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 *AMICUS CURIAE* ERIC S. LANDER IN SUPPORT OF NEITHER PARTY

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STATEMENT OF INTEREST OF *AMICUS CURIAE**

***Amicus Curiae* Eric S. Lander** was one of the principal leaders of the Human Genome Project (HGP), the international project that determined and made freely available the DNA sequence of the human genome. Dr. Lander directed the largest center in the HGP, which generated approximately one-third of the human genome sequence.

Dr. Lander is a geneticist, molecular biologist and mathematician. He serves as President and Founding Director of the Broad Institute of Harvard and MIT, a nonprofit biomedical research institution focused on genomic medicine. He is also Professor of Biology at the Massachusetts Institute of Technology and Professor of Systems Biology at Harvard Medical School. In addition, he has been a founder of several biotechnology firms.

Dr. Lander was elected a member of the U.S. National Academy of Sciences in 1997 and a member of the U.S. Institute of Medicine in 1999. He has received numerous major international awards for his research on the human genome.

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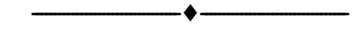
* Counsel for all parties have consented to the filing of this brief, and their consents have been lodged with the Clerk of this Court. No counsel for any party had any role in authoring this brief, and no person other than the named *amicus* and his counsel has made any monetary contribution to the preparation and submission of this brief. *See* Rule 37.

Dr. Lander also serves as Co-Chair of the President's Council of Advisors on Science and Technology (PCAST), an advisory group consisting of some of the nation's leading scientists and engineers, who directly advise the President and the Executive Office of the President. Importantly, however, Dr. Lander wishes to emphasize that this brief represents his own personal views. The brief is in no way intended as a statement of policy or position by the United States Government, the Broad Institute, Harvard, MIT, or any other entity.

In this case, the Federal Circuit held, among other things, that claims to isolated DNA fragments recite a composition of matter patent-eligible under 35 U.S.C. § 101. The assumption underlying this holding is that such fragments do not occur in Nature. As a leading genomic researcher, Dr. Lander has a strong interest in advising the Court that, in fact, such fragments routinely occur in Nature and that claims to such fragments create an insurmountable barrier to scientific innovation.



SUMMARY OF THE ARGUMENT

This case hinges on a scientific question: whether DNA fragments from a human chromosome are (1) products of Nature or (2) at least *similar enough* to products of Nature that they should not be considered "markedly different." *Diamond v. Chakrabarty*, 447 U.S. 303, 310 (1980).

The members of the Federal Circuit panel below agreed that the DNA of a *whole* human chromosome was a product of Nature. But the majority held that isolated DNA *fragments* of a human chromosome were *not* products of Nature.

Because the majority made (without citing scientific support) a foundational assumption that isolated DNA fragments of the human genome do not *themselves* routinely occur in Nature, it considered whether they are *similar enough* to products of Nature. Employing analogies, the panel members debated whether isolated DNA cleaved from a chromosome was akin to a leaf plucked from a tree, or a kidney surgically removed from a human body.

This reasoning-by-analogy was unnecessary because the majority's foundational assumption is demonstrably incorrect: it is well-accepted in the scientific community that (a) chromosomes are constantly being broken into DNA fragments by natural biological processes that break the covalent bonds within DNA chains; (b) these DNA fragments are ubiquitous in the human body, both within cells and in cell-free blood, urine, sputum and stool; and (c) these fragments cover the entire human genome and, in particular, include the BRCA1 and BRCA2 genes claimed by Myriad's patents. Myriad's claims thus include DNA fragments that are unambiguously products of Nature.

Under this Court's interpretation of 35 U.S.C. § 101, composition-of-matter patents on such pre-existing products of Nature are not permissible. Such products of Nature are "manifestations of . . . nature, free to all men and reserved exclusively to none." *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948).

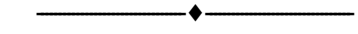
A patent on a product of Nature would authorize the patent holder to exclude everyone from observing, characterizing or analyzing, *by any means whatsoever*, the product of Nature. This barrier is inherently insurmountable: one cannot study a product of Nature if one cannot legally possess it. A molecule is one of the "basic tools" – indeed, the *essential* tool – for studying the molecule itself. *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972). A patent on a molecule that is a product of Nature would thus authorize a patent holder to wall off an entire domain of Nature from observation.

Finally, the majority held that a decision that isolated DNA fragments of the human genome are patent-ineligible would disrupt long-settled expectations and could wreak havoc on the biotechnology industry. The majority's concern is unfounded.

Most biotechnology products are protected by patents on *non-natural* DNA molecules, rather than *naturally occurring* genomic DNA. The biotechnology industry would not be substantially affected by a narrowly crafted decision here holding that (1) fragments of human genomic DNA are patent-ineligible

where the scientific evidence is clear that the claimed molecules themselves are routinely found in Nature and where the process for purification or synthesis of such molecules is routine but (2) human cDNAs are patent-eligible, because these molecules do not occur in Nature and have clearly different functional properties from related products of Nature.

On the contrary, such a narrowly crafted decision would foster scientific progress and technological innovation by guaranteeing an unfettered ability to study a remarkable product of Nature – the human genome. This ability will lead to countless discoveries about human disease, as well as an outpouring of medical invention with enormous consequences for human health.



ARGUMENT

This *amicus* brief provides information and perspective concerning several scientific issues at the center of the case – namely, whether (1) isolated DNA fragments of the human genome are products of Nature; (2) patents that foreclose the observation, characterization or analysis of products of Nature impede scientific progress and technological innovation; and (3) a narrowly crafted decision that isolated DNA fragments of the human genome are patent-ineligible would disrupt the biotechnology industry or instead would foster innovation.

I. THE FEDERAL CIRCUIT INCORRECTLY ASSUMED, WITHOUT CITING SCIENTIFIC EVIDENCE, THAT ISOLATED DNA FRAGMENTS OF THE HUMAN GENOME DO NOT OCCUR IN NATURE, WHEN IT IS WELL-ACCEPTED IN THE SCIENTIFIC COMMUNITY THAT THEY DO.

The human genome consists of 23 pairs of chromosomes, which together specify the instructions for life and harbor variations that can predispose to disease. Each chromosome contains a long DNA double helix, totaling approximately 3 billion nucleotides in length. The term "gene" typically refers to a nucleotide sequence, within a chromosome, that encodes instructions for proteins.[1]

[1] Myriad's patents concern the BRCA1 and BRCA2 genes. The BRCA1 gene, for example, consists of a region of ~81,000 nucleotides on Chromosome 17, which is 88 million nucleotides long. Todd M. Smith et al., *Complete Genomic Sequence and Analysis of 117 kb of Human DNA Containing the Gene BRCA1,* 6 Gen. Res. 1029 (1996); Eric S. Lander et al., *Initial Sequencing and Analysis of the Human Genome*, 409 Nature 860 (2001). The BRCA1 gene is transcribed into an initial RNA molecule, which is then spliced to yield a shorter mature RNA molecule and translated into the BRCA1 protein. Certain variations in the DNA sequence of the BRCA1 gene ("spelling differences") predispose women carrying them to develop early-onset breast cancer. The BRCA2 gene is on chromosome 13.

A. Myriad's patents cover isolated DNA fragments from the human genome.

Myriad's claims on the BRCA1 gene create a monopoly on any "isolated DNA" containing "at least" 15 consecutive bases from any DNA sequence that encodes a BRCA1 protein[2,3] – including from the human BRCA1 gene itself.

In the context of Myriad's patents, "isolated DNA" refers to "a free-standing portion of a larger, natural DNA molecule. Isolated DNA has been cleaved (*i.e.*, had covalent bonds in its backbone chemically severed) or synthesized to consist of just a fraction of a naturally occurring DNA molecule." *Association for Molecular Pathology v. United States Patent & Trademark Office,* 689 F.3d 1303, 1328 (Fed. Cir.), *cert. granted sub nom. Association for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 694 (2012). Isolated DNA has the identical nucleotide sequence as in the larger whole; it differs only in having been cleaved from the whole.

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[2] Claim 5 of the main patent at issue states: "5. An isolated DNA having at least 15 nucleotides of the DNA of claim 1." U.S. Patent No. 5,747,282 (issued May 5, 1998) ("'282 patent") col. 153 ll.66-67. Claim 1, in turn, describes the DNA of the full BRCA1 gene: "1. An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2." '282 patent col. 153 ll.57-59.

[3] We focus our arguments on claims regarding BRCA1. However, they apply *mutatis mutandis* to the analogous claims regarding BRCA2 in U.S. Patent No. 5,837,492 (issued November 17, 1998).

"Isolated DNA" thus refers not simply to *physical purification*,[4] but to a molecule that is *chemically distinct* from the larger DNA molecule of the entire chromosome. The Federal Circuit wrote that "isolated DNA is not just purified DNA. Purification makes pure what was the same material, but was combined, or contaminated, with other materials [whereas] . . . isolated DNA . . . has also been manipulated chemically [i.e., cleaved from a larger DNA]. . . ." 689 F.3d at 1328.

Myriad's claims to "isolated DNA" fragments of the human genome are extremely broad. They include any DNA fragment of chromosome 17 that contains *at least* 15 nucleotides of the region containing the BRCA1 gene. These fragments range in length from

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[4] "Purification" of an isolated DNA molecule from a mixture of other isolated DNA molecules has been straightforward since the invention in the 1970s of recombinant DNA ("gene cloning"). A molecular biologist can create a "library" of DNA molecules by (i) attaching genomic DNA fragments *en masse* to "vector" molecules, (ii) transferring the resulting molecules *en masse* into bacteria and (iii) growing the resulting bacteria on Petri plates. This process yields millions of separate bacterial colonies, each carrying an *individual* segment of DNA from the human genome. In this way, the first human recombinant library, produced in 1978, successfully "purified" all the fragments of the human genome from one another. Tom Maniatis et al., *The Isolation of Structural Genes from Libraries of Eucaryotic DNA*, 15 Cell 687 (1978); Richard M. Lawn et al., *The Isolation and Characterization of Linked Delta- and Beta-globin Genes from a Cloned Library of Human DNA*, 15 Cell 1557 (1978). Since then the challenge has thus not been purifying the fragments, but discovering their function.

15 nucleotides to nearly the *whole chromosome*.[5] In total, the claims cover more than *one quadrillion* distinct fragments from chromosome 17. *See* Fig. 1.

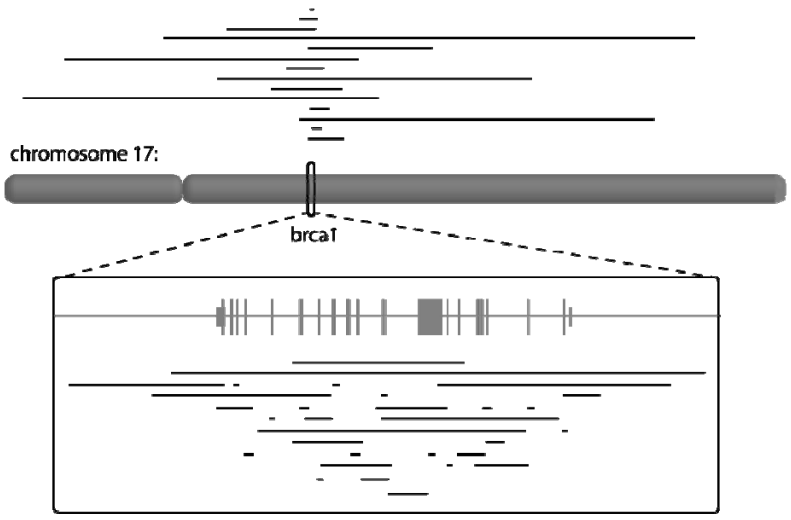

Figure 1: Examples of the many fragments of "isolated DNA" claimed by Myriad's patent on BRCA1. The fragments range in length from 15 nucleotides to many millions of nucleotides, and include any fragment that contains 15 nucleotides of the BRCA1 gene region.

[5] The concurrence below vastly understated the breadth of Myriad's claim 5. *See* 689 F.3d at 1341 ("I begin with the short isolated sequences such as those covered by claim 5 which is directed to 'an isolated DNA having at least 15 nucleotides of the DNA of claim 1.' This claim covers a sequence as short as 15 nucleotides and arguably as long as the *entire gene*." (emphasis added)). An isolated DNA fragment containing *virtually all of chromosome 17* qualifies as "an isolated DNA having at least 15 nucleotides of the DNA of claim 1."

B. The Federal Circuit assumed, without citing scientific evidence, that isolated DNA fragments of the human genome do not occur in Nature and therefore inappropriately used reasoning-by-analogy to decide whether such fragments are "similar" to or "markedly different" from products of Nature.

The central issue in the Federal Circuit's decision was (1) whether DNA fragments from a human chromosome are products of Nature or (2) if they are *not* products of Nature, whether they are *similar enough* to products of Nature that they cannot be considered "markedly different." *Chakrabarty*, 447 U.S. at 310.

The judges agreed that the DNA of a *whole* human chromosome was the patent-ineligible handiwork of Nature,[6] but they disagreed as to the status of an *isolated DNA fragment* of a human chromosome.[7]

The Federal Circuit began its analysis with a foundational assumption that the isolated DNA fragments claimed by Myriad (such as those shown in Figure 1) do not themselves occur in Nature:

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[6] *See* 689 F.3d at 1328, 1343 n.6, 1350.

[7] *See* 689 F.3d at 1325-33, 1340-43, 1350-58.

> The isolated DNA molecules before us are not found in nature. . . . In this case, the claimed isolated DNA molecules do not exist in nature within a physical mixture to be purified. They have to be chemically cleaved from their native chemical combination with other genetic materials. In other words, in nature, the claimed isolated DNAs are *covalently bonded* to such other materials. Thus, when cleaved, an isolated DNA molecule is not a purified form of a natural material, but a distinct chemical entity that is obtained by human intervention.

689 F.3d at 1325, 1329 (emphasis added).

The Federal Circuit cited no scientific support for its assertion that the claimed isolated DNA fragments do not occur in Nature.

Proceeding from this assertion, the Federal Circuit then sought to determine whether such isolated DNA fragments are fundamentally *similar* to products of Nature or are markedly "different from the natural products in 'name, character, and use.'" *Id.* at 1329 (quoting *Chakrabarty*, 447 U.S. at 309-10). The panel members debated whether cleaving a DNA fragment from a chromosome was akin to plucking a leaf from a tree, or surgically removing a kidney from a human body. *Id.* at 1332, 1347, 1352-53. Further, the panel members disagreed internally regarding whether the breaking of chemical covalent bonds rendered the fragments "materially different" from naturally occurring DNA. *Compare id.* at 1329-30

with id. at 1341 (Moore, J., conc.) *and id.* at 1350 (Bryson, J., conc. in part and diss. in part).

As shown in the next section, the Federal Circuit had no need to engage in this reasoning-by-analogy because the foundational assertion that the DNA fragments themselves do not occur in Nature is demonstrably incorrect.

C. It is well-accepted in the scientific community that isolated DNA fragments of the human genome – including many fragments covered by Myriad's patents – occur routinely in the human body and thus are products of Nature.

It has been well established for over 30 years that isolated DNA fragments of human chromosomes routinely occur in the human body. Moreover, these isolated DNA fragments span the entire human genome, including the BRCA1 and BRCA2 genes. Some of the abundant scientific evidence is summarized below.

Cell death occurs routinely in the human body, with many billions of cells dying every day.[8] When cells die, chromosomal DNA is broken into fragments

[8] Andrew G. Renehan et al., *What is Apoptosis, and Why Is It Important?,* 322 Br. Med. J. 1536 (2001).

as part of a carefully orchestrated natural process.[9] Nature provides the cell with specialized DNA-cleaving enzymes (called endonucleases); during cell death and other critical cellular processes, these enzymes have the specific function of breaking covalent bonds that otherwise hold together the DNA chain.[10]

The proper control of this natural process is so important that mutations that disrupt DNA-cleaving enzymes are associated with disease. For example, mutations that reduce the activity of a particular DNA-cleaving enzyme (called DNAse I) have been linked to the auto-immune disease lupus.[11] In another example, patients who lack either of two other genes encoding DNA-cleaving enzymes (involved in repairing DNA damage from ultraviolet light) have a serious disease called xeroderma pigmentosum, which often causes skin cancer.[12]

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[9] Jerry R. Williams et al., *Association of Mammalian Cell Death with a Specific Endonucleolytic Degradation of DNA*, 252 Nature 754 (1974).

[10] Xuesong Liu et al., *The 40-kDa Subunit of DNA Fragmentation Factor Induces DNA Fragmentation and Chromatin Condensation During Apoptosis*, 95 Proc. Natl. Acad. Sci. 8461 (1998).

[11] Hyoung Doo Shin et al., *Common DNase I Polymorphism Associated with Autoantibody Production Among Systemic Lupus Erythematosus Patients,* 13 Hum. Mol. Genet. 2343 (2004).

[12] Anneke M. Sijbers et al., *Xeroderma Pigmentosum Group F Caused by a Defect in a Structure-Specific DNA Repair*

(Continued on following page)

Isolated DNA fragments are not only present in cells, but also routinely found in cell-free blood. The quantity of freely circulating DNA fragments is especially high in the blood of many cancer patients.[13] Such fragments have also been found in substantial quantities in the blood of patients with viral infections,[14] exercise overtraining,[15] trauma,[16] and stroke,[17] and during pregnancy.[18]

The presence of freely circulating isolated DNA fragments in the blood is common enough that it can

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Endonuclease, 86 Cell 811 (1996); Thierry Nouspikel et al., *Mutations That Disable the DNA Repair Gene XPG in a Xeroderma Pigmentosum Group G Patient,* 3 Hum. Mol. Genet. 963 (1994).

[13] Maurice Stroun et al., *Isolation and Characterization of DNA from the Plasma of Cancer Patients*, 23 Eur. J. Cancer. Clin. Onc. 707 (1987).

[14] Tran Thi Ngoc Ha et al., *Elevated Levels of Cell-Free Circulating DNA in Patients with Acute Dengue Virus Infection*, 6 PLoS1 e25969 (2011).

[15] Ioannis Fatouros et al., *Cell-Free Plasma DNA as a Novel Marker of Aseptic Inflammation Severity Related to Exercise Overtraining*, 52 Clin. Chem. 1820 (2006).

[16] Nicole Y.L. Lam et al., *Time Course of Early and Late Changes in Plasma DNA in Trauma Patients,* 49 Clin. Chem. 1286 (2003).

[17] Timothy H. Rainer et al., *Prognostic Use of Circulating Plasma Nucleic Acid Concentrations in Patients with Acute Stroke*, 49 Clin. Chem. 562 (2003).

[18] H. Christina Fan et al., *Analysis of the Size Distributions of Fetal and Maternal Cell-Free DNA by Paired-End Sequencing,* 56 Clin. Chem. 1279 (2010).

be used for identifying genomic mutations in diseases such as cancer and cystic fibrosis.[19]

Studies of isolated DNA fragments in human blood have found that the fragments have a wide range of sizes. Fragments ranging from more than 80,000 bases to fewer than 100 bases are commonly seen.[20]

In pregnancy, both maternal and fetal DNA are found in the blood of the mother, with fragments smaller than 150 bases observed.[21] The presence of isolated fragments of fetal DNA in maternal blood has resulted in the ability to diagnose fetuses for chromosomal disorders (such as Down Syndrome) through sequencing of fetal DNA in maternal blood.[22]

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[19] George D. Sorenson et al., *Soluble Normal and Mutated DNA Sequences from Single-copy Genes in Human Blood*, 3 Cancer Epidemiol. Biomarkers Prev. 67 (1994).

[20] Mary Beth Giacona et al., *Cell-Free DNA in Human Blood Plasma: Length Measurements in Patients with Pancreatic Cancer and Healthy Controls*, 17 Pancreas 89 (1998); Florent Mouliere et al., *High Fragmentation Characterizes Tumour-Derived Circulating DNA*, 6 PLoS1 e23418 (2011).

[21] H. Christina Fan et al., *Analysis of the Size Distributions of Fetal and Maternal Cell-Free DNA by Paired-End Sequencing,* 56 Clin. Chem. 1279 (2010).

[22] H. Christina Fan et al., *Noninvasive Diagnosis of Fetal Aneuploidy by Shotgun Sequencing DNA from Maternal Blood*, 105 Proc. Natl. Acad. Sci. 16266 (2008).

Multiple studies[23] in leading journals have shown that the isolated DNA fragments in blood are so prevalent and cover the human genome so completely that it is "possible to unambiguously determine the whole genome sequence of a fetus from a teaspoon's worth of maternal blood."[24]

Inspection of the publicly available DNA sequence data from two of these studies confirms that (as expected) the isolated fragments of fetal DNA in maternal blood cover the BRCA1 and BRCA2 genes – and therefore include many of the isolated DNA fragments covered by Myriad's patents.[25]

Finally, the presence of isolated DNA fragments of human chromosomes is not limited to intact cells

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[23] H. Christina Fan et al., *Non-invasive Prenatal Measurement of the Fetal Genome*, 487 Nature 320 (2012); Jacob O. Kitzman et al., *Noninvasive Whole-Genome Sequencing of a Human Fetus*, 4 Sci. Transl. Med. 137ra76 (2012); Y.M. Dennis Lo et al., *Maternal Plasma DNA Sequencing Reveals the Genome-Wide Genetics and Mutational Profile of the Fetus*, 2 Sci. Transl. Med. 61ra91 (2010).

[24] Diana W. Bianchi et al., *Fetal Genes in Mother's Blood*, 487 Nature 304 (2012).

[25] BRCA1 and BRCA2 data from H. Christina Fan et al., *Non-invasive Prenatal Measurement of the Fetal Genome*, 487 Nature 320 (2012), are available at http://www.stanford.edu/~quake/brca. Data for Kitzman et al., *Noninvasive Whole-Genome Sequencing of a Human Fetus*, 4 Sci. Transl. Med. 137ra76 (2012), are available at the Genotypes and Phenotypes (dbGaP) database of the National Center for Biotechnology Information at the National Institutes of Health (http://www.ncbi.nlm.nih.gov/sites/entrez?db=gap, accession number phs000500.v1.p1).

and cell-free blood. DNA fragments are so pervasive as to be found in urine,[26] sputum[27] and stool.[28] Much research effort, both in the public and private sector, is underway to take advantage of the availability of these cell-free DNA fragments for diagnostic testing.[29]

In sum, it is well-accepted in the scientific community that (a) chromosomes are constantly being broken into DNA fragments by natural biological processes that break the covalent bonds within DNA chains; (b) these DNA fragments can be routinely found in the human body, within cells (both living and dying) as well as in cell-free blood, urine, sputum and stool; and (c) these fragments cover the entire human genome and, in particular, include many of the DNA fragments claimed by Myriad's patents.

The Federal Circuit thus erred with respect to the central issue in its analysis: isolated DNA

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[26] Ying-Hsiu Su et al., *Human Urine Contains Small, 150 to 250 Nucleotide-sized, Soluble DNA Derived from the Circulation and May Be Useful in the Detection of Colorectal Cancer*, 6 J. Mol. Diagn. 101 (2004).

[27] F. B. J. M. Thunnissen et al., *Sputum Examination for Early Detection of Lung Cancer*, 56 J. Clin. Pathol. 805 (2003); Miep A. van der Drift, *Circulating DNA Is a Non-invasive Prognostic Factor for Survival in Non-small Cell Lung Cancer*, 68 Lung Cancer 283 (2008).

[28] Kevin A. Boynton et al., *DNA Integrity as a Potential Marker for Stool-based Detection of Colorectal Cancer*, 49 Clin. Chem. 1058 (2003).

[29] Annemarie Ziegler et al., *Circulating DNA: A New Diagnostic Gold Mine?,* 28 Cancer Treatment Rev. 255 (2002).

fragments from the human genome, including those essential for determining a woman's risk of early-onset breast cancer and claimed in Myriad's patents, are products of Nature, not the handiwork of humans.

II. MYRIAD'S COMPOSITION-OF-MATTER CLAIMS ON ISOLATED FRAGMENTS OF GENOMIC DNA ARE INCONSISTENT WITH THIS COURT'S SECTION 101 JURISPRUDENCE BECAUSE THEY (1) ARE DIRECTED TO PRE-EXISTING PRODUCTS OF NATURE; (2) EXCLUDE OTHERS FROM OBSERVING, CHARACTERIZING OR ANALYZING THESE PRODUCTS OF NATURE BY ANY MEANS WHATSOEVER; AND (3) CREATE AN INSURMOUNTABLE BARRIER TO SCIENTIFIC PROGRESS AND TECHNOLOGICAL INNOVATION CONCERNING THESE PRODUCTS OF NATURE.

A. Composition-of-matter claims on products of Nature, such as Myriad's claims on naturally occurring DNA fragments of the human genome, are inconsistent with this Court's Section 101 Jurisprudence.

Section 101 of the Patent Act defines patentable subject matter:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful

> improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

35 U.S.C. § 101.

"The Court has long held that this provision contains an important implicit exception." *Mayo Collaborative Servs. v. Prometheus Labs*, 132 S. Ct. 1289, 1293 (2012). "Excluded from such patent protection are laws of nature, natural phenomena, and abstract ideas." *Diamond v. Diehr*, 450 U.S. 175, 185 (1981). The Court has written that "a new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter. . . . Such 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).

In *Chakrabarty*, the Court applied this rule to a human-made, genetically engineered bacterium carrying additional pieces of DNA:

> Judged in this light, respondent's micro-organism plainly qualifies as patentable subject matter. His claim is not to a hitherto unknown natural phenomenon, but to a non-naturally occurring manufacture or composition of matter – a product of human ingenuity "having a distinctive name, character [and] use."

Chakrabarty, 447 U.S. at 309-10 (quoting *Hartranft v. Wiegmann*, 121 U.S. 609, 615 (1887)).

Under *Chakrabarty* and *Mayo*, is a DNA molecule related to the human genome patent-eligible? The answer depends on the nature of the DNA molecule. It is instructive to compare patent claims for three types of DNA molecule:

> *(i) recombinant DNA including human genes* – for example, a novel DNA molecule, in which a human gene has been joined to other DNA containing regulatory sequences to control its expression and enable production of therapeutic protein in a factory. (Most economically valuable patents in the biotechnology industry are of this type.)
>
> *(ii) human cDNA* – that is, a DNA molecule that is obtained by taking a "spliced" messenger RNA from a human cell and using an enzyme to "reverse transcribe" it from RNA to DNA. (These DNA sequences encode human proteins and are often used for producing proteins in factories.)
>
> *(iii) human genomic DNA* – that is, a DNA molecule whose sequence is identical to a portion of the human genome. (Myriad's claim to a monopoly on diagnostics involving the BRCA1 gene rests on claims to genomic DNA.)

In the first case, the claim is clearly to "a nonnaturally occurring manufacture or composition of matter – a product of human ingenuity." *Chakrabarty*, 447 U.S. at 309. An invention involving a human gene in this manner is clearly patent-eligible.

In the second case, the question is closer but the answer is still clear. A cDNA molecule is closely related to the RNA from which it has been reverse transcribed: in particular, it has the same "information content." But it is produced by a transformative step[30] and is a distinct chemical entity that differs from both (i) the RNA (which is a different type of nucleic acid) and (ii) the genomic DNA from which the RNA was transcribed (which contains "intervening sequences"). For this reason, the Federal Circuit concluded, unanimously and correctly, that cDNA is patent-eligible.[31]

In the third case (the one relevant to Myriad's diagnostic monopoly at hand), the arguments for patent-eligibility under Section 101 evaporate. No transformative step is involved because, as shown above, isolated DNA fragments of the human genome occur routinely in Nature.

Claims, such as Myriad's, to isolated DNA fragments of the human genome thus are not directed to "a nonnaturally occurring manufacture or composition of matter – a product of human ingenuity," but rather to a product of Nature itself. *Chakrabarty*, 447 U.S. at 309.

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[30] It can be argued that the transformative step is straightforward, but this speaks to obviousness, not patent-eligibility under Section 101.

[31] *See* 689 F.3d at 1329, 1340-41, 1348.

A discovery about genomic DNA does not involve invention of a new composition of matter, but rather is more akin to discovery of a law of Nature pertaining to a product of Nature (for example, that a pre-existing DNA sequence is associated with a high-risk of breast cancer).

B. The rationale for barring patents on a product of Nature is strongest when a patent would wall off an entire domain of Nature from study and innovation.

A major purpose behind the "important, implicit exception" concerning "'[l]aws of Nature, natural phenomena, and abstract ideas'" is to avoid the "danger that the grant of patents . . . inhibit future innovation premised upon them." *Mayo*, 132 S. Ct. at 1293 (citation omitted); *see id.* at 1301; *Diehr*, 450 U.S. at 185.

The Court has noted that "phenomena of nature, though just discovered, . . . are not patentable, as they are the basic tools of scientific and technological work." *Gottschalk*, 409 U.S. at 67. In *Mayo*, this Court expanded upon *Gottschalk*, reasoning that the "monopolization of those tools through the grant of a patent might tend to impede innovation more than it would tend to promote it." *Mayo*, 132 S. Ct. at 1293.

"The Court has repeatedly emphasized . . . [the] concern that patent law not inhibit further discovery by improperly tying up the future use of laws of

nature." *Id.* at 1301. "[T]he underlying functional concern here is . . . how much future innovation is foreclosed relative to the contribution of the inventor." *Id.* at 1303.

It follows that the rationale against granting patents on the handiwork of Nature is strongest when a patent would create an insurmountable barrier to innovation.

Many patents that pertain to products of Nature do not create insurmountable barriers to innovation. For example, a monopoly on a particular method for studying a product of Nature would not preclude (and in fact might encourage) invention of an alternative method for studying the product of Nature. Similarly, a monopoly on a particular use or set of uses for a product of Nature – for example, to treat or prevent a disease – would not preclude (and in fact might encourage) development of alternative non-natural molecules that could substitute for (or improve upon) the product of Nature.

But the situation is different with respect to a composition-of-matter patent on a product of Nature (such as genomic DNA). Such a patent can be used to exclude everyone from observing, characterizing or analyzing, *by any means whatsoever*, the product of Nature. The exclusion is not limited to any particular method of analysis; it extends to all possible methods of analysis.

It is inherently impossible to circumvent this barrier. One cannot observe, characterize or analyze a

product of Nature if one cannot legally possess it. A molecule is one of the "basic tools" – indeed, an *essential* tool – for studying the molecule itself. *Gottschalk*, 409 U.S. at 67. Granting a monopoly on possessing a molecule that is a product of Nature authorizes a patent holder to wall off an entire domain of Nature from observation.

Science is the systematic and cumulative study of the natural world. It generates fundamental knowledge that not only serves human curiosity but also is the intellectual fuel for practical applications, including patentable invention. For scientific progress to proceed, scientists must have the ability to study the handiwork of Nature.

To illustrate the seriousness of this issue, suppose that a monopoly had been granted on the naturally occurring human immunodeficiency virus (HIV), responsible for AIDS, or on the nucleic acid molecule that is its genome. The patent holder would have been legally entitled to use his patent to block anyone from observing, characterizing or analyzing the virus by any means whatsoever. Scientists would not have been able to rapidly learn the secrets of this insidious virus; drug developers would not have been able to develop life-saving drugs; technologists would not have been able to develop effective diagnostics; and patients would not have been able to know their HIV status. All of this progress (which saved millions of lives and led to many patentable inventions) was possible only because observation, characterization, and analysis of the product of Nature were open to

all. To their credit, the discoverers of HIV obtained appropriately narrow patents that do not exclude others from observing, characterizing and analyzing naturally occurring HIV.

C. Myriad's composition-of-matter claims on genomic DNA are directed to pre-existing products of Nature; exclude others from observing, characterizing or analyzing these products of Nature by any means whatsoever; and create an insurmountable barrier to scientific innovation on these products of Nature with serious consequences for medical progress and technological innovation.

The isolated DNA fragments of the human genome claimed by Myriad are products of Nature, as shown above by abundant scientific evidence.

The composition-of-matter claims to these fragments allow the patent holder to exclude others from observing, characterizing or analyzing these products of Nature by any means whatsoever.

Such claims erect an insurmountable barrier to studying these DNA sequences, with serious consequences for innovation in medicine. For example, only a *subset* of BRCA1 mutations predispose to breast

cancer, while others are harmless.[32] To accurately predict a woman's risk of breast cancer, one must learn *which* mutations actually create a predisposition to the disease. This requires characterizing the BRCA1 gene in many thousands of women. Myriad's monopoly has seriously inhibited the ability of the scientific community to gather sufficient quantities of data to fully learn these laws of Nature.

III. A NARROWLY CRAFTED DECISION BY THIS COURT WOULD NOT UNDERMINE THE BIOTECHNOLOGY INDUSTRY AND INSTEAD WOULD FOSTER INNOVATION.

In the Federal Circuit's view, a decision that isolated DNA fragments are patent-ineligible would disrupt long-settled expectations and could wreak havoc on the biotechnology industry. *See* 689 F.3d at 1333, 1343-48. In fact, the Federal Circuit's concern is unfounded.

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[32] Francine Durocher et al., *Comparison of* BRCA1 *Polymorphisms, Rare Sequence Variants and/or Missense Mutations in Unaffected and Breast/Ovarian Cancer Populations*, 5 Hum. Mol. Genet. 835 (1996); Alison M. Dunning et al., *Common* BRCA1 *Variants and Susceptibility to Breast and Ovarian Cancer in the General Population*, 6 Hum. Mol. Genet. 285 (1997).

A. Most medically and commercially important biotechnology products depend on patent protection for non-naturally occurring DNA molecules, such as cDNAs and recombinant DNAs, rather than on products of Nature such as fragments of genomic DNA.

The vast majority of the medically and commercially important biotechnology products developed over the past quarter century are protected by patents on isolated DNA molecules that are *non-natural* compositions of matter, such as cDNA and recombinant DNA molecules – for such uses as artificially producing therapeutic proteins. Only a small fraction of products involve diagnostic claims to *naturally occurring* genomic DNA.

The biotechnology industry would not be substantially affected by a narrowly crafted decision holding that (1) fragments of human genomic DNA are patent-ineligible where the scientific evidence is clear that the claimed molecules themselves are routinely found in Nature and where the process for purification or synthesis[33] of such molecules is routine but (2) human cDNAs are patent-eligible, because

[33] If this Court does not wish to address the question of whether products of Nature are patent-ineligible under all circumstances, it can address the narrower question of whether products of Nature may be patented where their purification or synthesis is routine. As described *supra* in note 4, the physical purification of isolated DNA fragments has been routine since 1978.

these molecules do not occur in Nature and have clearly different functional properties from related products of Nature.[34]

B. The unfettered ability to observe, characterize and analyze the human genome will foster scientific progress and technological innovation.

Any concerns about unsettling expectations related to a limited number of diagnostic patents on human genomic DNA should be balanced against the innovation that will flow from unfettered access to this product of Nature.

Biomedicine stands on the verge of a revolution with major implications for human health. A decade ago, the scientific community completed the Human Genome Project, which revealed the complete genetic code of our species.[35] Over the past decade, stunning technological advances have reduced the cost of sequencing a human genome from billions of dollars to thousands of dollars – and it may fall in coming years to hundreds of dollars.[36] (For reference, Myriad charges approximately $3000 to sequence roughly four one-millionths of the human genome.)

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[34] *See supra* at 21.

[35] Eric S. Lander et al., *Initial Sequencing and Analysis of the Human Genome*, 409 Nature 860 (2001).

[36] Eric S. Lander, *Initial Impact of the Sequencing of the Human Genome*, 470 Nature 187 (2011).

The ability to read entire human genomes is unlocking critical secrets about cancer, diabetes, schizophrenia and many other diseases. Such studies involve identifying genetic variants associated with disease based on comprehensive genome studies of thousands of patients. These discoveries are making it possible to identify and prioritize targets for drug development, select patients for clinical trials and provide diagnostic and prognostic information.

Granting monopolies on the naturally occurring DNA of the human genome would impair the ability of patients to benefit from the fruits of this genetic revolution, by making it difficult or impossible to study the human genome as an integrated whole in scientific and medical settings. It would risk fencing off into a patchwork of private reserves the vast expanse of the human genome – one of the most remarkable "manifestations of . . . nature, [that should be] free to all men and reserved exclusively to none." *Funk Bros.*, 333 U.S. at 130.

CONCLUSION

It is well-accepted in the scientific community that isolated DNA fragments of the human genome – including isolated DNA fragments of the BRCA1 and BRCA2 genes – are found routinely in the human body and are thus patent-ineligible products of Nature. The biotechnology industry would not be substantially affected by a narrowly crafted decision here holding that (1) fragments of human genomic

DNA are patent-ineligible where the claimed molecules themselves are routinely found in Nature and where the process for purification or synthesis of such molecules is routine and (2) cDNAs are patent-eligible.

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