No. 12-398

IN THE

Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL.,

Petitioners,

—v.—

MYRIAD GENETICS, INC., ET AL.,

Respondents.

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

BRIEF FOR PETITIONERS

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QUESTION PRESENTED

Many patients seek genetic testing to see if they have mutations in their genes that are associated with a significantly increased risk of breast or ovarian cancer. Respondent Myriad Genetics obtained patents on two human genes that correlate to this risk, known as BRCA1 and BRCA2. These patents claim every naturally-occurring version of those genes, including mutations, on the theory that Myriad invented something patent-eligible simply by removing ("isolating") the genes from the body. Petitioners are primarily medical professionals who regularly use routine, conventional genetic testing methods to examine genes, but are prohibited from examining the human genes that Myriad claims to own.

The question presented is: Are human genes patentable?

LIST OF PARTIES

The petitioners are the Association for Molecular Pathology, American College of Medical Genetics and Genomics, American Society for Clinical Pathology, College of American Pathologists, Haig Kazazian, MD, Arupa Ganguly, PhD, Wendy Chung, MD, PhD, Harry Ostrer, MD, David Ledbetter, PhD, Stephen Warren, PhD, Ellen Matloff, M.S., Elsa Reich, M.S., Breast Cancer Action, Boston Women's Health Book Collective, Lisbeth Ceriani, Runi Limary, Genae Girard, Patrice Fortune, Vicky Thomason, and Kathleen Raker. The respondents are Myriad Genetics, Inc., and in their official capacity as directors of the University of Utah Research Foundation, Lorris Betz, Roger Boyer, Jack

Brittain, Arnold B. Combe, Raymond Gesteland, James U. Jensen, John Kendall Morris, Thomas Parks, David W. Pershing, and Michael K. Young. The United States Patent and Trademark Office (PTO) was dismissed as a defendant by the district court and that ruling was not appealed. Accordingly, the PTO is not a respondent here.

RULE 29.6 CORPORATE DISCLOSURE STATEMENT

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

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The order of this Court granting certiorari is reported at 133 S. Ct. 694 (2012). The opinion of the U.S. Court of Appeals for the Federal Circuit following remand from this Court is reported at 689 F.3d 1303 (Fed. Cir. 2012) (Pet. App. 2a-119a). This Court's order granting certiorari, vacating, and remanding in light of *Mayo Collaborative Services v. Prometheus Laboratories, Inc.* is reported at 132 S. Ct. 1794 (2012) (Pet. App. 1a). The Federal Circuit's original decision is reported at 653 F.3d 1329 (Fed. Cir. 2011) (Pet. App. 120a-231a). The district court opinion granting summary judgment to Petitioners and denying summary judgment to Respondents is reported at 702 F. Supp. 2d 181 (S.D.N.Y. 2010) (Pet. App. 232a-357a). An earlier opinion of the district court denying the motion to dismiss based, in part, on standing is reported at 669 F. Supp. 2d 365 (S.D.N.Y. 2009) (Pet. App. 358a-425a).

JURISDICTIONAL STATEMENT

The Federal Circuit's decision in this case following remand was issued on August 16, 2012, and this Court granted a timely petition for certiorari on November 30, 2012. Jurisdiction is conferred by 28 U.S.C. § 1254(1).

STATUTORY PROVISION

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

INTRODUCTION

Human genes are, of course, products of nature. Genetic variants, including mutations, are also products of nature. How genes work and whether variants are harmful or not are laws of nature. Respondents Myriad Genetics *et al*. did not invent any genes or variants or cause their significance, but they did obtain patent claims on two naturally-occurring human genes known as BRCA1 and BRCA2 (so named because one of the diseases to which the genes are linked is breast cancer). The claims are not limited to any form, variation, or structure of the BRCA1 or BRCA2 genes, and they cover the BRCA genes of every person in the United States, even genes that Myriad has never seen.

Myriad defends its claims on the grounds that a gene becomes a human invention when removed from the human body ("isolated"). Under this rationale, a kidney "isolated" from the body would be patentable, gold "isolated" from a stream would be patentable, and leaves "isolated" from trees would be patentable. This defense defies common sense and elevates the draftsman's art over the long-standing prohibition on patenting of products and laws of nature.

Because it is not possible to study or use the genes unless they are isolated, the claims have significant implications. The claims preempt any use of the genes for any purpose. This has serious and urgent consequences for patients today, who often cannot obtain information about their own genes and thus cannot make educated medical decisions about breast and ovarian cancer surveillance and treatment. Myriad has a monopoly on clinical

testing of *its* genes in the U.S., dictating the type and terms of BRCA genetic testing. Myriad has given women false negative results, while also barring other laboratories from testing genes to verify the accuracy of Myriad's results. Although Myriad has not exercised its authority to stop all research, Myriad's claims have had a proven chilling effect on research, as laboratories are dissuaded from pursuing scientific work that requires using the patented genes.

Even more disturbingly, because the claims reach all possible uses of the claimed genes, Myriad is authorized to block avenues of scientific inquiry. Myriad can prevent researchers from determining if mutations on the genes correlate with increased risk of other diseases. It can prevent researchers from determining whether the genes could be used in therapy, and if they could, Myriad can prevent that use or lay claim to it. Myriad can stop the development of new types of clinical testing of the genes that take advantage of recent scientific insights. If it were determined that the genes could be used for purposes not now known, such as a substitute for silicon chips in computers (a use currently being explored by companies), Myriad can prevent that use. Myriad can even prevent scientists from looking at their own genes.

This case does not involve a challenge to the method for removing BRCA1 and BRCA2 from the body, nor the process of testing the genes for mutations, nor any drugs developed as a result of scientific research involving the genes. The only question presented by this case is whether human genes can themselves be patented. Because the

patents grant exclusive rights over natural phenomena and create barriers to scientific progress and medical care, they must be held invalid.

STATEMENT OF THE CASE

The district court's opinion contains an extensive discussion of the science of DNA and genes, which was supplemented by the Circuit opinions. Pet. App. 254a-72a, 13a-20a.

a. *Nature of Human Genes and DNA*

Every human body contains genes that determine, in part, the structure and functions of the body. Pet. App. 255a-56a, 258a-59a; 1J.A. 130-31, 227-28. The structure and function of human genes are created by nature. Pet. App. 259-260a; 1J.A. 58-59, 63, 91-92, 130-31, 133, 135, 224-25, 232, 234-35, 264, 274-75, 688-89, 703-04, 707.

A gene is a segment of chromosomal DNA. Pet. App. 258a; 1J.A. 229-230.[1] DNA is composed of four repeating elements called nucleotides or bases. Pet. App. 257a. The nucleotides are products of nature. 1J.A. 132.

A gene is defined based on its naturally-occurring qualities. "Each gene is typically thousands of nucleotides long and usually 'encodes' one or more proteins, meaning it contains the information used by the body to produce those proteins." Pet. App. 258a. Nucleotides are represented by four letters, standing for each of the

[1] Because genes are simply segments of DNA, references to DNA in this brief are, unless otherwise noted, references to a DNA segment that constitutes the BRCA1 or BRCA2 genes.

four nucleotides that make up DNA: A (adenine), C (cytosine), T (thymine), and G (guanine). Pet. App. 257a. The linear order of the nucleotides is referred to as the nucleotide sequence or gene sequence or DNA sequence. Pet. App. 259a. The gene sequence is a product of nature and its role in creating proteins (polypeptides) is a law of nature. Pet. App. 260a.

Genes are chemicals, but they are unique because they are much more; they embody the information and instructions the body uses to function. Pet. App. 259a-60a, 355a-56a; 1J.A. 58-59, 130-33, 135-36, 232, 234-35, 561-62, 649-50, 680-81. They determine which polypeptides (proteins) will be made to do the work of the body. Pet. App. 258a, 266a-67a; 1J.A. 132-33, 227-30. Genes "define physical traits such as skin tone, eye color, and sex, in addition to influencing the development of conditions such as obesity, diabetes, Alzheimer's disease and bipolar disorder." Pet. App. 259a. The genes themselves embody laws of nature and the processes by which genes do these things are laws of nature. Pet. App. 257a-62a, 334a-37a; 1J.A. 229-30.

Genes vary from one individual to another. Genetic variants can be inherited or can develop after birth, but the process by which the changes occur is a law of nature and the resultant variant gene is a product of nature. Pet. App. 260a-61a, 270a, 378a; 1J.A. 38-45, 132-33,135-36, 224, 230-31. Genetic variants can be as small as a single deletion (ATAG becomes ATG) or single substitution (ATAG becomes CTAG). Pet. App. 260a-61a. They can also be large with the "addition or deletion of substantial chromosomal regions." Pet. App. 261a. Genetic variants can also "involv[e] the deletion or

duplication of up to millions of nucleotides." Pet. App. 261a. Variation in the human genome is very common. Pet. App. 260a; 1J.A. 230. There is not one gene that is "normal," with a few individuals having variants; much variation exists in the genes from one person to another. 1J.A. 230. Myriad claims every version of the BRCA1 gene, but lists just one version in the patents. Patent '282, FIG 10, 2J.A. 738-45. The capital letters in FIG 10 represent the nucleotides called "coding" and the lower case letters represent nucleotides called "non-coding," because they are thought to be unnecessary in the creation of the protein.

Variants can appear to be unimportant, correlate with an increased risk of disease or disorder ("mutations"), or have unknown significance ("variant of uncertain significance"). Pet. App. 18a, 261a; 1J.A. 231-32. The significance of the variant is created entirely by nature. Pet. App. at 270a; 1J.A. 58-59, 135-36, 224, 231-32.

Some mutations in the BRCA1 or BRCA2 genes correlate with an increased risk of breast and/or ovarian cancer. Pet. App. 20a, 278a, 309-310a; Patent '282, 1:20-30, 2J.A. 746. "Women with BRCA1 and BRCA2 mutations face up to an 85% cumulative risk of breast cancer as well as an up to 50% cumulative risk of ovarian cancer. . . . The existence of BRCA1 or BRCA2 mutations is therefore an important consideration in the provision of clinical care for breast and/or ovarian cancer." Pet. App. 278a; 1J.A. 205-06. As the district court found "mutations, along with any association with a propensity to develop a particular disease, are caused by nature. Therefore, the significance of any person's

gene sequence, including its relationship to any disease, is dictated by nature." Pet. App. 270a.

b. *Scientific Uses of Genes*

It is useful for pathologists, clinical laboratory scientists, other medical professionals, and researchers to conduct genetic testing for clinically significant alterations. Pet. App. 18a, 263a, 270a-72a, 378a, 380-81a; 1J.A. 58-59, 132-33, 209-10, 232. Sequencing methods are used to examine the precise order of the gene's nucleotides. Pet. App. 259a-60a, 263a, 270a-72a; 1J.A. 58-59, 133-35, 209-10, 223, 232-35; 2J.A. 854. Thousands of medical professionals around the world sequence genes daily, and the processes by which sequencing is done are not at issue here. Pet. App. 272a, 379a; 1J.A. 58-59, 125-26, 133-136, 218, 223, 232, 234-35. At the end of the sequencing process, the medical professional has a long string of the four letters (A, C, T, and G) that correspond to the four nucleotides. Pet. App. 257a, 378a; 1J.A. 58-59, 131-32, 230, 232. The structure, function, and sequence of the nucleotides are created entirely by nature. Pet. App. 260a, 343a; 1J.A. 234-35, 644-46, 653-54, 676, 688-89. After sequencing, the medical professional looks to see if there are variants; *e.g.*, whether natural processes have caused there to be a C where a T would commonly be. 1J.A. 58-59, 135-36, 232. *See, e.g.*, Pet. App. 426a (Patent '282, cl. 7(a)).

Myriad's patent claims have prevented labs other than Myriad from sequencing the BRCA1 and BRCA2 genes and looking to see if there are mutations, actions that are crucial to women and their families facing hereditary breast and ovarian cancer risk. *E.g.*, 1J.A. 60, 87-89, 219-220. In many

cases, the effect has been devastating. Some women have obtained testing from Myriad that gave them false negative results because Myriad did not include certain mutations in its standard testing. Tom Walsh et al., *Spectrum of Mutations in BRCA1, BRCA2, Chek2, and TP53 in Families at High Risk of Breast Cancer*, 295 J. Am. Med. Ass'n 1379, 1385-86 (2006). Women and their families make life-changing decisions based on testing provided by one company, without the option of seeking a second opinion. *See id.*; *see also* 1J.A. 76, 78-79, 119. District court plaintiffs Ceriani and Fortune, both breast cancer patients, sought critical testing recommended by their doctors but were denied when Myriad would not accept their insurance. 1J.A. 121-22, 118-119. Plaintiffs Raker and Thomason needed more extensive testing than offered by Myriad's standard test to screen for additional BRCA mutations but Myriad charged prohibitively for that testing. 1J.A. 75, 70-71. All of the plaintiff geneticists were willing to perform the tests for free or for an affordable cost but were prevented from doing so by Myriad's patent claims. *E.g.*, 1J.A. 60, 88-89, 221-22.

But because the patent claims are not limited to the use of the genes in BRCA1 or BRCA2 testing, the effects have been far greater. The patent claims have deterred research as other researchers, including plaintiffs Harry Ostrer, Wendy Chung, and David Ledbetter, are chilled from engaging in scientific work using these genes. 1J.A. 144-48, 220, 714-18. Plaintiff Runi Limary was told by Myriad that she has a "variant of uncertain significance," a result that only Myriad can further explain given their control over patients' BRCA genetic

information. 1J.A. 81-83; *see also* 1J.A. 61-62, 91, 113-14, 206-09, 222-23. And the research that has been deterred or prevented is not limited to research into breast and ovarian cancer, but to any research on these genes and their effects.

It is not currently possible to use genes, including looking at or sequencing them, without removing or "isolating" them from the body. Pet. App. 271a, 342a. The isolated gene, however, is not "markedly different" in either structure or function from a gene in the body. Most importantly, the nucleotides that make up DNA – or DNA's "information content" – remain the same. Pet. App. 270a. If that were not the case, Myriad's diagnostic use of the gene would be futile. After isolating and sequencing the gene utilizing conventional methods, Myriad reports to the person who provided the sample that the gene in the body does or does not have a harmful mutation because the isolated gene does or does not have that mutation. Pet. App. 278a-79a. If the "isolated" gene in the lab differed from the gene in the body, Myriad could not reach that conclusion. Pet. App. 224a. And classic experiments established that when isolated DNA is reinserted into the cell, it functions as it did previously. 1J.A. 650-53.

Isolation does separate the gene from other parts of the body to which it is normally attached. The gene in the body is normally surrounded by and sometimes attached to other things, including proteins, that are collectively called chromatin. Pet. App. 262a; 1J.A. 644-46, 685-86. But the gene sequence, the information it includes, and the laws it embodies are the same whether in or out of the body.

Pet. App. 262a, 336a; 1J.A. 644-46. Even if separation from the chromatin were considered to create a structural difference, DNA is separated from the chromatin in the body during several naturally-occurring processes; the gene separated from the chromatin can be found in the body. Pet. App. 264a.

Isolation also separates the chromosome into fragments, breaking the bonds that link the pieces of the chromosome itself. Once again, the gene sequence, the information it includes, and the laws it embodies are the same whether the gene is in the body or contained in fragments made during the isolation process. But even if cutting the chromosome into pieces were considered to constitute a structural change, gene fragments exist in the body. These fragments result from naturally-occurring processes that break the bonds that hold the full chromosome together.[2] Those fragments are

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[2] Nature breaks the bonds that hold together the full chromosome (1) every time gametes are produced during the normal process of meiotic recombination; (2) during the cellular process by which cells make copies of themselves; (3) when DNA experiences a double strand break (which then is often repaired). *See* Wolf-Dietrich Heyer et al., *Holliday Junctions in the Eukaryotic Nucleus: Resolution in Sight?*, 28 Trends in Biochemical Sci. 548 (2003); *see also* Robyn L. Maher et al., *Coordination of DNA Replication and Recombination Activities in the Maintenance of Genomic Stability*, 112 J. of Cellular Biochemistry 2672 (2011).

The entire fetal and maternal genome can also be found in short fragments with broken covalent bonds in maternal plasma, and DNA can also be found in the blood of those suffering from cancer. Y.M. Dennis Lo et al., *Maternal Plasma DNA Sequencing Reveals the Genome-Wide Genetic and Mutational Profile of the Fetus*, 2 Sci. Translational Med. 61ra91 at 1 (2010); Maurice Stroun et al., *Isolation and*

identical to the fragments created by Myriad when it isolates the gene.[3]

c. *The Patents*

Petitioners challenge nine patent claims on human genes. None of the challenged claims is limited to any particular use of the genes, any form of recombinant DNA, or a therapy (including a drug) involving the genes. None is limited to a method of looking at the gene. All of the claims are to the genes themselves and reach all structures and uses of the gene.

The key claims are claim 1 of Patent '282 and claim 1 of Patent '492. Those claims reach any "isolated DNA" that will create the proteins

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Characterization of DNA from the Plasma of Cancer Patients, 23 Eur. J. Cancer & Clinical Oncology 707 (1987).

[3] In the process of isolating a gene, DNA is fragmented and covalent bonds are broken. The scientist, however, does not decide or control the size or composition of the fragments; they are of random length and composition. Indeed, if a scientist were to isolate a gene of a person on Monday, and then do so again on Tuesday, it is likely the fragments would have a different size and composition. Many fragments are likely to include a portion of the BRCA1 or BRCA2 gene and a portion of the adjacent DNA. Bruce Alberts et al., *Molecular Biology of the Cell* Ch. 8 (4th ed. 2002); Robert L. Nussbaum et al., *Thompson and Thompson Genetics in Medicine* Ch. 4 (7th ed. 2007); Harvey Lodish et al., *Molecular Cell Biology* Ch. 7-8 (4th ed. 2000).

In addition, scientists sequencing genes after isolation generally do not chemically stitch the fragments back together to form longer segments, such as an entire gene. *See* 1J.A. 690-91. Sequencing generally relies on computers to recreate the gene sequence without creating a molecule or chemical that is an entire gene. *Id.*

naturally created by the BRCA1 and BRCA2 genes. More specifically, Patent '282, claim 1 reaches the BRCA1 gene:

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

Pet. App. 426a. SEQ ID No. 2 refers to a lengthy sequence of amino acids set forth in the patent. Patent '492, claim 1 is virtually identical, reaching the BRCA2 gene.

> An isolated DNA molecule coding for a BRCA2 polypeptide, said DNA molecule comprising a nucleic acid sequence encoding the amino acid sequence set forth in SEQ. ID. No. 2.

Pet. App. 427a.

All of the remaining claims use alternate terms to define the same genes or duplicatively claim alternate forms of the genes.

All nine claims use the same definitions of the two key terms: "isolated" and "DNA." "Isolated" is defined as: "An 'isolated' … nucleic acid (*e.g.* an RNA, DNA, or a mixed polymer) is one which is substantially separated from other cellular components which naturally accompany a native human sequence or protein . . ." Patent '282, 19:8-12, 2J.A. 755. This definition of "isolated" comports with the ordinary understanding of the term in the field and there is no dispute between the parties over the meaning of the term.

"DNA" is defined broadly. The claims reach "all forms of mutations" (Patent '282, 12:31-32, 2J.A. 751) and "all allelic [nucleotide] variations" (Patent '282, 19:35-40, 2J.A. 755). They reach any DNA if it is as little as 60% similar to the specified DNA (Patent '282, 24:19, 2J.A. 757) and any DNA that creates proteins as little as 30% similar to the specified proteins (Patent '282, 24:62-63, 2J.A. 757). They reach all fragments of both the DNA and the proteins. *See* Patent '282, 6:26-28, 2J.A. 748 ("comprising all, or a portion of the BRCA1 locus or of a mutated BRCA1 locus, preferably at least 8 bases"); Patent '282, 19:1-5, 2J.A. 755 (reaches DNA that "can … produce … the polypeptide or a fragment thereof"); Patent '282, 19:41-43, 2J.A. 755 (reaches DNA that produces "fragment, homolog, or variant" of proteins); Patent '282, 20:34-35, 2J.A.755 (fragments as short as 15 nucleotides); Patent '282, 20:63-65, 2J.A. 755 (fragments as short as 8 nucleotides); Patent '282, 25:33-35, 2J.A. 758 (fragments as short as 5 amino acids). In 1998, Myriad wrote to one of the plaintiffs, Dr. Kazazian, and said specifically that the patents covered "any fragments of the BRCA1 gene." 1J.A. 168-69.

The claims also reach other forms of genetic material. They include "RNA, cDNA, genomic DNA, synthetic forms . . . ." Patent '282, 19:51-53, 2J.A. 755.[4] They reach DNA with or without "all coding sequences, all intervening sequences and regulatory elements." Patent '282, 19:35-40, 2J.A. 755. They

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[4] cDNA, or complementary DNA, is discussed in Section II, *infra*. In short, it is DNA without the non-coding regions (regions seemingly unnecessary in creating the protein/polypeptide).

reach DNA modified by "methylation" or other naturally-occurring biochemical or chemical modifications or not so modified. Patent '282, 19:53-55, 2J.A. 755; *see also* Pet. App. 263a.

The key claims (Patent '282, claim 1 and Patent '492, claim 1) define the genes by the function given to the genes by nature and are not limited to any particular molecular structure or any particular use. Pet. App. 426a-27a. Because nature dictates that numerous DNA sequences can result in those polypeptides (proteins), 1J.A. 685-86, these claims unquestionably reach all uses of multiple compositions created by nature and defined by laws of nature, whether or not Myriad or anyone else has identified those compositions.

Claim 2 of Patent '282 defines the exact same gene by referring to a sequence of nucleotides that in nature represents one version of the BRCA1 gene. It reads:

> The isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID No. 1.

Pet. App. 426a. This sequence reference is to a nucleotide sequence listed in the patent. Because the patents define the term "DNA" used in this claim identically to claim 1 to include all versions of the nucleotide sequence (and more), the sequence referenced is solely illustrative.

Indeed, if the claim reached only the specific sequence identified in the table, it would be confounding to geneticists who would not know if they infringed (*i.e.*, found that identical sequence) until they infringed (sequenced the gene). The claim

would also be useless to Myriad. It is unlikely that more than a few people possess that exact sequence. If the specified sequence were the only sequence covered, it would not reach any sequence with any variants, mutations, or alterations. There is nothing in the patents to suggest that variants including non-coding regions are excluded from the definition of DNA.

The remaining claims are alternate descriptions, duplicative of the key claims, though three are of extraordinary breadth. Claim 6 of Patent '492 reaches any isolated BRCA2 DNA with a mutation that is "associated with a susceptibility to cancer." It reads:

> An isolated DNA molecule coding for a mutated form of the BRCA2 polypeptide set forth in SEQ ID No. 2, wherein said mutated form of the BRCA2 polypeptide is associated with a susceptibility to cancer.

Pet. App. 427a. The claim reaches any BRCA2 gene with harmful mutations regardless of whether another geneticist is the one who finds the mutation and identifies it as associated with any type of cancer. Indeed, for another geneticist to look for and find such a mutation would be infringing.

Claims 5 and 6 of patent '282 reach any segment of the BRCA1 DNA as short as 15 nucleotides. Claim 5 reaches any segment as short as 15 nucleotides that will create the proteins or any portion of the protein. Pet. App. 426a. Claim 6 reaches any 15 nucleotides of the BRCA1 gene. *Id.* More specifically, the claims read:

> 5. An isolated DNA having at least 15 nucleotides of the DNA of claim 1.
>
> 6. An isolated DNA having at least 15 nucleotides of the DNA of claim 2.

Because the claims reach DNA having "at least" 15 nucleotides, they reach longer sequences as well, including the entire gene. They also reach other genes. Because DNA is composed solely of the four nucleotides, there is extensive repetition in the genome. And, because the BRCA1 gene is large, it includes a huge number of 15 nucleotide sequences. Fifteen (15) nucleotide sequences from the BRCA1 gene can be found in virtually every other gene in the body. 1J.A. 631-34, 662-72. Moreover, as Judge Bryson indicated, claim 6 reaches nucleotide sequences in the non-coding regions as well as the coding regions throughout the genome. Pet. App. 114a.

The other claims, claim 1 of patent '473, claim 7 of patent '282, and claim 7 of patent '492, reach more specific, identified mutations. Pet. App. 426a, 428a. For example, claim 7 of '282 reads:

> An isolated DNA selected from the group consisting of: (a) a DNA having the nucleotide sequence set forth in SEQ ID No. 1 having T at nucleotide position 4056 . . .

These claims represent nothing more than Myriad describing a gene that contains some of the mutations caused by nature that nature has caused to be significant. Any geneticist must infringe (isolate the gene with the mutation) before she can determine that she has infringed (look to see if the

composition includes the specified mutation). As with all the claims, they are not limited to any particular use.

d. *Proceedings Below*

This lawsuit began in 2009 with the filing of a complaint in the United States District Court for the Southern District of New York against the PTO, as well as the patent holders, Myriad Genetics and the directors of the University of Utah Research Foundation.[5] Plaintiffs included four national organizations of physicians, geneticists, researchers, clinicians, and other health professionals with a combined total of over 150,000 members, as well as six of the nation's leading geneticists, two genetic counselors, two women's health and breast cancer organizations, and six individual women who have been diagnosed with or are at risk of hereditary breast or ovarian cancer. Pet. App. 240a-48a.

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

The complaint challenged fifteen claims from seven different patents. Pet. App. 297a-303a. Nine

[5] The University of Utah Research Foundation is an owner or co-owner of each of the patents containing the challenged claims, Pet. App. 248a, and has acted jointly with Myriad throughout the litigation.

of the challenged claims from three patents cover the BRCA1 or BRCA2 genes.[6]

Defendants moved to dismiss in the district court largely on the grounds that plaintiffs lacked standing. Pet. App. 361a. The court denied that motion. Pet. App. 412a. Both plaintiffs and Myriad subsequently moved for summary judgment, and the PTO moved for judgment on the pleadings. Pet. App. 237a. The district court granted plaintiffs' motion for summary judgment and denied Myriad's motion. *Id*. The constitutional claims against the PTO were dismissed based on the doctrine of constitutional avoidance. *Id*. at 357a.

The district court's 153-page, comprehensive opinion, Pet. App. 232a-357a, began by discussing the standard set by this Court for determining if a patented composition of matter – like the "isolated" DNA at issue here – has been sufficiently changed so that it is no longer a law or product of nature. Pet. App. 320a-23a (citing *Diamond v. Chakrabarty*, 447 U.S. 303 (1980); *Funk Bros. Seed Co. v. Kalo Inoculant Co.,* 333 U.S. 127 (1948); and *American Fruit Growers, Inc. v. Brogdex Co.,* 283 U.S. 1 (1931)).

The district court considered Myriad's arguments regarding both structural and functional differences between "isolated" DNA and the DNA inside the human body, ultimately concluding that none caused "isolated" genes to be "markedly different," *Chakrabarty*, 447 U.S. at 310, from genes in the body. Pet. App. 333a-44a. In holding that

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[6] The complaint also challenged some method claims, none of which is now before the Court.

patents on isolated DNA claim laws and products of nature, the district court emphasized that the functionality of genes is based on their unique status as the embodiment of the information the body uses.

> [T]he information encoded by DNA reflects its primary biological function: directing the synthesis of *other* molecules in the body – namely, proteins, "biological molecules of enormous importance" which "catalyze biochemical reactions" and constitute the "major structural materials of the animal body."

Pet. App. 335a. The district court found that in isolating a gene, Myriad did not "alter its essential characteristic – its nucleotide sequence that is defined by nature and central to both its biological function within the cell and its utility as a research tool in the lab." Pet. App. 342a. To the extent any claims reached cDNA, the court also invalidated those claims for largely the same reason. Pet. App. 339a.

Myriad appealed to the Federal Circuit. Plaintiffs did not appeal the dismissal of the PTO, although plaintiffs continued to raise their First Amendment claims against the University of Utah defendants. The United States did, however, participate in the proceedings on the initial appeal and remand as *amicus curiae,* largely supporting plaintiffs.

A divided panel of the Federal Circuit reversed. The panel first dismissed all but one of the plaintiffs on the grounds that unless they had been

personally threatened by Myriad, they did not have standing. Pet. App. 32a-42a. Each panel member wrote a separate opinion discussing the patentability of human genes. Judge Lourie held that in analyzing whether an "isolated" gene has "markedly different characteristics" from what is found in nature, the functionality of the gene is irrelevant. Pet. App. 55a. He held that "isolated" DNA is structurally different from DNA on the sole basis that in the process of removing DNA from the rest of the chromosome to which it is attached, a covalent bond is broken. Pet. App. 51a-57a.

Judge Moore, by contrast, found that both structure and function were relevant in determining if a composition is "markedly different" from what is found in nature. Pet. App. 85a. She found that a full-length "isolated" gene "does not clearly have a new utility and appears to simply serve the same ends devised by nature." Pet. App. 85a-86a. She wrote: "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." Pet. App. 86a. She nevertheless found full-length genes to be patentable because of the PTO's practice of granting gene patents and industry reliance on that practice. *Id.* She also opined that small fragments of the gene would be patentable because they could be used as probes or primers, while recognizing that none of the patents claims is limited to small fragments.[7] *See* Pet. App. 82a.

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[7] Probes and primers are pieces of DNA that are used in laboratories as part of the process of identifying or making

In his dissenting opinion, Judge Bryson held that the genes were not patentable. Pet. App. 102a. He reasoned:

> 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.

Pet. App. 110a.

Plaintiffs sought reconsideration by the panel on the grounds that the majority had introduced facts not in the record and that those facts were wrong. Specifically, plaintiffs noted that fragments of DNA with broken covalent bonds are created both in the body and in the "isolation" process; therefore, the breaking of a covalent bond did not distinguish "isolated" DNA from DNA in the body. Pls.-Appellees' Pet. for Panel Reh'g 4, *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office*, 653

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copies of DNA. Pet. App. 264a-65a, 340a-41a. None of the challenged patent claims is limited to use as probes or primers.

F.3d 1329 (Fed. Cir. 2011); *see* 1J.A. 688-89. Rehearing was denied without opinion.[8]

This Court granted plaintiffs' petition for certiorari, vacated and remanded for further proceedings in light of *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012). Upon remand, each panel member adhered to his or her previous views.

Judge Lourie's consideration of *Mayo* was limited to two short paragraphs, which purported to distinguish *Mayo* on the ground that its reference to the preemptive effect of the invalidated patent in that case was applicable only to "laws of nature," not "products of nature." Rejecting the findings of the district court that DNA is a unique composition in its embodiment of natural laws, Judge Lourie ruled that the patents in this case do not claim a law of nature. Pet. App. 56a.

Judge Moore, unlike Judge Lourie, thought that *Mayo* "clearly ought to apply equally to manifestations of nature (composition claims)." Pet. App. 79a. Even so, she did not alter her conclusion or analysis in any material way to reflect *Mayo*'s holdings. Neither she nor Judge Lourie even referred to this Court's apparent rejection of her "reliance" argument in *Mayo*. 132 S. Ct. at 1305.

Judge Bryson's dissenting opinion applied this Court's reasoning in *Mayo*. "Has the applicant made

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[8] Myriad also filed a petition for panel rehearing, arguing that plaintiff Harry Ostrer lacked standing. The petition was denied without opinion. 1J.A. 19. Myriad raised the standing issue again following the *Mayo* remand, and the Federal Circuit rejected the argument in its second opinion. Pet. App. 25a n.6.

an 'inventive' contribution to the product of nature? Does the claimed invention involve more than 'well-understood, routine, conventional' elements. Here, the answer to those questions is no." Pet. App. 112a. He also rejected the majority's deference to prior PTO practice, noting that it "give[s] the PTO lawmaking authority that Congress has not accorded it." Pet. App. 119a.

All three judges held that cDNA was patentable subject matter, *e.g.,* Pet. App. 47a-48a, 80a-81a, 98a, ignoring the district court's findings that none of the claims is limited to cDNA, that cDNA results from natural phenomena, and that cDNA sequences are found in the human genome. Pet. App. 268a, 339a. None of the Circuit judges addressed the claim to DNA with cancer-associated mutations or the other four claims that reach other mutations. None of the Circuit judges addressed Petitioners' constitutional claims.

Petitioners again sought review by this Court and the petition was granted, limited to Question 1: "Are human genes patentable?"

SUMMARY OF ARGUMENT

Myriad's patents on BRCA1 and BRCA2 violate long-established precedent that prohibits the patenting of laws and products of nature. *Chakrabarty*, 447 U.S. at 309. The Court's seminal Section 101 cases describe three different ways to evaluate patents to determine whether they impermissibly claim natural phenomena: whether the patented composition has markedly different characteristics from any found in nature, *id.* at 310; whether the patent is based on an inventive concept,

Mayo, 132 S. Ct. at 1294; and whether the patent preempts use of the underlying product or law of nature, foreclosing future innovation out of proportion with the patentee's contribution, *id.* at 1301-03. When these three standards are applied to Myriad's claims, it is clear that the patents on isolated DNA must be found invalid.

First, isolated DNA does not have markedly different characteristics from any found in nature. Isolated DNA is simply removed from its natural environment; its structure and function remain the same. It also embodies the same genetic information – a law of nature – as in the body. The difference in structure discussed by the Federal Circuit majority opinion is based on a scientific misunderstanding, but even if correct, isolated DNA still could not be considered "markedly different" from the DNA in the body.

Second, patents on isolated DNA are not based on any inventive concept. Isolation was a routine, conventional activity at the time these patents were obtained. The only addition to the progress of science disclosed by these claims is the law of nature itself: that this DNA encodes for the BRCA1 or BRCA2 gene or protein. As in *Funk Brothers*, Myriad's discovery is simply of nature's handiwork. *See* 333 U.S. at 131.

Third, patenting isolated DNA ties up all basic uses of the BRCA1 and BRCA2 genes, foreclosing more future innovation than the underlying discovery could reasonably justify. *See Mayo*, 132 S. Ct. at 1301. Because isolation is required for any serious study, examination, or clinical or commercial use of the genes, these patents preempt all such

activity. The patents exclude using the genes for research, clinical genetic testing, and the development of therapies. And these fears are not hypothetical; in practice, Myriad has used its patents to shut down clinical care and impede research.

The Court need not reach the question of whether cDNA, or complementary DNA, is patentable. Myriad has never argued that any of its claims are limited to cDNA, nor could it given the definitions in the patents. Even if some claims were so limited, cDNA's structure is dictated by nature and created by natural processes. Its function is likewise dictated by nature. It is neither inventive nor markedly different from DNA, and patenting it preempts use of a basic scientific and technological tool.

Patent-eligibility cannot be satisfied by the PTO's policy of issuing patents on isolated DNA and the industry reliance on such patents. This Court has never deferred to the PTO's Section 101 determinations, especially where, as here, they violate this Court's own precedent. Moreover, in *Mayo*, the Court rejected the same arguments about industry reliance made by Prometheus and Myriad, as amicus.

Finally, these patents run afoul of the First Amendment because they lock up the body of knowledge about these two genes. Myriad (and specifically in this context, the University of Utah) has the right to exclude all others from examining these genes in any context. Such restrictions on an entire field of knowledge give control over thought and pure information, in violation of the Constitution.

ARGUMENT

I. "ISOLATED DNA" IS NOT PATENTABLE SUBJECT MATTER UNDER SECTION 101.

The patenting of isolated DNA violates long-established precedent that prohibits the patenting of laws of nature, natural phenomena, products of nature, and abstract ideas. *Chakrabarty*, 447 U.S. at 309; *see also J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 134 (2001) ("'the relevant distinction' for purposes of § 101 is . . . 'between products of nature, whether living or not, and human-made inventions'"). "[T]hese exceptions have defined the reach of the statute as a matter of statutory *stare decisis* going back 150 years." *Bilski v. Kappos*, 130 S. Ct. 3218, 3225 (2010) (citing *Le Roy v. Tatham,* 55 U.S. 156, 174-75 (1853)). "Phenomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work." *Mayo*, 132 S. Ct. at 1293 (quoting *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972)). This Court has explained repeatedly that "[s]uch discoveries are 'manifestations of . . . nature, free to all men and reserved exclusively to none.'" *Chakrabarty*, 447 U.S. at 309 (quoting *Funk Bros.,* 333 U.S. at 130). Otherwise, "there is a danger that the grant of patents that tie up their use will inhibit future innovation premised upon them." *Mayo*, 132 S. Ct. at 1301; *see also Funk Bros.*, 333 U.S. at 130-31.

Laws of nature, products of nature, and abstract ideas are not patentable based "on the more

fundamental understanding that they are not the kind of 'discoveries' the statute was enacted to protect." *Parker v. Flook*, 437 U.S. 584, 593 (1978). A product of nature does not become a patentable invention based on utility, novelty, hard work, or the need to recoup investment. *See Mayo*, 132 S. Ct. at 1304. Nor can clever draftsmanship – such as adding the word "isolated" – rescue a claim that otherwise falls short of Section 101 scrutiny. The Court's "cases warn us against interpreting patent statutes in ways that make patent eligibility 'depend simply on the draftsman's art' without reference to the 'principles underlying the prohibition against patents for [natural laws].'" *Id.* at 1294 (quoting *Flook*, 437 U.S. at 593).

The central question in this case is whether "isolated DNA" is an unpatentable product or law of nature or a patentable invention. In *Mayo*, *Chakrabarty*, *Funk Brothers*, and *American Fruit Growers*, this Court has identified at least three different ways of distinguishing a product or law of nature from a patentable invention: whether the composition has any markedly different characteristics from any found in nature; whether the patent is based on an inventive concept; and whether the patent ties up use of the underlying natural phenomena. The three ways do not appear to be independent tests but ways of approaching the central question that must be applied on a case-by-case basis. When each is applied to the patent claims challenged in this case, the claims must be held invalid. Isolated DNA does not have markedly different characteristics from any found in nature, it is not based on an inventive concept, and patenting it

preempts a huge number of valuable applications, far more than the underlying discovery can justify.

A. Isolated DNA Does Not Have Markedly Different Characteristics From Any Found In Nature.

In *Diamond v. Chakrabarty,* the last case in which this Court considered whether a composition of matter was patentable subject matter under Section 101, the Court held that a patent-eligible composition must have "a distinctive name, character [and] use" and "markedly different characteristics from any found in nature," *Chakrabarty*, 447 U.S. at 309-10 (alteration in original) (citation omitted). These criteria are consistent with the Court's statements in earlier Section 101 cases, including *Funk Brothers* and *American Fruit Growers,* and should guide the patent-eligibility determination here. Isolated DNA does not meet this standard.

Chakrabarty involved patents on bacteria that had been genetically-engineered to contain two or more plasmids, each capable of breaking down a component of crude oil, thus allowing the bacteria to degrade oil. *Id.* at 305. In concluding that the *Chakrabarty* bacterium was not a product of nature, the Court did not simply ask whether the bacterium was naturally-occurring, as had the Patent Office Board of Appeals below. *Id.* at 306 n.3. Instead, the Court delved deeper, examining the key characteristics of the claimed composition, including structure and function, to determine whether it was the work of nature.

Comparing the unpatentable combination of bacteria in *Funk Brothers* with the genetically-

engineered and patentable *Chakrabarty* bacterium, the Court in *Chakrabarty* concluded that the latter has "markedly different characteristics from any found in nature," while the former's discovery is "nature's handiwork." *Id.* at 310. The *Chakrabarty* bacterium was both structurally and functionally different from the bacterium in its natural state, containing new genetic material and becoming capable of degrading oil in its new form. By contrast, the challenged patent in *Funk Brothers* was based on a naturally-occurring phenomenon; namely, the ability of certain "isolated" bacteria to efficiently fix nitrogen without inhibiting each other. Even though the bacteria did not exist together naturally and even though their aggregate nitrogen-fixing capability had been newly identified and had commercial utility, the Court invalidated the patent because the patent holder did "not create [a] state of inhibition or of non-inhibition in the bacteria." 333 U.S. at 130. The *Funk Brothers* bacteria did not have markedly different characteristics because their qualities were the work of nature, not of the patentee. *Funk Brothers* and *Chakrabarty* teach that the conditions of section 101 cannot be satisfied when compositions function as they would naturally, even when human ingenuity led to their packaging in a more useful form.

These cases drew on principles laid out in *American Fruit Growers*, in which the Court also grappled with the change necessary to create a patentable invention. The Court rejected the patenting of a fruit that had been treated with mold-resistant borax, even though the "complete article is not found in nature" and despite its "treatment, labor and manipulation." 283 U.S. at 11-12. The Court

said: "There is no change in the name, appearance, or general character of the fruit. It remains a fresh orange fit only for the same beneficial uses as theretofore." *Id*. at 12. Even though the treated fruit had enhanced functionality because it would not rot as quickly, the primary use of the fruit remained the same – for human consumption – and thus the chemical treatment did not give it a "distinctive name, character or use." *Id*.

Under this precedent, the patents on isolated DNA improperly claim products and laws of nature. Isolated DNA does not have markedly different characteristics from DNA in the body – either in structure or function. Only because isolated DNA is not markedly different can Myriad tell patients if they face an increased risk of breast or ovarian cancer after performing diagnostic testing.

The claims' definition of the patented DNA based on biological characteristics, and the sheer number of molecules that are accordingly patented, provide key evidence that the claims reach products and laws of nature. The patents define the claim terms so broadly that they include the BRCA1 and BRCA2 genes of every person. They reach "all forms of mutations" or variations. Patent '282, 12:31-32, 2J.A. 751. They reach any DNA if it is as little as 60% similar to the specified DNA and any DNA that creates proteins as little as 30% similar to the specified proteins. Patent '282, 24:19, 2J.A. 757; Patent '282, 24:60-64, 2J.A. 757. They reach all fragments of both the DNA and the proteins. The claims also reach other forms of genetic material, including "RNA, cDNA, genomic DNA, synthetic forms…" Patent '282, 19:51-53, 2J.A. 755. They

reach DNA with or without "all coding sequences, all intervening sequences and regulatory elements." Patent '282, 19:35-40; 2J.A. 755. They reach DNA modified by "methylation" or other biochemical or chemical modifications or not so modified. Patent '282, 19:56-67, 2J.A. 755; *see also* Pet. App. 263a. Thus while Myriad asserts that it has patented "a composition," it has actually patented hundreds of millions of compositions, most of which have as yet unidentified structures and functions, and all of which have been created by nature.

Even without resort to the patents' definitions of the claim terms, the claim language itself reaches a huge number of compositions, based on their naturally-occurring characteristics. Claim 1 of Patent '282 covers DNA that codes for all versions of the specified BRCA1 protein. The claim does not specify a particular gene that Myriad created or identified, but instead reaches any form of the gene that exists in nature. Claim 6 of Patent '492 reaches any isolated DNA coding for a mutated form of the BRCA2 polypeptide associated with susceptibility to cancer. The claim does not specify any of the mutations that are covered by the claim, nor the type of cancer that might be associated with a mutated form. Claims 5 and 6 of Patent '282 claim DNA sequences with as few as 15 nucleotide bases; small DNA segments sharing 15 nucleotide bases of the BRCA1 gene appear throughout the human genome. 1J.A. 631-34, 661-68. The claims do not seek to claim one or more specific genes (or even gene fragments) intentionally created and made different by the inventor, but instead claim every one of the segments that occur in nature.

Three of the four lower court judges correctly found that the structure of an isolated full-length gene is not markedly different from DNA in the body. Pet. App. 85a-86a, 102a-13a, 333a-44a. They rejected Myriad's argument that separating a gene from other parts of the body with which it is bound makes it structurally different. In so holding, they implicitly or explicitly acknowledged that Myriad's argument improperly confuses chromatin, the proteins and other elements attached to DNA in a cell, with the DNA itself. *See* 85a-86a, 108a, 337a-38a.

Judge Lourie found the structure was markedly different when a chromosome was split into constituent pieces such as genes. Pet. App. 51a-52a. As noted, he was simply wrong that fragments of chromosomes, with broken covalent bonds, do not appear in the body. *See infra*, p.10-11 n. 2. He was simply wrong in his implicit view that scientists isolating genes choose where to break covalent bonds. *See infra*, p. 11 n.3. But even were he correct, the idea that a piece of nature is patentable by breaking it into its constituent parts is fundamentally erroneous. Hydrogen separated from the oxygen to which it is bound in water is still a product of nature.

Likewise, removing DNA from its natural environment does not automatically create "markedly different characteristics." Many natural products must be physically separated from their natural environments in order to be used by mankind, but under *Funk Brothers,* that is not sufficient to render them patentable. The strains of bacteria in *Funk Brothers* were "isolated," removed from their natural environment, and aggregated so

as to more efficiently fix nitrogen without inhibiting each other. 333 U.S. at 129-30. Nevertheless, they could not be patented. *Id*. at 132.

Judge Lourie focused narrowly on minor chemical changes incidental to isolation and viewed DNA's functional characteristics as irrelevant even though DNA's function is inherent in the claims. Pet. App. 55a. ("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.") DNA is foremost an informational molecule, embodying the genetic code. Pet. App. 259a-60a, 334a-43a; 1J.A. 58-59, 130-33, 135-136, 232, 234-35, 561-62, 649-50, 680-81. "Today the idea that DNA carries genetic information in its long chain of nucleotides is so fundamental to biological thought that it is sometimes difficult to realize the enormous intellectual gap that it filled." Bruce Alberts et al., *Molecular Biology of the Cell* 98 (3d ed. 1994) (also noting "DNA is relatively inert chemically," *id.* at 104). Other chemicals in the human body remain the same, albeit in different quantities, from person to person. For example, H_2O, HOH and OH_2 all describe and represent the exact same water molecule; the nucleotide sequences of TAA, ATA and AAT encode entirely different amino acids. 1J.A. 676. Accordingly, the patents describe DNA by its nucleotide sequence, not the sugars and phosphates that make up its backbone, or the covalent bonds in between. 1J.A. 661-73, 676. There is no reading of the patent claims, case law, or science that justifies privileging the breaking of covalent bonds over all else (including other types of bonds and any analysis

of function) in making patent eligibility determinations.

Turning to an analysis of functional differences between isolated genes and unisolated ones, Myriad has argued that genes are patentable because they can be used outside the body in ways they cannot be used inside the body. This argument not only ignores the breadth of the challenged claims, which are not limited to any such new uses, but it also fundamentally misunderstands the product of nature doctrine. Gold does not become patentable once taken out of a stream because it can be used in jewelry; kidneys do not become patentable once taken out of a body because they can be transplanted. Put another way, one potential use unspecified by the patent claim does not justify a patent on the product of nature itself and all uses of it. *See Mayo*, 132 S. Ct. at 1293-94.

None of the nine claims challenged is limited to a particular use or function.[9] Indeed, the two key claims themselves define "isolated DNA" according to a naturally-occurring function – namely, "coding for"

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[9] While claims 5 and 6 of '282 reach very short gene fragments, they reach full-length genes as well; both include DNA of *at least* 15 nucleotides. Thus, the discussion by Judge Moore analyzing the uses of gene fragments as primers and probes, App. at 82a-83a, must be rejected as dicta. None of the claims is limited to gene fragments, and none is limited to uses as primers and probes. *See infra*, pp. 11-17. And as a majority of the Federal Circuit and the district court held, scientists cannot use full-length genes as primers because they are too long. Pet. App. 85a, 115a; 1J.A. 673-74. Similarly, full-length genes cannot be used as probes unless altered by a process called fluorescence. Pet. App. 85a; 1J.A. 672-74*; see also* 1J.A. 656, 693.

a naturally-occurring polypeptide. *See*, *e.g.*, Pet. App. 426a (Claim 1 of Patent '282). Because this blueprint is the essential characteristic of DNA and remains the same before and after isolation, "isolated" DNA does not have markedly different characteristics from any found in nature, nor a distinctive name, character, or use. Both are DNA, the protein coded for by each is the same, and their use in storing and transmitting information about a person's heredity is identical. Indeed, classic experiments demonstrated that isolated DNA, once introduced into other cells and incorporated into chromosomes, would perform the very same function as it did while in the body. 1J.A. 650-53. The isolated DNA molecules "serve the ends nature originally provided and act quite independently of any effort of the patentee." *Funk Bros.,* 333 U.S. at 131. As the district court held, "DNA, and in particular the ordering of its nucleotides, therefore serves as the physical embodiment of laws of nature – those that define the construction of the human body." Pet. App. 335a. Only because this most basic function of DNA is not changed by isolation can Myriad perform its diagnostic tests and tell patients if they are at an increased risk of breast or ovarian cancer.

B. The Challenged Claims Are Not Based On Any Inventive Concept But Instead Claim Products And Laws Of Nature.

In *Mayo*, the Court highlighted another method of determining patent-eligibility found in its precedent – whether the patent is based on an "inventive concept." 132 S. Ct. at 1294, 1297. *Mayo* asked, does the claim arise from an "'inventive

concept,' sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself"? *Id.* at 1294. Does it "add enough" or "simply append[] conventional steps, specified at a high level of generality, to laws of nature [or] natural phenomena"? *Id.* at 1300.

Mayo and *Funk Brothers* elaborate on the inventive concept analysis. In *Mayo*, the Court found that the claims were not inventive, despite transformations that occurred during the administration of a drug and determination of metabolite levels, because nothing of significance was added to the law of nature – the patient's response to a drug. The steps of administering a drug and determining metabolite levels were routine, conventional science. *Id.* at 1297-98. The only addition in the patent claim was the identification by Prometheus of the metabolite levels that indicate drug efficacy. *Id.* at 1297. The claims simply "inform a relevant audience about certain laws of nature." *Id.* at 1298. In *Funk Brothers*, even though the patentee arguably advanced the field because his combination of bacteria "contributed utility and economy to the manufacture and distribution of commercial inoculants," 333 U.S. at 130-31, the Court found that Section 101 was not satisfied. The only addition by the patentee was the discovery of the natural qualities of the bacteria: "[T]here is no invention here unless the discovery that certain strains of the several species of these bacteria are non-inhibitive and may thus be safely mixed is invention. But we cannot so hold without allowing a patent to issue on one of the ancient secrets of nature now disclosed." *Id.* at 132.

Myriad identified the naturally-existing gene, which embodies the natural law that some naturally-occurring mutations of that gene increase a woman's risk of breast and ovarian cancer. Myriad isolated those genes, but isolation of DNA was a well-known technique at the time these patents were sought, and continues to be a routine, conventional preparatory step for using human genes in research and clinical practice. 1J.A. 642-43, 689. The only addition of the "isolated" DNA claims to the progress of science is disclosure of a natural genetic sequence created by a natural law itself – the fact that this sequence of DNA encodes for the BRCA protein and embodies information important for understanding a person's heredity and disease susceptibility. The claimed composition is a discovery of nature's handiwork. *Chakrabarty*, 447 U.S. at 310. And while isolation is needed to use the sequence to identify the law of nature in a particular person's gene, the genetic sequence "itself exists in principle apart from any human action." *Mayo*, 132 S. Ct. at 1297. Just as administering a drug triggered manifestation of a person's natural metabolism of thiopurine in *Mayo*, isolating DNA merely makes visible a person's inherited genetic makeup.

Perhaps the most obvious illustration of the lack of an "inventive" concept in Myriad's claims is claim 6 of Patent '492. It reaches any isolated BRCA2 DNA that is "associated with a susceptibility to cancer." Pet. App. 427a. Myriad has identified a gene in the body, but now claims any mutations created by nature that are found by anyone at any time and are "associated with a susceptibility to cancer." Myriad surely cannot claim to have invented mutations identified by others.

In some ways, the inventive concept analysis overlaps with the "markedly different characteristics from any found in nature" standard discussed *supra*, particularly when compositions of matter are at issue. The focus on inventive concept is helpful, however, in explaining the difference between novelty and utility inquiries and the Section 101 exceptions, which lower courts sometimes have blurred. The inventive concept required to satisfy Section 101 depends on determining whether what the inventor has "added" to the field is a product or law of nature, or whether the inventor has transformed it into more. Although it is possible that the novelty or utility criteria would be satisfied by the new discovery of a natural phenomenon or a discovery of its utility, Section 101 *per se* precludes such patents. *See Mayo*, 132 S. Ct. at 1303-04. *See also In re Marden*, 47 F.2d 958, 959 (C.C.P.A. 1931) (rejecting patent on pure vanadium, because "pure vanadium is not new in the inventive sense, and, it being a product of nature, no one is entitled to a monopoly of the same").

Other cases apply the inventive concept analysis and offer further support for the invalidity of these claims. The Third Circuit held that a patent applicant named Coolidge could not patent "[s]ubstantially pure tungsten having ductility and high tensile strength," despite the superiority of purified tungsten over its naturally-occurring, brittle form. *Gen. Elec. Co. v. De Forest Radio Co.,* 28 F.2d 641, 643 (3d Cir. 1928).

> Naturally we inquire who created pure tungsten. Coolidge? No. It existed in nature and doubtless has existed there

> for centuries. The fact that no one before Coolidge found it there does not negative its origin or existence.

Id. at 643. *General Electric* confirms that courts must examine whether the composition and any characteristics specified in the claims were invented by the patentee or were the work of nature. *See also In re Marden*, 47 F.2d 957 (C.C.P.A. 1931) (rejecting patent on purified uranium); *In re Marden*, 47 F.2d at 958 (rejecting patent on purified vanadium); *In re Merz*, 97 F.2d 599 (C.C.P.A. 1936) (rejecting patent on purified ultramarine). In the early case of *Ex Parte Latimer,* the Patent Commissioner rejected a patent on fibers extracted from pine needles that could more easily be spun and woven. 1889 Dec. Comm'r Pat. 123 (1889). The applicant did not invent the length, strength, or fineness of the fibers; "[n]ature made them so and not the process by which they are taken from the leaf or the needle." *Id.* at 125. *Cf. Am. Wood Paper Co. v. Fibre Disintegrating Co.*, 90 U.S. 566, 593-94 (1874) (finding that cellulose derived from wood and useful for making paper was unpatentable).

Myriad did not invent the isolated DNA. Myriad did not invent any of the characteristics of DNA that are incidental to its isolation. Myriad did not invent the length, composition, or function of the BRCA1 or BRCA2 genes; human biology determined these qualities of the two genes. Pet. App. 106a-07a, 339a, 342a-44a.

C. The Challenged Claims Preempt Uses Of Products And Laws Of Nature.

As *Mayo* reaffirmed, a key aspect of the product or law of nature analysis turns on whether the patent preempts use of the laws and products of nature. Does the patent "risk disproportionately tying up the use of the underlying natural laws, inhibiting their use in the making of further discoveries"? 132 S. Ct. at 1294. Patents on natural phenomena present roadblocks to scientific inquiry and innovation, thus running counter to the constitutional mandate that patents "promote the progress of science." U.S. Const. art. I § 8, cl. 8; *Chakrabarty*, 447 U.S. at 315. "[M]onopolization of [basic scientific and technological] tools through the grant of a patent might tend to impede innovation rather than it would tend to promote it." *Mayo,* 132 S. Ct. at 1293. Thus, the Court's precedents "warn us against upholding patents that claim processes that too broadly preempt the use of a natural law." *Id.* at 1294*; see also Bilski*, 130 S. Ct. at 3231 ("Allowing petitioners to patent risk hedging would pre-empt use of this approach in all fields, and would effectively grant a monopoly over an abstract idea."); *Funk Bros.,* 333 U.S. at 130 ("The qualities of these bacteria, like the heat of the sun, electricity, or the qualities of metals, are part of the storehouse of knowledge of all men. . . . He who discovers a hitherto unknown phenomenon of nature has no claim to a monopoly of it which the law recognizes."); *O'Reilly v. Morse*, 56 U.S. 62, 113 (1853) (The patentee's claim on any machinery or process using electric current to mark characters at a distance "shuts the door against inventions of other persons . .

. ."). The preemption inquiry under Section 101 is determined by whether the patent claim authorizes the patentee to foreclose use of a product or law of nature. *Bilski*, 130 S. Ct. at 3230.

Claims on isolated DNA impermissibly preempt scientific and medical work, far beyond what Myriad's contribution can justify.[10] *See Mayo*, 132 S. Ct. at 1301. The challenged claims cover all isolated forms of the naturally-occurring genes, whether previously identified or not. Some, like claim 6 of '492, expressly claim additional laws of nature (mutations that correlate with an increased risk of cancer), whether previously identified or not. All of the claims reach all uses of the genes in DNA, cDNA, or RNA form and all variants and fragments of the genes, including future uses not yet identified or technically achievable. And because isolation is a necessary step in any serious study, research, or clinical or commercial use of the native DNA, the patents raise the same concerns about patenting a "building-block" that has previously troubled the Court. *See id.* at 1303. They also undermine the patent system by giving Myriad the right to any applications of isolated DNA without disclosing them or even having done the work to develop them. *See*

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[10] While Myriad's work should be credited, it is important to recognize that Myriad built upon the contributions of others. The process of isolation has been performed since as early as 1869. Pet. App. 255a n.3 (citing Ralf Dahm, *Discovering DNA: Friedrich Miescher and the Early Years of Nucleic Acid Research*, 122 Hum. Genetics 565 (2008)). Other scientists discovered the locus of the BRCA1 gene years before Myriad sequenced it, and the federal government poured millions of dollars of funding into the search for the gene. Pet. App. 272a-78a; 1J.A. 247-52.

Morse, 56 U.S. at 113 ("And if he can secure the exclusive use by his present patent he may vary it with every new discovery and development of the science, and need place no description of the new manner, process, or machinery, upon the records of the patent office . . . he claims an exclusive right to use a manner and process which he has not described and indeed had not invented, and therefore could not describe when he obtained his patent."). These patents thus tie up all basic uses of the genes, "foreclose[ing] more future innovation than the underlying discovery could reasonably justify." *Mayo*, 132 S. Ct. at 1292.

Because the patent claims reach all uses of the two human genes, Myriad has the authority to prevent all study of them. When patent exclusivity extends to genes, science is seriously undermined.

> From the point of view of scientific research, human genetic sequences are as basic as you can get in terms of biological information. They are as basic as the elements in the periodic table. Patenting a gene or genetic sequence impedes scientific progress much the same way that patenting a naturally occurring element such as oxygen or gold would impede science.

1J.A. 136 (statement of Nobel Prize-winning biologist John Sulston); *see also* Rep. of the Sec'y's Advisory Comm. on Genetics, Health, and Soc'y, *Gene Patents and Licensing Practices and their Impact on Patient Access to Genetic Tests* 90 (Apr. 2010) (hereinafter "SACGHS Report") (US gene patent law "not only threatens medical progress, it may also drive

valuable genetic research" to other countries); Francis S. Collins, *The Language of Life: DNA and the Revolution in Personalized Medicine* 113 (2010) ("The information contained in our shared instruction book is so fundamental, and requires so much further research to understand its utility, that patenting it at the earliest stage is like putting up a whole lot of unnecessary toll booths on the road to discovery."). Nobel Prize-winning economist Joseph Stiglitz stated that gene patents held by Myriad and others "did not contribute to the store of knowledge, but they impeded innovation in several ways." 1J.A. 708-09.

The effect of the patents has been to prevent and deter research. Pet. App. 290a-92a; 1J.A. 144, 257-58, 623-24, 708-10, 714-18. The contested claims have inhibited others' willingness to engage in research. Over half of all labs surveyed as part of a government-funded study reported "deciding not to develop a new clinical genetic test because of a gene patent or license." 1J.A. 144. Another study found that 46% of surveyed geneticists felt that gene patents had "delayed or limited their research." *Id.* Some geneticists have felt a deep discomfort with conducting research on the BRCA genes because Myriad has prohibited them from disclosing genetic information to research subjects and sharply limited what it considers to be research. 1J.A. 59-60; Kimberly Blanton, *Corporate Takeover Exploiting the U.S. Patent System*, Boston Globe Mag., Feb. 24, 2002, at 10. And scholars looking closely at gene patents found they had "persistent negative effects on subsequent scientific research." Heidi L. Williams, *Intellectual Property Rights and Innovation: Evidence from the Human Genome* ii

(Nat'l Bureau of Econ. Research, Working Paper No. 16213, 2010). *See also* 1J.A. 708-09 ("The Myriad and similar patents … impeded innovation in several ways…more significant perhaps is the impediment to follow-up research…[and] even for basic research…"); 1J.A. 717-18; SACGHS Report at 63-65; Sam Kean, *The Human Genome (Patent) Project*, 331 Sci. 530 (Feb. 4, 2011) (describing high barriers faced by biotechnology companies, including patents that are impossible to circumvent and the millions of dollars required to investigate relevant patent claims and to attempt to negotiate licensing deals).

These patents bar access to people's genetic information. In *Mayo*, the Court suggested that a claim on a new drug would not raise the concern that invalidated Prometheus' patents because another company could develop another drug treating the same condition without infringing. *Mayo*, 132 S. Ct. at 1302-03. In contrast, the "isolated" DNA claims are claims that do preempt future use of laws and products of nature because another entity cannot invent a gene that embodies a person's BRCA1 and BRCA2 genetic information. 1J.A. 135-36. The claims that specifically claim DNA with as few as 15 nucleotide bases preempt scientific work to an even greater extent, because sequences sharing at least 15 nucleotides of the BRCA1 gene appear throughout the genome. Pet. App. 226a-27a; 1J.A. 631-35, 663-72.

These patents preclude using the DNA for the development of drugs, instruments, and treatment methods. Although the BRCA genetic testing Myriad offers is a useful application of isolated DNA, this value is dwarfed by the potential applications of

isolated DNA in new therapeutics, biomedical devices and instruments, and sequencing technologies. *See* Jonathan D. Rockoff & Jess Bravin, *Gene Patents Face Reckoning*, Wall St. J., Dec. 30, 2012 (describing companies, even those which control gene patents, that believe ending gene patents could be a "positive development . . . because it would open new opportunities to develop new testing services based on gene discoveries."). Some of these new applications might relate to breast and ovarian cancer, and some might not[11]; yet, they all are precluded by the patents if they require using the BRCA DNA. Myriad has used the challenged claims to prevent clinical testing of these genes by any other lab, even when others could do so at lower cost, to confirm results, or to ensure testing quality. Many women, upon obtaining results from Myriad, wish to get a second opinion before they make life-changing medical decisions, such as obtaining or refraining from prophylactic surgery. Women cannot obtain confirmatory testing through other labs except for one small set of mutations. Pet. App. 288a-89a; SACGHS Report at 33-34. Myriad also prevents others from providing testing at a lower price, or for free, and only 130 million of America's 308 million people currently receive insurance coverage for their testing. 1J.A. 536.

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[11] The BRCA genes have been linked to other cancers, including prostate and pancreatic. *See, e.g.*, Srinath Sundararajan et al., *The Relevance of BRCA Genetics to Prostate Cancer Pathogenesis and Treatment*, 9 Clinical Advances in Hematology & Oncology 748 (2011); Kathleen M. Murphy et al., *Evaluation of Candidate Genes MAP2K4, MADH4, ACVR1B and BRCA2 in Familial Pancreatic Cancer: Deleterious BRCA2 Mutations in 17%*, 62 Cancer Res. 3789 (2002).

These claims give rise to the same concern expressed by this Court in *Mayo* regarding how patents "threaten to inhibit the development of more refined treatment recommendations." *Mayo,* 132 S. Ct. at 1302. The "isolated" DNA claims allow Myriad to dictate the standard of testing that is offered. It is undisputed that for several years, Myriad was performing tests that did not identify all known mutations. Women with mutations not detected by Myriad's tests were and continue to be given falsely reassuring results. 1J.A. 61, 151, 210, 220-21, 258; Robert Langreth, *Myriad Stymies Cancer Answers by Impeding Data Sharing*, Bloomberg, Dec. 28, 2012. Indeed, Myriad continues to separate testing for large genetic rearrangements from its standard testing, even though national guidelines recommend that patients receive such testing. Nat'l Comprehensive Cancer Network, *NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast and Ovarian* HBOC-2, MS-14-15 (2012). Moreover, Myriad's monopoly on the BRCA genes prevents other laboratories from including these genes when clinically assaying the over twenty genes now known to be associated with hereditary risk for breast and ovarian cancer or when using next generation testing methods. *See, e.g.*, Tom Walsh et al., *Detection of Inherited Mutations for Breast and Ovarian Cancer Using Genomic Capture and Massively Parallel Sequencing*, Proc. Nat'l Acad. Sci. 3 (2010); Hilmi Ozcelik et al., *Long-Range PCR and Next-Generation Sequencing of BRCA1 and BRCA2 in Breast Cancer*, 14 J. Molecular Diagnostics 419, 467 (2012); SACGHS Report at 39-40; *see also* 1J.A. 59-60, 86-91, 208-11, 219-24, 623; Fed. Cir. App. A2813.

The patents also have interfered with deepening our knowledge about these genes. Scientists routinely share information about the importance of particular genes and particular gene mutations. 1J.A. 137-39. Because the patents have authorized Myriad to maintain a monopoly on clinical testing, they have permitted Myriad to control a huge amount of data on the nature and significance of variants in the BRCA1 and BRCA2 genes. For the last several years, Myriad has refused to share that data with the scientific community and has no obligation to collaborate with others. Pet. App. 289a-93a; 1J.A. 62, 91, 206-09; Andrew Pollack, *Despite Gene Patent Victory, Myriad Genetics Faces Challenges*, N.Y. Times, Aug. 24, 2011; *see also* 1J.A. 136-39. If additional labs could engage in testing, the scientific community would know considerably more, particularly about those alterations of the gene whose significance is not now known. 1J.A. 62, 113-14, 222-23. Through its patents, Myriad not only commands the law of nature that is embodied by the BRCA genes, but also the laws of nature relating to how the BRCA genes function in tandem with other genes and genetic factors and how the genes might be linked to diseases other than breast and ovarian cancer – key scientific insights required for the development of personalized medicine. 1J.A. 138-39.

Despite *Mayo*'s concerns about the impact of patents on innovation, the Federal Circuit majority refused to consider how the patents preempt use of laws and products of nature, impeding clinical and scientific work. Pet. App. 43a-44a, 58a-59a. The wide-ranging harmful impact of these patents has led the medical and scientific establishment, including the American Medical Association, the

American Society of Human Genetics, and patient advocacy groups, to oppose them.

Because virtually every conceivable scientific use of DNA requires that it be isolated, and because the patents do not specify a single BRCA molecule or a single use of the DNA but instead cover all of them, the patents give exclusivity over the BRCA1 and BRCA2 genes itself, and their preemptive effect mandates a finding of invalidity.

II. cDNA IS NOT PATENTABLE SUBJECT MATTER.

Although Myriad has *never* asserted that any of its claims are limited to cDNA, and Petitioners agree that none of the challenged claims is limited to cDNA, the Department of Justice (and Judges Lourie and Bryson of the Federal Circuit after remand) thought one or more claims were limited to cDNA. Pet. App. 47a n.9, 100a. The judges and DOJ apparently relied on the description of the sequence listed in the patent's table (Patent '282, 2J.A. 779) rather than the definition of DNA as used in the patent claim. Patent '282, 19:51-53, 2J.A. 755, 822.

This Court need not and should not reach the question of the patentability of cDNA. The challenged claims define "isolated DNA" to include a variety of types of compositions including genomic DNA (DNA with coding and non-coding regions) and cDNA (DNA with coding regions). *See*, *e.g.*, Patent '282, 19:14-18, 19:51-53, 2J.A. 755. Thus, if the definitions of DNA that Myriad insisted upon in its patents are credited, as they must be, a ruling finding isolated DNA unpatentable would defeat all of the challenged claims.

If, however, the Court interprets any of the challenged claims to be limited to just cDNA and chooses to address the patent-eligibility of cDNA, it should find that claims on cDNA impermissibly claim products and laws of nature.

At the simplest level, cDNA is identical to DNA except the non-coding regions have been removed. Myriad does not decide which nucleotides to remove. Nature dictates which are coding and which are not. Thus, comparing the capital letters listed in patent '282, FIG 10 (which is DNA with coding regions in capital letters and non-coding regions in small letters) with SEQ ID. NO.1 reveals that they are identical. 2J.A. 738-45. They are not "markedly different" in structure; only the parts nature has made seemingly unnecessary are removed. If DNA is analogized to a newspaper, cDNA is the identical newspaper without the ads.

cDNA and DNA also are not "markedly different" in function. Definitionally, they encode the same polypeptide/protein. BRCA1 or BRCA2 cDNA "codes for" or creates the BRCA1 or BRCA2 polypeptide.

Equally importantly, the non-coding regions are removed in the body by nature. In the process of making a protein, the DNA is first converted into mRNA by a naturally-occurring process. mRNA is fundamentally DNA but does not contain the non-coding regions.[12] Pet. App. 265a-67a. To go to cDNA,

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[12] It is admittedly more complicated. As noted above, DNA consists of four nucleotides: A, G, T, and C. Pet. App. 257a. Each uniquely binds to (or connects with) a binding partner. Thus, A always binds to T and C always binds to G. Pet. App. 258a; 1J.A. 234. When mRNA is made in the cell, the

the mRNA is removed from the body and converted into cDNA by repeating the complementary binding process that nature has dictated to re-create the coding regions of the original DNA. Pet. App. 266a-69a. Thus, if the DNA sequence was a GCGTAT, the mRNA sequence will be CGCUTU, and the cDNA sequence will once again be GCGTAT as it was in the original DNA.[13]

There is no scientific or legal distinction between isolated genomic DNA and cDNA that warrants treating their patent eligibility differently. Their characters and functions are both dictated by nature, not the patentee, and therefore neither has "markedly different characteristics from any found in nature." The critical difference, exclusion of the non-coding regions, is accomplished entirely within the cell, by natural processes, without any human intervention. cDNA "is an exact copy of one of the protein coding sequences encoded by the original genomic DNA . . . In this respect, cDNA contains the identical protein coding informational content as the DNA in the body . . ." Pet. App. 268a; *see also* Pet. App. 339a ("not only are the coding sequences contained in the claimed DNA identical to those

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nucleotide in the DNA is replaced by its binding partner. Pet. App. 15a, 266a. Thus, if the DNA nucleotides are GCG, the mRNA nucleotides made by the body will be a CGC. mRNA also utilizes a chemical called uracil (U), in place of DNA's T which binds to A. Pet. App. 15a, 266a. These changes are analogous to the simplest of all codes, in which the letter A is always replaced by B and B by C. The substance has not changed and the changes are made by the body. Finally, mRNA has different endings from DNA, called untranslated regions.

[13] Of course, the full cDNA sequence excludes the non-coding regions.

found in native DNA, the particular arrangement of those coding sequences is the result of the natural phenomena of RNA splicing.") As a result, cDNA simply does not have "markedly different characteristics from any found in nature."

Although cDNA is frequently created in the laboratory using the above-described process, scientists have documented the existence of the BRCA1 pseudogene1, a segment of the BRCA1 cDNA, in the human genome. Pet. App. 268a; 1J.A. 658-59, 674-75. A ruling that DNA is not patentable because it is a product of nature necessarily would require a ruling that pseudogenes (or cDNA) are not patentable for the same reason.

Even though cDNA is generally made in the laboratory, that fact alone does not render it patentable subject matter. The nucleotide sequence of cDNA is dictated by nature, not by the lab technician; indeed, the technician does not even know the sequence beforehand. And presumably, the fruit at issue in *American Fruit Growers* was not treated while still on the tree; nor were the *Funk* strains of bacteria isolated and combined in their natural habitat. *Chakrabarty* would not have presented a close question if the legal standard turned on whether the bacterium was created in the laboratory or in the wild. The setting for the creation of the patented composition does not determine its patent eligibility. Nor is the synthetic nature of the composition decisive. In *Cochrane v. Badische Anilin & Soda Fabrik*, the Court held that an artificial version of a natural red dye called alizarine that was produced by manipulating another compound through acid, heat, water, or distillation could not be

patented. 111 U.S. 293, 311 (1884). Although the artificial version was brighter than observed in nature and prepared through a new, man-made process, it was unpatentable because of its similarity to the natural product. That it was synthesized, rather than naturally-occurring, did not make it a patentable composition of matter, though the process of synthesizing artificial alizarine could be patented. *Id.* Lastly, the fact that cDNA does not include non-protein-coding sequences found in DNA does not transform it into an invention. As the Court said in *American Fruit Growers*, "every change in an article is the result of treatment, labor, and manipulation," but the key question remains, is it no longer a product of nature? 283 U.S. at 12.

There is no inventive concept in cDNA. The process resulting in cDNA was known long before Myriad obtained its patents and is not before the Court. 1J.A. 675; Jeffrey Ross et al., *In Vitro Synthesis of DNA Complementary to Purified Rabbit Globin mRNA*, 69 Proc. Nat. Acad. Sci. USA 264 (1972). cDNA is a composition whose structure and function is dictated by and created by nature.

Lastly, patenting cDNA preempts use of a basic scientific tool that serves as the basis for many genetic discoveries. For example, many genetic engineering experiments involve producing and tinkering with cDNA. Any foreseeable innovations that apply genetic engineering techniques in developing new ways of repairing mutated genes would require utilizing cDNA. cDNA is also the basis for RNA sequencing that is used to quantify

how a gene is functioning.[14] Furthermore, cDNA is modified and used in the development of recombinant drugs or therapeutic proteins. Finding ways to change cDNA to produce a more useful protein are true discoveries worthy of patent protection; the baseline cDNA is not.

Given cDNA's biological relationship to naturally-occurring mRNA, its existence in the naturally-occurring human genome, its creation based on the naturally-occurring biological machinery of the cell, and its status as a "basic scientific and technological tool," cDNA is not patentable subject matter.

III. THE COURT SHOULD DECIDE THE PATENTABILITY OF HUMAN GENES WITHOUT REGARD TO INDUSTRY RELIANCE ON PATENT OFFICE PRACTICE.

Judge Moore thought full-length genes were not patentable subject matter but provided the critical vote upholding the challenged claims because the PTO has long approved patents on genes and industry has relied upon them. The PTO's practice is largely irrelevant. Were it not, it would be unusual, not routine, for courts to invalidate patents. For example, roughly 37% of all patents challenged on obviousness grounds were held invalid. *See* Univ. of Houston Law Center Inst. for Intell. Prop. & Info.

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[14] RNA analysis is distinct from genetic sequencing in measuring a different type of gene malfunction. *See, e.g.*, Gina Kolata, *In Treatment for Leukemia, Glimpses of the Future*, N.Y. Times, July 8, 2012, at A1 (describing how researchers found the cause for one oncologist's leukemia using RNA sequencing).

Law, Full Calendar Year 2011 Report, http://www.patstats.org/2011_Full_Year_Report.html. Moreover, the U.S. government, in the course of this litigation, has filed two briefs arguing that isolated DNA is not patentable.

That the PTO's practice is based on written guidelines is equally irrelevant. The 2001 PTO Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001) are guidelines for patent examiners, not binding on this Court. *See Hill-Rom Co., Inc. v. Kinetic Concepts, Inc.*, 209 F.3d 1337, 1341 n.* (Fed. Cir. 2000). They are also remarkably free of any analysis of their rationale, simply stating that "isolated" genes do not exist in the body. Not only is this incorrect, but it misapprehends this Court's analysis for distinguishing products or laws of nature from inventions.

Perhaps more troubling is Judge Moore's view that patentees attain "adverse possession" on products or laws of nature, Pet. App. 119a, if industry has relied on them. Presumably, industry relies on any issued patent. But more importantly, this Court confronted and flatly rejected this argument in *Mayo*. 132 S. Ct. at 1304-05 (referring to the industry reliance argument of Prometheus and "several amici"); Brief for Myriad Genetics, Inc., as Amicus Curiae Supporting Respondent, *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289 (2012) (No. 10-1150), 2011 WL 5373694.

It is not for the Court to balance policy considerations and dole out special patent protection for DNA. The Court stated that such special protection must be expressly required by Congress: "And we must recognize the role of Congress in

crafting more finely tailored rules where necessary. We need not determine here whether, from a policy perspective, increased protection for discoveries of diagnostic laws of nature is desirable." *Mayo*, 132 S. Ct. at 1305 (citations omitted). The *Bilski* concurrence, approving the invalidation of a business method patent, similarly noted that Congress, not the Court, should select the policy that best serves the constitutional aim, "[a]nd absent a discernible signal from Congress, we proceed cautiously when dealing with patents that press on the limits of the 'standard written into the constitution,'" 130 S. Ct. at 3253 (citation omitted)*; see also Microsoft Corp. v. AT&T Corp.* 550 U.S. 437, 458 (2007) ("[O]ur precedent leads us to leave in Congress' court the patent-protective determination AT&T seeks."); *Eli Lilly & Co. v. Medtronic, Inc.,* 496 U.S. 661 (1998) (finding exemption from infringement where statute was ambiguous as to scope of exemption).

It is not clear that Congress could constitutionally abolish the product or law of nature doctrine in whole or in part, but it has not done so with respect to human genes. This Court should apply long-standing doctrine without regard to PTO deference and industry reliance and find the challenged claims unpatentable.

IV. PATENT CLAIMS ON ISOLATED DNA ALSO VIOLATE THE FIRST AMENDMENT BECAUSE THEY AMOUNT TO A GRANT OF EXCLUSIVE CONTROL OVER A BODY OF KNOWLEDGE.

The First Amendment limits the reach of intellectual property laws. In copyright, where the

potential conflict is more obvious, this Court has suggested that doctrines, like the idea/expression distinction, that are incorporated into statute are required by the First Amendment. *Harper & Row Publishers, Inc. v. Nation Enters.*, 471 U.S. 539, 556 (1985); *Eldred v. Ashcroft,* 537 U.S. 186, 219 (2003). *See also Salinger v. Colting*, 641 F. Supp. 2d 250, 255 (S.D.N.Y. 2009), *rev'd on other grounds*, 607 F.3d 68 (2d Cir. 2010); *Maxtone-Graham v. Burtchaell*, 631 F. Supp. 1432, 1435 (S.D.N.Y. 1986). Although the section 101 doctrine prohibiting patenting of natural phenomena has not been described previously as compelled by the First Amendment, there can be little doubt that granting patents that give control over an entire body of knowledge would violate the First Amendment. Indeed, the Court's concern about tying up basic scientific and technological tools highlights the priority placed on preventing patents that impede scientific thought and innovation. *Mayo*, 132 S. Ct. at 1293*; see also* Gary L. Francione, *Experimentation and the Marketplace Theory of the First Amendment*, 136 U. Pa. L. Rev. 417, 428 (1987).

For a typical invention, such as a carburetor, others can examine how the new carburetor functions once the patent is published and develop a better carburetor using different materials or methods. By contrast, if "isolated" oxygen were patented, no one could invent a new oxygen, and no one could study how it reacts in numerous scientific contexts without the patentee's permission. Similarly, once a human gene is patented, nobody can invent a new human gene, and nobody can access

that particular human genetic information.[15] *See* 1J.A. 63, 139. Because patent claims on the isolated BRCA1 and BRCA2 DNA prevent access to each person's genetic information, and accordingly deprive scientists of the opportunity to examine and study the genes, they are fundamentally different from patents on carburetors.

Indeed, rather than leading to a greater understanding or a better product, the patent claims challenged in this case exclude others from further work with naturally-occurring genes. *E.g.*, 1J.A. 139, 148, 152. Myriad has used its exclusive authority to amass an enormous amount of information critical to the health of every American. Myriad refuses to allow others to obtain the information themselves or to share the information with the medical and scientific communities. The claims thus give entire control over a body of knowledge and over pure information to Myriad. That, under the First Amendment, is impermissible. *See Ashcroft v. Free Speech Coal.,* 535 U.S. 234, 253 (2002) ("First Amendment freedoms are most in danger when the government seeks to control thought or to justify its laws for that impermissible end. The right to think is the beginning of freedom . . . .")*; see also* John A. Robertson, *The Scientist's Right to Research: A Constitutional Analysis*, 51 S. Cal. L. Rev. 1203, 1217-18 (1977) (concluding that "[i]f the first amendment serves to protect free trade in the dissemination of ideas and information, it must also protect the necessary preconditions of speech, such

[15] Genes with new sequences can be invented, of course, that have never existed in nature. Those are not at issue here.

as the production of ideas and information through research.").

The serious constitutional violation raised by these patent claims provides an additional reason for the Court to construe the statute to find the claims invalid. The district court found it unnecessary to reach the constitutional questions, invoking the doctrine of constitutional avoidance. Pet. App. 357a. However, if the Court finds the claims valid under the statute, it should find them unconstitutional under the First Amendment.

CONCLUSION

For the foregoing reasons, the patent claims should be held invalid.

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