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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 *AMICI CURIAE* UNIVERSITY OF BALTIMORE/JOHNS HOPKINS UNIVERSITY CENTER FOR MEDICINE & LAW, AND LAW PROFESSORS GREGORY DOLIN, M.D., *ET AL.* IN SUPPORT OF RESPONDENTS

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STATEMENT OF INTEREST OF *AMICI CURIAE*[1]

Amicus curiae University of Baltimore School of Law/ Johns Hopkins School of Medicine Center for Medicine & Law is a joint venture between the two universities dedicated to research in the areas of health care law, pharmaceutical and medical technology innovation, increased patient access to health care, and improved understanding of medical technology by the public.

Professor Gregory Dolin, M.D., Co-Director Center for Medicine and Law, University of Baltimore School of Law, Johns Hopkins University School of Medicine, Professor Adam Mossoff, Senior Scholar & Co-Director of Academic Programs, Center for the Protection of Intellectual Property, George Mason University and Professor Mark F. Schultz, Southern Illinois University School of Law, Senior Scholar & Co-Director of Academic Programs, Center for the Protection of Intellectual Property, George Mason University School of Law are *amici curiae* law professors teach patent law and have published peer-reviewed articles in several law reviews discussing patent eligibility of inventions under Section 101 of the Patent Act, particularly as it relates to genetic materials.

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1. No counsel for a party authored this brief in whole or in part and no party of counsel for a party made a monetary contribution intended to fund the preparation or submission of this brief. No persons other than *amici curiae* or their counsel made a monetary contribution to its preparation or submission. The parties have all either filed blanket waivers with the Court or have explicitly consented to the filing of this brief.

All *amici* are exceptionally familiar with both patent laws and the underlying science, and have an interest that the Patent Act be applied properly, pursuant to the prescriptions of Congress and this Court, and consistent with the underlying scientific principles.

SUMMARY OF ARGUMENT

Genetic medicine is among the most active and promising areas of scientific research. Laboratory synthesized strands of DNA—derived yet distinct from naturally occurring DNA—play a central role in this research, as well as in the commercial diagnostic and therapeutic tools that it generates.

These synthetic DNA strands differ from their natural counterparts in several significant ways: The synthetic strands are not found directly in nature, but rather are constructed or isolated using inventive laboratory techniques. The synthetic strands are smaller, isolated, and focused, while natural DNA incorporates massive genomic information unrelated to a specific gene, mutation, or disease. The synthetic strands possess unique molecular structures and chemical properties unlike anything found in nature. Perhaps most importantly, the synthetic strands provide useful functionality that their natural counterparts lack, specifically in the critical areas of diagnosis and therapy.

Petitioners contend that these synthetic strands are nevertheless mere discoveries latent in natural DNA rather than new inventions eligible for patent protection. Such an assertion misstates both the applicable law and the underlying facts.

From a factual perspective, the differences between natural and synthetic DNA strands are manifest. An inventive step that works from a natural beginning to craft a new item, possessing some similarities to its natural parent but with different forms and properties, distinguishes invention from discovery. There is no place in nature to which one could turn to find an object identical to the claimed inventions—or an object that functions in an identical manner.

From a legal perspective, this Court has long interpreted Section 101 of the Patent Act to define patent-eligible subject matter broadly; anything "made by man" should qualify. Given that the claimed inventions cannot be found anywhere in nature, the analysis should be straightforward. In fact, ample precedent, including this Court's most recent interpretations of Section 101, supports the conclusion that concrete inventions—such as the synthetic DNA strands that the Respondents claim—are patentable, while abstract ideas are not.

Petitioners and their *amici* also rely on public policy arguments against patenting genetic materials. Yet few if any of those purported policy concerns differ from those raised in objection to therapeutic inventions of all sorts. Congress has heard these arguments many times since the first genetic patent was issued more than thirty years ago, and rejected all such entreaties. In that time, Congress has incorporated numerous new rules and limitations on biologic and therapeutic patents—but never the broad, sweeping prohibition that Petitioners now seek.

Congressional policy favoring the patentability of genes is neither capricious nor mistaken. The entire

raison d'être of the patent system is the promotion of science and the useful arts. Every patent granted, like any grant of exclusive rights, imposes costs on those seeking to use inventions already invented. We bear those costs willingly because we have concluded that the costs are outweighed by the benefits stemming from the fruits of increased inventive activity. Genetic research is hardly an exception. The difficulty in devising useful inventions like those at issue here, coupled with the ease of copying genetic products once invented, argue strongly in favor of patent protection.

Petitioners have asked this court to overrule the Federal Circuit's ruling that synthetic DNA strands are patentable subject matter. We urge this Court instead to follow scientific fact, legal precedent, public policy, and Congressional judgment by affirming the Federal Circuit.

ARGUMENT

I. Isolated DNA Sequences and cDNA are Different from Native, Naturally Occurring DNA.

The patents at issue here are directed to new and distinct chemical entities that are not present in nature. The overall chemical structure, and often the very sequence of the DNA subunits in the claimed products, differs radically from anything that occurs in nature. Never before has Congress or this Court concluded that a new, man-made chemical entity is not patentable subject matter.

A. Human Genes in Their Native State are Chemically Bound to Other Genes and Proteins, Giving them Particular and Unique Chemical and Physical Properties

A DNA molecule consists of two strands of a repetitive sugar-phosphate chain called deoxyribose. *See* BRUCE ALBERTS ET. AL., MOLECULAR BIOLOGY OF THE CELL 98 (3rd ed. 1994). Each strand is a long, unbranched polymer composed of four types of subunits: bases known as adenine, cytosine, guanine, and thymine ("A," "C," "G," and "T," respectively) leading to a structure resembling four kinds of beads strung on a necklace. *Id.* Each adenine base on one strand is paired with a thymine base on the other, and each cytosine base is paired with a guanine base, generating strands that are complementary, not identical. *Id.* at 99. The DNA molecule can be visualized as a zipper with each strand serving as tape and the A, C, T, G base pairs forming the teeth. Unlike a regular zipper, though, a molecule of DNA is neither straight nor flat. Instead, in its "native" state (i.e., the state it assumes naturally inside a living organism) the DNA molecule is twisted into a spiral ladder shape, giving rise to the famous "double-helix" model. *Id.*

Each DNA molecule is packaged in a separate chromosome. *Id.* at 337. The DNA is associated with chromosomal proteins (such as histones) that pack the DNA molecule in an orderly way to protect it from damage and to regulate gene expression. *Id.* at 342; Rajesh C. Rao, *Alternatives to Embryonic Stem Cells and Cloning: A Brief Scientific Overview*, 9 YALE J. HEALTH POL'Y L. & ETHICS 603, 605 (2009). Each chromosome is thus far more complex than a long, twisted ladder; it is a three-dimensional structure of coiled and packed DNA.

Each chromosome contains numerous genes, and the full set of an organism's chromosomes carries the entirety of its genetic information—its "genome." Because the human genome contains upwards of 20,000 genes but only twenty-three pairs of chromosomes, each chromosome must contain hundreds or thousands of genes. *See* Erik Lillquist & Charles A. Sullivan, *The Law and Genetics of Racial Profiling in Medicine*, 39 HARV. C.R.-C.L. L. REV. 391, 410 (2004). Although each cell contains its organism's entire genome, not all genes are expressed or "turned on" at all times.[2] ALBERTS, *supra* at 401. In order to allow for such differential gene expression, cells identify which genes to express through various cellular mechanisms like chemical modification of the DNA molecule or protein binding to relevant segments of DNA in order to turn it "on" or "off." *Id.* at 402-04, 449.

The overall chemical and physical properties of native DNA emerge from this combination of factors: the entire sequence of base pairs (rather than a particular isolated fragment); the chemical modification of its nucleotides; the association with proteins such as histones; and the overall packaging into superstructures such as chromosomes. Each of these factors plays a role in defining and controlling native DNA's molecular weight, chemical charge, three dimensional structure, responsiveness to particular chemicals and enzymes, availability of electrons for other chemical reactions, and every other property.

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2. If all genes were turned on in all cells all of the time, cell differentiation would be impossible. In other words, cells would not be able to differentially develop into liver cells, brain cells, blood cells, skin cells, etc. That they actually do so is the result of certain genes being expressed in certain cells but not in others.

B. Human DNA is a Set of Genetic Instructions for Proteins — The Building Blocks of Life

The "function" of DNA is to provide a set of genetic instructions for the production of other critical molecules: proteins.[3] *See* Gregory Dolin, *Exclusivity Without Patents: The New Frontier of FDA Regulation for Genetic Materials*, 98 IOWA L. J. 1399, ___ (2013), available at http://papers.ssrn.com/sol3/papers.cfm?abstract_id=2020112 at *21.

Amino acids are the building blocks of proteins, and DNA codes for amino acids. *Id.* at *21-22. This coding operates by grouping nucleotides together in groups of three. Mathematically, each triad drawn from the set of four nucleotides defines a potentially distinct code, yielding sixty-four distinct possible values, or "codons."[4] *Id.* For reasons not wholly understood, genes have non-coding regions (known as "introns") that are interspersed among coding regions (known as "exons"). ALBERTS, *supra* at 341. Indeed, the majority of the genetic material, consists of the non-coding regions. *Id.*

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3. Portions of DNA also code for other molecules such as structural RNAs. However, encoding proteins is the primary function of most of the DNA.

4. Mathematically, four letters, each used alone, would result in just four permutations. If four letters were used two at a time, sixteen permutations are possible. Only if four letters are used three at a time will the number of permutations (sixty-four) exceed twenty. This results in the genetic code being "degenerate" where multiple codons may code for the same amino acid. For example, codons CGT, CGC, CGA, CGG, AGA, and AGG all code for the same amino acid – arginine. At the same time, only a single codon (ATG) codes for amino acid methionine. *Dolin*, supra at *21-22.

Mutations in a codon sequence, which may occur, for example, by adding or deleting a nucleotide or by changing one nucleotide into another, often result in coding an incorrect amino acid, leading to a defective or completely nonfunctional protein. *Id.* at 102-03. Thus, when diagnosing genetic disorders, it is important to compare the subject sequence to both the normal sequence and all known mutations. *Dolin*, *supra* at *23.

Those diagnostic comparisons require a few further definitions and steps. First, recall that DNA's two strands are complements, not mirror images; the complement of an AAA sequence, for example, is TTT. Next, only one of these complementary strands—known as the "sense" strand—codes for amino acids; its complement is known as the "anti-sense" strand. *Id.* at *24. Diagnosis and treatment require identifying the "sense" strand coding a particular protein, a difficult challenge because both strands contain sense and anti-sense regions. *See* ALBERTS, *supra* at 227. Natural cellular mechanisms, working *in vivo*, can differentiate between the sense and anti-sense strands in native DNA that embodies a complete genetic code. *Id.* Laboratory tools and techniques capable of distinguishing sense from anti-sense strands require innovation and inventiveness beyond the use of natural mechanisms.

C. Production and Processing of RNA is an Intermediate Step in Translating the Genetic Code into Protein Structure

The "decryption" of DNA's genetic code into a protein structure occurs in two steps: transcription and translation. For present purposes—namely understanding

why the patent claims at issue describe invented, rather than natural, phenomena—transcription is far more significant than translation.

The process begins when the DNA region containing the relevant active gene is "transcribed" into a corresponding RNA molecule. RNA is comprised of nucleotides attached to a single strand of a sugar molecule called ribose (as opposed to the dual strands of deoxyribose in DNA). *Id.* at 60. The transcription from DNA to RNA copies A, C, and G nucleotides directly, while replacing all T (thymine) nucleotides with U (uracil) nucleotides. *Id.* at 104.

In addition to the replacement of Ts with Us, RNA and DNA differ in several other significant ways. Unlike the native DNA strand that contains multiple genes, only some of which are active, an RNA molecule contains only a single active gene. *Id.* at 340. In a similar vein, single-stranded RNA transcribes only sense regions, never anti-sense regions. *Dolin*, *supra* at *26. Also unlike DNA, RNA lacks the bound histones that fold DNA into the complex chromosomal structures. *Id.* RNA does, however, possess several features that native DNA lacks: a special methylated guanine nucleotide known as a "5' cap" on one side of the strand, and a long tail of 100 to 200 adenine nucleotides, known as a "poly-A tail," on the other. *Id.* These structures, which do not code for amino acids, promote the RNA's stability and permit cellular mechanisms to verify that an RNA strand is intact before decoding it to produce proteins. ALBERTS, *supra* at 369-70.

Before that production can begin, however, a further pre-processing step, known as "RNA splicing," removes non-coding introns from the RNA and splices the

remaining exons together in an uninterrupted string known as "messenger RNA," or mRNA. *Dolin*, *supra* at *27. That sets the stage for the "translation" step, where cellular mechanisms read the mRNA, one codon at a time, to produce the final protein structure. *See* ALBERTS, *supra* at 232–36.

All told, even though the DNA dictated the critical sequence of nucleotides in the mRNA molecule, the two molecules differ quite significantly. The removal of a majority of the genetic code; the subsequent splicing, the introductions of the 5' cap and the poly-A tail; the substitution of uracil for thymine; and the use of a different sugar all render the resultant mRNA a very different molecule from the DNA from which it was derived.

D. Laboratory Created cDNA Molecules that are Used to Identify and Treat Disease are Structurally Different from Native State DNA and RNA

Though mRNA serves as the template for protein synthesis, scientists typically have little choice but to work with DNA when studying genes because only active genes produce mRNA and, consequently, proteins. An inactive gene coding a dangerous mutation—such as a cancer—will thus be asymptomatic. Because genetic research attempts to identify such dangers *before* they pose an active threat to their host organism, geneticists *must* study the molecules containing all of that organism's genetic information, inactive as well as active. The only molecules possessing that property are DNA. *See Dolin*, *supra* at *27-28.

In order to locate and identify the quiescent gene on a complex DNA molecule packed with thousands of other genes, scientists create "probe" molecules that bind to the region of interest and locate the targeted gene. *Id.* at *28-30. Because DNA contains two complementary strands with each nucleotide sequence binding to its complement, these laboratory-created probes bind to complementary regions of native DNA. The process for creating such probes is well-known: "reverse transcription" of an mRNA molecule creates a copy of an *in vivo* anti-sense DNA strand's coding regions, known as "complementary DNA," or cDNA (because it is complementary to the mRNA template). *See* ALBERTS, *supra* at 300-03.

Nature does not create cDNA; only laboratory scientists do. cDNA is thus a completely man-made molecule. It differs from the templating mRNA molecule in at least three ways, and from native *in vivo* DNA in at least four ways.

A comparison of mRNA and cDNA reveals that: First, the cDNA is not a copy of the mRNA because it is a double-stranded rather than a single stranded molecule. Second, as a DNA molecule, it uses thymine rather than uracil. Third, the sugar backbones of the mRNA and cDNA strands differ; the mRNA's is ribose while the cDNA's is deoxyribose. *See Dolin*, *supra* at *29-30.

A comparison of native DNA and cDNA reveals that: First, the cDNA has no introns. Second, since the cDNA is a laboratory-produced molecule, it is not subjected to cellular regulation such as chemical modification of various nucleotides. Third, cDNA is not part of a larger structure such as a chromosome. Fourth, because

cDNA is complementary to the mRNA, it has a region complementary to the poly-A tail—a region not present in the *in vivo* DNA. *See id.*

In short, *nothing* about cDNA is "naturally occurring." cDNA is a completely artificial construct useful for studying naturally occurring DNA.

E. Laboratory Created and Isolated DNA Molecules Possess Functions that Native State DNA and RNA Lack

Laboratory-synthesized cDNA molecules are useful as probes to identify genes *in vivo*. While the cDNA strand *as a whole* is not complementary to any *in vivo* DNA sequence (i.e., because cDNA lacks introns), the overlap is sufficient for the cDNA to attach itself to, or "hybridize" with, the native DNA. *See id.* at *30. The points of hybridization, in turn, allow scientists to identify the endpoints of each native gene, to excise each gene using specific (and known) enzymes (i.e., create "isolated" DNA), and to employ well-known (and mostly automated) methods to discover the sequence of each gene. *Id.*

The genetic sequence, once discovered, presents multiple opportunities for scientific advancement, most immediately by helping researchers probe, test, and identify genetic predispositions for cancer and other diseases. *See id.* at *31-32. In some cases, medical scientists can go further by generating genetic therapies for diseases thus diagnosed. *Id.* The ability to isolate and to work with "full" genes (i.e., those with introns present) opens new opportunities for working with transgenic animal (i.e., animals with a foreign gene inserted into

their native genome) studies and for treatment of certain diseases (though such experimental interventions are currently in their infancy). *Id.* at *32. Finally, knowledge of the genetic sequence of one gene helps advance research into other genes and biological processes. Diseases and other characteristics are often controlled not by a single gene but by a combination of genes working together. *See id.* at *32-33. In these situations, the expression of some genes is directly affected by expression of others. Given the complex nature of genetic expression, scientists need to build upon, and work with, earlier genetic discoveries in order to continue their exploration.

Various opponents of genetic patents have attempted to draw analogies between genetic research and mining to convince the court that the claims at issue are discoveries rather than inventions. *See Ass'n for Molecular Pathology v. USPTO*, 689 F.3d 1303, 1350 (Fed. Cir. 2012) (Bryson, J., concurring in part and dissenting in part). Such analogies are inapt. The chemical and physical properties of a mineral are fixed and do not change when miners extract the mineral from soil or mineralogists extract it further from ore into an isolated form. Electrical conductivity, reactivity to acids or bases, melting points, or reactivity to other metals remain natural constants. By way of contrast, *all of these properties* of isolated DNA and cDNA differ from those of corresponding native DNA.

Taken together then, isolated DNA and cDNA are more than merely new inventions; they are new inventions that serve distinct and important functions unachievable using only elements found in nature. Unlike their natural counterparts, these laboratory-synthesized molecules lack chemical modification of particular nucleotides; do

not associate with binding proteins such as histones; are not part of superstructures such as chromosomes; and have molecular weights, charges, and responsiveness to chemicals and enzymes that differ from native DNA. *See id.* at *68. By any reasonable definition, isolated DNA and cDNA are "not nature's handiwork, but [the inventor's] own." *Diamond v. Chakrabarty*, 447 U.S. 303, 310 (1980).

II. Prior Decisions of this Court Make Clear that Laboratory-Created Chemical Compounds are Patent Eligible

Since at least 1853, this Court has drawn a line between patent-eligible inventions and patent-ineligible discoveries. *See Le Roy v. Tatham*, 55 U.S. 156, 174-175 (1853). However, it has never mattered whether the invention "is produced by chemical agency or combination; or by the application of discoveries or principles in natural philosophy known or unknown before his invention." *O'Reilly v. Morse*, 56 U.S. 62, 119 (1854). Patent eligibility has always meant that the invention was "not nature's handiwork, but [the inventor's] own," *Chakrabarty*, 447 U.S. at 310, and that the patent described it "in a manner so full and exact, that any one skilled in the science to which it appertains, can, by using the means he specifies, without any addition to, or subtraction from them, produce precisely the result he describes." *O'Reilly*, 56 U.S. at 119. Although the Court has excluded from patent eligibility "[t]he laws of nature, physical phenomena, and abstract ideas," 447 U.S. at 309, it has consistently held that an invention that "come[s] from the application of the law of nature to a new and useful end," *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948), is indeed worthy of patent protection under § 101 (and its predecessors). *See Diamond v. Diehr*, 450 U.S. 175, 187-188 (1981).

Part I, *ante*, explained why isolated DNA and cDNA are neither "nature's handiwork" nor "natural phenomena." Rather, they are produced in the laboratory as the "handiwork" of the inventor, through the application of laws of nature, which are taken "from the laboratory of the philosopher, and ma[de] the servant of man." *O'Reilly*, 56 U.S. at 132. As this Court held in *The Telephone Cases*, when "[t]he art consists in so controlling the force [of nature] as to make it accomplish the [inventor's] purpose," the claims to such art are in fact eligible for patent protection. 126 U.S. 1, 532 (1888).

The late Chief Judge Markey once observed "'[o]nly God works from nothing. Men must work with old elements.'" *Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556 n.3 (Fed. Cir. 1985) (quoting Howard T. Markey, *Why Not the Statute?*, 65 J. Pat. & Trademark Off. Soc'y 331, 334 (1983)). That the isolated DNA and cDNA molecules claimed by the Respondents are derived from a naturally occurring substance does not and should not change the analysis. Indeed, in the field of biological and medical science most, if not all, substances are derived and purified from naturally occurring compounds. In fact, as far back as 1873 Louis Pasteur was issued a patent on purified yeast. *See* U.S. Patent No. 141,072. Neither Congress nor this Court have ever viewed such lineage as a reason to deny patent eligibility to the derived products.

A. As a Matter of Science, the Claims in Myriad's Patents are Indistinguishable from Claims in Chakrabarty's Patents

In *Diamond v. Chakrabarty*, Dr. Ananda Chakrabarty sought to patent a known species of bacterium that he endowed with new biological properties. 447 U.S. at 305.

His "inventive process" essentially merged the DNA of one bacterium with the DNA of another. *See* U.S. Patent No. 4,259,444, col. 2, ll. 38-46. As Dr. Chakrabarty explained in his disclosure, both of the merged DNA molecues (known as plasmids) were naturally occurring and well known, as were the bacteria that carried each of the plasmids. *Id.* Furthermore, the methods for inserting foreign plasmids into a new host were also well known in the art by the time Dr. Chakrabarty created his transgenic bacterium. *Id.* at col. 2, ll. 8-28.

Although there was much concern over permitting patents on living organisms, *see Chakrabarty*, 447 U.S. at 316 (describing concerns "that genetic research may pose a serious threat to the human race, … [that it] may spread pollution and disease, that it may result in a loss of genetic diversity, and that its practice may tend to depreciate the value of human life."), the Court correctly concluded that Congress had consciously crafted the "subject-matter provisions of the patent law … in broad terms to fulfill the constitutional and statutory goal of promoting 'the Progress of Science and the useful Arts.'" *Id.* at 315. Applying these broad Congressionally-defined contours, the Court concluded that the microorganisms that Dr. Chakrabarty invented are not a "natural phenomenon, but [] a nonnaturally occurring manufacture or composition of matter – a product of human ingenuity 'having a distinctive name, character and use.'" *Id.* at 309-10 (quoting *Hartranft v. Wiegmann*, 121 U.S. 609, 615 (1887)).

From the scientific perspective though, the key to Dr. Chakrabarty's invention was not the bacterium, but the plasmid – the DNA – that he created in his laboratory and ultimately transfected into the claimed bacterium. *See*

U.S. Patent No. 4,259,444, col. 2, ll. 38-55. The invention worked only because the bacterial DNA coded for enzymes that provided a degradative pathway for a variety of hydrocarbons. *Id.* at col. 3, ll. 5-23. Had Dr. Chakrabarty sought to patent the newly created plasmid (or combination of plasmids), he likely would have achieved the same legal result. This hypothetical patent would have had the same reach as the patent that ultimately issued, and the subject matter of that hypothetical patent would still have been "a product of human ingenuity 'having a distinctive name, character and use,'" even though each component was both known and naturally occurring.

The case at hand cannot be distinguished in a meaningful way. The Respondents claim isolated DNA and cDNA sequences that are capable of hybridizing to native DNA. These sequences have "a distinctive name, character and use" different from sequences that occur in nature. It is these man-made fragments that are useful and used in diagnosing predisposition to breast cancer. In *Chakrabarty*, the invention consisted of inserting two separate known pieces of DNA into a single cell in order to cause that cell to express both genes. U.S. Patent No. 4,259,444, col. 10, ll. 46-52. The case at bar, at the very least with respect to cDNA, is identical. As discussed in Part I, creating cDNAs is a multi-step process that includes excising pieces of DNA from the native sequence and annealing the remaining pieces together. The only difference between this process and the patent eligible process in *Chakrabarty* is that here, all pieces of the DNA come from a single organism, while in *Chakrabarty*, each piece of DNA was sourced from a different organism. This distinction should not be relevant to a determination of patent eligibility of the subject matter; the fundamental

inventive process and the ultimate inventive result are the same in both cases.

A similar analysis applies to isolated DNA. Although isolated DNA includes only the process of cutting DNA segments from a larger molecule and does not include re-annealing, the isolated DNA claimed by the Respondents still differs from anything that occurs in nature. Not only does the isolated compound have different chemical and physical properties, it also has a "distinctive … use." Unlike naturally occurring chromosomal DNA, isolated and purified DNA can be used to specifically identify and differentiate normal from mutated *in vivo* DNA sequences. *See Dolin*, *supra* at *27-33. Because human intervention is required to produce isolated DNA, the isolated DNA is chemically and physically different from naturally occurring DNA. Because that newly-invented isolated DNA has a distinct purpose and uses, it is patent eligible subject matter.

B. Isolated DNA and cDNA are Patent Eligible Under the Principles and Logic of *Parke-Davis*

Courts and commentators have long viewed *Parke-Davis & Co. v. H. K. Mulford Co.*, 189 F. 95 (C.C.S.D.N.Y. 1911), as a clear and correct statement of patentability in the field of biologic arts. In *Parke-Davis*, Judge Hand concluded that adrenaline, extracted from the adrenal gland and purified to be both therapeutically and commercially useful, was "a new thing," not a naturally occurring substance—and thus eligible for patent protection. *Id.* at 103. Though adrenaline is indeed a naturally occurring compound produced by the body's adrenal glands, its medicinal uses emerge only after

isolation and purification. *See* Michael D. Davis, *The Patenting of Products of Nature*, 21 RUTGERS COMPUTER & TECH. L.J. 293, 326 (1995). The process of isolation and purification therefore took the naturally occurring product from the state of nature "and ma[de it] the servant of man" by giving it a new utility.

The Fourth Circuit adopted the *Parke-Davis* approach in *Merck & Co. v. Olin Mathieson Chem. Corp.*, 253 F.2d 156 (4th Cir. 1958). There again, the patentee patented an isolated and purified form of a naturally occurring chemical compound – in that case, vitamin B-12. Faced with a challenge to the patent under the "product of nature" doctrine, the Fourth Circuit concluded that the patentee

> has produced a medicine indisputably beneficial to mankind -- something new in a useful art, such as our patent policy was intended to promote. … And it makes no difference, so far as patentability is concerned, that the medicine thus produced is lifted out of a mass that contained, chemically, the compound [in question] -- where the one is therapeutically available and the others were therapeutically unavailable – patentability would follow."

Id. (quoting *Kuehmsted v. Farbenfabriken of Elberfeld Co.*, 179 F. 701, 705 (7th Cir. 1910)).

What underlies the holdings in *Parke-Davis*, *Merck*, and *Kuehmsted* is the understanding that patent laws exist to "promote the Progress of Science and useful Arts," U.S. Const., Art. I, §8, cl. 8, and that inventions

which create new medical therapies do in fact "promote the Progress of Science." That Constitutional utilitarian justification has always underpinned the patent system, *see* Adam Mossoff, *Rethinking the Development of Patents: An Intellectual History*, 1550-1800, 52 HASTINGS L. J. 1255, 1256 n.7 (2001), and its implications should be instructive in any consideration of the proper scope of patent eligibility—including the present one. *See Dolin*, *supra* at *40-46. From the perspective of public policy, the relevant question is thus whether granting patents on genetic compounds isolated and purified from their natural state to make them diagnostically and therapeutically useful would spur innovation in excess of the costs implicit in any grant of exclusive rights. *See id.* at *78-79. Given the extraordinarily high capital cost and the inherent uncertainty of genetic research, compounded by the negligible cost of copying new discoveries, the answer should be clear. The patent system is necessary to motivate scientific research and to protect the commercially viable discoveries emerging from the research laboratories. *See id.* at *91.

C. *Prometheus* and *Funk Brothers* are Not to the Contrary

This Court's own precedents, at the very least from *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948) through the more recent *Mayo Collaborative Services v. Prometheus, Inc.*, 566 U.S. ___, 132 S. Ct. 1289 (2012), support a holding that isolated and purified DNA and cDNA are patent eligible subject matter.

In *Funk Bros.*, the Court concluded that a particular mixture of bacteria, though useful for agricultural

purposes, is not patent eligible subject matter because the claimed invention was "hardly more than an advance in the packaging of the inoculants." 333 U.S. at 131. In the Court's view, the aggregation of bacteria into a single package was "no more than the discovery of some of the handiwork of nature and hence is not patentable."[5] *Id.* The Court's decision ultimately rested on the absence of any inventive step whatsoever. In the view of the Court, the *Funk Bros.* "inventor" did *nothing* to modify the bacteria in the mixture, and the mixture resulted in no individual strains of bacteria acquiring a new "range of their utility. Each species has the same effect it always had. … Their use in combination does not improve in any way their natural functioning. They serve the ends nature originally provided and act quite independently of any effort of the patentee." *Id.* In contrast, unlike naturally occurring DNA, isolated DNA and cDNA serve important diagnostic and therapeutic purposes, thereby giving these man-made molecules a new "range of utility," making them serve the ends different from what nature originally provided, and causing them to act only because of the "effort of the patentee" who created these particular molecules precisely to allow such therapeutic and diagnostic interventions.

Similarly, in *Prometheus*, the Court concluded that a patent on optimizing the level of a particular drug in a body does not satisfy § 101 requirements because the claim merely embodied the scientific truth that too little

5. In the view of the *amici*, *Funk Bros.*, was incorrectly decided and should be overruled. However, as described below, the patents at issue in the present case would satisfy even the overly broad "product of nature" exception articulated in *Funk Bros.*

of the drug is ineffective, while too much is poisonous. The claimed method in *Prometheus* simply "set forth laws of nature-namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a [the] drug will prove ineffective or cause harm," and directed the treating physician to increase an ineffective or decrease a harmful dosage of the drug. 132 S. Ct. at 1296. In other words, the patents claiming the method of administering the drug did nothing more than recite the method by which the immutable law of nature works. The human involvement in the claimed method was merely a "conventional [and] obvious, … insignificant post-solution activity." *Id.* at 1298 (internal citations and quotations omitted). The *Prometheus* Court, however, cautioned against "too broad" an application of the principle that "[p]henomena of nature, … are not patentable," *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972), because such "an interpretation … could eviscerate patent law. For all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas." 132 S. Ct. at 1293.

Applying the *Prometheus* principles to the present case, it becomes clear that the invention the Respondents claim is patent eligible subject matter. Extracting DNA from the chromosome, separating coding from non-coding regions, re-annealing these regions, and/or reverse transcribing DNA sequence from an RNA molecule, are neither "conventional [nor] obvious, [nor] insignificant post-solution activit[ies]." Indeed these activities lie at the very heart of molecular and medical genetics research. While no one disputes that all breakthroughs in molecular and medical genetics "embody, use, reflect, rest upon, or apply laws of nature [and] natural phenomena," *the*

results of this research remain well within the ambit of patent protection. The decision in *Prometheus* did not alter the dichotomy that "'[w]hile a scientific truth, or the mathematical expression of it, is not a patentable invention, a novel and useful structure created with the aid of knowledge of scientific truth may be,'" *Diamond v. Diehr*, 450 U.S. 175, 188 (1981) (quoting *Mackay Radio & Telegraph Co. v. Radio Corp. of America*, 306 U.S. 86, 94 (1939)), instead re-affirming it. *Prometheus*, 132 S. Ct. at 1294.

The DNA molecules that Respondents claim are not natural phenomena, but rather "novel and useful structure[s] created with the aid of knowledge of scientific truth," *Diehr*, 450 U.S. at 188, and therefore deserving of patent protection. Holding otherwise would expand the scope of the "products of nature" exception to patent eligibility far beyond its original scope and purpose: ensuring that monopolization of scientific principles not impede innovation by foreclosing access to the "basic tools of scientific and technological work." *Gottschalk*, 409 U.S. at 67.

There is no evidence to suggest that patents on man-made genetic materials impede medical research and scientific progress in any way that differs from the effects of other therapeutic patents.[6] Thus, excluding man-made

6. As one study has shown, these patents are almost never asserted against an entity using genetic materials as a basic research tool. *See* Christopher M. Holman, *The Impact of Human Gene Patents on Innovation and Access: A Survey of Human Gene Patent Litigation*, 76 UMKC L. Rev. 295, 343 (2007). Indeed the study was able to identify only a single case involving the "actual sale of a cloned human gene *per se* as opposed to the sale

DNA molecules from patent eligibility would accomplish the opposite of what the "products of nature" exception was meant to achieve. Instead of keeping "manifestations of … nature, free to all men and reserved exclusively to none," *Funk Bros.*, 333 U.S. at 130, denying patent eligibility to man-made DNA molecules would significantly reduce the incentives impelling research medical and molecular genetics research forward, thus delaying the discovery of new and useful diagnostic and therapeutic tools, and retarding, rather than promoting the "progress of science," *see Dolin*, *supra* at *91, all without any palpable increase in the access to the tools of research. *See* Christopher M. Holman, *The Impact of Human Gene Patents on Innovation and Access: A Survey of Human Gene Patent Litigation*, 76 UMKC L. Rev. 295, 352-61 (2007) (stating that patents on DNA have had no negative impact on research or access to research tools, and may have in fact had positive impact).

III. It is Up to Congress, Not the Courts to Define The Limits of Patentability.

The first application for a patent on genetic materials was filed in 1978 and issued as a patent in 1982. U.S. Patent No. 4,363,877 (filed Apr. 19, 1978) (issued Dec. 14, 1982). Calls immediately arose to deny patents to such applications. *See, e.g.*, Robert P. Merges, *Intellectual Property in Higher Life Forms: The Patent System and Controversial Technologies,* 47 Md. L. Rev. 1051, 1058-60 (1988) (discussing ethical objections to patenting

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of a product incorporating the gene (for example, the transgenic mouse []), or the use of the gene in the production of a product or the performance of a service." *Id.* at 343-44.

genetic materials and living organisms); Rebecca S. Eisenberg, *Proprietary Rights and the Norms of Science in Biotechnology Research*, 97 YALE L.J. 177 (1987) (discussing perceived conflicts between the intellectual property regime and the norms of scientific research). Numerous parties have lobbied Congress to deny patent protection to genetic materials. *See* Joel J. Garris, *The Case for Patenting Medical Procedures*, 22 AM. J. L. AND MED. 85, 107 (1996). In the ensuing decades, individual members of Congress have introduced several bills attempting to limit or to end the patenting of genetic materials; not a single one has progressed beyond the committee stage. *See, e.g.*, H.R. 977, 110th Cong. (2007); H.R. 3967, 107th Cong. (2002); H.R. 977, 110th Cong. (2007); S. 2111, 100th Cong., 2d Sess. (1988); H.R. 3119, 100th Cong., 1st Sess. (1987). The implication is clear: Congress believes that genetic materials are patentable subject matter, and sees little reason to alter that *status quo* in any way. *See Dolin*, *supra* at *71-74.

Congress has amended the Patent Act several times since the issuance of that first genetic patent in 1982—without ever restricting genetic patents. In 1984, for example, Congress amended the Patent Act to declare that "[i]t shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention … solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products." 35 U.S.C. § 271(e)(1). Similarly, in 1996, Congress immunized medical practitioners from charges of infringement resulting from practicing patented medical techniques. 35 U.S.C. § 287(c)(1). Starting in 2004,

Congress has on a yearly basis enacted a ban on the use of federal funds "to issue patents on claims directed to or encompassing a human organism." *See* Consolidated Appropriations Act, 2006, Pub. L. No. 109-149, § 509, 119 Stat. 2833, 2880 (2006); Consolidated Appropriations Act, 2005, Pub. L. No. 108-447, § 626, 118 Stat. 2809, 2920 (2005); Consolidated Appropriations Act, 2004, Pub. L. No. 108-199, § 634, 118 Stat. 3, 101 (2004). In 2011, Congress wrote this restriction into the substantive Patent Act. *See* Leahy-Smith America Invents Act, Pub. L. No. 112-29, § 4, 125 Stat. 284, 340 (2011) (amending 35 U.S.C. § 101). In short, over the years, Congress has considered and adopted several mechanisms that limited the scope of the Patent Act either by proscribing the issuance of patents to certain technologies or limiting the ability of patent holders to enforce their patents against a particular class of alleged infringers. Congress, however, consciously chose not to exclude man-made genetic materials from the reach of the Patent Act. *See Dolin*, *supra* at *71-74.

"Congress, not the courts, must define the limits of patentability." *Chakrabarty*, 447 U.S. at 315. Congress has time and again chosen to define the patent eligible subject matter broadly. As this Court stated just three Terms ago, "Section 101 … precludes the broad contention that the term[s of § 101] categorically exclude[]" any particular type of inventions. *Bilski v. Kappos*, 561 U.S. ___, ___, 130 S. Ct. 3218, 3228 (2010). As in *Bilski*, "[t]he argument that [human genes] are categorically outside of § 101's scope is further undermined by the fact that federal law explicitly contemplates the existence of at least some [human gene] patents." *Id.* Section 101 of the Patent Act, as recently amended by the Leahy-Smith America Invents Act, currently prohibits issuance of patents "on a claim

directed to or encompassing a human organism." 35 U.S.C. § 101(a). If § 101 were construed to categorically exclude patents on human genes from its scope, the limitation added by the Leahy-Smith America Invents Act would have been superfluous, as any patent directed to a human organism would necessarily encompass a patent on genetic material. According such a construction to § 101 "would violate the canon against interpreting any statutory provision in a manner that would render another provision superfluous." *Bilski*, 130 S.Ct at 3228.

The Petitioners' arguments have, thus far, not carried the day in either Congress or the Executive Branch. Nothing prevents them from continuing to press their arguments in those arenas. However, they should not be permitted to use this Court to upset the considered judgment of Congress developed over nearly three decades of debate on the issue, and that of the Executive Branch, which, having considered the argument and concerns raised, has continued to issue patents on man-made genetic materials. *See J.E.M. Ag Supply v. Pioneer Hi-Bred Int'l*, 534 U.S. 124, 144-45 (2001) (concluding that courts should not disturb a long and consistent practice by the USPTO which has been acquiesced in by Congress). As this Court has itself recognized, it is

> without competence to entertain these arguments -- either to brush them aside as fantasies generated by fear of the unknown, or to act on them. The choice [the Court is] urged to make is a matter of high policy for resolution within the legislative process after the kind of investigation, examination, and study that legislative bodies can provide and courts

> cannot. That process involves the balancing of competing values and interests, which in our democratic system is the business of elected representatives. Whatever their validity, the contentions now pressed on [the Court] should be addressed to the political branches of the Government, the Congress and the Executive, and not to the courts.

Chakrabarty, 447 U.S. at 317 (1980).

IV. The Functionality Standard Relied on by the Petitioners and Some Amici Does not Make Sense in the Context of Biological Medicine.

Petitioners and some *amici* have argued that man-made DNA ought to be ineligible for patent protection because its function does not differ from naturally occurring DNA. *See, e.g.*, Pet. Br. at 34-35; Br. of Fifteen Law Professors at 37-38; Br. of Am. Med. Ass'n, et al., at 24-26. This argument is both incorrect as a factual matter and, if taken to its logical conclusion, nonsensical in the context of biological medicine.

As an initial matter, isolated DNA and cDNA possess important functional capabilities that naturally occurring DNA lacks. While it is true that both the natural and the artificial molecules code for the same amino acid sequence, the functional similarities stop there. The only function of the naturally occurring DNA is to provide a code for the ultimate amino acid sequence, which is derived after the DNA is transcribed and translated. Although isolated DNA and cDNA are also capable of producing proteins (given the proper biological environment), they have

functions beyond protein production, and they are used for those functions rather than for protein production: isolated DNA and cDNA serve diagnostic functions by binding to *in vivo* DNA and helping to identify genetic mutations. *See* Part I.C, *supra*.

Furthermore, biological medicine works precisely because the therapeutic agent can simulate the function of a naturally occurring substance, often (as here) in addition to its other functions. For example, laboratory produced insulin is useful only because it serves the same function (and operates in the same manner) as insulin produced by pancreas *in vivo*. Yet, that has never been cause to deny patents for a variety of insulin analogues. For example, the UPSTO issued U.S. Patent No. 5,618,913 was issued in 1997 for insulin aspart (marketed as NovoLog/RapidLog). The insulin analogue described in the patent acts in the exact same manner as naturally produced insulin does, and is indeed chemically identical to naturally occurring insulin but for modification in the single amino acid. See FDA, NovoLog Insulin Aspart Label, available at http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4254b_13_04_KP%20InsulinAspartFDAlabel102005.pdf.[7] Despite these similarities in structure and identity of function, there has never been any question that these insulin molecules satisfy § 101 of the Patent Act. Similarly, low molecular weight heparin (an anti-coagulant) has the same function as naturally occurring heparin that

7. Other patents have issued on similar insulin analogues. *See, e.g.*, U.S. Patent No. 5,750,497 (covering insulin determir, which differs from naturally occurring insulin by a single amino acid); U.S. Patent No. 5,656,722 (covering insulin glargine, which differs from the naturally occurring insulin by just three amino acids).

is produced by mast cells. Yet U.S. Patent No. 4,990,502 (issued Feb. 5, 1991) protects it. ("Low molecular weight heparins of regular structure, their preparation and their biological uses.").[8]

Adopting the Petitioners' and *amici*'s functionality analysis would eviscerate an entire field of scientific and medical exploration. By categorically denying patent protection to the fruits of such research, the Court would seriously undermine the incentives to engage in this painstaking and extraordinarily expensive endeavor. Such an approach would privilege chemical-based medical treatments (with all the attendant side-effects) over biological ones (which replace the naturally occurring substance that, due to disease, is not produced in sufficient quantities). Under the Petitioners' view, the traditional chemical drugs would continue to be patent eligible because the particular chemical would have no naturally occurring counter-part, while the biological therapeutic agent modeled on the agent produced *in vivo* would not be patent eligible. Given the evolution of medicine towards biologic treatments, such a result would be not only anomalous, but highly detrimental to the "progress of science" and to improvements in medical therapeutics.

V. Any Questions About Novelty and Scope of Prior Art Must be Answered by Applying Sections 102 and 103 of the Patent Act.

Petitioners and some *amici* argue that the claims to isolated DNA and cDNA lack an "inventive step" that transforms a "product of nature" into patent eligible

8. A number of other patents covering variations of heparin have been issued as well.

subject matter. *See, e.g.*, Pet. Br. at 35-39; Br. of Nat'l Women's Health Network, et al., at 29-30; Br. of Academics in Law, Medicine, Health Policy and Clinical Genetics at 25-31. This argument confuses and conflates separate requirements of the Patent Act into a single inquiry under § 101.

Judge Giles Rich – one of the crafters of the Patent Act of 1952 – described the system thus:

> Achieving the ultimate goal of a patent under those statutory provisions involves, to use an analogy, having the separate keys to open in succession the three doors of sections 101, 102, and 103, the last two guarding the public interest by assuring that patents are not granted which would take from the public that which it already enjoys (matters already within its knowledge whether in actual use or not) or potentially enjoys by reason of obviousness from knowledge which it already has.
>
> …
>
> The first door which must be opened on the difficult path to patentability is § 101 (augmented by the § 100 definitions) ... whether [the] invention is patentable or not.
>
> …
>
> If the invention, as the inventor defines it in his claims … falls into any one of the named categories, he is allowed to pass through to the

> second door, which is § 102; "novelty and loss of right to patent" is the sign on it.
>
> The third door, under the 1952 Act, is § 103 . …
>
> …
>
> Section 103 … refers to the difference between the subject matter sought to be patented and the prior art, meaning what was known before as described in section 102. If this difference is such that the subject matter as a whole would have been obvious at the time [the invention was made] to a person [ordinarily] skilled in the art, then the subject matter cannot be patented.
>
> If the inventor holds the three different keys to the three doors, his invention (here assumed to be "useful") qualifies for a patent, otherwise not.

In re Bergy, 596 F.2d 952, 960-62 (C.C.P.A. 1979). Thus, the issue of whether the patentee was sufficiently inventive or merely made a conventional and obvious change or improvement is not to be analyzed under § 101, but rather under § 103.

It may well be that as knowledge and skill in molecular and medical genetics evolve, some genetic discoveries will fail § 103 analyses. *See generally Dolin*, *supra* at *83-91. As the Federal Circuit recognized in *In re Kubin*, "an obviousness finding [is] appropriate where the prior art 'contain[s] detailed enabling methodology for practicing the claimed invention, a suggestion to modify the prior art

to practice the claimed invention, and evidence suggesting that it would be successful.'" 561 F.3d 1351 (Fed. Cir. 2009) (quoting *In re O'Farrell*, 853 F.2d 894, 902 (Fed. Cir. 1988)). As the art of molecular genetics continues to evolve and the methodology for isolating and purifying DNA and for creating cDNA becomes more "detailed" and "enabling," the evidence that modification of prior art "would be successful" will become stronger and stronger, and the granting of exclusive patent rights will become more and more limited. *See Dolin*, *supra* at *83-91.

Petitioners, however, have chosen not to challenge Respondents' patents on the grounds of obviousness;[9] instead, they have chosen to import the obviousness inquiry into the § 101 patent eligibility analysis. This approach is contrary to well-established principles of patent law and to the intent of Congress that, in 1952, specifically separated the patent eligibility and obviousness inquiries into the different sections of the Patent Act. The Court should not entertain the Petitioners' attempt to rewrite the Patent Act and conflate what should be separate inquiries into a single issue.

9. The *amici* express no view on the issue of obviousness with respect to Respondents' patents.

CONCLUSION

The Federal Circuit correctly held isolated DNA and cDNA to be patent-eligible subject matter and should be affirmed.

Respectfully submitted,

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