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

AMICI CURIAE BRIEF FOR ACADEMICS IN LAW, MEDICINE, HEALTH POLICY AND CLINICAL GENETICS IN SUPPORT OF NEITHER PARTY

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INTEREST OF THE *AMICI CURIAE*[1]

Amici Curiae are academics in law, medicine, health policy and clinical genetics. Collectively, they have advised governments in the United States, Canada, South Africa, the United Kingdom and Australia, as well as international organizations including the Organisation for Economic Co-operation and Development (OECD), the European Union and the World Health Organization on human gene patents and life science innovation. Specifically, they chaired a task force of the Secretary's Advisory Committee on Genetics, Health and Society on human gene patents, testified before Congress on genetic testing, drafted guidelines for the OECD on the licensing of genetic inventions, prepared a report for the OECD on intellectual property management in the life sciences, prepared Opinions for the European Commission on intellectual property issues in life sciences, drafted reports for the U.S. Congress, prepared multiple case studies on gene patenting in the United States and prepared submissions for Australian law reform inquiries into gene patenting.

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1. The petitioners have filed a letter of blanket consent to filing *amicus* briefs and this letter is lodged with the Clerk. The respondents granted consent to *amici* on January 9, 2013 via electronic mail. Pursuant to this Court's Rule 37.6, the *amici* submitting this brief and their counsel hereby represent that no party to this case nor their counsel authored this brief in whole or in part, and that no person other than *amici*, using research funds provided by Value Addition through Genomics and GE3LS (VALGEN), paid for or made a monetary contribution toward the preparation and submission of this brief.

has authored an extensive case study of Myriad Genetics and its patenting policies and was the Expert Consultant who drafted the OECD Guidelines on the Licensing of Genetic Inventions. He practiced law in the areas of intellectual property licensing and financing of small to medium-sized technology companies and has provided judicial education in the United States, Canada and France on questions of intellectual property, property and the life sciences. He also heads intellectual property and technology transfer research within the Value Addition through Genomics and GE3LS (VALGEN), a publicly financed research project on agriculture and crop biotechnology and is co-lead of intellectual property within a Genome Canada funded project on commercialization and personalized medicine.

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Dr. Dianne Nicol, Ph.D., L.L.M., is a Professor of Law in the Faculty of Law at the University of Tasmania, Australia and Deputy Director of the Centre for Law and Genetics, based at the University of Tasmania. She has conducted research and written extensively on intellectual property in biotechnology and commercialization of biomedical research.

SUMMARY OF ARGUMENT

The *BRCA1* and *BRCA2* genes, the patent-eligibility of which is contested in this case, are sequences of DNA that specify the production of protein molecules involved in detecting and repairing DNA damage. All human genes are made of molecules of deoxyribonucleic acid (DNA) that are transcribed into ribonucleic acid (RNA). DNA is the chemical storage and transmission medium of genetic information. It stores information within cells and it transmits genetic information from cell to cell, organism to organism, and generation to generation. RNA is a molecule that is essential in the translation of genetic information into proteins and possesses several regulatory functions within cells. The impugned composition-of-matter claims in this case thus constitute human genes as they claim the concrete embodiments of those genes.

This Court has recognized that 35 U.S.C. § 101 contains a single exception to patentable subject matter that comprises three components: laws of nature, abstract ideas and phenomena of nature. While *Mayo v. Prometheus*, 132 S.Ct. 1289 (2012) is this Court's latest

statement on the purpose and nature of this exception, it builds on a century and a half of consistent jurisprudence. According to *Mayo,* this exception is crucial to achieving the overarching aim of patent law to facilitate rather than inhibit innovation.

Mayo builds on *Diamond v. Chakrabarty,* 447 U.S. 303 (1980), which distinguished between claims to naturally occurring compounds and claims to inventions. According to *Chakrabarty*, to constitute an invention constituting patentable subject matter, the claimed compound must possess a 'markedly different' function than does the natural compound.

DNA inherently possesses a dual nature that has a decisive impact in determining whether the claimed inventions are 'markedly different' from their natural counterparts. First, DNA is the embodiment of information in the order of its base pairs, forming a quaternary code analogous to the binary code used in computer software. Second, it is a physical chemical with bonds, folding and other physical characteristics that determine its biochemical properties. The reduction of DNA to either a chemical or to pure information—and thus ignoring its dual nature—has led courts below, the parties and commentators to misapply the 'markedly different' test.

Because one of the natural functions of DNA and RNA is to store and transmit information, a 'markedly different' function must be something beyond these. Yet, the specification does not recite any such function in relation to many of the molecules falling within the impugned claims.

Further, the impugned claims attempt to capture the genetic information embodied within human genes. In fact, the specification specifically recites the use of the invention to retrieve this information. Information does not, however, constitute patentable subject matter under precedents of both this Court and of the Federal Circuit.

This Court held in *Diamond v. Diehr*, 450 U.S. 175 (1981) that the addition of insignificant post-solution activity does not convert a claim over unpatentable subject matter into one that was eligible for patent protection. Isolating a human gene is an example of such insignificant post-solution activity. Moreover, in the context of diagnostics, isolation is merely a byproduct of the real purpose, which is to exactly copy the information stored in a person's DNA. While the step of isolation may require technical skill, the legal test of significance of the activity is based on whether the activity itself gives a markedly different function to the invention. When the purpose of creating a DNA molecule is to reveal the genetic information it embodies—as is the case when conducting diagnostic tests or in doing science to study the *BRCA1/2* genes—isolation does not provide any additional function to a gene beyond its natural information storage function. Therefore, making an exact copy and 'isolating' the DNA is not sufficient in itself to convert the copied DNA into a patentable invention. In addition, claims over human genes that possess no function beyond their ability to store the *natural* genetic information recorded on human genes cannot be patented.

In constrast, both natural and altered DNA and RNA that possess functions beyond information storage and transmission are eligible for patent protection. To claim

naturally-occurring isolated sequences, patent claims would need to be restricted to the use of the molecule for the additional function. For altered DNA and RNA molecules, the invention can normally be protected using composition-of-matter claims, provided they also satisfy §§ 102, 103, and 112 as well as § 101 utility.

ARGUMENT

The question before this Court—are human genes patentable?—asks whether and under which circumstances the molecular unit of human heredity, in the form of strands of deoxyribonucleic acid (DNA) and/or ribonucleic acid (RNA) (*see* Helen Pearson, *Genetics: What is a Gene?*, 441 NATURE 398 (2006)), constitute patentable subject matter under 35 U.S.C. § 101. DNA strands may contain the sequence of entire human genes without any deletions or editorial changes (genomic DNA or gDNA), sequences of messenger RNA that correspond (through transcription) to that gDNA, sequences of DNA that (through reverse transcription) correspond to the messenger RNA that is translated into proteins by cellular ribosomal complexes (complementary DNA or cDNA), and smaller strands of either DNA or RNA.

In the context of the present case, nine patent claims fall within the above understanding of human genes: claims 1, 2, 5, 6 and 7 of the 5,747,282 patent ('282 patent), claims 1, 6 and 7 of the 5,837,492 patent ('492 patent) and claim 1 of the 5,693,473 patent ('473 patent). These claims read, collectively, over gDNA sequences, cDNA sequences and RNA sequences, ranging in length from 15 base pairs to the entire, unedited, gene sequence for *BRCA1* and *BRCA2*.

While the context in which this case is set—health care innovation—demonstrates the social and ethical importance of the question before the Court, its answer can be determined solely on the basis of this Court's precedents on patent eligibility that stretch back well over a century. The latest of these, *Mayo v. Prometheus*, 132 S.Ct. 1289 (2012), is simply the most recent in a long and consistent line of jurisprudence.

The Effect of Broad Claims over Human Genes on Innovation

While perhaps more socially and politically charged than most patent law issues (*See, e.g.*, E. Richard Gold & Julia Carbone, *Myriad Genetics: In the Eye of the Policy Storm,* 12 (4) GENETICS MED. S39 (2010) (April supplement)), legal controversies over the patenting of human genes can be resolved through the application of this Court's precedents. Peter Yun-Hyoung Lee, *Inverting the Logic of Scientific Discovery: Applying Common Law Patentable Subject Matter Doctrine to Constrain Patents on Biotechnology Research Tools,* 19 HARV. J.L. & TECH. 79, 82 (2005).

Nowhere is the impact of broad claims over human genes more evident than in the field of human genetic testing. In a study of US and European patents affecting such testing, researchers found that, out of the 22 inherited diseases studied, 16 diseases are subject to at least one blocking patent. Isabelle Huys, *et al.*, *Legal Uncertainty in the Area of Genetic Diagnostic Testing,* 27 NATURE BIOTECHNOLOGY 903, 904 (2009).

Recent advances in DNA sequencing have led to a dramatic increase in the efficiency and scope of genetic

testing. Yet the grant of patents over human genes has impeded innovation in this domain. This problem has emerged in developing a new and more comprehensive approach to test those at risk of breast and ovarian cancer. 'Deep sequencing' tests of over twenty genes are comparable in cost to the two-gene *BRCA1/2* sequence-based test offered by the Respondents. Tom Walsh et al., *Detection of Inherited Mutations for Breast and Ovarian Cancer Using Genomic Capture and Massively Parallel Sequencing*, 107 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES 12629, 12631 (2010). Commercial laboratories have begun to offer comprehensive genetic testing in a single test of almost all genes—that notably leaves out *BRCA1/2*, the human genes subject to the claims in question—that may explain inherited risk of breast or ovarian cancer.

For example, Ambry Genetics, a commercial diagnostic genetics laboratory, recently began offering sequencing of a panel of cancer genes. AMBRY GENETICS http://www.ambrygen.com/tests/breastnext (last visited December 13, 2012). The Ambry Genetics panel has the potential to be a very useful clinical test but its utility is severely undermined by the fact that the Ambry Genetics panel does not include *BRCA1/2*. These exclusions are attributable to infringement liability from the patents at issue in this case. The lack of coverage of *BRCA1/2* forces a clinician to order two expensive tests serially from two different providers when one comprehensive test would not only be less expensive, but provide more timely results to patients. As the Respondents have never licensed the sequence-based testing of *BRCA1/2* (although they have licensed testing for known individual mutations, a distinction often incompletely explained by Respondents) Respondents' patents prevent the

development of a comprehensive sequence-based test of the twenty-some known genes associated with breast and ovarian cancer. While cross-licensing would theoretically enable the development of truly comprehensive tests, the industry has failed to engage in this practice for more than a decade, preferring instead to maximize revenue from single genetic tests.

In developing diagnostic tests, patent incentives play a much smaller role than in drug discovery or therapeutic biological molecules: "[P]atents have not caused irreparable harm in genetic diagnostics, but neither have they proven greatly advantageous . . . One justification for gene patents is that they speed up the development of tests. But the patent incentive is usually not necessary." Robert Cook-Deegan et al., *The Dangers of Diagnostic Monopolies,* 458 NATURE 405, 405 (2009). Out of 10 clinical conditions studied, researchers found that "in no case was the exclusive licensee [with control over the patents] the first to market." Julia Carbone et al., *DNA Patents and Diagnosis: Not a Pretty Picture,* 28 NATURE BIOTECHNOLOGY 784, 788 (2010).

This is not to say that patents have no place in the field of genetic diagnostics. In two of ten clinical conditions studied (Mercator Genetics for hemochromatosis and Myriad Genetics for breast and ovarian cancer), researchers at Duke University found that patents played a positive role in enticing private investment to supplement the public investment in genetics research. 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); Subhashini Chandrasekharan, et al., *Impact of Gene Patents and Licensing Practices on Access to Genetic Testing for Hereditary Hemochromatosis,* 12 Genetics in Medicine S155 (2010). Despite positive outcomes being in the minority, these two cases illustrate that patents can contribute to health innovation.

The key to preserving the benefits of patents while avoiding their costs is to develop a sufficiently clear bright-line rule, as suggested by *Mayo,* 132 S.Ct. at 1303, that differentiates unpatentable human genes that inhibit innovation from 'markedly different' inventions that facilitate it. Thus, the question is *not* whether the Respondents ought to receive a patent for their work; the answer to that question is likely 'yes'. Rather, the question is whether the Respondents claimed too broadly so as not only to claim their contributions to health and science but also to exclusively control any study and use of the natural function of human genes.

A Question of Law, Not Science

This Court specifically warned against conflating legal and scientific determinations in *Diamond v. Chakrabarty,* 447 U.S. 303 (1980) and in *Mayo.* In both cases, this Court held that its role was limited to making legal determinations and not the subtle parsing of scientific knowledge and opinion.

In *Chakrabarty*, the petitioner asked the Court to resist granting a patent over a genetically-created bacterium because "[s]cientists, among them Nobel laureates. . . [suggest] that genetic research may pose a serious threat to the human race, or, at the very least,

that the dangers are far too substantial to permit such research to proceed apace at this time." *Chakrabarty,* 447 U.S. at 316. This Court held that its role was to provide a legal interpretation of the patent statute, not to engage in science: "What is more important is that we are without competence to entertain these arguments—either to brush them aside as fantasies generated by fear of the unknown, or to act on them." *Chakrabarty,* 447 U.S. at 317.

Similarly, in *Mayo*, this Court held that the determination of the scope of exceptions to patentable subject matter under § 101 was a legal question, not one that depended on a deep understanding of science: "Courts and judges are not institutionally well suited to making the kinds of judgments needed to distinguish among different laws of nature. And so the 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." *Mayo,* 132 S.Ct. at 1303.

The Federal Circuit in the decision below conflated the legal question it posed—do isolated DNA molecules constitute patentable subject matter under § 101?—with the scientific determination of how one can isolate DNA molecules. For example, the majority stated as follows:

> As the above description indicates, isolated DNA is not just purified DNA. Purification makes pure what was the same material, but was combined, or contaminated, with other materials. Although isolated DNA is removed from its native cellular and chromosomal environment, it has also been manipulated

> chemically so as to produce a molecule that is markedly different from that which exists in the body.

Association for Molecular Pathology v. USPTO, 689 F.3d 1303, 1328 (Fed. Cir. 2012) ("*AMP v USPTO*").

> In this case, the claimed isolated DNA molecules do not exist in nature within a physical mixture to be purified. They have to be chemically cleaved from their native chemical combination with other genetic materials . . . . In fact, some forms of isolated DNA may require no purification at all, because DNAs can be chemically synthesized directly as isolated molecules.

AMP v. USPTO at 1329.

These passages reveal a troubling conflation of science and law (in addition to the mistake of reducing the claimed invention to the process through which the Federal Circuit speculated it may have been produced). Rather than determine whether the claimed invention falls within the *legal* meaning of invention under § 101, the Federal Circuit answered the question of whether a scientist would use the same processes to *isolate* as to *purify* DNA molecules. The result of this approach was for the Federal Circuit, the actor entrusted with the duty to determine the legal question posed by § 101, to delegate its determination of patent eligibility to scientists and their processes.

There are two strong prudential reasons why this Court in both *Chakrabarty* and *Mayo* held that it was inappropriate to engage in a fine analysis of science when

answering the legal question of whether a purported invention constitutes patentable subject matter.

First, determinations of patent-eligibility do not change over time but become established standards in the law. They do not, in particular, depend on the state of knowledge available to the person of skill in the art, whether at the moment of invention, of filing, of patent grant or of claim construction. As scientific knowledge undergoes rapid change, it is inappropriate to link a determination of patent eligibility to the particular understanding of the science at any one moment because that understanding could soon be out of date.

Second, as the decision of the majority in the Federal Circuit illustrates, deciding questions of patent eligibility on the basis of the science—or the particular technical procedural arcana of purification or isolation—leads courts to engage in speculative assessments of the state of scientific knowledge. Because subject matter eligibility is a pure question of law, the courts are not assisted by expert evidence in these determinations and thus must make their own findings about the science involved. This is precisely the confusion that the Federal Circuit introduced in the present case.

The majority opinion in the Federal Circuit misunderstood a seminal 1960s text on chemistry to hold that the defining characteristic of the DNA molecule is its set of *covalent* bonds. ("But a covalent bond is the defining boundary between one molecule and another, and the dissent's citation of Linus Pauling's comment that covalent bonds 'make it convenient for the chemist to consider [the aggregate] as an independent molecular

species' underlines the point." *AMP. v. USPTO* at 1329.) The correct citation of the text reveals, however, that the defining characteristic of a molecule is a *chemical* bond, which includes "electrostatic bonds [which encompass both ionic and hydrogen bonds], covalent bonds and metallic bonds." Linus Pauling, The Nature of the Chemical Bond and the Structure of Molecules and Crystals: An Introduction to Modern Structural Chemistry 5 (3d ed. 1960). Thus, a covalent bond in the Pauling text is but one type of chemical bond that defines a molecule. The result of this misreading of the Pauling text was that the Federal Circuit majority focused exclusively on covalent bonds, when electrostatic bonds play at least as critical a role in the function of DNA as the unique storage and transmission medium of biological information.

Because of this Court's concerns over separating legal from scientific questions, it held, in *Mayo,* 132 S.Ct. at 1305, that courts ought not to engage in too fine an analysis of the science underlying the exceptions to patentability even if this results in different effects in different fields of technology. With this caution in mind, we turn to this Court's elucidation of the exception to patentable subject matter in § 101.

A Single Exception Residing in 35 U.S.C. § 101

This Court has many times recognized that there are limits to the scope of § 101. It has encapsulated these in a judicially-elaborated exception relating to laws of nature, natural phenomena and abstract ideas (e.g., *Mayo; Bilski v. Kappos*, 130 S. Ct. 3218 (2010); *Diamond v. Diehr*, 450 U.S. 175 (1981); *Chakrabarty,* 447 U.S.; *Gottschalk v. Benson*, 409 U.S. 63 (1972); *Parker v. Flook*, 437 U.S. 584

(1978); *Rubber Tip Pencil Company v. Howard*, 87 U.S. 498 (1874); *LeRoy v. Tatham*, 55 U.S. 156 (1852); *O'Reilly v. Morse* 56 U.S. (15 How.) 62 (1853)). In particular, this Court in *Mayo* provided a clear and straightforward understanding of the independent role played by this exception. This understanding has four elements.

First, *Mayo* brushed aside any uncertainties introduced by the Federal Circuit (*MySpace Inc., v. GraphOn Corp.*, 672 F.3d 1250 (2012)) over whether a § 101 determination of patentable subject matter must take place prior to any §§ 102, 103, and 112 or § 101 utility analyses. ("These considerations lead us to decline the Government's invitation to substitute §§ 102, 103, and 112 inquiries for the better established inquiry under § 101." *Mayo,* 132 S.Ct. at 1304.) "[T]o shift the patent-eligibility inquiry entirely to these later sections risks creating significantly greater legal uncertainty, while assuming that those sections can do work that they are not equipped to do." *Mayo,* 132 S.Ct. at 1304. That is, *Mayo* made clear that determination of patent-eligibility is the first step in the analysis of the validity of any patent claim. While for most claims this step is so evident that it can effectively be skipped, courts must logically determine whether the claim reads over a patent-eligible invention before determining whether that invention complies with the substantive criteria of novelty, utility and obviousness, as well as those relating to description and enablement.

Second, § 101 implicitly contains *one* overarching exception with three components—laws of nature, natural phenomena and abstract ideas—and not three distinct exceptions. ("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." *Mayo,* 132 S.Ct. at 1293, citations omitted, emphasis added.) The three components are simply different ways to address aspects of one central, principled exception rather than constituting three, narrow, watertight and independent exceptions. This is illustrated in *Mayo* by the Court's reliance on cases falling into each of the three components (*O'Reilly v. Morse*, (15 How.) 62 (1854) with respect to laws of nature; *Funk Brothers Seed Col v. Kalo Inoculant Col*, 333 U.S. 127 (1948) and *Chakrabarty* regarding natural phenomena; *Diamond v. Diehr*, 450 U.S. 175 (1981), *Parker v. Flook*, 437 U.S. 584 (1978), and *Bilski v. Kappos*, 130 S.Ct. 3218 (2010) dealing with abstract ideas) to elucidate the central purpose underlying the exception. In fact, the *Mayo* Court held that two cases, *Diehr* and *Flook*, both of which relate to *abstract ideas*, were "most directly on point" in relation to the *law of nature* at issue in *Mayo*. *Mayo,* 132 S.Ct. at 1298.

Third, the underlying purpose behind the exception is to avoid the "danger that the grant of patents that tie up [the] use [of laws and principles] 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." *Mayo,* 132 S.Ct. at 1301, citations omitted. The Court recognized that patent law must consider both the facilitative and inhibitory effects of patents so as to maximize innovation:

> Patent protection is, after all, a two-edged sword. On the one hand, the promise of exclusive

> rights provides monetary incentives that lead to creation, invention, and discovery. On the other hand, that very exclusivity can impede the flow of information that might permit, indeed spur, invention, by, for example, raising the price of using the patented ideas once created, requiring potential users to conduct costly and time-consuming searches of existing patents and pending patent applications, and requiring the negotiation of complex licensing arrangements.

Mayo, 132 S.Ct. at 1305.

Fourth, the exception flows from the policy inherent in the patent laws as passed by Congress, not from definitions and concepts deriving from particular branches of science. ("[P]atent law's general rules must govern inventive activity in many different fields of human endeavor, with the result that the practical effects of rules that reflect a general effort to balance these considerations may differ from one field to another." *Mayo,* 132 S.Ct. at 1305). That is, the determination of patent eligibility is, as argued earlier, a pure question of law and not one that ought be delegated to scientists or technicians.

As the question of the patent-eligibility of human genes has never been directly raised, the application of this unitary principle (with three components) to the claims in issue provides a straightforward means of answering that question.

'Markedly Different' Refers to Functional Difference

Mayo made clear that there is a single, underlying, purpose behind the judicially recognized exception to patent-eligibility under § 101: that claims may not encompass so much intellectual territory that they diminish, as opposed to facilitate, the flow of information that is essential to further innovation. While stated using contemporary language, this purpose has long been embedded in this Court's decisions concerning all three facets of the exception.

This Court's elucidation of the exception in *Chakrabarty* embodies this purpose. There, this Court held that, to constitute patentable subject matter, the claimed invention must possess "markedly different characteristics from any found in nature". *Chakrabarty,* 447 U.S. at 310. In contrast to the claimed invention in *Funk Brothers*, which the *Chakrabarty* Court stated had no "different use" than what was found in nature, Chakrabarty's invention carried out a new and useful function. *Chakrabarty,* 447 U.S. at 310. ("This human-made. . . bacterium is capable of breaking down multiple components of crude oil. Because of this property, which is possessed by no naturally occurring bacteria, [the] invention is believed to have significant value. . . ." *Chakrabarty,* 447 U.S. at 305).

By focusing on the functional difference between the claimed invention and its natural counterpart, the *Chakrabarty* Court was able to distinguish between inventions that contributed to future innovation (those that have a markedly different function) and those that hindered innovation (those that tied up an important natural phenomenon that lay at the heart of a great swath of potential innovation).

It is through an understanding of this underlying purpose—as highlighted in *Mayo*—that it becomes clear that the *Chakrabarty* test is related to functional instead of simply structural differences between claimed inventions and their natural counterparts. While a structural difference will usually result in a functional difference, it is the functional and not the structural difference that meets the legal test of patent eligibility.

Applying *Chakrabarty* in light of *Mayo*, the question before the Court reduces to whether claims reading over human genes or parts of them are functionally different from those same genes occurring in their natural form. Where the function of the claimed invention is 'markedly different' from that of the natural counterpart, it is patent-eligible; where the claimed invention carries out the same function as the natural counterpart, it is not.

DNA's Dual Nature

DNA inherently has a dual nature. It is both a molecule and medium for storing genetic information for operations within a cell and transmitting that information from cell to cell, organism to organism, and generation to generation: "DNA sequences are not simply molecules; they are also information. Knowing the DNA sequence for the genome of an organism provides valuable scientific information that can open the door to future discoveries." Rebecca S. Eisenberg, *How Can You Patent Genes?*, 2 Am. J. Bioethics, 30 Nov. 2010, at 3, 4 (2002). Because of this duality, the granting of patents over DNA has been controversial with scientists, physicians and policy-makers: "[T]he central problem with human DNA sequence patents today is that they not only provide their

holders with control over the invention itself—the physical molecule—but also over access to the particular health information coded in individual genes." E. Richard Gold, *Gene Patents and Medical Access*, 49 INTELL. PROP. F. 20, 24 (2002).

Information is the building block of ideas and concepts. As such, information is understood not to constitute patentable subject matter:

> Patent rights are not well adapted to protecting information, particularly information about the natural world. Given that independent discovery of such information is quite likely to happen without the efforts of any particular patent holder, excessive protection of such information as intellectual property may slow down subsequent research more than it promotes the original data collection.

Rebecca S. Eisenberg, *Patenting Genome Research Tools and the Law*, 326 COMPTES RENDUS BIOLOGIES 1115, 1118 (2003); *see also In re Comiskey*, 554 F.3d 967, 978-980 (Fed. Cir. 2009).

An applicant cannot simply impose a new function on information by restricting the claim to a particular technological environment. *See, e.g.*, *Diamond v. Diehr*, 450 U.S. at 191 ("A mathematical formula as such is not accorded the protection of our patent laws, and this principle cannot be circumvented by attempting to limit the use of the formula to a particular technological environment.") (citations omitted).

Similarly, an applicant cannot turn an unpatentable claim to information into a patentable claim simply by limiting the invention to a particular medium without also indicating the additional function that embodying this information on that medium accomplishes. *See In re Bradley*, 600 F.2d 807, 812 (C.C.P.A. 1979). This conclusion is illustrated through a consideration of the 'printed matter' doctrine in *King Pharmaceuticals, Inc. v. Eon Labs, Inc.,* 616 F.3d 1267 (Fed. Cir. 2010).

"Roughly stated, [the 'printed matter' doctrine] dictates that 'information recorded in [a] substrate or medium' is not eligible for patent protection—regardless of how nonobvious and useful it is—if the advance over the prior art resides in the 'content of the information.'" Kevin E. Collins, *Semiotics 101: Taking the Printed Matter Doctrine Seriously,* 85 IND. L.J. 1379, 1380 (2010) ("*Semiotics 101*").

King Pharmaceuticals involved a claim to dispensing a known medicine while informing patients to take the medicine with food and another claim to dispensing that medicine in conjunction with a printed label that informed the patient to take the medicine with food. The Federal Circuit rejected both claims, noting that:

> In an analogous context, we have held that '[w]here the printed matter is not functionally related to the substrate, the printed matter will not distinguish the invention from the prior art in terms of patentability.' . . . In such cases, we have recognized that the printed matter is not independently patentable . . .

King Pharmaceuticals, 616 F.3d at 1278-79 (citations omitted).

The Federal Circuit held that there was no functional relationship between the information provided—to take the medicine with food—and the medicine itself. *Id.* at 1279.

While the information of taking medicine with food does not constitute patentable subject matter in itself, that information could result in a patentable invention if limited to an embodiment in a specific medium or to a context in which doing so has a functional advantage. This was the case in *In re Gulack,* 703 F.2d 1381 (Fed Cir. 1983), in which the Federal Circuit held as patentable an invention consisting of a series of numbers that, when printed on a circular band, served the function of educating about number theory. While the information itself was too abstract to be patented, that information when recorded on the particular medium served a specific function that neither the numbers themselves nor their being printed on another medium—for example, a sheet of paper—accomplished. *See Id.* at 1386-87.

Despite the fact that the *King Pharmaceuticals* Court applied the 'printed matter' doctrine under 35 U.S.C. § 103, the same analysis can be applied often more persuasively under 35 U.S.C. § 101. *See, e.g.*, *In re Nuijten*, 500 F.3d 1346, 1365 (Fed. Cir. 2007) (Linn, J., concurring-in-part and dissenting-in-part); *Semiotics 101* at 1380 n. 1 ("The Federal Circuit grounds the printed matter doctrine alternately in 35 U.S.C. §§ 101 & 103, but there is no principled basis for the statutory distinction").

One of the critical rulings in *King Pharmaceuticals* was the court's extension of the printed matter' doctrine to a large range of media:

> Although these 'printed matter' cases involved the addition of printed matter, such as written instructions, to a known product, we see no principled reason for limiting their reasoning to that specific factual context.

King Pharmaceuticals, 616 F.3d at 1279.

While information cannot be claimed *as* information, even when embodied in a medium, it is nonetheless clear that when the restriction of the information to a particular medium serves some function beyond imposing a physical limit on the claim, then the claim recites patentable subject matter:

> More than mere abstraction, the data structures are specific electrical or magnetic structural elements in a memory. According to Lowry, the data structures provide tangible benefits: data stored in accordance with the claimed data structures are more easily accessed, stored, and erased. . . . In short, Lowry's data structures are physical entities that provide increased efficiency in computer operation.

In re Lowry, 32 F.3d 1579, 1583-1584 (Fed. Cir. 1994).

When the invention involves information that is necessarily tied to the medium on which information is stored, as were the data structures in *In re Lowry*,

then the invention constitutes patentable subject matter under § 101. On the other hand, where the embodiment of information on a particular medium implies no particular function beyond holding the information it contains, then that limitation cannot save the claim from invalidity under § 101.

The case law thus treats the two aspects of human genes differently. To the extent that a claim reads over DNA or RNA that carries out the information storage and transmission function of a human gene, it does not constitute patentable subject matter. On the other hand, claims relating to DNA and RNA would satisfy the patentable subject matter test when the patent is directed to a biochemical function attached to the form of molecule claimed (*e.g.*, gDNA, RNA or cDNA) that goes beyond simple storage and transmission of the information encoded in the gene. For example, DNA (even if identical to a natural sequence) within a construct for gene therapy, inserted into a bacterium or other organism to produce a given protein, modified to have new characteristics, forming a replicon, tagged as a probe, or DNA injected into the body to encode proteins that elicit a vaccine response, would all have this additional function.

Isolation Constitutes Insignificant Post-solution Activity

Diehr further developed this Court's elaboration on the underlying purpose of the § 101 exception, particularly in relation to its discussion of *Parker v. Flook*, 437 U.S. 584 (1978). In *Flook*, the patent applicant claimed "a formula for computing an updated alarm limit," *Flook*, 437 U.S. at 586, to help an operator identify when to terminate a

chemical reaction. The *Diehr* Court explained that, while the applicant had argued that the calculation of the alarm limit was a critical component of the underlying chemical reaction, in reality, the alarm limit constituted nothing more than insignificant post-solution activity. *Diehr*, 450 U.S. at 191.

The Court's discussion of function and post-solution activity further reveals the workings of the § 101 exception:

> Similarly, insignificant post-solution activity will not transform an unpatentable principle into a patentable process. To hold otherwise would allow a competent draftsman to evade the recognized limitations on the type of subject matter eligible for patent protection. On the other hand, when a claim containing a mathematical formula implements or applies that formula in a structure or process which, when considered as a whole, *is performing a function which the patent laws were designed to protect* (*e. g.*, transforming or reducing an article to a different state or thing), then the claim satisfies the requirements of § 101.

Diehr, 450 U.S. at 191-192 (citations omitted; emphasis added).

It is thus not just any human intervention that converts a natural law, an abstract idea or (as in the present case) a phenomenon of nature into patentable subject matter: that human intervention must also result in a markedly different function. As *Chakrabarty* made clear, that function must be other than the function of

the phenomenon of nature; that is, in this case, it must be something other than the storage and transmission of genetic information.

The Federal Circuit placed much emphasis on the fact that the impugned claims were restricted to 'isolated' molecules:

> Accordingly, *BRCA1* and *BRCA2* in their isolated states are different molecules from DNA that exists in the body; isolated DNA results from human intervention to cleave or synthesize a discrete portion of a native chromosomal DNA, imparting on that isolated DNA a distinctive chemical identity as compared to native DNA.

AMP v. USPTO at 1328.

The majority in the Federal Circuit arrived at this conclusion not on the basis of applying the legal test of patentable subject matter as elucidated by this Court in *Mayo*, *Chakrabarty* and *Flook* but on the basis of its own, disputable, scientific inquiry into the process of isolating and synthesizing human genes. In ignoring the required inquiry into whether the step of isolation gives rise to a 'markedly different' function (*Chakrabarty,* 447 U.S. at 310) or a "function which the patent laws are designed to protect" (*Diehr,* 450 U.S. at 192), the Federal Circuit effectively substituted a 'chemical structural difference test' for the legal one. In doing so, it not only introduced a legal error but as noted earlier, in misunderstanding the scientific texts from which it quoted, scientific error as well.

To determine whether isolation of a human gene *by itself* introduces a markedly different function as required by *Chakrabarty* and *Diehr*, one must return to the natural function of those genes: to store and transmit information. Since isolation does nothing to alter or improve this function, the answer, following this Court's precedents, is clear: no.

The answer would be different if, in addition to isolation, a new function were introduced. DNA molecules used to treat a disease by gene transfer or to make a therapeutic protein would not be merely isolated but have an additional, patent-eligible, function. Here, however, the 'isolated' molecule, like the original, has no function beyond the storage and transmission of information.

In fact, the only function suggested in the specification of the '282 patent for an isolated, unaltered and unedited molecule of gDNA (as included within Claim 1 of that patent) is to extract the *information* stored on it. '282 Patent, col. 12, ll. 42-44 ("The finding of *BRCA1* mutations thus provides both diagnostic and prognostic *information*") (emphasis added); *Id.* at col. 28, ll. 26-28 ("Results of these tests and interpretive *information* are returned to the health care provider for communication to the tested individual") (emphasis added).

Beyond the fact that the specification does not suggest any function above the natural one of storing and transmitting information, any attempt to 'improve' the molecule by altering its sequence would make it useless for diagnostic purposes because it would no longer accurately convey the genetic information contained within the tested person's cells. Indeed, the only value to

the isolated molecule is that the sequence of base pairs exactly corresponds to that of the human gene in a specific person's cells. Modifying the molecule in any way destroys this correspondence and renders the molecule useless for diagnostic purposes. A purported 'invention' that cannot, even theoretically, improve on the underlying natural phenomenon can hardly be considered an invention.

While claiming an 'isolated' gDNA molecule implies there has been some type of human intervention, that intervention does not give rise to a 'markedly different' function as required by *Chakrabarty*. Rather, the intervention constitutes the type of insignificant post-solution activity so criticized in *Diehr*. The claim is, in substance, a claim to the information contained in the human gene masquerading as a composition-of-matter claim. Since a claim to information cannot be saved by limiting it to a particular storage medium, the addition of the requirement of isolation adds "insignificant post-solution activity" to an otherwise unpatentable claim. *Diehr,* 450 U.S. at 191.

Respondents assert, in both their brief to this Court prior to the grant of *certiorari*, and before the Federal Circuit, that claims over 'isolated' DNA molecules are sufficiently narrow in scope as to not prevent the use of currently available technologies to identify mutations such as whole genome sequencing. Yet, beyond the fact that its patents have prevented the development of new diagnostic tests such as the Ambry Genetics panel, this assertion has never been evaluated: "Because no court in the United States has ever addressed this issue head-on, it is impossible to entirely rule out the possibility that a court would interpret a claim to an

isolated DNA molecule in the extremely broad sense . . . " Christopher M. Holman, *Debunking the Myth that Whole-Genome Sequencing Infringes Thousands of Gene Patents*, 30 NATURE BIOTECHNOLOGY 240, 242 (2012). While Respondents have argued in these proceedings that the claims in issue do not prevent a number of general diagnostic approaches, they have not committed themselves to this position. Under the Federal Circuit's jurisprudence on issue estoppel, the Respondents will be free to argue that a particular diagnostic test falling within one of those general diagnostic approaches infringes on its claims. *SanDisk Corp. v. Memorex Products Inc.*, 415 F.3d 1278 at 1291 (Fed. Cir. 2005). Until a court has interpreted the Respondents' claims, one cannot be certain of their scope.

In addition, the Respondents' argument is not relevant. Simply because a post-solution activity, here isolation, restricts some, but not all, uses of human genes does not render it any more eligible for patent protection. As this Court warned in *Diehr*, the principle prohibiting patents on laws of nature, abstract ideas and phenomena of nature "cannot be circumvented by attempting to limit the use . . . to a particular technological environment." *Diehr*, 450 U.S. at 191. The question is not, therefore, which activities the Respondents say do not fall within the scope of their claims, but whether the Respondents have invented something that has a 'markedly-different' function from that which occurs in nature.

Where the patent applicant identifies a function in addition to that of information storage and transfer for an isolated but otherwise unaltered and unedited DNA or RNA molecule, the applicant is—provided the

invention also satisfies §§ 102, 103, and 112 and the utility requirement in § 101—entitled to a claim over the use of that molecule for that new function. Claims in this form provide the inventor with appropriate recognition for his or her contribution without encumbering future innovators with claims reading over the natural function of those molecules. That this is a rational and balanced solution is illustrated by the fact that both Germany and France, two important competitors in the world of health innovation, have arrived at this same position. Section 1a(4) of Germany's *Patentgesetz* (Patent Law), 1981 BGBI as amended, requires that claims reading over molecules identical to a whole or part of a human gene must be restricted to the specific utility (industrial application) identified by the inventor. Similarly, Article L611-18 of France's *Code de propriété intellectuelle* (Intellectual Property Code) limits a claim reading over a component of the human body, including the entire or partial sequence of a human gene, to the utility specified by the inventor.

Claims at Issue

Claim 1 of the '282 patent is illustrative of the composition of matter claims in this case. It claims: "An isolated DNA coding for a *BRCA1* polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2." SEQ ID NO:2 is the naturally occurring sequence of the protein encoded by the *BRCA1* gene. To interpret this claim, recourse must be made to the specification, which defines the term DNA and describes the functions attached to DNA. *In re Suitco Surface, Inc.*, 603 F.3d 1255, 1260 (Fed. Cir. 2010) ("Rather, claims should always be read in light of the specification and teachings in the underlying patent").

The specification demonstrates that the use of the term 'DNA' as used in Claim 1 refers to unaltered genomic DNA, cDNA and altered forms of both. '282 Patent, col. 19, ll. 51-56. ("The polynucleotide compositions of this invention include RNA, cDNA, genomic DNA, synthetic forms, and mixed polymers, both sense and antisense strands, and may be chemically or biochemically modified or may contain non-natural or derivatized nucleotide bases, as will be readily appreciated by those skilled in the art.") Claim 1 restricts the set of DNA to those that have been 'isolated'. 'Isolate' and its cognates are used in many different senses in the patent specification but the explicit definition provided is as follows: "An 'isolated' or 'substantially pure' nucleic acid (e.g., an RNA, DNA or a mixed polymer) is one which is substantially separated from other cellular components which naturally accompany a native human sequence or protein, e.g., ribosomes, polymerases, many other human genome sequences and proteins." '282 Patent, col. 19, ll. 8-13. Thus, the inventors made clear that Claim 1 of the '282 patent includes, among other forms of DNA, isolated but otherwise unaltered gDNA. As noted earlier, the specifications provide no function for this gDNA other than its natural function of storing and transmitting information.

On the other hand, the specification does attribute functions beyond information storage to other molecules (i.e., other than the full gDNA molecule) falling within the broad scope of Claim 1 of the '282 patent. For example, the specification states that isolated cDNA coding for the SEQ ID NO.2 may be used in gene therapy (the genomic DNA being well known at the time to be too large for insertion within a vector. *See generally,* Joseph Sambrook & David W. Russell, Laboratory Cloning; A Laboratory

MANUAL (3d ed. 2001)). One function attributed to small portions of isolated DNA is their use as probes or primers for diagnostic or other purposes. These are non-trivial functions and their protection, through the grant of a patent, would facilitate rather than lessen innovation. Thus, if considered alone, these molecules could have been claimed for their use in relation to their additional function (beyond information storage and transmission).

The respondents did not, however, separate out their claims, preferring the broader scope of Claim 1 of the '282 patent as drafted. If they had adopted a more conservative patent strategy, they could have saved a substantial and important component of Claim 1 of the '282 patent and other impugned claims. In particular, the respondents could have adopted a less broad definition of DNA that excluded, in this case, unaltered gDNA, which specifies the protein defined by SEQ ID NO:2 and could have formulated their claims as a method of use of DNA for any of the non-natural functions. Potentially valuable subsequences of gDNA, particularly those found in the non-coding intron regions, could have given rise to valid claims under a number of circumstances. As an example, if a piece of DNA is found to bind competitively to an enhancer or promoter region in one of these introns, it could have the workings of a therapeutic molecule rather than of a storage medium for information and would be patentable for this function. Additionally, therapeutic molecules that target the intron sequences (e.g., to promote or inhibit gene expression) would constitute patentable subject matter as they have additional biochemical function. The respondents could (and did, in unchallenged claims) claim probe molecules that bind to specific sequences of interest, or primers to direct DNA synthesis.

Other claims of the impugned composition of matter claims, such as Claims 5 and 6 of the '282 patent, appear on their surface to be less broad, but in reality cover virtually any human gene. In particular, these claims include any molecule containing at least any given 15 base pair sequence occurring within any DNA sequence that would produce the *BRCA1* protein in SEQ ID 2. Claim 5 specifies over 1.6 million 15 base pair sequences, and an indefinite (thus infinite) number of DNA molecules that contain those sequences. Thomas B. Kepler, Colin Crossman and Robert Cook-Deegan, *Metastasizing Patent Claims on BRCA1,* 95 GENOMICS 312, 312 (2010). Searches of DNA sequences available before the patent was issued show that chromosome 1 alone had 340,000 sequences that fit this description, and the average gene would include 14 sequences conforming to the claim—including several genes already in the public domain before the patent application was filed. *Ibid* at 313. Subsequent analysis by the same authors indicates that long DNA sequences of well over 100 base pairs—which would be unique if DNA sequences were truly random—are found repeatedly in the human genome. Remarks to the United States Patent Office, Observations from Studies of Patenting and Licensing Practices that Affect DNA-Based Clinical Testing, app. b. (Jan. 10, 2013), http://www.genome.duke.edu/centers/cpg/sec-27study/documents/Cook-DeeganCpGstmtforUSPTOroundtable10Jan2013presentationdraft-1.docx; permission to cite obtained. The effect of the outcome of these studies is that anybody conducting a diagnostic test—whether in the course of discovery science or the study of another disease—on virtually any human gene would almost certainly produce isolated DNA molecules meeting the description of Claims 5 and 6, and thus infringe the '282 patent.

A reading of some of the non-impugned claims in the '282 patent reveal that they, in contrast with the claims examined above, constitute patentable subject matter. These would include Claims 8 to 13, all of which involve the use of the polynucleotide as a biochemical agent in addition to or instead of as an information storage and transmission medium. Whether these claims will survive a utility, novelty, non-obviousness, written description or enablement analysis is a separate question that does not arise in this case.

CONCLUSION

Following this Court's jurisprudence, human genes are patentable when claims are directed to a function that is markedly different from the genes' natural functions of genetic information storage and transmission. Hence, where the claim reads over a molecule corresponding to a naturally occurring human gene sequence, the claim must be restricted to the use of that molecule for that additional function. Where the claim reads over molecules corresponding to an altered version of the human gene sequence, unless the alteration is insignificant (e.g., if one base pair is substituted for another without changing the coding for, in the appropriate coding frame, the amino acid), then that molecule may be eligible as a composition-of-matter claim.

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