Association For Molecular Pathology et al v. United States Patent and Trademark Office et al Doc. 154

UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

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

Plaintiffs,

-against-

UNITED STATES PATENT AND TRADEMARK OFFICE; MYRIAD GENETICS; 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.

No. 09 Civ. 4515 (RWS)

ECF Case

DEFENDANTS' RULE 56.1 STATEMENT OF MATERIAL FACTS

Pursuant to Local Civil Rule 56.1, Defendants Myriad Genetics ("Myriad") 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, or alleged to have been named in their official capacity, as directors of the University of Utah Research Foundation (the "Directors") (collectively, Myriad and the Directors are referred to as the "Defendants"), submit the following statement of material facts in support of their motion for summary judgment.

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STATEMENT OF MATERIAL FACTS

In the view of the Myriad Defendants, there should be few or no facts that are material to the resolution of their motion for summary judgment. Plaintiffs have presented three legal claims in their Complaint: (1) whether the challenged patent claims cover patent-eligible subject matter under 35 U.S.C. § 101; (2) whether the patent claims violate the First Amendment to the U.S. Constitution; and (3) whether the patent claims violate the Patent Clause (Article I, Section 8, Clause 8) of the U.S. Constitution. Each of these is a legal issue, and will be determined as a matter of law by the Court. "Whether a claim is drawn to patent-eligible subject matter under § 101 is an issue of law." *In re Bilski*, 545 F.3d 943, 951 (Fed. Cir. 2008) (*en banc*), *cert. granted*, 129 S. Ct. 2735 (2009). Likewise, the two constitutional issues pose questions of law. *See, e.g., Peel v. Attorney Registration & Disciplinary Comm'n of Ill.*, 496 U.S. 91, 108 (1990) (First Amendment); *Eldred v. Ashcroft*, 537 U.S. 186, 199-218 (2003) (Article I, Section 8, Clause 8). Resolution of each of these questions should depend only upon a proper construction of the patent claims at issue (specifically, whether the product claims cover "isolated" DNA, and whether the method claims include "transformative" steps); patent claim construction, too, is conducted as a matter of law. *See, e.g., Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1454 (Fed. Cir. 1998) (*en banc*).

Nonetheless, the Myriad Defendants set forth the following limited statement of undisputed facts, as it may be helpful to the Court in resolving the issues in this case.

DNA IS A CHEMICAL COMPOSITION

1. "DNA" stands for deoxyribonucleic acid, which is a chemical compound made up of deoxyribonucleotides linked by a phosphodiester backbone. Kay ¶¶ 14, 125; Linck ¶ 70.

2. A DNA molecule is composed of several chemical elements, namely Carbon, Hydrogen, Oxygen, Nitrogen, and Phosphorus. These chemical elements make up repeating units that are connected to form a strand or polymer of the DNA molecule. Kay ¶¶ 14, 125.

3. DNA can exist as single strand or as double strand molecule. Kay ¶ 14.

4. The repeating units of DNA are known as nucleotides. The standard nucleotides in vertebrate DNA contain four different bases: Adenine, Thymine, Cytosine, and Guanine. These bases are linked together by chemical bonds via a sugar-phosphate backbone. Kay ¶¶ 14, 125.

5. As shorthand for convenience, scientists often denote nucleotides by the first letter of the names of their bases: "A" for Adenine; "G" for Guanine; "T" for Thymine; and "C" for Cytosine. Kay ¶¶ 14, 125.

6. A nucleotide sequence is a scientific notation understood in the field of human genetics as the primary structure of the DNA molecule, akin to formulae that represent chemical compounds, e.g., H_2O represents 2 atoms of hydrogen and 1 atom of oxygen that form the molecule water. Kay ¶ 127; Schlessinger ¶ 19; Doll ¶ 31; Linck ¶ 45.

7. A nucleotide sequence or a DNA sequence is a description of the linear order of nucleic acids that make up the polynucleotide; it is not itself a chemical compound. Kay ¶ 10; Doll ¶31.

8. DNA as it is found in the human body, i.e., native DNA, is one integral component of chromosomes. Chromosomes are complex structures that carry genes which are located

in most cells of the human body. Proteins represent another integral component of chromosomes. These proteins are bound to the DNA molecules in the chromosomes and modulate the structure and function of the DNA molecules to which they are bound. Kay ¶ 131; Schlessinger ¶ 12.

9. Thus, native DNA is never found floating freely in cells of the body, but is packaged along with proteins to form chromosomes. Kay ¶ 131.

10. The dynamic interaction between chromosomal proteins and native DNA in the body has a major role in establishing which genes are active and which are inactive and the level of their activity. Kay ¶ 132.

11. In addition, the chromosomal proteins mediate the interplay between the native DNA and the rest of the cell. Kay ¶ 132.

12. Chemical modifications of the DNA molecule, *e.g.*, methylation, can have a major impact on the function of the DNA molecule in the body. Accordingly, there are many factors in the cell, so-called epigenetic factors, which can influence native DNA and consequently the presentation of a trait. Kay ¶ 132.

13. The body does not have a mechanism for isolating genes. Kay ¶ 143. Schlessinger ¶ 11; Linck ¶ 52.

14. An "isolated DNA" or "isolated DNA molecule" is DNA that has been extracted from the cell and excised from the chromosome, or chemically synthesized. Kay ¶¶ 17, 137.

15. An isolated DNA is made by the hand of the scientist. Kay ¶ ¶ 17, 137.

16. To isolate DNA molecules from the body, the entire genome must be extracted from tissues or cells of the body and the chromosomal proteins must be removed. Kay ¶ 133.

17. To isolate a specific gene of interest, relevant DNA fragments must be excised from the genome. Kay ¶ 133.

18. The dynamic chemical, physical, and functional interaction between DNA and chromosomal proteins is therefore eliminated from an isolated DNA molecule. Kay ¶ 133.

19. An isolated complementary DNA, or "cDNA" molecule is an artificial construct that does not exist in the body and is structurally and functionally different from both native DNA and RNA (**r**ibo**n**ucleic **a**cid). Kay ¶¶ 148, 164; Linck ¶ 48.

20. In the cell, RNA is generated by a process called transcription. The RNA transcribed from one gene is processed into one or more messenger RNAs ("mRNAs") through a process called alternative splicing. Thus a single gene may give rise to various different mRNA molecules, which in turn give rise to various different proteins through a process called translation. Kay ¶¶ 149-152; Schlessinger ¶¶ 13-14.

21. A cDNA molecule is synthesized from a mRNA in a reaction catalyzed by a protein known as reverse transcriptase. cDNA received its name because each base in the cDNA can bind to a base in the mRNA from which the cDNA is synthesized. In other words, it is "complementary" to the mRNA from which it is synthesized. Kay ¶ 161.

22. Several steps are required to construct a cDNA, involving many molecular biology techniques. First, mature RNA is isolated from the tissues or cells of an organism. cDNA is then synthesized from the mature RNA using reverse transcriptase. Kay ¶ 165.

23. In this process, the bases of the RNA serve as clamps while the chemical bonds between the nucleotides of the newly forming cDNA strand are formed. Uracil binds to and thereby acts as a clamp for Adenine, Thymine for Adenine, Guanine for Cytosine, and Cytosine for Guanine. Kay ¶ 165.

24. Initially, the cDNA is single stranded but the second strand can be synthesized to form a double stranded cDNA molecule. Kay ¶ 166.

25. The synthesis of cDNA from very long mRNA molecules, such as BRCA1 and BRCA2, often does not result in a cDNA strand that is as long as the mRNA chain. Instead, not unlike a puzzle, several cDNA fragments have to be pieced together to arrive at a composite full length cDNA. Kay ¶ 166.

26. Isolated DNA molecules are distinct from any substance found in the human body. Kay ¶ 137.

ISOLATED DNA IS DIFFERENT IN KIND FROM NATURALLY OCCURRING DNA

27. Once a DNA molecule is isolated, it gains new properties which, in its native state, it did not possess. These new properties impart the isolated DNA molecules with new characteristics and new utilities. These new functions make isolated DNA molecules useful as tools for many biotechnological applications such as, for example, diagnostic

assays to identify and detect potentially harmful human genetic alterations. Kay ¶¶ 134, 138; Schlessinger ¶ 28; Doll ¶¶ 27-29.

28. Unlike native DNA, isolated DNA can be used as a probe, a diagnostic tool that a molecular biologist uses to target and bind to a particular portion of DNA, allowing it to be detectable using laboratory machinery. Native DNA cannot be used this way. Kay ¶ 138; Schlessinger ¶ 29.

29. Isolated DNA can also be used as another diagnostic tool, a "primer," which can be used in "sequencing" DNA, a method used by a molecular biologist to determine the primary structure of a DNA molecule. In sequencing, a primer binds to, or "hybridizes" with, a DNA target, such as a BRCA1/2 genomic DNA, or a cDNA to form a hybridization product that acts as a substrate for the enzymes used in the sequencing reaction. Kay ¶ 138; Schlessinger ¶ 30.

30. Native DNA does not have the chemical, structural, or functional properties that make isolated DNA so useful to the molecular biologist. Native DNA cannot be used as molecular tools, such as probes and primers, and cannot be used to detect mutations. Nor can it be used in sequencing reactions to determine the structure of a DNA molecule. Kay ¶ 139.

31. Extraction, excision, and purification from cellular components, or synthesizing DNA directly from its nucleotide components, is essential to be able to use the isolated DNA molecules as primers or probes. Thus, only isolated DNA molecules have the required chemical, structural and functional properties important for use as diagnostic tools and in the claimed diagnostic methods. Kay ¶ 139.

32. cDNA, like other isolated DNA molecules that are extracted, excised or synthesized, can be a useful tool for researchers as primers and probes in biotechnological and diagnostic applications. Kay ¶ 162.

33. Moreover, when a scientist wants to express a specific protein in a cell that does not normally express that protein to learn more about the protein, the scientist can transfer the cDNA that codes for the protein to a recipient cell. If the cDNA is operatively linked to a promoter that initiates transcription from the cDNA, the recipient cell will then express the protein of interest. Kay ¶ 163.

34. cDNA is structurally different from native DNA in human cells. Kay ¶ 168.

35. First, cDNA made from an mRNA does not contain introns in contrast to native human genes, which contains many intronic sequences. Second, cDNA can contain nucleotides that correspond to the poly-adenine tail of mRNA, which does not exist in native DNA. Third, because it is not associated with proteins as with native DNA and because it lacks a 5' cap, no protein can be produced from an isolated cDNA molecule without introduction of regulatory structures. Fourth, the sugar-phosphate backbone of native DNA is usually chemically modified, e.g., by methylation. In contrast, the sugar-phosphate backbone of cDNA is not modified. Finally, as discussed above, isolated cDNA can serve as a probe, as a target for a probe, and as a template for a polymerase chain reaction ("PCR"), all of which native mRNA cannot do. Kay ¶ 168.

36. cDNA is also functionally different from native DNA. Kay ¶ 169.

37. First, native DNA contains regulatory regions. These regulatory regions are not

present in cDNA because they are not present in the mRNA from which the cDNA was synthesized. Second, because cDNA does not contain intronic sequences, mRNA can be transcribed from cDNA without the need for splicing. Third, introducing a cDNA alone into a cell does not give rise to protein production from that cDNA. Fourth, native DNA and chromosomal proteins form a functional unit; isolated or synthetic cDNA, however, is not associated with chromosomal protein and can thus be used as a molecular tool in various biotechnological applications. Kay ¶ 169.

38. As with native DNA, cDNA is structurally different from RNA, both pre-mRNA and mature mRNA. Kay ¶ 170.

39. First, the set of bases in DNA is different from the set of bases in RNA. While the four bases in DNA are Adenine, Cytosine, Guanine, and Thymine, the four bases in RNA are Uracil, Adenine, Cytosine, and Guanine. Second, the sugar-phosphate backbone in DNA is chemically different from the sugar-phosphate backbone of RNA. This difference in structure allows DNA to form the famous double helix. Kay ¶ 170.

40. cDNA is also functionally different from mRNA. Kay ¶ 171.

41. First, cDNA is a much more stable molecule than mRNA. Second, protein can be translated directly from mRNA, whereas protein cannot be directly translated from cDNA, but requires the additional step of RNA transcription. Third, in the body, tens of thousands different mRNA molecules are present. Synthesized cDNA, on the other hand, is generated in the laboratory, commonly as a homogenous population of molecules of the same kind to study the properties and functions of a specific gene of interest. Kay ¶ 171.

42. The physical form of a DNA molecule can significantly impact its function and the information it can yield. Kay ¶ 141.

43. The usefulness of isolated BRCA1/2 DNA molecules is based on their ability to target and interact with native DNA, or isolated BRCA1/2 DNA molecules themselves, which is a function of their own individual structure and chemistry. Kay ¶ 138.

44. Only isolated DNA molecules have the required chemical, structural and functional properties important for use as diagnostic tools. Kay ¶¶ 139, 174.

DNA SEQUENCING

45. A DNA sequence cannot be obtained by "looking" at genes. One cannot detect or determine the sequence of a human subject's genes by mere inspection. Detection of a gene marker requires breaking open the cells of a tissue sample, and extracting and excising the native DNA. Kay ¶ 187

46. The gene, mRNA and allele are in the body and must be obtained from a patient's tissue sample in order to be sequenced. The cells of the tissue sample must be broken open and a sample of DNA or RNA or allele extracted from the cells. cDNA can be synthesized using mRNA obtained from the patient sample. Various types of patient samples can be used, for example, a blood, tumor tissue, or non-tumor tissue samples. Kay ¶ 186.

47. The DNA has to be isolated from these samples and put through sequencing reactions in order to obtain the sequence. This is transformative—the blood sample no longer resembles blood, and the patient's tissue no longer resembles the tissue. Kay ¶ 186.

48. To determine a DNA sequence of a patient for diagnostic purposes, a biological sample, such as a blood sample, from the patient must be processed. Native DNA or mRNA must be purified from the patient sample. Kay ¶ 178.

49. The purification of native DNA of the entire genome, however, does not result in the purification of a single gene. Given that the human genome is over three billion nucleotides long, this initial purification step is still a long way from obtaining the sequence of a specific gene. To put things in perspective, the size of the BRCA1 cDNA relates to the size of the entire genome approximately as a grain of sand to the height of the observation floor of the Empire State Building. Kay ¶178.

50. Similarly, purification of mRNA from a patient sample yields a mixture of thousands or tens of thousands of different mRNA molecules. Even if cDNA is synthesized from this pool of mRNA molecules, the resulting cDNA molecules are similarly a mixture of thousands or tens of thousands of different cDNAs. Kay ¶ 179.

51. To initiate the sequencing reaction at the desired location of a target in the sample, a primer is used. A primer is an artificial DNA fragment, usually between 15 and 30 nucleotides long, that binds specifically to the target nucleotide. The nucleotide sequence of the primer is complementary to the sequence of the target such that the bases of the primer and the bases of the target bind to each other. Kay ¶¶ 177, 183.

52. Thus, to sequence a particular target within a sample, at least part of the target sequence must be known to design a suitable primer. The initial sequencing of a target sequence requires ingenuity far beyond the mere application of routine laboratory techniques and usually involves a significant amount of trial and error. Kay ¶ 179.

53. Target-sequence specific primers can also be used to initiate polymerase chain reaction ("PCR"), a technique that can be employed to synthesize and isolate specific target DNA fragments for sequencing. For example, PCR can be used to synthesize a fragment of genomic DNA. The resulting fragment can then be sequenced. However, to do so, at least part of the sequence of the target DNA molecule must be known so that the target specific primer can be designed. Thus, the use of PCR requires knowledge of at least part of the sequence of the target DNA to design these specific primers. Kay ¶ 184.

54. After diagnostic sequencing, the patient's sample, such as blood or tissue, is no longer blood or tissue but has been processed to obtain DNA. The DNA has then been subjected to a sequencing reaction. At the end, instead of blood or tissue, the clinician has the chemical structure of a small portion of the patient's DNA. Kay ¶ 185.

55. For example, using a set of molecular tools, such as a diagnostic probe or a primer that can specifically bind to a BRCA1/2 DNA molecule in a tissue sample, the patient's native DNA is analyzed to determine if the structural composition is the same or different from the normal native gene. These molecular diagnostic tools were designed based on their ability to bind to and form a stable chemical structure with a target gene. Kay ¶ 187.

56. To detect a mutation in the *BRCA1* and *BRCA2* genes, the first step typically is to obtain a sufficient amount of the genomic DNA corresponding to the *BRCA1* and *BRCA2* genes from a patient's tissue sample (e.g., blood). This step is typically done by enzymatic synthesis to connect different nucleotide molecules into a DNA chain using a genomic DNA molecule from the patient sample as a template. Critchfield ¶ 40.

57. To obtain a sufficient quantity of the genomic DNA, the enzymatic synthesis is performed by PCR (polymerase chain reaction) to duplicate the DNA molecule exponentially. Critchfield ¶ 40.

58. However, there is a limit in the size of the genomic DNA fragment that can be made by PCR (about several hundred base pairs). The *BRCA1* and *BRCA2* genes are large in size each being over 70,000 base pairs long, and can not be amplified or duplicated into a single DNA fragment. Critchfield ¶ 40.

59. Under the current state of the art, the only practical way to obtain a sufficient amount of *BRCA1* or *BRCA2* genomic DNA for mutation detection purpose is to PCR amplify the genomic DNA in segments. Typically, each coding exon (an exon that codes for part of the protein) of the *BRCA1* and *BRCA2* genes, including a small adjacent portion of the flanking introns, is separately amplified by PCR into one or more amplified DNA fragments, also called "amplicons." The *BRCA1* and *BRCA2* genes have a total of 48 coding exons containing over 15,700 nucleotide base pairs. More than 50 amplicons are typically produced, and each is subsequently interrogated for the presence or absence of mutations. Critchfield ¶ 40.

Dated: New York, New York
December 23, 2009

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By: /s/ Brian M. Poissant

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CERTIFICATE OF SERVICE

This is to certify that on December 23, 2009, a true and correct copy of the foregoing document has been served on all counsel of record via the court's ECF system.

/s/ Brian M. Poissant
Brian M. Poissant