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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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

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 routin e 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.

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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.

"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 ma terial, 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 fragment s range in length from

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 i

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

Isolated DNA fragments are not only present in cells, but also routinely fo und in cell-free blood. The quantity of freely circulati ng 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).

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

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 availabl

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

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

II. MYRIAD'S COMP OSITION-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, CHARAC-TERIZING OR ANALYZING THESE PRODUCTS OF NATURE BY ANY MEANS WHATSOEVER; AND (3) CREATE AN INSURMOUNTABLE BARRIER TO SCI-ENTIFIC PROGRESS AND TECHNOLOG-ICAL INNOVATION CONCERNING THESE PRODUCTS OF NATURE.

A. Composition-of-matter claims on

> 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 subje ct 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 inv olved 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.

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 co ntribution 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 exa mple, 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 exte nds 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 pro-

all. To their credit, the di scoverers of HIV obtained appropriately narrow patent s 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 th ese laws of Nature.

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

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.

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.

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CONCLUSION

It is well-accepted in th e 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 pate nt-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 purifica tion or synthesis of such molecules is routine and (2) cDNAs are patent-eligible.

Respectfully submitted,

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