No. 12-398

In the Supreme Court of the United States

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 OF GENEDX AND LAW PROFESSORS AS *AMICI CURIAE* IN SUPPORT OF PETITIONERS

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TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases: **Page(s)**

TABLE OF AUTHORITIES—Continued

Constitution and statutes:..... Page(s)

Miscellaneous: ..... Page(s)

TABLE OF AUTHORITIES—Continued

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INTEREST STATEMENT OF *AMICI CURIAE*

Amici are GeneDx and law professors whose scholarship and teaching focuses on patent law and related fields.[1] *Amicus* GeneDx is a diagnostic laboratory that was started for the purpose of providing molecular diagnoses for patients and families with rare and

[1] Pursuant to this Court's Rule 37.6, no counsel for a party authored this brief in whole or part, and no person or entity made any monetary contribution to the preparation or submission of the brief. The petitioners in this case have filed a letter giving blanket consent to the filing of *amicus* briefs in this case. The respondents have specifically consented to the filing of this *amicus* brief.

ultra-rare hereditary disorders. The company was formed by National Institutes of Health (NIH) scientists who wished to provide diagnostic services to the families with histories of genetic disorders. GeneDx has discovered several genes linked to rare skin disorders and has never attempted to patent such genes. As long as the federal courts uphold patents on human genes linked to disorders that NIH scientists or patients wish tested, GeneDx is unable to assist such families. The small market for rare disorder testing services, combined with the large investment in time and effort to develop new tests, makes paying license fees to gene patent owners an absolute deterrent to developing diagnostics for patients suffering from most rare disorders. Gene patents have accordingly had a negative impact on the development and availability of genetic tests for patients and families, especially those with rare disorders.

Amici law professors are Linda J. Demaine, Aaron X. Fellmeth, and Dennis Karjala, Professors of Law at the Arizona State University, Sandra Day O'Connor College of Law. Law faculty have an interest in ensuring that the Patent Act is interpreted to reflect accurately the constitutional limits on Congress's power to grant patents, the historical underpinnings of U.S. patent law, and the public policies the Constitution and Patent Act seek to promote.

SUMMARY OF ARGUMENT

The U.S. Constitution grants Congress no power to issue patents on products of nature, nor has Congress sought to exercise such a power. The Supreme Court has accordingly held patents on natural phenomena invalid long and consistently. Scientific and technological innovation has benefited from this policy.

However, the policy has come under threat by the U.S. Patent and Trademark Office (PTO) and certain federal courts, which have granted and upheld patents on "isolated," natural human genes as well as cDNA copies of them. Such genes and cDNA are products of nature regardless of whether they have been "purified," removed from larger molecules, or synthesized using well-known methods to copy the coding portions of natural human DNA.

Judge Lourie's opinion below treats natural human DNA as if it were an industrial chemical whose physical structure determines its properties. He treated the human chromosome as the relevant molecule, so that any natural chemical contained in that chromosome is not a "product of nature," in his opinion.

This conclusion reflects a fundamental misconception about DNA molecules. Living DNA cannot be compared to inert industrial chemicals. DNA molecules and chromosomes may have identical physical structures while producing wildly different proteins and other biochemicals; it is the order of nucleotides that determines the gene's biological function. One who merely replicates the order of nucleotides by "isolating" a gene or part of a gene is claiming the

essence and *raison d'être* of the gene. All protein-coding genes exist to express proteins; by claiming the natural sequence of DNA coding for a natural protein, a patent applicant claims a portion of the blueprint of life itself.

The Federal Circuit also relied on a lower court decision from 1911, holding that when a product of nature has been so altered to have greater therapeutic or commercial value, it becomes patentable subject matter. Although lower courts have increasingly relied on this theory, it is the wrong standard for determining the patentability of products of nature. This Court has never held, and should not hold, that some human intervention that increases the inherent therapeutic or commercial value of a product of nature *ipso facto* justifies treating the result as a new and distinct product susceptible to patenting.

Instead, the Court should continue to hold that a product of nature must be transformed into a new article with a markedly different name, character, and use to qualify as patentable subject matter. As this "substantial transformation test" applies to human DNA, "isolated" genes fail to qualify as patentable subject matter. The essence of a human gene is its ability to express a specific protein; therefore, any molecule that merely extracts or copies the gene's sequence of nucleotides to express that same protein is insufficiently different from the natural gene. If the new molecule performs the same biological function as the natural gene, it is the same product of nature.

By similar logic, a cDNA molecule that merely copies the protein-coding portions of a human gene (exons) is a gene with its regulatory nucleotide sequences omitted. It performs precisely the same biological function as the natural and "isolated" genes, in the same way, and merely represents an attempt to patent the natural gene. Moreover, the concept of omitting the non-coding region of a DNA molecule (introns) is not a human innovation, it is a well-known natural process. Messenger RNA, a natural molecule used in the process of gene translation, is a single-stranded copy of the gene with the introns omitted. A cDNA is "synthetic" only in the sense that it is a double-stranded version of the mRNA molecule, with the complementary strand dictated by the same laws of nature that dictate DNA's complementary strand. There is nothing remotely inventive about it.

If products of nature are unpatentable subject matter, biologically insignficant modifications to products of nature should also be unpatentable. The substantial transformation test draws a reasonably bright line between insignificantly altered products of nature and man-made inventions; is consistent with Supreme Court precedent; and avoids the many negative repercussions of patents that confer an effective monopoly on fundamental biological components of the human body.

ARGUMENT

I. Products of nature are not patentable subject matter.

The U.S. Constitution authorizes Congress to grant patents only to "Inventors" for their "Discoveries." U.S. CONST. art. 1, sec. 8, cl. 8. The term "discoveries," as used in this clause, is a term of art. It refers not to preexisting facts that any person might come upon, but rather as a synonym for "inventions," being the product of human ingenuity. *See* Linda Demaine & Aaron Fellmeth, *Reinventing the Double-Helix*, 55 STAN. L. REV. 303, 367-74 (2002). The Constitution thereby establishes that a newly discovered product of nature is not patentable subject matter, because it was not "invented" by any person.

Consistent with this limitation on congressional power, Congress drafted the 1952 Patent Act to authorize a patent on any "new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof." 35 U.S.C. § 101. Newly perceived products of nature are by definition not "new," but preexist the human perception of them. Although Congress has several times considered amendments to the Patent Act that touch on the question of whether products of nature are patentable, such as the Plant Patent Act of 1930, 46 Stat. 703, ch. 497, *codified as amended at* 35 U.S.C. §§ 161-64, it has never endorsed the patenting of natural phenomena of any kind.

This Court has accordingly long held that patents may not be granted on products of nature. *E.g.*,

Diamond v. Chakrabarty, 447 U.S. 303, 309, 313 (1980). Never has the Court strayed from this firm rule. "[T]o transform an unpatentable law of nature into a patent-eligible *application* of such a law, one must do more than simply state the law of nature while adding the words 'apply it.'" *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S.Ct. 1289, 1294 (2012).

That the discovery of a product of nature may have been difficult, costly, uncertain, and scientifically groundbreaking is and has always been irrelevant. "Products of nature are nonstatutory subject matter. This defect cannot be remedied by a showing of novelty, utility, or non-obviousness." John M. Conley & Robert Makowski, *Back to the Future: Rethinking the Product of Nature Doctrine as a Barrier to Biotechnology Patents (Part II)*, 85 J. PAT. & TRADEMARK OFF. SOC'Y 371, 391 (2003). In any case, genes are not difficult, costly, or uncertain to discover. Using modern sequencing technology, the entire human genome can now be sequenced with certainty within a week at the cost of a few thousand dollars.

This conclusion is consistent with the policies the Framers sought to promote in the Constitution's Intellectual Property Clause. Products of nature, thought as yet undiscovered, exist in the public domain; they are *res communis*, "free to all men and reserved exclusively to none." *Chakrabarty*, 447 U.S. at 309. They are elemental components of the physiology of living organisms, a functioning ecology, or the chemistry of the universe. The innate curiosity of

homo scientificus and the structure of universities, which reward faculty and students finding new facts about nature, together provide sufficient incentive to research natural phenomena. No patent incentive is generally required for such fundamental discoveries. Moreover, because products of nature are the fundamental building blocks of all matter and life, a patent on a product of nature risks investing the patentee with a power to tax or entirely prevent research on vast and uncharted fields of knowledge. Such a power may generally be expected to extend far out of proportion to the effort and insight invested in discovering the product of nature.

II. Human genes, including isolated human DNA sequences, are products of nature unless transformed into a new product with a different biological function.

That an "isolated" human gene remains a product of nature is evident from the fact that the person claiming such a gene "invented" nothing. He merely used well-known techniques for severing a string of nucleic acids from their surrounding chromosomal matrix. In fact, it is perfectly possible to obtain a patent without even having performed the act of severing the gene from the chromosome; success in "isolating" the gene is so certain using standard laboratory techniques that a patent applicant need merely sequence the gene (as discussed below, also using well known and mostly automated techniques invented by others) and submit the patent application claiming the "isolated" gene as an "invention." Yet,

there is no invention in isolating a gene, and without invention, Congress has no power to grant a patent under the Constitution.

Nonetheless, some 30 years ago, the U.S. Patent and Trademark Office (PTO) began granting patents on human genes in their natural state, with the word "isolated" affixed to the claim. Judge Lourie of the U.S. Court of Appeals for the Federal Circuit believes that isolated human DNA is patentable subject matter, because is it not "found in nature" as such. *Association for Molecular Pathology v. United States Patent & Trademark Office*, 689 F.3d 1303, 1325 (Fed. Cir. 2012). His and Judge Moore's opinions seem to recognize that, to constitute patentable subject matter, an invention must be "man-made," "the product of human ingenuity," "markedly different" from what exists in nature, and have a "distinctive name, character, and use." *Id.* at 1325-26, 1329 (Lourie, J.), 1339 (Moore, J.).

These opinions also admit that an "isolated" human protein-coding gene contains the same biological information (that is, it codes for the same protein) as the natural gene existing in the human body. Like that natural gene, the isolated DNA sequence serves the sole biological function of expressing a specific protein. However, Judge Lourie believes that isolated genes qualify as patentable subject matter because they have a "distinctive chemical structure." *Id.* at 1328. By this, he means that a "chemical" is defined as a group of atoms covalently bonded to one another; by severing some of those bonds, a person creates a

different "chemical." Because in nature a DNA molecule is "intertwined with various proteins," under this view, a chromosome is a single "molecule." *Id.* Based on this belief, Judge Lourie reasoned that "isolated" natural DNA satisfies this Court's precedents distinguishing products of nature from patentable inventions, because the isolated DNA has been cleaved from the chromosome by human intervention. *Id.* at 1328, 1330; *see also id.* at 1341-42 (Moore, J., concurring). Judge Moore further concluded that this chemical manipulation satisfies the criteria for a 1911 lower court decision, *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F. 95 (C.C.S.D.N.Y. 1911), , *aff'd in part, rev'd in part*, 196 F. 496 (2d Cir. 1912), presumably because the isolated gene has commercial uses to which the natural gene cannot be put while remaining in the chromosome.

These opinions make much of the "human intervention" involved in isolating DNA from the chromosome, calling the resulting product "man-made" repeatedly throughout. However, neither opinion argues that human intervention alters the biological use of the DNA in the claims at issue. The opinions try to minimize the significance of DNA's biological function, calling it "irrelevant," and preferring to focus on the differences between the chemical structure of the assumed product of nature (a chromosome) and the chemical structure of the much smaller, isolated (or "purified") gene. *See Association for Molecular Pathology*, 689 F.3d at 1330 (Lourie, J.), 1343 (Moore, J.).

These opinions are correct in asserting that an isolated gene is a product of human intervention, in much the same way that (as Judge Bryson put it) a kidney is the product of human intervention when excised from a human body. *Id.* at 1352-53 (Bryson, J., concurring in part and dissenting in part). But the input of skill and labor no more takes kidneys out of the realm of products of nature when "isolated" than does the DNA sequence of nucleotides. The fact that removing the nucleotides is performed by a geneticist or biochemist "in the laboratory," *id.* at 1325, is no more significant than the fact that the isolation of the kidney is performed by a surgeon in an operating room.[2] Nor does the "skill, knowledge, and effort" required to isolate the DNA matter, *id.* at 1332, if the result is a product of nature (although the process of isolating it may well be patentable subject matter). In any case, as noted, sequencing and isolating a human

[2] One especially egregious error Judge Lourie made in rejecting this comparison was to suggest that removing a human kidney requires little skill, knowledge, or effort. *Id.* at 1332. He is greatly underestimating both the difficulties of surgery and the ease of sequencing and isolating DNA. It is especially ironic that he tried to buttress his argument that courts should let sleeping dogs lie by noting that the PTO issued 2,645 patents claiming isolated DNA over the past twenty-nine years. The number leaps to 40,000 if DNA-related patents of human genes are included, according to his opinion. If DNA requires such exceptional knowledge, skill, and effort to sequence and isolate, it is strange that there should be such a massive proliferation of DNA patents.

gene has long been well within the skill of any ordinary biochemist.

The argument that removing DNA from a chromosome is distinguishable because it converts the DNA to a "different molecular entity" misses the point. The gene is not merely an inert "chemical entity" like sodium chloride or ammonia, it is a biological component, an integral, defining, and biologically *functional* part of human life. Its physical structure does not define it; different chromosomes and genes can have the identical macrostructures while having radically differing functions. A gene is defined by its sequence of nucleotides. It is composed of an arrangement of nucleotides that, in the specific order they exist in nature, expresses a specific protein or RNA product. A change to that order is likely to change the protein. Expressing a specific protein is the very reason for the protein-coding gene's existence. To claim the sequence of nucleotides coding for the protein is to claim the natural gene and its biological function. It is to claim a portion of life's blueprint.

Judge Moore's attempt to distinguish a patent on a natural product like a human kidney from a patent on an isolated gene fails as well. The *Parke-Davis* case does not set forth the correct standard for invention. *Parke-Davis* relied on the fact that the patent applicant had done something to confer greater therapeutic and commercial value on the product of nature as the basis for accepting the resulting "purified" chemical as a new, synthetic product. But increasing a natural product's therapeutic or commercial value

does not automatically make the resulting product patentable subject matter. The excised kidney, like the isolated gene, is "for every practical purpose a new thing commercially and therapeutically," *Parke-Davis*, 189 F. at 103, *quoted in Association for Molecular Pathology*, 689 F.3d at 1339. A kidney removed from a human body can be used as a life-saving transplant; one currently in a body cannot. The attempt to distinguish the cases is strained and unconvincing.

This Court has long and consistently denied the patentability of natural phenomena that have been insignificantly altered. *See Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S.Ct. 1289 (2012) (correlation between the presence of drug in the bloodstream and the biologically effective dosage of the drug); *American Fruit Growers, Inc. v. Brogdex Co.*, 283 U.S. 1, 11-12 (1931) (natural fruit treated with mold-resisting chemical); *cf. Winans v. Denmead*, 56 U.S. (15 How.) 330, 341 (1853) ("Under our law a patent cannot be granted merely for a change of form.... Merely to change the form... is the work of a constructor, not of an inventor; such a change cannot be deemed an invention."). A policy of awarding patents for minor alterations of a product of nature improves in no way on a policy of allowing patents on products of nature. A patent applicant may be expected to make trivial alterations to natural products in order to bring them within the scope of patentable subject matter or adapt them to commercial needs. *De minimis non curat lex* "is part of the established background of legal principles against which all

enactments are adopted, and which all enactments (absent contrary indication) are deemed to accept." *Wisconsin Department of Revenue v. William Wrigley, Jr., Co.*, 505 U.S. 214, 231 (1992).

A certain line of district and appellate court cases, illustrated by Judge Learned Hand's opinion in *Parke-Davis* and on which Judge Moore especially relied, has contradicted this Court's doctrine denying the patentability of minor variants of products of nature. *See generally* Demaine & Fellmeth, *supra*, at 334-39 (describing the line of cases). In *Parke-Davis*, the district court held that a new process for purifying the human hormone adrenaline could justify a product patent on the resulting relatively pure adrenaline, because the purer adrenaline was therapeutically and commercially more valuable than less pure adrenaline. 189 F. at 102-03. *Parke-Davis* conflated the invention of a process with the invention of its resulting product in weighing the ingenuity of the purification process in favor of the the ingenuity of the resulting product. It also conflated the utility of an innovation with its patentability. The relevant question is not whether some modicum of human intervention has conferred greater therapeutic or commercial value on a product of nature. As noted above, a kidney does not become commercially or therapeutically valuable until removed from the human body, but its removal does not render it patentable subject matter. The pertinent question is whether it has transformed the product of nature into a new and markedly different

product with a distinctive name, character, and use.[3] *Diamond v. Chakrabarty*, 447 U.S. 303, 309-10 (1980).

This Court has never held, and should not now hold, that a new-found product of nature becomes patentable merely because a human act has given it more practical or commercial utility, or even a different overall chemical structure. On the contrary, in *Funk Brothers Seed Co. v. Kalo Inoculant Co.,* 333 U.S. 127 (1948), this Court decisively rejected the argument that minor alterations to a product of nature rendered it patentable. In that case, the patentee had packaged together several strains of naturally occurring plant-inoculating bacteria. The patent was based on the discovery that, although many strains of inoculating bacteria inhibit each other from assisting plants in fixing nitrogen for growth and metabolism when combined, certain strains had no inhibitory effect on other strains and could usefully be packaged together as an inoculant for multiple crops. The applicant accordingly claimed a combination of natural bacteria. The Court held that, because the bacteria continued to perform their natural function in the way they always had, the patent applicant had not invented a patentable product.

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[3] In *Chakrabarty*, this Court used the classic customs law formulation "name, character, and use," but, as discussed in Demaine & Fellmeth, *supra*, at 394-95, a change in name serves at most as an indirect and unreliable indicator of change in character and use.

The *Funk Brothers* decision was based on the recognition that allowing patents on insubstantial modifications of products of nature does not serve the patent law's goal of encouraging innovation. Although it is reasonable to take issue with the application of that principle on the facts before the Court at that time, the fundamental premise is sound. *Funk Brothers* followed a long line of cases rejecting the patentability of both products of nature and insubstantial variations on previously known substances. If *Parke-Davis* was not very widely followed by other courts before the *Funk Brothers* decision, it certainly was not followed afterward. *See generally* Demaine & Fellmeth, *supra*, at 334-45 (recounting the history of case law dealing with patents on purified products of nature).

However, with the adoption of the 1952 Patent Act, the tide soon turned, and the *Parke-Davis* reasoning began to dominate federal jurisprudence. Appellate courts began approving patents on purified products of nature, justifying the patent by the technical differences between the product of nature and increased therapeutic or commercial value of the purified substance. *See generally* Demaine & Fellmeth, *supra*, at 349-60. It is not entirely clear why lower courts began departing from this Court's precedents after the adoption of the Act. One possible reason, supported by the fact that most such decisions related to pharmaceutical and biochemical patents, is that courts considered improvements in the field of health and medicine more urgent than in other fields having

less direct and immediate effect on human welfare. They may have believed that a looser patent policy would be helpful to foster medical advances and reinterpreted the law accordingly.

Another possibility is that courts read the language of the new Patent Act as signalling a congressional desire to abandon or minimize the prohibition on patenting products of nature, because the Act included no such prohibition *expressis verbis*. On this theory, Section 103 of the Act forbade patents on variants of prior art (defined in Section 102 of the Act, 35 U.S.C. § 102) that would have been obvious at the time of invention. *See* 35 U.S.C. § 103. But Section 102 of the Act does not include undiscovered products of nature in its catalog of prior art. *Ergo*, the courts may have reasoned, obvious variants on undiscovered products of nature may be patented under the Patent Act. In short, "the Act seems to sanction by omission the patenting of obvious derivatives of naturally occurring phenomena." Demaine & Fellmeth, *supra*, at 383. If this hypothesis is correct, then these courts must have been unaware of, or must have ignored that, undiscovered products of nature do in fact qualify as prior art under the Patent Act. All human DNA is already in public use in this country, 35 U.S.C. § 102(a), by all persons whose body use that DNA biologically. Moreover, the courts improperly interpreted the codification of the scattered patent statutes as repudiating Supreme Court and CCPA precedents prohibiting patents on insignificantly altered products of nature.

Whatever the reason for this departure from this Court's precedents, the *Parke-Davis* reasoning gained ascendancy when the Court of Customs and Patent Appeals endorsed it in In re *Bergstrom*, 427 F.2d 1394 (C.C.P.A. 1970). There, the CCPA rejected the "consistent principle . . . that a claim to a purified material cannot be allowed unless the purified material exhibits properties and utilities not possessed by the unpurified material." *Id.* at 1398. Instead, the court relied on the tautology that, if the applicant sought a patent on a product of nature purer than its natural form, the applicant was not seeking to patent a product of nature in the first place. *Id.* at 1401-02. The Federal Circuit endorsed this line of reasoning in *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 1206-07 (Fed. Cir. 1991), *cert. denied sub nom. Genetics Institute v. Amgen, Inc.*, 502 U.S. 856 (1991), and this new doctrine has represented federal jurisprudence ever since, though never endorsed by this Court.

The Federal Circuit's decision below follows and ratifies the *Parke-Davis* and *Amgen v. Chugai* line cases, mistaking the mere fact of human intervention using some knowledge, skill, or effort for the functionally inconsequential removal of natural DNA from its surroundings, as a basis for denying the status of a human gene as a product of nature. These are not, have never been, and should not be, the proper criteria for determining whether a product of nature has been transformed into patentable subject matter under this Court's jurisprudence.

Nonetheless, because of the Federal Circuit's current policy, the effective rule in practice is currently that a product of nature constitutes patentable subject matter as long as it has been somehow altered, no matter how trivially, by human intervention, giving it a superior practical use—typically a therapeutic, diagnostic, or research use—it did not have in its natural, unaltered state. This has allowed many patent applicants to successfully claim products of nature by merely qualifying the claims with the talismanic words "isolated," "purified," or "synthesized." *See* Demaine & Fellmeth, *supra*, at 358-59; Conley & Makowski, *supra*, at 394. Patent lawyers in the past three decades have openly used this formula to monopolize any commercial use of human genes. For example, one patent prosecutor advised fellow practitioners: "The discovery of a product in nature, although not an invention, may well lead to an invention *by the proper use of claim language*." Karl Bozicevic, *Distinguishing "Products of Nature" from Products Derived from Nature*, 69 J. PAT. & TRADEMARK OFF. SOC'Y 415, 426 (1987) (emphasis added). Notice that he said not "by inventive activity," but by the phrasing of the patent application. While patent prosecutors may celebrate the triumph of semantics over substance, it is bad law and bad policy. "Because the distinction between a statutory invention and a nonstatutory product of nature is one of substance rather than form, cases should not be resolved on the basis of incantations. . . . The case law simply does not support the existence of linguistic safe harbors." Conley & Makowski, *supra*, at 392.

The reasoning of these decisions leads to potentially absurd results by *reductio ad absurdum*:

> If any naturally occurring substance that cannot be found in purified form in nature were patentable the first time it was isolated and purified, then the first person to purify water could have patented it; the first person to strain blood cells out of blood could have patented pure plasma because plasma always contains blood cells in its natural state; and for that matter, the first person to climb up a banana tree, pull down a fruit, and peel it would have merited a patent on "isolated and purified" banana fruit, because in nature bananas always grow on trees and with peels.

Demaine & Fellmeth, *supra*, at 391.

As this Court recognized in *Mayo Collaborative Services v. Prometheus Laboratories,* 132 S.Ct. 1289, 1293 (2012), ultimately, all inventions are traceable back to products of nature and natural phenomena, which supply the particles, atoms and laws that make up all matter in the universe and allow it to interact. This Court has not had occasion to formulate a precise test for distinguishing products of nature from patentable inventions based on them, but it has clearly indicated factors that should be considered in the analysis.

Specifically, this Court rejected a patent on a natural citrus fruit treated with borax to resist mold on the ground that the resulting fruit had no "new or distinctive form, quality, or property. . . . There is no

change in the name, appearance, or general character of the fruit." *American Fruit Growers, Inc. v. Brogdex Co.*, 283 U.S. 1, 11-12 (1931). In *Funk Brothers v. Kalo Inoculant*, part of the Court's rationale for invalidating the patent was that the claimed combination of bacteria did not alter the utility of any one of the bacteria species: "No species acquires a different use." 333 U.S. 127, 131 (1948). The Court's opinion upholding the patent on a recombinant bacterium in *Chakrabarty*, relied heavily on the fact that the bacterium was "markedly different" from any naturally occurring bacterium, and had "a distinctive name, character [and] use." *Chakrabarty*, 447 U.S. at 309-10.

From these and other cases, Demaine and Fellmeth determined that the Court has been using a "substantial transformation test" similar to the one traditionally used in customs law for determining the country of origin of a good from one country subjected to processing steps in another. Under this test, a preexisting product or combination of products traditionally becomes a new and different article if subjected to processing steps that cause the precursors to lose their identities and become "a new article having a new name, character, and use." *United States v. Gibson-Thomsen*, 27 C.C.P.A. 267, 273 (1940).

Demaine and Fellmeth articulated and justified this test as consistent with this Court's precedent in determining whether a product of nature had been sufficiently altered to qualify as an invention. Demaine & Fellmeth, *supra*, at 393-407. As noted,

the Federal Circuit seems to have accepted that this test is the appropriate one, but it misapplied the test on the facts before it. The character of a human protein-coding gene is a double-helical molecule composed of nucleotides arranged for the production of a specific protein. The biological "use" of a protein-coding gene is the production of a specific protein. The character and use of the gene in its natural state and in "isolated" DNA is precisely the same. It is not even marginally different; much less is it "markedly different."

The Court should uphold its previous decisions requiring a substantial transformation of a product of nature to qualify it as patentable subject matter. As Demaine and Fellmeth argued, in the context of a protein-coding gene, a substantial transformation does not occur unless the gene has been so altered as to acquire a new and different biological function, which means producing something other than the protein for which the natural gene codes. *See id.* No other alteration to a natural biochemical is sufficient to avoid conferring a monopoly on all meaningful uses of the product of nature. *See id.*

The substantial transformation test articulated by this Court, as interpreted by Demaine and Fellmeth, fulfills the policy purposes of the patent law. It is clear in application, because only changes to a gene sequence that result in a new, synthetic protein would qualify as patentable subject matter. In other words, it draws a bright line between merely applying an idea taken from nature to a practical context (i.e.,

discovering a law of nature and "applying it") and creating something meaningfully different and man-made, an "invention." It is consistent with this Court's precedents, discussed above, because any change to the gene's biological function necessarily and markedly changes the gene's character and use. In contrast, an alteration that does not change the gene's biological function but merely uses it in a different context or adjusts the rate of expression would not qualify, because no invention has occurred with respect to that gene.[4] As Demaine and Fellmeth concluded:

> Transformation of biological function is not the same as change of context. For example, if a natural protein is discovered to promote cell growth in nature, the fact that the protein is only useful for therapeutic purposes after being purified, concentrated, or otherwise modified does not by itself render the modified protein "new." This is merely a change of context, not a transformation of biological function. If the protein's function is the same in the therapeutic context (e.g., promoting cell

[4] For example, isolating the gene from the chromosome and using in an assay, or transfecting a vector with a clone of a natural gene to create a cell line would not qualify as a substantial transformation. The artificial cell line itself or the process of creating it could, however, qualify as patentable subject matter, because the biological function of the cells will have been altered by causing them to produce unnatural proteins.

> growth) as its function in nature, then no change of utility has occurred, and merely adjusting the form of the substance cannot work a substantial transformation on it. The same analysis applies to DNA molecules. If a naturally occurring DNA molecule has the useful function of coding for Protein X, then no purified or otherwise altered version of that DNA molecule can be "new" unless its claimed function is fundamentally different than coding for Protein X. Without a change in biological function, the DNA molecule lacks adequate creative input to qualify as an invention; it is little more than a molecule found in nature with superficial modifications.

Demaine & Fellmeth, *supra*, at 400.

The test also fits well with other key patent doctrines, such as the prohibition on patenting obvious innovations, 35 U.S.C. § 103, and the Doctrine of Equivalents. Section 103 of the Patent Act is the statutory codification of key federal jurisprudence defining "invention." As noted, merely extracting or reproducing a portion of a natural DNA molecule is not an invention, and the act of isolating human genes and cloning them is always obvious based on prior art. The Doctrine of Equivalents, as articulated by this Court, allows a patent owner to seek protection against nonliteral infringement of the claims when the accused product performs substantially the same function in substantially the same way to

achieve the same result. *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 608 (1950).

A man-made gene that does not perform the same biological function as a natural gene would pass these tests and qualify as nonobvious and nonequivalent. If a product of nature is not patentable subject matter, neither should be an obvious modification of the natural product. The substantial transformation test achieves this outcome without discouraging meaningful technological advances. *See generally* Demaine & Fellmeth, *supra*, at 406 (discussing the advantages of the test).

Finally, because the U.S. Court of Appeals for the Federal already interprets the substantial transformation test in the customs law context, the test will already be familiar to it.

When the law is uncertain, courts should consider whether the policy consequences of one interpretation or another serves the legislative purpose. As noted, the Constitution does not authorize Congress to grant patents to encourage all knowledge of any kind whatsoever, but only to encourage "Discoveries." U.S. CONST. Art. I, sec. 8, cl. 8. The Patent Act, too, authorizes patents only for those who "invent" a new and useful product. 35 U.S.C. § 101. Judge Lourie claimed that his interpretation of the Patent Act serves the patent law's policy purposes by encouraging innovation, *Association for Molecular Pathology*, 689 F.3d at 1331, while in the same breath insisting that "it is ultimately for Congress" to weigh the policy consequences of overturning the case law holding

human DNA patentable, *id.* at 1330-31. This is a rather disingenuous self-contradiction. In any case, Congress has never blessed the patenting of human genes; it was lower courts themselves that engaged in their own act of invention to create a policy of allowing patents on human genes, in defiance of this Court's precedents disapproving of patents on very similar purified products of nature. To claim that it is Congress, not the courts, that should reverse lower court decisions usurping Supreme Court precedents is absurd. Despite considerable industry lobbying in favor of allowing gene patents and public sentiment opposed to such patents, Congress has chosen not to legislate on the subject. It clearly prefers to leave this issue to the courts.

Using the substantial transformation test, as advocated here, serves the purposes of patent law. It encourages technological innovation beyond mere copying of human genes without imposing excessive tollbooth costs on biotechnology research. It avoids at least three negative repercussions that would seriously undermine the public policies promoted by the Patent Act.

First, allowing patents on isolated human genes over-rewards the *least* difficult, costly, and inventive stage of the development process of pharmaceuticals, assays, and other downstream therapeutic inventions. An efficient patent system would grant patents conferring a scope of protection no greater than what was invented—an observation made by Jeremy Bentham two hundred years ago. 2 JEREMY BENTHAM, THE

RATIONALE OF REWARD ch. IX (1825). By awarding patents conferring a legal monopoly on exceedingly broad and largely unknown downstream medical research uses of the gene, gene patents awards a windfall on upstream researchers of basic biology while creating barriers to the more difficult and exacting research closer to therapeutic end-uses.

Second, unlike the great majority of inventions, it is exceedingly difficult to "invent around" human genes for, by way of example, ascertaining a patient's susceptibility to gene-linked disorders or creating biologically necessary human proteins. Isolating natural genes or reproducing them, or their coding regions, is the only efficient and predictable method of making natural genes scientifically and commercially available on a large scale. Demaine & Fellmeth, *supra*, at 418. Allowing patents on isolated human genes gives the first person to sequence the gene an effective exclusionary right not just to that gene itself, but to the protein it produces and all uses of the gene in any later medical invention, including cell lines for the production of the protein, assays to detect the presence of the gene in medical patients, and any other use later discovered.[5]

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[5] Patents on "isolated and purified" natural human proteins have also been sanctioned by the Federal Circuit, and are even more problematic than the patenting of human genes. It is at least theoretically possible to produce pharmaceutically viable human proteins through methods other than recombinant technology, such as pure chemical protein synthesis. A patent on a human protein by the

Third, because of the difficulty of inventing around basic building blocks of nature and the fact that multiple genes may be involved in any given medical condition, there is a risk of creating an "anticommons" by which the owner of any one human gene patent can hold up or block the development of important medical diagnostics and therapies, and in any case would raise the costs of basic medical research through higher license search costs and stacking of license fees on top of each other. Monopolization of products of nature "through the grant of a patent might tend to impede innovation more than it would tend to promote it." *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S.Ct. 1289, 1293 (2012); *see* Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCI. 698 (1998). Far from promoting the progress of scientific innovation, such patents tend to retard progress, as the empirical

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first person to express it through a vector transfected with the cDNA clone of a human gene monopolizes a constituent element of the human body even though someone else may be able to develop an entirely different and nonobvious method for synthesizing that protein chemically. *See* Aaron Xavier Fellmeth, *The Challenge to Patent Law of Pure Chemical Protein Synthesis*, 23 NATURE BIOTECH. 547 (2005). By adopting the substantial transformation test proposed here with regard to all natural biochemicals, this Court reaffirm the invalidity of such "gold rush" tactics that attempt to monopolize products of nature found but not invented by the patent applicant.

evidence suggests it has already done. *See* Julia Carbone et al., *DNA Patents and Diagnostics: Not a Pretty Picture*, 28 NATURE BIOTECH. 784 (2010); Michelle R. Henry et al., *DNA Patenting and Licensing*, 297 SCI. 1279 (2002); Mildred K. Cho et al., *Effects of Patents and Licenses on the Provision of Clinical Genetic Testing Services*, 5 J. MOLECULAR DIAGNOSTICS 3 (2003); Robert Cook-Deegan & Chistropher Heaney, *Patents in Genomics and Human Genetics*, 11 ANN. REV. OF GENOMICS & HUM. GENETICS 383 (2010); Kurt Eichenwald, *Push for Royalties Threatens Use of Down Syndrome Test*, N.Y. TIMES, May 23, 1997, at A1.

In short, patents on "isolated and purified" human genes are not just bad law, they are bad public policy. The Court should reaffirm its long-held jurisprudence denying the patentability of insignificantly altered products of nature. It should specifically approve a substantial transformation test to weed out patents on biologically identical derivatives of human genes and other natural biochemicals.

III. cDNA sequences copying human DNA are products of nature unless substantially transformed into a new product with a different biological function.

Some of the claims in this case, such as claim 2, involve complementary DNA (cDNA) rather than "isolated" human DNA. cDNA corresponds to the portion of the natural DNA sequence that codes for a protein (exons). By omitting the non-coding regions

of the gene (introns, typically comprising up to 30% of the sequence), scientists may create a cDNA molecule that they can later transfect into a vector (i.e., a host cell) for regulated expression of the protein, which can be used as a living protein factory for the production of pharmaceuticals or for the screening of drug candidates that are intended to act on the protein to resolve a disorder.

This Court should treat a cDNA molecule having the same nucleotide sequence as the coding region of a natural gene no differently from that gene itself. If a human gene is product of nature, so too is its coding region, and by extension a copy through cDNA or otherwise of the gene's coding region. The coding region is as much a product of nature as the DNA molecule as a whole. It is, indeed, its essence. "[D]espite its nominal chemical distinctiveness, [cDNA derived from a human gene] is functionally indistinguishable from natural DNA and RNA. It contains exactly the same genetic information as its natural counterpart. It can do precisely the same work as a naturally occurring gene—protein synthesis—and it employs precisely the same processes to do it, whether in the body or in the laboratory." Conley and Makowski, *supra*, at 394. A cDNA copy of a human gene has precisely the same function—to express a specific protein—that the gene has in its natural state. "The geneticist who discovers that a particular sequence produces a particular protein and isolates that sequence no more creates the protein-producing nature of the sequence than the *Funk*

Brothers Seed patentee created the noninhibitory nature of the *Rhizobium* bacteria." Demaine & Fellmeth, *supra*, at 409.

The U.S. government argued below that cDNA copies of human DNA are patentable subject matter if they pass a "magic microscope test," meaning that nowhere in the human body can a cDNA sequence be found as such. *Association for Molecular Pathology*, 689 F.3d at 1326. In effect, the government proposed a new test, under which a DNA molecule copied literally from the chromosome is a product of nature, while a molecule such as cDNA, which copies the most important part of the natural DNA molecule, is patentable subject matter, because the cDNA molecule is not found in nature in that precise form.

The government's attempt to distinguish a product merely extracted from nature (an "isolated" natural gene) from a product extracted from an extract of nature (the exon sequence of a natural gene) is a distinction without a difference. cDNA may be one step removed from the natural gene (its introns are not copied), but it is a simple step to accomplish and is equivalent for all biological purposes. As Judge Lourie correctly observed below, isolated genes are also not found *as such* in nature. This Court should reject the government's proposed distinction between products of nature and inventions. Exact identity to the product of nature is not the appropriate test for determining patentable subject matter. The Court should not sanction the patenting of *any* biologically insignificant alteration of a human gene without

more, regardless of how much of the natural DNA sequence is omitted. A person claiming the cDNA sequence of a natural gene no more created that sequence than he created the gene itself.

Moreover, the argument that cDNA differs substantially from the natural gene ignores the role of messenger ribonucleic acid (mRNA) in gene expression. mRNA is a natural molecule that conveys information from the DNA to the ribosome during natural translation of coding DNA into proteins. Like a cDNA molecule, *the mRNA molecule contains only the coding region of the gene*. "The notion of removing introns, regions of a DNA sequence that do not code for proteins, is not a human invention. In fact, during the process of natural DNA transcription, an mRNA molecule is created as a copy of a gene in preparation for protein synthesis. During the creation of the mRNA, only the exons are reproduced." Demaine & Fellmeth, *supra*, at 408. The only significant difference between an mRNA molecule and its correlative cDNA molecule is that the former is single-stranded and the latter is double-stranded.[6] Scientists who create cDNA merely use well-known techniques for converting a natural mRNA molecule into cDNA. Indeed, *even this process happens naturally*; cells create processed pseudogenes in just this way. In fact, an important function of cDNA in biotechnology

[6] RNA also has a ribose sugar instead of deoxyribose sugar in its backbone and substitutes uracil for thymine in its base composition. These differences do not affect the amino acid sequence conveyed by the sequence of bases.

is to reproduce the natural mRNA so that it can be translated into the natural protein. The cDNA is a mere replica of natural mRNA and pseudogenes.

This Court should apply the substantial transformation test to find that cDNA versions of naturally occurring human genes, if they merely "isolate and purify" those genes by copying the non-coding regions, do not constitute patentable subject matter. As with merely "isolated" genes, the biological function of the cDNA is identical to that of the natural gene—the expression of a specific protein. Only if the cDNA is altered to perform protein expression in a "markedly different" way than the nature gene—generally by expressing an unnatural protein—should the cDNA be considered patentable subject matter.

CONCLUSION

For the foregoing reasons, the judgment below should be reversed.

Respectfully submitted,

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