteristics of DNA.

In light of DNA's unique qualities as a physical embodiment of information, none of the structural and functional differences cited by Myriad between native *BRCA1/2* DNA and the isolated *BRCA1/2* DNA claimed in the patents-in-suit render the claimed DNA "markedly different." This conclusion is driven by the overriding importance of DNA's nucleotide sequence to both its natural biological function as well as the utility associated with DNA in its isolated form. The preservation of this defining characteristic of DNA in its native and isolated forms mandates the conclusion that the challenged composition claims are directed to unpatentable products of nature.

Myriad argues that the § 101 inquiry into the subject matter patentability of isolated DNA should focus exclusively on the differences alleged to exist between native and isolated DNA, rather than considering the similarities that exist between the two forms of DNA. See, e.g., Myriad Reply at 8-9 ("[T]he observation that isolated DNA and native DNA share this single property [i.e. the same protein coding sequences] is irrelevant to the critical issue of whether there are *differences* in their properties. It is the *differences* that are legally relevant to the novelty inquiry under Section 101, not the properties held in common." (emphasis in original)); Myriad Br. at 8. Setting aside the fact that considerations such as novelty are irrelevant for § 101 purposes, see Bergy, 126 596 F.2d at 960-61, Myriad offers no authorities supporting such an approach. To the contrary, the Supreme Court has held that "[i]n determining the eligibility of [a] claimed process for patent protection under § 101, [the] claims must be considered as a whole." Diehr, 450 U.S. at 188. Similarly, the Federal Circuit has expressly held that "[i]n the final analysis under § 101, the claimed invention, as a whole, must be evaluated for what it is." In re Grams, 888 F.2d 835, 839 (Fed. Cir. 1989) (quoting In re Abele, 684 F.2d 902, 907 (C.C.P.A. 1982)).

Were Myriad's approach the law, it is difficult to discern how any invention could fail the test. For example, the bacterial mixture in Funk Brothers was unquestionably different from any preexisting bacterial mixture; yet the Supreme Court recognized that a patent directed to the mixture, considered as a whole, did no more than patent "the handiwork of nature." 333 U. S. at 131. There will almost

inevitably be some identifiable differences between a claimed invention and a product of nature; the appropriate § 101 inquiry is whether, considering the claimed invention as a whole, it is sufficiently distinct in its fundamental characteristics from natural phenomena to possess the required "distinctive name, character, [and] use." Chakrabarty, 447 U.S. at 309-10.

None of Myriad's arguments establish the distinctive nature of the claimed DNA. Myriad's argument that association of chromosomal proteins with native DNA establishes the existence of "structural differences" between native and isolated DNA relies on an incorrect comparison between isolated DNA and *chromatin*, which are indeed different insofar as chromatin includes chromosomal proteins normally associated with DNA. The proper comparison is between the claimed isolated DNA and the corresponding native DNA, and the presence or absence of chromosomal proteins merely constitutes a difference in purity that cannot serve to establish subject matter patentability. See Gen. Elec., 28 F.2d at 642-43; Marden I, 47 F.2d at 957-58; Marden II, 47 F.2d at 1059.

Myriad also attempts to rely on its assertion that native DNA contains intron sequences that are absent in the claimed *BRCA1/2* DNA. However, some of the claims, such as claim 1 of the '282 patent, are directed broadly to DNA "coding for a BRCA1 polypeptide." Native *BRCA1* DNA, by definition, encodes the *BRCA1* protein; thus claim 1 of the '282 patent would cover purified *BRCA1* DNA possessing the exact same structure found in the human cell,

introns and all.<sup>52</sup> See also '492 patent, claim 1 (similarly claiming isolated DNA "coding for a BRCA2 polypeptide"). In addition, several of the composition claims are directed to isolated DNA containing as few as 15 nucleotides of the *BRCA1* coding sequence, see, e.g., '282 patent, claims 5 & 6, and at least some of these short DNA sequences will be found within a single exon of the native *BRCA1* gene sequence. See Adam Pavlicek, et al., Evolution of the Tumor Suppressor *BRCA1* Locus in Primates: Implications for Cancer Predisposition, 13 Human Molecular Genetics 2737, 2737 (2004) (noting *BRCA1* exons range from 37 to 3427 nucleotides in length). Therefore, for these small DNA fragments, the existence of introns in native *BRCA1* DNA is completely irrelevant to the question of structural differences when comparing these short DNA molecules with native *BRCA1* DNA.

More generally, the fact that the *BRCA1/2* cDNA molecules covered by the composition claims-in-suit contain only the protein coding exons and not the introns found in native DNA does not render these cDNAs and their native counterparts "*markedly different*." The splice variants represented by these cDNAs are the result of the naturally occurring splicing of pre-mRNA into mature mRNA. Therefore, not only are the coding sequences contained in the claimed DNA identical to those found in native DNA, the particular arrangement of those coding sequences is the result of the natural

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<sup>52</sup> To the extent a claim reads on unpatentable subject matter, the entire claim must be deemed invalid. See Titanium Metals Corp. of Am. v. Banner, 778 F.2d 775, 782 (Fed. Cir. 1985).



phenomena of RNA splicing. Finally, at least in the case of *BRCA1*, the claimed cDNA sequences are actually found in the human genome in the form of a naturally occurring pseudogene. See Mason Supp. Decl. ¶ 18.<sup>53</sup>

Myriad's argument that the functional differences between native and isolated DNA demonstrates that they are "markedly different" relies on the fact that isolated DNA may be used in applications for which native DNA is unsuitable, namely, in "molecular diagnostic tests (e.g., as probes, primers, templates for sequencing reactions), in biotechnological processes (e.g. production of pure *BRCA1* and *BRCA2* protein), and even in medical treatments (e.g. gene therapy)." Myriad Reply at 9; see also Myriad Br. at 30-32.

Isolated DNA's utility as a primer or a molecular probe (for example, for Southern blots) arises from its ability to "target and interact with other DNA molecules," that is, the ability of a given DNA molecule to bind exclusively to a specific DNA target sequence. Myriad Br. at 33;

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<sup>53</sup> Native DNA is sometimes methylated, but that methylation is preserved when the DNA is extracted and purified. Nussbaum Decl. ¶ 20. Since the claimed "isolated DNA" includes DNA extracted and purified from the body, methylation of DNA in the body does not distinguish native DNA from the claimed DNA. In addition, DNA in the body also exists in a non-methylated state, just as the synthesized DNA claimed in the patents would not be methylated. More importantly, while methylation affects the transcription of a gene in the body, it does not have any impact on the genetic information contained within the DNA. Indeed, DNA is demethylated and remethylated as it passes from the germline of one generation to the next. Nussbaum Decl. ¶ 28.

see Kay Decl. ¶ 138. Thus, for example, a 24 nucleotide segment of isolated *BRCA1* DNA can be used as a primer because it will bind only to its corresponding location in the *BRCA1* gene. However, the basis for this utility is the fact that the isolated DNA possesses the identical nucleotide sequence as the target DNA sequence,<sup>54</sup> thus allowing target specific hybridization between the DNA primer and the portion of the target DNA molecule possessing the corresponding sequence. Kay Decl. ¶¶ 135-36, 138. In contrast, another 24 nucleotide segment of DNA possessing the same nucleotide composition but a different nucleotide sequence would not have the same utility because it would be unable to hybridize to the proper location in the *BRCA1* gene.<sup>55</sup> Indeed, Myriad implicitly acknowledges this fact when it states that the usefulness of isolated DNA molecules "is based on their ability to target and interact with other DNA molecules, which is a function of *their own individual structure and chemistry.*" Myriad Br. at 33 (emphasis added). Therefore, the cited utility of the isolated DNA as a primer or probe is primarily a function of the nucleotide sequence identity between native and isolated *BRCA1/2* DNA.

Similarly, the utility of isolated DNA as a sequencing target relies on the preservation of native DNA's nucleotide sequence. Indeed, one need look no further than Myriad's BRACAnalysis testing, which

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<sup>54</sup> To be precise, the isolated single-stranded DNA molecule utilized as a primer or probe has the identical sequence as the complementary DNA strand to the DNA strand containing the target DNA sequence. The description in the text is meant to serve as a short-hand description of this relationship.

<sup>55</sup> The same reasoning applies with respect to the use of isolated DNA as a probe. Kay Decl. ¶¶ 135-36.

relies on the sequencing of isolated DNA (i.e. the PCR amplified exons of *BRCA1/2*), to determine the sequence of the corresponding DNA coding sequences found in the cell. The entire premise behind Myriad's genetic testing is that the claimed isolated DNA retains, in all relevant respects, the identical nucleotide sequence found in native DNA. The use of isolated *BRCA1/2* DNA in the production of *BRCA1/2* proteins or in gene therapy also relies on the identity between the native DNA sequences and the sequences contained in the isolated DNA molecule. Were the isolated *BRCA1/2* sequences different in any significant way, the entire point of their use - the production of *BRCA1/2* proteins - would be undermined.

While the absence of proteins and other nucleotide sequences is currently required for DNA to be useful for the cited purposes, the purification of native DNA does not alter its essential characteristic – its nucleotide sequence that is defined by nature and central to both its biological function within the cell and its utility as a research tool in the lab. The requirement that the DNA used be "isolated" is ultimately a technological limitation to the use of DNA in this fashion, and a time may come when the use of DNA for molecular and diagnostic purposes may not require such purification. The nucleotide sequence, however, is the defining characteristic of the isolated DNA that will always be required to provide the sequence-specific targeting and protein coding ability that allows isolated DNA to be used for the various applications cited by Myriad. For these reasons, the use of isolated DNA for the various purposes cited by Myriad does not establish the existence of differences "in kind" between native and

isolated DNA that would establish the subject matter patentability of what is otherwise a product of nature. See Am. Fruit Growers, 283 U.S. at 11.

Finally, the isolated *BRCA1/2* DNA claimed in Myriad's patents bears comparison to the bacterial mixture in Funk Brothers. In explaining why the claimed mixture of bacteria did not constitute an invention, the Court observed that the first part of the claimed invention was the "[d]iscovery of the fact that certain strains of each species of these bacteria can be mixed without harmful effect to the properties of either" which was "a discovery of their qualities of non-inhibition. It is no more than the discovery of some of the handiwork of nature and hence is not patentable." 33 U.S. at 131. The Court went on to observe that the second part of the claimed invention was [t]he aggregation of select strains of the several species into one product[, ] an application of that newly discovered natural principle. But however ingenious the discovery of that natural principle may have been, the application of it is hardly more than an advance in the packaging of the inoculants." Id.

According to Myriad, the invention claimed in its patents required the identification of the specific segments of chromosomes 17 and 13 that correlated with breast and ovarian cancer (*BRCA1* and *BRCA2*) followed by the isolation of these sequences away from other genomic DNA and cellular components. Myriad Reply at 6 ("By identifying these particular *BRCA* DNAs and isolating them away from other genomic DNA and other cellular components, the inventors created the claimed isolated *BRCA* DNA molecules."). Like the discovery of the mutual non-inhibition of the bacteria in Funk Brothers,

discovery of this important correlation was a discovery of the handiwork of nature - the natural effect of certain mutations in a particular segment of the human genome. And like the aggregation of bacteria in Funk Brothers, the isolation of the *BRCA1* and *BRCA2* DNA, while requiring technical skill and considerable labor, was simply the application of techniques well-known to those skilled in the art. See Parthasarathy Decl. ¶ 19. The identification of the *BRCA1* and *BRCA2* gene sequences is unquestionably a valuable scientific achievement for which Myriad deserves recognition, but that is not the same as concluding that it is something for which they are entitled to a patent. See Funk Bros., 33 U.S. at 132 ("[O]nce nature's secret of the non-inhibitive quality of certain strains of the [nitrogen-fixing bacteria] was discovered, the state of the art made the production of a mixed inoculant a simple step. Even though it may have been the product of skill, it certainly was not the product of invention.").

Because the claimed isolated DNA is not markedly different from native DNA as it exists in nature, it constitutes unpatentable subject matter under 35 U.S.C. § 101.

#### **D. The Method Claims are Invalid Under 35 U.S.C. § 101**

"Phenomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work." Benson, 409 U.S. at 67. However, "an application of a law of nature or mathematical formula to a known structure or process may well be deserving of patent

protection." Bilski, 545 F.3d at 953 (quoting Diehr, 450 U.S. at 187). In Bilski, the Federal Circuit set forth "the definitive test to determine whether a process claim is tailored narrowly enough to encompass only a particular application of a fundamental principle rather than pre-empt the principle itself." Id. at 954. Under this "machine or transformation" test, "[a] claimed process is surely patent-eligible under § 101 if: (1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing." Id. In addition, "the use of a specific machine or transformation of an article must impose meaningful limits on the claim's scope to impart patent-eligibility," and "the involvement of the machine or transformation in the claimed process must not merely be insignificant extra-solution activity." Id. at 961-62. In other words, the "transformation must be central to the purpose of the claimed process." Id. at 962. In particular, the Bilski court held that "adding a data-gathering step to an algorithm is insufficient to convert that algorithm into a patent-eligible process." Id. at 963 (citing Grams, 888 F.2d at 840; Meyer, 688 F.2d at 794). "A requirement simply that data inputs be gathered - without specifying how is a meaningless limit on a claim to an algorithm because every algorithm inherently require the gathering of data inputs." Id. (citing Grams, 888 F.2d at 839-40). "Further, the inherent step of gathering data can also fairly be characterized as insignificant extra-solution activity." Id. (citing Flook, 437 U.S. at 590).

**1. The claims for "analyzing" and "comparing" DNA sequences are invalid under § 101**

Claim 1 of the '999 patent is directed to the process of "analyzing" a *BRCA1* sequence and noting whether or not the specified naturally-occurring mutations exist. The claimed process is not limited to any particular method of analysis and does not specify any further action beyond the act of "analyzing." Similarly, claim 1 of the '001, '441, and '857 patents as well as claim 2 of the '857 patents are directed to "comparing" two gene sequences to see if any differences exist and do not specify any limitations on the method of comparison.

Myriad argues that these method claims should not be viewed as mental processes because they incorporate a transformation step and therefore satisfy the "transformation" prong of the Bilski "machine or transformation" test. In support of its position, Myriad relies primarily on the Federal Circuit's holding in Prometheus, 581 F.3d 1336. There, the Federal Circuit considered a patent containing claims directed to methods for calibrating the proper dosage of thiopurine drugs by measuring metabolites in subjects having gastrointestinal disorders. Id. at 1343-50. The patentees had discovered a correlation between metabolite levels in a patient's blood and the therapeutic efficacy of a dose of the drug. Based on this correlation, the patentees claimed methods to optimize therapeutic efficiency while minimizing side effects by determining metabolite levels and identifying a need to adjust drug dosage upward or downward based on

the levels. Id. at 1339-40. A representative claim asserted by the patentee in Prometheus claimed:

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

(a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and

(b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder,

wherein the level of 6-thioguanine less than about 230 pmol per  $8 \times 10^8$  red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject

and

wherein the level of 6-thioguanine greater than about 400 pmol per  $8 \times 10^8$  red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

Id. at 1340.

In concluding that the claimed methods satisfied the requirements of § 101, the Federal Circuit held that the relevant transformation for purposes of the "machine or transformation" test was



the transformation of the human body as well as the chemical and physical changes of the drug's metabolites. Id. at 1346 (stating that "claims to methods of treatment," were "always transformative when a defined group of drugs is administered to the body to ameliorate the effects of an undesired condition". Because the transformative steps were central to the claimed treatment methods, they satisfied the "machine or transformation" test. Id. at 1346-47. The court went on to hold that the "determining" step alone was transformative and central to the claimed methods since "determining the levels of [the metabolites] 6-TG or 6-MMP in a subject necessarily involves a transformation, for those levels cannot be determined by mere inspection." Id. at 1347.

Myriad argues that just as the act of "determining" metabolite levels in Prometheus was found to involve the transformation of human blood, so too should "analyzing" or "comparing" *BRCA1/2* gene sequences be construed to incorporate physically transformative steps (i.e. the isolation and sequencing of DNA<sup>56</sup> ) that would satisfy the Bilski "machine or transformation" test. Myriad further asserts that these transformations are "central to the purpose of the claims," id. at 1347, because "Myriad's method claims each require the transformation of a tissue or blood sample in order to isolate the patient's DNA." Myriad Br. at 35.

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<sup>56</sup> The challenged method claims are also directed to analyzing and comparing RNA and cDNA sequences, but for purposes of this opinion, the discussion will be framed in terms of analyzing and comparing DNA sequences.

The claims in Prometheus, however, are distinguishable from the method claims in dispute here. In Prometheus, "determining metabolite levels in the clinical samples taken from patients" was found to be transformative because the act of "determining metabolite levels" was itself construed to include the extraction and measurement of metabolite concentrations, such as high pressure liquid chromatography. See Prometheus, 581 F.3d at 1347. Indeed, neither party in Prometheus disputed that "determining" metabolite levels in samples taken from patients was, in and of itself, transformative."<sup>57</sup>

In contrast, the language of the method claims-in-suit and the plain and ordinary meanings of the terms "analyzing" or "comparing" establish that the method claims-in-suit are directed only to the abstract mental processes of "comparing" or "analyzing" gene sequences. Although Myriad asserts that the challenged method claims are directed to comparing DNA molecules rather than DNA sequences, the language of the claims belies such an interpretation. While the purpose of the claimed method is, for example, to "detect a germline alteration in a BRCA1 gene," see '999 patent, col. 161: 17-18, the *method* actually claimed is "analyzing a *sequence* of a BRCA1 gene." '999 patent, col. 161: 20-21 (emphasis added); see also '001 patent, col. 144:2-17 ("A method . . . which comprises gene comparing a first sequence selected from the

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<sup>57</sup> The issue with respect to the "determining" step was not whether it was transformative, but whether that transformation was central to the claimed invention. Id.

group consisting of a BRCA1 gene from said tumor sample with a second sequence selected from the group consisting of BRCA1 gene from a nontumor sample . . . wherein a difference in the sequence of the BRCA1 gene . . . indicates a somatic alteration in the BRCA1 gene."); '857 patent, col. 169:40-45 ("A method . . . which comprises comparing the nucleotide sequence of the suspected mutant BRCA2 allele with the wild-type BRCA2 nucleotide sequence . . .").

Similarly, the inclusion of the phrases "from a human subject" or "from a nontumor sample" in the claims serve only to specify the identity of the DNA or RNA sequence to be "analyzed" or "compared," i.e., from a human sample as opposed to an animal sample or cell culture, and do not, as Myriad argues, establish that the claims should be read to include the physical transformations associated with obtaining DNA from those sources.<sup>58</sup> In addition, the passages from the '999 specification cited by Myriad describing the process by which DNA sequences are obtained cannot serve to redefine the scope of the

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<sup>58</sup> Whether acts are "transformative" in the context of the "machine or transformation" test for process claims is distinct from the question of whether those acts would render the resulting product patentable subject matter. See, e.g., *Am. Wood-Paper*, 90 U.S. (23 Wall.) at 593-94 (noting that a party may be entitled to a patent on a process for purifying a natural product but not the final product itself if the final product is not different "in kind" from the natural product); *Merz*, 97 F.2d at 601 (same). Therefore the description of DNA purification and sequencing as "transformative acts" in the context of the challenged process claims is not inconsistent with the conclusion that the isolated DNAs claimed in the challenged patents constitute unpatentable subject matter.

challenged claims without violating the prohibition against importing claim limitations from the specification. See Phillips, 415 F.3d at 1320.

By the same token, the transformative steps associated with isolating and sequencing DNA described in the unchallenged dependent claims cannot be used to establish that the challenged claims include transformative events. To do so would violate the doctrine of claim differentiation, which presumes that "different words or phrases used in separate claims . . . indicate that the claims have different meanings and scope." Karlin Tech., Inc. v. Surgical Dynamics, Inc., 177 F.3d 968, 972 (Fed. Cir. 1999). Because claim differentiation "prevents the narrowing of broad claims by reading into them the limitations of narrower claims," Clearstream Wastewater Sys., Inc. v. Hydro-Action, Inc., 206 F.3d 1440, 1446 (Fed. Cir. 2000), the dependent claims serve only to illustrate the breadth of the challenged claims and reinforce the conclusion that what is claimed are mental processes independent of any physical transformations. See Phillips, 415 F.3d at 1314-15 ("[T]he presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim.").<sup>59</sup>

Myriad also argues that because isolating and sequencing DNA are required for "analyzing" or

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<sup>59</sup> The patent examiner's reasons for allowance, cited by Myriad, are precisely the legal conclusions concerning the patentability of the claimed methods being challenged by Plaintiffs. Moreover, the examiner's reasons of allowance cannot serve to define the scope of claim terms. See ACCO Brands, Inc. v. Micro Sec. Devices, Inc., 346 F.3d 1075, 1079-(Fed. Cir. 2003).

"comparing" DNA sequences, Prometheus allows those transformative acts to be incorporated into the process claims for purposes of the § 101 analysis. See Myriad Reply at 12. Myriad thus seeks to rely on transformations not actually claimed by the method claims-in-suit to satisfy the Bilski "machine or transformation" test. Neither Prometheus nor any other authority supports such an expansive approach to the application of this test. Prometheus held only that the term "determining," as used in the claims at issue, referred to acts that included manipulations that satisfied the "machine or transformation" test. Id. Nowhere did Prometheus suggest that preparatory physical transformations required for the performance of, but not included in, claims directed to mental processes should be incorporated into the claim for purposes of the § 101 analysis. Not only would such an approach be inconsistent with the prohibition on the importation of claim limitations from the specification, it would effectively vitiate the limitations to claiming mental processes provided by the "machine or transformation" test since "to use virtually any natural phenomenon for virtually any useful purpose could well involve the use of empirical information obtained through an unpatented means that might have involved transforming matter." Metabolite Labs., 548 U.S. at 136 (Breyer, J., dissenting). Therefore the preparatory transformations relating to obtaining DNA sequences cannot be relied on to satisfy the requirements of § 101.

Even if the challenged method claims were read to include the transformations associated with isolating and sequencing human DNA, these transformations would constitute no more than

"data-gathering step[s]" that are not "central to the purpose of the claimed process." Bilski, 545 F.3d at 962-63. In Grams, the Federal Circuit considered a patent directed to a method of diagnosing an abnormal condition in an individual. The claimed method consisted of two steps: (1) "performance of Clinical laboratory tests on an individual to obtain data for the parameters," and (2) "analyz[ing] that data to ascertain the existence and identity of an abnormality . . . ." 888 F.2d at 837. Concluding that the essence of what was claimed was the mathematical algorithm for analyzing the clinical data, and that the sole physical process - laboratory testing - was merely data-gathering to obtain clinical data, the court held the patent invalid under § 101 for claiming a mathematic algorithm. Id. at 840.

The method claims-in-suit present a closely analogous situation. The essence of what is claimed is the identification of a predisposition to breast cancer based on "analyzing" or "comparing" *BRCA1/2* gene sequences. See, e.g., '857 patent, claim 2 ("A method for diagnosing a predisposition for breast cancer in a human subject which comprises comparing the [BRCA2 gene sequence] from said subject with the [ ] sequence of the wild-type BRCA2 gene . . ."). As in Grams, isolation and sequencing of DNA from a human sample, even if incorporated into the method claims-in-suit, would represent nothing more than data-gathering steps to obtain the DNA sequence information on which to perform the claimed comparison or analysis. Moreover, in the absence of a specified method for isolating and sequencing DNA, "[a] requirement simply that data inputs be gathered - without specifying how - is a meaningless limit on a claim to an algorithm because

every algorithm inherently requires the gathering of data inputs." Bilski, 545 F.3d at 963 (citing Grain, 888 F.2d at 839-40). Consequently, even if the method claims-in-suit were construed to include the physical transformations associated with isolating and sequencing DNA, they would still fail the "machine or transformation" test under § 101 for subject matter patentability.

## **2. The Claim for "Comparing" the growth rate of Cells is invalid under § 101**

Claim 20 of the '282 patent is directed to "comparing" the growth rates of cells in the presence or absence of a potential cancer therapeutic. Specifically, the claim recites a method for identifying potential cancer therapeutics by utilizing cells into which an altered *BRCA1* gene known to cause cancer has been inserted. Thus modified to mimic cancerous cells in the body, these cells are then grown in either the presence or absence of a potential cancer therapeutic, and the growth rates of the cells are compared to determine the effect of the potential therapeutic.

Unlike the method claims directed to "analyzing" or "comparing" DNA sequences, claim 20 arguably recites certain transformative steps, such as the administration of the test compound.<sup>60</sup>

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<sup>60</sup> It is questionable whether the two transformations cited by Myriad are relevant transformations for purposes of the § 101 inquiry. Under Prometheus, the administration of a test compound is transformative only if it effects a change in cell growth. See Prometheus, 581 F.3d at 1346 (finding "administering" of a drug transformative since it resulted in changes to both the patient and the drug metabolites). If the test compound had no effect on the cells, it is unclear whether

However, the essence of the claim, when considered in its entirety, is the act of comparing cell growth rates and concluding that "a slower growth of said host cell in the presence of said compound is indicative of a cancer therapeutic." '282 patent, col. 156: 25-27.

This claimed "process" is, in fact, the scientific method itself, and claim 20 seeks to patent a basic scientific principle: that a slower rate of cell growth in the presence of a compound indicates that the compound may be a cancer therapeutic. The recited transformative steps, as in Grams, represent nothing more than preparatory, data-gathering steps to obtain growth rate information and do not render the claimed mental process patentable under § 101. See Grams, 888 F.2d at 840 ("The presence of a

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there would be any basis to view its administration as working a "transformation" since there would be no transformation with respect to the cells (i.e. there was no change in their growth rate) and there would also presumably be no transformation with respect to the test drug (i.e, it was not metabolized).

The other alleged "transformation" cited by Myriad is the insertion of DNA into cells to create the "transformed eukaryotic cell" for treatment with the test compound. Kay Decl. ¶ 57. Even more that its expansive interpretation of the method claims for analyzing DNA sequences for § 101 purposes, Myriad's attempt to rely on transformations associated with the creation of a starting product for its claimed process is unsupported by the law and demonstrates the limitlessness of Myriad's interpretation of Prometheus and the "machine or transformation" test.



physical step in the claim to derive data for the algorithm will not render the claim statutory").<sup>61</sup>

### **E. The Constitutional Claims Against the USPTO Are Dismissed**

As determined above, the patents issued by the USPTO are directed to a law of nature and were therefore improperly granted. The doctrine of constitutional avoidance, which states that courts should not reach unnecessary constitutional questions, thereby becomes applicable. See, e.g., Allstate Ins. Co. v. Serio, 261 F.3d 143, 149-50 (2d Cir. 2001) ("It is axiomatic that the federal courts should, where possible, avoid reaching constitutional questions.") (citing Sector Motor Serv., Inc. v. McLaughlin, 323 U.S. 101 (1944) ("If there is one doctrine more deeply rooted than any other in the process of constitutional adjudication, it is that we ought not to pass on questions of constitutionality . . . unless such adjudication is unavoidable")); see also Ashwander v. TVA, 297 U.S. 288,347 (1936) (Brandeis, J., concurring) ("[I]f a case can be decided on either of two grounds, one involving a constitutional question, the other a question of statutory construction or general law, the Court will decide only the latter."). This doctrine bears on the consideration of Plaintiffs' claims that the USPTO's policy permitting the grant of the Myriad patents violates Article I, Section 8, Clause 8 and the First Amendment of the Constitution.

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<sup>61</sup> Because Plaintiffs' motion for summary judgment with respect to its claims against Myriad is granted on the basis of 35 U.S.C. § 101, its Constitutional claims need not be addressed.

The Plaintiffs have not addressed these authorities and have contended that "the doctrine of constitutional avoidance is inapplicable" because the invalidation of Myriad's claims pursuant to 35 U.S.C. § 101 will not necessarily invalidate the USPTO's policy [in granting the patents]." Pl. Reply at 43. However, a decision by the Federal Circuit or the Supreme Court affirming the holding set forth above would apply to both the issued patents as well as patent applications and would be binding on all patent holders and applicants, as well as the USPTO. See Koninklijke Philips Electronics N.V. v. Cardiac Science, 590 F.3d 1326, 1337 (Fed. Cir. 2010) ("We remind the district court and the [USPTO] Board that they must follow judicial precedent. . . ."). Thus, to the extent the USPTO examination policies are inconsistent with a final, binding ruling, the USPTO would conform its examination policies to avoid issuing patents directed to isolated DNA or the comparison or analysis of DNA sequences. See USPTO Reply Memo, at 4.

With the holding that the patents are invalid, the Plaintiffs have received the relief sought in the Complaint and the doctrine of constitutional avoidance precludes this Court from reaching the constitutional claims against the USPTO. See Allstate Ins. Co. v. Serio, 261 F.3d 143, 149-50 (2d Cir. 2001); USPTO Br. at 4. Plaintiffs' claims for constitutional violations against the USPTO are therefore dismissed without prejudice.

## **VIII. CONCLUSION**

For the reasons set forth above, Plaintiffs' motion for summary judgment is granted in part, Myriad's motion for summary judgment is denied, the USPTO's motion for judgment on the pleadings is granted, and the claims-in-suit are declared invalid pursuant to 35 U.S.C. § 101.

Submit judgment on notice.

It is so ordered.

**New York, N.Y.**

**April 2, 2010**

**Robert W. Sweet**  
**U.S.D.J.**

UNITED STATES DISTRICT COURT  
SOUTHERN DISTRICT OF NEW YORK

ASSOCIATION FOR MOLECULAR PATHOLOGY, ET. AL.,      09 Civ. 4515  
*Plaintiffs,*      OPINION

--against--

UNITED STATES PATENT AND  
TRADEMARK OFFICE, ET AL.,  
*Defendants.*

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## TABLE OF CONTENTS

I.	PRIOR PROCEEDINGS.....	243a
II.	THE COMPLAINT AND THE AFFIDAVITS .....	244a
	A. The Plaintiffs.....	244a
	B. The Defendants.....	257a
	C. <i>BRCA1</i> and <i>BRCA2</i> .....	258a
	D. Enforcement of the Patents-in-Suit .....	262a
III.	THE PARTIES' CONTENTIONS .....	265a
IV.	THERE IS SUBJECT MATTER JURISDICTION OVER THE CLAIMS AGAINST THE USPTO.....	269a
V.	THERE IS STANDING .....	273a
	A. The Plaintiffs Have Standing to Sue the USPTO for Constitutional Violations.....	273a
	B. The Plaintiffs Have Established Standing to Sue Myriad and the Directors .....	277a
	1. Affirmative Acts by the Defendants .....	281a
	2. Meaningful Preparations for Infringing Action .....	288a
VI.	JURISDICTION EXISTS OVER THE DIRECTORS .....	293a
VII.	THE ALLEGATIONS OF CONSTITUTIONAL VIOLATIONS ARE ADEQUATE.....	303a
VIII.	CONCLUSION.....	306a

**Sweet, D.J.**

In this action the Plaintiffs challenge certain patent claims granted to defendants Myriad Genetics and the Director<sup>1</sup> of the University of Utah Research Foundation ("UURF") (collectively, "Myriad") by defendant United States Patent and Trademark Office ("USPTO") (collectively, the "Defendants"). The identified patent claims (the "patents-in-suit" or the "claims-in-suit") cover two human genes known as *BRCA1* and *BRCA2* (collectively, "*BRCA1/2*" or the "*BRCA* genes"). Compl. ¶¶ 37, 55-80. The claims-in-suit also cover certain mutations in those genes, the mental act of comparing different forms of the *BRCA* genes, and the correlations between certain genetic mutations and an increased risk of breast and/or ovarian cancer. Id.

The Plaintiffs allege that these patents are unlawful under each of (1) the Patent Act, 35 U.S.C. § 101 (1952), (2) Article I, Section 8, Clause 8 of the United States Constitution, and (3) the First and Fourteenth Amendments because they cover products of nature, laws of nature and/or natural phenomena, and abstract ideas or basic human knowledge or thought. Compl. ¶ 102.

The Defendants now move, pursuant to Rules 12 (b) (1), (b) (2), and (b) (6), Fed. R. Civ. P., to dismiss Plaintiffs' complaint (the "Complaint") for lack of subject matter jurisdiction, lack of personal jurisdiction, and failure to state a claim.

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<sup>1</sup> Defendants Lorris Betz, Roger Boyer, Jack Brittan, Arnold B. Combe, Raymond Gesteland, James U. Jenson, John Kendall Morris, Thomas Parks, David W. Pershing, and Michael K. Young. For purposes of this opinion, they will be referred to as the "Directors" or the "UURF Directors."

This action is unique in the identity of the parties, the scope and significance of the issues presented, and the consequences of the remedy sought. The Plaintiffs in this action comprise a broad range of parties, including researchers, genetic counselors, medical and/or advocacy organizations, and women facing the threat of breast cancer or who are in the midst of their struggle with the illness. The challenges to the patents-in-suit raise questions of difficult legal dimensions concerning constitutional protections over the information that serves as our genetic identities and the need to adopt policies that promote scientific innovation in biomedical research. The widespread use of gene sequence information as the foundation for biomedical research means that resolution of these issues will have far-reaching implications, not only for gene-based health care and the health of millions of women facing the specter of breast cancer, but also for the future course of biomedical research.

Based on the conclusions set forth below, the motions to dismiss are denied.

## **I. PRIOR PROCEEDINGS**

The Complaint in this action was filed on May 12, 2009.

The Plaintiffs moved for summary judgment pursuant to Rule 56, Fed. R. Civ. P., on August 26, 2009.

Defendants' motion to dismiss and Plaintiffs' motion for jurisdictional discovery<sup>2</sup> were heard and

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<sup>2</sup> Defendants' motion to dismiss incorporates, by reference, challenges to the exercise of personal jurisdiction over the



marked fully submitted on September 30, 2009, and Plaintiffs' motion for summary judgment was stayed pending resolution of Defendants' motion to dismiss.

## **II. THE COMPLAINT AND THE AFFIDAVITS**

The following allegations, taken from the Complaint and the affidavits submitted by the parties in connection with Defendants' motion to dismiss, are accepted as true for the purpose of resolving the motions to dismiss.

### **A. The Plaintiffs**

Plaintiff the Association for Molecular Pathology ("AMP") is a not-for-profit scientific society dedicated to the advancement, practice, and science of clinical molecular laboratory medicine and translational research based on the applications of genomics and proteomics. AMP members participate in basic and translational research aimed at broadening the understanding of gene/protein structure and function, disease processes, and molecular diagnostics, and provide clinical medical services for patients, including diagnosis of breast cancer. Compl. ¶ 7.

Plaintiff the American College of Medical Genetics ("ACMG") is a non-profit organization of clinical and laboratory geneticists seeking to improve health through the practice of medical genetics.

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Directors raised in Defendants' opposition to Plaintiffs' motion for jurisdictional discovery. Consequently, the arguments concerning personal jurisdiction set forth by the parties in connection with Plaintiffs' motion for jurisdictional discovery will be considered here.

AMCG strives to 1) promote excellence in medical genetics practice and the integration of translational research into practice; 2) promote and provide medical genetics education; 3) increase access to medical genetics services and integrate genetics into patient care; and 4) advocate for and represent providers of medical genetics services and their patients. Compl. ¶ 8.

Plaintiff the American Society for Clinical Pathology ("ASCP") is the largest and oldest organization representing pathologists and laboratory professionals. ASCP members design and interpret the tests that detect disease, predict outcome, and determine the appropriate therapy for the patient. Compl. ¶ 9.

Plaintiff the College of American Pathologists ("CAP") is a national medical society representing board-certified pathologists and pathologists in training who practice anatomic pathology and laboratory medicine worldwide. The CAP is an advocate of high-quality and cost-effective medical care. Compl. ¶ 10.

The affidavits submitted by the Plaintiffs state that members of AMP, ACMG, ASCP, and CAP are ready, willing, and able to engage in research and clinical practice involving the *BRCA1/2* genes if the patents-in-suit were to be invalidated. For example, Madhuri Hegde, Ph.D. ("Dr. Hegde"), is a member of AMP and ACMG and serves as an Associate Professor in the Department of Human Genetics at Emory University School of Medicine, Adjunct Assistant Professor at the University of Texas M.D. Anderson Cancer Center, and Senior Laboratory Director at the Emory Genetics Laboratory. He

currently conducts research on human genes in addition to supervising one of the largest and most technologically advanced clinical laboratories in the country. The laboratory sequences and analyzes approximately sixty genes every day for sequence variants and their clinical significance. Dr. Hegde has personally sequenced the *BRCA1/2* genes while at the Auckland Hospital in New Zealand, and his lab would begin sequencing and analyzing *BRCA1/2* genes for clinically significant variants within weeks if the patents-in-suit were invalidated. Hegde Decl. ¶¶ 3-12.<sup>3</sup>

Roger Hubbard, Ph.D. ("Dr. Hubbard"), a member of ASCP, is the President and Chief Executive Officer, Molecular Pathology Laboratory Network, Inc. ("MPLN"), and an Adjunct Associate Professor at the University of Tennessee Medical Center/Knoxville, Department of Pathology. MPLN offers molecular diagnostics and cytogenetic testing services that target hematological malignancies, oncology, and medical diseases. MPLN currently sequences genes and has the personnel, experience and equipment to analyze the *BRCA* genes. They currently receive inquiries every few weeks from a hospital or laboratory asking them to analyze the *BRCA* genes, but they do not do so as solely because of the patents-in-suit. If the patents-in-suit were to be invalidated, Dr. Hubbard and MPLN would immediately consider doing testing in their laboratory. Hubbard ¶¶ 1-4, 6, 8-9.

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<sup>3</sup> For purposes of this opinion, references to the parties' declarations will be in the format [Declarant Name] ¶ [paragraph number].

Jeffrey Kant, M.D., Ph.D. ("Dr. Kant"), a member of AMP and CAP, is the Director of the Division of Molecular Diagnostics in the Department of Pathology at the University of Pittsburgh Medical Center and a Professor Pathology and Human Genetics at the University of Pittsburgh. As part of his responsibilities, he supervises a clinical laboratory that analyzes human genes and is experienced in sequencing and analyzing genes for inherited diseases. His laboratory currently tests nine genes, including five related to hereditary predisposition for cancer. His laboratory was asked in the late 1990s to engage in the sequencing and analysis of *BRCA 1/2*, but declined to do so because of the patents-in-suit. If the patents-in-suit were to be invalidated, Dr. Kant would immediately consider doing full gene testing for the *BRCA* genes. Kant ¶¶ 1-2, 4-6.

Plaintiff Haig Kazazian, Jr., M.D. ("Dr. Kazazian"), is the Seymour Gray Professor of Molecular Medicine in Genetics in the Department of Genetics at the University of Pennsylvania School of Medicine. He is the previous chair of the Department. Kazazian ¶ 1, 2. Plaintiff Arupa Ganguly, Ph.D. ("Dr. Ganguly"), is an Associate Professor in the Department of Genetics at the Hospital of the University of Pennsylvania. Ganguly ¶ 1. Drs. Kazazian and Ganguly have served as co-Directors of the University of Pennsylvania Genetic Diagnostic Laboratory ("GDL") since 1995. Kazazian ¶ 3; Ganguly ¶ 2. The GDL provides state-of-the-art DNA-based diagnostic testing for a variety of genetic conditions and diseases, as well as prenatal and predictive testing and genetic counseling services. Kazazian ¶ 3.

Starting in 1996, the GDL was providing *BRCA1* genetic testing services to approximately 500 women per year. *Id.* ¶ 4. By late 1996, the GDL had designed and provided a similar test for the *BRCA2* gene. *Id.* Following Dr. Kazazian's and the University of Pennsylvania's receipt of a series of cease-and-desist letters from Myriad in 1998 and 1999, described *infra*, the GDL ceased its *BRCA1/2* genetic testing services. *Id.* ¶ 5-7; Ganguly ¶ 4-10. If the patents-in-suit were to be invalidated, the GDL possesses the technological capability necessary to begin performing *BRCA1/2* testing again within a matter of weeks, and Drs. Ganguly and Kazazian have the desire to consider doing so. Kazazian ¶ 11; Ganguly ¶ 14.

Plaintiff Wendy Chung, M.D., Ph.D. ("Dr. Chung"), is the Herbert Irving Professor of Pediatrics and Medicine in the Division of Molecular Genetics at Columbia University and is the Director of Clinical Genetics and Director of Clinical Oncogenetics. She is also a member of ACMG. Dr. Chung is a human geneticist whose current research includes research on the *BRCA* genes, for which she has received grants of over \$1 million. Dr. Chung is a co-investigator of the Breast Cancer Family Registry, funded by the National Cancer Institute of the National Institute of Health. The goal of the Registry is to collect and study families with multiple cases of breast and/or ovarian cancer and to study genetic and environmental factors influencing cancer susceptibility and clinical outcomes. As part of her research, Dr. Chung's lab sequences human genes, including the *BRCA1/2* genes of research subjects to determine whether there exist alterations in the gene sequences and investigate their clinical

significance. Because of the patents-in-suit, Dr. Chung does not tell the research subjects in her studies the results of the analysis of their *BRCA* genes. Dr. Chung's clinical diagnostic laboratory at Columbia University sends samples to Myriad for any analysis of *BRCA1/2* in order to tell the subjects the results and use the results clinically. It does not do *BRCA* testing on its own because of the patents-in-suit. If the patents-in-suit were to be invalidated, Dr. Chung would begin clinical testing of *BRCA1/2* immediately. Her clinical laboratory has the personnel, expertise to do various forms of *BRCA1/2* sequencing and would be able to offer genetic testing that is more comprehensive than the testing currently offered by Myriad. Chung Decl. ¶ 1, 4, 8-9, 11-14, 16-18.

Plaintiff Harry Ostrer, M.D. ("Dr. Ostrer"), is a Professor of Pediatrics, Pathology and Medicine, Director of the Human Genetics Program in the Department of Pediatrics at the New York University ("NYU") Langone Medical Center, and a member of ACMG. As Director of the Human Genetics Program, Dr. Ostrer helped establish the Molecular Genetics Laboratory ("MGL") at the NYU Langone Medical Center, one of the largest academic genetic testing laboratories in the United States. Dr. Ostrer's work through the MGL has focused on understanding the genetic basis of development and disease, including genetic susceptibility to breast cancer. Dr. Ostrer is actively engaged in identifying genes that convey the risk of breast cancer and may mitigate the effects of mutations in *BRCA1/2*. His laboratory has the ability to evaluate *BRCA1/2* gene sequences, including in custom-designed tests that may be more cost-effective than Myriad's current

offerings. However, because of Myriad's assertions of the patents-in-suit, Dr. Ostrer sends all of his patient samples to Myriad for *BRCA1/2* analysis. If the patents-in-suit were to be invalidated, Dr. Ostrer would immediately begin clinical sequencing of the *BRCA1/2* genes. His laboratory possesses all of the personnel, expertise, and facilities necessary to do various types of sequencing of the *BRCA1/2* genes, including full sequencing, detection of deletions and rearrangements, and searches for large rearrangements that Myriad currently does not offer as a service. If the patents-in-suit were to be invalidated, Dr. Ostrer would also tell patients involved in his current research program the results of their *BRCA1/2*-related genetic screening. Ostrer Decl. ¶¶ 1-5; 8-10.

Plaintiff David Ledbetter, Ph. D. ("Dr. Ledbetter"), is the Robert W. Woodruff Professor of Human Genetics and Director of the Division of Medical Genetics at the Emory University School of Medicine. He is also a diplomat of the American Board of Medical Genetics (Clinical Cytogenetics) and a Founding Fellow of the ACMG. He has previously served as the Director of the Kleberg Cytogenetics Laboratory at Baylor College of Medicine and in the Senior Executive Service of the federal government as Branch Chief of the Diagnostic Development Branch at the National Center for Human Genome Research (now the National Human Genome Research Institute). He was also the founding Chair of the Department of Human Genetics at the University of Chicago where he held the Marjorie I. and Bernard A. Mitchell Professor of Human Genetics. As Director of the Division of Medical Genetics, Dr. Ledbetter is

responsible for very large genetic testing laboratories at the Emory University School of Medicine which provide clinical testing services for patients and families with genetic diseases, including biochemical, cytogenetics, and molecular genetics testing. The genetic testing laboratory utilizes state-of-the-art technology and has the personnel, experience, expertise, and facilities necessary to conduct comprehensive mutation analysis (including full gene sequencing and high-resolution deletion/duplication analysis) of any human gene, including the *BRCA* genes. If the patents-in-suit were to be invalidated, Dr. Ledbetter would begin offering comprehensive *BRCA1/2* testing and would likely have an operational program within one month's time. Ledbetter Decl. ¶¶1, 3-4, 8-10, 18.

Plaintiff Stephen T. Warren, Ph.D. ("Dr. Warren"), is the William Patterson Timmie Professor of Human Genetics and Professor of Biochemistry and Professor of Pediatrics at Emory University as well as a past President of the American Society of Human Genetics. He personally supervises genetic research at Emory University and is also responsible for the Emory Genetics Laboratory. Dr. Warren is ready, willing, and able to being *BRCA1/2* genetic testing if the patents-in-suit were to be invalidated. Compl. ¶ 17.

Plaintiff Ellen Matloff, M. S. ("Ms. Matloff"), is Director of the Yale Cancer Genetic Counseling Program and a Research Scientist in the Department of Genetics at the Yale University School of Medicine. Ms. Matloff advises women on the desirability of obtaining an analysis of their genes to determine if the women have the genetic mutations



that correlate with an increased risk of breast and/or ovarian cancer. Ms. Matloff also arranges for such genetic analysis and advises women on the significance of the results. As a result of the patents-in-suit, Ms. Matloff is currently required to utilize Myriad's testing services for analysis of *BRCA1/2*. If the patents-in-suit were to be invalidated, Ms. Matloff would immediately begin sending samples from women who are appropriate candidates for *BRCA* gene analysis to laboratories other than Myriad, such as the laboratories of Drs. Chung, Ledbetter, and Ostrer, for gene sequencing as well as large rearrangement testing. Matloff Decl. ¶¶ 1, 4, 10-15.

Plaintiff Elsa W. Reich, M.S. ("Ms. Reich"), is a Professor of Pediatrics in the Human Genetics Program at the NYU School of Medicine Department of Pediatrics, where she has served as a genetic counselor since 1974. Ms. Reich provides risk assessment and information to women and men about their risk of having a heritable form of cancer and advises them on the potential utility of obtaining an analysis of their genes to determine if they have genetic mutations that correlate with an increased risk of developing breast cancer, ovarian cancer, or other malignancies. The genes of most interest to be analyzed are the *BRCA1/2* genes. If a patient requests this testing, Ms. Reich sends samples to Myriad and explains the results to the patient. If the patents-in-suit were to be invalidated, Ms. Reich would immediately begin sending samples, including ones previously tested by Myriad, to other laboratories, such as those of Drs. Chung, Ostrer, and Ledbetter for *BRCA1/2* testing. Reich Decl. ¶¶ 1-3, 7-9, 14-15.

Plaintiff Breast Cancer Action ("BCA") is a national organization of approximately 30,000 members based in San Francisco, California that works with researchers to encourage innovative approaches to unresolved issues in breast cancer. Members of Breast Cancer Action have had their *BRCA* genes analyzed or sought analysis to determine if they have genetic mutations that correlate with an increased risk of breast and/or ovarian cancer. In some instances, members have been unable to obtain testing at a laboratory of their choice or choose to be tested at a laboratory that would share data with researchers. In other instances, members have been unable to obtain genetic testing because of the high cost of the test. Members have also received ambiguous genetic test results from Myriad that show they have a genetic variant of uncertain significance, but have been unable to obtaining testing from a second laboratory. BCA staff and volunteers also provide information to members of the public about genetic analysis but have been unable to refer patients to labs other than Myriad. If the patents-in-suit were to be invalidated, BCA and its members would immediately begin utilizing other alternatives to Myriad's *BRCA1/2* testing services in addition to publicizing the existence of such alternatives, such as the laboratories of Drs. Chung and Ostrer. Compl. ¶ 19; Brenner Decl. ¶¶ 2-3, 7, 9.

Plaintiff Boston Women's Health Book Collective ("BWHBC"), doing business as Our Bodies Ourselves ("OBOS"), is a women's health education, advocacy, and consulting organization that seeks to educate women about health, sexuality, and reproduction. OBOS staff provides information to

members of the public about genetic analysis, but does not, as a result of the patents-in-suit, refer their readers to or publicize genetic testing services at laboratories other than Myriad. BWHC also does not advocate for researchers and clinicians to perform *BRCA* testing as a result of the patents-in-suit. If the patents-in-suit were to be invalidated, BWHC and OBOS are ready, willing, and able to provide information about testing options offered by labs other than Myriad and would directly benefit from any increased research on *BRCA1/2*. Compl. ¶ 20; Norsigian Decl. ¶¶ 2-3.

Plaintiff Lisbeth Ceriani ("Ms. Ceriani") is a 43-year-old single mother who was diagnosed with cancer in both breasts in May 2008. Ms. Ceriani's oncologist and genetic counselor recommended that she obtain *BRCA1/2* genetic testing to determine whether she should consider further surgery in order to reduce her risk of ovarian cancer. Because Myriad refused to accept Ms. Ceriani's insurance, however, her blood samples would not be processed unless she paid for the service out-of-pocket. Ms. Ceriani is unable to pay the full cost out-of-pocket and, to date, has not been tested and cannot determine her best medical course of action. Were Ms. Ceriani able to obtain genetic testing from Myriad, she would also want verification of the results of the *BRCA1/2* test before deciding whether to undergo removal of her ovaries. If the patents-in-suit were to be invalidated, Ms. Ceriani would pursue *BRCA1/2* genetic testing through laboratories other than Myriad, such as those of Drs. Chung and Ostrer. She would also seek verification of her *BRCA1/2* test results at a second lab. Ceriani Decl. ¶¶ 2-5, 7-11.

Plaintiff Runi Limary ("Ms. Limary") is a 32-year-old Asian-American woman who was diagnosed with aggressive breast cancer in November 2005. Following her diagnosis, she sought *BRCA1/2* genetic testing on the advice of her doctor. However, she was unable to be tested by Myriad until two years later, when she obtained insurance that provided coverage for the test. Her test results informed her that she possessed a "genetic variant of uncertain significance" in her *BRCA1* gene frequently identified in women of Asian descent and other racial minorities but whose significance as an indicator of predisposition to cancer was unclear. However, her test did not examine all known types of mutations in her *BRCA* genes, including known large rearrangements. Ms. Limary seeks additional resources for testing and research that could reveal the significance of her genetic variant, including whether it is correlated with an increased risk of breast or ovarian cancer, and could allow her to make an informed decision about her future medical treatment. If the patents-in-suit were to be invalidated, Ms. Limary would immediately pursue additional *BRCA1/2* genetic testing through other laboratories, such as those of Drs. Chung and Ostrer. Such testing would include additional analysis to determine the significance of her *BRCA1* variant of unknown significance. Limary Decl. ¶¶ 2-6, 8-9.

Plaintiff Genae Girard ("Ms. Girard") is a 39-year-old woman who was diagnosed with breast cancer in 2006. Shortly after her diagnosis, she obtained *BRCA1/2* genetic testing from Myriad and tested positive for a deleterious mutation on the *BRCA2* gene. She sought, but was unable to obtain a second opinion confirming the test result before

making any decisions concerning prophylactic bilateral breast surgery and ovarian surgery. IF the patents-in-suit were to be invalidated, Ms. Girard would immediately pursue *BRCA1/2* genetic testing through other laboratories, such as those of Drs. Chung and Ostrer. Girard Decl. ¶¶ 2-5, 10.

Plaintiff Patrice Fortune ("Ms. Fortune") is a 48-year-old woman who was diagnosed with breast cancer in February 2009. Because Ms. Fortune has a family history of breast cancer, her genetic counselor and oncologist advised her to seek *BRCA1/2* genetic testing. However, as a result of incomplete coverage for Myriad's test by Ms. Fortune's health insurance, Ms. Fortune would be required by Myriad to pay the full out-of-pocket cost for her genetic testing. Because Ms. Fortune currently works in unpaid positions while receiving treatment for her cancer, she cannot afford the cost of Myriad's genetic testing. If the patents-in-suit were to be invalidated, Ms. Fortune would immediately seek testing through other laboratories, such as those of Drs. Chung and Ostrer, in addition to seeking a second opinion by another lab before making any major decisions about her treatment. Fortune Decl. ¶¶ 2-5, 8.

Plaintiff Vicky Thomason ("Ms. Thomason") is a 52-year-old woman who was diagnosed with ovarian cancer in 2006. She obtained *BRCA1/2* genetic testing from Myriad in 2007 at the advice of her doctor and genetic counselor and was found to be negative for mutations covered by that test. However, in light of her family history of cancer, her genetic counselor advised her that she was an appropriate candidate for the additional *BRCA1/2* genetic testing offered by Myriad that looks for large

genetic rearrangements that are not detected by Myriad's standard genetic test. However, Ms. Thomason's insurance will not cover the entire cost of Myriad's additional test, and Ms. Thomason is unable to afford the extra cost. If the patents-in-suit were to be invalidated, Ms. Thomason would immediately seek *BRCA1/2* testing, including the large rearrangement testing that she currently cannot afford, through other laboratories, such as those of Drs. Chung and Ostrer. Thomason Decl. ¶¶ 2-6, 8, 10.

Plaintiff Kathleen Raker ("Ms. Raker") is a 42-year-old woman whose mother and maternal grandmother died from breast cancer. She obtained *BRCA1/2* genetic testing from Myriad in 2007 and was found to be negative for mutations covered by that test. However, her genetic counselor advised her that she could still face hereditary risks for breast cancer due to a mutation in her *BRCA* genes that could not be detected by Myriad's standard test, but might be detected by Myriad's test for large rearrangements. Ms. Raker is unable to afford the cost of Myriad's additional testing and, to date, has not received this testing. Without those results, she cannot determine the risk of cancer she or her children face. If the patents-in-suit were to be invalidated, Ms. Raker would immediately pursue *BRCA1/2* testing through other laboratories, such as those of Drs. Chung and Ostrer. Raker Decl. ¶¶ 2-3, 5-7, 8-9, 11-12.

## **B. The Defendants**

The USPTO is an agency of the Commerce Department of the United States. Compl. ¶ 27. The Plaintiffs assert only their claims' for constitutional

violations against the USPTO.

Myriad is a for-profit corporation located in Salt Lake City, Utah, doing business throughout the United States. Myriad Genetics is a co-owner of one of the patents-in-suit and holds the exclusive licenses for the remaining ones. It is currently the sole clinical provider of full sequencing of the BRCA genes in the United States. Compl. ¶ 28.

The Directors are directors of the UURF, a not-for-profit corporation located in Salt Lake City, Utah, that the Plaintiffs allege is operated, supervised, and/or controlled by the University of Utah. The UURF is an owner or part-owner of all of the patents-in-suit.<sup>4</sup> Compl. ¶ 29.

### **C. *BRCA1* and *BRCA2***

The human body is composed of cells. Contained in the nucleus of each cell are the genes that serve as the blueprints used by the body to create the proteins and gene products required for its function. Human genes are composed of unique combinations of four DNA<sup>5</sup> nucleotides (i.e., bases) referred to by the letters A, T, C, and G. The sequence of each gene reflects the string of hundreds or thousands of A, T, C, and G nucleotides that make up the gene. Each gene has a normal, or "wild-type"

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<sup>4</sup> The United States of America, represented by the Secretary of Health and Human Services, is an additional owner of the '001, '441, '897, and '282 patents. Endo Recherche, Inc., of Quebec, Canada, HSC Research and Development Limited Partnership of Toronto, Canada, and the Trustees of the University of Pennsylvania are additional owners of the '492 and '857 patents. Compl. ¶ 30.

<sup>5</sup> DNA, which stands for deoxyribonucleic acid, is a chemical compound made by the body. Compl. ¶ 34.

sequence of nucleotides. Compl. ¶¶ 33, 35, 36.

The sequence of any given human gene varies in nature from one person to another and frequently varies from the "wild-type" sequence. Some of the variations, referred to as "mutations" or "variants," can impact the body's ability to create proteins necessary for sound health. These mutations can include individual nucleotide substitutions (e.g., a T where G would normally appear in a gene), individual nucleotide deletions (e.g. a G being deleted altogether from a particular location in a gene), or much larger variations (e.g. a section of a gene containing numerous nucleotides is deleted or displaced). Mutations can be inherited from an individual's parents as well as be acquired during an individual's lifetime. Id.

To find out if the nucleotide sequence of a person's gene differs from the normal, or "wild-type" nucleotide sequence for the gene, a genetic researcher or clinician can sequence the person's gene to determine its nucleotide sequence. Once the sequence of the gene has been obtained, the researcher or clinician can examine the entire sequence to see if the A, T, C, and Gs encode a healthy sequence, a sequence with mutations known to be associated with cancer, or a sequence with one or more variants of uncertain significance. Alternatively, the researcher or clinician can sequence and examine a small section of the gene where a particular mutation or variant is known to occur. The methods by which researchers or clinicians identify the sequence of either the whole gene or any part thereof are not patented in the claims at issue here and are well known in the field.



Compl. ¶ 36.

In the 1990s, a number of genetic researchers around the world began looking for a human gene that correlated with an increased risk of breast and/or ovarian cancer. Many of those researchers, including the researchers who ultimately formed Myriad, were funded, at least in part, by the federal government. Researchers, using techniques widely available in the profession, determined in 1990 that one gene that correlated with an increased risk of breast and/or ovarian cancer was located in the body on chromosome 17. Another research team that was eventually associated with Myriad, using techniques widely available in the profession, sequenced the precise gene, which was named *BRCA1* because of its correlation with breast cancer susceptibility. These researchers subsequently formed Myriad. Myriad sought, and ultimately obtained, several patents on this human *BRCA1* gene. Researchers also began looking for other genes similar to *BRCA1*, and Myriad, using techniques widely available in the profession, subsequently identified *BRCA2* and obtained a series of patents over the human *BRCA2* gene. As a result, Myriad holds, either through ownership or exclusive license, numerous patents relating to the human *BRCA1* and *BRCA2* genes. Compl. ¶¶ 41-45.

The patents for *BRCA1/2* were granted by the USPTO pursuant to a formal written policy that provides that naturally occurring genes can be patented if they are "isolated from their natural state and purified." Compl. ¶ 50. According to USPTO policy, an "isolated and purified" gene includes one that is simply removed from the body and separated

from the other contents of the cell. Compl. ¶ 51. However, the information dictated by the gene is identical whether it is inside or outside of the body, and an "isolated and purified" human gene performs the same function as the human gene in a person's body. *Id.* USPTO policy also permits patenting of comparisons or correlations created by nature, but identified by a patent holder. Compl. ¶ 53.

Everyone carries the *BRCA1* and *BRCA2* genes, but the sequence of each person's *BRCA* genes can differ. Compl. ¶ 37. Certain mutations in the genes are correlated with an increased risk of breast and/or ovarian cancer and may also be associated with other cancers, such as prostate and pancreatic cancers. *Id.* Women with these mutations have an approximately 40-85% lifetime risk of developing breast cancer. Compl. ¶ 39. Approximately 5-10% of women who develop breast cancer are likely to have a mutation in their *BRCA1* or *BRCA2* genes predisposing them to breast cancer and which they inherited from their parents. Compl. ¶ 38.

A *BRCA1/2* genetic test result that is positive for one of these mutations can have a substantial impact on a woman's medical decisions and health. Many women will obtain earlier and more vigilant screening for breast and/or ovarian cancers, and some women may choose to have prophylactic surgery to remove their breasts and/or ovaries in order to reduce the risk of future cancers. Compl. ¶ 40.

#### **D. Enforcement of the Patents-in-Suit**

In the late 1990s, the GDL at the University of Pennsylvania was engaged in providing *BRCA1* genetic testing services to women. Kazazian Decl. ¶ 4. Around this time, Dr. Kazazian, one of the co-Directors of the GDL, met with Dr. Mark Skolnick ("Dr. Skolnick"), the Chief Science Officer at Myriad. During the meeting, Dr. Skolnick informed Dr. Kazazian that Myriad planned to stop the *BRCA1* and *BRCA2* testing being done by the GDL. Kazazian Decl. ¶ 6. Shortly thereafter, on or about May 29, 1998, Dr. Kazazian received a letter from William A. Hockett, Director of Corporate Communications for Myriad which asserted that Myriad is "the patent holder for the *BRCA1* gene" covering, among other things "composition of matter covering the *BRCA1* gene [and] any fragments of the *BRCA1* gene." Ganguly Decl. ¶ 5. The letter further offered the University a collaboration license of very limited scope. *Id.*

On or about August 26, 1998, Dr. Kazazian received a cease-and-desist letter from George A. Riley of O'Melveny & Myers, LLP, asserting that the Dr. Kazazian's commercial testing activities infringed the patents-in-suit and demanding that he cease "all infringing testing activity." Ganguly Decl. ¶ 6.

On or about June 10, 1999, the University of Pennsylvania general counsel, Robert Terrell, received a letter from Christopher Wright, Myriad's General Counsel, asserting that Dr. Kazazian's *BRCA* testing activities infringed the patents-in-suit and demanding that the university cease all such commercial genetic testing services. Ganguly Decl. ¶

7. In a subsequent letter to the University dated September 22, 1999, Myriad reiterated its belief that the genetic testing activities being performed at the GDL infringed the patents-in-suit and repeated its demand that such activities cease. Ganguly Decl. ¶ 9.

As a result of these letters, the University of Pennsylvania advised Drs. Kazazian and Ganguly to discontinue their *BRCA1/2* testing, which they did. Kazazian Decl. ¶ 7; Ganguly Decl. ¶ 10.

During this same period, Dr. Harry Ostrer was sending patient samples to Dr. Kazazian for *BRCA1/2* related genetic screening. Ostrer Decl. ¶ 5. On May 21, 1998, Dr. Ostrer also received a letter from William Hocket similar to that sent to Dr. Kazazian. The letter notified Dr. Ostrer of Myriad's patents and offered him a license for *BRCA1/2*-related genetic testing. Ostrer Decl. ¶ 7. Because of the narrow scope of the proposed license, Dr. Ostrer did not enter into a licensing agreement with Myriad. Id.

On or about September 15, 1998, Gregory Critchfield, the President of Myriad, sent a letter to Dr. Susan Nayfield of the National Cancer Institute ("NCI"). Ganguly Decl. Ex. 7. The letter assured Dr. Nayfield that Myriad would not interfere with research activities supported by the NCI in any way, but noted that Myriad had, over the past several months, sent several laboratories engaged in the "commercial testing" of the *BRCA1* gene draft license agreements defining the conditions under which those laboratories would be allowed to conduct commercial genetic testing. Id.

On or about September 2, 1999, a Myriad representative sent a letter to a Georgetown laboratory demanding that it no longer sent genetic samples to the GDL for testing because such testing infringed the patents-in-suit. Ganguly Decl. ¶ 13. As a result of the letter, Georgetown stopped sending samples to the GDL for *BRCA1/2* screening. Id.

In December 2000, the director of the Yale DNA Diagnostics Laboratory (the "YDL") received a letter from Myriad directing that the YDL cease the *BRCA1/2* genetic testing that was being conducted in the laboratory because the testing allegedly infringed the patents-in-suit. Matloff Decl. ¶ 7. Following receipt of the letter, the laboratory ceased offering such genetic testing. Id.

In 2005, Ms. Matloff telephoned Myriad to inquire whether it was permissible for the YDL to perform genetic screening of the *BRCA* genes that looked for large rearrangement mutations. Matloff Decl. ¶ 8. Several scientific studies had demonstrated that Myriad's full sequencing test missed large rearrangements that are also correlated with cancer risk. Myriad informed Ms. Matloff that this large rearrangement testing could not be done by the Yale laboratory because it would infringe the patents-in-suit. Id.

Myriad has also engaged in litigation to assert its rights under the patents-in-suit. In 1997 and 1998, Myriad filed suit against Oncormed, a company offering competing *BRCA1/2* genetic testing. See Myriad Genetics v. Oncormed, 2:97-cv-922 (D. Utah); Myriad Genetics v. Oncormed, 2:98-cv-35 (D. Utah). In November 1998, Myriad sued the University of Pennsylvania for infringing its *BRCA* patents. See

Myriad Genetics v. Univ. of Pennsylvania, 2:98-cv-829 (D. Utah). Although the lawsuit was dismissed after the University agreed to cease its *BRCA* testing, the dismissal was "without prejudice." See 2:98-cv-829 (D. Utah) (docket entry 3).

As a result of these efforts, it is widely understood within the research community that Myriad has taken the position that any *BRCA1/2* related activity infringes its patents and that Myriad will assert its patent rights against parties engaged in such activity. See, Ostrer Decl. ¶¶ 5-6; Chung Decl. ¶ 15; Hubbard Decl. ¶ 7; Kant Decl. ¶ 4; Matloff Decl. ¶¶ 7-9; Reich Decl. ¶ 5; see also Mildred K. Cho, et al., Effects of Patents and License on the Provision of Genetic Testing Services, 5 J. Molecular Diagnostics 3 (2003) (reporting that nine clinical genetic testing laboratories ceased *BRCA1/2* testing as a result of Myriad's patents).

### III. THE PARTIES' CONTENTIONS

The Plaintiffs challenge the validity of claims 1, 2, 5, 6, 7, and 20 of patent 5,747,282 (the "'282 patent") ; claims 1, 6, and 7 of patent 5,837,492 (the "'492 patent"); claim 1 of patent 5,693,473 (the "'473 patent"); claim 1 of patent 5,709,999 (the "'999 patent"); claim 1 of patent 5,710,001 (the "'001 patent"); claim 1 of patent 5,753,441 (the "'441 patent"); and claims 1 and 2 of patent 6,033,857 (the "'857 patent").

The Plaintiffs divide the claims-in-suit into four categories. The first category of claims, which include claims 1, 2, 5, and 6 of the '282 patent and claim 1 of the '492 patent, cover isolated, non-mutated forms of *BRCA1* and *BRCA2* as well as

fragments of *BRCA1* of 15 nucleotides or more. The second category of claims, which includes claim 1 of the '473 patent, claim 7 of the '282 patent and claims 6 and 7 of the '492 patent, cover isolated forms of *BRCA1* and *BRCA2* that contain mutations that may or may not have any correlation with an increased risk of breast and ovarian cancer. The third category of claims, comprised of claim 1 of the '999 patent, covers any method of analyzing an individual's *BRCA1* gene to determine whether the individual's gene contains an inherited mutation. The fourth category of claims, which includes claim 1 of the '001 patent, claim 1 of the '441 patent, and claims 1 and 2 of the '857 patent, covers comparison of a patients' *BRCA1* and *BRCA2* gene sequences with the normal *BRCA1* and *BRCA2* gene sequences to determine whether there are differences that would indicate a genetic predisposition to breast cancer. Claim 20 of the '282 patent, which the Plaintiffs include in this fourth category of claims, covers a method of examining the growth of cells containing a mutated form of *BRCA1* following their treatment with a potential therapeutic compound. None of the claims in the fourth category of claims are limited to "isolated" DNA.

The Plaintiffs allege that because human genes are products of nature, laws of nature, and/or natural phenomena, and abstract ideas or basic human knowledge or thought, the claims-in-suit are invalid for violating Article 1, section 8, clause 8 of the United States Constitution, the First and Fourteenth Amendments to the Constitution, and 35 U.S.C. § 101 of the patent statute. Compl. ¶ 52, 54.

According to the Plaintiffs, these genes exist

as naturally occurring products of nature, and Myriad did not invent, create, or in any way construct or engineer the genes. Rather, Myriad located them in nature and described their informational content as it exists and functions in nature. According to the Plaintiffs, Myriad did not invent, create, or in any way construct the differences that may be found when a patient's *BRCA1/2* gene sequences are compared to the normal *BRCA1/2* gene sequences or the correlations between certain mutations in *BRCA1/2* and an increased risk of breast and/or ovarian cancer. Compl. ¶¶ 46, 48.

Myriad currently offers two types of tests: the Comprehensive BRCAAnalysis Test and the BRCAAnalysis Rearrangement Test ("BART"). The Comprehensive BRCAAnalysis Test costs over \$3000; BART costs approximately \$600, although Myriad will offer BART testing for free to some women who meet certain criteria. Compl. ¶ 92, 94. Although Myriad's tests examine many mutations known to correlate with a predisposition to breast and/or ovarian cancer, they do not look for all mutations known to correlate with breast and/or ovarian cancer. Ledbetter Decl. ¶ 16. The Plaintiffs allege that Myriad's patents on *BRCA1/2* have allowed it to bar any other entity from conducting genetic testing on the *BRCA* genes despite the ability of other clinical laboratories, such as the laboratories of Drs. Chung, Ostrer, and Ledbetter, to do so and the desire of patients, such as Ms. Limary and Ms. Girard, to seek such alternative testing. Compl. ¶ 84. As a result, any person seeking testing of their *BRCA1/2* genes is required to utilize Myriad's tests. Compl. ¶ 90.



According to the Plaintiffs, Myriad also has the ability to prevent researchers from conducting any research examining the *BRCA* genes. Compl. ¶ 96. Myriad has permitted some scientists to conduct pure research on *BRCA1/2*, but the Plaintiffs allege that Myriad has no official policy permitting such research and has not publicized its willingness to allow such research. Compl. ¶ 97. The Plaintiffs allege that the patents on the *BRCA* gene sequences deny researchers access to genomic information which, unlike other patented inventions, cannot be "invented around" or built upon to foster scientific progress. Commpl. ¶ 88. As a result, researchers are chilled from engaging in research on *BRCA1/2* as well as research on other genes that may interact with *BRCA1/2*. Compl. ¶ 98. Included in such activities would be the development of new tests for breast and/or ovarian cancer that might be linked to *BRCA1/2*. The Plaintiffs assert that this infringes on quality medical practice and compromises quality assurance and improvement of testing. Compl. ¶ 101; Ledbetter Decl. ¶ 23.

The Defendants have moved to dismiss the claims against them pursuant to Fed. R. Civ. P. 12(b) (1) on the grounds that the Court lacks subject matter jurisdiction over Plaintiffs' claims against the USPTO and that the Plaintiffs lack standing to bring this declaratory judgment action. The Defendants have also moved to dismiss the claims against the UURF Directors pursuant to Fed. R. Civ. P. 12(b) (2) on the grounds that the Court lacks personal jurisdiction over the Directors. Finally, the Defendants move to dismiss the constitutional claims pursuant to Fed. R. Civ. P. 12(b) (6) for failure to sufficiently plead a claim.

#### IV. THERE IS SUBJECT MATTER JURISDICTION OVER THE CLAIMS AGAINST THE USPTO

The USPTO has moved to dismiss the Complaint, pursuant to Rule 12(b)(1), on the grounds that the Court lacks subject matter jurisdiction over the Plaintiffs' claims. A claim is "properly dismissed for lack of subject matter jurisdiction under Rule 12(b)(1) when the district court lacks the statutory or constitutional power to adjudicate it." Makarova v. United States, 201 F.3d 110, 113 (2d Cir. 2000). "When jurisdiction is challenged, the plaintiff 'bears the burden of showing by a preponderance of the evidence that subject matter jurisdiction exists.'" Arar v. Ashcroft, 532 F.3d 157, 168 (2d Cir. 2008) (quoting APWU v. Potter, 343 F.3d 619, 623 (2d Cir. 2003)). "[J]urisdiction must be shown affirmatively, and that showing is not made by drawing from the pleadings inferences favorable to the party asserting it." Shipping Fin. Servs. Corp. v. Drakos, 140 F.3d 129, 131 (2d Cir. 1998) (citation omitted). As such, the Court may rely on evidence outside the pleadings, including declarations submitted in support of the motion and the records attached to these declarations. See Makarova, 201 F.3d at 113 ("In resolving a motion to dismiss . . . under Rule 12(b)(1), a district court . . . may refer to evidence outside the pleadings. ").

The Plaintiffs premise their assertion of subject matter jurisdiction on 28 U.S.C. §§ 1331 & 1338(a).<sup>6</sup> 28 U.S.C. § 1331 vests the district courts

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<sup>6</sup> Although Plaintiffs also cite 28 U.S.C. § 2201 as a basis for jurisdiction, "[i]t is settled law that the Declaratory Judgment Act, 28 U.S.C. § 2201 (1994), does not enlarge the jurisdiction of

with subject matter jurisdiction for "all civil actions arising under the Constitution." The USPTO, however, asserts that the Court lacks subject matter jurisdiction over Plaintiffs' claims against them in light of the "comprehensive scheme Congress established to govern patent grants."<sup>7</sup> Hitachi Metals, Ltd. v. Quigg, 776 F. Supp. 3, 7 (D.D.C. 1991). According to the USPTO, the existence of this comprehensive statutory scheme reflects Congress' intention to preclude judicial challenges of the type brought by the Plaintiffs.

The cases cited by the USPTO, however, involved claims alleging statutory violations for which the Patent Act provided a remedy. The issue before the courts, then, was whether the existence of a comprehensive statutory scheme that addressed the alleged statutory violation precluded the right to also seek judicial review of the alleged violations. See Syntex (U.S.A.), Inc. v. U.S. Patent & Trademark Office, 883 F.2d 1570, 1572-74 (Fed. Cir. 1989) (concluding remedy provided by patent statute for alleged statutory violations precluded private judicial

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the federal courts . . . and that a declaratory judgment action must therefore have an independent basis for subject matter jurisdiction." Concerned Citizens of Cohocton Valley, Inc. v. N.Y. State Dep't of Env'tl. Conservation, 127 F.3d 201, 206 (2d Cir. 1997) (citing Skelly Oil Co. v. Phillips Petroleum Co., 339 U.S. 667, 671 (1950)).

<sup>7</sup> The USPTO also argues that sovereign immunity serves to bar this action. Courts, however, routinely entertain actions against federal agencies alleging violations of the Constitution. See, e.g., Reno v. ACLU, 521 U.S. 844 (1997). As Plaintiffs note in their Complaint, the only claims raised against the USPTO are of a constitutional nature. Compl. ¶ 27.

remedy for those claims);<sup>8</sup> Hallmark Cards, Inc. v. Lehman, 959 F. Supp. 539, 543 (D.D.C. 1997) (concluding Congress' statutory framework providing means to challenge issuance of Certificates of Correction "implicitly preclude[d]" a right to judicial relief); Hitachi Metals, 776 F. Supp. at 7-8 (finding statutory scheme for administrative and judicial review of patent reissue decisions precluded third-party judicial challenges to reissue process).

In Bush v. Lucas, 462 U.S. 367 (1983), cited by the USPTO, the Supreme Court considered whether an employee subjected to adverse employment action as a result of his criticism of the federal agency employing him could maintain a suit against the agency for violation of his First Amendment rights. Id. at 369-72. Noting that "the ultimate question on the merits . . . may appropriately be characterized as one of 'federal personnel policy,'" id. at 380-81, the Court went on to describe Congress' "repeated consideration of the conflicting interests involved in providing job security, protecting the right to speak freely, and maintaining discipline and efficiency in the federal workforce." Id. at 385. The result, the Court concluded, was an "elaborate, comprehensive scheme" within which "Constitutional challenges to agency action, such as First Amendment claims raised by petitioner, are fully cognizable." Id. As a result, the Court was presented with a question "quite different from the typical remedial issue confronted by a common-law court" since the issue

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<sup>8</sup> The Syntex opinion noted in passing that the plaintiff had pled a violation of the 5<sup>th</sup> Amendment, but included no discussion concerning the claim in its analysis of subject matter jurisdiction.

was not whether a judicial remedy should be created where none existed, but rather whether a judicial remedy should be created where a plaintiff was merely dissatisfied by the statutory remedy Congress provided for his alleged wrong. Id. at 388.

While the USPTO notes the existence of a comprehensive scheme to redress violations of the Patent Act, it cites to no comparable statutory scheme providing a remedy for persons who complain about the constitutionality of patents issued by the USPTO and/or the policies and practices of the USPTO. See Block v. Cmty. Nutrition Inst., 467 U.S. 340, 349 (1984) ("[W]hen a statute provides a detailed mechanism for judicial consideration of particular issues at the behest of particular persons, judicial review of those issues at the behest of other persons may be found to be impliedly precluded." (emphasis added)); see generally Marbury v. Madison, 5 U.S. 137 (1803). In such circumstances, the Supreme Court has held that Congress did not intend to preclude enforcement of federal rights through private actions. See Wright v. Roanoke, 479 U.S. 418, 427-28 (1987) (citing absence of statutorily defined private judicial remedy for alleged violation of federal housing law as evidence that Congress did not intend to foreclose private right of action). Indeed, even when Congress has created a statutory remedy, if that remedy is not coextensive with the remedy provided by the Constitution, plaintiffs may still bring a separate action to enforce the Constitution. See Fitzgerald v. Barnstable Sch. Comm., \_\_\_ U.S. \_\_\_, 129 S. Ct. 788, 796-978 (2009).

The novel circumstances presented by this action against the USPTO, the absence of any

remedy provided in the Patent Act, and the important constitutional rights the Plaintiffs seek to vindicate establish subject matter jurisdiction over the Plaintiffs' claim against the USPTO.<sup>9</sup> See, e.g., Reno v. ACLU, 521 U.S. 844 (1997); Mace v. Skinner, 34 F.3d 854, 859-60 (9th Cir. 1994).

## V. THERE IS STANDING

### A. The Plaintiffs Have Standing to Sue the USPTO for Constitutional Violations

The "judicial power . . . defined by Art. III is not an unconditioned authority to determine the constitutionality of legislative or executive acts" but, rather, is limited to the resolution of "cases" and "controversies." Valley Forge Christian Coll. v. Ams. United for Separation of Church & State, Inc., 454 U.S. 464, 471 (1982); Lujan v. Defenders of Wildlife, 504 U.S. 555, 559-60 (1992). An "essential and unchanging part" of that limitation is the doctrine of standing. Lujan, 504 U.S. at 560. Indeed, "[t]he Art. III doctrine that requires a litigant to have 'standing' to invoke the power of a federal court is perhaps the most important of these doctrines." Allen v. Wright, 468 U.S. 737, 750 (1984). "At an irreducible minimum, Art. III requires the party who invokes the court's authority to show (1) that he personally has suffered some actual or threatened injury as a

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<sup>9</sup> Although the USPTO suggests that finding subject matter jurisdiction over Plaintiffs' constitutional claims would open the gates to a flood of challenges to patents based on alleged constitutional violations, it is difficult to see how a colorable claim for constitutional violations could arise out of patents for more commonly patented inventions, such as computer chips or carburetors.

result of the putatively illegal conduct of the defendant, that (2) the injury fairly can be traced to the challenged action, and (3) is likely to be redressed by a favorable decision." Valley Forge, 454 U.S. at 472 (internal citations omitted).<sup>10</sup>

Beyond these constitutional requirements, a plaintiff must also satisfy certain prudential standing requirements, based on the principle that the judiciary should "avoid deciding questions of broad social import where no individual rights would be vindicated." Phillips Petroleum Co. v. Shutts, 472 U.S. 797, 804 (1985). Prudential standing requires, inter alia, that a party "assert his own legal interests rather than those of third parties," id. at 804, and that a claim must not be a "generalized grievance" shared in by all or a large class of citizens, Warth v. Seldin, 422 U.S. 490, 499 (1975). Prudential standing also addresses whether "the constitutional or statutory provision on which [a plaintiff's] claim rests properly can be understood as granting persons in the plaintiff's position a right to judicial relief." See id. at 499-500. Thus, the litigant's complaint must fall within the "zone of interests to be protected or regulated by the statute or constitutional guarantee in question." Valley Forge, 454 U.S. at 475.

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<sup>10</sup> The USPTO's challenge to Plaintiffs' standing is intertwined with its challenge to Plaintiffs' subject matter jurisdiction. See Syntex, 882 F.2d at 1573 ("The standing and reviewability inquiries tend to merge. A plaintiff cannot claim standing based on violation of an asserted personal statutorily-created procedural right when Congress intended to grant that plaintiff no such right." (quoting Banzhaf v. Smith, 737 F.2d 1167, 1170 n.\* (D.C. Cir. 1984))).

The Defendants allege that it is well established that third parties do not have standing to challenge the USPTO's issuance of a patent. The authorities cited by the USPTO, however, address a party's standing to bring claims for statutory violations and establish only that the existence of a comprehensive framework within the Patent Act designed to address certain statutory violations may demonstrate Congressional intent to foreclose a judicial remedy for those violations. See Syntex, 882 F.2d at 1572-74; Hitachi Metals, 776 F. Supp. at 7-8; Godtfredsen v. Banner, 503 F. Supp. 642, 644-45 (D.D.C. 1980) (finding statutory remedies for claims of examiner error during interference proceedings precluded judicial review of the proceedings prior to the exhaustion of administrative remedies).<sup>11</sup> As discussed supra in Section IV, these cases do not, as the USPTO suggests, establish that the remedial scheme provided by the Patent Act for statutory violations divests the Plaintiffs of standing to assert constitutional claims for which the Patent Act

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<sup>11</sup> Animal Legal Defense Fund, 932 F. 2d 920 (Fed. Cir. 1991), cited by the USPTO, did not involve allegations of constitutional violations. Moreover, the court's analysis of standing turned on the specific APA provisions involved and was, in substance, a finding that no legally cognizable right was violated. See id. at 929-30. The court's holding also turned on the fact that no patents on animals had been granted and therefore any harm that might occur in the future from such patents was speculative. Id. at 933. The same cannot be said here, where patents over *BRCA1/2* have already been granted and have been used to present Plaintiffs from engaging in clinical analysis of the *BRCA1/2* genes, from informing women about testing options other than by Myriad, and from obtaining genetic testing or second opinions. Plaintiffs alleged harms are therefore not the type of speculative harms at issue in Animal Legal Defense Fund.



provides no remedy.

The USPTO also argues that the Plaintiffs do not have standing because the injuries alleged are not "fairly traceable" to the USPTO's allegedly improper conduct. The "fairly traceable" requirement "examines the causal connection between the assertedly unlawful conduct and the alleged injury." Allen, 468 U.S. at 753 n.19. While the USPTO is correct that Myriad's refusal to license its patent broadly contributes to Plaintiffs' alleged injuries, the patents were issued by the USPTO, in accordance with its policies and practices. It is those policies and practices that the Plaintiffs allege are unconstitutional. The injury alleged is therefore "fairly traceable" to the USPTO .

Finally, the USPTO argues that Plaintiffs' claim against it fails to meet the redressibility requirement, which "examines the causal connection between the alleged injury and the judicial relief requested." Allen, 468 U.S. at 753 n.9. The Plaintiffs ask the Court to enjoin the Defendants from taking any actions to enforce the challenged claims in Myriad's patents. Fairly included in this prayer for relief is a request that the Court declare unconstitutional the USPTO's policies and practices with respect to the challenged claims and similar classes of claims. Granting Plaintiffs' request for relief would serve to render the claims-at-issue definitionally invalid. As a result, the Plaintiffs would be allowed to engage in conduct currently prohibited by Myriad's patents, and the alleged injuries would be redressed.

## **B. The Plaintiffs Have Established Standing to Sue Myriad and the Directors**

Article III limits federal jurisdiction to disputes involving an actual "case or controversy," and not merely "a difference or dispute of a hypothetical or abstract character." Aetna Life Ins. Co. v. Haworth, 300 U.S. 227, 240 (1937). As the Supreme Court has recently observed, there exists no bright-line rule for determining whether an action satisfies the case or controversy requirement. MedImmune, Inc. v. Genentech, Inc., 549 U.S. 118, 127 (2007). Rather, "[t]he difference between an abstract question and a 'controversy' contemplated by the Declaratory Judgment Act is necessarily one of degree, and it would be difficult, if it would be possible, to fashion a precise test for determining in every case whether there is such a controversy." Md. Cas. Co. v. Pac. Coal & Oil Co., 312 U.S. 270, 273 (1941). Consequently, "the analysis must be calibrated to the particular facts of each case." Cat Tech LLC v. TubMasters, Inc., 528 F.3d 871, 879 (Fed. Cir. 2008).

"Whether an actual case or controversy exists so that a district court may entertain an action for a declaratory judgment of non-infringement and/or invalidity is governed by Federal Circuit law." MedImmune, Inc. v. Centocor, Inc., 409 F.3d 1376, 1378 (Fed. Cir. 2005) (citations omitted), rev'd on other grounds, 549 U.S. 118 (2007). "The purpose of the Declaratory Judgment Act . . . in patent cases is to provide the allegedly infringing party relief from uncertainty and delay regarding its legal rights." Goodyear Tire & Rubber Co. v. Releasomers, Inc.,

824 F.2d 953, 956 (Fed. Cir. 1987). As the Federal Circuit has explained:

[A] patent owner . . . attempts extrajudicial enforcement with scare-the-customer-and-run tactics that infect the competitive environment of the business community with uncertainty and insecurity . . . . Before the Act, competitors . . . were rendered helpless and immobile so long as the patent owner refused to grasp the nettle and sue. After the Act, those competitors were no longer restricted to an in terrorem choice between the incurrence of a growing potential liability for patent infringement and abandonment of their enterprises; they could clear the air by suing for a judgment that would settle the conflict of interests.

Elecs. for Imaging, Inc. v. Coyle, 394 F.3d 1341, 1346 (Fed. Cir. 2005) (quoting Arrowhead Indus. Water, Inc. v. Ecolochem, Inc., 846 F.2d 731, 735 (Fed. Cir. 1988), overruled on other grounds by MedImmune, 549 U.S. 118).

The Federal Circuit's jurisprudence governing a party's standing to seek a declaratory judgment of patent invalidity was recently revised by the Supreme Court in MedImmune, 549 U.S. 118. There, the Supreme Court considered whether the licensee of a patent had standing to seek a judgment declaring the underlying patent invalid, unenforceable, or not infringed without first breaching or terminating the license agreement. Id.

at 137. In concluding that subject matter jurisdiction existed over the plaintiff's declaratory judgment claim, the Supreme Court rejected the Federal Circuit's "reasonable apprehension of suit" test as conflicting with the Court's precedent. Id. at 132 n.11; see also Revolution Eyewear, Inc. v. Aspex Eyewear, Inc., 556 F.3d 1294, 1297 (Fed Cir. 2009) (observing that "the Federal Circuit's requirements, specific to patent cases, that there be both a threat or other action by the patentee sufficient to create a reasonable apprehension of infringement suit, and present activity that could constitute infringement or concrete steps taken with the intent to conduct such activity, were more rigorous than warranted by the principle and purpose of declaratory actions").<sup>12</sup> Instead, the Court held that the jurisdictional analysis was properly based on an examination of "all the circumstances." MedImmune, 549 U.S. at 127.

Under the "all the circumstances" test, "the question in each case is whether the facts alleged, under all the circumstances, show that there is a substantial controversy, between the parties having adverse legal interests, of sufficient immediacy and reality to warrant the issuance of a declaratory

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<sup>12</sup> Under the "reasonable apprehension of suit" test, determining whether a party seeking a declaratory judgment of invalidity possessed the necessary standing required examining (1) "whether the declaratory judgment plaintiff actually produced or was prepared to produce an infringing product;" and (2) "whether conduct by the patentee had created on the part of the declaratory judgment plaintiff a reasonable apprehension that the patentee would file suit of the allegedly infringing activity continued." Sony Elecs. Inc v. Guardian Media Techs., Ltd., 497 F.3d 1271, 1283 (Fed. Cir. 2007).

judgment." Id. at 127 (quoting Md. Cas. Co., 312 U.S. at 273). This "more lenient legal standard facilitates or enhances the availability of declaratory judgment jurisdiction in patent cases," and, accordingly, there is now an "ease of achieving declaratory judgment jurisdiction." Micron Tech. v. Mosaid Techs. Inc., 518 F.3d 897, 902 (Fed. Cir. 2008). Courts in this district have likewise recognized that since MedImmune, "the trend is to find an actual controversy, at least where the declaratory judgment plaintiff's product arguably practices a patent and the patentee has given some indication it will enforce its rights." Diamonds.net LLC v. IDEX Online, Ltd., 590 F. Supp. 2d 593, 597-98 (S.D.N.Y. 2008).

Although MedImmune did not define the precise contours of the "all the circumstances" test, guidance is provided by other courts' standing analysis. First, there must be some affirmative act by the defendant relating to enforcement of its patent rights. See, e.g., Prasco, LLC v. Medicis Pharm. Corp., 537 F.3d 1329, 1338-39 (Fed. Cir. 2008); SanDisk Corp. v. STMicroelectronics, Inc., 480 F. 3d 1372, 1380-81 (Fed. Cir. 2007) ("[J]urisdiction generally will not arise merely on the basis that a party learns of the existence of a patent owned by another or even perceives such a patent to pose a risk of infringement, without some affirmative act by the patentee."). Second, the declaratory judgment plaintiff must have undertaken "meaningful preparation to conduct potentially infringing activity." Cat Tech LLC, 528 F.3d at 880. This inquiry ensures that a party does not seek a declaratory judgment "merely because it would like an advisory opinion on whether it would be liable for patent infringement if it were to initiate some merely

contemplated activity." Arrowhead, 846 F.2d at 736 (citations omitted). Whether there exists "sufficient 'preparation' is a question of degree to be resolved on a case-by-case basis." Id. (citing Md. Cas. Co., 312 U.S. at 273).

### **1. Affirmative Acts by the Defendants**

The Defendants assert that in order to satisfy the "affirmative act" requirement for declaratory judgment standing, there must be some act by the Defendants directed towards the Plaintiffs. As an initial matter, the Defendants have, in fact, taken specific affirmative acts toward Drs. Kazazian and Ganguly.<sup>13</sup> Moreover, other courts have recognized that "an overt, specific act toward the declaratory judgment plaintiff is not required to demonstrate the existence of an actual controversy." Edmunds Holding Co. v. Autobyte, Inc., 598 F. Supp. 2d 606, 610 (D. Del. 2009).

The cases cited by the Defendants unquestionably considered the absence of "affirmative acts" directed towards the plaintiff in finding a lack of standing to bring the declaratory judgment action. None of the cases, however, establish a requirement that only acts directed towards the plaintiff could be considered for purposes of the standing analysis or even that there must exist

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<sup>13</sup> The Defendants argue that the cease-and-desist letters addressed to the University of Pennsylvania cannot be viewed as affirmative acts directed towards Dr. Ganguly. However, the letters were designed to stop the *BRCA1/2* testing being conducted by the lab jointly overseen by Drs. Kazazian and Ganguly, and Defendants seek to draw an overly formalistic distinction.

acts specifically directed towards the plaintiffs in order to establish standing. Instead, in most of the cases, the dismissal was based on a lack of any legally cognizable acts by the defendant upon which a declaratory judgment could be established. See, e.g., Prasco, 537 F.3d at 1334, 1340 (observing that the plaintiff's only basis for standing was the plaintiff's allegation that its product did not infringe the defendants' patents); Indigodental GMBH & Co. KG v. Ivoclar Vivadent, Inc., No. 08 Civ. 7657 (RJS), 2008 WL 5262694, at \*2 (S.D.N.Y. Dec. 10, 2008) (concluding that "Plaintiff had done little more than become aware of Defendant's patent"); Document Sec. Sys., Inc. v. Adler Techs., Inc., No. 03-CV-6044, 2008 WL 596879, at \*10 -\*11 (W.D.N.Y. Feb. 29, 2008) (finding single page of deposition testimony and an unrelated patent litigation insufficient basis for standing); Broadcom Corp. v. Qualcomm Inc., No. 08cv1829 WQH (LSP), 2009 WL 684835, at \*6 (S.D. Cal. Mar. 12, 2009) (citing, as the basis for its holding, plaintiff's failure "to specify any affirmative act by the defendants" that would support jurisdiction); Impax Labs., Inc v. Medicis Pharm. Corp., No. C-08-0253 MMC, 2008 WL 1767044, at \*2 (N.D. Cal. Apr. 16, 2008) (finding plaintiff's filing of an Abbreviated New Drug Application coupled with defendant's public statements of intent to enforce patents insufficient to create an "actual controversy"); The Wooster Brush Co. v. Bercom Int'l, LLC, No. 5:06CV474, 2008 WL 1744782, at \*4 -\*5 (N.D. Ohio Apr. 11, 2008) (finding defendant had never engaged in any activity that would suggest the plaintiffs infringed its patent); Baker Hughes Oilfield Operations, Inc. v. Reedhycalog UK, Ltd., No. 2:05-CV-931, 2008 WL 345849, at \*2 -\*3 (D. Utah Feb. 6,

2008) (dismissing case where letters from defendant did not indicate that it thought plaintiffs were infringing its patents).<sup>14</sup>

A requirement that there be a specific, affirmative act directed towards the plaintiff to establish standing to seek a declaratory judgment of patent invalidity would be inconsistent with the Supreme Court's mandate that the Court examine "the facts alleged, under all the circumstances," in assessing the existence of a case or controversy. See MedImmune, 549 U.S. at 127 (quoting Md. Cas. Co., 312 U.S. at 273). As the Federal Circuit has previously stated:

Article III jurisdiction may be met where the patentee takes a position that puts the declaratory judgment plaintiff in the position of either pursuing arguably illegal behavior or abandoning that which he claims a right to do. We need not define the outer boundaries of declaratory judgment jurisdiction, which will

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<sup>14</sup> In Geospan Corp. v. Pictometry Int'l Corp., 598 F. Supp. 2d 968 (D. Minn. 2008), the court observed that the only instances post-MedImmune in which declaratory judgment jurisdiction had been found to exist were those in which the defendants had engaged in some form of activity against the plaintiff. *Id.* at 970. It did not, however, state a general rule that actions directed towards the plaintiff were required to establish subject matter jurisdiction over a declaratory judgment action, nor how such a requirement would be consistent with the "all the circumstances" test. To the extent that Geospan may be read to set forth such a requirement concerning a defendant's relevant "affirmative acts," the Court declines to adopt a similar holding.



depend on the application of the principle of declaratory judgment jurisdiction to the facts and circumstances of each case.

SanDisk, 480 F.3d at 1381. In light of these principles, an examination of the totality of Myriad's conduct relating to the patents-in-suit is appropriate.

The Defendants raise several challenges to the legal significance of the acts relied on by the Plaintiffs to establish standing. First, the Defendants argue that Myriad's 1998 letter to Dr. Kazazian is too old to serve as the basis for a case or controversy. The Federal Circuit cases cited by the Defendants in support of their argument, however, predate MedImmune and examined the timeliness of letters in the context of the now-defunct "apprehension of suit" test. See Sierra Applied Scis., Inc. v. Advanced Energy Indus., Inc., 363 F.3d 1361, 1374 (Fed. Cir. 2004); Cygnus Therapeutics Sys. v. ALZA Corp., 92 F.3d 1153, 1159 (Fed. Cir. 1996). Given the recent changes to the standing analysis for declaratory judgment claims, those cases no longer serve as controlling authorities. See Benitec Austl., Ltd. v. Nucleonics, Inc., 495 F.3d 1340, 1346 (Fed. Cir. 2007) (questioning holdings in prior cases applying the "reasonable apprehension of suit" test for declaratory judgment jurisdiction in light of MedImmune). Furthermore, the Defendants cite no authority that would preclude the Court from considering the letter as part of "all the circumstances."

While the district court cases cited by the Defendants correctly applied the "all the circumstances" test in dismissing the declaratory

judgment actions, they are also distinguishable from the present situation. In Avante, the affirmative act cited by the plaintiff consisted of a single, brief infringement suit lasting a few weeks. See Avante Int'l Tech., Inc. v. Hart Intercivic, Inc., No 08-832-GPM, 2009 WL 2431993, at \*3 (S.D. Ill. July 31, 2009). In Edmunds Holding, the court's dismissal turned on the a finding that "[n]one of the facts adduced by [the plaintiff] established that [the defendant] believe[d] [the plaintiff] to be infringing the '517 patent." Edmunds Holding, 598 F. Supp. 2d at 610. While the Court agrees that an 11-year old letter may not, alone, be sufficient to establish declaratory judgment jurisdiction, those are not the circumstances presented here. Myriad's assertions of its patent rights consist not only of the letter to Dr. Kazazian, but a continuing course of conduct over a period of several years. In addition, Defendants' prior efforts to prevent the Plaintiffs and other similarly situated parties from engaging in *BRCA1/2* testing establish that Plaintiffs' planned activities would be considered infringing by the Defendants. The totality of the circumstances, as alleged by the Plaintiffs, cannot be said to be comparable to the circumstances presented by Avante and Edmunds.

The Defendants also dispute the relevance of prior litigation to the standing analysis. The Defendants argue at the outset that only litigation brought against the Plaintiffs may be considered by the Court in its jurisdictional analysis; none of the cited cases, however, supports such a rule,<sup>15</sup> and, as

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<sup>15</sup> Prasco held only that the particular prior lawsuit in question did not establish the existence of a case or controversy between the parties in light of the absence of any other evidence that the

discussed supra, this approach is inconsistent with the premise of the "all the circumstances" test. Further, although the lawsuits brought by Myriad against Oncormed and the University of Pennsylvania were dismissed, both serve as evidence of Myriad's willingness to assert its rights granted by the patents-in-suit against others. See Prasco, 537 F.3d at 1341 ("Prior litigious conduct is one circumstance to be considered in assessing whether the totality of the circumstances creates an actual controversy."). Finally, the suit against the University of Pennsylvania was dismissed without prejudice and therefore would not bar a new infringement action by Myriad against the University of Pennsylvania or Drs. Kazazian and Ganguly. Consequently, Myriad's prior litigations involving the patents-in-suit are fairly included in the Court's standing analysis.

The Plaintiffs cite counsel's August 11, 2009 letter to Defendants' counsel requesting a waiver of claims against intended *BRCA*-related activities and Defendants' subsequent refusal to grant such a waiver as evidence in support of the existence of subject matter jurisdiction. See Ravicher Decl. Ex. 1. However, the presence or absence of jurisdiction must be determined on the facts existing at the time

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defendants had taken a position adverse to the plaintiff's position. See Prasco, 537 F.3d at 1340, 1341 n.9. It did not set forth a general rule concerning the consideration of prior litigation. The court in Edmunds similarly did not prohibit consideration of prior litigation directed to third parties. See Edmunds, 598 F. Supp. 2d at 610 (distinguishing cases cited by the plaintiff in support of its assertion of the existence of case or controversy).

the complaint under consideration was filed. GAF Bldg Materials Corp. v. Elk Corp. of Dallas, 90 F.3d 479, 483 (Fed. Cir. 1996) (citing Arrowhead, 846 F.2d at 734 n.2). Because the filing of the Complaint predated the August 11, 2009 letter, the letter does not factor into the standing analysis.

Taken together, Plaintiffs' allegations establish the existence of sufficient "affirmative acts" by the Defendants for purposes of declaratory judgment jurisdiction. The Defendants have asserted their right to preclude others from engaging in *BRCA1/2* genetic testing through personal communications, cease-and-desist letters, licensing offers, and litigation. The result, as alleged by the Plaintiffs and supported by affidavits, is the widespread understanding that one may engage in testing at the risk of being sued for infringement liability by Myriad. This places the Plaintiffs in precisely the situation that the Declaratory Judgment Act was designed to address: the Plaintiffs have the ability and desire to engage in *BRCA1/2* testing as well as the belief that such testing is within their rights, but cannot do so without risking infringement liability.<sup>16</sup>

In light of "all the circumstances," there exists a sufficiently "real and immediate injury or threat of future injury that is caused by the defendants" to satisfy the "affirmative act" requirement for a declaratory judgment action. Prasco, 537 F.3d at

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<sup>16</sup> Indeed, in light of the widespread knowledge of Myriad's *BRCA1/2* patents and the breadth of the relevant claims, a finding of patent infringement would likely be considered willful and result in treble damages. See 35 U.S.C. § 284.

1339; see also Adenta GmbH v. OrthoArm, Inc., 501 F.3d 1364, 1370 (Fed. Cir. 2007); Micron Tech., 518 F.3d at 899 (patentee "pursues a systematic licensing and litigation strategy").

## **2. Meaningful Preparations for Infringing Action**

The Defendants also assert that the Plaintiffs have failed to demonstrate the existence of "meaningful preparation" to engage in infringing activity.

With respect to the researcher Plaintiffs, the Defendants argue that the Plaintiffs allege only that they are "ready, willing, and able" to infringe expressions of desire and ability are insufficient to establish "meaningful preparations" without reference to specific preparatory activities. However, the "meaningful preparation" inquiry properly focuses on whether the Plaintiffs are meaningfully prepared to engage in the infringing act such that the court's decision would serve as more than an "advisory opinion." See Cat Tech LLC, 528 F.3d at 879; SanDisk, 480 F.3d at 1381 ("[A] party need not risk a suit for infringement by engaging in the identified activity before seeking a declaration of its legal rights."). Where plaintiffs' normal course of business renders them meaningfully prepared to engage in the infringing activity at issue, the lack of some identifiable preparatory effort separate and apart from their normal activities cannot, without more, serve as the basis for finding that there has been no "meaningful preparation" for purposes of declaratory judgment jurisdiction. To hold otherwise would render those most prepared to engage in infringing activity, i.e., those for whom essentially no

additional preparation is required to perform the infringing activity, the parties least likely to satisfy the standing requirements for a declaratory judgment action.

The Defendants also cite Benitec, 495 F.3d 1340, and Mega Lift Sys., LLC v. MGM Well Services, Inc., No. 6:08 CV 420, 2009 WL 1851919 (E.D. Tex. June 29, 2009), in support of their assertion that the researcher Plaintiffs' preparation is insufficient as a matter of law to establish standing. In Benitec, the Federal Circuit found the plaintiff's plans to adapt its human gene silencing technology for use in the animal husbandry and veterinary markets insufficiently immediate for standing purposes. Benitec, 495 F.3d at 1349. The court based its holding on the fact that (1) the plaintiff had merely stated that it "expect[ed]" to begin work "shortly" on adapting its existing gene silencing technology to livestock; (2) the plaintiff had provided insufficient information for the court to assess whether the plaintiff's planned activities would be infringing; and (3) the parties agreed that the plaintiff's planned activities would fall within the safe harbor provision to infringement under 35 U.S.C. § 271 (e)(1). See Benitec, 495 F. 3d at 1349. In Mega Lift, the district court relied on the fact that the plaintiff had failed to include in its complaint any "allegation about its readiness to manufacture and sell" the future product that was the subject of the declaratory judgment action. Mega Lift, 2009 WL 1851919, at \*4.

The factual circumstances, as set forth in the Plaintiffs' affidavits, render Benitec and Mega Lift distinguishable on their facts and demonstrate

sufficient preparation by the researcher Plaintiffs to establish standing. The Plaintiffs have demonstrated that the researcher Plaintiffs are poised to begin *BRCA1/2* testing and that the patents-in-suit present the only obstruction to doing so.<sup>17</sup> See, e.g., Chung Decl. ¶¶ 13, 15-18; Ledbetter Decl. ¶¶ 8-9. All are established human geneticists whose laboratories are routinely engaged in genetic testing and therefore possess the necessary equipment and expertise to immediately begin performing *BRCA1/2* genetic testing. Compl. ¶¶ 11-16; Kazazian Decl. ¶¶ 3-5, 8-11; Ganguly Decl. ¶¶ 3, 14; Chung Decl. ¶¶ 17-18, 21; Ostrer Decl. ¶¶ 8-10, 13; Ledbetter Decl. ¶¶ 18-19 (speaking for himself and Dr. Warren). Moreover, Drs Kazazian, Ganguly, and Ostrer had previously engaged in *BRCA1/2* testing prior to Myriad's assertion of its patent rights against them.<sup>18</sup> See Kazazian Decl. ¶¶ 4-10; Ganguly Decl. ¶¶ 3-10. Consequently, the researcher Plaintiffs are meaningfully prepared to begin "BRCA testing to advance research and/or to offer . . . an important service to the public" and "could do so

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<sup>17</sup> The affidavits also establish that the proposed BRCA testing would infringe the claims-in-suit and provide sufficient information to satisfy the Federal Circuit's requirement that "the existence of a case or controversy [ ] be evaluated on a claim-by-claim basis." Jervis B. Webb Co. v. Southern Sys., Inc., 742 F. 2d 1388, 1399 (Fed. Cir. 1984).

<sup>18</sup> Defendants argue that Drs. Kazazian and Ganguly state only that they would "consider" engaging in infringing Myriad's patents, and that such speculative intent cannot satisfy the "meaningful preparation" prong. However, the proper focus of this inquiry is whether the plaintiffs are meaningfully prepared, not whether they have made a final, conclusive decision to engage in the infringing activity. See Cat Tech LLC, 528 F.3d at 879 (describing inquiry as requiring "a showing of 'meaningful preparation' for making or using that product").

within a matter of weeks." Ganguly Decl. ¶ 14; see also Ledbetter Decl. ¶ 18.<sup>19</sup>

Plaintiffs' affidavits similarly establish that members of the various medical organizations, represented by the organizations under the "doctrine of associational standing," are, like the researcher Plaintiffs, also meaningfully prepared and possess the desire to engage in *BRCA1/2* testing were the patents-in-suit invalidated. See, e.g., Hegde Decl. I 6-12; Hubbard Decl. ¶ 3-9; Kant Decl. ¶ 4-6.

The remaining non-researcher Plaintiffs have also established the existence of sufficient "meaningful preparations" to satisfy this prong of the standing inquiry. As an initial matter, the non-researcher Plaintiffs cannot be found to have failed to satisfy the meaningful preparation requirement on the grounds that the researcher Plaintiffs have not yet chosen to engage in infringing *BRCA* testing. Potential contributory infringers, such as the non-researcher Plaintiffs, may very well understand the precise nature of, and be prepared to take advantage of, the services of a potential infringer were the latter not prevented from offering those services by a third party's assertion of its patent rights. Here, it is alleged that the researcher Plaintiffs would offer infringing *BRCA1/2* genetic testing services of the

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<sup>19</sup> According to Plaintiffs' counsel, all that would be required to begin genetic testing would be to order the necessary oligonucleotides specific to the *BRCA1/2* genes, a delay of less than a month. Although Defendants raise the possibility that state certification may, in some instances, be required in order for Plaintiffs to engage in clinical *BRCA* testing, they have offered no evidence suggesting that this would constitute a delay of sufficient length to render the dispute of insufficient immediacy to warrant judicial intervention.



type the non-researcher Plaintiffs would solicit or encourage others to solicit. The Defendants cite no authorities establishing that only potential direct, and not potential contributory infringers can have standing in a declaratory judgment action.<sup>20</sup>

The Plaintiffs have set forth sufficient factual allegations to establish that the non-researcher Plaintiffs are meaningfully prepared to engage in contributory infringement so as to render the controversy between them and the Defendants of "sufficient immediacy and reality." MedImmune, 549 U.S. at 126 (citation omitted) ; see, e.g., Matloff Decl. ¶¶ 4, 10-15; Reich Decl. ¶¶ 3, 7-11, 14-15; Brenner Decl. ¶¶ 2-3, 9; Ceriani Decl. ¶ 11; Limary Decl. ¶ 9; Girard Decl. ¶ 10; Fortune Decl. ¶ 8; Thomason Decl. ¶ 10. Indeed, for these Plaintiffs, whose infringing activity would constitute nothing more than taking advantage of alternatives to Myriad's *BRCA1/2* testing or encouraging others to do the same, it is difficult to conceive what more "meaningful preparation" would be required.<sup>21</sup>

The contentions of the Defendants in urging the Plaintiffs' lack of standing to bring a declaratory

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<sup>20</sup> Animal Legal Defense Fund, cited by Defendants, addressed the standing of a third party to challenge the findings of a PTO Examiner during examination of a patent and has no bearing on standing in the context of a declaratory judgment action. See Animal Legal Defense Fund, 932 F.2d, 920, 930 (Fed. Cir. 1991) ("A third party has no right to intervene in the prosecution of a particular patent application to prevent issuance of an allegedly invalid patent.").

<sup>21</sup> Similarly, it is difficult to envision what preparatory activity would be required to infringe the claims-in-suit covering the comparison of the *BRCA1/2* gene sequence.

judgment action present a stark alternative: the deliberate violation of the patents-in-suit in order to challenge their constitutionality and validity. The risks, expense, and uncertainty of that protracted litigation process to compel the Defendants to defend the patents-in-suit are well known and recognized. Under the unique circumstances of this action and the pendency of the Plaintiffs' motion for summary judgment, the declaratory judgment procedure is preferable. It offers a far speedier and potentially less risky and protracted route to a resolution of the direct and fundamental issues. See Elecs. for Imaging, 394 F.3d at 1346.

For the foregoing reasons, the Plaintiffs possess the necessary standing to bring their claims against the Defendants.

## **VI. JURISDICTION EXISTS OVER THE DIRECTORS**

The Defendants have moved to dismiss the Directors as defendants, pursuant to Fed. R. Civ. P. 12(b) (2), for lack of personal jurisdiction. In considering this challenge to personal jurisdiction, Federal Circuit law applies because the jurisdictional issue is "intimately involved with the substance of the patent laws." Autogenomics, Inc. v. Oxford Gene Tech, Ltd., 566 F.3d 1012, 1016 (Fed. Cir. 2009) (quoting Avocent Huntsville Corp. v. Aten Int'l Co., 552 F.3d 1324, 1328 (Fed. Cir. 2008)).

"In the procedural posture of a motion to dismiss, a district court must accept the uncontroverted allegations in the plaintiff's complaint as true and resolve any factual conflicts in the affidavits in the plaintiff's favor." Elecs. for

Imaging, 340 F.3d at 1349 (internal citations omitted). Furthermore, because discovery has not yet been conducted, the Plaintiffs need only make a prima facie showing that the Directors are subject to personal jurisdiction. Avocent, 552 F.3d at 1329; Elecs. for Imaging, 340 F.3d at 1349.

"Determining whether personal jurisdiction exists over an out-of-state defendant involves two inquiries: whether a forum state's long-arm statute permits service of process, and whether the assertion of personal jurisdiction would violate due process." Avocent, 552 F.3d at 1329 (quoting Inamed Corp. v. Kuzmak, 249 F.3d 1356, 1359 (Fed. Cir. 2001)). "[D]ue process requires only that in order to subject a defendant to a judgment in personam, if he be not present within the territory of the forum, he have certain minimum contacts with it such that the maintenance of the suit does not offend traditional notions of fair play and substantial justice." Int'l Shoe Co. v. Washington, 326 U.S. 310, 316 (1945) (internal quotations omitted).

The Supreme Court has distinguished between "general" and "specific" forms of personal jurisdiction. General jurisdiction requires that a defendant have "continuous and systematic" contacts with the forum state. Helicopteros Nacionales de Columbia, S.A. v. Hall, 466 U.S. 408, 415-16 (1984). Minimum contacts establishing specific jurisdiction exist where "the defendant has purposefully directed his activities at residents of the forum and the litigation results from alleged injuries that arise out of or relate to those activities." Burger King Corp. v. Rudzewicz, 471 U.S. 462, 472-73 (1985) (internal quotes and citations omitted). "Once it has been

decided that a defendant purposefully established minimum contacts within the forum State, these contacts may be considered in light of other factors to determine whether the assertion of personal jurisdiction would comport with 'fair play and substantial justice.'" Id. (quoting Int'l Shoe, 326 U.S. at 320). Relevant factors include "'the burden on the defendant,' 'the forum State's interest in adjudicating the dispute,' 'the plaintiff's interest in obtaining convenient and effective relief,' 'the interstate judicial system's interest in obtaining the most efficient resolution of controversies,' and the 'shared interest of the several States in furthering fundamental substantive social policies.'" Id. at 477 (quoting World-Wide Volkswagen Corp. v. Woodson, 444 U.S. 286, 292 (1980)).

In an action seeking a declaratory judgment of patent invalidity, the Federal Circuit has held that specific jurisdiction exists if "(1) the defendant purposefully directed its activities at residents of the forum, (2) the claim arises out of or relates to those activities, and (3) the assertion of personal jurisdiction is reasonable and fair." Breckenridge Pharm., Inc. v. Metabolite Labs, Inc., 444 F. 3d 1356 (Fed. Cir. 2006). "The first two factors correspond with the 'minimum contacts' prong of the International Shoe analysis, and the third factor corresponds with the 'fair play and substantial justice' prong of the analysis." Inamed, 249 F.3d at 1360. With respect to the last prong, the burden of proof is on the defendant, which must "present a compelling case that the presence of some other considerations would render jurisdiction unreasonable." Burger King, 471 U.S. at 476-77.

The Plaintiffs assert claims against the Directors not in their individual capacities, but in their capacity as state officials, pursuant to Ex parte Young, 209 U.S. 123 (1908). The threshold question is whether, for purposes of the personal jurisdiction analysis, the contacts of the Directors as individuals or as state officials should be examined.

Under Ex parte Young, state officials are treated as state actors for all but Eleventh Amendment sovereign immunity issues, regardless of whether the conduct in question is authorized by state law. See Florida Dep't of State v. Treasure Salvos, Inc., 458 U.S. 670, 697 (1982) (suit for relief against a state officer is not barred by the Eleventh Amendment); Home Tel. & Tel. v. Los Angeles, 227 U.S. 278, 282-85 (1913) (officer sued in his official capacity treated as state actor for 14th Amendment purposes). As a result, an official capacity action is, in all but name, a suit against the governmental entity. Kentucky v. Graham, 473 U.S. 159, 165-66 (1985) ("Official capacity suits . . . 'generally represent only another way of pleading an action against an entity of which an officer is an agent.'" (quoting Monell v. N.Y. City Dep't of Social Servs., 436 U.S. 658, 690 n.55 (1978))); see also Will v. Mich. Dep't of State Police, 491 U.S. 58, 71 (1989) ("[A] suit against a state official in his or her official capacity is not a suit against the official but rather is a suit against the official's office. As such, it is no different from a suit against the State itself." (internal citations omitted)). Consistent with these principles, official capacity defendants may assert only those defenses available to the governmental entity, rather than those available to the defendant as an individual. Graham, 473 U.S. at 165-66; see

also Will, 491 U.S. at 71.<sup>22</sup>

When confronted with the issue of specific personal jurisdiction<sup>23</sup> over a non-forum state official, courts routinely examine the contacts of the state officials in their capacity as representatives of the state, rather than their contacts with the forum in their individual capacity. See, e.g., Stroman Realty, Inc. v. Wercinski, 513 F.3d 476, 484 (5th Cir. 2008) (examining extent of defendant's contact with forum as a representative of the state of Arizona);<sup>24</sup> Grand River Enters. Six Nations, Ltd. v. Pryor, 425 F3d. 158, 166 & n.2 (2d Cir. 2005)

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<sup>22</sup> The treatment of state officials sued in their official capacities by the Federal Rules of Civil Procedure reflects this conception of official capacity suits. Those officials need not be identified by name; they are automatically replaced as parties by their successors; and any relief granted is automatically binding not just on the named individual but on his or her successor. See Fed. R. Civ. P. 17(d), 25(d); Hafer v. Melo, 502 U.S. 21, 25 (1991).

<sup>23</sup> Because specific personal jurisdiction exists over the Directors, Plaintiffs' general personal jurisdiction arguments are not addressed here

<sup>24</sup> Defendants cite language in Stroman which they assert refutes Plaintiffs' position. See Defs.' Mem. of Law in Opp. to Pls.' Mot. to Conduct Jurisdictional Disc. at 4 (citing Stroman, 513 F.3d at 485 ("Even if the State of Arizona itself - as a sovereign state, subject to Eleventh Amendment protections - derived a benefit from any 'effects' in Texas generated by the action of the Commissioner, the benefit does not run to those officials in their individual capacity, stripped of their sovereign immunity cloak.")). The cited language, however, in addition to being dicta, is taken from the discussion of whether a "commercial benefit" accrued to the state. It does not establish that the contacts of the official's department are not imputed to her as an official defendant for purposes of personal jurisdiction.

(analyzing contacts of state attorneys general with New York as representatives of their states).

The Defendant's rely on Great Western United Corp. v. Kidwell, 577 F.2d 1256 (5<sup>th</sup> Circuit, 1978), rev'd on other grounds by Leroy v. Great Western United Corp., 443 U.S. 173 (1979), for their assertion that the jurisdictional analysis properly focuses on the contacts of the Directors as individuals with New York. In Great Western, the Court of Appeals considered whether a court in the Northern District of Texas could assert personal jurisdiction over Idaho officials enforcing an Idaho law that had "substantial consequences" in the forum. Great Western, 557 F.2d at 1265, 1267. The Defendants argue that the Fifth Circuit's opinion established that because as state cannot authorize unconstitutional action, a suit for injunctive relief against a state official in his official capacity cannot be viewed as a suit against the state. Instead, it must be viewed as a suit against the official as a private individual, and the contacts to be examined for purposes of personal jurisdiction must be the contacts of the defendant as an individual, rather than as an extension of the state.

The discussion in Great Western cited by the Defendants, however, did not address the question of personal jurisdiction. Instead, the Fifth Circuit considered only the narrow issue of whether the Idaho official was immune from suit outside of Idaho. See id. at 1265 ("Initially McEldowney contends that his status as a state official means that even though he may be sued under Ex Parte Young . . . he may not be sued outside Idaho without his consent."

(citation omitted)).<sup>25</sup> In contrast, when the court turned to the issue of "whether due process permits a court in Texas to exercise jurisdiction over the Idaho official who has enforced the Idaho takeover law [against a Texas corporation]," id. at 1266, the Fifth Circuit examined the actions of the defendants as representatives of the state, not as individual defendants. See, e.g., id. at 1267 (evaluating defendants' contacts with the forum by examining activities relating to the enforcement of the Idaho takeover statute). On the basis of those contacts, the court concluded that exercising personal jurisdiction over the Idaho officials pursuant to the Texas long arm statute did not violate considerations of due process. Id. at 1266.

The Defendants also rely on Pennington Seed, Inc. v. Produce Exch. No. 299, 457 F.3d 1334 (Fed. Cir. 2006). There, the Federal Circuit's opinion contained no discussion about the proper analysis for considering a state official's contacts with a forum for personal jurisdiction purposes, instead finding that there were no allegations that the university officials had the necessary contacts with the forum. Id. at 1344. The court's observation concerning the location of the officials' residences was made only in passing to note that even that fact failed to establish purposeful activity directed to the forum. Id.

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<sup>25</sup> To the extent the Fifth Circuit's discussion may be viewed more broadly as establishing that a state official sued in his official capacity should be treated as an individual defendant, such a holding is at odds with subsequent Supreme Court caselaw. See Hafer, 502 U.S. at 26; Will, 491 U.S. at 71; Graham, 473 U.S. at 165-66.



In light of the foregoing, the question of jurisdiction over the Directors should be resolved based upon the Directors' contacts, as representatives of the state, with New York.

Under New York C.P.L.R. § 302(a) (1), specific jurisdiction exists where a defendant "transacts any business within the state or contracts anywhere to supply goods or services in the state." A party "transacts business" when it "purposefully avails [itself] of the privilege of conducting activities within [New York], thus invoking the benefits and protections of its laws." McKee Elec. Co. v. Rauland-Borg Corp., 20 N.Y.2d 377, 382 (1967) (citation omitted). Here, the Directors have entered into an exclusive license agreement that permits Myriad to market the UURF's products and services in New York and creates continuing obligations for UURF.<sup>26</sup> As a result, the Directors have purposefully availed themselves of the privilege of conducting business in New York. Because the claims in this case are directly related to that license agreement and to Defendants' patent enforcement activities that have occurred in New York, the requisite "articulable nexus" between the cause of action and the business activity is present. See, e.g., Credit Lyonnais Sec. (U.S.A.), Inc. v. Alcantara, 183 F.3d 151, 153 (2d Cir. 1999). Consequently, specific personal jurisdiction over the Directors exists under New York's long arm statute. See N.Y. C.P.L.R. § 302(a) (1) (2008).

The exercise of specific personal jurisdiction over the Directors also comports with considerations of due process. The Federal Circuit has established

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<sup>26</sup> See infra.

that in the context of an action seeking a declaration of patent invalidity, due process considerations are satisfied when the defendants have (1) engaged in cease-and-desist efforts directed to parties in the forum state or attempted to license the patents at issue in the forum state;<sup>27</sup> and (2) entered into an exclusive license agreement with an entity that markets and sells its products and services in the forum state. See Breckenridge, 444 F.3d at 1366; see also Avocent, 552 F.3d at 1333-35; Akro Corp. v. Luker, 45 F.3d 1541, 1546 (Fed Cir. 1995); Genetic Implant Sys. v. Core-Vent Corp., 123 F.3d 1455, 1458-59 (Fed. Cir. 1997). The critical requirement for purposes of establishing due process is that the license agreement impose continuing obligations on the patentee, such as the right to enforce or defend the patents, so that the patentee maintains an ongoing relationship with the licensee operating within the forum that goes beyond the mere receipt of royalty income. See Breckenridge, 444 F.3d at 1366. The personal jurisdiction analysis of the Directors' contacts with the forum state thus turns on "the defendant's relationship with its exclusive licensee." Id. at 1365; see also Akro, 45 F.3d at 1546-47.

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<sup>27</sup> Although Defendants appear to assert that only cease-and-desist letters sent to a party in the forum may be relied upon to establish subject matter jurisdiction, the Federal Circuit has stated that offers to license may also serve as the requisite first point of contact with the forum. See Breckenridge, 444 F.3d at 1366 ("Thus, the crux of the due process inquiry should focus first on whether the defendant has had contacts with parties in the forum state beyond the sending of cease and desist letters or mere attempts to license the patent at issue there.").

Here, the Defendants have attempted to license the patents-in-suit to Dr. Ostrer, a resident of New York.<sup>28</sup> See Ostrer Decl. ¶ 7 & Ex. 2. They have also caused or participated in direct in-person cease-and-desist efforts that occurred in New York. Kazazian Decl. ¶ 6. In addition, the agreement between Myriad and UURF creates ongoing obligations on the part of the UURF beyond the mere receipt of royalty payments. As set forth in the standard licensing term sheet, UURF's policy is to retain the right to enforce licensed patents and to initiate proceedings regarding them. Ravicher Aff. Ex. 7. Myriad, of course, has a similar ability to take action enforcing the patents as demonstrated by its actions to enforce the patents-in-suit.<sup>29</sup> See supra. Both UURF and Myriad appear to have obligations relating to the enforcement and maintenance of the patents at issue in this lawsuit which establishes that the Directors have purposefully directed their activities at New York as a matter of law.<sup>30</sup> See, e.g., Avocent, 55 F.3d at 1336 ("[W]hen the patentee enters into an exclusive license or other obligation relating to the exploitation of the patent by such licensee or contracting party in the forum . . . the

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<sup>28</sup> While the offer to license made to Dr. Ostrer was sent on Myriad Genetics' letterhead, Plaintiffs assert that Myriad and UURF acted together in asserting the rights granted by the patents-in-suit. See, e.g., Compl. IT 29, 49.

<sup>29</sup> Neither party contests that Myriad purposefully engages in business in New York, where it both solicits and sells a significant volume of its testing services.

<sup>30</sup> In addition, both the Directors and Myriad are represented jointly by counsel, further suggesting the existence of an ongoing relationship between the two entities. See Breckenridge, 44 F.3d at 1367.

patentee may be said to purposefully avail itself of the forum and to engage in activity that relates to the validity and enforceability of the patent."); Breckenridge, 444 F.3d at 1366; Akro, 45 F.3d at 1546.

In addition, the claims in this suit directly relate to the license agreement between the Defendants and their efforts to enforce the patents. See, e.g., Akro, 45 F.3d at 1548-49 ("[The patentee's] exclusive license agreement with [the plaintiff's] local competitor Pretty Products undoubtedly relates to [the plaintiff's] challenge to the validity and enforceability of the '602 patent."). Finally, the Defendants have not presented other considerations that would render it unfair or unjust for the Court to exercise jurisdiction over them.

Consequently, the Court's exercise of personal jurisdiction over the Directors satisfies the requirements of due process.

## **VII. THE ALLEGATIONS OF CONSTITUTIONAL VIOLATIONS ARE ADEQUATE**

In ruling on a motion to dismiss made pursuant to Rule 12(b) (6), the Court must accept all well-pleaded factual allegations in the complaint as true. Erickson v. Pardus, 551 U.S. 89, 94 (2007) (citing Bell Atl. Corp. v. Twombly, 550 U.S. 544, 555 (2007)). In addition, the Court must "construe[ ] the complaint liberally" and "draw[ ] all reasonable inferences in the plaintiff's favor." Chambers v. Time Warner, Inc., 282 F.3d 147, 152 (2d Cir. 2002) (citing Gregory v. Daly, 243 F.3d 687, 691 (2d Cir. 2001)). The question before the court "is not whether a

plaintiff will ultimately prevail but whether the claimant is entitled to offer evidence to support the claims." Villager Pond, Inc. v. Town of Darien, 56 F.3d 375, 378 (2d Cir. 1995) (quoting Scheuer v. Rhodes, 416 U.S. 232, 235-36 (1974)). Consequently, the complaint should not be dismissed on a motion for judgment on the pleadings unless it appears beyond doubt that the plaintiff can prove no set of facts in support of its claims that would entitle it to the relief it seeks. Faconti v. Potter, 242 Fed. App'x 775, 777 (2d Cir. 2007).

The USPTO challenges the sufficiency of Plaintiffs' complaint in light of the Supreme Court's recent holding in Ashcroft v. Iqbal, 129 S.Ct. 1937 (2009). Iqbal set forth "[t]wo working principles" to guide a court's analysis of a complaint's sufficiency. Id. at 1949. "First, the tenet that a court must accept as true all of the allegations contained in a complaint is inapplicable to legal conclusions." Id. "Second, only a complaint that states a plausible claim for relief survives a motion to dismiss." Id. at 1950.

In this case, the Plaintiffs have pled sufficient factual allegations to satisfy the standard set forth in Iqbal. The Complaint alleges the existence of a specific, written policy for the patenting of genes and the parameters of the policy. Compl. ¶ 50. The policy, contained in the Federal Register, Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001), is alleged by the Plaintiffs to be applied to a series of specific patents and patent claims. Compl. passim. The Plaintiffs describe each application of the policy in considerable detail. See, e.g., Compl. ¶¶ 55-80. Similar allegations and specificity apply to the Plaintiffs' allegations of the USPTO's

practices. See, e.g., Compl. ¶¶ 53-54.

The Complaint further alleges that the information encoded in the *BRCA1/2* genetic sequences, rather than being the result of an inventive process, exists in nature. See Compl. ¶¶ 34, 46, 51, 55-60. The Complaint also alleges that the existence of certain mutations in *BRCA1/2* and their correlation with an increased risk of breast and/or ovarian cancer constitutes nothing more than a naturally occurring phenomenon. See Compl. ¶¶ 61-80. Based on these factual allegations, the Plaintiffs assert that the patents-in-suit grant Myriad ownership rights over products of nature, laws of nature, natural phenomena, abstract ideas, and basic human knowledge and thought in violation of the First Amendment's protections over freedom of thought. Compl. ¶¶ 52, 54. In addition, the Plaintiffs assert that Myriad's ownership of correlations between certain *BRCA1/2* mutations and an increased risk of breast and/or ovarian cancer has inhibited further research on *BRCA1/2* as well as genes that interact with *BRCA1/2*. See, e.g., Compl. ¶¶ 96-98, 101. As a result, the patents-in-suit are alleged to violate Article I, section 8, clause 8 of the Constitution which directs Congress to "promote the Progress of Science and useful Arts . . . ." Compl. ¶¶ 52, 54.

The facts alleged in the Complaint are plausible, specific, and form a sufficient basis for Plaintiff's legal arguments. Consequently, the pleading requirements as set forth in Iqbal are satisfied.

**VIII. CONCLUSION**

For the reasons stated above, Defendants' motion to dismiss the Complaint is denied.

Defendants' opposition to Plaintiffs' motion for summary judgment will be due December 2, 2009. Plaintiffs' reply will be due on December 9, 2009, and argument will be heard on December 11, 2009, at ten o'clock in the forenoon in Courtroom 18C, unless good cause is shown to alter the date of the submissions.

It is so ordered.

**New York, N.Y.**

**November 1, 2009**

**Robert W. Sweet  
U.S.D.J.**

## CLAIMS

Claims 1, 2, 5, 6, and 7 of patent 5,747,282 ('282)

1. An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID No. 2.

2. The isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID No. 1.

5. An isolated DNA having at least 15 nucleotides of the DNA of claim 1.

6. An isolated DNA having at least 15 nucleotides of the DNA of claim 2.

7. An isolated DNA selected from the group consisting of:

(a) a DNA having the nucleotide sequence set forth in SEQ ID No. 1 having T at nucleotide position 4056;

(b) a DNA having the nucleotide sequence set forth in SEQ ID No. 1 having an extra C at nucleotide position 5385;

(c) a DNA having the nucleotide sequence set forth in SEQ ID No. 1 having G at nucleotide position 5443; and



(d) a DNA having the nucleotide sequence set forth in SEQ ID No. 1 having 11 base pairs at nucleotide position 189-199 deleted.

Claims 1, 6, and 7 of patent 5,837,492 ('492)

1. An isolated DNA molecule coding for a BRCA2 polypeptide, said DNA molecule comprising a nucleic acid sequence encoding the amino acid sequence set forth in SEQ ID No. 2.

6. An isolated DNA molecule coding for a mutated form of the BRCA2 polypeptide set forth in SEQ ID No. 2, wherein said mutated form of the BRCA2 polypeptide is associated with a susceptibility to cancer.

7. The isolated DNA molecule of claim 6, wherein the DNA molecule comprises a mutated nucleotide sequence set forth in SEQ ID No. 1.

Claim 1 of patent 5,693,473 ('473)

1. An isolated DNA comprising an altered BRCA1 DNA having at least one of the alterations set forth in Tables 12A, 14, 18, or 19 with the proviso that the alteration is not a deletion of four nucleotides corresponding to base numbers 4184-4187 in SEQ. ID No. 1.