United States Court of Appeals for the Federal Circuit

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, THE AMERICAN COLLEGE OF MEDICAL GENETICS, THE AMERICAN SOCIETY FOR CLINICAL PATHOLOGY, THE 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,
Plaintiffs-Appellees,

v.

UNITED STATES PATENT AND TRADEMARK OFFICE,
Defendant,

and

MYRIAD GENETICS, INC.,
Defendant-Appellant,

and

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,

IN THEIR OFFICIAL CAPACITY AS DIRECTORS OF THE UNIVERSITY OF UTAH RESEARCH FOUNDATION,
Defendants-Appellants.

2010-1406

Appeal from the United States District Court for the Southern District of New York in Case No. 09-CV-4515, Senior Judge Robert W. Sweet.

Decided: August 16, 2012

CHRISTOPHER A. HANSEN, American Civil Liberties Union Foundation, of New York, New York, argued for plaintiffs-appellees. With him on the brief were SANDRA S. PARK, ADEN FINE, and LENORA M. LAPIDUS. Of counsel on the brief were DANIEL B. RAVICHER and SABRINA Y. HASSAN, Public Patent Foundation, Benjamin N. Cardozo, School of Law, of New York, New York.

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Before LOURIE, BRYSON, and MOORE, *Circuit Judges*.

Opinion for the court filed by *Circuit Judge* LOURIE.
Opinion concurring in part filed by *Circuit Judge* MOORE.
Opinion concurring in part and dissenting in part filed by *Circuit Judge* BRYSON.

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. *Ass'n 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. *Ass'n 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.

This appeal has returned to us as, a petition for certiorari having been filed from our decision of July 29, 2011, the Supreme Court of the United States granted the petition, vacated our decision, and remanded the case to us for further consideration in light of its decision in *Mayo Collaborative Services v. Prometheus, Inc.*, 566 U.S. ___, 132 S. Ct. 1289 (2012). *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 132 S. Ct. 1794 (2012). We invited and received briefing by the parties and interested amici and held oral argument on July 20, 2012. Our decision on remand follows. It both decides the issues that were before us in the original appeal and evaluates the effect of *Mayo* on those issues.

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 because each of the claimed molecules represents a nonnaturally occurring

composition of matter. We also reverse the district court's decision that Myriad's method claim to screening potential cancer therapeutics via changes in cell growth rates of transformed cells is directed to a patent-ineligible scientific principle. We affirm the court's decision, however, 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.*, 669 F. Supp. 2d 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.

'282 patent col.153 l.55 – col.154 l.56.[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; the latter sequence is colloquially referred to as cDNA. *Id.* 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 claims 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 col.161 ll.17-25 (emphases added).

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[1] In addition to representative claims 1, 2, and 5 of the '282 patent, other claims to isolated DNA molecules at issue in this appeal include: claims 6 and 7 of the '282 patent; claims 1, 6, and 7 of the '492 patent; and claim 1 of the '473 patent.

> 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 col.155 ll.2-17 (emphasis added).[2]

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

[2] The claims currently before us that recite methods of "analyzing" or "comparing" *BRCA* sequences are: claims 1 of the '999, '001, and '441 patents and claims 1 and 2 of the '857 patent.

> 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.

'282 patent col.156 ll.13–24 (emphases added).

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.[3] The human genome, the entirety of human genetic information, contains approximately 22,000 genes, which form the basis of human inheritance. The majority of genes act by guiding the production of polypeptide chains that form proteins. Proteins in turn make up living matter and catalyze a variety of 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,[4] together via a sugar-

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[3] The district court's opinion, *SJ Op.*, 702 F. Supp. 2d at 192-203, contains a detailed and comprehensive discussion of the science involved in this case. We repeat only the basics here.

[4] Covalent bonds are chemical bonds characterized by the sharing of electrons between atoms in a molecule.

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.

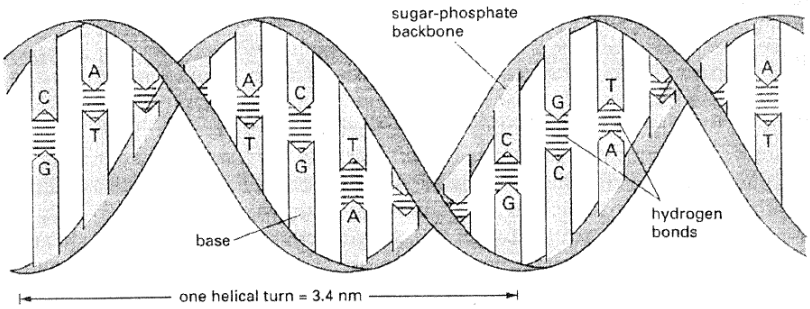

Figure 1

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 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"). During transcription, the DNA double helix is unwound and each nucleotide on the non-coding, or template, DNA strand is used to make a complementary, single-stranded RNA molecule that mirrors 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, followed by "splicing" the exons 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 excising the introns and splicing of the exons to produce an mRNA containing only exon sequences.

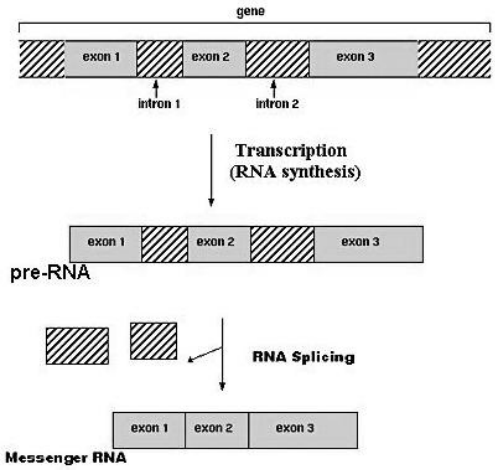

Figure 2

Following transcription and splicing, the resulting mRNA is "translated" into the encoded protein. Genes, and their corresponding mRNAs, encode proteins via three-nucleotide combinations called codons. Each codon triplet 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 AUG 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.

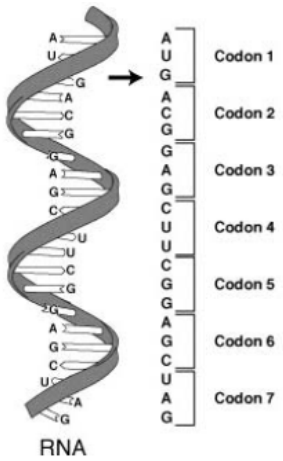

Figure 3

Changes, or mutations, in the sequence of a human gene can alter the production, structure, and/or 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 *G*CU to *C*CU changes an alanine in the encoded protein to a proline. Larger scale variations include the deletion, rearrangement, or duplication of larger DNA segments—ranging from several hundreds to over a million nucleotides—and can 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 disease risk.

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 comprising a single extended DNA molecule wrapped around proteins called histones, as shown in Figure 4 below.

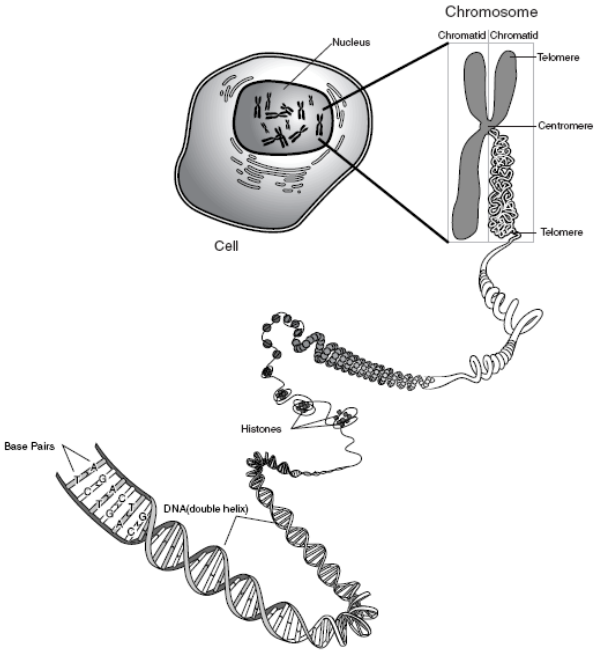

Figure 4

Each chromosome contiguously spans millions of bases and encompasses many discrete genes. 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 chromosomal gene sequence.

II.

Certain 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 therapy 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.[5]

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 Officer 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 U.S. patents covering the isolated *BRCA1* gene and diagnostic

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[5] 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 resulting 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 such patent, the '492 patent, issued on November 17, 1998.

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 alterations 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 the 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, which 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 covered by 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. Dr. Ostrer[6] 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,

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[6] On July 27, 2011, two days before we issued our initial, now-vacated decision in this case, Myriad notified the court that Dr. Ostrer was leaving NYU to assume a position at the Albert Einstein College of Medicine and Montefiore Medical Center, effective August 29, 2011. In response, Plaintiffs submitted a supplemental declaration from Dr. Ostrer stating that, in his new position, he still seeks to undertake BRCA diagnostic testing, still has the resources and expertise to conduct such testing, and would immediately do so if Myriad's patents were invalidated. Following remand from the Supreme Court, we have also received from Myriad a related "suggestion of mootness" and motion to remand or dismiss. We declined the suggestion and denied the motion. We now review this case on the facts and arguments briefed and presented to us.

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.*, 669 F. Supp. 2d 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.*, 702 F. Supp. 2d 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) (en banc), *aff'd on other grounds*, *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 *Mayo* 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.*, 702 F. Supp. 2d at 234-35 (citing *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, 628 F.3d 1347, 1350 (Fed. Cir. 2010), *rev'd,* 132 S. Ct. 1289 (2012)). 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 justici-

able 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. Pac. 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. STMicroelecs., 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 in light of 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 un-

dertake the *BRCA*-related activities that they desire because of Myriad's enforcement of its patent rights covering *BRCA1/2*.[7] 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" 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

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[7] 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.

"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 Pennsyl-

vania, 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 avoid 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.*, Appellants' Br., 2010 WL 4600106, at 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.[8]

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[8] 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.").

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 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 the first oral argument in this case 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 the asserted claims and decline to 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.

Although we affirm the district court's decision to exercise declaratory judgment jurisdiction over this case, we do so on narrower grounds. The district court failed to limit its jurisdictional holding to affirmative acts by the patentee directed at specific Plaintiffs, *see SanDisk*, 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.*, 669 F. Supp. 2d 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 on isolated DNA sequences 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. The various organizational plaintiffs in this suit in particular were not the target of any enforcement action or offered license agreements by Myriad and had made no preparation to undertake potentially infringing activities. They accordingly suffered no injury and thus lack standing to bring this action. *See Prasco*, 537 F.3d at 1338-42; *Cat Tech*, 528 F.3d at 880-81.

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. Subject Matter Eligibility

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, natural phenomena, and abstract ideas' are not patentable." *Mayo*, 132 S. Ct. at 1293 (quoting *Diamond v. Diehr*, 450 U.S. 175, 185 (1981)). The Court has also referred to those exceptions as precluding the patenting of 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 Bros. 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, its method claims directed to "analyzing" or "comparing" DNA sequences, and its claim to a method for screening potential cancer therapeutics. We address each in turn. Before reviewing the applicability of the Supreme Court's *Mayo* holding to the claims of the Myriad patents, however, it is important to state what this appeal is not about. It is not about whether individuals suspected of having an increased risk of developing breast cancer are entitled to a second opinion. Nor is it about whether the University of Utah, the owner of the instant patents, or Myriad, the exclusive licensee, has acted improperly in its licensing or enforcement policies with respect to the patents. The question is also not whether is it desirable for one company to hold a patent or license covering a test that may save people's lives, or for other companies to be excluded from the market encompassed by such a patent—that is the basic right provided by a patent, *i.e.*, to exclude others from practicing the patented subject matter. It is also not whether the claims at issue are novel or nonobvious or too

broad. Those questions are not before us. It is solely whether the claims to isolated BRCA DNA, to methods for comparing DNA sequences, and to a process for screening potential cancer therapeutics meet the threshold test for patent-eligible subject matter under 35 U.S.C. § 101 in light of various Supreme Court holdings, particularly including *Mayo*. The issue is patent eligibility, not patentability.

We would further note, in the context of discussing what this case is not about, that patents on life-saving material and processes, involving large amounts of risky investment, would seem to be precisely the types of subject matter that should be subject to the incentives of exclusive rights. But disapproving of patents on medical methods and novel biological molecules are policy questions best left to Congress, and other general questions relating to patentability and use of patents are issues not before us. As will be seen, on the limited questions before us, we conclude that the composition claims and the screening claim involving growing a transformed host cell meet the standards for patent eligibility, while the claimed methods for "analyzing" or "comparing" do not.

A. Composition Claims: Isolated DNA Molecules

i.

The principal claims of the patents before us on remand relate to isolated DNA molecules. *Mayo* does not control the question of patent-eligibility of such claims. They are claims to compositions of matter, expressly authorized as suitable patent-eligible subject matter in § 101. As to those claims, the issue of patent-eligibility remains, as it was on the first appeal to this court, whether they claim patent-ineligible products of nature. We hold that they do not. The isolated DNA molecules before us are not found in nature. They are obtained in

the laboratory and are man-made, the product of human ingenuity. While they are prepared from products of nature, so is every other composition of matter. All new chemical or biological molecules, whether made by synthesis or decomposition, are made from natural materials. For example, virtually every medicine utilized by today's medical practitioners, and every manufactured plastic product, is either synthesized from natural materials (most often petroleum fractions) or derived from natural plant materials. But, as such, they are different from natural materials, even if they are ultimately derived from them. The same is true of isolated DNA molecules.

ii.

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 manufacture or composition of matter" with "a distinctive name, character, and use." Appellants' Br., 2010 WL 4600106, at 41-42 (quoting *Chakrabarty*, 447 U.S. at 309-10). Myriad contends that isolated DNA does not exist in nature and that isolated DNAs, unlike native DNAs, can be used as primers and probes for diagnosing cancer. Moreover, Myriad asserts that an ultimately-derived-from "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. Regarding *Mayo*, Myriad argues that the Supreme Court's decision did not address or alter the established patent-eligibility test for composition claims, such that the standards announced in *Chakrabarty* still govern this appeal. To the extent that the general principles discussed in *Mayo* bear on the DNA claims, Myriad maintains that isolated DNA represents a nonnatural, man-made invention distinct from the lack of human ingenuity underlying the method claims there at issue.

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 part of the same nucleotide sequence as native DNAs, they do not have any "markedly different" characteristics. Furthermore, according to Plaintiffs, the isolated DNA claims preempt products and laws of nature, excluding anyone from working with the *BRCA* genes and the genetic information they convey. Under *Mayo*, Plaintiffs assert that any structural differences relative to the chromosomal *BRCA* genes do not add "enough" to the underlying natural genetic sequences to render Myriad's isolated DNA molecules patentable under § 101.

The government as amicus curiae does not defend the longstanding position of the PTO, a government agency, 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,[9] 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 the first oral argument, the government illustrated its position by way of a so-called "magic microscope" test (an invention in and of itself, although probably not patent-eligible). Oral Arg. at 46:50-47:50. According to the government's test then, if an imaginary microscope could focus in on the claimed DNA molecule as it exists in the human body, the claim covers ineligible subject matter. The government thus argued 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 contended, because an imaginary microscope could not focus *in vivo* on a cDNA 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.

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[9] 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. We agree.

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.

iii.

While *Mayo* and earlier decisions concerning method claim patentability provide valuable insights and illuminate broad, foundational principles, the Supreme Court's decisions in *Chakrabarty* and *Funk Brothers* set out the primary framework for deciding the patent eligibility of compositions of matter, including isolated DNA molecules.[10]

In *Chakrabarty*, the Court addressed the question whether a man-made, living microorganism is a patent-

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[10] Other Supreme Court decisions cited by the parties and amici relating to patented manufactures and compositions of matter were decided based on lack of novelty, not patent-eligible 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)).

eligible 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 patent-eligible 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 the mixed bacterial cultures found unpatentable in *Funk Brothers*, again casting this case, more relating to 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 that 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 cooperative qualities 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 applying the newly discovered bacterial compatibility to create a mixed 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 oil-degrading bacteria from the mixed cultures 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.

One distinction, therefore, between products of nature and 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 arrayed in useful combinations or harnessed to exploit newly discovered properties, have similar characteristics as in nature, and compositions that human intervention has given "markedly different," or "distinctive," characteristics. *Id.* (citing *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, the challenged claims are drawn to patent-eligible subject matter because the claims cover molecules that are markedly different—have a distinctive chemical structure and identity—from those found 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. Natural DNA exists in the body as one of forty-six large, contiguous DNA molecules. Each of those DNA molecules is condensed and intertwined with various proteins, including histones, to form a complex tertiary structure known as chromatin that makes up a larger structural complex, a chromosome. *See supra*, Figure 3. Inside living cells, the chromosomes are further encapsulated within a series of membranes and suspended in a complex intracellular milieu.

Isolated DNA, in contrast, is a free-standing portion of a larger, natural DNA molecule. 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 approximately 10,200 nucleotides and *BRCA1* to just around 5,500 nucleotides. Furthermore, claims 5 and 6 of the '282 patent cover isolated DNAs, *e.g.*, primers or probes, having as few as fifteen nucleotides of a *BRCA* sequence. Accordingly, *BRCA1* and *BRCA2* in their isolated states are different molecules from DNA that exists in the body; isolated DNA results from human intervention to cleave or synthesize a discrete portion of a native chromosomal DNA, imparting on that isolated DNA a distinctive chemical identity as compared to native DNA.

As the above description indicates, isolated DNA is not just purified DNA. Purification makes pure what was the same material, but was combined, or contaminated, with other materials. Although isolated DNA is 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. 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, albeit being "for every practical purpose a new thing commercially and therapeutically." 189 F. 95, 103 (C.C.S.D.N.Y. 1911). Judge Learned Hand's opinion for

the district court in that oft-cited case held the purified "Adrenalin" to be patent-eligible subject matter. *Id.* The *In re Marden* cases are similarly inapposite, directed as they are to the patent ineligibility of purified natural elements—ductile uranium, 47 F.2d 957 (CCPA 1931), and vanadium, 47 F.2d 958 (CCPA 1931)—that are inherently ductile in purified form. While purified natural products thus may or may not qualify for patent under § 101, the isolated DNAs of the present patents constitute an *a fortiori* situation, where they are not only purified; they are different from the natural products in "name, character, and use." *Chakrabarty*, 447 U.S. at 309-10.[11]

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

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[11] *In re Bergy*, relating to a purified microorganism, 596 F.2d 952, 967-68 (CCPA 1979), was once a companion case to *Chakrabarty* but was vacated by the Supreme Court and remanded for dismissal as moot when the inventors withdrew their claim from the pending application. *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 nonobvious claims to synthetically produced, substantially pure 2-methyl-2-pentenoic acid, 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 obvious).

isolated DNA molecules do not exist in nature within a physical mixture to be purified. They have to be chemically cleaved from their native chemical combination with other genetic materials. In other words, in nature, the claimed 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 that is obtained by human intervention. *See Chakrabarty*, 447 U.S. at 313 ("the relevant distinction [is] between products of nature . . . and human-made inventions"). In fact, some forms of isolated DNA may require no purification at all, because DNAs can be chemically synthesized directly as isolated molecules.

The above analysis holding the isolated DNA molecules to be patent-eligible subject matter applies to all of the asserted composition claims on appeal in this case. However, as the government has pointed out, claim 2 of the '282 patent is narrower than claim 1 and reads only on cDNAs, which lack the non-coding introns present in the genomic *BRCA1* gene.[12] While, as we have held, all of the claimed isolated DNAs are eligible for patent as compositions of matter distinct from natural DNA, the claimed cDNAs are especially distinctive, lacking the non-coding introns present in naturally occurring chromosomal DNA. They are even more the result of human intervention into nature and are hence patent-eligible subject matter. The government, as noted earlier, has agreed with that conclusion. Br. United States, 2010 WL 4853320, at 14-17.

The dissent disparages the significance of a "chemical bond," presumably meaning a covalent bond, in distin-

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[12] Claims 2 and 7 of the '282 patent and claim 7 of the '492 patent recite isolated cDNA molecules.

guishing structurally between one molecular species and another. But a covalent bond is the defining boundary between one molecule and another, and 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 connect different chemical moieties to one 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, albeit a key one: the information content contained in isolated and native DNAs' nucleotide sequences. 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 nonobviousness 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. 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 by their functions. In

fact, many different materials may have the same function (*e.g.*, aspirin, ibuprofen, and naproxen).

The district court in effect created a categorical rule excluding isolated genes from patent eligibility. *See SJ Op.*, 702 F. Supp. 2d 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 *Diehr*, 450 U.S. at 182), 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). Contrary to the conclusions of the district court and the suggestions of Plaintiffs and some amici, § 101 applies equally to all putative inventions, and isolated DNA is not and should not be considered a special case for purposes of patent eligibility under existing law. *See, e.g.*, *SJ Op.*, 702 F. Supp. 2d at 185 ("DNA represents the physical embodiment of biological information, distinct in its essential characteristics from any other chemical found in nature."); Appellees' Suppl. Br. at 4-5 ("Unlike other chemicals, the information encoded by DNA reflects its primary biological function . . . .").

Under the statutory rubric of § 101, isolated DNA is a tangible, man-made composition of matter defined and distinguished by its objectively discernible chemical structure. Whether its unusual status as a chemical entity that conveys genetic information warrants singular treatment under the patent laws as the district court did is a policy question that we are not entitled to address. *Cf. Nat'l Fed'n of Indep. Bus. v. Sebelius*, 132 S. Ct. 2566, slip op. at 6 (2012) ("[W]e possess neither the expertise nor the prerogative to make policy judgments. Those

decisions are entrusted to our Nation's elected leaders, who can be thrown out of office if the people disagree with them."). Congress is presumed to have been aware of the issue, having enacted a comprehensive patent reform act during the pendency of this case, and it is ultimately for Congress if it wishes to overturn case law and the long practice of the PTO to determine that isolated DNA must be treated differently from other compositions of matter to account for its perceived special function. 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 earlier 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 Supreme Court in *Mayo* focused on its concern that permitting patents on particular subject matter would prevent use by others of, in *Mayo*, the correlation recited in the method claims. Plaintiffs argue here that they are preempted from using the patented DNA molecules. The answer to that concern is that permitting patents on isolated genes does not preempt a law of nature. A composition of matter is not a law of nature. Moreover, as indicated earlier, a limited preemption is inherent in every patent: the right to exclude for a limited period of time. 35 U.S.C. § 154(a)(1) ("Every patent shall contain . . . a grant to the patentee, his heirs or assigns, of the right to exclude others from making, using, offering for sale, or selling the invention throughout the United States . . . ."). When the patent expires, the public is entitled to practice the invention of the patent. That is true of all inventions; during the term of the patent, unauthorized parties are "preempted" from practicing the patent, but only for its limited term. The seven patents being challenged here all expire by December 18, 2015.[13] Any preemption thus is limited, very limited in the case of the present patents. Moreover, patents are rarely enforced against scientific research, even during their terms.

The remand of this case for reconsideration in light of *Mayo* might suggest, as Plaintiffs and certain amici state, that the composition claims are mere reflections of a law of nature. Respectfully, they are not, any more than any product of man reflects and is consistent with a law of nature. Everything and everyone comes from nature, following its laws. But the compositions here are not

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[13] Specifically, the '441 patent will expire on August 12, 2014; the '473 patent will expire on December 2, 2014; the '999 and '001 patents will expire on January 20, 2015; the '282 patent will expire on May 5, 2015; and the '492 and '857 patents will expire on December 18, 2015.

natural products. They are the products of man, albeit following, as all materials do, laws of nature.

The dissent indicates that "elemental lithium (like other elements) would not be patentable subject matter, even if it could only be extracted from nature through an isolation process." But the isolation here is not a simple separation from extraneous materials, but conversion to a different molecular entity. And again, these facts are not before us, so we do not attempt to evaluate the patentability of one form of lithium over another. Courts decide cases; they do not draft comprehensive legal treatises. Suffice it to say, however, that if lithium is found in the earth as other than elemental lithium because it reacts with air and water to form, for example, lithium oxide or lithium hydroxide, it is a different material. A lithium compound is not 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, easily done by anyone. Creating a new chemical entity is the work of human transformation, requiring skill, knowledge, and effort. *See Mayo*, 132 S. Ct. at 1294 ("While a scientific truth . . . is not a patentable invention, a novel and useful structure created with the aid of knowledge of scientific truth may be.") (quoting *Mackay Radio & Tel. Co. v. Radio Corp. of Am.*, 306 U.S. 86, 94 (1939)).

The dissent also mentions several times in its opinion the "breathtaking[]" 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 under § 101, not the adequacy of the patents' disclosure to support particular claims. Nor is it lack of patentability for obviousness, as the dissent intimates, that is before us.

The dissent finally attempts to analogize the creation of the isolated DNAs in this case to the removal of a kidney from the human body, indicating that the latter does not create patent-eligible subject matter, hence the claimed isolated DNAs also do not. Such an analogy is misplaced. Extracting a kidney from a body does not result in a patent-eligible composition, as an isolated gene has been and should be. A kidney is an organ, not a well defined composition of matter or an article of manufacture specified by § 101. No one could confuse extensive research needed to locate, identify, and isolate a gene with the extraction of an organ from a body. One is what patents are intended to stimulate research on and hence are properly patent eligible, and the other, while obviously essential to human wellbeing, is not what patents are understood to cover under the patent statute. An isolated DNA is properly characterized as a composition of matter under § 101; no one would so characterize an isolated body organ.

Finally, our decision that isolated DNA molecules are patent eligible comports with the longstanding practice of the PTO and the courts. 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 Con-

gress 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 Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1347 (Fed. Cir. 2010) (en banc) (upholding a written description requirement separate from enablement based in part on *stare decisis*).

In this case, the PTO has issued patents relating 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 relating to, in non-native form, 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 and investing communities, the decision must come, not from the courts, but from Congress. The dissent mentions possible "adverse effects" that may occur if isolated DNAs are held to be patent eligible. But, respectfully, it is the adverse effects on innovation that a holding of ineligibility might cause. Patents encourage innovation and even

encourage inventing around; we must be careful not to rope off far-reaching areas of patent eligibility.

Accordingly, we once again conclude that claims 1, 2, 5, 6, and 7 of the '282 patent; claims 1, 6, and 7 of the '492 patent; and claim 1 of the '473 patent directed to isolated DNA molecules recite patent-eligible subject matter under § 101. *Mayo* does not change that result. In so doing, we reiterate that the issue before us is *patent eligibility*, not *patentability*, about which we express no opinion.

II. Method Claims

We turn next to Myriad's challenged method claims. This court in its now-vacated decision of July 29, 2011, had held method claims 1 of the '999, '001, and '441 patents, as well as method claims 1 and 2 of the '857 patent—all of which consist of analyzing and comparing certain DNA sequences—not to be patent-eligible subject matter on the ground that they claim only abstract mental processes. In light of the Supreme Court's decision in *Mayo*, we reaffirm that prior holding. The Court made clear that such diagnostic methods in that case essentially claim natural laws that are not eligible for patent. Without expressly analyzing the instant method claims in the context of the Court's reasoning, but in light of the Court's holding, and in view of our own prior reasoning, set forth herein below, those method claims cannot stand.

In our prior decision, however, we reversed the district court's holding that claim 20 of the '282 patent was not eligible for patent. We did so on the ground, *inter alia*, that, in addition to the step of comparing the cells' growth rates, the claim also recites the steps of growing transformed cells and determining those growth rates. We relied on the fact that those steps were transformative. Although the Court has now held that certain transformative steps are not necessarily sufficient under § 101

if the recited steps only rely on natural laws, we once again, even in light of *Mayo*, arrive at the same conclusion of patent-eligibility because at the heart of claim 20 is a transformed cell, which is made by man, in contrast to a natural material.

A. Methods of "Comparing" or "Analyzing" Sequences

Myriad argued that its claims to methods of "comparing" or "analyzing" *BRCA* sequences satisfy the machine-or-transformation test 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 merely 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 responded 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 renew our conclusion 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 intellec-

tual 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: one looks at the first position in a first sequence; determines the nucleotide sequence at that first position; looks at the first position in a second sequence; determines the nucleotide sequence at that first position; determines 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 alteration; and repeats the process 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 patent-eligible 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 that is claimed.

To avoid this result, Myriad attempts to read into its method claims additional, allegedly 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 such 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. That may be true, but the claims only recite mental steps, not the structure of physical DNA molecules.

Accordingly, Myriad's challenged method claims are indistinguishable from the claims the Supreme Court found invalid under § 101 in *Mayo*. In *Mayo*, the patents claimed methods for optimizing the dosage of thiopurine drugs administered to patients with gastrointestinal disorders. 132 S. Ct. at 1295. As written, the claimed methods included the steps of (a) "administering" a thiopurine drug to a subject, and/or (b) "determining" the drug's metabolite 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. *Prometheus*, 628 F.3d at 1357. However, the Supreme Court held that the steps of administering and determining, combined with a correlative "wherein" clause, were not sufficiently transformative of what was otherwise a claim to a natural law. That holding governs Myriad's claims to methods of "comparing" and "analyzing" DNA sequences.

Myriad's other claims do not even include a *Mayo*-like step of "determining" the sequence of *BRCA* genes by, *e.g.*, isolating the genes from a blood sample and sequencing them, or any other putatively 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 are only directed to the abstract mental process of comparing two nucleotide sequences. As such, we hold claims 1 of the '999 patent, '001 patent, and '441 patent and claims 1 and 2 of the '857 patent invalid under § 101 for claiming patent-ineligible processes.

B. Method of Screening Potential Cancer Therapeutics

Lastly, we turn to claim 20 of the '282 patent, directed to a method for screening potential cancer therapeutics via changes in cell growth rates of transformed cells. The parties agree that those transformed cells arose from human effort; *i.e.*, they are not natural products. Plaintiffs nonetheless challenge claim 20 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. Plaintiffs therefore contend that claim 20 is indistinguishable from the claims held ineligible in *Mayo*. We disagree.

Claim 20 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. Claim 20 thus recites a screening method premised on the use of "transformed" host cells. Those cells, like the patent-eligible cells in *Chakrabarty*, are not naturally occurring. Rather, they are derived by altering a cell to include a foreign gene, resulting in a man-made, transformed cell with enhanced function and utility. *See* '282 patent col.27 ll.28-33. The claim thus includes more than the abstract mental step of looking at two numbers and "comparing" two host cells' growth rates.

In *Mayo*, the Supreme Court invalidated claims directed to the relationship between concentrations of certain metabolites in the blood and the likelihood that a particular dosage of a thiopurine drug will be optimum, stating that steps of "administering" and "determining," coupled with a correlative "wherein" clause, were insufficient to differentiate the claimed method from the natural laws encompassed by the claims. In short, "to transform an unpatentable law of nature into a patent-eligible *application* of such a law, one must do more than simply state the law of nature while adding the words 'apply it'." 132 S. Ct. at 1294.

Here, claim 20 does do more; it does not simply apply a law of nature. Of course, all activity, whether chemical, biological, or physical, relies on natural laws. But, more to the point here is that claim 20 applies certain steps to

transformed cells that, as has been pointed out above, are a product of man, not of nature. The Court, in its evaluation of the *Mayo* method claims, found that the additional steps of those claims were not sufficient to "transform" the nature of the claims from mere expression of natural laws to patent-eligible subject matter. By definition, however, performing operations, even known types of steps, on, or to create, novel, *i.e.*, transformed subject matter is the stuff of which most process or method invention consists. All chemical processes, for example, consist of hydrolyzing, hydrogenating, reacting, etc. In situations where the objects or results of such steps are novel and nonobvious, they should be patent-eligible. It is rare that a new reaction or method is invented; much process activity is to make new compounds or products using established processes. Thus, once one has determined that a claimed composition of matter is patent-eligible subject matter, applying various known types of procedures to it is not merely applying conventional steps to a law of nature. The transformed, man-made nature of the underlying subject matter in claim 20 makes the claim patent-eligible. The fact that the claim also includes the steps of determining the cells' growth rates and comparing growth rates does not change the fact that the claim is based on a man-made, non-naturally occurring transformed cell—patent-eligible subject matter.

Furthermore, 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. Accordingly, we hold that claim 20 of the '282 patent recites patent-eligible subject matter under § 101. Whether such processes, including claim 20, meet other

tests for patentability, such as novelty or nonobviousness, is not before us.

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, including cDNAs, we affirm the district court's grant of summary judgment with regard to Myriad's method claims directed 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 of novel, man-made transformed cells.

AFFIRMED IN PART and REVERSED IN PART

COSTS

Costs to Myriad.

United States Court of Appeals for the Federal Circuit

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, THE AMERICAN COLLEGE OF MEDICAL GENETICS, THE AMERICAN SOCIETY FOR CLINICAL PATHOLOGY, THE 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,
Plaintiffs-Appellees,

v.

UNITED STATES PATENT AND TRADEMARK OFFICE,
Defendant,

and

MYRIAD GENETICS, INC.,
Defendant-Appellant,

and

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,

IN THEIR OFFICIAL CAPACITY AS DIRECTORS OF THE UNIVERSITY OF UTAH RESEARCH FOUNDATION,
Defendants-Appellants.

2010-1406

Appeal from the United States District Court for the Southern District of New York in case No. 09-CV-4515, Senior Judge Robert W. Sweet.

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 join the majority with respect to claims to isolated cDNA sequences, and concur in the judgment with respect to isolated DNA 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 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, 3226 (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) ("[S]uch terms as 'the work of nature' and the 'laws of nature' . . . are vague and malleable . . . . 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 when an invention does not exist in nature in the claimed state, it may still be directed to subject matter that is not patentable. 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. *Funk Bros.*, 333 U.S. 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 309-10. 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,[1] purified vitamin B-12, another natural product, was also held patentable subject matter within the meaning of 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] princi-

[1] 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.

ple. . . . 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. *General Electric 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.

II.

We reconsider whether the claims at issue in this case are directed to patentable subject matter following the remand from the Supreme Court in light of its opinion in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012) (*Prometheus*). While the *Prometheus* decision does not control the outcome in this case, it is nonetheless instructive regarding the scope of the law of nature exception. As an initial matter, the *Prometheus* discussion of laws of nature (process claims) clearly ought to apply equally to manifestations of nature (composition claims). Myriad's argument that *Prometheus* is constrained to methods is an untenable position.

As the *Prometheus* court explained: "If a law of nature is not patentable, then neither is a process reciting a law of nature, unless that process has additional features that provide practical assurance that the process is more than a drafting effort designed to monopolize the law of nature itself." *Id.* at 1297. *Prometheus* did not, however, overturn *Funk Brothers* or *Chakrabarty*; cases clearly more analogous to the one before us. Using the framework of *Funk Brothers* and *Chakrabarty* in conjunction with the direction of *Prometheus*, the applicable principles are: (1) laws of nature/manifestations of nature are not patentable; (2) a composition of matter with "markedly different characteristics" from that found in nature with

the potential for significant utility is directed to patentable subject matter.

Does the isolation process change the DNA from an unpatentable manifestation of nature into a patentable composition of matter? *Id.* at 1299. Does the claimed isolated DNA 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.

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, 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 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 cDNA, even if those sequences are inspired by a natural template. I therefore join the majority opinion with respect to the claims to cDNA sequences.[2]

DNA sequences that have the same pattern of DNA bases as a natural gene, in whole or in part, present a more difficult issue. Unlike the isolated cDNA molecules, whose sequence is not present in nature, the isolated

[2] 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.

DNA claims include nucleotide sequences which are found in the human body, albeit as part of a much larger molecule, the chromosome. To the extent the majority rests its conclusion on the chemical differences between genomic and isolated DNA (breaking the covalent bonds), I cannot agree that this is sufficient to hold that the claims to human genes are directed to patentable subject matter. I agree that isolated genes are a different molecule and are therefore not squarely analogous to unpatentable minerals, created by nature without the assistance of man. 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.

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 do this. 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. In *Prometheus*, the Supreme Court held that the claims at issue were not directed to patentable subject matter because they merely "set forth laws of nature—namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm." 132 S. Ct. at 1296-97. The claimed relationship was "a consequence of the ways in which thiopurine compounds are metabolized by the body—entirely natural processes." *Id.* at 1297.

There is no suggestion that the human body naturally uses 15-mers as primers to synthesize DNA, or that the attendant process of "probing" a patient's DNA to detect a mutation is somehow a natural law. The ability to use a short strand of DNA as a primer or probe to determine whether a patient has a mutation is a new and important utility substantially different from the role of that DNA as it occurs in nature. Indeed, many of the plaintiffs in this case submitted declarations indicating that they wanted to either offer such testing or receive such testing. Unlike *Prometheus*, the claims to short isolated strands of DNA are not directed to the relationship between the mutation and cancer, but rather to a new tool that can be used to determine if that relationship exists. The short isolated DNA sequences have markedly different properties which are directly responsible for their new and significant utility. *Chakrabarty*, 447 U.S. at 309-10. It is not the chemical change alone, but that change combined with the different and beneficial utility that leads me to conclude that small isolated DNA fragments are patentable subject matter. *Id.* at 310.

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, and he has molded the retained portion into a product that bears little resemblance to that which occurs naturally." Dissent at 11-12. 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.[3] 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.[4] 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." 447 U.S. at 310.

Turning now to the longer strands of isolated DNA, isolated strands which include most or all of the gene present a more difficult case. Some of the claims at issue, for example '282 patent claim 5, are genus claims, drafted

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[3] If adding functionality to a naturally occurring molecule, for example adding a lipid chain, is a creation of man then removing functionality, for example truncating a natural DNA sequence or protein to yield smaller molecules with new properties should also be. 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.

[4] 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?

broadly enough to include both short fragments as well as the entire 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. Unlike 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."). 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.

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. The scope of the law of nature/manifestation of nature exception was certainly enlarged in *Prometheus*. But we do not decide this case on a blank canvas. 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.[5] 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.[6]

III.

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 . . . that DNA molecule does

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[5] *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).

[6] 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.

not occur in that isolated form in nature . . . ." 66 Fed. Reg. 1092, 1093 (Jan. 5, 2001). I do not agree with the dissent's characterization of the PTO position as perfunctory. The PTO concluded that isolated DNA is patentable because it is different from what is found in nature – the process of synthesizing it or isolating it changes it. While the PTO lacks substantive rule making authority, it is not without expertise in this area. 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, it granted patents to human genes in the early 1980s, and subsequently issued thousands of patents on "isolated DNA." Majority at 54. 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." *Id.* 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 longstanding 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, now argues that the Patent Office's published guidelines are incorrect and a misstatement of the law. In place of these guidelines, the government suggested that a "magic microscope" would provide a useful metaphor for guiding our section 101 analysis. 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. Creating the claimed isolated DNA sequences therefore results in a distinctly unnatural molecule.[7] Even the dissent agrees that the isolated DNA molecules at issue require cleaving chemical bonds, though it disputes the importance of the resulting distinct

[7] 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 currently 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.

"'molecular species.'" Dissent at 7 (quoting Linus Pauling, *The Nature of the Chemical Bond* 6 (3d ed. 1960)).

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 20. 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 government 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 government argues in this case. Instead the government 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. *Chakrabarty*, consistent with the broad language of the statute, allowed additional patents where none previously existed. In contrast, the government 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 Congress.

Nevertheless, the government 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 government 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 invitation is tempting, but I decline the opportunity to act where Congress has chosen not to. Congress 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." 149 Cong. Rec. E2417-01. 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.[8] Far from oblivious to the patenting of genes, Congress introduced and declined to pass several bills

[8] "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." 149 Cong. Rec. E2417-01 (emphasis added); *see also* 157 Cong. Rec. E1177-04 (resubmitting this testimony in the context of the current patent reform legislation).

which would put a moratorium on gene patents,[9] authorize funding for the study of whether genes ought to be patentable,[10] and exempt from patent infringement anyone who uses patented genes for non-commercial research purposes or medical practitioners who use genetic diagnostic tests.[11] 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).

The judiciary cannot engage in an *ad hoc* innovation-based analysis, which is why the exceptions to patentability apply only to the clearest cases: a new mineral discovered in the earth, or a new plant found in the wild, or $E=mc^2$, or the law of gravity. It is Congress, with "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), who must decide whether it is necessary to change the scope of section 101

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[9] 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).

[10] The Genomic Science and Technology Innovation Act of 2002 (H.R. 3966).

[11] 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.

to exclude the kind of isolated DNA claims at issue here. It is not clear to me that *Chakrabarty*, *Funk Brothers*, or *Prometheus* leads inexorably to the conclusion that isolated DNA molecules are not patentable subject matter. I decline the invitation to broaden the law of nature exception.

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.").

IV.

"The rule that the discovery of a law of nature cannot be patented rests . . . on the . . . fundamental understanding that they are not the kind of 'discoveries' that the statute was enacted to protect." *Flook*, 437 U.S. at 593. Is an isolated kidney patentable? Probably not, but as far as I can tell nobody ever thought isolating organs from someone's body was the kind of discovery "that the statute was enacted to protect." In contrast, purifying or isolating natural products has historically been exactly the kind of discovery protected by the patent statutes. There is a century-long history of affirming patent protection for isolated and purified biological products ranging from hormones to vitamins to proteins to antibiotics. These inventions must have seemed miraculous at the time, providing previously unknown therapeutic options to treat sickness. The fact that these molecules might have existed in nature did not foreclose patent protection in

view of the extraordinary benefits accessible to man after isolation.

The Patent Office has, for more than a decade, affirmatively stated its belief that isolated DNA is patentable for the same reasons as isolated vitamins or hormones. There is no indication from Congress that this view is wrong; to the contrary, it appears Congress also believes DNA is patentable. This long-term policy of protecting isolated DNA molecules has resulted in an explosion of innovation in the biotechnology industry, an industry which, unlike the financial services industry or even the software industry, depends on patents to survive. Holding isolated DNA not patentable would destroy long settled industry expectations for no reason other than a gut feeling that DNA is too close to nature to be patentable, an arbitrary decision based on a judge-made exception. I believe that isolated DNA fragments, which have both chemical changes from the naturally occurring genomic DNA as well as new utility, are "the kind of 'discoveries' that the statute was enacted to protect." I therefore decline to extend the "laws of nature" exception to include isolated DNA sequences.

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 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 choice we are urged to make is a matter of high policy for resolution within the legislative process after the kind of investigation, examination, and study that legislative bodies can provide and courts cannot." *Id.* at 317. 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 will not strip an entire industry of the property rights it has invested in, earned, and owned for decades unchallenged under the facts of this case.

United States Court of Appeals for the Federal Circuit

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, THE AMERICAN COLLEGE OF MEDICAL GENETICS, THE AMERICAN SOCIETY FOR CLINICAL PATHOLOGY, THE 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,
Plaintiffs-Appellees,

v.

UNITED STATES PATENT AND TRADEMARK OFFICE,
Defendant,

and

MYRIAD GENETICS, INC.,
Defendant-Appellant,

and

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,

IN THEIR OFFICIAL CAPACITY AS DIRECTORS OF THE UNIVERSITY OF UTAH RESEARCH FOUNDATION,
Defendants-Appellants.

2010-1406

Appeal from the United States District Court for the Southern District of New York in case No. 09-CV-4515, Senior Judge Robert W. Sweet.

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 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 the court's decision, if sustained, 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.[1] 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

[1] 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.

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 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 DNA 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.'" 447 U.S. 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 one another. 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 that are 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.[2] 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.[3] 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." 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

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[2] 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.

[3] 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.

(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.

If the changes in the DNA molecule that occur as part of the process of isolation render the gene claims patentable, the same analysis would seem to apply to chemical elements that do not appear in their atomic form in nature. For example, 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 it seems plain that elemental lithium (like other elements) would not be patentable subject matter, even if it could only be extracted from nature through an isolation process.

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. 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 would code 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. It is true that the claimed molecules have been cleaved and that they possess terminal groups that differ from those found on naturally occurring genes. The majority attaches significance to those facts. But the function of the isolated DNA molecules is attributable not to the nature of the isolation process or to the identity of the terminal groups on the molecules; the

function of the claimed molecules is dictated by the nucleotide sequence of the gene—a sequence that is determined by nature and that appears in nature exactly as it appears in the claimed isolated DNA. 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.

Another example underscores the problem with characterizing the isolated gene as a patentable invention. A human kidney is a product of nature; it does not become a patentable invention when it is removed from the body, even if the patentee has developed an improved procedure for extracting the kidney, and even if the improved procedure results in some physical or chemical changes to the

kidney at the points where the kidney was attached to the host body. But if that is so, then why should an isolated gene be treated differently for purposes of section 101? While the isolation of a gene involves the alteration of a single molecule, it is difficult to accept that it should make a difference, for purposes of patentability, whether the isolated substance is part of a single molecule, as in the case of the BRCA genes, or part of a very large aggregation of molecules, as in the case of a kidney.

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, and he has molded

the retained portion into a product that bears little resemblance to that which occurs naturally. 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.[4] 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 a purer version of ultramarine, but recognizing that if a claimed article is "of such

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[4] 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.

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; 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. 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.

The Supreme Court's recent decision in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289, 1293 (2012), does not decide this case, but the Court's analysis is nonetheless instructive. In *Mayo*, which involved method claims, the representative claim involved the steps of administering a drug to a subject, determining a metabolite concentration in the subject's blood, and inferring the need for a change in dosage based on that metabolite concentration. *Id.* at 1295. The Court found that the method was not directed to patent-eligible subject matter because it contributed nothing "inventive" to the law of nature that lay at the heart of the claimed invention, i.e., "the relationships between the concentration in the blood of certain thiopurine metabolites and the likelihood that the drug dosage will be ineffective or induce harmful side-effects." *Id.* at 1294. The Court examined "whether the claims do significantly more than simply describe these natural relations" and whether the "claims add *enough* to their statements of the correlations to allow the processes they described to qualify as patent-eligible processes that apply natural laws." *Id.* at 1297 (emphasis in original). In concluding that the claims did not add "enough" to the natural laws, the Court was particularly persuaded by the fact that "the steps of the claimed processes . . . involve well-understood, routine, conventional activity previously engaged in by researchers in the field." *Id.* at 1294.

Just as a patent involving a law of nature must have an "inventive concept" that does "significantly more than simply describe . . . natural relations," *Mayo*, 132 S. Ct. at 1294, 1297, a patent involving a product of nature should have an inventive concept that involves more than merely incidental changes to the naturally occurring product. In cases such as this one, in which the applicant claims a composition of matter that is nearly identical to a product of nature, it is appropriate to ask whether the applicant has done "enough" to distinguish his alleged invention from the similar product of nature. Has the applicant made an "inventive" contribution to the product of nature? Does the claimed composition involve more than "well-understood, routine, conventional" elements? Here, the answer to those questions is no.

Neither isolation of the naturally occurring material nor the resulting breaking of covalent bonds makes the claimed molecules patentable. We have previously stated that "isolation of interesting compounds is a mainstay of the chemist's art," and that "[i]f it is known how to perform such an isolation doing so 'is likely the product not of innovation but of ordinary skill and common sense.'" *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1302 (Fed. Cir. 2007), quoting *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 421 (2007). Similarly, the structural changes ancillary to the isolation of the gene do not render these claims patentable. The cleaving of covalent bonds incident to isolation is itself not inventive, and the fact that the cleaved molecules have terminal groups that differ from the naturally occurring nucleotide sequences does nothing to add any inventive character to the claimed molecules. The functional portion of the composition—the nucleotide sequence—remains identical to that of the naturally occurring gene.

The majority suggests that I have "focus[ed] not on the differences between isolated and native DNAs, but on one similarity: their informational content." In light of *Mayo*, that approach seems appropriate. The informational content of the nucleotide sequences is the critical aspect of these molecules; the terminal groups added to the molecules when the covalent bonds are broken—to which the majority and concurring opinions attribute such significance—are not even mentioned in the claims. The nucleotide sequences of the claimed molecules are the same as the nucleotide sequences found in naturally occurring human genes. In my view, that structural similarity dwarfs the significance of the structural differences between isolated DNA and naturally occurring DNA, especially where the structural differences are merely ancillary to the breaking of covalent bonds, a process that is itself not inventive.

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.[5] The end product is a human-made invention with

[5] 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.

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 is not entitled to such broad protection. *See Mayo*, 132 S. Ct. at 1301, 1303 (examining "how much future innovation is foreclosed relative to the contribution of the inventor" and warning of the "danger" that overly broad patent claims might "foreclose[] more future invention than the underlying discovery could reasonably justify").

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.

The other claim to a short segment of DNA, 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 numerous molecular variations, but also any sub-sequence of those molecules, including portions that fall in the undefined range of those molecules denoted "vvvvvvvvvvvvv." 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").

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 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 has twice 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 on either occasion 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 conclude 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 microorgan-

isms 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 the government's brief in that case) 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.[6] There is no collective right of adverse possession to intellectual property, and we should not create one. 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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[6] 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.