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

DECLARATION OF DR. SEAN TAVTIGIAN

I, Sean V. Tavtigian, declare:

1. In 1984 I received a B.A. with a joint major in biology and chemistry from Pomona College, Claremont, California. In 1992 I received a Ph.D. in molecular biology and biochemistry from the California Institute of Technology, Pasadena, California. I am currently an associate professor in the Department of Oncological Sciences at the University of Utah School of Medicine.

2. I was employed by Myriad Genetics, Inc. ("Myriad") between 1993 and 2002. At Myriad I held several senior positions, including Vice President, Director of Cancer Research, and Director of the (research) Sequencing and Genotyping Core at the time of my departure.

3. As a senior scientist at Myriad during the period between 1993 and 1996, I oversaw the laboratory and external collaborations components of the company's *BRCA2* positional cloning project. In particular, Dr. Alexander Kamb and I at Myriad collaborated with Dr. Jacques Simard of the University of Laval in Quebec, Canada, Dr. Johanna M. Rommens of the Hospital for Sick Children in Toronto, Canada, and Drs. Fergus Couch and Barbara L. Weber of the University of Pennsylvania in the discovery and characterization of the *BRCA2* gene in late 1995. I am one of the named inventors in United States Patent Nos. 5,709,999, 5,710,001, 5,747,282, 5,753,441, 5,837,492 & 6,033,857.

4. In discovering and characterizing *BRCA2*, Myriad and its collaborators used much the same positional cloning approach used for *BRCA1* and described in some detail in Defendant Myriad's Declaration of Donna Shattuck.

5. On December 21, 1995, at the culmination of this effort, Myriad filed patent application serial no. 08/576,559 in the United States Patent and Trademark Office disclosing the full structure of the *BRCA2* cDNA and protein.

6. A short time later the Institute of Cancer Research (ICR), one of Myriad's competitors in the search for *BRCA2* led by Michael Stratton, claimed to have discovered the *BRCA2* gene. *See* Wooster *et al.*, NATURE 378:789-92 (1995) (Exhibit 2). In this publication and its accompanying patent applications, ICR set forth what it believed to be the cDNA and protein structures for *BRCA2*.

7. As it turned out, ICR's proposed BRCA2 structure was incomplete at one end and contained a serious error at the other. More specifically, the N-terminus of what ICR called the BRCA2 protein was missing more than 280 amino acids (more than 1,000 base pairs in the cDNA and the first eight protein coding exons of the genomic structure). ICR recognized the potential for such a shortfall, stating "the N terminus of the BRCA2 protein may well be missing from the above sequence." *See* Exhibit 2, Figure 2 and legend.

8. Fully characterizing the 5' end of the *BRCA2* cDNA would have required significant additional work on the part of ICR. In arriving at the full-length *BRCA2* cDNA structure, Myriad sequenced and pieced together numerous clones using a variety of processes, including a technique called **R**apid **A**mplification of **c**DNA **E**nds (RACE). However, even knowing the full cDNA structure was not enough to fully characterize the gene since the structure of the resulting protein would be unknown. Though ICR apparently had the right reading frame, researchers (such as Myriad and its collaborators) still needed to definitively find the start and stop codons, a difficult task in a gene that has an open reading frame of more than 10,000 base pairs.

9. Despite these difficulties, Myriad succeeded in fully characterizing the *BRCA2* gene and submitted its full BRCA2 cDNA structure to a public database called Genbank the same day the Wooster article was published.

10. Beyond missing the N-terminus, ICR's proposed BRCA2 structure contained a much subtler and potentially more disruptive error at its C-terminus. Specifically, ICR's "*BRCA2*" structure mistakenly fused a portion of the actual *BRCA2* cDNA with a totally unrelated region of a different chromosome. This was

not a rare splice variant; it was a potentially catastrophic error, i.e., a chimeric artifact. As shown in Exhibits 3 & 4, respectively, ICR's proposed "BRCA2" protein structure[1] was missing the last 812 amino acids of true BRCA2[2] and ICR's "*BRCA2*" cDNA[3] was missing the final 3,352 nucleotides of true *BRCA2*,[4] corresponding to the last ten coding exons of the gene structure. Exhibit 5 shows that, instead of being from *BRCA2*, the final 266 nucleotides of ICR's "*BRCA2*" cDNA sequence are from a region of the sequence of the X chromosome. Moreover, in contrast to their description of potential N-terminal incompleteness, the ICR's publication gives no warning about potential error at the C-terminus, strongly suggesting that the ICR team was unaware of their error (i.e., the publication mentions the possibility of additional structure at the 5' end but treats the 3' end as complete and correct).

11. Imagine claiming to have found a life-saving drug, but publishing (and filing a patent application on) the correct structure of only a portion of the molecule, and mistakenly including several side groups from a completely unrelated molecule in the structure. Beyond throwing off researchers hoping to study the drug's properties, the unrelated side groups would likely detract from the drug's therapeutic efficacy and might even make the drug harmful.

12. As with the N-terminus, Myriad correctly determined the C-terminal structure of the *BRCA2* cDNA and, in so doing, corrected ICR's errors. This is noteworthy for two reasons. First, the process of determining the correct C-terminal structure was difficult. ICR's "BRCA2" structure was missing the final

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[1] ICR's "BRCA2" protein sequence is shown in Figure 2 of the Wooster publication.
[2] True BRCA2 protein sequence herein corresponds to SEQ ID NO:2 of US Patent no. 5,837,492.
[3] ICR's "*BRCA2*" cDNA sequence corresponds to SEQ ID NO:15 from PCT patent application publication WO/1997/019110.
[4] True *BRCA2* cDNA sequences herein corresponds to SEQ ID NO:1 of US Patent no. 5,837,492.

3,352 nucleotides of true *BRCA2* as well as 10 full exons and most of an eleventh exon. More importantly, however, researchers provided with ICR's structure alone would have had no immediate reason to doubt its correctness or undertake the laborious process of determining the correct structure. For instance, as revealed from their PCT patent sequence, ICR's proposed "BRCA2" protein structure had a stop codon at the C-terminal end, suggesting that end of the protein coding sequence had been cloned. Moreover, the Wooster publication stated "Contiguity of the transcription unit was confirmed by reverse-transcription-polymerase chain reaction (RT-PCR) on cDNA and sequence analysis." Two paragraphs later, they went on to say "...including 300 bp of 3' untranslated sequence..." Together with the Figure 2, these two statements indicate that Wooster et al. thought that their sequence included a *bona fide* BRCA2 translation termination signal and were unaware that their sequence was chimeric. Further, the more than 3,000 nucleotides and 10-plus exons missing from the C-terminal end of ICR's "*BRCA2*" structure are around the size of an average genes entire cDNA.

13. While the technologies used for DNA cloning and gene sequencing are standard, the discovery and characterization of genes is by no means routine. ICR's difficulties and Myriad's successes in characterizing *BRCA2* underscore the monumental nature of the discovery and characterization of the *BRCA1* and *BRCA2* genes (*see, e.g.*, D. Mason ¶ 33, D. Parthasarathy ¶ 19). Moreover, we should keep in mind that BRCA2 did not "have" to be a protein coding gene. Had BRCA2 been, for instance a regulatory snRNA, the cloning techniques of the mid-1990s may have been unable to find it.

14. More importantly, however, I disagree with plaintiffs' allegations that "[g]ene patents are not necessary to further scientific discovery and the development of diagnostics." *See* D. Leonard ¶ 20; *see also*, D. Sulston ¶ 38, D. Cho ¶ 17, etc. I also question plaintiffs' suggestion that academic groups (ICR is given as an example) are more generous with the genetic information they gather. *See, e.g.*, D. Sulston ¶¶ 29-33 ("From the very beginning of the Human Genome Project, most scientists and even some private companies recognized the importance of keeping the genome freely available to all.").

15. In the case of BRCA2, patents were necessary to drive forward research and also to incentivize public disclosure of genetic sequences. For example, despite the prevailing "best practices" of the day, ICR never submitted its proposed BRCA2 protein structure to a public database when it produced the Wooster publication (such submissions are routinely required by scientific journals today). The Wooster publication gave a partial BRCA2 protein sequence, but I know of no publication nor any public database submission by ICR that gives the corresponding DNA structure (which is the most important thing for a BRCA2 diagnostic test).

16. Indeed, I only discovered the true nature of ICR's errors when ICR's patent application (PCT publication no. WO/1997/019110) published with a partial cDNA structure (which was then entered automatically in Genbank). In contrast, Myriad submitted its *BRCA2* cDNA structure to the publicly available Genbank database the day after filing its patent applications. Given Plaintiffs' allegations about patents discouraging public disclosure, it is particularly ironic that ICR's

errors only came to light because the sequences were published in a patent application.

17. If Myriad had not published the full *BRCA2* cDNA structure, *see* Tavtigian *et al.*, *The Complete* BRCA2 *Gene and Mutations in Chromosome 13q-Linked Kindreds*, NATURE GENETICS 12:333-7 (1996), it is difficult to say when ICR's mistake would have been discovered or how much progress in BRCA2 research would have been delayed. The incentive provided by patents was critical in the discovery of the true structure of BRCA2.

18. In his declaration, John Sulston suggests Myriad has improperly claimed the discoveries of others. *See* D. Sulston ¶ 31. Specifically, Sulston alleges:

> Myriad used its patent applications to claim rights over the entire BRCA2 gene, including the mutations that had been identified by ICR. Myriad has since claimed proprietary rights for all diagnostic testing for the BRCA genes. One of their tests focuses on one of the mutations discovered by the ICR team that is commonly found among Ashkenazi Jews from central and eastern Europe. Thus, by having a patent on the gene as a whole, Myriad was able to claim scientific findings made by others.

19. As I discussed above, ICR's efforts fell far short of characterizing the full *BRCA2* cDNA and instead would have led BRCA researchers astray if not for Myriad's correction.

20. I also disagree with Sulston's description of the discovery of the Ashkenazi mutation. ICR may have discovered the mutation (i.e., that a nucleotide change occurs at this position in the structure of *BRCA2*), it was Myriad who discovered its significance (i.e., that it is a founder mutation commonly found among Ashkenazi Jews from central and eastern Europe). Neuhausen *et al.*,

Recurrent BRCA2 *6174delT Mutations in Ashkenazi Jewish Women Affected by Breast Cancer*, NATURE GENETICS, 13:126-8 (1996). In fact, the European Patent Office, despite its more stringent absolute novelty requirements, granted Myriad a patent on the use of this mutation for determining risk in patients of Ashkenazi ancestry.

Pursuant to 28 USC § 1746, I declare under penalty of perjury that the foregoing is true and correct.

Sean V. Tavtigian, Ph.D

Executed on 12/21, 2009

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