No. 12-398

IN THE

Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, *et al.*,

Petitioners,

v.

MYRIAD GENETICS, INC., *et al.*,

Respondents.

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

BRIEF OF PROFESSOR EILEEN M. KANE AS *AMICUS CURIAE* IN SUPPORT OF PETITIONERS

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INTEREST OF *AMICUS CURIAE*

Professor Eileen M. Kane teaches patent law and intellectual property law in the United States, and her legal scholarship has focused on the intersection of patent law and the life sciences, with particular attention to the field of genetics.[1] Professor Kane has a Ph.D. in molecular biology and is a registered attorney before the United States Patent and Trademark Office. She has no financial interest in the above referenced case. This brief is submitted because of the continuing importance of striking a balance between the patent system and the public domain.

SUMMARY OF THE ARGUMENT

DNA is a unique molecule in the life sciences because it is the chemical repository of inheritance, written in the language of the genetic code. Genes are nature's formulas of the genetic code. Modern genetic science has been defined by the imperative to discover the full set of genes in the human genome.

Are human genes patentable? Not everything can be patented. This Court's careful application of the patentable subject matter doctrine of 35 U.S.C. § 101 has provided guardianship for the "storehouse of knowledge" (*Funk*

1. Petitioners' letter of consent to file amicus briefs is on file with the Court; Respondents' emailed consent is attached to this brief. This brief was not authored in whole or in part by counsel for any party and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. No person other than amicus curiae made a monetary contribution to its preparation or submission.

Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 130 (1948)) and the "basic tools" (*Gottschalk v. Benson*, 409 U.S. 63, 67 (1972)) that comprise the intellectual inputs for patentable inventions. The Court has been quite clear that the "laws of nature, natural phenomena, and abstract ideas" are not patentable. *Diamond v. Diehr*, 450 U.S. 175, 185 (1981). The underlying rationale for these exclusions is that scientific advances originate from widely available basic knowledge, and therefore, patenting the intellectual substrates of a field has an adverse effect on its progress. In *Mayo Collaborative Services v. Prometheus Laboratories, Inc.,* 132 S. Ct. 1289 (2012), this Court recently confirmed the requirement for an "inventive concept" in order to establish patentable subject matter that is derived from the natural world.

Genes are not invented. This Court's jurisprudence provides the basis for concluding that patent claims on human genes violate long-standing prohibitions against patenting laws of nature and products of nature. This brief presents two theories of patent ineligibility, grounded in the Court's precedent, that disqualify genes as patentable subject matter: specific and general. First, the gene is a DNA molecule with a specific patent ineligibility that results from its unique property as the repository of the genetic code. The genes are the naturally occurring embodiments of the genetic code. The patenting of genes preempts the use of the genetic code and therefore preempts a law of nature. Second, the gene is a DNA molecule that is generally ineligible for patenting in view of the product of nature doctrine, which requires an inventive conversion of a natural product to secure patent rights. The isolated gene of the challenged patent claims retains natural structure in order to execute natural function. It is a product of nature, and as such, cannot be patented.

In determining patentable subject matter, *Mayo* requires the Court to measure any inventive contribution against the foreclosure of future innovation. That calculation leads to the conclusion that gene patenting exhibits an acute asymmetry: the absence of any inventive contribution is coupled with a damaging effect on the ability of scientists and medical practitioners to freely utilize the most basic discoveries of genetic science, with adverse consequences for the development of innovative advances in genetic medicine. Genes do not constitute patentable subject matter, and the patent claims should be invalidated.

ARGUMENT

I. The Exclusion of Laws and Products of Nature from Patenting Is Necessary to Generate Inventive Achievement

The boundaries of patentable subject matter are critical to a functioning patent system that encourages inventive achievement. Just last year, in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), this Court revisited the doctrine of patentable subject matter as applied to the life sciences. Mayo involved patent claims to methods for determining optimal pharmaceutical dosing by using the correlations between metabolite levels and drug toxicity, which the Court characterized as a "law of nature." *Id.* at 1296. The Court unanimously concluded that the patent claims lacked any inventive contribution beyond merely reciting the correlations; it stated that the steps recited in the method claim "add nothing of significance to the natural laws themselves," and that the claims were thus invalid under 35 U.S.C. § 101. *Id.* at 1302.

Mayo made several general points regarding the necessity and rationale for the use of the patentable subject matter doctrine of 35 U.S.C. § 101. First, the Court reaffirmed the necessity for performing an eligibility analysis in the examination of a proposed invention for compliance with the patent statute. The Court explicitly declined an invitation to avoid patentable subject matter questions by substituting the other doctrinal requirements for patentability (*e.g.*, utility under 35 U.S.C. § 101, novelty under 35 U.S.C. § 102, nonobviousness under 35 U.S.C. § 103, and the disclosure doctrines of 35 U.S.C. § 112), noting that "to shift the patent eligibility inquiry entirely to these later sections risks creating significantly greater legal uncertainty." *Id.* at 1304.

Second, *Mayo* reaffirmed the complexity of the patentable subject matter inquiry, noting that the reach of 35 U.S.C. § 101 is not without limit: "The Court has long held that this provision contains an important implicit exception. '[L]aws of nature, natural phenomena, and abstract ideas' are not patentable." *Id.* at 1293 (quoting *Diamond v. Diehr*, 450 U.S. 175, 185 (1981)). The Court defined the policing of patentable subject matter by these categorical exclusions as a necessary predicate to maintaining a common stock of scientific knowledge in the public domain. "[T]he cases have endorsed a bright-line prohibition against patenting laws of nature, mathematical formulas and the like, which serves as a somewhat more easily administered proxy for the underlying 'building block' concern." *Id.* at 1303. Several years earlier, this Court had also reiterated the continuing relevance of these exclusions: "The concepts covered by these exceptions are 'part of the storehouse of knowledge of all men …free to all men and reserved exclusively to none.'" *Bilski v. Kappos*,

130 S. Ct. 3218, 3225 (2010) (quoting *Funk Bros. Seed Co. v. Kalo Inoculant Co.,* 333 U.S. 127, 130 (1948)).

These modern statements from *Mayo* and *Bilski* echo the Court's observation from 40 years ago: "Phenomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work." *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972). The sum of these pronouncements from the Court signals that it regards the patentable subject matter doctrine as providing a guardianship of the "basic tools," the "building blocks" and the "storehouse of knowledge" of science – all of which are to be protected from private appropriation when 35 U.S.C. § 101 is applied with the precision demanded by this Court's jurisprudence.

The challenged composition of matter claims recite the naturally occurring wild-type genes or naturally occurring mutated genes that correspond to the native human BRCA1 and BRCA2 genes, although described in the claim language of "isolated DNA" (Claims 1, 2, and 7 of U.S. Patent No. 5,747,282, Claims 1, 6, and 7 of U.S. Patent No. 5,837,492 and Claim 1 of U.S. Patent No. 5,693,473). Patent claims that comprise fragments of the BRCA1 gene can also operate to cover the use of the full-length gene (Claims 5 and 6 of U.S. Patent No. 5,747,282); as a result, their validity is subject to the same eligibility analysis.

Although the challenged patent claims to "isolated DNA" can be classified as compositions of matter with respect to the formal categories of inclusion detailed in 35 U.S.C. § 101, the analysis does not end there. Patent claims must not capture the basic knowledge tools that are

essential for maintaining the vibrant intellectual climate of a technological field. "Patent law seeks to avoid the dangers of overprotection just as surely as it seeks to avoid the diminished incentive to invent that underprotection can threaten. One way in which patent law seeks to sail between these opposing and risky shoals is through rules that bring certain types of invention and discovery within the scope of patentability while excluding others." *Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.,* 548 U.S. 124, 127 (2006) (Breyer, J., dissenting from the dismissal of the writ of certiorari as improvidently granted). The application of the law of nature doctrine and the product of nature doctrine to the isolated genes of the challenged patent claims is necessary to discern whether such claims impermissibly appropriate subject matter that belongs in the public domain. Detailed examination reveals that isolated genes remain products of nature, and their patenting preempts a law of nature. As such, they fail to meet this Court's standards for patentable subject matter.

II. The Gene Has a Specific Patent Ineligibility Because Its Patenting Preempts a Law of Nature

A. The Genes are the Natural Embodiments of the Genetic Code, Which Is a Law of Nature

Unraveling the biochemical infrastructure of inheritance revealed an underlying law of nature that explained the unique structure of DNA. "Only when the structure of DNA was discovered in the early 1950's did it become clear how the hereditary information in cells is encoded in DNA's sequence of nucleotides." Bruce Alberts et al., MOLECULAR BIOLOGY OF THE CELL 299, 4th edition (2002). The molecular design of DNA

was then understood to convey an informational code that accounted for its ability to function as the chemical repository of inheritance. A genetic code was discovered and deciphered, revealing a set of equivalences that link a specific DNA nucleotide sequence to a specific protein sequence. *Id.* at 336. The gene functions as a template according to the genetic code. "The genetic code is not the message itself but the 'dictionary' used by the cell to translate from the four-letter language of nucleic acid to the 20-letter language of protein." Frances Crick, *The Genetic Code III*, 215 Scientific American 55 (1966). The correlation between DNA and protein is central to the gene patent claims at issue. Claim 1 of U.S. Patent No. 5,747,282 is a representative illustration of reliance on the genetic code when it simply claims "an isolated DNA coding for a BRCA1 polypeptide." "[T]he relation itself exists in principle apart from any human action." *Mayo*, 132 S. Ct. at 1297.

The leading historian of the genetic code noted that the universality of the genetic code across the biological world was especially significant because "it would elevate the genetic code to the pedestal of universal laws of nature, a privilege usually reserved for the Olympian reaches of physics." Lily E. Kay, Who Wrote The Book Of Life?: A History Of The Genetic Code 276 (2000). The realization that the genetic code functioned as a natural law in the biological sciences led scientists to refer to the DNA-protein relation as the "central dogma" of molecular biology. Alberts et al., Molecular Biology of the Cell, at 301.

The genetic code, therefore, is equivalent in status to the laws of physics previously recognized as unpatentable

laws of nature in this Court's patentable subject matter jurisprudence. "The laws of nature, physical phenomena, and abstract ideas have been held not patentable. Thus, a new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter. Likewise, Einstein could not patent his celebrated law that $E=mc^2$; nor could Newton have patented the law of gravity. Such discoveries are 'manifestations of….nature, free to all men and reserved exclusively to none.'" *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980) (quoting *Funk Bros.*, 333 U.S. at 130). This recitation of unpatentable scientific laws by the Court provides a firm basis for concluding that the discoveries of scientific equivalences, whether the metabolite-toxicity relationship in *Mayo* or the genetic code in this case, cannot be patentable subject matter; in fact, these are precisely the kinds of intellectual achievements that must be segregated from the patent system so that they can be used freely by all. The designation of the genetic code as a law of nature has implications for the patenting of its natural embodiments, which are the genes.

Genes are nature's exemplars of the genetic code – as such, they embody the law of nature. The conversion of the genetic code into a human organism is accomplished by the set of formulas that are individually encapsulated as the genes. The gene, while formally described as a chemical compound, is functionally explained as a template. The dynamic gene operates by the laws of the genetic code. Activation of a gene initiates a sequence of metabolic events that unfold to accomplish the ultimate objective of generating a protein from a gene, a process generally known as gene expression. Extensive scientific efforts have been expended to locate and characterize

the genes and to sequence the full human genome, finally culminating in the efforts of the Human Genome Project. International Human Genome Sequencing Consortium, *Finishing the Euchromatic Sequence of the Human Genome*, 431 Nature 931 (2004). The human genes are the natural formulas of the genetic code that are embedded in the human genome.

The use of the genetic code in genetic medicine is accomplished by research into the behavior of the genes, which dictate the structure and function of the human organism. While the science is novel and paradigm-shifting, its impact is explained by its use of the naturally occurring molecules, the genes, to arrive at a precise and individualized account of an individual's genetic and biochemical identity. "[T]he ultimate consequences of the integration of genomics into medical research and medical practice are likely to be revolutionary." Alan F. Guttmacher and Francis S. Collins, *Realizing the Promise of Genomics in Biomedical Research*, 294 J. Am. Med. Ass'n 1399 (2005). The use of the genes is critical because these molecules carry the natural templates of the human organism. Thus, scientists must draw on the fundamental and uninvented principles of genetics to in order to develop practical applications for use in genetic medicine.

Despite the technical work that underlies the identification and sequencing of the natural genes, there can be no dispute that such efforts do no more than reveal a natural blueprint. "The genome sequence is a discovery, not an invention." John Sulston & Georgina Ferry, The Common Thread: A Story Of Science, Politics, Ethics, And The Human Genome 266 (2002). Accordingly, because the genes are the natural embodiments of the genetic

code, the eligibility analysis of these molecules necessarily implicates the effect of patenting on the availability of this underlying law of nature. More precisely for patent law, this question is generally framed as investigating whether a law of nature is preempted by the grant of a patent claim, an outcome that conflicts with this Court's precedents. "The rule that the discovery of a law of nature cannot be patented rests, not on the notion that natural phenomena are not processes, but rather on the more fundamental understanding that they are not the kind of discoveries that the statute was enacted to protect." *Parker v. Flook*, 437 U.S. 583, 593 (1978).

B. The Patenting of Genes Preempts the Genetic Code, and Is Invalid According to the Court's Prohibition Against Patenting Laws of Nature

Although the Court has repeatedly stated that laws of nature, natural phenomena and abstract ideas are not patentable subject matter, the Court has been alert to possible preemption of the underlying idea through patenting practices. The Court recently elaborated on the underlying rationale for the law of nature exception when it cautioned against "the kind of risk that underlies the law of nature exception, namely the risk that a patent on the law would significantly impede future innovation." *Mayo*, 132 S. Ct. at 1304. The preemption analysis from the Court's jurisprudence provides the analytic tool for avoiding such risk. The claimed mathematical process in *Benson* provided such an example: "The mathematical formula involved here has no substantial practical application except in connection with a digital computer, which means that if the judgment below is affirmed, the patent would wholly pre-empt the mathematical formula

and in practical effect would be a patent on the algorithm itself." *Benson*, 409 U.S. at 71-72 (1972).

Preemption of fundamental subject matter has been the focus of the two most recent patentable subject matter cases from this Court. Just last year, the Court defined a persistent concern from its jurisprudence when it noted that its cases "warn us against upholding patents that claim processes that too broadly preempt the use of a natural law." *Mayo*, 132 S. Ct. at 1294. Applying that warning to its analysis of the medical treatment claims in *Mayo*, the Court found preemption of an uninvented correlation between drug metabolism and toxicity when it reasoned that "upholding the patents would risk disproportionately tying up the use of the underlying natural laws, inhibiting their use in the making of further discoveries." *Id.* In 2010, the Court employed a preemption analysis in concluding that the patenting of a method for hedging the risk of price changes had too broad an occlusive effect. "Allowing petitioners to patent risk hedging would preempt use of this approach in all fields, and would effectively grant a monopoly over an abstract idea." *Bilski*, 130 S. Ct. at 3231 (2010).

The preemption analysis can be applied to the isolated DNA claims at issue, because the claimed genes embody the most fundamental law of nature from biology, the genetic code. The issued patents in this case unambiguously document the natural identity of the claimed BRCA1 gene: "The nucleic acids of the present invention will possess a sequence which is either derived from, or substantially similar to a *natural* BRCA1-encoding gene or one having substantial homology with a *natural* BRCA1-encoding gene or a portion thereof." U.S. Patent No. 5,747,282,

column 19, lines 44-48 (italics added). The natural identity of the claimed BRCA2 gene is similarly described: "The nucleic acids of the present invention will possess a sequence which is either derived from, or substantially similar to a *natural* BRCA2-encoding gene or one having substantial homology with a *natural* BRCA2-encoding gene or a portion thereof." U.S. Patent No. 5,837,492, column 18, lines 29-33 (italics added). Although the patent claims are formally directed to "isolated DNA," the actual DNA sequence is the sequence of the "natural" wild-type or mutated gene, as the patents describe.

The patents claim to the isolated DNA at issue cover natural and uninvented expressions of the genetic code, and have preemptive effect. The genetic code, which is an unpatentable law of nature, does not effectively reside in the public domain if private rights are held in DNA gene sequences, so that the use of the nature's expressions of the genetic code - the genes - are controlled through patent rights. The patenting of genes, therefore, results in effective preemption of the genetic code, an outcome that conflicts with the Court's dictate that the laws of nature should remain in the public domain, free for all to use. Eileen M. Kane, *Splitting the Gene: DNA Patents and the Genetic Code*, 71 Tenn. L. Rev. 707, 753 (2004).

The question presented in this case offers the Court an opportunity to resolve patent eligibility for the entire class of human genes, which comprise the human genome. A proper patentable subject matter analysis of one gene patent claim will resolve the patent eligibility for the class of molecules, because the relevant analysis is generic and not gene-specific. The human genome can be understood as the compilation of nature's formulas for the construction

of the human organism. Each and every gene patent has preemptive effect because it withdraws the use of one of nature's genetic formulas; an outcome that allows "a patent to issue on one of the ancient secrets of nature now disclosed." *Funk Bros.*, 333 U.S. at 131.

The merger doctrine from copyright law supplies a relevant theoretical framework for understanding preemption in the context of genetic science. According to this doctrine, if an uncopyrightable idea has a set of finite expressions, then property rights in the expressions are tantamount to ownership of the underlying idea; effectively, the idea and the expressions merge. *Baker v. Selden*, 101 U.S. 99 (1879). The genes are nature's finite set of embodiments of the genetic code. Moreover, they are not modular or redundant - each embodiment is unique. The grant of private rights to the embodiments of the genetic code results in an effective grant of rights to the code itself. At the level of the human genome, the patenting of genes can be viewed as a merger problem writ large - if the embodiments of the underlying law of nature are subject to private appropriation through patent rights, then the underlying law of nature has itself entered the private domain. Kane, *supra,* at 754. Such an outcome does not comport with the *Mayo* requirement that "to 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*, 132 S. Ct. at 1294 (italics in original). Because the correlation between a DNA sequence and its cognate protein is a law of nature, and this correlation is central to the patent claims at issue, the claims are fatally analogous to the patent claims invalidated in *Mayo*, which failed to demonstrate "more than a drafting effort

designed to monopolize the law of nature itself." *Id.* at 1297. "The question before us is whether the claims do significantly more than simply describe these natural relations. To put the matter more precisely, do the patent claims add *enough* to their statements of the correlations to allow the processes they describe to qualify as patent eligible processes that *apply* natural laws?" *Id.* (italics in original). In this case, patent claims to isolated genes simply "inform a relevant audience about certain laws of nature." *Id.* at 1298. They do no more.

The Federal Circuit did not consider a law of nature analysis to be relevant to its analysis of composition of matter claims. "[P]ermitting patents on isolated genes does not preempt a law of nature." *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 689 F.3d 1303, 1331 (Fed. Cir. 2012). The court then acknowledged that "limited preemption" could be tolerated, but it then mischaracterized the concept of preemption ("a limited preemption is inherent in every patent). *Id.* However, preemption refers, in this Court's jurisprudence, to instances where patenting can block access to certain unpatentable forms of subject matter. That definition of preemption is independent of technological field or claim format, and it does not support a quantification of preemption. In fact, *Mayo* explicitly declined to "draw distinctions among laws of nature." *Mayo*, 132 S. Ct. at 1303. The Federal Circuit thus failed to apply all relevant analytic tools from this Court's jurisprudence in its eligibility analysis of isolated genes, and it did not fully consider the complexity of the DNA molecule. The duality of DNA as both chemical and template requires a bifurcated legal analysis that draws on both process-based and product-based doctrines of eligibility developed in

patentable subject matter jurisprudence to derive analytic principles suitable for the eligibility analysis of a gene. Contrary to the court's assertion that a "categorical rule" is created by a DNA-specific eligibility analysis, the law of nature analysis of patented genes is necessitated by the multidimensional nature of the gene, and it is a logical application of well-established eligibility criteria from this Court. Gene patenting results in the preemption of a law of nature, the genetic code, and, consequently, the isolated genes do not constitute patentable subject matter.

III. The Gene Has a General Patent Ineligibility As a Product of Nature

A. The Isolated Gene Retains a Natural Structure Dictated by Natural Function, and is Not Markedly Different from the Cellular Gene

When considering whether a genetically engineered bacterium became an invented product, the Court noted that the patentable subject matter inquiry must distinguish "between products of nature, whether living or not, and human-made inventions." *Chakrabarty*, 447 U.S. at 313. The distinction between a product of nature and an invented product was further defined by the Court when it recognized that an inventive conversion of a natural product would require the demonstration of "markedly different characteristics" in a claimed product. *Id.* at 310. The Court recognized that patent eligibility could be satisfied by a "product of human ingenuity" "having a distinctive name, character [and] use." *Id.* at 309-10.

In order to apply this Court's standard to the present case, the comparison of the "isolated DNA" in the

composition of matter claims on wild-type and mutant genes to the naturally occurring genes has two separate inquiries. Formally, these are the questions of structure and function. Is the isolated DNA structurally identical to the native gene? Does the isolated DNA function in the same manner as the native gene? However, these questions converge for DNA. The structure of the isolated DNA of the patent claims is not chosen, and certainly not invented, but required - because it will provide the natural function of the gene.

Structure and function converge in the patent claims at issue. Claim 1 of U.S. Patent No. 5,747,282 is representative of this convergence when it claims "an isolated DNA coding for a BRCA1 polypeptide" – claiming a molecule with a structure that will allow it to execute its normal function, which is to encode the BRCA1 protein. The patent claim simply "reports" that a particular DNA sequence encodes the amino acid sequence that constitutes a natural protein.

The isolated DNA of the patent claims is a product of nature's design. While Claim 1 of U.S. Patent No. 5,747,282 reports a DNA sequence defined by "coding," other challenged claims report DNA coding sequences written in complementary DNA (cDNA) format (*e.g.*, Claim 2 of U.S. Patent No. 5,747,282). A purified gene is often claimed as an isolated cDNA - the abbreviated, message-bearing form of the gene. Alberts et al., Molecular Biology of the Cell, at 503. The cDNA molecule is produced by routine, conventional laboratory protocols. Jonathan Pevsner, Bioinformatics and Functional Genomics 302, 2nd edition (2009). The goal of recovering the gene sequence as a cDNA is to preserve the "natural"

informational content of the molecule so that it is identical to the native gene. The patents in this case document the functional identity - and therefore structural identity - of the isolated BRCA1 DNA to native genes, describing "a sequence which is either derived from, or substantially similar to a *natural* BRCA1-encoding gene," U.S. Patent No. 5,747,282, column 19, lines 45-46 (italics added); the identity of isolated BRCA2 DNA to the native genes is noted by "a sequence which is either derived from, or substantially similar to a *natural* BRCA2-encoding gene," U.S. Patent No. 5,837,492, column 18, lines 30-31 (italics added). Those statements simply report that structure will implement function for the isolated DNA molecules, and that the function is nothing more than the mechanical reproduction of nature's blueprint. This conclusion applies to all challenged patent claims – whether primarily defined by function ("coding for") or primarily defined by structure (cDNA). All such claims have identical effect, which is to claim patent rights on a naturally occurring BRCA1 or BRCA2 gene. In fact, any deviation from the natural DNA sequence would compromise the use of the isolated DNA as the functional equivalent of the cellular gene, as the patented molecules provide the foundation for Myriad's BRCA1 and BRCA2 genetic tests. The mimicry of the native gene undermines any assertion that an inventive alteration has occurred.

In *Funk Bros.*, this Court considered whether the repackaging of natural bacterial strains in a mixed inoculant created a patent-eligible product. The Court concluded that neither structure or function were altered in the claimed bacterial product: "The bacteria perform in their natural way. 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." *Funk Bros.,* 333 U.S. at 131. By analogy, the isolated genes retain a structure that allows their natural function to be maintained, and "serve the ends nature originally provided." *Id.* They are products of nature, and cannot be patented.

B. There is No Inventive Conversion of the Isolated Gene, and it Remains an Unpatentable Product of Nature

The tests derived from this Court's jurisprudence for identifying an unpatentable product of nature focus on difference. The "markedly different characteristics" required by *Chakrabarty* are further amplified with reference to "having a distinctive name, character [and] use." *Chakrabarty*, 447 U.S. at 309-310. *Funk Bros.* examined the properties of the claimed bacterial inoculant to determine if they reflected any inventive input. "The qualities of these bacteria, like the heat of the sun, electricity, or the qualities of metals, are part of the storehouse of knowledge of all men. They are manifestations of laws of nature, free to all men and reserved exclusively to none." *Funk Bros.,* 333 U.S. at 130. The Court stated that the inventor had simply made a "discovery of some of the handiwork of nature." *Id.* at 131. No human intervention accounted for the properties exhibited by the bacteria, and the Court did not conflate discovery with invention.

In *American Fruit Growers, Inc. v. Brogdex Co.*, 283 U.S. 1 (1931), directed to a claimed invention of a chemically-treated orange, the Court decided that the

addition of borax to the rind of an orange to increase its longevity did not confer a patentable distinction, when compared to an unadulterated orange, to create an article of manufacture, stating that "[a]ddition of [the] borax to the rind of [the] natural fruit does not produce from the raw material an article for use which possesses a new or distinctive form, quality, or property." *Id.* at 11. The Court's cases suggest that the comparison of a claimed invention to a natural product must be comprehensive and thorough, and consider all relevant properties in determining whether an inventive conversion has been accomplished.

In view of these precedents, the Federal Circuit utilized an unduly narrow lens to compare the isolated DNA at issue with the naturally occurring genes. "We recognize that biologists may think of molecules in terms of their uses, but genes are in fact materials having a chemical nature and, as such, are best described in patents by their structures rather than by their functions." *Ass'n for Molecular Pathology*, 689 F.3d. at 1330. This statement ignores the fact that the patent claims themselves merge structure with function. Claim 1 of U.S. Patent No. 5,747,282 is representative of this convergence when it claims "an isolated DNA coding for a BRCA1 polypeptide." Claim 2 of the same patent claims a cDNA molecule - which has a structure solely defined by its functional coding requirements.

The analytic error of focusing on structure to the exclusion of function is compounded by an idiosyncratic definition of the structural features that are accorded inventive weight. "[I]n nature, the claimed isolated DNAs are covalently bonded to such other materials. Thus, when

cleaved, an isolated DNA molecule is not a purified form of a natural material, but a distinct chemical entity that is obtained by human intervention." *Id.* at 1329. The Federal Circuit erred in elevating the cleavage of a covalent bond during the excision of DNA into a transformative act that conferred patent eligibility. Instead, it is a routine technical operation that facilitates the removal of the gene from its native environment to an isolated state. Moreover, there is no basis in this Court's precedents for characterizing any specific chemical manipulation of natural subject matter as an eligibility-conferring maneuver.

The comparative analysis from the Federal Circuit overlooks several features of the isolated DNA at issue. The chemical cleavage that produces an isolated gene is not a manipulation that alters the intrinsic properties of the isolated product. The isolated DNA retains the naturally occurring nucleotide sequence, which the appellate court did not regard as relevant. "[I]t is the distinctive nature of DNA molecules as isolated compositions of matter that determines their patent eligibility rather than their physiological use or benefit." *Id.* at 1330. When the court declared that "the patent eligibility of an isolated DNA is not negated because it has similar informational properties to a different, more complex natural material," it failed to credit the fact that all of the chemical processing of the claimed DNA was actually driven by a genetic objective: to recover an isolated gene with an intact informational character. *Id.* No inventive conversion can be detected when the objective is simply to capture the naturally occurring genetic template and transport it outside the cell, and such repackaging cannot confer patent eligibility to the natural product. The isolated gene is thus more

akin to the aggregated bacterial inoculant in *Funk Bros.*: "Even though it may have been the product of skill, it certainly was not the product of invention." *Funk Bros.*, 333 U.S. at 132.

The starting materials for the patent claims are the native BRCA1 and BRCA2 genes, and the processing that produces the claimed genes does not produce a nonnaturally occurring product, as both structure and function remain intact. There is no demonstration of the inventive conversion required by this Court for the patent eligibility of naturally-derived subject matter. As such, the isolated genes are products of nature, and do not constitute patentable subject matter.

IV. This Court's Precedent Requires That A Patent Not Exact More in Costs Than It Provides in Benefits

A. An Asymmetry Between Inventive Contribution and the Foreclosure of Innovation is Prohibited by *Mayo*

Just last year, in *Mayo*, this Court was very clear about the need to measure the potentially preemptive or inhibitory effect of a patent against the magnitude of any inventive contribution provided by its subject matter. "[T]he underlying functional concern here is a *relative* one: how much future innovation is foreclosed relative to the contribution of the inventor." *Mayo*, 132 S. Ct. at 1303 (italics in original). In the view of the Court, the most troubling scenario is presented when a patent involving a natural law or product but lacking any inventive contribution has an occlusive impact on technological innovation because it removes basic knowledge from

the public domain. "And so there is a danger that the grant of patents that tie up their use will inhibit future innovation premised upon them, a danger that becomes acute when a patented process amounts to no more than an instruction to 'apply the natural law,' or otherwise forecloses more future invention than the underlying discovery could reasonably justify." *Id.* at 1301. To apply the *Mayo* formulation, the inventive contribution must be assessed, and compared to any foreclosure of innovation, in order to identify illegitimate patenting that exacts more in costs than it provides in benefits. The need for symmetry has been noted by this Court before. "The Patent Clause itself reflects a balance between the need to encourage innovation and the avoidance of monopolies which stifle competition without any concomitant advance in the 'Progress of Science and useful Arts.'" *Bonito Boats v. Thunder Craft Boats*, 489 U.S. 141, 146 (1989).

Mayo further considered how the discovery of natural laws and products were affected by the availability of patent rights, rejecting any invitation to lessen inventive standards in order to stimulate scientific discovery. *Mayo* explicitly recognized that even if patenting were to encourage research into laws of nature and basic scientific principles, the cost of patenting basic scientific knowledge would still be too high: "These statements reflect the fact that, even though rewarding with patents those who discover new laws of nature and the like might well encourage their discovery, those laws and principles, considered generally, are 'the basic tools of scientific and technological work.'" *Mayo*, 132 S. Ct. at 1301 (quoting *Benson*, 409 U.S. at 67). Patent rights are reserved for truly inventive work, and patent claims to natural laws and products controvert both *Mayo* and the essential patent bargain. "A patent by its very nature is affected with a

public interest. As recognized by the Constitution, it is a special privilege designed to serve the public purpose of promoting the 'Progress of Science and useful Arts.'" *Precision Instrument Mfg. Co. v. Auto. Maint. Mach. Co.*, 324 U.S. 806, 816 (1944) (quoting U.S. CONST. art I, § 8, cl. 8).

The *Mayo* framework for granting patent rights for actual inventive achievement is broadly applicable to all patent claims, whether to products (*e.g.*, compositions of matter) or methods. Although *Mayo* was directed to the patent eligibility of method claims, the *Mayo* formulation is grounded in the underlying purposes of the patent system, and is not technology-specific or claim-dependent. Consequently, *Mayo*'s formulation can be squarely applied to the composition of matter claims at issue here.

B. Gene Patents Exemplify the Asymmetry Between Invention and Occlusion that *Mayo* Prohibits

The application of the *Mayo* formulation asks whether there is an inventive contribution that is commensurate with any foreclosure of innovation. In fact, this case reveals an acute asymmetry: the isolated BRCA1 and BRCA2 genes at issue are not invented, but the patenting of these genes has severely limited innovative development in the field of genetic testing, with adverse consequences for genetic medicine. Thus, this case is a paradigmatic illustration of the "danger" from illegitimate patenting that *Mayo* warned about.

First, as the foregoing analyses in *Parts II* and *III*, *supra*, have detailed, the "isolated DNA" claims are directed to or derived from naturally occurring wild-type

or mutant forms of the BRCA1 and BRCA2 genes or, in the case of patent claims on DNA fragments, have a scope that can include naturally occurring genes. The presentation of a native gene as an "isolated DNA" molecule in the patent claims is the result of routine, well-established protocols in the field of molecular biology that do not alter or enhance the naturally occurring DNA sequence of the gene, and are conceptually analogous to the additional steps in the invalidated *Mayo* method claims which "add nothing of significance to the laws of nature." *Mayo,* 132 S. Ct. at 1299. Because the "isolated DNA" retains natural structure and function, the patent claims capture products of nature and preempt a law of nature.

The genes are basic scientific tools which have no effective substitutes. Rochelle C. Dreyfuss and James P. Evans, *From Bilski Back to Benson: Preemption, Inventing Around and the Case of Genetic Diagnostics*, 63 Stan. L. Rev. 1349, 1371 (2011). This fact only heightens the importance of rectifying the fact that such singular tools of biological science have been captured by patenting despite the absence of an inventive justification. The absence of any inventive contribution in the challenged patent claims violates the Court's standard for patentable subject matter, and provides the first part of the analysis for the *Mayo* formulation.

Second, the *Mayo* formulation requires an assessment of whether any foreclosure of innovation is the result of the patent grant. The patenting of DNA – as genes – removes critical scientific tools from widespread use in research and medicine by genetic scientists and medical practitioners, with adverse consequences for patients. The BRCA1 and BRCA2 genetic testing field is a signature

example of how unjustified patent claims have exerted undue weight in limiting the development of breast cancer and ovarian cancer genetic medicine. The record in this case is replete with instances where scientists had to abandon the offering of genetic testing services, doctors could not provide genetic information as a part of medical care, and patients encountered limited or faulty genetic testing options for the BRCA1 and BRCA2 genes, all as a result of the restrictive climate created by these patents. *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office*, 702 F. Supp. 2d 181, 205-207 (S.D.N.Y. 2010).

Genetic testing can be used to identify disease susceptibility, to establish diagnostic status, and to design personalized therapeutic regimens in medical care. Restrictive management of gene patents with critical diagnostic significance limits peer assessment, and reduces the available testing options for patients. Robert Cook Deegan et al., *Impact of Gene Patents and Licensing Practices on Access to Genetic Testing for Inherited Susceptibility to Cancer: Comparing Breast and Ovarian Cancers with Colon Cancers*, 12 Genetics in Medicine S15 (2010).

When a patent holder dominates a clinical field as the sole provider of genetic testing services, as Myriad has done for the BRCA1 and BRCA2 genes, patients are adversely affected. "Where patents and licensing practices have created a sole provider of a genetic test, patient access to those tests has suffered in a number of ways." The Secretary's Advisory Committee on Genetics, Health and Society (SACGHS), *Gene Patents and Licensing Practices and Their Impact on Patient Access*

to Genetic Tests 3 (2010) [hereinafter "SACGHS"]. If the sole commercial provider of a particular genetic test does not offer a comprehensive genetic analysis, the test will not provide the most accurate assessment of genetic status, and compensatory genetic testing to correct deficiencies may be prohibited by the patent holder. An artificially constrained genetic testing climate can result in patients receiving incomplete test results that cannot be relied on for medical decision making. *Ass'n for Molecular Pathology,* 702 F. Supp. 2d at 206.

Myriad's limitations on commercial genetic testing for the BRCA1 and BRCA2 genes to determine the risk of hereditary breast and ovarian cancer have limited the ability of women to seek second opinions or confirmatory analysis of laboratory results. *Id.* at 207. This scenario is even more troubling because some of the patients receiving BRCA1 and BRCA2 genetic testing from Myriad had genetic mutations that were not detected by Myriad's testing protocols, and these women received false negative test results. Tom Walsh et al., *Spectrum of Mutations in BRCA1, BRCA2, CHEK2, and TP53 in Families at High Risk of Breast Cancer*, 295 J. Am. Med. Ass'n 1379, 1386 (2006). Where exclusive control of the relevant patent portfolio for a particular disease field has frustrated a competitive genetic testing environment - as is the case for the BRCA1 and BRCA2 genes - the consequences for patients are very real. The clinical standard of care becomes a function of the marketplace, rather than the laboratory, commercial objectives trump scientific merit, and patients encounter a distorted set of options for medical care. Eileen M. Kane, *Patent-Mediated Standards in Genetic Testing*, 2008 Utah L. Rev. 835, 849. This outcome highlights the importance of

the patent eligibility questions posed by this litigation, and validates *Mayo*'s persistent focus on a cost-benefit analysis to determine the legitimacy of a patent grant.

It has been argued that gene patents are necessary to incentivize genetic research and the development of genetic tests. *Ass'n for Molecular Pathology*, 702 F. Supp. 2d at 211. The SACGHS undertook a comprehensive analysis on the need for and impact of patents affecting genetic testing, and asked whether the availability of patent rights stimulates scientific curiosity and engagement in genetic science. "[T]his information suggests that scientists are motivated to conduct genetic research by reasons other than patents, suggesting that discoveries will be sought regardless of the availability of intellectual property rights." SACGHS at 23. According to the SACGHS, the steady march of genetic research was not a patent-induced phenomenon. "[P]atents are not needed for much of U.S. basic genetic research to occur." *Id.* at 2.

Are gene patents essential for encouraging the development of in-house genetic testing services by commercial laboratories, such as for the BRCA1 and BRCA2 genetic tests? The SACGHS concluded that they were not. "[P]atent derived exclusive rights are neither necessary nor sufficient conditions for the development of genetic test kits and laboratory-developed tests. In the area of laboratory-developed tests particularly, where development costs are not substantial, patents were not necessary for the development of several genetic tests." *Id.* at 35. The genetic tests offered by Myriad fall into the latter category of laboratory-developed tests. Any assertions that the invalidation of gene patents will have devastating consequences on biomedical innovation

cannot be reconciled with the empirical research demonstrating that gene patents do not incentivize much of the progress in genetic science and are not critical for the commercialization of testing services.

The lack of incentives provided by gene patents does not equate to an absence of impact when they have been granted. Gene patents, although unnecessary, are costly. This paradox only magnifies the harm created by the patenting of genes. Petitioners have amply demonstrated the limitations on research and patient care that have been created with the issuance of the BRCA1 and BRCA2 gene patents. Illegitimate gene patent claims in force have constrained the set of knowledge tools in the public domain, a consequence that has foreclosed innovation in the genetic testing field by imposition of a chilling effect. That was documented by the SACGHS in its review of Myriad's impact on the legal climate in which genetic research takes place. "Myriad therefore cannot fully elude responsibility for any chilling effect on research, because the company could fully anticipate that others would refrain from research for fear of being sued for infringement." SACGHS at A-27.

The concerns over the inhibitory effects of gene patenting received Congressional attention during the enactment of the America Invents Act of 2011 (AIA), Pub. L. 112–29 (2011). As a consequence, the AIA included a mandate that directed the United States Patent and Trademark Office to undertake a study on "effective ways to provide independent, confirming genetic diagnostic test activity where gene patents and exclusive licensing for primary genetic diagnostic tests exist." *Id.*, Section 27. Congress specifically asked for an assessment of "the impact that the current lack of independent second opinion

testing has had on the ability to provide the highest level of medical care to patients and recipients of genetic diagnostic testing, and on inhibiting innovation to existing testing and diagnoses." *Id*. Legislative scrutiny of the consequences from issuing a specific class of patents – on human genes - is further evidence that such patents have an undue adverse impact on medical care.

The application of *Mayo's* formulation for identifying illegitimate patenting (invention vs. occlusion) leads to the inescapable conclusion that gene patenting has demonstrable costs, while failing to provide commensurate benefits. Moreover, available evidence has failed to document that gene patents have provided critical incentives for genetic medicine, further compounding the error of granting such patents. Gene patenting exhibits the asymmetry that *Mayo* warned about: the absence of any inventive contribution is coupled with a damaging effect on the ability of scientists and medical practitioners to freely utilize the most basic discoveries of genetic science, with adverse consequences for the development of innovative advances in genetic medicine.

The toll exacted on genetic science and medicine from the grant of illegitimate gene patents can be reversed by this Court's invalidation of the gene patent claims. Although both the executive branch (SACGHS) and the legislative branch (Congress) of the U.S. government have contended with limiting the harm created by gene patenting, this Court has the authority to squarely address the validity of gene patents by performing an exacting eligibility analysis of the challenged patent claims, using the standards that have been developed to define the boundaries of the patent system. While bioethical and human rights objections have been raised to the patenting of genes,

it is clear that this Court's jurisprudence provides the basis for declaring that the discoveries of genetic science, including human genes, cannot be patented, in view of the law of nature and product of nature exclusions. The Court has an opportunity to restore the set of "basic tools" for genetic science, and to invalidate gene patenting for the benefit of scientists, medical practitioners, and patients who wish to use isolated genes in research and medical care. This Court's precise application of 35 U.S.C. § 101 will allow creative applications of fundamental knowledge to emerge and legitimately solicit legal protection, and ensure that the intellectual substrates for genetic science remain unowned.

CONCLUSION

For the foregoing reasons, the Court should reaffirm that patents may not issue for laws of nature or products of nature, and hold that the violation of these prohibitions invalidates patent claims to human genes under 35 U.S.C. § 101.

Respectfully submitted,

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