No. 2010-1406

United States Court of Appeals

FOR THE FEDERAL CIRCUIT

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, THE AMERICAN COLLEGE OF MEDICAL GENETICS, THE AMERICAN SOCIETY FOR CLINICAL PATHOLOGY, THE COLLEGE OF AMERICAN PATHOLOGISTS, HAIG KAZAZIAN, MD, ARUPA GANGULY, PHD, WENDY CHUNG, MD, PHD, HARRY OSTRER, MD, DAVID LEDBETTER, PHD, STEPHEN WARREN, PHD, ELLEN MATLOFF, M.S., ELSA REICH, M.S., BREAST CANCER ACTION, BOSTON WOMEN'S HEALTH BOOK COLLECTIVE, LISBETH CERIANI, RUNI LIMARY, GENAE GIRARD, PATRICE FORTUNE, VICKY THOMASON, and KATHLEEN RAKER,

Plaintiffs-Appellees,

—v.—

UNITED STATES PATENT AND TRADEMARK OFFICE,

Defendant,

—and—

MYRIAD GENETICS, INC.,

Defendant-Appellant,

—and—

LORRIS BETZ, ROGER BOYER, JACK BRITTAIN, ARNOLD B. COMBE, RAYMOND GESTELAND, JAMES U. JENSEN, JOHN KENDALL MORRIS, THOMAS PARKS, DAVID W. PERSHING, and MICHAEL K. YOUNG, in their official capacity as Directors of The University of Utah Research Foundation,

Defendants-Appellants.

ON APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE SOUTHERN DISTRICT OF NEW YORK, IN CASE NO. 09-CV-4515, SENIOR JUDGE ROBERT W. SWEET

SUPPLEMENTAL BRIEF FOR APPELLEES

DANIEL B. RAVICHER
SABRINA Y. HASSAN
PUBLIC PATENT FOUNDATION (PUBPAT)
BENJAMIN N. CARDOZO
SCHOOL OF LAW
55 Fifth Avenue, Suite 928
New York, NY 10003
(212) 790-0442

CHRISTOPHER A. HANSEN
SANDRA S. PARK
ADEN FINE
LENORA M. LAPIDUS
AMERICAN CIVIL LIBERTIES UNION
FOUNDATION
125 Broad Street, 18th Floor
New York, NY 10004
(212) 549-2606

Attorneys for Plaintiffs-Appellees

June 15, 2012

CERTIFICATE OF INTEREST

Counsel for the Plaintiffs-Appellees, Association for Molecular Pathology; American College of Medical Genetics; American Society for Clinical Pathology; College of American Pathologists; Haig Kazazian, MD; Arupa Ganguly, PhD; Wendy Chung, MD, PhD; Harry Ostrer, MD; David Ledbetter, PhD; Stephen Warren, PhD; Ellen Matloff, M.S.; Elsa Reich M.S.; Breast Cancer Action; Boston Women's Health Book Collective; Lisbeth Ceriani; Runi Limary; Genae Girard; Patrice Fortune; Vicky Thomason; and Kathleen Raker certifies the following:

1. The full name of every party or amicus represented by me is:

Association for Molecular Pathology; American College of Medical Genetics and Genomics; American Society for Clinical Pathology; College of American Pathologists; Haig Kazazian, MD; Arupa Ganguly, PhD; Wendy Chung, MD, PhD; Harry Ostrer, MD; David Ledbetter, PhD; Stephen Warren, PhD; Ellen Matloff, M.S.; Elsa Reich M.S.; Breast Cancer Action; Boston Women's Health Book Collective; Lisbeth Ceriani; Runi Limary; Genae Girard; Patrice Fortune; Vicky Thomason; and Kathleen Raker.

2. The name of the real party in interest represented by me is:

Same as above.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

None.

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court are:

American Civil Liberties Union Foundation (Christopher A. Hansen; Sandra S. Park; Lenora M. Lapidus; Aden Fine); Public Patent Foundation (PUBPAT), Benjamin N. Cardozo School of Law (Daniel B. Ravicher; Sabrina Y. Hassan).

Christopher A. Hansen

Christopher A. Hansen
Counsel for Plaintiffs-Appellees

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Other Authorities

STATEMENT OF THE ISSUES AND SUMMARY OF ARGUMENT[1]

Plaintiffs-Appellees challenge certain claims covering human genes on the grounds that they are unpatentable subject matter under the law/product of nature doctrine. On July 29, 2011, this court held that some of those claims (those covering "isolated" DNA and one covering a method) were valid, and found several method claims invalid. *Ass'n for Molecular Pathology v. U.S. Patent and Trademark Office*, 653 F.3d 1329, 1350 (Fed. Cir. 2011), *vacated*, 132 S. Ct. 1794 (2012). On March 26, 2012, the United States Supreme Court granted Plaintiffs' petition for a writ of *certiorari*, vacated this court's judgment, and remanded the case to this court for further proceedings in light of *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012). On April 30, 2012, this court ordered the parties to file supplemental briefs addressing the applicability of *Mayo* to the "isolated DNA claims and to method claim 20 of the '282 patent." Order, April 30, 2012, Dkt. Entry (D.E.) 275.

Mayo reemphasized and gave new vigor to three principles for determining whether a law/product of nature has been "transformed" into something patentable. First, courts must examine whether the patent claims preempt what is unpatentable – such as laws and products of nature – a question that was unaddressed by the

[1] Plaintiffs have nothing to add to the jurisdictional statement, statement of the case, and statement of facts found in their answering brief. Brief for the Appellees, Nov. 30, 2010.

original majority or concurring opinions. Second, the Court made clear that what is patented must be based on an "inventive concept" or "add enough" to the natural phenomena, or as it has said in other cases, have "markedly different characteristics from any found in nature." Under *Mayo* and previous Supreme Court precedent, trivial chemical transformations cannot meet this test. Third, the Court held that the role of the courts is to decide whether claims fall within the law/product of nature doctrine without regard to industry reliance and the Patent Office's approval of patents. A fair application of these three principles to this case should lead this court to issue a new opinion and judgment affirming the district court as to the isolated DNA claims and claim 20 of the '282 patent.

ARGUMENT

I. UNDER *MAYO* AND OTHER SUPREME COURT PRECEDENT, THE ISOLATED DNA CLAIMS ARE INVALID BECAUSE THEY PREEMPT USE OF LAWS AND PRODUCTS OF NATURE.

When patents "risk disproportionately tying up the use of the underlying natural laws, inhibiting their use in the making of further discoveries" *Mayo*, 132 S. Ct. at 1294, they should be found to be invalid under the law/product of nature doctrine. Citing its previous cases, including cases examining composition claims such as *Diamond v. Chakrabarty*, 447 U.S. 303 (1980) and *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948), the Court held that the law/product of nature doctrine is a robust doctrine that prohibits the patenting of

laws of nature, natural phenomena, or abstract ideas because "they are the basic tools of scientific and technological work." *Mayo*, 132 S. Ct. at 1293. "[M]onopolization of those tools through the grant of a patent might tend to impede innovation rather than it would tend to promote it." *Id.*

Although this doctrine should not be interpreted overly broadly, *id.*, the entire thrust of the Court's unanimous opinion is that this circuit defined it far too narrowly in its *Mayo* decisions. A fundamental component of the Court's examination is whether the patent "otherwise forecloses more future invention than the underlying discovery could reasonably justify." *Id.* at 1301. It is clear that patents on "isolated" DNA that claim laws and products of nature impermissibly foreclose future scientific work and innovation.

In *Mayo*, the Court concluded that the patents covered a law of nature – the relationship between certain metabolite levels and drug efficacy in a patient. Although the claims involved human intervention, they monopolized this naturally-occurring relationship and thus were invalid.

> While it takes a human action (the administration of a thiopurine drug) to trigger a manifestation of this relation in a particular person, the relation itself exists in principle apart from any human action. The relation is a consequence of the ways in which thiopurine compounds are metabolized by the body – entirely natural processes. And so a patent that simply describes that relation sets forth a natural law.

Id. at 1297. *See also id.* at 1294 (Supreme Court's precedents "warn us against upholding patents that claim processes that too broadly preempt the use of a natural

law"); *Bilski v. Kappos*, 130 S. Ct. 3218, 3231 (2010) ("Allowing petitioners to patent risk hedging would pre-empt use of this approach in all fields, and would effectively grant a monopoly over an abstract idea."); *Funk Bros.*, 333 U.S. at 130 ("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. . . . He who discovers a hitherto unknown phenomenon of nature has no claim to a monopoly of it which the law recognizes"); *O'Reilly v. Morse*, 56 U.S. 62, 113 (1853) (the patentee's claim on any machinery or process using electric current to mark characters at a distance "shuts the door against inventions of other persons"). The central inquiry in these cases has been: Does the patent seek to claim a "'manifestation of . . . nature, free to all men and reserved exclusively to none"? *Mayo*, 132 S. Ct. at 1293 (citing *Chakrabarty*, 447 U.S. at 309 (quoting *Funk Bros.*, 333 U.S. at 130)).

The "isolated" DNA claims in this case patent laws of nature and products of nature. The law is the correlation between the patented DNA and the BRCA proteins it encodes, which in turn correspond to traits such as risk for breast and ovarian cancers. The product is the DNA itself.

Both the district court and Myriad's own expert recognized DNA as a blueprint for all of the proteins, cells, and organs that make up the human body. A216-17; A4837-38. Unlike other chemicals, the information encoded by DNA

"reflects its primary biological function: directing the synthesis of other molecules in the body – namely, proteins." A217. This naturally-occurring relationship between DNA and proteins is at the heart of the patent claims, which themselves define the patented DNA based on its coding for a polypeptide. *See, e.g.*, claim 1, '282 patent ("An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID No.2"). "DNA, and in particular the ordering of its nucleotides, therefore serves as the physical embodiment of laws of nature – those that define the construction of the human body." A217. The point of these claims and the sole use of them by Myriad is to uncover the informational qualities, the laws of nature that they embody.

The laws of nature covered by the patent claims – the encoding relationship between a DNA molecule and a protein, and the correlations between genetic mutations and disease – exist independently, whether the DNA is isolated or not. Indeed, "isolated" DNA can be reinserted into the cell and will then code for proteins and transmit the same traits as previously. A6969-72. The isolated DNA molecules "serve the ends nature originally provided and act quite independently of any effort of the patentee." *Funk Bros.*, 447 U.S. at 131. Just as administering a drug triggered manifestation of a person's natural metabolism of thiopurine in *Mayo*, isolating DNA merely makes visible a person's inherited genetic makeup.

There are several aspects of the specific claims in this case that establish that they are unduly preemptive of laws/products of nature and therefore invalid. First, because humans did not invent DNA, it is not possible to invent around the claims. In *Mayo*, the Court suggested that a claim on a new drug would not raise the concern that invalidated Prometheus' patents because another company could develop another drug treating the same condition without infringing. *Mayo,* 132 S. Ct. at 1302-03. In contrast, the "isolated" DNA claims are claims that do preempt future use of laws and products of nature because another entity cannot invent a DNA molecule that encodes for the same protein and embodies a person's BRCA1 and BRCA2 genetic information. A2445-46. As a consequence, no other laboratory in the U.S. has been able to provide clinical testing of these genes, whether at lower cost, to confirm results, or to ensure testing quality.

Indeed, the parts that result from breaking down a naturally-occurring thing are probably never patentable, because a patent on any such building block of nature would preempt all of its uses. This is particularly true with isolated DNA, because Myriad never precisely isolates a BRCA1 or BRCA2 molecule with specific ends, but instead obtains random fragments that are the building blocks of the genes and chromosomes. Pls.-Appellees' Pet. for Panel Reh'g 6-7, Aug. 25, 2011, D.E. 263. In contrast, recombining aspects of nature may be patentable if

the result is "markedly different" in structure and function and does not preempt use of a law or product of nature.

Second, the disputed claims are broader than those invalidated in *Mayo*. The claims in *Mayo* covered one method of manipulating the natural law and could be characterized as on "narrow laws that may have limited applications." *Mayo*, 132 S. Ct. at 1302. The isolated DNA composition claims, by contrast, preclude every imaginable manufacture and use of the claimed subject matter. A7016, A7060-63. They thus monopolize the law correlating every human's BRCA1/2 genes to particular proteins and disease risk. They reach hundreds of millions of molecules.

For example, claim 6 of patent '492 reaches any isolated DNA molecule coding for a mutated form of the BRCA2 polypeptide, wherein the mutated form is associated with susceptibility to cancer. The claim does not specify the mutations nor the type of cancer that might be associated with a mutated form; yet, it preempts others' work into these very questions.

Claims 5 and 6 of patent '282 cover any isolated DNAs "having **at least** 15 nucleotides" of the BRCA1 gene. A664. The claims reach the entire BRCA1/2 genes and are therefore invalid. *See Ass'n for Molecular Pathology*, 653 F.3d at 1365 (Moore, J., concurring) ("For this claim to be patent eligible, all of the sequences ranging from the 15 nucleotide sequence to the full gene must be patentable subject matter."). Dicta as to the patentability of short segments of

DNA should be avoided. And, as explained by experts and the dissenting opinion, those claims preempt scientific work to an even greater extent because molecules sharing at least 15 nucleotides of the BRCA1 gene appear throughout the genome. *Id.* at 1378-79 (Bryson, J., concurring in part and dissenting in part); A7017-7021; A7215-30. The ability to use short DNA segments as primers or probes does not mitigate the impediments the patents pose to innovation, because the challenged claims are not limited to these uses.[2]

Third, these patents give rise to the same concern expressed by *Mayo* that Prometheus' patents "threaten to inhibit the development of more refined treatment recommendations (like that embodied in Mayo's test), that combine Prometheus' correlations with later discovered features of metabolites, human physiology or individual patient characteristics." *Mayo*, 132 S. Ct. at 1302. The "isolated" DNA claims inhibit the development of more refined and advanced genetic testing, such as testing for large genetic rearrangements that are not detected by Myriad's standard "Comprehensive BRACAnalysis" but is recommended for all patients receiving BRCA genetic testing, simultaneous testing of the over twenty genes now known to be associated with hereditary risk for breast and ovarian cancer, and whole genome sequencing. *See, e.g.*, Tom Walsh et al., *Spectrum of Mutations in BRCA1, BRCA2, Chek2, and TP53 in Families at High Risk of Breast Cancer,* 295

[2] Plaintiffs did not challenge claims limited to the use of short segments of DNA as probes or primers. *See, e.g.*, Patent '473, claims 4 and 5. A358.

J. of the Am. Med. Ass'n 1379, 1385-86 (2006) (finding a 12% false negative rate for patients from high risk families); Nat'l Comprehensive Cancer Network, NCCN Clinical Practice Guidelines in Oncology - Genetic/Familial High-Risk Assessment: Breast and Ovarian, at MS-15 (2012) (recommending that patients advised to seek BRCA genetic testing receive large rearrangement testing); Tom Walsh et al., *Detection of Inherited Mutations for Breast and Ovarian Cancer Using Genomic Capture and Massively Parallel Sequencing*, 107 PNAS 12629, 12631-32 (2010) (estimating that testing of 21 genes correlated to breast and ovarian cancer, including BRCA1 and BRCA2, could be done for less than $500 per sample); Jacob O. Kitzman et al., *Noninvasive Whole-Genome Sequencing of a Human Fetus*, 4 Sci. Translational Med. 137ra76, at 1 (2012) (showing that the whole fetal genome can be sequenced using "cell-free" DNA, or naturally-occurring DNA fragments, found in the mother's plasma); Sec'y Advisory Comm. on Genetics, Health, and Soc'y, Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests (2010) (hereinafter "SACGHS Report"). *See also* A2649-50, A2775, A2813, A2934-36, A2978-81, A3022.

Moreover, these claims pose a barrier to the development of targeted cancer therapies. Although the scientific community identified years ago a class of drugs effective in patients with BRCA mutations, there is recent evidence that the patents in this case have impeded the availability of these new treatments. *See* Susan M.

Domcheck et al., *Challenges to the Development of New Agents for Molecularly Defined Patient Subsets: Lessons from BRCA1/2 - Associated Breast Cancer*, 29 J. on Clinical Oncology 4224 (2011).

> The US Food and Drug Administration requires an approved companion diagnostic test that will define the population of interest before approval is granted for an agent directed toward that population. There is presently no US Food and Drug Administration approved diagnostic test for determining germline BRCA status, although mutation results have been used for more than a decade to make major decisions about preventive surgeries.

Id. at 4225. The patents, and the inability of others to seek regulatory approval to provide BRCA testing (as laboratories have done in the context of other drugs that are prescribed based on genetic testing), stand in the way of access to effective treatments for patients with BRCA mutations and their doctors. *Id.* The promise of personalized medicine through targeted therapies has not materialized for the patient community most directly affected by BRCA mutations. *Id.* at 4226; *see also* Brief for Canavan Foundation et al. as Amici Curiae Supporting Petitioners at 3-4, *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 132 S. Ct. 1794 (2012) (No. 11-725) (joined by Facing Our Risk of Cancer Empowered, the only national nonprofit organization devoted to hereditary breast and ovarian cancer).

Finally, the contested claims (and similar claims) have already inhibited research. Over half of all labs surveyed as part of an NHGRI-funded study reported "deciding not to develop a new clinical [BRCA] test because of a gene patent or license." A2672. A similar study found that 46% felt that gene patents

had "delayed or limited their research." A2672-73. Another researcher looking closely at patenting genes found that it had "persistent negative effects on subsequent scientific research." Heidi L. Williams, *Intellectual Property Rights and Innovation: Evidence from the Human Genome* 27 (Nat'l Bureau of Econ. Research, Working Paper No. 16213, 2010). *See also* A7064 ("The Myriad and similar patents … impeded innovation in several ways…more significant perhaps is the impediment to follow-up research…[and] even for basic research…"); SACGHS Report at 53-54.[3]

The claims curtail the ability of scientists to examine human genes. Because scientific work relies on using DNA after it has been isolated, and because the patents do not specify a single BRCA molecule or a single use of the DNA but instead cover all of them, the patents give exclusivity over the BRCA1 and BRCA2 DNA itself, and their preemptive effect mandates a finding of invalidity.

II. THE ISOLATED DNA CLAIMS ARE NOT BASED ON AN INVENTIVE CONCEPT AND DO NOT ADD ENOUGH TO THE LAWS AND PRODUCT OF NATURE TO BECOME PATENTABLE.

Mayo reiterated that this court must analyze whether the patents sufficiently apply or change the law or product of nature to create a patentable invention. *Mayo* asked, does the claim arise from an "'inventive concept' sufficient to ensure

[3] Plaintiffs recognize that Myriad states it has not fully enforced its patent rights against activity it deems to be research. The preemption question, however, must be decided on the authority given Myriad by the patents, not Myriad's actions. That authority allows Myriad to stop research.

that the patent in practice amounts to significantly more than a patent upon the natural law itself"? Does it "add enough" or "simply append[] conventional steps, specified at a high level of generality to laws of nature [or] natural phenomena"? *Mayo*, 132 S. Ct. at 1300. Or, as the Court previously has stated, does what is patented have "markedly different characteristics from any found in nature"? *Chakrabarty*, 447 U.S. at 310. In *Mayo*, the Court found that the claims were not inventive, despite transformations that occurred during the administering of a drug and determining metabolite levels, because nothing of significance was added to the law of nature – the patient's response to a drug. The claims simply "inform a relevant audience about certain laws of nature." 132 S. Ct. at 1298. Accordingly, they did not change the law of nature into something patentable.

Likewise, although the discovery of the BRCA genes should be credited, the contested claims simply do not cover a patent-eligible invention. Isolation of DNA was a well-known technique at the time these patents were sought, and continues to be a routine, conventional preparatory step for using human genes in research and clinical practice. A6963; A7037. The only addition of the "isolated" DNA claims to the progress of science is disclosure of the natural law itself – the fact that this DNA encodes for the BRCA protein and embodies the information needed to understand a person's heredity and disease susceptibility.

Considering "isolated" DNA not only as a law but also a product of nature leads to the same conclusion. The majority in this case and, to a lesser extent the concurrence, relied on the fact that a fragment of DNA consists of a different chemical composition than a strand of full-length DNA. *Ass'n for Molecular Pathology*, 653 F.3d at 1352 ("cleaving … a portion of a native chromosomal DNA imparts on that isolated DNA a distinctive chemical identity"); *Id.* at 1363 (man creates isolated DNA by "chemically altering the larger polymer to cleave off adjacent portions").[4] For the majority, this distinction was dispositive.

This misplaced emphasis on chemical change is directly analogous to the circuit's analysis in *Mayo.* There, the remand panel of this court upheld the patents in part on the basis that the determination of the metabolite levels caused a chemical transformation. *Prometheus v. Mayo*, 628 F.3d 1347, 1356-7 (Fed. Cir. 2010), *rev'd*, 132 S. Ct. 1289 (2012). That analysis was rejected by the Supreme Court. The determination of metabolite levels "could be satisfied without transforming the blood, should science develop a totally different system for determining metabolite levels that did not involve such a transformation." *Mayo*,

[4] As plaintiffs argued in their Petition for Panel Rehearing, the question is not whether a fragment of DNA is chemically different from the whole DNA, but whether isolated DNAs, with covalent bonds broken, are found in nature or not. They are. Moreover, the court's discussion of the chemical changes represents a misunderstanding of the "isolation" process. Thus, for the reasons stated in the earlier petition, the DNA is not patentable under the law/product of nature doctrine. Pls.-Appellees' Pet. for Panel Reh'g 1-11, Aug. 25, 2011, D.E. 263.

132 S. Ct. at 1303. And importantly, the Court said "[i]n stating that the 'machine or transformation' test is an '*important and useful clue*' to patentability, we have neither said nor implied that the test trumps the 'law of nature' exclusion." *Id.*

Thus, even if something is transformed by human intervention, the law/product of nature doctrine may render it invalid. In this case, should science develop a method of cleaving a gene's covalent bonds while the DNA remains in the body, can it be seriously argued that the DNA fragments so created, but floating in the body, would be patentable subject matter? If not, then the routine steps involved in isolating the fragments from the body cannot, under *Mayo,* be sufficient to make them patentable upon removal. In fact, such DNA fragments already exist naturally in the body. *Infra,* pp. 14-15. Conversely, if the claim in *Mayo* had been a composition claim covering the blood transformed by administration of thiopurine and/or the steps necessary "to extract the metabolites from a bodily sample and determine their concentration," *Prometheus,* 628 F.3d at 1357, can it be argued that Prometheus could have patented the "transformed" blood? Considering that the Supreme Court in *Mayo* invalidated the method as not sufficiently transforming the blood, it seems inconceivable that the Court would have upheld a composition claim that blocked every use of that blood.

Moreover, BRCA1 and BRCA2 fragments, with covalent bonds broken, naturally exist in the body. For example, such DNA fragments result from the

naturally-occurring processes of meiotic recombination or double strand breaks. Fetal and maternal genomes, including BRCA1 and BRCA2 fragments, exist in the maternal plasma of pregnant women, and these fragments can be used to sequence the entire fetal genome. *See* Kitzman, *supra*, at 9. And BRCA1 and BRCA2 fragments can be found in the blood of cancer patients. Pls.-Appellees' Pet. for Panel Reh'g 1-11, Aug. 25, 2011, D.E. 263.

The concurrence also relied, in part, on the diagnostic utility of small fragments of DNA. *Ass'n for Molecular Pathology*, 653 F.3d at 1365. Diagnostic testing is, as the Supreme Court said repeatedly in *Mayo*, a "well-understood, routine, conventional activity" that for other genes had been and is "engaged in by researchers in the field." *Mayo*, 132 S. Ct. at 1294. That activity is insufficient to transform a product of nature into a patentable composition. Just as the utility of using the "transformed" blood in *Mayo* for diagnosis was insufficient to make that process patentable, so too the utility of using "isolated" DNA for diagnosis is insufficient to make "isolated" DNA patentable. *See also* pp. 7-8, *supra*.

The decision in *Mayo* is also relevant to the patentability of cDNA. First, Myriad has never argued that a single one of the challenged claims is limited to cDNA in its briefs. Brief for the Appellees at 13, Nov. 30, 2010; Reply Brief for the Appellants, Dec. 22, 2010. Thus, the court's earlier discussion of the patent eligibility of cDNA is entirely dicta and should not be repeated. Plaintiffs do not

dispute that a process for creating cDNA may be patentable under Section 101; as a composition, however, it is not patent-eligible. cDNA results from the biological machinery of the cell, wherein naturally-occurring RNA creates its complement. A2608, A6974-75, A7023. The order and effect of the cDNA sequence is dictated by a law of nature, not by humans. Accordingly, the composition is not "inventive" as defined by the Supreme Court. It may take human action to create cDNAs (though in other instances, cDNAs do exist naturally in the body through naturally-occurring reverse transcription and are naturally reinserted into the genome, A6974-75, A7013-14, A7023-24). Yet, cDNA has value because it is used to inform about a patient's genetic code – just as the method challenged in *Mayo* informs doctors about a naturally-occurring reaction to a drug. *See also Cochrane v. Badische Anilin & Soda Fabrik*, 111 U.S. 293, 311 (1884) (holding that an artificial version of naturally-occurring alizarine could not be patented because it was not a "new composition of matter"). cDNA is not markedly different in structure, function, or preemptive effect and thus not patentable subject matter.

III. *MAYO* REJECTS THE IDEA THAT INDUSTRY RELIANCE IS A FACTOR IN APPLYING THE LAW/PRODUCTOF NATURE DOCTRINE.

Myriad submitted a brief *amicus curiae* in the Supreme Court in *Mayo*. In that brief, Myriad argued that an entire industry was "built on the settled

expectations of the incentive provided by strong patent protection," including the patents at issue in *Mayo.* Brief for Myriad Genetics, Inc. as *Amicus Curiae* Supporting Respondent at 12, *Mayo Collaborative Servs. v. Prometheus Labs.*, 132 S.Ct. 1289 (2012) (No. 10-1150). Myriad cited its own BRACAnalysis test as "an excellent example" of this phenomenon. *Id.* at 15. Myriad concluded that the Supreme Court should "tread very carefully when asked…to upset those expectations." *Id.* at 16.

Somewhat similarly, both the majority opinion and, to an even greater extent, the concurrence in this case emphasized the relevance of the settled expectations of the industry and/or the PTO. Thus, the majority suggested that "[i]f the law is to be changed, and DNA inventions excluded from the broad scope of § 101 contrary to the settled expectation of the inventing community, the decision must come not from the courts, but from Congress." *Ass'n for Molecular Pathology*, 653 F.3d at 1355. The concurrence relies heavily on the idea that "we must be particularly wary of expanding the judicial exception to patentable subject matter where both settled expectations and extensive property rights are involved." *Id*. at 1367 (Moore, J., concurring).

In *Mayo*, the Supreme Court addressed this proposition for patents relating to the same field as gene patents and unequivocally rejected it. The Court noted that there are strong countervailing interests, citing *amicus* briefs by the medical

community, including one filed by two of the plaintiffs in this case. *Mayo*, 132 S. Ct. at 1304-05. Patent "exclusivity can impede the flow of information that might permit, indeed spur, invention ..." *Id.* at 1305. The claims will tie up "critical scientific data that must remain widely available if physicians are to provide sound medical care." *Id*. (quoting Brief for American College of Medical Genetics et al. as *Amicus Curiae* 7). The Supreme Court concluded that the courts should not emphasize reliance by industry or deference to the PTO at the expense of the harms that occur with patenting basic laws/products of nature. *See id*. at 1304-05.

Plaintiffs and their *amici* (the same organizations quoted approvingly by the Supreme Court in *Mayo*) identified at length the harms caused by these patents. Brief for Appellees at 18-20, Nov. 30, 2010. There is considerable evidence that the claims have impeded clinical practice and research. *See, e.g.*, SACGHS Report at 2-4. For periods of time, Myriad was engaged in testing that was known to be inadequate, supplying some patients with erroneous results. Many patients could not afford to receive testing. The claims may well be preventing life-saving research and treatment. *See supra,* at pp. 8-11.

This court should follow the approach of the Supreme Court.[5] This court should not consider deference to the PTO or reliance by industry. Instead, it

[5] Plaintiffs recognize that there are Supreme Court statements, cited by the concurrence in this case, that imply the opposite. *See Ass'n for Molecular Pathology*, 653 F.3d at 1368. Those cases did not involve determining what is

should apply fairly the law/product of nature doctrine without regard to those factors. According to the Supreme Court, the burden on Congress, if it disagrees, is not to broaden the law/product of nature doctrine to prevent patentability of genes, but to narrow it to allow patentability of genes.

IV. CLAIM 20 IS INDISTINGUISHABLE FROM THE CLAIMS FOUND INVALID IN *MAYO*.

This court upheld Claim 20 of the '282 patent with an analysis that relied heavily on the remand panel's opinion in *Mayo*. The court found the "growing" and "determining" steps of Claim 20 transformative in the same way that the remand panel found the "administering" and "determining" steps transformative in *Mayo*. *Ass'n for Molecular Pathology*, 653 F.3d at 1357-8. The court found that the Claim 20 steps were "central to the purpose" of the claim, as the remand panel had found the *Mayo* steps "central." *Id.* The court found the claim non-preemptive, emphasizing the narrow nature of the preemption, as the remand panel had done with the *Mayo* claim. *Id.*

The Supreme Court in *Mayo* addressed each of these rationales and rejected them. The processes in Claim 20, like those in *Mayo* "set forth laws of nature" – namely the effect of a drug. "A patent that simply describes that relation sets forth

---

unpatentable under Section 101, and *Mayo*'s analysis is definitive. *See also Chakrabarty*, 447 U.S. at 306-07 (approving patent over objections by the Commissioner of Patents and Trademarks). In addition, *Mayo* at least makes clear that deference is not warranted when the issue is whether a patent is invalid under Section 101 in the context of medical care. *Mayo*, 132 S. Ct. at 1305.

a natural law." *Mayo*, 132 S. Ct. at 1297. Both claims involve nothing more than "well-understood, routine, conventional activity already engaged in by the scientific community." *Id.* at 1298. Permitting both claims preempt medical and scientific activity. *See id.* at 1305. Further, even if the court in this case were correct that Claim 20 was minimally preemptive, the Supreme Court has held that limited preemption is sufficient to invalidate the claim. *Id.* at 1303.

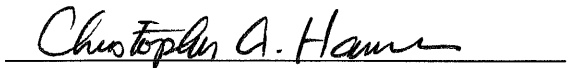
Because Claim 20 is indistinguishable from *Mayo* it should be invalidated.

CONCLUSION

For these reasons, plaintiffs respectfully ask this court to affirm the district court's holdings in all respects.

Dated: June 15, 2012

Respectfully submitted,



Christopher A. Hansen
Sandra S. Park
Aden J. Fine
Lenora M. Lapidus
American Civil Liberties Union Foundation
125 Broad Street, 18th Floor
New York, NY, 10004
(212) 549-2606

Daniel B. Ravicher
Sabrina Y. Hassan
Public Patent Foundation (PUBPAT)
Benjamin N. Cardozo School of Law
55 Fifth Avenue, Suite 928
New York, NY 10003

CERTIFICATE OF SERVICE

I hereby certify that on this 14th day of June, 2012, I caused the original and eleven true and correct copies of the foregoing Supplemental Brief for Appellees to be mailed to the Court via FedEx overnight; two copies to be served upon counsel for Appellants via FedEx overnight; and two copies of the Brief to be served upon the counsel of record listed below via first-class United States mail.

Gregory A. Castanias
Jones Day
51 Louisiana Avenue, N.W.
Washington, D.C. 20001
Counsel for Defendants-Appellants

Bruce Vignery
AARP Foundation Litigation
601 E Street, NW
Washington, DC 20049
Counsel for Amicus AARP

Mary M. Calkins
Foley and Lardner
3000 K Street, N.W., Suite 500
Washington, DC 20007
Counsel for Amicus Alnylam Pharmaceuticals

Barbara R. Rudolph
Finnegan, Henderson, Farabow, Garrett & Dunner
901 New York Avenue, N.W.
Suite 1100
Washington, DC 20001-4413
Counsel for Amicus American Intellectual Property Law Association

Lori B. Andrews
Chicago-Kent College of Law
Illinois Institute of Technology College of Law
565 West Adams Street
Chicago, IL 60661
Counsel for Amici American Medical Association et al.

Seth P. Waxman
Wilmer Hale
1875 Pennsylvania Avenue, N.W.
Washington, DC 20006
Counsel for Amici Biotech Industry Organization et al.

Erik P. Belt
McCarter & English
265 Franklin Street
Boston, MA 02110
Counsel for Amicus Boston Patent Law Association

John L. Hendricks
Hitchcock Evert LLP
750 North St. Paul Street
Suite 1110
Dallas, Texas 75201
Counsel for Amici Canavan Foundation et al.

Larry Frierson
The Law Offices of Larry Frierson
3265 Lake County Highway
Calistoga, CA 94515
Counsel for Amici Cancer Council Australia and Luigi Palombi

Christopher M. Holman
5100 Rockhill Road
Kansas City, MO 64110
Counsel for Amici Christopher Holman et al.

Jennifer Gordon
Baker Botts
30 Rockefeller Center
New York, NY 10112
Counsel for Amicus Croplife International

E. Richard Gold
Faculty of Law, McGill University
3664 Peel Street
Montreal, Quebec H3A 1W9
Counsel for Amici E. Richard Gold et al.

Eileen M. Kane
Penn State Dickinson School of Law
328 Katz Building
University Park, PA 16802
Counsel for Amicus Professor Eileen N. Kane

James J. Kelley
Eli Lilly and Company
Lilly Corporate Center, Drop Code 1104
Indianapolis, IN 46285
Counsel for Amicus Eli Lilly and Company

Erika R. George
Loyola University Chicago School of Law
25 E. Pearson
Chicago, IL 60611
Counsel for Amici Erika R. George and Kali N. Murray

Maxim H. Waldbaum
Schiff Hardin
900 Third Avenue, 23rd Floor
New York, NY 10022
Counsel for Amicus Fédération Internationale des Conseils en Propriété Industrielle (FICPI)

David S. Forman
Finnegan, Henderson, Farabow, Garrett & Dunner
901 New York Avenue, N.W.
Washington, DC 20001-4413
Counsel for Amicus Genetic Alliance

William G. Gaede, III
McDermott, Will & Emery
275 Middlefield Rd., Suite 100
Menlo Park, CA 94025
Counsel for Amici Genomic Health et al.

J. Timothy Keane
Harness, Dickey & Pierce
7700 Bonhomme Avenue, Suite 400
St. Louis, MO 63105
Counsel for Amici Gilead Sciences et al.

Herbert C. Wamsley
McDonnell, Boehnen, Hulbert & Berghoff
300 South Wacker Drive
Chicago, Illinois 60606
Counsel for Amicus Intellectual Property Owners Association

George Kimbrell
International Center for Technology Assessment
660 Pennsylvania Ave., Suite 302
Washington, D.C. 20003
Counsel for Amici International Center for Technology Assessment et al.

Judy Deleon Jarecki-Black
Merial Limited
3239 Satellite Blvd.
Duluth, GA 30096
Counsel for Amicus Merial Limited

Kent D. McClure
Animal Health Institute
1325 G Street, NW, Suite 700
Washington, DC 20005
Counsel for Amicus Animal Health Institute

Debra L. Greenfield
UCLA Center for Society and Genetics
Box 957221, 1323 Rolfe Hall
Los Angeles, CA 90095
Counsel for Amici National Women's Health Network et al.

Aaron Stiefel
Kaye Scholer
425 Park Avenue
New York, NY 10022
Counsel for Amicus Novartis Corp.

Kurt G. Calia
Covington & Burling
1201 Pennsylvania Avenue, N.W.
Washington, DC 20004-2401
Counsel for Amicus Pharmaceutical Research and Manufacturers of America

Thomas Kowalski
Vedder Price PC
1633 Broadway, 47th Floor
New York, NY 10019
Counsel for Protein Sciences Corporation

Jacqueline D. Wright-Bonilla
Foley and Lardner
3000 K Street, N.W., Suite 500
Washington, DC 20007
Counsel for Amici Rosetta Genomics et al.

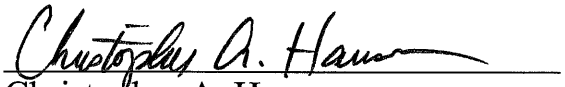
Andrew Chin
University of North Carolina
School of Law
160 Ridge Road, CB #3380
Chapel Hill, North Carolina 27599-3380
Counsel for Amicus Scholars of Biotechnology Patent Law

Francis Pizzulli
718 Wilshire Blvd
Santa Monica, CA 90401
Counsel for Amicus Southern Baptist Convention

Mark R. Freeman
U.S. Department of Justice
950 Pennsylvania Avenue, N.W., Room 7237
Washington, DC 20530-0001
Counsel for Amicus United States

Krista L. Cox
Universities Allied for Essential Medicines
2625 Alcatraz Ave, #180
Berkeley, CA 94705
Counsel for Amicus Universities Allied for Essential Medicines

Ann M. McCrackin
University of New Hampshire School of Law
2 White Street
Concord, NH 03301
Counsel for Amicus University of New Hampshire School of Law



Christopher A. Hansen
Counsel for Plaintiffs-Appellee

CERTIFICATE OF COMPLIANCE

1. This brief complies with this Court's order of April 30, 2012, because it is 20 pages, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii) and Federal Circuit Rule 32(b).

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of the Federal Rule of Appellate Procedure 32(a)(6), because it has been prepared in a proportionally spaced typeface using Microsoft Word 2010 in Times New Roman 14 point font.

Dated: June 15, 2012

Christopher A. Hansen
Counsel for Plaintiffs-Appellees