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.

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* ROSETTA GENOMICS, LTD., ROSETTA GENETICS, INC., AND GEORGE MASON UNIVERSITY IN SUPPORT OF DEFENDANTS-APPELLANTS, SUPPORTING REVERSAL

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TABLE OF CONTENTS

Page

IDENTITY AND INTEREST OF AMICI CURIAE 1

AUTHORITY TO FILE 2

ARGUMENT 2

I. INTRODUCTION 2
- A. Procedural History 2
- B. This Brief Only Addresses Patentability of "Isolated DNA" Claims 5

II. IMPACT OF GENE PATENTS AND CLAIMS RECITING "ISOLATED DNA" 6
- A. Abolishing Gene Patents Will Deter, Not Promote, Innovation 6
- B. Patent Claims Directed to "Isolated DNA" Stimulate Data Sharing and Innovation 10

III. PATENTABILITY UNDER 35 U.S.C. § 101 – "ISOLATED DNA" CLAIMS 15
- A. *Chakrabarty* and *Funk Brothers* 18
  1. Isolated DNA are new, changed, markedly, and qualitatively different from native DNA 22
  2. Isolated DNA have many different uses and effects, as well as improved function, as compared to native DNA 25
  3. Isolated DNA serve more than "ends nature originally provided" and do not exist nor act independently of human effort 27
- B. Other Relevant Legal Precedent and USPTO Position 28
  1. USPTO Has Issued Tens of Thousands of Gene Patents 29
  2. Congress Has Refused To Abolish Gene Patents, Despite Ample Opportunity 30
  3. Other Legal Considerations 31

IV. CONCLUSION 33

TABLE OF AUTHORITIES

Page

FEDERAL CASES

Am. Fruit Growers, Inc. v. Brogdex Co.,
283 U.S. 1 (1931) 19

Association for Molecular Pathology, et al. v. U.S. Patent and Trademark Office, et al.,
702 F.Supp.2d 181 (S.D.N.Y. 2010) ..... *Passim*

Bilski v. Kappos,
130 S.Ct. 3218 (2010) 5, 17-18

Diamond v. Chakrabarty,
447 U.S. 303 (1980) ..... *Passim*

Diamond v. Diehr,
450 U.S. 175 (1981) 17-18

Funk Bros. Seed Co. v. Kalo Inoculant Co.,
333 U.S. 127 (1948) ..... *Passim*

Hartranft v. Wiegmann,
121 U.S. 609 (1887) 20

In re Bilski,
545 F.3d 943 (Fed. Cir. 2008) 5

In re Fisher,
421 F.3d 1365 (Fed. Cir. 2005) 31

Intervet Inc. v. Merial Ltd.,
617 F.3d 1282 (Fed. Cir. 2010) 3, 17, 22, 31

J.E.M. AG Supply, Inc. v. Pioneer Hi-Bred Int'l.,
534 U.S. 124 (2001) 28

Parke-Davis & Co. v. H.K. Mulford & Co.,
189 F. 95 (S.D.N.Y. 1911), *aff'd in part*, 196 F. 496 (2d Cir. 1912) 32

Shell Dev. Co. v. Watson,
149 F. Supp. 279 (D.C. 1957) 19-20

U.S. v. Dubilier Condenser Corp.,
289 U.S. 178 (1933) 17

FEDERAL STATUTES

35 U.S.C. § 101 ..... *Passim*

35 U.S.C. § 112 11

RULES

Federal Rule of Appellate Procedure 29(a) 2

REGULATIONS

Utility Examination Guidelines, 66 Fed. Reg. 1092 (2001) 8, 29, 31

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H.R. 977: "Genomic Research and Accessibility Act"
(introduced on February 9, 2007, in 110th Congress) 30

H.R. Rep. No. 1923, 82d Cong., 2d Sess., 6 (1952) 19

Secretary's Advisory Committee on Genetics, Health and Society (SACGHS): Public Consultation Draft Report on Gene Patents and Licensing Practices and the Impact on Patient Access to Genetic Tests, 75 (2009) 14

S. Rep. No. 1979, 82d Cong., 2d Sess., 5 (1952) 19

Congressional Testimony of James A. Severson at hearing on "Gene Patents and Other Genomic Inventions," House Committee on Judiciary, Subcommittee on Courts and Intellectual Property, July 13, 2000 ..... 7, 13

IDENTITY AND INTEREST OF AMICI CURIAE

Rosetta Genomics, Ltd., and its wholly-owned subsidiary Rosetta Genomics, Inc., (collectively "Rosetta") create and market minimally-invasive molecular tests based on the use of nucleic acids found in the human body, and the technical platforms used to conduct these tests. Rosetta has launched three diagnostic tests for cancer and is currently developing additional tests for the diagnosis of additional human cancers. Through its research and development efforts, Rosetta is also the owner of numerous patents claiming isolated nucleic acid sequences. *See, e.g.,* U.S. Patent Nos. 7,618,814; 7,592,441; 7,250,496; 7,217,807; and 7,642,348. Thus, issues raised in this case are of great importance to Rosetta.

George Mason University ("GMU") is a public university located in Virginia. The university includes numerous laboratories and facilities conducting cutting-edge research in the biosciences, including cancer research and proteomics. Its new biomedical research laboratory is one of 13 nationwide being built with the help of a $25 million grant from the National Institute of Allergy and Infectious Diseases. Certain research conducted by the universities' scientists is incorporated into patent applications covering cancer diagnostics. See, for example, U.S. Patent Publication No. 2009/0275546. Thus, issues raised in this case are of great importance to George Mason University.

AUTHORITY TO FILE

All parties have consented in writing to the filing of this amicus brief by Rosetta and GMU. Consequently, in accordance with Federal Rule of Appellate Procedure 29(a) (amicus brief may be filed "if the brief states that all parties have consented to its filing"), no motion for leave to file has been submitted.

ARGUMENT

I. Introduction

A. Procedural History

This case has generated significant public comment regarding so called "gene patents." The ACLU and Plaintiffs-Appellees have welcomed, and in fact encouraged, the public attention and resulting controversy. These groups ask questions such as: Should for-profit corporations be able to charge large sums of money for important medical products, especially when many patients have inadequate health insurance? Do patents, especially gene patents, promote or impede important science and medical choices? According to Plaintiffs-Appellees, judicial abolition of gene patents is the simplest way to resolve these difficult public policy questions.

This simplistic viewpoint both mischaracterizes and misunderstands what motivates scientific innovation, and ignores the high cost and risks of failure associated with placing any medical product into the hands of doctors and patients.

If Plaintiffs-Appellees' negative position regarding subject matter patentability of isolated nucleic acids became law, many goals of the biotechnology community—innovation, public dissemination of scientific knowledge, and practical application of medical advances—would be subverted.

At the district court, Plaintiffs-Appellees successfully exploited the fact that "neither the Supreme Court nor [the Federal Circuit] has directly decided the issue of the patentability of isolated DNA molecules" under 35 U.S.C. § 101.[1] In fact, in apparent agreement with assertions and assumptions of Plaintiffs-Appellees, the district court invalidated every single "isolated DNA" composition claim at issue in this case under § 101. In the process, the district court became the first U.S. court to conclude that "isolated DNA" compositions correspond to unpatentable products of nature—irrespective of whether such chemical compositions ever exist in nature. Citing no case law for the proposition, the district court unilaterally opines that because DNA manifests "a physical embodiment of information," isolated DNA is not "markedly different" from native DNA.[2]

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[1] *Intervet Inc. v. Merial Ltd.*, 617 F.3d 1282, 1293, (Fed. Cir. 2010) (J. Dyk, concurring-in-part, dissenting-in-part).

[2] *Association for Molecular Pathology, et al. v. U.S. Patent and Trademark Office, et al.*, 702 F.Supp.2d 181, 229 (S.D.N.Y. 2010).

The district court appears to have created this premise in an effort to obliterate patentability of compositions comprising DNA in particular, without necessarily challenging patentability of all compositions somehow derived or isolated from products existing in nature. That said, the district court's sweeping reasoning applies not only to "isolated DNA" *per se*, but also to any man-made compositions comprising isolated nucleic acids. Examples of such compositions include cDNA, plasmids, vaccines, PCR probes, interfering or micro RNA, nucleotide-based biologics, recombinant cells, transgenic animals, and compositions involved in gene therapy. In other words, the district court's reasoning has the potential to negatively impact almost every patent portfolio involving recombinant DNA/RNA technology.

The district court decision glosses over the fact that other U.S. courts—not to mention thousands of patentees, the U.S. Patent and Trademark Office ("USPTO") and the biotech industry as a whole—have consistently assumed and relied upon patent eligibility of claims directed to isolated DNA compositions.

While the district court opinion is not binding precedent, the Federal Circuit's review of this decision presents an opportunity to issue a precedential decision that will have significant implications for thousands of patentees, including *amici*, and the entire biotechnology industry. A decision against subject matter patentability by this court would significantly undermine biotechnology

innovation, as well as the viability of relevant industries such as those providing biologics (and biosimilars), personalized medicine and diagnostics, just to name a few. Because of the importance of this issue, *amici curiae* submit this brief.

B. This Brief Only Addresses Patentability of "Isolated DNA" Claims

This brief will not address certain issues presented by the case, and specifically will not address subject matter patentability of Myriad's diagnostic method claims. Although an important issue, other pending cases consider patentability of diagnostic method claims and may offer better vehicles to resolve this complex area of law in light of the Supreme Court's recent decision in *Bilski*.[3]

Because *amici* are not aware of any other pending Federal Circuit or Supreme Court case that concerns subject matter patentability of composition claims directed to genetic material, this brief addresses the issue of patentability of Myriad's "isolated DNA" claims on appeal here. The issue at hand, i.e., whether such composition claims recite patent-eligible subject matter under § 101, is a question of law that this court reviews *de novo*.[4]

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[3] *Bilski v. Kappos*, 130 S.Ct. 3218 (2010).

[4] *In re Bilski*, 545 F.3d 943, 951 (Fed. Cir. 2008).

Amici respectfully request that this Court reverse the district court's decision regarding Myriad's "isolated DNA" claims and find in favor of subject matter patentability regarding at least the composition claims at issue in this case.

II. Impact of Gene Patents and Claims Reciting "Isolated DNA"

A. Abolishing Gene Patents Will Deter, Not Promote, Innovation

Contrary to Plaintiffs-Appellees short-sighted view, abolishing patents on genetic inventions will have more of a dampening effect on research and development ("R&D") in relevant medical fields than any patent right could ever have.

Abolishing patent rights for genetic technology will certainly, at minimum, deter "translational" research and innovation. A closer examination of the position of Plaintiffs-Appellees at the district court indicates it to be a relatively narrow one, i.e., that abolishing gene patenting could stimulate, or at least will not deter, some *basic research* performed at the bench at universities and non-profit research institutions. Plaintiffs-Appellees scientists, for example, wish to ensure that their specific research in the laboratory or clinic is not deterred.

Plaintiffs-Appellees fail to consider or acknowledge, however, the astronomical costs and inherent large risks associated with "translating" basic

science to something actually used by patients.[5] The reality is that most "translational" aspects of genetic innovations (i.e., going from laboratory to market to bedside) are not funded or even performed by scientists or clinicians at non-profit entities. These entities usually do not have the finances or know-how needed to obtain FDA-approval, to scale up for mass production and clinical use, or to properly commercialize and distribute therapeutic products.[6] Thus, without patent protection, gene based products "in many instances would not have reached the public."[7]

While for-profit companies perform much of the important basic research in biotechnology, they perform nearly all "translational" or "applied" research and development. These companies are often funded by investors who are able to take large financial risks. The patent system provides some prospect of reward so that investors can hope to recoup, at minimum, the high costs associated with R&D and

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[5] *See, e.g.*, Skolnick Decl., A4803:10, A4804:15, A4805:17 and A4805-6:18; Critchfield Decl., A3657-8:41 (both cited in district court opinion).

[6] *Cf.*, Testimony of James A. Severson, Then-President, Cornell Research Foundation, and Then-President, Association of University Technology Managers, at hearing on "Gene Patents and Other Genomic Inventions," House Committee on Judiciary, Subcommittee on Courts and Intellectual Property, July 13, 2000 ("Severson Congressional Testimony"), pages 4-6, http://www.autm.net/AM/Template.cfm?Section=Bayh_Dole_Act&Template=/CM/ContentDisplay.cfm&ContentID=1375.

[7] *Id.* at 3-4.

then "translating" a specific innovation into a viable benefit for patients. Without such incentives, the entire U.S. system for developing biomedical therapies for patient use will become unworkable, as it necessarily will lead to a significant financial loss for any initial innovator.

This significant loss will occur, not in small part, due to the fact that other non-innovating for-profit entities will have every incentive to piggyback and freeload off the significant effort and investment of original innovators. As explained by the USPTO, "[o]ther researchers may discover higher, better or more practical uses, but they are advantaged by the starting point that the original disclosure provides."[8]

In fact, if gene patents no longer exist, particularly in a difficult economy, many biotech/pharma companies may have no choice but to shut down or greatly reduce their basic and applied R&D activities. Such companies will either freeload off the work of others or rely on previously established products. Biotech/pharma companies, who are otherwise solely responsible for getting products to doctors and patients, will have neither the finances nor the potential of future returns needed to attract necessary investment to support continued efforts to innovate. Without a viable patent system or other meaningful exclusive rights, innovators

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[8] Utility Examination Guidelines, 66 Fed. Reg. 1092, 1094, Comment (7) (Jan. 5, 2001).

will be immediately subject to competition by others who will take advantage of the innovator's investment in basic and applied R&D while providing nothing in return. This phenomenon will deter anyone from being an initial innovator, or from investing in entities doing the basic research.

In the context of the current case, abolishing gene patents also may effectively kill the relatively new diagnostic and personalized medicine industries altogether, especially in the current economy. Diagnostic and other biotech companies and investors will be unwilling and/or unable to make the needed upfront financial investments.[9]

In short, without involvement of for-profit groups/investors, most basic research will stay exactly where it will start—in academia or with other non-profit basic research institutions.[10] Very little basic research will go beyond initial stages through clinical development to lead to improved patient well being. The long term effect of Plaintiffs-Appellees' position will likely be that the availability of new diagnostics and treatments will slow to a trickle, and eventually dry up. It will ultimately lead to a downturn in innovation and reduce the number of new diagnostic, prevention and treatment options available to patients.

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[9] *See, e.g.*, Critchfield Decl., A3649:25; Linck Decl., A4422-3:74-75 (both cited in district court opinion).

[10] Skolnick Decl., A4805:18.

B. Patent Claims Directed to "Isolated DNA" Stimulate Data Sharing and Innovation

Notably, no party in this case disagrees with the premise that "data sharing is the key" to innovation.[11] All parties appear to believe that keeping relevant information "in the public domain" "encourage[s] research and development and [] maximize[s] its benefit to society."[12] As the district court notes, however, "[t]here exists deep disagreement ... concerning effects of gene patents on the procession of scientific knowledge."[13] Nevertheless, the district court apparently summarily assumes that gene patents negatively impact scientific knowledge and innovation in biotech and biomedical fields. As discussed in below, evidence cited in the district court's opinion, in fact, fails to support such an assumption.

Specifically, other than citing an idea "postulated" in law review journals, the district court opinion refers to two studies offered by Plaintiffs-Appellees: (1) the Murray study; and (2) the Cho study.[14] Dr. Murray devised her study "to gauge the impact of gene patenting on public knowledge that utilized the time lag

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[11] *Ass'n for Molecular Pathology*, 702 F.Supp.2d at 208.

[12] *Id.* (citing Sulston Decl., A2447:33).

[13] *Id* at 207-208, 211 (stating that "there exists a sharp dispute concerning the impact of patents directed to isolated DNA on genetic research and consequently the health of society.")

[14] *Id.* at 208-209.

between publication of papers on a gene sequence and the issuance of a patent claiming that gene sequence."[15]

The district court does not consider nor critique whether the methodology used in the Murray study actually provides relevant information. In fact, the Murray study merely assesses the number of citations to one published paper per case before and after a patent issues. Such information provides no valid information regarding the impact of gene patents on public knowledge, data sharing, or innovation in genetic and recombinant DNA/RNA fields. As just one example, the Murray study ignores the fact that in light of 35 U.S.C. § 112, the filing of a patent application often stimulates innovators to publicly disclose all relevant aspects of their invention to satisfy the written description, enablement and best mode requirements, rather than keep choice data or information secret. It is also worth noting that the Murray study considers gene patents only, without analyzing other types of patents. No evidence suggests that the asserted "impact" of gene patents differs from that observed with patents in any other area of technology.

As understood by the district court, the Cho study indicates that 53% of "laboratory directors" "*decided* not to develop a new clinical test because of the

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[15] *Id.* at 208.

existence of a gene patent or license."[16] The Cho study also states that 67% "*believed* that gene patents decreased their ability to conduct research."[17] Likewise, others asked by the American Society of Human Genetics "*felt* that patents had delayed or limited their research."[18] In other words, the Cho study reports the *perceptions* of certain basic researchers regarding the impact of patents on their research, but does not explore the validity of those perceptions. One should not dictate patent policy based on perceptions that are not grounded in legal reality, however. Like the Murray study, the Cho study fails to illuminate whether gene patents actually increase or decrease public knowledge and innovation. Both studies similarly fail to assess whether gene patents differ in this regard, as compared to other types of patents.

Furthermore, many in academia disagree with the hypotheses presented in the Murray and Cho studies. For example, as stated by James Severson in 2000, then-President of the Cornell Research Foundation (a not-for-profit subsidiary of Cornell University), and then-President of the Association of University Technology Managers ("AUTM"), "patents to genetic discoveries made during university research can be pursued without disrupting the core values of

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[16] *Ass'n for Molecular Pathology*, 702 F.Supp.2d at 208 (emphasis added).

[17] *Id.* (emphasis added).

[18] *Id.* (emphasis added).

publication and sharing of information, research results, materials, and know-how."[19] This AUTM President also testified regarding passage of the Bayh-Dole Act, which granted universities, small businesses and non-profit institutions control of intellectual property, including gene patents, stemming from government funded research:

> *By all accounts*, this relatively simple change in the rules [via the Bayh-Dole Act] for the management of innovations *has had a profound impact on the development and commercialization of inventions made at universities*, and on the economy.[20]

In other words, many academic researchers understand that the ability of universities to obtain and manage gene patents has a profoundly positive impact on innovation.

In making its assumptions, the district court opinion also completely side-steps the question of what "isolated DNA" claims actually encompass, and ignores the possibility that someone may take advantage of information disclosed in a patent specification while working around patent claims. The district court opinion likewise fails to adequately address other noteworthy points. As recently explained in the scientific journal *Nature*:

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[19] Severson Congressional Testimony, page 1; *see also* AUTM's current website at http://www.autm.net/Bayh_Dole_Act.htm (citing the testimony).

[20] Severson Congressional Testimony, page 3 (emphasis added).

> A survey last year revealed that for more than 40,000 gene patents, only six instances of litigation came up in relation to diagnostic testing (C. M. Holman, *Science* 322, 198-199, 2008). All six were settled or dismissed within a year and a half, suggesting that the scale of litigation is not as high as some suspected. Reports of researchers being blocked from access to patented DNA sequences or being sued for infringement are extremely rare, and workarounds are not difficult from a legal perspective.[21]

Gene patents, therefore, do not block researchers from access to patented DNA sequences. Moreover, "workarounds" are viable.

Regarding Myriad's gene patents in particular, as recently stated by the Secretary's Advisory Committee on Genetics, Health, and Society ("SACGHS"), which advises the Secretary of Health and Human Services:

> Myriad's monopoly and enforcement activities may have inhibited research—more clearly, clinical research on the use of genetic testing rather than basic research. Nonetheless, a considerable amount of research has proceeded, and any chilling effect has been at the margins.[22]

In other words, even the Myriad patents at issue in this appeal have not impeded

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[21] *Property rights: The granting of patents on human genes has so far not been the disaster it was predicted to be*, 458 NATURE 386 (2009).

[22] *Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS): Public Consultation Draft Report on Gene Patents and Licensing Practices and the Impact on Patient Access to Genetic Tests* (2009), page 75, http://oba.od.nih.gov/oba/SACGHS/SACGHS%20Patents%20Consultation%20Draft%203%209%202009.pdf.

R&D in relevant scientific areas, or even patient or clinical access to tests.[23]

In fact, Myriad's patents have significantly stimulated relevant research. Over 18,000 scientists have conducted research on the *BRCA1* and *BRCA2* genes, and have published more than 7,000 papers on those genes since Myriad's patents issued.[24] Such scientists include eight Plaintiffs-Appellees and their declarants in this case, who have themselves published over 48 scientific papers on the *BRCA1* and *BRCA2* genes.[25]

III. Patentability under 35 U.S.C. § 101 – "Isolated DNA" Claims

As acknowledged by the district court, isolated DNA is not merely information, but a chemical compound, i.e., a physical molecule.[26] That notwithstanding, the district court decision heavily relies on the notion that DNA are "physical carriers of information"[27]

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[23] *See also* Myriad Defendants' Memorandum of Law (1) In Support of Their Motion for Summary Judgment and (2) In Opposition to Plaintiffs' Motion for Summary Judgment ("Myriad's District Court Summary Judgment Memo"), A3444, A3484, (citing Parvin Decl., A4502-3:3-6; Baer Decl., A3613-5:3-6; Li Decl., A4382-4:3-6; Critchfield Decl., A3639:3, A3643-4:13).

[24] Myriad's District Court Summary Judgment Memo, A3439 and A3444.

[25] *Id.* at A3484.

[26] *Ass'n for Molecular Pathology*, 702 F.Supp.2d at 192-93.

[27] *Id.* at 228-229. Without citing basis, the district court also assumes that because DNA supposedly differs from other chemicals and biological molecules in

The district court's legal reasoning regarding isolated DNA claims is stated succinctly in the following paragraph of the opinion:

> In light of DNA's unique qualities as a physical embodiment of information, none of the structural and functional differences [between native and isolated DNA] render the DNA "markedly different." . . . The preservation of this defining characteristic of DNA in its native and isolated forms mandates the conclusion that the challenged composition claims are directed to unpatentable products of nature.[28]

In other words, the district court assumes that because DNA manifests "a physical embodiment of information" (where DNA sequence = information), isolated DNA cannot be "markedly different" from DNA as it exists in nature, and all isolated DNA, therefore, corresponds to unpatentable subject matter. The district court's opinion cites no legal basis in support of this premise, and *amici curiae* believe none exists. Many other naturally-occurring molecules manifest "a physical embodiment of information." For example, an amino acid sequence in a protein determines its three-dimensional structure and biological properties.

Indeed, the district court has devised for the first time a new and devastatingly sweeping interpretation of the law, in direct contradiction to Supreme Court precedent. As the Court has repeatedly cautioned, "courts 'should not read

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this way, relying on such a notion to invalidate claims will not negatively impact the biotech industry. *Id.* at 228 n.51.

[28] *Id.* at 229.

into the patent laws limitations and conditions which the legislature has not expressed.'"[29] By severely limiting subject matter patentability as it relates to genetic inventions, the district court's opinion does exactly that.

In a recent case addressing infringement of "isolated DNA" claims, Judge Dyk wrote a concurring-in-part and dissenting-in-part opinion suggesting that he also questions whether "isolated DNA" composition claims are patentable under § 101.[30] Judge Dyk's opinion is noteworthy because it indicates: (1) one Federal Circuit judge's thoughts after reading the district court's decision here and the Supreme Court decision in *Bilski*; and (2) Supreme Court decisions that this judge believes are most relevant, *Chakrabarty* and *Funk Brothers*.[31]

Amici curiae appreciate these two citations and agree that these cases are pertinent to the issue at hand. *Chakrabarty* and *Funk Brothers* constitute two rare Supreme Court cases that address subject matter patentability of biologic

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[29] *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980) (quoting *U.S. v. Dubilier Condenser Corp.*, 289 U.S. 178, 199 (1933); *see also Diamond v. Diehr*, 450 U.S. 175, 182 (1981).

[30] *Intervet*, 617 F.3d 1282 at 1293.

[31] *Chakrabarty*, 447 U.S. 303; *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948).

composition claims.[32]

A. *Chakrabarty* and *Funk Brothers*

As noted in *Bilski* and *Chakrabarty*, Supreme Court precedent provides three exceptions to § 101 broad patent-eligibility principles: laws of nature, physical phenomenon, and abstract ideas.[33] The *Bilski* case itself, as well as many cases cited therein (such as *Benson*, *Flook* and *Diehr*), discuss "laws of nature" and "abstract idea" exceptions as applicable to method claims. Such cases do not provide much guidance, however, on what might qualify as an unpatentable "physical phenomenon" in a composition claim.

Chakrabarty, on the other hand, sheds light upon the "physical phenomenon" exception. In this case, the Supreme Court addressed subject matter patentability of claims directed to man-made bacteria. The bacteria comprised two or more exogenous (outside) plasmids containing DNA sequences that expressed proteins involved in hydrocarbon degradation pathways. Thus, the claimed bacteria possessed a non-naturally occurring ability to break down crude oil components that was conferred by DNA present in the plasmids that Chakrabarty

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[32] Some commentators interpret *Funk Brothers* differently, suggesting it does not relate to § 101. Regardless, nothing in *Funk Brothers* indicates that isolated DNA corresponds to unpatentable subject matter.

[33] *Bilski*, 130 S.Ct. at 3225 (quoting *Chakrabarty*, 447 U.S. at 309).

had inserted into the bacteria.

In *Chakrabarty*, the Court first broadly defined the term "manufacture" in § 101 as "the production of articles for use from raw or prepared materials by giving to these materials new forms, qualities, properties, or combinations, whether by hand-labor or by machinery."[34] The Court also defined "composition of matter" to include "all compositions of two or more substances and . . . all composite articles, whether they be the results of chemical union, or of mechanical mixture, or whether they be gases, fluids, powders or solids."[35] The Court then made its famous assessment "that Congress intended statutory subject matter to 'include anything under the sun that is made by man.'"[36] The Court also noted, however, that one may not patent "a new mineral discovered in the earth or a new plant found in the wild."[37]

Against this backdrop, the Court determined that Chakrabarty's bacteria qualified as patentable subject matter. As explained by the Court, Chakrabarty's

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[34] *Chakrabarty*, 447 U.S. at 308 (quoting *Am. Fruit Growers, Inc. v. Brogdex Co.*, 283 U.S. 1, 11 (1931)).

[35] *Id.* (quoting *Shell Dev. Co. v. Watson*, 149 F. Supp. 279, 280 (D.C. 1957)).

[36] *Id.* at 309 (quoting S. Rep. No. 1979, 82d Cong., 2d Sess., 5 (1952); H.R. Rep. No. 1923, 82d Cong., 2d Sess., 6 (1952)).

[37] *Id.* at 309.

claim was "not to a hitherto unknown natural phenomenon, but to a nonnaturally occurring manufacture or composition of matter—a product of human ingenuity 'having a distinctive name, character [and] use.'"[38]

The Court also distinguished Chakrabarty's man-made bacteria from the mixture of bacteria claimed in *Funk Brothers*. Unlike Chakrabarty's claims directed to bacteria comprising exogenous plasmids (i.e., plasmids that did not exist in the bacteria in nature), claims in *Funk Brothers* recited mixtures of naturally existing bacteria and their naturally occurring, inherent properties. The bacteria in *Funk Brothers* did not comprise exogenous plasmids or DNA, nor any other man-made material.

As explained by the Court, patentability of Chakrabarty's bacteria "is underscored dramatically" by a comparison of inventions in the two cases.[39] Specifically, in *Funk Brothers* (as described in *Chakrabarty*):

> the patentee had discovered that there existed in nature certain species of root-nodule bacteria which did not exert a mutually inhibitive effect on each other. He used that discovery to produce a mixed culture capable of inoculating the seeds of leguminous plants. Concluding that the patentee had discovered "only some of the handiwork of nature," the Court ruled the product nonpatentable:

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[38] *Chakrabarty*, 447 U.S. at 309-310 (quoting *Hartranft v. Wiegmann*, 121 U.S. 609, 615 (1887).

[39] *Id.* at 310.

> "Each of the species of root-nodule bacteria contained in the package infects the same group of leguminous plants which it always infected. *No species acquires a different use*. The combination of species *produces no new bacteria, no change in the six species of bacteria, and no enlargement of the range of their utility*. Each species *has the same effect it always had*. The bacteria *perform in their natural way*. Their use in combination *does not improve in any way their natural functioning*. *They serve the ends nature originally provided and act quite independently of any effort of the patentee*."[40]

When discussing Chakrabarty's bacteria, the Court then stated:

> Here, by contrast, *the patentee 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*; accordingly it is patentable subject matter under § 101.[41]

When looking at these two Supreme Court cases, one must consider what actually distinguishes the man-made bacteria in *Chakrabarty* from the bacteria in *Funk Brothers*. Chakrabarty created bacteria containing exogenous plasmids, each plasmid encoding different enzymes that degraded unique hydrocarbons. On the other hand, the *Funk Brothers* bacteria were unaltered, naturally existing bacteria strains. Notably, Chakrabarty's bacteria were capable of degrading a broader range of hydrocarbons thereby more effectively treating oil spills than bacteria

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[40] *Chakrabarty*, 447 U.S. at 310 (quoting *Funk Bros.*, 333 U.S. at 131) (emphasis added).

[41] *Id.* at 310 (emphasis added).

found in nature. Chakrabarty's claimed bacteria provided "markedly different characteristics from any found in nature," and "the potential for significant utility."[42]

The above-quoted factors relied upon by the Court in *Chakrabarty* and *Funk Brothers* indicate that claims directed to "isolated DNA" are akin to Chakrabarty's man-made bacteria, and therefore constitute patentable subject matter. The science at hand makes it abundantly clear that an isolated DNA composition "is qualitatively different from the product occurring in nature such that it would pass the test laid out in *Funk Brothers* and *Chakrabarty*."[43]

1. Isolated DNA are new, changed, markedly, and qualitatively different from native DNA

Like the man-made bacteria in *Chakrabarty*, "isolated DNA" differs chemically in size and composition from anything that naturally exists in nature.[44] Isolated DNA is not "nature's handiwork," but is man-made. Contrary to Plaintiffs-Appellees' scientifically erroneous assertions to the district court,[45] the human body does not have a mechanism for isolating DNA, and consequently,

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[42] *Chakrabarty*, 447 U.S. at 310.

[43] *Intervet*, 617 F.3d at 1294 (J. Dyk, concurring-in-part, dissenting-in-part).

[44] Petricoin Decl., A6766:11, A6767:15, A6768-9:18-19, A6771:24.

[45] *See, e.g.*, Plaintiff's Memorandum of Law in Support for Summary Judgment dated Aug. 26, 2009, A1670.

isolated DNA is not found in the body.[46] The expression of proteins is a complex process that involves the production of mRNA and protein through transcription and translation in the naturally-occurring environment of the cell, surrounded by many other cellular components. At no time during this process is DNA "removed from its naturally occurring environment."[47]

More specifically, while a human body transcribes a gene into mRNA, which is then translated into a protein, the human body never, at any time, produces "isolated DNA." Human genes are located on chromosomes, which are large DNA structures. A single chromosome includes numerous genes and other DNA sequences, such as promoters, transcription factors, enhancers and termination sequences ("regulatory sequences"). A gene is located on one of the two strands of DNA (the coding strand) within a chromosome, and remains in place—and intact—during the gene expression process. To make a protein, a human body transcribes a gene into an mRNA molecule, which itself binds to other cellular components, such as RNA processing enzymes and multiple ribosomes. Each ribosome translates the mRNA into a polypeptide chain, that is, the ribosome-mRNA complex guides the assembly of amino acids into a polypeptide.

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[46] Petricoin Decl., A6772:25.

[47] Petricoin Decl., A6772:26.

As part of this process, a human body never isolates or purifies genes or mRNA from their naturally occurring environment.[48]

When isolated DNA claims recite specific sequences (e.g., SEQ ID NOs), the sequences usually do not include any (much less all) endogenous regulatory sequences. In addition, isolated DNA does not exist within a native chromatin structure (as native genes do within a chromosome), and isolated DNA often presents a different pattern of methylation as compared to a naturally occurring gene.[49] Moreover, when claims recite cDNA molecules, such molecules do not include introns (untranscribed DNA) that are normally present between exons (transcribed DNA) in genes as they naturally occur in the body.[50] Thus, there are many ways in which "isolated DNA" is no longer surrounded by, or regulated by, its natural environment.[51]

The district court states that "when DNA is copied, or replicated," or "when a particular portion of DNA is transcribed into RNA," such "segments of DNA

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[48] Petricoin Decl., A6772:27.

[49] *Id.* at A6768:18, A6773:29.

[50] *Id.* at A6767:15 (also noting that genomic *BRCA1* and *BRCA2* genes contain introns).

[51] *Id.* at A6771:24.

exist dissociated from the proteins normally bound to it."[52] Dissociation of certain proteins during such processes, however, does not mean that short segments of DNA, e.g., genes, within a chromosome are somehow naturally "isolated" and/or "purified" within a cell. In fact, even when DNA within a chromosome undergoes replication or transcription, a particular gene never dissociates from the chromosome strand itself. It is not simply the case that "native DNA, unlike purified or synthesized DNA, is not *typically* found floating freely in cells of the body," as stated by the district court.[53] Rather, native DNA, such as native genes, *never* naturally exist in an isolated form.[54]

2. Isolated DNA have many different uses and effects, as well as improved function, as compared to native DNA

The environment of a DNA molecule dictates not only its structure, but also its uses.[55] Isolated DNA has many different uses *in vitro* and *in vivo*, and many different effects when expressed outside a native environment. Isolated DNA, therefore, provides an "enlargement of the range of [the] utility," as compared to a

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[52] *Ass'n for Molecular Pathology*, 702 F.Supp.2d at 196.

[53] *Ass'n for Molecular Pathology*, 702 F.Supp.2d at 196 (emphasis added).

[54] Petricoin Decl., A6772:26-27.

[55] *Id.* at A6768-9:18; *see also* Linck Decl., A4412:48.

native DNA molecule.[56]

For instance, isolated DNA can be used in recombinant techniques to make purified protein in a large amount, in a form and manner that never exists inside the body.[57] Isolated DNA allows one to isolate an expressed protein in a purified form in large quantity that might otherwise be difficult, expensive or even impossible to obtain.[58] Isolated DNA and recombinant techniques can also avoid undue burden on a humans or animals, as might otherwise be needed to extract a sufficient amount of a protein of interest.[59]

Furthermore, isolated DNA may be used as a primer for synthesis of DNA in a polymerase chain reaction ("PCR").[60] In addition, one can use isolated DNA to create a transgenic animal, such as a mouse over-expressing a human gene of interest.[61] In the case of *BRCA1* and *BRCA2* isolated DNAs in particular, such

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[56] *Funk Bros.*, 333 U.S. at 131; *see also* Petricoin Decl., A6766:11, A6769-71:20-24.

[57] Petricoin Decl., A6770-1:22.

[58] *Cf., id.* at A6770-1:22 (stating that "[p]rior to production ... through cloning of isolated DNA, [human growth hormone] was extracted from the pituitary glands of cadavers and therefore there was a very limited supply of [it.]")

[59] *Id.*

[60] *Id.* at A6769-70:21.

[61] *Id.* at A6771:23.

molecules are useful for, *inter alia*, diagnosing a predisposition to breast and ovarian cancer. Such uses correspond to significant and important improvements on the function of any naturally occurring DNA molecule.

3. Isolated DNA serve more than "ends nature originally provided" and do not exist nor act independently of human effort

Isolated DNA do not merely "serve the ends nature originally provided."[62] The many uses of isolated DNA, such as those discussed above, as well as a vast number of other uses and properties, are unique to isolated DNA and cannot be duplicated with naturally-occurring DNA.[63]

It is also clear that isolated DNA, by definition, cannot "act quite independently of any effort of the patentee."[64] Isolated DNA are necessarily obtained by the hand of man, who must use highly sophisticated genetic and molecular techniques to identify and isolate DNA molecules of interest.[65] Dr. Sulston, a declarant at the district court for Plaintiffs-Appellees, also recognizes that "many *inventive* steps have been necessary to allow us to extract and read a

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[62] *Funk Bros.*, 333 U.S. at 131.

[63] Petricoin Decl., A6769-71:21-23.

[64] *Funk Bros.*, 333 U.S. at 131; *see also* Petricoin Decl., A6769:20.

[65] Petricoin Decl., A6773-4:30-31.

genetic sequence . . . ."[66]

Similarly, without human intervention, an isolated DNA molecule has no practical function or real world use.[67] Simply put, unless a human somehow physically uses an isolated DNA molecule in some manner, that chemical entity has little to no biological activity or impact, in sharp contrast to native DNA existing in a organism.

B. Other Relevant Legal Precedent and USPTO Position

In *J.E.M. v. Pioneer Hi-Bred*, the Supreme Court held that newly developed plant breeds corresponded to patentable subject matter under § 101.[68] The fact that the USPTO had issued "some 1800 utility patents for plants, plant parts and seeds" over a period of at least 16 years influenced the Court, as did Congress' failure to abolish such patent rights. As stated by the Court's majority opinion: "As in *Chakrabarty*, we decline to narrow the reach of § 101 where Congress has given us no indication that it intends this result."[69]

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[66] Sulston Decl., A2442-3:17 (emphasis added).

[67] Petricoin Decl., A6769:20.

[68] *J.E.M. AG Supply, Inc. v. Pioneer Hi-Bred Int'l.*, 534 U.S. 124, 145-46 (2001).

[69] *Id.* (citing *Chakrabarty*, 447 U.S. at 315-316).

1. USPTO Has Issued Tens of Thousands of Gene Patents

Over nearly twenty years, the USPTO has issued tens of thousands of patents directed to isolated nucleic acids. Even today, the USPTO continues to follow its long-standing position that "an inventor's discovery of a gene can be the basis for a patent on the genetic composition isolated from its natural state and processed through purifying steps that separate the gene from other molecules naturally associated with it."[70]

As such, an adverse decision here could negatively impact thousands of existing patents. For example, a search conducted on September 22, 2010, on the USPTO website for U.S. issued patents filed within the last 17 years (i.e., since September 22, 1993), having claims reciting: (isolated or purified) and (nucleotide or DNA or RNA or "nucleic acid" or "SEQ ID NO"), brought up 23,710 patents alone. Likewise, a search conducted on the USPTO website for U.S. issued patents filed within the last 17 years having claims reciting "SEQ ID NO" brought up 35,504 patents. These search results are consistent with information recently presented in *Nature* and *Science* discussing "more than 40,000 gene patents."[71]

Presumably, the vast majority of these U.S. patent are still valid today. For

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[70] Utility Examination Guidelines, 66 Fed. Reg. at 1093, Comment (1).

[71] 458 *Nature* 386 (citing C. M. Holman, 322 *Science* 198-199 (2008)).

example, a search on Westlaw® in "ALLFEDS" (containing all U.S. district court, U.S. court of appeals or Supreme Court opinions) for decisions including the terms: (patent) and (isolated or purified) and (nucleotide or DNA or RNA or "nucleic acid" or "SEQ ID NO") identified 204 cases.[72] Even assuming all 204 cases invalidated a patent (not possibly the case), it would only affect a very small percentage of issued patents. As noted in the *Nature* editorial, "[r]eports of researchers being blocked from access to patented DNA sequences or being sued for infringement are extremely rare," despite the fact that tens of thousands of relevant U.S. valid gene patents currently exist.[73]

2. Congress Has Refused To Abolish Gene Patents, Despite Ample Opportunity

It is noteworthy that Congress recently considered, but chose not to take, the drastic action proposed by Plaintiffs-Appellees and propagated by the district court.[74] Congress has every reason to refuse to take such action. Gene patents,

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[72] All above searches were conducted on September 22, 2010. The search did not consider whether any court addressed claim validity or infringement, the same patents on appeal or remand, etc.

[73] 458 *Nature* 386.

[74] *See* H.R. 977: "Genomic Research and Accessibility Act" (a bill that never became law, introduced by Rep. Xavier Becerra [D-CA31] on February 9, 2007, in 110th Congress) (proposing to amend 35 U.S.C. "to prohibit the patenting of human genetic material") (http://www.govtrack.us/congress/bill.xpd?bill=h110-977).

such as those directed to isolated DNA, have allowed genetic research and the biotechnology industry to grow and thrive. As just one example, as noted above, over 18,000 scientists (including Plaintiffs-Appellees and their declarants) have conducted research on the *BRCA1* and *BRCA2* genes, and have published more than 7,000 papers on those genes since Myriad's relevant patents issued.[75]

3. Other Legal Considerations

Other than the district court here, and Judge Dyk speaking for himself in *Intervet*, no case has ever suggested that claims directed to isolated DNA are unpatentable subject matter under § 101. By contrast, the USPTO and the Federal Circuit have squarely addressed and acknowledged utility of gene-related inventions under § 101.[76] As noted by the USPTO, "[p]atenting compositions or compounds isolated from nature follows well-established principles, and is not a new practice."[77] Indeed, a substantial body of case law supports subject matter

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[75] Myriad's District Court Summary Judgment Memo, A3439, A3444 and A3484 (citing numerous declarations in support).

[76] *See, e.g.,* USPTO Utility Examination Guidelines, 66 Fed. Reg. at 1093, Comments (1) and (3); *In re Fisher*, 421 F.3d 1365, 1372 (Fed. Cir. 2005).

[77] Utility Examination Guidelines, 66 Fed. Reg. at 1093, Comment (2) (citing numerous cases).

patentability of chemical compounds, such as DNA, that are isolated from nature.[78]

Judge Learned Hand of the Southern District of New York wrote a pivotal early decision, *Parke-Davis*.[79] In this case, the court upheld patentability of claims directed to purified adrenalin. The prior art understood that the adrenal gland contained a bioactive substance, but it was not until the claimed invention that this substance existed in a purified form having a therapeutic use. Judge Hand stated that the inventor "was the first to make it available for any use by removing it from the other gland-tissue.... It became for every practical purpose a new thing commercially and therapeutically. That was a good ground for a patent."[80] Likewise, it was not until identification and purification of the *BRCA1* and *BRCA2* genes that the isolated nucleotide sequences could be used in a variety of highly important and beneficial methods including disease diagnosis.

In his concurrence in *Funk Brothers*, Justice Frankfurter notes the following:

> It only confuses the issue [] to introduce such terms as 'the work of nature' and the 'laws of nature.' For these are vague and malleable terms infected with too much ambiguity and equivocation. Everything that happens may be deemed 'the work of nature,' and any

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[78] *See, e.g.*, Linck Decl., A4404-10:29-42, A4413-25:50-77; Rebecca S. Eisenberg, *Genetics and the Law: Patenting the Human Genome*, 39 Emory. L.J. 721, 727 & n.27 (1990) (listing "a substantial body of case law" on point).

[79] *Parke-Davis & Co. v. H.K. Mulford & Co.*, 189 F. 95 (S.D.N.Y. 1911), *aff'd in part and rev'd in part*, 196 F. 496 (2d Cir. 1912)

[80] *Id.* at 103.

> patentable composite exemplifies in its properties 'the laws of nature.' *Arguments drawn from such terms for ascertaining patentability could fairly be employed to challenge almost every patent.*[81]

Similarly, one must take great care when determining that an entire subject matter is an unpatentable physical phenomenon. Nearly everything is arguably a physical phenomenon, i.e., directly or tangentially involves a product of nature, which can lead to a slippery slope of undermining all patents. It is exactly this slippery slope that Plaintiffs-Appellees pursue today.

IV. Conclusion

Isolated DNA is a man-made, non-naturally occurring composition of matter, and not simply a sequence or "a physical embodiment of information." Isolated DNA is removed from the environment in which it naturally occurs, and therefore is significantly changed in the process. It has a different chemical structure and many unique properties and uses, as compared with naturally-occurring nucleotide sequences. Isolated DNA only comes about as a result of human intervention. Isolated DNA has "markedly different characteristics," as compared to DNA that exists in nature, just like the man-made bacteria containing exogenous plasmids in *Chakrabarty* differs from the naturally occurring bacteria in

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[81] *Funk Bros*, 333 U.S. at 134-35 (emphasis added).

Funk Brothers. As such, isolated DNA composition claims, such as the ones at issue in this case, correspond to patentable subject matter under 35 U.S.C. § 101.

Respectfully submitted,

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