Appeal No. 2010-1406

In the United States Court of Appeals for the Federal Circuit

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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

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BRIEF OF *AMICUS CURIAE* LAW PROFESSOR CHRISTOPHER M. HOLMAN IN SUPPORT OF NEITHER PARTY

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Dated June 11, 2012

CERTIFICATE OF INTEREST

Amicus Curiae Christopher M. Holman certifies the following:

1. The full name of every party or *amicus curiae* represented by me is Christopher M. Holman.

2. The name of the real parties in interest (if the party named in the caption is not the real party in interest) represented by me is Christopher M. Holman.

3. All parent corporations and any publicly held companies that own 10 percent of the stock of the party or *amicus curiae* represented by me are: None.

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

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TABLE OF CONTENTS

TABLE OF AUTHORITIES

STATEMENT OF INTEREST OF *AMICUS CURIAE*

Amicus curiae is a professor who teaches and write about biotechnology patent law and policy. *Amicus* has a Ph.D. in molecular biology and extensive experience as a scientist and patent attorney working in the biotechnology industry. *Amicus* has no personal interest or stake in the outcome of this case. No part of this brief was authored by counsel for any party, person, or organization besides *amicus*. My sole interest in this case is maintenance and development of a sensible patent system that accurately reflects science and which provides appropriate incentives for innovation, particularly in biotechnology. Pursuant to Fed.R.App.P. 29(a), all parties to this appeal have consented to the filing of this amicus brief.

STATEMENT OF AUTHORSHIP AND FUNDING

Pursuant to Fed.R.App.P. 29(c)(5), this brief was authored by Christopher M. Holman on his own behalf. No party or party's counsel authored this brief in whole or in part. No party or party's counsel funded the preparation of this brief. Counsel for Appellees assisted with the submission of this brief. No other person funded or participated in the preparation or submission of this brief.

ARGUMENT

I. Introduction

This Court's original decision focused largely on structural and functional differences between the claimed isolated DNA molecules and their naturally occurring counterparts (i.e., native genomic DNA and messenger RNA (mRNA)), and on the scope of the claims, particularly the extent to which the claims would preempt current and potential research and diagnostic testing activities. *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office*, 653 F.3d 1329, (Fed. Cir. 2011) ("*Myriad I*"). *Mayo* appears to bolster the relevance of these considerations in assessing patent eligibility. *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012). Unfortunately, in *Myriad I* this Court made a number of assumptions regarding the nature of the claimed subject matter that were unsupported at best, and in some instances clearly mistaken.

The unusual posture of the case has likely contributed to the problem. There has been no specific allegation that any particularly technology infringes any of the challenged claims, and in fact my research indicates that no US court has ever addressed the question of whether an isolated DNA claim would be infringed by any form of DNA sequencing or diagnostic testing. Christopher M. Holman, *Trend in Human Gene Patent Litigation*, Science 322:198-99 (2008). As a consequence,

the claims have yet to be adequately construed, and their purported preemptive effect remains entirely speculative.

This case has serious ramifications extending well beyond the context of genetic diagnostic testing, particularly with respect to biotherapeutics. I am filing this brief in the hope that this Court will not decide the patent eligibility of the isolated DNA claims based on unfounded assumptions as to the nature of the claimed subject matter and the potential impact of the claims (and so-called “gene patents” in general) on research and diagnostic testing.

II. Isolated DNA Is Not Simply DNA That Has Been Cleaved and Extracted from Native Chromosomal DNA

Statements in *Myriad I* suggest that some members of this Court are under the impression that the claims encompass native genomic DNA that has been simply "cleaved" from the chromosome and “extracted” from the cell, in a process analogous to separating cotton fiber from cottonseed, or purifying human adrenaline from human tissue. While the imagery of cleaving a piece of DNA out of the chromosome might serve as a useful metaphor for explaining difficult concepts to non-biologists, like the "magic microscope” it misrepresents the biology and obscures the very real distinction between the claimed DNA and native chromosomal DNA. Properly construed, the challenged claims are limited to synthetic DNA molecules that are structurally and functionally distinguishable from their native counterparts.

The isolation of genomic DNA, as described in the Myriad patents, and as generally practiced by biologists, is fundamentally different from the isolation of other biomolecules, such as proteins, lipids, or the purified adrenaline claimed in *Parke-Davis*. The distinction arises out of the unique ability of DNA to self-replicate, *i.e.*, to serve as a template for the synthesis of copies retaining the nucleotide sequence of the original DNA molecule.

Other biomolecules, for example proteins, cannot serve as the bases for their own replication, and so to isolate a human protein from a human source entails separating the protein of interest from other proteins and cellular constituents, resulting in a purified preparation of protein molecules originating from a native source. This is not the approach taken in isolating human genomic DNA, and for a variety of technical reasons such an approach would generally be infeasible for the purification of a human gene such as *BRCA1/2*. Instead of literally isolating gene sequences directly from chromosomal DNA, biologists create genomic DNA libraries comprising synthetic DNA molecules that retain the nucleotide sequence of genomic DNA, and isolated the "genomic DNA" from this synthetic source.

Although a full technical description of the process would exceed the 15 page limit of this amicus brief, a brief overview might be helpful.[1] A biologist seeking to isolate a human genomic gene begins by extracting chromosomal DNA

[1] A complete description can be found in reference sources such as J. Sambrook et al., MOLECULAR CLONING: A LABORATORY MANUAL, Chap. 9 (1989 2nd Edition).

from a sample of human cells, and then cleaving the long chromosomal DNA strands into shorter fragments. These DNA fragments are then inserted into DNA vectors capable of replication in a host cell. The vectors are subsequently introduced into cells, typically bacterial or yeast, which can be grown in culture. The cells multiply, and as they do the recombinant vector DNA, including the fragment originating from the human chromosome, is replicated.

The resulting collection of vector-containing cells is referred to as a "genomic DNA library." The cells comprising the library contain DNA that retains the primary sequence of genomic DNA, but the DNA molecules themselves did not originate in the human chromosome, but instead were synthesized as copies outside the body. Single cells can be isolated from this mixture, and used to create a culture of cells that all comprise the same fragment of genomic DNA. To isolate a gene of interest, a biologist screens the library to identify and isolate a pure cell culture that comprises a DNA fragment that includes the gene.

Once the DNA sequence of a gene has been determined, there is generally little reason to go back and repeat this process, since the sequence information of the DNA can be used to synthesize further copies by more convenient means. For example, as described in a brief I submitted in the first iteration of this case, conventional BRCA genetic testing involves using techniques such as PCR to amplify DNA molecules representing fragments of a patient's full-length BRCA

gene. *Brief of Amici Curiae Christopher M. Holman and Robert Cook-Deegan in Support of Neither Party*, 2010 WL 4853323,*16. In short, genetic testing does not involve cleaving the BRCA gene out of a native chromosome, but rather synthetic copies produced outside the body.

Today, once the sequence of a gene has been determined, the technology is available to easily synthesize a DNA molecule corresponding in sequence to the full-length gene. In fact, there are many laboratory techniques available for making "isolated" DNA that would arguably fall within the scope of the challenged claims, but all essentially involve synthetic DNA that originates outside the native context of the human chromosome.

More particularly, the isolation of the BRCA1 gene as described in U.S. Patent No. 5,747,282 (the ‘282 patent) employees the general methodologies described above. For example, the patent describes how the inventors "isolated" the BRCA1 gene from cloned DNA residing in yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), P1 and cosmid clones (*i.e.,* genomic DNA libraries), and explains that P1 clones were “isolated” using PCR primers. col. 7, l. 52 – col. 8, l. 5.The ‘282 patent does not describe isolating DNA by extracting it directly from native human chromosome, and to do so would make little sense, since that is simply not how DNA was, or is, isolated.

It is true that the process of initially isolating the BRCA genes involved extracting native chromosomal DNA from human cells, and cleavage of that native DNA into fragments. But these are merely intermediate steps in the preparation of the genomic DNA library, from which the genes were actually isolated, and would not fall within a reasonable construction of the claims.

Of course, one might argue that a literal reading of the claims would cover bulk extracted chromosomal DNA, or fragments of native DNA used in the preparation of a library, since they would inherently include a BRCA gene. But to give the claims such a broad interpretation would render them anticipated by the extraction and cleavage of chromosomal DNA, and the preparation of genomic DNA libraries, activities that were routine and widely described in printed publications long before the isolation of *BRCA1/2*. J. Sambrook et al., MOLECULAR CLONING: A LABORATORY MANUAL, Chapter 9 (1989 2nd Edition). To give the claims such a broad construction would not only be inconsistent with the disclosure, and with the general practices of molecular biologists, it would assume that the patent examiner issued claims that are invalid on their face in view of prior art of which the examiner had to be aware.

Not only does the claimed DNA originate outside the body, it has distinct functional and structural characteristics that distinguish it from native genomic DNA. It is important to bear in mind that the information content of genomic DNA

extends beyond the primary sequence of nucleotides, *i.e.*, the order in which G, A, T and C appear. There are other structural modifications of genomic DNA, referred to as epigenetics, which play an important role in regulating gene expression in the native chromosome. http://en.wikipedia.org/wiki/Epigenetics.

For example, one of the most common epigenetic modifications of genomic DNA in human is DNA methylation, a structural modification of certain cytosine bases that occurs at millions of locations throughout the native human genome. Yingying Zhang and Albert Jeltsch, *The Application of Next Generation Sequencing in DNA Methylation Analysis*, Genes 85-101, 86 (2010). The methylation pattern of genomic DNA plays a critical role in regarding gene expression, that not only varies from individual to individual, but also varies from cell to cell in a individual, and changes over time.

Significantly, the methylation pattern of human genomic DNA is lost when it is amplified in a host cell (e.g., a DNA library) or by laboratory techniques such as PCR. Genes 85-101, 87. Thus, the methylation of genomic DNA, along with other epigenetic modifications, are not retained by the isolated DNA. In short, the claimed DNA not only does not originate from a native source, it is structurally different in a way that significantly affects function.

III. The DNA of Claims 1 and 2 of the '282 Patent Are Not Fundamentally Different to an Extent That Would Justify Different Patent Eligibility Status

The US government argues that isolated cDNA is so fundamentally different from isolated genomic DNA that the two forms of DNA should be treated differently for purposes of patent eligibility, and some of the judges of this Court appear to have to some extent accepted this argument. *Brief for the United States as Amicus Curiae in Support of Neither Party*, 2010 WL 4853320. However, a closer look at the nature of these molecules and how they are prepared reveals that they are quite analogous and should not warrant disparate patent eligibility status.

The methodology for producing cDNA is entirely analogous to the methodology for isolating genomic DNA. J. Sambrook et al., MOLECULAR CLONING: A LABORATORY MANUAL, Chapter 8 (1989 2nd Edition). As a first step, messenger RNA (mRNA) is extracted from human cells. This collection of mRNA molecules will comprise many different sequences, generally representing all of the proteins that are being expressed by the cells. The extracted mRNA is analogous to the extracted genomic DNA described above. mRNA is structurally very similar to DNA, and contains the sequence information of the gene. However, mRNA is a single-stranded molecule that cannot self-replicate like DNA and is less chemically stable.

To address these issues, scientists use the extracted mRNA molecules as templates to synthesize double-stranded cDNA molecules retaining the sequence information of mRNA, but which are more stable and can self-replicate. These

double-stranded cDNA molecules are inserted into vectors which are then introduced into cells, resulting in a cDNA library entirely analogous to a genomic DNA library as described above. This library can be screened to isolate a cDNA corresponding to a gene of interest, *e.g.*, a cDNA encoding a BRCA protein.

Significantly, the resulting isolated cDNA is entirely analogous to the claimed isolated genomic DNA. In both cases the DNA did not actually originate in the cell, but it retains the informational content of a native polynucleotide sequence. In the case of cDNA, the sequence of an mRNA molecule, and in the case of isolated genomic DNA, the sequence of genomic DNA.

In its brief the US argues that cDNAs are synthetic molecules "engineered" by scientists to exclude introns and other regulatory regions, but in fact a cDNA is nothing more than a rote copy of a naturally occurring mRNA molecule. The "engineering" to exclude introns and other regulatory regions is accomplished entirely within the cell, by natural processes, without any human intervention.

Judge Moore opined that claim 2 of the ‘282 patent can be distinguished from claim 1 in that it is limited to a cDNA molecule (1) having “a completely different nucleotide sequence than the RNA” upon which it is based, and (2) because “DNA has a different chemical structure than RNA, including a different base (T instead of U, respectively) and sugar units (deoxyribose instead of ribose, respectively).” 653 F.3d at 1364. The first purported distinction is based on a

fundamental misunderstanding of the nature of cDNA, perhaps attributable to the inadequate claim construction in this case. Isolated cDNA is generally a double-stranded molecule, a first strand that is complementary to the RNA in which is based, and a second strand having the identical sequence. The ‘282 patent clearly states that SEQ ID NO: 1 is the coding sequence for the protein, i.e., is the same sequence as the mRNA. col. 19, ll. 49-50

Regarding the second basis, it is true that RNA includes small chemical differences relative to DNA, but these changes are of the same order as the difference between methylated genomic DNA and its isolated counterpart discussed above. The difference between deoxyribose and ribose is a single oxygen atom, the difference between T and U (thymine and uracil) is a methyl group attached to the ring at the 5 position, i.e., thymine is 5-methyluracil. This is essentially the same structural modification that occurs in the methylation of genomic DNA, i.e., methylation at the 5 position in the cytosine ring. The structural differences between RNA and DNA are functionally significant, as reflected in the increased stability of cDNA relative to RNA, but methylation of native genomic DNA also performs an important functional role in mediating epigenetic regulation of gene expression.

IV. Unfounded Assumptions Regarding the Utility of Isolated Genomic DNA

In assessing patent eligibility of the claimed DNA, the judges apparently viewed as significant the extent to which the claimed DNA had markedly different utility than its naturally occurring counterpart. But again, the analysis seemed to be based on inaccurate or unjustified assumptions.

For example, Judge Moore concluded that short DNA fragments have sufficient utility for patent eligibility because they can be used as primers and probes, but that "the isolated full length gene does not clearly have a new utility and appears to simply serve the same ends devised by nature, namely to act as a gene encoding a protein sequence." 653 F.3d at 1365, 1367. But the single most important category of biotechnology products, both economically and therapeutically, are protein therapeutics such as recombinant human erythropoietin and insulin. Prior to the biotechnology revolution, these human proteins could only be derived from a human source, and thus not in the quantity necessary for use as a drug. It would be unwise for the court to dismiss this important use of isolated DNA as insufficient to warrant patent eligibility, particularly when the parties who would most affected by this, biotechnology companies that produce biotech drugs (as well as patients that might benefit) are not parties to the litigation.

Judge Bryson, on the other hand, concluded that "cDNA has a utility not present in the naturally occurring BRCA DNA and mRNA because cDNA can be attached to a promoter and inserted into a non-human cell to drive protein

expression." 653 F.3d at 1379. But intron-containg genomic genes can also be used to express human proteins in non-human cells, refuting this artificial dichotomy between the DNA of claims 1 and 2. Kuan-Teh Jeang et al., *A Baculovirus Vector Can Express Intron-Containing Genes*, 61 J. OF VIR. 1761 (1987).

V. Unfounded Assumptions As To the Impact of Isolated DNA Patents on Genetic Testing and Whole Genome Sequencing

Judge Bryson assumes that some of the challenged DNA composition claims "effectively preempt any attempt to sequence the BRCA genes, including whole-genome sequencing." 653 F.3d at 1374. But there our many alternate methodologies for sequencing DNA, including revolutionary next-generation technologies capable of determining the sequence of single molecules, without necessitating any isolation of specific DNA sequences. Judge Bryson provides no explanation as to how the challenged claims would necessarily be infringed by any, let alone all of these methodologies.

A method of DNA sequencing would only infringe if it entails making or using an isolated DNA molecule falling within the scope of the claim. Although many critics of gene patents incorrectly assume that any patent claim that recites a gene sequence necessarily forecloses any research or diagnosis relating to that gene, this court should bear in mind that "the name of the game is the claim," and maintain its focus on a fact-based comparison of the properly construed claim to an allegedly infringing product.

As I have explained elsewhere, including in the brief I submitted with Robert Cook-Deegan in the first iteration of this case, there is no basis for assuming that all forms of DNA sequencing, especially next-generation single molecule methods, would necessarily entail the production of isolated DNA falling within the scope of the properly construed claims. Claims reciting the full-length gene would not be infringed by conventional BRCA testing, for example, which is based on the amplification and analysis of fragments of the gene. 2010 WL 4853323 at *16. The analysis of the DNA fragment claims is less straightforward, in our previous brief we explained why the claims would most likely be invalid under sections 102, 103 and or 112 if they were to be construed so broadly as to preclude all forms of DNA sequencing. 2010 WL 4853323.

Judge Bryson goes on to assume that unless this Court declares the broader isolated DNA claims patent ineligible whole genome sequencing will be impeded by thousands of gene patents. 1379-1380. This brief is rapidly approaching its fifteen page limit, so I will simply refer this Court to two of my articles which basically demonstrate that the widespread perception that 20% of human genes are patented is a myth based upon the misreading of a single "Policy Perspective" article published in Science, and that the concern that whole genome sequencing and multiplex testing will result in the infringement of thousands of gene patents is entirely unfounded. Christopher M. Holman, *Will Gene Patents Derail the Next-*

Generation of Genetic Technologies?: A Reassessment of the Evidence Suggests Not, 80 UMKC L. REV. 563 (2012), available at SSRN: http://ssrn.com/abstract=2001574 or http://dx.doi.org/10.2139/ssrn.2001574; and Christopher M. Holman, *Debunking the Myth That Whole Genome Sequencing Infringes Thousands of Gene Patents*, 30 NATURE BIOTECHNOLOGY 240 (2012).

CONCLUSION

A determination by this court that any of the challenged isolated DNA claims is patent ineligible could cause serious unintended collateral damage to biotechnology, and should not be made cavalierly based on an overly simplistic and imprecise interpretation of the claims and speculation as to their potential preemptive effect.

Respectfully submitted,

Christopher M. Holman
Amicus Curiae

June 11, 2012

CERTIFICATE OF SERVICE

I, Christopher M. Holman, hereby certify that I caused a copy of the foregoing Brief of *Amicus Curiae* Law Professor Christopher M. Holman in Support of Neither Party to be served this 8th day of June, 2012, by email upon each of the following sets of Counsel:

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