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, JOHNKENDALL 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,

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

BRIEF OF *AMICI CURIAE* GILEAD SCIENCES, INC., CONFLUENCE LIFE SCIENCES, INC. AND EUCLISES PHARMACEUTICALS, INC., IN SUPPORT OF NEITHER PARTY

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14 June 2012

CERTIFICATE OF INTEREST
AMICUS PARTY GILEAD SCIENCES, INC.

Counsel for the *amicus curiae*, Gilead Sciences, Inc., certifies the following:

1. The full names of every amicus represented by me are Gilead Sciences, Inc., Confluence Life Sciences, Inc. and Euclises Pharmaceuticals, Inc.

2. There are no real parties in interest associated with the amicus parties listed.

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 *amicus curiae*, Gilead Sciences, Inc., did not appear in the trial court. The name of the attorney who will be appearing before this Court on behalf of the amicus party is J. Timothy Keane of Harness, Dickey & Pierce, P.L.C.

Dated: 14 June 2012

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2. There are no real parties in interest associated with the amicus parties listed.

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.

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2. There are no real parties in interest associated with the amicus parties listed.

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 *amicus curiae*, Euclises Pharmaceuticals, Inc., did not appear in the trial court. The name of the attorney who will be appearing before this Court on behalf of the amicus party is J. Timothy Keane of Harness, Dickey & Pierce, P.L.C.

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TABLE OF CONTENTS

STATEMENT OF AUTHORSHIP & FUNDING

In compliance with Fed.R.App.P. 29(c)(5), this brief was authored by J. Timothy Keane of Harness, Dickey and Pierce, P.L.C., which funded this Amicus Brief. No party or party's counsel authored this brief in whole or in part. No party or party's counsel funded the preparation or submission of this brief.

TABLE OF AUTHORITIES

Page

CASES

STATUTES

STATEMENT OF INTEREST OF AMICI CURIAE

The decision of the District Court for the Southern District of New York, that the patent claims at issue in this case are not §101 includable, was erroneous. If the decision were applied broadly, it could disrupt the expectations of large numbers of chemical and biotechnology patent holders and researchers who have depended on the patent system to secure rights to valuable intellectual property and to attract necessary capital and investment. The amicus parties are organizations that rely on chemical and biotechnology patents; each has a strong interest in ensuring the stability of the patent system as it relates to chemical and biotechnology inventions.

Gilead Sciences, Inc. is a research-based biopharmaceutical company that discovers, develops and commercializes innovative medicines in areas of unmet need.

Confluence Life Sciences, Inc. is a research-based biopharmaceutical company that is engaged in research and development to commercialize innovative medicines in the field of inflammation and oncology.

Euclises Pharmaceuticals, Inc. is a research-based biopharmaceutical company that is engaged in research and development to commercialize innovative medicines in the field of inflammation and oncology.

I. STATEMENT OF CASE

This is not a "gene patenting" case. This case is an inquiry as to scope of includable substances, specifically cDNA nucleotide sequences, within the statutory class of "composition of matter" under 35 U.S.C. §101, which provides:

> **Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.** [1]

At issue here is whether a synthetic, man-made sequence of nucleotides forming a "composition of matter", which is both "new and useful", is §101-includable.

Enacted in 1952, 35 U.S.C. §101 "embodied Jefferson's philosophy that 'ingenuity should receive a liberal encouragement'," and "Congress intended statutory subject matter to 'include any thing under the sun that is made by man'." [2] **The 1952 Act is a re-codification of prior case law. In 1980, the Supreme Court's decision in *Diamond v. Chakrabarty,* as well as subsequent case law, firmly established the principle that patent-eligibility under §101 should have broad scope.**

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[1] 35 U.S.C. §101.
[2] *Diamond v. Chakrabarty*, 447 U.S. 303, 308-309 (1980) (citation omitted).

Defendant-Appellant Myriad Genetics, Inc. ("Myriad") invented a synthetic sequence of nucleotides (a chemical compound) which has never existed in nature. This new compound is a "made-by-man" chemical compound useful as a probe in life-saving diagnosis of human genetic pre-disposition to ovarian and breast cancer to a high degree of certainty.[3]

This "new and useful" chemical compound is defined in Claim 2 of Myriad U.S. Patent No. 5,747,282 ("U.S.'282") as a cDNA sequence recited as SEQ ID NO:1 ("Myriad Synthetic cDNA"). [4]

In holding Myriad Synthetic cDNA unpatentable, [5] **the District Court of Southern District of New York ("S.D.N.Y.") erred, in two respects:**

1) **As a matter of Patent Law, the S.D.N.Y. Court failed to recognize the "made-by-man" standard, as embedded in §101 of the 1952 Patent Act, as the fundamental standard for determining whether a new chemical substance is §101-includable subject-matter.**

---

[3] Myriad Synthetic cDNA is useful as a chemical probe to identify cancer-inducing gene-mutations. A woman who tests positive has, on average, an 82% lifetime risk of developing breast cancer and a 44% risk of developing ovarian cancer. These pre-symptomatic individuals, employing appropriate preventive therapies, can reduce their risk of developing breast cancer by approximately 50% (as reported in Journal of the National Cancer Institute), and can lower their risk of developing ovarian cancer by approximately 60% (as reported in New England Journal of Medicine). See: Hall MJ, Reid JE, Burbidge LA *et. al. BRCA1 and BRCA2 mutations in women of different ethnicities undergoing testing for hereditary breast-ovarian cancer*. Cancer. 2009; 115(10):2222-2233. doi: 10.1002/cncr.24200.; *See also* Swisher Decl. ¶¶ 11-13.

[4] The DNA claims at issue in this case are Claims 1, 2, 5, 6 and 7 of U.S. Patent No. 5,747,282 ("U.S.'282"); Claim 1 of U.S. Patent No. 5,693,473 ("U.S.'473"); and Claims 1, 6 and 7 of U.S. Patent No. 5,837,492 ("U.S.'492"). This Brief, however, shall address primarily U.S. '282 Claim 2 reciting cDNA sequence of SEQ. ID No:1.

[5] *Assoc. for Molecular Pathology v. USPTO,* 702 F.Supp.2d 181 (S.D.N.Y., 2010).

2) **As factual error, the S.D.N.Y. Court misapplied the "markedly different" test, first asserted in pre-1952 case law, in its analysis of structural and functional characteristics of Myriad Synthetic cDNA.**

Because the S.D.N.Y. Court erred in questions of both law and fact, in a manner contrary to statutory intent and meaning of §101 as well as all applicable case law, the CAFC properly reversed holdings of the S.D.N.Y. Court as to adverse finding on §101-includability. [6] **Following grant of Petition for Writ of Certiorari, from the earlier CAFC decision, the U.S. Supreme Court remanded this case to the Court of Appeals Federal Circuit ("CAFC") for disposition in view of rulings in the Supreme Court decision in the *Prometheus* case.**[7]

II. FACTUAL BACKGROUND

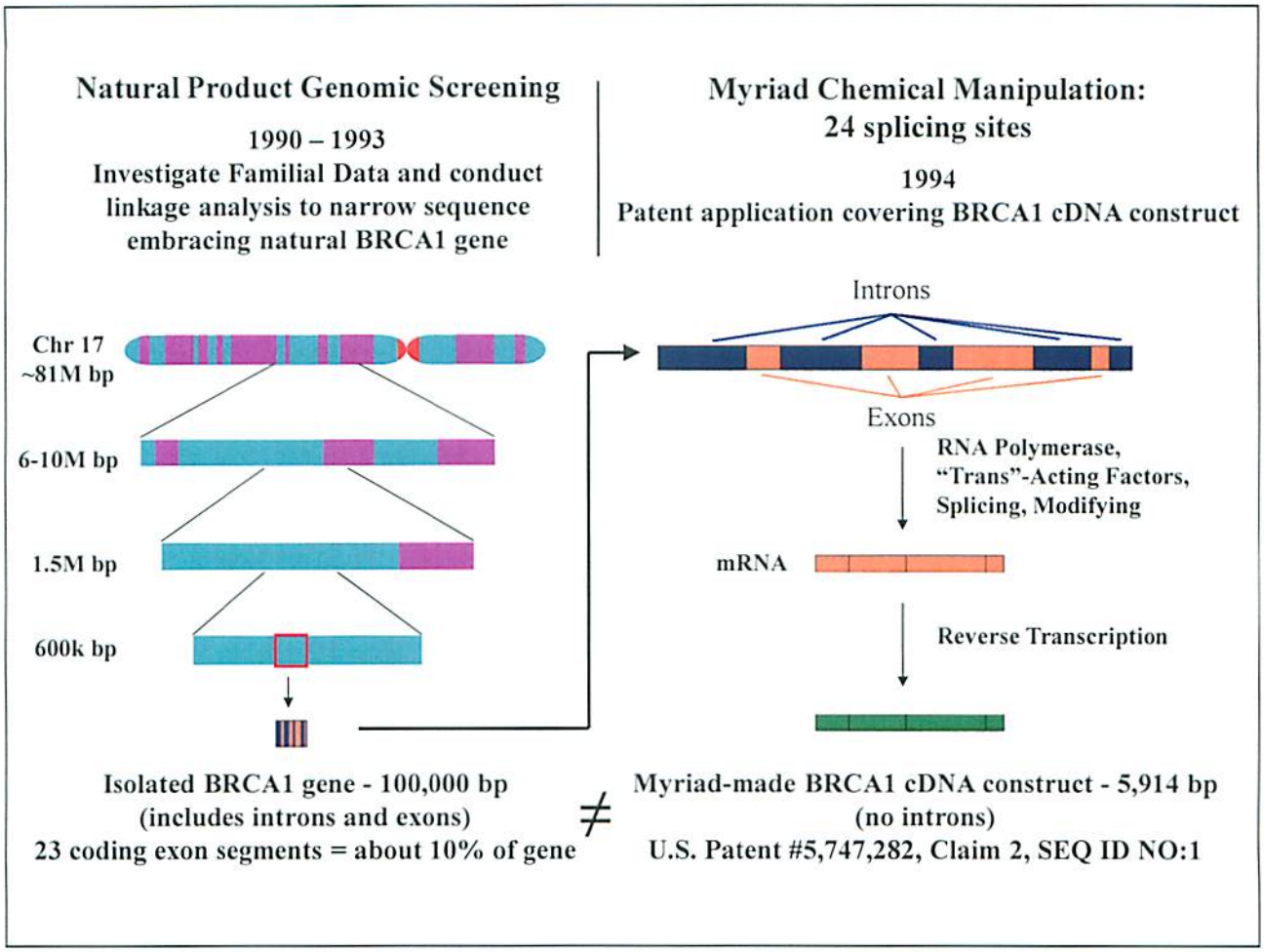
After years of intensive investigation and engineering, Myriad researchers identified a chemical compound having a sequence of nucleotides which never existed before in nature. Synthesis of this made-by-man cDNA sequence resulted from a lengthy series of transformative steps starting with identification of a genetic territory within Chromosome 17 (comprising ~81 million DNA base pairs) that housed BRCA1 gene. Using familial genetic

[6] The patentability of process claims at issue is not discussed herein. Only patent eligibility under §101 of U.S. '282 Claim 2 cDNA sequence is discussed herein. This Amicus Brief does not discuss novelty, obviousness, and other patentability issues under 35 U.S.C. §102, §103, and §112.

[7] *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 566 U.S. ___, 132 S.Ct. 1289 (2012)

histories correlated with cancer-occurrence, Myriad researchers identified genetic defects in natural BRCA1 gene as a likely source of cancer pre-disposition. Further genetic-marker-screening and chemical synthesis resulted in a 5,914 bp synthetic cDNA sequence characterized by an uninterrupted coding sequence, which does not, and cannot, occur in nature. This synthetic cDNA is useful as an effective and highly-efficient probe for diagnosis of ovarian and breast cancer genetic pre-disposition. The highlights of Myriad's discovery process resulting in Myriad Synthetic cDNA are illustrated in Figure 1, as follows:

Figure 1: Transformative-Steps to Make Myriad Synthetic cDNA BRCA1-Probe Recited in U.S. '282 Claim 2



Natural Product Genomic Screening:

Multipoint linkage analysis was used to localize and refine from Chromosome 17 (~81 million bp) chromosomal region (6-10 million bp)[7] embracing the BRCA1 gene locus (1.5 million bp)[8], which was subsequently identified and mapped using positional cloning.[9] Candidate cDNA clones for

[7] (US '282 at col. 9 and col. 46, lines 34-38).
[8] (US '282 at col. 9 and col. 46, lines 45-46).
[9] Shattuck Decl., ¶ 4.; US '282 at col. 46-49.

the BRCA1 genetic locus were identified by genomic analysis of the contig region and detailed maps of transcripts for the target chromosomal region (600,000 bp) were constructed to provide 65 candidate expressed-sequences (selected by hybridization, direct screening of cDNA library, and random sequencing of subclones).[10] The candidate sequences were then screened within the target chromosomal region, and 21 of the screened sequences were found to constitute the isolated BRCA1 gene (100,000 bp) including introns and exons.[11]

Chemical Transformative Steps:

The isolated BRCA1 gene was then transcribed to produce a molecule of mRNA. During this step, the mRNA was chemically cleaved, breaking covalent bonds between the nucleotide sequences constituting introns and the nucleotide sequences constituting exons in the newly-formed RNA molecule. The remaining exon segments of the mRNA were then spliced, forming new covalent bonds linking the previously cleaved exon nucleotide sequences through ≥ 20 splicing events. This transformative step produced mRNA in which the introns were excised from the molecule and the 23 coding exons were covalently linked via splicing at 24 splicing sites. The mRNA was then

[10] (US '282 at col. 49-52).
[11] (US '282 at col. 54 and FIGS 10A-H).

reverse transcribed to produce a full length, intron-free complementary DNA (cDNA) construct, SEQ ID NO:1 (5,914 bp) [12] **of U.S.'282 Claim 2.**

III. ARGUMENT

A. CAFC Properly Recognized "Made By Man" As Fundamental Standard In Subject-Matter Inquiry Under §101

1. Broad Statutory Threshold of 35 U.S.C. §101

The Supreme Court in *Diamond v. Chakrabarty* held that microorganisms produced by genetic engineering are eligible for patent protection under 35 U.S.C. §101.[13] **As interpreted by *Chakrabarty*, "[i]n choosing such expansive terms as 'manufacture' and 'composition of matter,' (modified by the comprehensive 'any'), Congress plainly contemplated that the patent laws would be given wide scope."** [14] **The Court in *Chakrabarty* reviewed the legislative history since the Patent Act of 1793, including the Committee Reports accompanying the 1952 Act, and concluded that "Congress intended statutory subject matter to 'include any thing under the sun that is made by man'."** [15] **Thus, the current statutory design is to set a**

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[12] (US '282 at col. 53).
[13] *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).
[14] *Chakrabarty*, at 308.
[15] *Id.* at 309 (citation omitted).

broad, welcoming threshold to "embod[y] Jefferson's philosophy that 'ingenuity should receive a liberal encouragement'." [16]

Of course, such a broad construction does not mean that §101 is without limit. §101 qualifies specified categories of patentable subject matter by the phrase "new and useful". The *Chakrabarty* Court upheld the rule that laws of nature, physical phenomena, and abstract concepts are not patentable.[17] The *Chakrabarty* Court emphasized that "Congress thus recognized that the relevant distinction was not between living and inanimate things, but between products of nature, whether living or not, and human-made inventions." [18] Thus, under *Chakrabarty*, the fundamental question, beside utility and subject matter category inquiries, should be whether the invention is truly "made by man", i.e., whether the invention is "the result of human ingenuity and research." [19]

2. Case Law Supports §101 To Include Anything "Made-By-Man"

Consistent with the broad interpretation as set forth in *Chakrabarty*, other courts have upheld §101-includability of synthetic compounds and

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[16] *Id.* at 308-309
[17] *Id.* at 309
[18] *Id.* at 313 (emphasis added).
[19] *Id.*

isolated or purified natural substances. [20, 21] **Up to present case, there is no reported case law in past 60 years (since discovery of existence of natural DNA consisting of nucleotide sequences) declaring that a synthetic cDNA compound is excludable from §101.**

All prior applicable case law has consistently given §101 broad interpretation to conform to the legislative intent of the 1952 Patent Act that any useful subject matter "made by man", or involving transformative steps, or intervention by man, satisfies the statutory requirement of §101. Up to the

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[20] Case law finding synthetic compounds and materials as §101-includable:

a. *In re Folkers*, 344 F.2d 970 (C.C.P.A. 1965) (Quinones having electron-transport property are useful);
b. *In re Bergy*, 596 F.2d 952, 960 (C.C.P.A. 1979) (microbe having synthetic DNA plasmid is statutory);
c. *Amgen v. Chugai*, 927 F.2d 1200 (Fed. Cir. 1991) (DNA encoding for natural-EPO is patentable);
d. *Fiers v. Revel*, 984, F.2d 1164 (Fed. Cir. 1993) (isolated DNA is patentable);
e. *J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Intern., Inc.*, 534 U.S. 124 (2001) (new hybrid corn seed is statutory);
f. *Plant Genetic Sys. v. DeKalb Genetics Corp.*, 175 F.Supp.2d 246 (D.Conn. 2001) (genetically-modified seeds are statutory);
g. *Chiron v. Genentech*, 268 F.Supp.2d 1148 (E.D.Cal. 2002) (Monoclonal antibody binding to breast-cancer antigen);
h. *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, (Fed. Cir. 2003) (recombinant DNA characterized as "non-natural");
i. *Monsanto v. Good*, 2004 WL 1664013 (D.N.J. 2003) (Soybean chimeric gene is statutory);
j. *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331 (Fed. Cir. 2005)(PHC hemihydrate is synthetic man-made compound as "manufacture" or "composition-of-matter");
k. *Genentech v. Insmed*, 436 F.Supp.2d 1080 (N.D.Cal. 2006) (Insulin-like human growth factor is statutory even without utility).

[21] Case law finding purified compounds as §101-includable:

a. *Parke-Davis & Co. v. H. K. Mulford Co.*, 189 F.95, 103 (S.D.N.Y. 1911) (isolated and purified natural adrenaline salt is patentable);
b. *Kuehmsted v. Farbenfabriken of Elberfeld Co.*, 179 F. 701 (7th Cir. 1910) (Purified aspirin is new, useful & patent-eligible);
c. *Merck & Co., Inc. v. Olin Mathieson Chem. Corp*, 253 F .2d 156 (4th Cir. 1958) (naturally occurring vitamin B_{12} in purified form is patentable);
d. *In re Kratz*, 592 F.2d 1169 (C.C.P.A. 1979) (purified 2-methyl-2-pentenoic acid, a chemical compound naturally responsible for the flavor of strawberries, was held to be patentable);
e. *In re Bergstrom*, 427 F.2d 1394 (C.C.P.A. 1970) (purified prostaglandin compounds are new);
f. *Schering Corp. v. Amgen, Inc.*, 18 F.Supp.2d 372 (D. Del.1998) (the substantially pure DNA encoding recombinant human interferon-like peptide as substantially-pure DNA sequence is statutory subject matter), affirmed 222 F.3d 1347, (Fed.Cir. 2000).

present S.D.N.Y. decision, in every case which a court has explicitly or implicitly evaluated §101-includability of a synthetic DNA molecule, the court has ruled for inclusion.

3. CAFC Properly Found Myriad cDNA Claim as Meeting "Markedly Different" Test to Determine §101-Includability

To the extent that the Supreme Court in *Chakrabarty* imposed a "markedly different characteristics" requirement into the statutory language of §101, Myriad U.S. '282 Claim 2 fully satisfies such standard.

B. New DNA Molecules Synthesized By Biotechnology Are §101-Includable

Under *Chakrabarty*, "natural product" or "natural phenomena" are exclusions to the broad scope of §101.[22] Under *Chakrabarty's* interpretation of the "new and useful" requirements in §101, an invention is patentable if:

-- 1) It belongs to a statutory category of subject matter (process, machine, manufacture, or composition of matter).

-- 2) It is "made by man" (i.e., non-naturally occurring substance); and

-- 3) It has practical utility.

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[22] *Chakrabarty*, at 309.

Myriad U.S. '282 Claim 2 synthetic cDNA molecule meets all three requirements.

Firstly, cDNA molecules are chemical entities that consist essentially of carbon, hydrogen, oxygen, nitrogen and phosphorous elements. There is no fundamental difference between a cDNA sequence and other chemicals for purposes of patent law – they are all compositions of matter includable in §101.[23]

Secondly, Myriad Synthetic cDNA is clearly a made-by-man substance. For claims covering a synthetic substance, the human intervention is making (i.e., to chemically modify, synthesize and isolate) a compound from building blocks (which, in turn, can be basic chemicals such as nucleotides). Myriad Synthetic cDNA molecule contains the entire coding sequence of the BRCA1/2 diagnostic protein and such cDNA does not exist in nature. Unlike Myriad Synthetic cDNA molecule, the naturally-occurring DNA of Chromosome 17 has fragments of the BRCA-gene coding sequence (in the form of exons and

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[23] Some historical perspective is beneficial here. John J. Doll, former Acting Undersecretary of the USPTO, observes that Plaintiffs' arguments, in many ways, resemble those voiced 30 to 40 years ago when polymer chemistry was an emerging technology. The concerns raised in the current case are similar to those raised when polymers were first patented:

> "At that time, it was argued that patents on the building blocks of basic polymers would devastate the industry. In fact, no such disaster occurred. For example, the issuance in 1965 of a basic patent broadly claiming...ethylene-propylene-diene monomer ("EPDM") rubber ... did not preclude the later issuing of patent to different inventors for several copolymers of this type." Doll Decl. ¶ 25.

introns) scattered across an 81 million base-pair DNA sequence.[24] Myriad did not simply purify or extract the claimed DNA from natural sources (i.e., enrich an existing natural product by removing unwanted components). Rather, Myriad synthesized U.S. '282 Claim 2 cDNA sequence *de novo* from basic nucleotide components, which are themselves artificially synthesized compounds (e.g., oligonucleotide primers). Figure 1 (above) shows the key transformation steps used in Myriad identification and synthesis of the entire cDNA coding sequence from the chromosomal gene, [25] each of which represents careful, laborious and creative efforts by Myriad researchers over a decade.

Thus, but for Myriad's transformative synthetic activity, Myriad Synthetic cDNA would not have come into existence as a chemical entity. After identifying the coding sequence, the human intervention here transforms nucleotide building blocks into a non-natural composition of matter, which is surely sufficient to render Myriad Synthetic cDNA the result of human ingenuity, and which is not the handiwork of nature.

Finally, Myriad Synthetic cDNA is indisputably useful as a diagnostic tool, as evidenced by Myriad's medical and economic success employing

[24] Myriad Synthetic DNA is not a natural gene. A gene is "integrated into the chromosome and are not broken or detached from the chromosome." Kay Decl. ¶ 27. Myriad Synthetic cDNA does not have the same ordering of nucleotides as the native BRCA1/2 genetic sequence.

[25] See Factual Background, *supra*.

Myriad Synthetic cDNA compound useful to predict genetic pre-disposition to breast and ovarian cancer.[26]

Therefore, under the statutory construction set forth in *Chakrabarty*, Myriad Synthetic cDNA is no doubt patent-eligible subject-matter under §101.

C. *Prometheus* Does Not Compel Reversal of Earlier CAFC Decision on §101-Includability

In its July 2011 decision, the CAFC properly reversed the District Court of Southern District of New York, on matters of law and fact, as to §101-includability, of Myriad U.S. '282 Claim 2 cDNA sequence.

§101-includability of Myriad cDNA is fundamentally consistent with the Supreme Court's holding in *Chakrabarty*, and fully supported by firmly established case law developed since enactment of the 1952 Patent Act.

Nothing in the Supreme Court decision in *Prometheus* directs the CAFC to alter its earlier finding of U.S. '282 Claim 2 cDNA sequence as being §101-eligible.

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[26] See the description of BRAC*Analysis*™, Crichtfield Decl. ¶¶ 26-30; Skolnick Decl. ¶¶ 19-23.

IV. CONCLUSION

A. CAFC Myriad Decision Should Not Be Reversed on Basis of *Prometheus*

Prometheus claims at issue before the U.S. Supreme Court were directed to a diagnostic method, which the Court found, recited routine, conventional "administering" & "data-measuring" steps already widely used in the medical community. The critical "point-of-novelty" of the claim required a mathematical correlation between data-measuring steps. Further, the Court found that these *Prometheus* claim steps:

--- (a) "when viewed as a whole" applied a "law of nature" without sufficient "transformation of the substance" of the claim; and

--- (b) did not satisfy test in *Diamond v. Diehr* of transforming a claimed process into an "inventive" application of underlying formula ("law of nature").

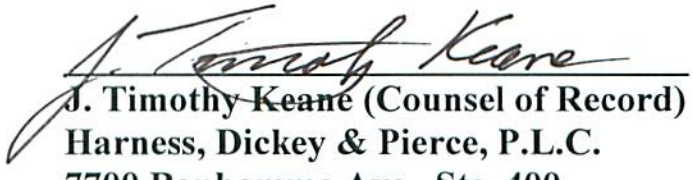
These Supreme Court findings on *Prometheus* do not apply to Myriad Synthetic cDNA because:

--- (a) No "<u>transformative</u> outcome" was yielded by *Prometheus* claims, whereas Myriad Synthetic cDNA is a made-by-man application of at least 20 <u>transformative</u> steps resulting in a sequence of nucleotides that has <u>not</u>, and could <u>not</u>, exist in nature.

--- (b) Myriad Synthetic cDNA "transformative outcome" fully meets the *Diehr* standard of §101-eligible subject-matter that is not mere application of a "mathematical formula" or "law of nature."

Dated: 14 June 2012

Respectfully submitted,



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CERTIFICATE OF SERVICE

This is to certify that on 14 June 2012 two true and correct copies of the foregoing document were served on the following registered counsel of record via FedEx (overnight delivery).

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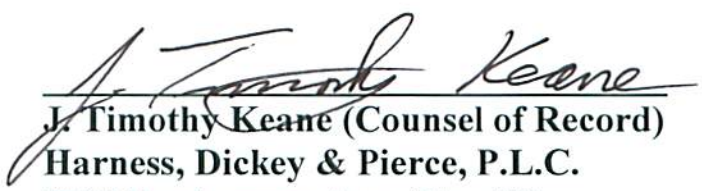

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14 June 2012

CERTIFICATE OF COMPLIANCE

1. This brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7)(B). The brief contains 2,055 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii).

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6). This brief has been prepared in a proportionally spaced typeface using Microsoft Word 2003 in Times New Roman 14 point font.

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