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. AND BIOGENERATOR IN SUPPORT OF DEFENDANTS-APPELLANTS AND URGING REVERSAL

J. Timothy Keane (Counsel of Record)
Harness, Dickey & Pierce, P.L.C.
7700 Bonhomme Ave., Ste. 400
St. Louis, MO 63105
Telephone: 314-726-7500
tkeane@hdp.com

Counsel for Amici Curiae

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TABLE OF CONTENTS

Page

TABLE OF AUTHORITIES

Page

CASES

STATUTES

OTHER AUTHORITIES

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 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 patents; each has a strong interest in ensuring the stability of the patent system as it relates to chemical inventions.

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

BioGenerator is a Missouri non-profit corporation that works closely with university technology transfer offices, researchers, entrepreneurs, community leaders and the investment community, to identify promising plant and life science technologies with sufficient potential to form a start-up company.

I. STATEMENT OF CASE

This is not a "gene patent" case. This case is an inquiry as to scope of includable substances 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 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") has 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 DNA sequence recited as SEQ ID NO:1 ("Myriad Synthetic DNA"). [4]

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

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[3] Using Myriad Synthetic DNA 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").

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

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.**

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 DNA.**

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 and all applicable case law, its decision should be reversed as to its adverse finding on §101-includability. [6]

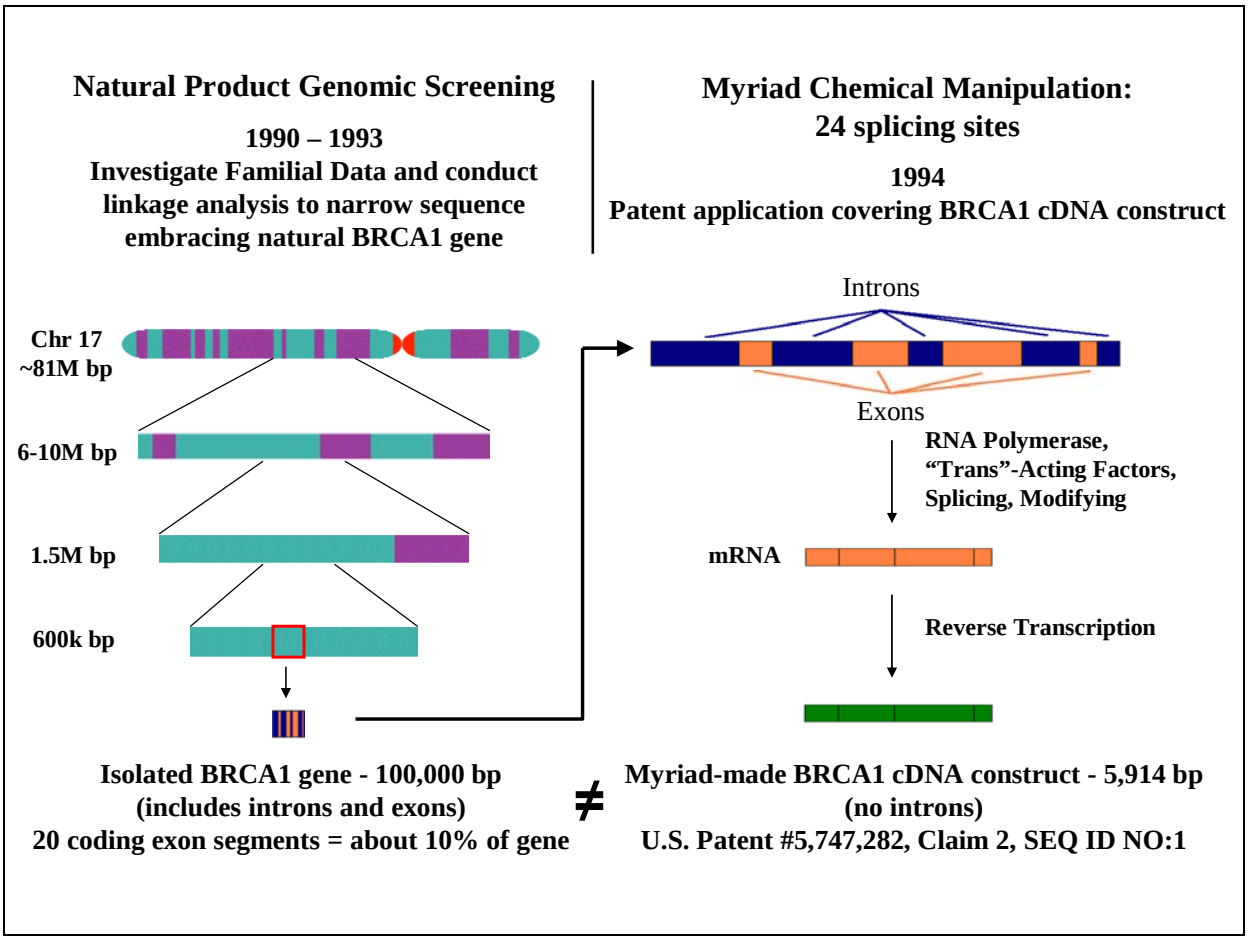
II. FACTUAL BACKGROUND

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 DNA sequence resulted from a lengthy series of transformative steps starting with

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

identification of a genetic territory within Chromosome 17 (comprising ~81 million DNA base pairs) that housed BRCA1 gene (comprising ~84,000 DNA base pairs). Using familial genetic 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 synthetic DNA sequence of ~6,000 base-pairs characterized by an uninterrupted coding sequence, which does not occur in nature. This synthetic DNA is useful as an effective and highly-efficient probe for diagnosis of ovarian and breast cancer genetic pre-disposition. The highlights of Myriad's process resulting in Myriad synthetic DNA are illustrated in Figure 1, as follows:

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



After initial localization of BRCA1 natural gene to Chromosome 17 (~81 million base pairs), the BRCA1 gene had to be localized to a region small enough to effectively use positional cloning to identify the genetic sequence. The coding exons were subsequently identified and combined to make Myriad Synthetic DNA compound. Each labor-intensive transformative-step took a team of dedicated Myriad scientists months to accomplish, totaling to about 10 years:

-- 1) Localize to Mfd15 (D17S250)–42D4 (D17S588) by multipoint linkage analysis (6-10 million base pairs).[7]

-- 2) Refine region to THRA1-D17S183.[8]

-- 3) Further refine region to THRA-D17S78. [9]

-- 4) Identify BRCA1 gene locus between D17S776 and D17S78 (1.5 million base pairs).[10]

-- 5) Construct physical map of the D17S776–D17S78 region using positional cloning:

(a) Obtain DNA samples from large, well-documented families with inherited breast cancer;

(b) Identify appropriate polymorphic markers in the BRCA1-gene region;

(c) Type individuals from suitable families with suitable polymorphic markers to yield a sufficiently small chromosomal region containing the BRCA1 gene;

(d) Identify the genetic structure within that small chromosomal region;

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[7] (US '282 at col. 9 and col. 46, lines 34-36).
[8] (US '282 at col. 46, lines 35-37).
[9] (US '282 at col. 46, lines 38).
[10] US '282 at col. 9 and col. 46, lines 45-56.

(e) Identify causal mutations in genetic sequences that correlate with breast cancer in a statistically significant manner, but not with control or non-cancer patients.[11]

-- 6) Identify candidate cDNA clones for BRCA1 genetic locus by genomic analysis of contig region (set of overlapping DNA segments derived from the same source).[12]

-- 7) Construct detailed maps of transcripts for 17q21 chromosomal region D17S1321–D17S1324 (600,000 base pairs).[13]

-- 8) Within D17S1321–D17S1324 region, screen 65 candidate expressed sequences selected by hybridization, direct screening of cDNA library, and random sequencing of P1 subclones.[14]

-- 9) Combine 21 sequences (SEQ ID NOS. 14-34) to obtain an intermediate synthetic DNA construct (100,000 base pairs).[15]

-- 10) Transcribe the intermediate synthetic DNA construct to mRNA.

-- 11) After intron excision, transcribe 23 coding exons to produce a full-length, intron-free DNA construct, SEQ ID NO: 1 (5,914 base pairs) [16]

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[11] Shattuck Decl., ¶ 4.; US '282 at col. 46-49.
[12] US '282 at col. 49-52.
[13] US '282 at col. 52.
[14] US '282 at col. 52, lines 43-46.
[15] US '282 at col. 54 and FIGS 10A-H.
[16] US '282 at col. 53.

Myriad gathered an extensive and well-documented collection of kindred family data for 17q-linked breast and ovarian cancer, including Kindred 2082, which alone contained 51 breast cancer cases and 22 ovarian cases. Such familial-genetic compilations provided guidance for scientists to carry out positional cloning (Step 5 above).[17] **During the chemical synthesis of Myriad Synthetic DNA, segments of selected DNA sequence were combined to give an intermediate synthetic DNA construct (Step 9). The intermediate synthetic DNA construct had an open reading frame of 5,914 nucleotides distributed over about 100,000 base pairs. If an incomplete open reading frame were mistakenly believed to be complete, mutations located in the overlooked portion would have been missed and the entire coding sequence not properly identified. Every nucleotide in the final DNA construct had to be correctly placed so that the open reading frame was preserved.**[18] **Synthesis of a ~6,000 base-pair nucleotide-construct containing the putative BRCA1 region was guided by this arduous and costly data-collection and evaluation.**

[17] Shattuck Decl. ¶ 11, 12; US '282, 38: 51-53.
[18] Shattuck Decl. ¶ 27.

III. ARGUMENT

A. S.D.N.Y. Failed to Recognize "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.[19] **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."** [20] **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'."** [21] **Thus, the current statutory design is to set a broad, welcoming threshold to "embod[y] Jefferson's philosophy that 'ingenuity should receive a liberal encouragement'."** [22]

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[19] *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).
[20] *Chakrabarty*, at 308.
[21] *Id.* at 309 (citation omitted).
[22] *Id.* at 308-309

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 ideas are not patentable.[23] 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." [24] **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 it is "the result of human ingenuity and research."** [25]

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 isolated or purified natural substances. [26, 27] **Up to present case, there is no**

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[23] *Id.* at 309
[24] *Id.* at 313 (emphasis added).
[25] *Id.*
[26] 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);

reported case law in past 60 years (since discovery of existence of natural DNA consisting of nucleotide sequences) declaring that a synthetic DNA compound is excludable from §101.

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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).

[27] 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).

Exemplary of judicial determinations in §101-includable cases, the Court in *In re Bergstrom* held that purified prostaglandin compounds (e.g., pure PGE_2 and pure PGE_3) are "not 'naturally occurring'" because they "do not exist in nature in pure form, and appellants have neither merely discovered, nor claimed sufficiently broadly to encompass, what has previously existed in fact in nature's storehouse, albeit unknown, or what has previously been known to exist." [28]

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 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. S.D.N.Y. Erred By Imposing "Markedly Different" Test to Determine §101-Includability

After reviewing case law stretching from *American Wood-Paper* [29] to *Chakrabarty*, the S.D.N.Y. Court concluded that "purification of a product of

[28] *In re Bergstrom*, at 1401.
[29] *American Wood-Paper v. The Fibre Disintegrating Co.*, 90 U.S. 566 (1874).

nature, without more, cannot transform it into patentable subject matter. Rather, the purified product must posses 'markedly different characteristics' [from a product of nature] in order to satisfy the requirement of §101." [30]

i. "Marked Difference" As Requirement For §101 Includability?

In *Chakrabarty*, the Supreme Court contrasted Chakrabarty's genetically modified bacterium (patentable subject matter) with the bacterial mixture in *Funk Brothers* (unpatentable subject matter), [31] **stating that Chakrabarty "has produced a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility. His discovery is not nature's handiwork, but his own. . ."** [32] **Thus, the Supreme Court described a *sufficient* condition for a substance to be man-made, as opposed to "nature's handiwork." There is no reasonable basis for the S.D.N.Y. Court to infer from this statement that the Supreme Court had imposed a "markedly different characteristics" requirement into the statutory language of §101, especially when the Supreme Court concluded,**

[30] *Assoc. for Molecular Pathology*, at 227.
[31] *Funk Bros. Seed Co. v. Kalo Inoculant Co.* 333 U.S. 127 (1948).
[32] *Chakrabarty*, at 310.

from legislative history, that patentable subject matter must be broadly interpreted to include "anything under the sun that is made by man." [33]

ii. "Made-By-Man" Standard Should Not Be Replaced by Narrower Interpretation of §101

The "made-by-man" standard denotes human activity or intervention. In *Funk Brothers*, the only human intervention is the simple mixing of the bacteria into one product, with each "serv[ing] the ends nature originally provided and act[ing] quite independently of any effort of the patentee." [34] **Such intervention is "hardly more than an advance in the packaging of the inoculants."** [35] **Therefore, a sufficient level of human intervention is required for an invention to be "made by man." Accordingly, the USPTO indicates that the test for patentable subject matter (including living organism) is whether "the invention is the result of human intervention."** [36]

The S.D.N.Y. Court substituted the "markedly different" test for the "made-by-man" standard. But, these two legal standards are not interchangeable. The "markedly different" test is a narrower interpretation of the statutory language and may not be applied without violating the

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[33] *Chakrabarty*, at 309.
[34] *Funk Bros. Seed Co.*, at 442.
[35] *Id.*
[36] *Manual of Patent Examining Procedure* §2105 (2008).

legislative intent of §101, as well as the broad statutory interpretation set forth in *Chakrabarty*. [37] **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). This "making" is the cause, and the "marked difference" from the starting material is the result. The focus of §101 should be the "made-by-man" aspect of a human endeavor, and a court should not confuse the standard for §101-includability by imposing a "marked difference" test.**

iii. S.D.N.Y. Court Ignored Post-1952 Case Law

In formulating the "markedly different" test, the S.D.N.Y. Court mainly relied on pre-1952 case law. [38] **Surprisingly, the S.D.N.Y. Court treated *In re***

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[37] *Chakrabarty*, at 309.

[38] *Assoc. for Molecular Pathology*, at 222-227, the cases relied upon by the District Court include:

a. *American Wood-Paper v. The Fibre Disintegrating Co.*, 90 U.S. 566 (1874). Extract obtained by purification of cellulose pulp not patent-eligible. Distinction: Myriad Synthetic DNA requires human ingenuity and transformative actions beyond mere purification.
b. *Cochrane v. Badische Anilin & Soda Fabrik*, 111 U.S. 293 (1884). Artificial version of natural red dye is not new composition of matter and thus not patent-eligible. Distinction: Myriad Synthetic DNA is new, man-made composition of nucleic acids that differ in structure and in function from native genetic material.
c. *American Fruit Growers v. Brogdex Co.* 283 U.S. 1 (1931). Orange coated with borax not patent-eligible because no changes occurred to character of fruit. Distinction: Myriad Synthetic DNA possesses new properties and capabilities attributable to new structure distinct from natural product.

***Bergstrom* and *In re Kratz* as presenting "issues of novelty and anticipation rather than the question of patentable subject matter."** [39] **In both cases, the CCPA affirmed patentability of a purified natural substance,** [40] **a result predicated on recognition that isolated DNA is patentable subject matter under §101 of the 1952 Patent Act. Further, the S.D.N.Y. Court ignored cases decided in light of *Chakrabarty* upholding §101-includability of synthetic compounds and isolated or purified natural substances, supra.** [41]

The 1952 Patent Act is a re-codification of prior case law. In light of *Chakrabarty's* broad interpretation of §101, any analysis on patentable subject matter must start from the statutory text and the legislative intent extending patent eligibility to "anything under the sun that is made by man." Therefore, fundamentally inconsistent with the holding in *Chakrabarty* and the leading case law, the S.D.N.Y. Court here truncated the "made-by-man" standard by replacing it with the "markedly different" test.

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d. *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948). Discovery of non-inhibitive qualities of mixture of different strains of bacteria not patent-eligible because no changes occurred in structure or function. Distinction: Myriad synthetic DNA is new, man-made compound and not work of nature.

[39] *Assoc. for Molecular Pathology*, at 226.
[40] *In re Bergstrom*, 427 F.2d 1394 (C.C.P.A. 1970); In re Kratz, 592 F.2d 1169 (C.C.P.A. 1979).
[41] See footnote 26 and 27

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

Under *Chakrabarty*, "natural product" or "natural phenomena" are exclusions to the broad scope of §101.[42] 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.

Myriad Synthetic DNA molecule meets all three requirements.

First, DNA molecules are chemical entities that consist essentially of carbon, hydrogen, oxygen, nitrogen and phosphorous elements. There is no fundamental difference between DNA and other chemicals for purposes of patent law – they are all compositions of matter includable in §101.[43]

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[42] *Chakrabarty*, at 309.

[43] 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

Secondly, Myriad Synthetic DNA is clearly a made-by-man substance. Myriad Synthetic DNA molecule contains the entire coding sequence of the BRCA1/2 diagnostic protein and does not exist in nature. Unlike Myriad Synthetic DNA molecule, the naturally-occurring DNA of Chromosome 17 has fragments of the BRCA-gene coding sequence (in the form of exons) scattered across an 81 million base-pair DNA sequence.[44] **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 the DNA sequence *de novo* from basic nucleotide components, which are themselves artificially synthesized compounds (e.g., oligonucleotide primer). There are at least 11 major steps in the identification and synthesis of the entire DNA coding sequence from the chromosomal gene,** [45] **each of which represents the careful, laborious and creative efforts by Myriad researchers over a decade.**

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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.

[44] 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 DNA do not have the same ordering of nucleotides as the native BRCA1/2 genetic sequence.

[45] See Factual Background, *supra*.

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

Finally, Myriad Synthetic DNA is indisputably useful as a diagnostic tool, as evidenced by Myriad's medical and economic success employing Myriad Synthetic DNA compound useful to predict genetic pre-disposition to breast and ovarian cancer.[46]

Therefore, under the statutory construction set forth in *Chakrabarty*, Myriad Synthetic DNA is no doubt patentable subject matter under §101.

C. "Markedly Different" Standard Confirms Myriad Synthetic DNA as "New & Useful"

1. S.D.N.Y. Test: Distinctive Form, Quality, Or Property

The S.D.N.Y Court observed that "this requirement [set forth in *Chakrabarty*], that an invention possess 'markedly different characteristics'

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

for purposes of §101 reflects the oft-repeated requirement that an invention have 'a new or distinctive form, quality, or property' from a product of nature." [47] **However, the S.D.N.Y. Court misapplied this requirement to the facts of this present case by finding that Myriad Synthetic DNA was neither structurally nor functionally distinct from natural product. This finding constitutes clear error on a question of fact.** [48]

2. Structural Differences

Myriad Synthetic DNA, as a chemical entity, does not exist in nature. It is the product of a series of synthetic steps that (1) produce the coding sequences identified in the chromosomal DNA, and (2) assemble them into a DNA molecule in which the complete nucleotide sequence encodes the polypeptide sequence of BRCA1/2 protein. Myriad Synthetic DNA contains the entire coding sequence of BRCA1/2 in an uninterrupted sequence (~ 6000 base pairs), while in nature, fragments of BRCA1/2 coding sequences are scattered across the chromosomal DNA (81 million base pairs on Chromosome 17) that also contains regulatory sequences, such as introns. The S.D.N.Y. Court did not explain why a man-made structural change of this scale (i.e., reduction of the size of DNA sequence from the natural product's

[47] *Assoc. for Molecular Pathology*, at 223, citing *Am. Fruit Growers*, 283 U.S. at 11. (emphasis added).
[48] *Id.* at 227-232.

81 million base pairs to the synthetic molecule's 6000 base pairs) "does not render these cDNA and their native counterparts 'markedly different'." [49]

Myriad Synthetic DNA must be obtained in an essentially pure form, free from cellular components. To the contrary, natural DNA (such as the native BRCA1 gene embedded in Chromosome 17) within chromatin complexes with histone proteins. Such protein complex is critical for the natural DNA's tight chromosomal packing. Variations in chromatin density and exposure to the intracellular environment modulate the function of natural DNA. "Tight packing is also vital for the functioning of genes at various stages of the cell cycle." [50] **"The structure of the chromatin regulates access to genes of molecules required for transcription and gene expression."** [51] **Myriad Synthetic DNA does not possess other cellular components (e.g., histone proteins) that determine the packing of natural DNA. In fact, chromosomal packing, while preserving natural DNA function, is completely irrelevant to (and thus is not the structural basis of) the function of Myriad Synthetic DNA.**

[49] *Id.* at 230.
[50] Atherly *et al.*, *The Science of Genetics*, ISBN:0030292328 (2000), at 293.
[51] Petricoin Decl. ¶ 16.

The S.D.N.Y. Court also mentioned that Myriad's "claimed cDNA sequences are actually found in the human genome in the form of a naturally occurring pseudogene."[52] **But §101-includability of Myriad's Synthetic DNA remains unchallenged by the S.D.N.Y. Court's assessment because:**

-- 1) The sequence identity of the putative pseudogene to Myriad Synthetic DNA is not substantiated by evidence;

-- 2) The putative pseudogene has not been isolated from its cellular environment to a level of purity comparable to that of Myriad Synthetic DNA; and

-- 3) The Myriad U.S.'282 Claim 2 recites Myriad Synthetic DNA only, and does not embrace any naturally-found nucleotide sequence.

Thus, the S.D.N.Y. Court clearly erred by ignoring three crucial structural features distinguishing Myriad Synthetic DNA from any natural DNA:

-- 1) Reduction of molecular size from natural-gene 84,000 base-pair length to 5,914 base-pair sequence;

-- 2) Excision of non-coding intron-segments from natural gene; and

-- 3) Elimination of chromosomal packing directed by chromatin and other cellular components which maintain natural gene structure and function.

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[52] *Assoc. for Molecular Pathology*, at 230.

Thus, the S.D.N.Y. Court's observation is clearly erroneous that "[t]he entire premise behind Myriad's genetic testing is that the claimed isolated DNA retains, in all relevant respects, the identical nucleotide sequence found in native DNA."[53]

3. Functional Property Is Inseparable From Structural Characteristics

The S.D.N.Y. Court decided that the function of Myriad Synthetic DNA is not "markedly different" from that of natural DNA, even though Myriad Synthetic DNA may be used as a molecular probe in the diagnosis of cancer,[54] **which is a property not possessed by natural DNA. The S.D.N.Y. Court further concluded that "the use of isolated DNA for the various purposes cited by Myriad does not establish the existence of differences 'in kind' between native and isolated DNA that would establish the subject matter patentability of what is otherwise a product of nature."** [55]

The function of a DNA molecule is inseparable from its physical form, quality and molecular structure. The distinctive form and quality of Myriad Synthetic DNA is manifest in its purity (free of other cellular content) and structure (complete uninterrupted coding sequence). The purity and

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[53] *Id.* at 231.
[54] *Id.*
[55] *Id.* at 232, citing *Am. Fruit Growers*, 283 U.S. at 11.

distinctive structure of Myriad Synthetic DNA forms the basis of its distinctive property and function. For example, Myriad Synthetic DNA is not subject to alternative splicing and does not give rise to different sequential combinations of coding exons because it does not contain introns or the 43 intron/exon junctions present in the natural DNA. [56] **The most distinctive functional feature of Myriad Synthetic DNA is its practical utility as a molecular probe for the diagnosis of ovarian or breast cancer in women.** [57] **In contrast, the natural DNA does not have this specific, practical use. Thus, by having a utility not contained in natural DNA, Myriad Synthetic DNA differs wholly from natural DNA "in kind" with respect to its function.**

The mere fact that a synthetic DNA molecule performs a natural information-carrying function should not be outcome-determinative in the factual inquiry for distinctive function or property. Every human invention is based upon application of some natural law, using basic materials that nature provides. Given the problem the invention at issue is set to resolve (i.e., diagnosis of genetic pre-disposition for cancer), the focus instead should be on the fact that Myriad Synthetic DNA not only contains the entire natural genetic information encoding the target protein, but also is practically used as

[56] US '282 at col. 53, Table 9.
[57] US '282, col. 2, lines 59-61, citing Easton et al., *Am. J. Hum. Genet.*, 52:678-701 (1993).

a research and diagnostic tool, which cannot be accomplished by natural DNA in the human body.

Thus, a court must not analyze the functional distinction (i.e. "difference in kind") of the Myriad Synthetic DNA without taking into consideration its structural distinction from natural DNA and the level of human intervention in achieving such non-natural structure. The S.D.N.Y. Court over-emphasized the general information-carrying function of Myriad Synthetic DNA as a basic genetic material, but ignored the specific utility of this molecule as a diagnostic tool – a human-engineered function that is targeted at probing genetic diseases by design.

IV. CONCLUSION

The District Court of Southern District of New York erred as a matter of law in altering the scope of §101-includability, from "anything under the sun that is made by man", to one requiring "markedly different characteristics" from natural products.

As a matter of patent law, such a narrow interpretation of §101-includability is fundamentally inconsistent with the Supreme Court's holding in *Chakrabarty,* and is directly incompatible with the firmly established case law following enactment of the 1952 Patent Act.

In its factual determination, the S.D.N.Y. Court was clearly erroneous in:

-- 1) Ignoring (without explanation) the structural distinctions of Myriad Synthetic DNA as compared to natural DNA;

-- 2) Over-emphasizing the general information-carrying function of Myriad Synthetic DNA; and

-- 3) Failing to recognize the specific, human-engineered, and practical utility of Myriad DNA molecule as a diagnostic tool for genetic disease that is unachievable by natural DNA.

For these reasons, the S.D.N.Y. Court's exclusion of Myriad Synthetic DNA from scope of §101-includable subject-matter should be reversed.

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Respectfully submitted,

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J. Timothy Keane (Counsel of Record)
Harness, Dickey & Pierce, P.L.C.
7700 Bonhomme Ave., Ste. 400
St. Louis, MO 63105
Telephone: 314-726-7500
tkeane@hdp.com

Counsel for Amici Curiae
Gilead Sciences, Inc.
and
BioGenerator