ASSOCIATION FOR MOLECULAR PATHOLOGY v MYRIAD GENETICS, INC – A DISTINGUISHABLE DECISION?

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A representative Myriad patent considered by the Supreme Court in the above proceedings covered isolated DNA coding for the wild-type BRCA1 gene. However, it disclosed only a partial sequence of the gene and did not disclose its isolation as a free-standing molecule. For those reasons a claim which on reasonable interpretation covered the wild-type gene was open to objection on the grounds of lack of written description and lack of enablement, which objections though not formally in issue were readily apparent to a knowledgeable reader. These reasons may have provided a subtext, coupled with the functional rather than structural nature of much of the claim, for the finding that patent-eligible novelty should be considered from the standpoint of a geneticist and not from that of a chemist. From that standpoint, isolation of the BRCA1 gene created no material difference in the structure or utility of the DNA, the ability to sequence the gene if and when isolated being only a consequence of its possession. Against that factual background the holding that genes are not patent-eligible *simply* because they have been isolated appears open to development in future cases and its relevance e.g. to intron-free bacterial genes or to plant genes is questioned. Doubts are also expressed whether full-length sequences either of the wild-type gene or of the corresponding cDNA are needed for clinical testing, in which case the suspicion of Justice Sotomayor may have been well-founded that much of the argument, as between the parties, was in reality about nothing.

What was disclosed and what was claimed

It is common ground that the patents in issue concern a medical breakthrough. However, a subtext to the decisions at all levels in this litigation may have been a disjuncture between the disclosed technical achievements, what was enabled or foreseeable in the patent specifications as filed, and the wide scope of the subject-matter claimed Although Justice Thomas expressed the court's opinion in terms of general propositions of law, all cases are fact-sensitive and the disjuncture, which is readily apparent to non-technical readers, discernibly played a part in shaping the outcome. In terms of the US statute, the unexpressed background issues were lack of written description and lack of enablement under 35 USC §112(a) at least insofar as the claims extend to wild-type genes as full-length sequences. Where issues are not raised by the parties it is, of course, open to a court to disregard them, but it is suggested that that in *Myriad* these issues were appreciated both by the dissent in the CAFC and by the Supreme Court and were more influential than might appear at first sight.

Myriad discovered the precise location and sequence the BRCA1 and BRCA2 genes, mutations in which can dramatically increase an individual's risk of developing breast and ovarian cancer. US Patent 5,782,282 which related to the BRCA1 gene was

treated as representative. It describes mapping of the BRCA1 gene to a 600 kb region of chromosome 17 adjacent marker D17S855 as shown in Fig. 4:

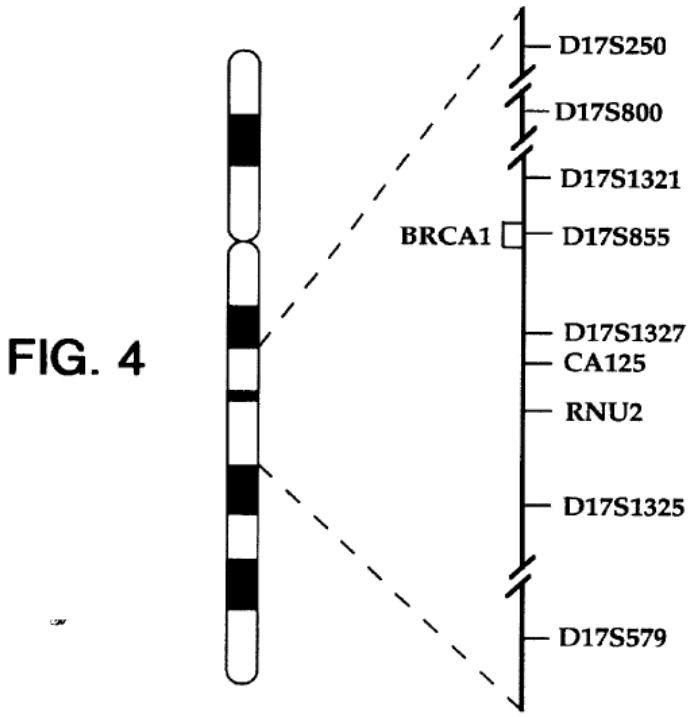

FIG. 4

Only a partial sequence of the wild-type gene is disclosed in the '282 patent. Fig 10 lists the partial sequence and includes all 24 BRCA1 exons together with their 5' and 3' flanking sequences, portions of which are also listed in a table in Example 8. Many introns are only partly shown with “indefinite” regions being indicated by the letters “vvvvvvvvvv”. Overall only 24,000 of the full ~81,000 bp are listed.

The sequence data was obtained by probing human yeast artificial chromosome (YAC) or human bacterial artificial chromosome (BAC) libraries commercially available e.g. from Clontech, sequencing hybridization-selected cDNA fragments and reconstructing longer sequences by merging data for overlapping fragment sequences using computer software. The sequence listing in Fig. 10 therefore represents data in computer memory rather than physical molecules or parts of molecules obtained by cutting chromosomal DNA or fragments thereof at chosen locations. Although not featuring in any of the judicial opinions, Wikipedia (which arguably represents what is well-known to a skilled person) discloses that the practical upper limit for PCR is about 10,000 bp, well below the length of the wild-type BRCA1 gene, so that even if a full-length gene had been isolated, the ability to multiply it and put it to practical use has to be regarded as not proven.

Finding sequence variants by amplification of the 23 coding exons from the DNA of a patient and comparison to corresponding wild type sequences is disclosed in Example 8, as is allele-specific screening of genomic DNA from carriers, but these experiments fall short of involving the full-length gene in isolated form. None of the remaining examples discloses isolation of the full-length wild-type gene as a free-standing molecule either *in vitro* or predictively.

Claim 1 reads:
"An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2" (i.e. the full-length BRCA1 protein sequence).

The word "an" indicates that what is being claimed is a sequence having the desired properties and therefore excludes a library of overlapping shorter sequences each having part of the code for the whole polypeptide. The reference to DNA is arguably more than a mere place-holder for the word "means" and suffices to avoid the provisions of §112(f); compare *Linear Technology v Impala,* CAFC, 2004 where the word "circuit" was held to imply well-understood structure and therefore also to avoid §112(f). Beyond that, however, the claim is wholly functional since it covers all DNA sequences that code for the polypeptide and mentions no specific sequence or genus of DNA sequences. It has been suggested that sequence structure is implicit since the genetic code maps the base sequence directly to the amino acid sequence of the polypeptide and that this has been known for many decades. However this suggestion does not take account of variability through codon degeneracy (not considered in the various opinions) which applies to 18 of the 20 amino acids in the polypeptide and to the STOP codon. A second source of variability is sequence length which could be anywhere from the 5,500 bp of the relevant cDNA to ~81,000 bp for the full-length wild-type gene. A third source of variability is mutation or natural variability within introns. As will be seen, lack of structural definition in claim 1 formed part of the chain of reasoning leading to the outcome.

The two most representative sequences covered by the claim are firstly the full-length wild-type BRAC1 gene and secondly the laboratory-produced cDNA which also encodes the polypeptide. It is logical to assume that when the word "gene" appears on the various opinions it is the full-length wild-type DNA sequence in isolated form that the court has in mind, and that judicial attention was focused on it since cDNA is claimed in claim 2.

"DNA" as Myriad argued before Judge Sweet at first instance means a real and tangible molecule, a chemical composition made up of deoxyribonucleotides linked by a phosphodiester backbone and not mere information. That argument is repeated in their reply brief for the Supreme Court, in which they further argued that the words "encoding" or "coding for" are commonly used in DNA patent claims to recite physical structure, not function, citing *In re Deuel*, 51 F.3d 1552, 1557-58 (Fed. Cir. 1995).

"Isolated DNA" as construed by Judge Sweet means a segment of DNA nucleotides existing free from other cellular components normally associated with native DNA, including proteins and other DNA sequences comprising the remainder of the genome. In their reply brief to the Supreme Court Myriad argue that isolation required separation of the specific DNA of interest from the rest of the DNA in the body and even from the rest of the fragmented DNA that may be present in a test tube outside the body. In their subsequent respondent's brief they argue that the specific isolated BRCA1 and BRCA2 molecules, once defined, are either separated from surrounding genomic and cellular matter at precise locations chosen by the Myriad inventors or assembled in a laboratory in the case of cDNA.

Unfortunately for Myriad, and as apparent from what has been said above, at least so far as disclosure of the full-length or wild-type BRCA1 on which much judicial attention has been focused this picture resides in the realm of science-fiction rather than reality. Neither the wild-type DNA as a free-standing molecule nor methods of cleaving a larger sequence at precise locations of choice to create it is described.

Written description requires either complete and correct sequencing or physical possession of the sequence and making it available in a public depository, see *Sanofi-Aventis v Pfizer*, Federal Circuit, 5th November 2013 (**patents4life, 6 November 2013**) and cases cited therein including *Enzo Biochem, Inc. v. Gen-Probe Inc*., 323 F.3d 956 (Fed. Cir. 2002). For the wild-type BRCA1 gene neither is reported, so that insofar as that gene is covered by claim 1 an objection of lack of written description would have been strongly arguable. Also since the procedures needed for isolation of a complete wild-type BRCA1 gene as a physical molecule are not described and were self-evidently not well-known in the art at the application date, the exception in *Hybritech, Inc. v. Monoclonal Antibodies, Inc*., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987) is not available. Therefore it is strongly arguable that the '282 disclosure also does not enable the wild-type BRCA1 gene.

If the disjunction between firstly claim scope and the arguments of Myriad's counsel and secondly the level of technical knowledge disclosed in '282 had been less pronounced, it is possible that differences of opinion in the Federal Circuit would not have surfaced and the case might never have found its way to the Supreme Court.

In contrast, the disclosure in '282 of cDNA coding for the BRCA1 polypeptide is complete. Example 8 discloses that ESTs for three independent contigs representing portions of BRCA1 when used as hybridization probes in Northern analysis detected a single transcript of about 7.8 kb in breast mRNA suggesting that they represent portions of a single gene. Further research led to the construction of a composite full-length sequence of 5,941 bp for BRCA1 cDNA, which is disclosed in the specification and is also deposited with GeneBank. That sequence covers all 1863 amino acids of the BRCA1 polypeptide. In an experiment, a portion of the cDNA is expressed in *E. coli*, the expressed polypeptide is purified by gel elution and is used e.g. to immunise rabbits and mice to generate antibodies against mutant forms of the BRCA1 gene (Example 12). BRCA1 cDNA is covered by claim 2 which reads: The isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID NO:1. It will be appreciated that claim 2 does not suffer from the same written description and enablement issues as claim 1

Isolated DNA having at least 15 nucleotides of the wild-type DNA of claim 1 is claimed in dependent claim 5 and isolated DNA having at least 15 nucleotides of the cDNA of claim 2 is claimed in claim 6. Objections to each of these claims are discussed below.

Full-length sequence patent eligibility

Judge Lourie argued that the patent-eligibility of the full-length BRCA1 gene should be considered from the standpoint of a chemist. He emphasized the distinctness of the molecular species being claimed and the role that chemical bond rupture could play in establishing such distinctness:

> "Isolated DNA … is a free-standing portion of a larger, natural DNA molecule. Isolated DNA has been cleaved (i.e., had covalent bonds in its backbone chemically severed) or synthesized to consist of just a fraction of a naturally occurring DNA molecule. For example, the BRCA1 gene in its native state resides on chromosome 17, a DNA molecule of around eighty million nucleotides … In contrast, isolated BRCA1 … with introns consists of just 80,000 or so nucleotides. And without introns …BRCA[1] shrinks to just around 5,500 nucleotides …Accordingly, BRCA in [its] isolated state [is a different molecule] from DNA that exists in the body; isolated DNA results from human intervention to cleave or synthesize a discrete portion of a native chromosomal DNA, imparting on that isolated DNA a distinctive chemical identity as compared to native DNA…
>
> The dissent disparages the significance of a "chemical bond," presumably meaning a covalent bond, in distinguishing structurally between one molecular species and another. But a covalent bond is the defining boundary between one molecule and another, and the dissent's citation of Linus Pauling's comment that covalent bonds "make it convenient for the chemist to consider [the aggregate] as an independent molecular species" underlines the point. The covalent bonds in this case connect different chemical moieties to one another."

It will be apparent that the above argument is based on the premise that the necessary human intervention had indeed been disclosed, i.e. cleavage of longer DNA (e.g. the 600 kb sequence adjacent marker D17S855) at precise locations of choice to give the wild-type BRCA1 as a single full-length sequence in an isolated state. Possibly for that reason neither Judge Moore nor Judge Bryson in the Federal Circuit had been convinced that breaking chemical bonds was the key to patent-eligibility.

The contrary view is that what matters is the informational content of the gene and that it should be evaluated from the standpoint of a geneticist and not that of a chemist. That view was explained by Judge Bryson in his dissent, who supported his view by the absence of any DNA sequence information in claim 1 of the '282 patent:

> "If we are to apply the conventional nomenclature of any field to determine whether Myriad's isolated DNA claims are "new," it would seem to make more sense to look to genetics, which provides the language of the claims, than to chemistry. Aside from Myriad's cDNA claims, its composition claims are not defined by any particular chemical formula. For example, claim 1 of the '282 patent covers all isolated DNAs coding for the BRCA1 protein, with the protein being defined by the amino acid sequence encoded by the naturally occurring BRCA1 gene."

In the Supreme Court Justice Thomas approved that reasoning in the following language which also draws attention to the absence of sequence information:

> "Nor are Myriad's claims saved by the fact that isolating DNA from the human genome severs chemical bonds and thereby creates a nonnaturally occurring molecule. Myriad's claims are simply not expressed in terms of chemical composition, nor do they rely in any way on the chemical changes that result from the isolation of a particular section of DNA. Instead, the claims understandably focus on the genetic information encoded in the BRCA1 and BRCA2 genes."

He went on to doubt whether Myriad intended the claim to be structural and limited to a unique molecule since its scope would then be narrow:

> "If the patents depended upon the creation of a unique molecule, then a would-be infringer could arguably avoid at least Myriad's patent claims on entire genes (such as claims 1 and 2 of the '282 patent) by isolating a DNA sequence that included both the BRCA1 or BRCA2 gene and one additional nucleotide pair. Such a molecule would not be chemically identical to the molecule "invented" by Myriad. But Myriad obviously would resist that outcome because its claim is concerned primarily with the information contained in the genetic sequence, not with the specific chemical composition of a particular molecule."

The origins of this line of reasoning may only become fully apparent on going through the totality of the briefs filed. In oral argument Justice Sotomayor explained that she had an analytical problem: it was very difficult to conceive how you can patent a sequential numbering system by nature (sic) in the same way that she had a problem in thinking that someone could get a patent on computer binary code merely because they throw a certain number of things on a piece of paper in a certain order. A further source may have been the fact pattern in EPO Appeal case T 1213/05 *Breast and ovarian cancer/UNIVERSITY OF UTAH* which Myriad cited to the Supreme Court in their reply brief and which concerned one of the European equivalents to the US '282 patent. In that case the disclosure of the cDNA sequence for BRCA1 in a priority document differed from that in the European patent as filed in 15 nucleotide residues, nine of which lead to amino-acid exchange and six of which were silent. These differences led to denial of priority which, coupled with an intervening publication, gave rise to lack of novelty objections and resulted in significant limitation of the European claims. It will be noted that sequence errors were also an issue in the recent CAFC decision in *Sanofi-Aventis v Pfizer*, mentioned above.

In his dissent, Judge Bryson further relied on *Diamond v Chakrabarty* 447 US 303 (1989) and held that as between what is claimed and what is found in nature the focus should be firstly on the similarity in structure and secondly on the similarity in utility. His analysis, which continued to be from the standpoint of a geneticist rather than a chemist, emphasized the absence of any new utility for the isolated wild-type BRCA1 gene and was as follows:

> "The structural differences between the claimed "isolated" genes and the corresponding portion of the native genes are irrelevant to the claim limitations, to the functioning of the genes, and to their utility in their isolated form. The use to which the genetic material can be put, i.e., determining its sequence in a clinical setting, is not a new use; it is only a consequence of possession. In order to sequence an isolated gene, each gene must function in the same manner in the laboratory as it does in the human body. Indeed, that identity of function in the isolated gene is the key to its value. The naturally occurring genetic material thus has not been altered in a way that would matter under the standard set forth in *Chakrabarty*. For that reason, the isolation of the naturally occurring genetic material does not make the claims to the isolated BRCA genes patent-eligible."

Justice Thomas agreed that *Chakrabarty* was central to the enquiry, and that qualifying subject-matter had to be a product of human ingenuity having a distinctive name, character and use. In relation to the wild-state gene Myriad had not created anything. Genes and the information that they encode are not patent-eligible under §101 simply because they have been isolated from the surrounding genetic material.

In contrast where there was a well-defined new molecular entity with new and identifiable utility the associated claim received judicial support. All three Justices of the CAFC held that the subject-matter of claim 2 was patent-eligible and their decision was unanimously affirmed by the Supreme Court.

Short segments

As a further part of his dissent Judge Bryson doubted the novelty and written description of claims to short segments. For example as regards short segments of cDNA he objected:

> "I disagree with the court as to the two claims to short segments of DNA having at least 15 nucleotides. Claim 6 of the '282 patent covers any sequence of the BRCA1 cDNA that is at least 15 nucleotides long. That claim encompasses each BRCA1 exon, even though each exon is naturally defined by transcription. Moreover, because small sequences of DNA are repeated throughout the three billion nucleotides of the human genome, the claim covers portions of the cDNA of more than 4% of human genes. It also covers portions of the DNA of nearly all human genes. Accordingly, efforts to sequence almost any gene could infringe claim 6 even though Myriad's specification has contributed nothing to human understanding of other genes. Myriad is not entitled to such broad protection."

Similar doubts were expressed by Justice Thomas. In the Supreme Court patentability of short segments of wild-type DNA had become moot, but written description was doubted by Judge Lourie:

> "The other claim to a short segment of DNA, claim 5 of the '282 patent, is breathtakingly broad. That claim covers any segment of the DNA defined by claim 1, provided that the segment is at least 15 nucleotides long. Claim 1, in

turn, covers any isolated DNA that codes for the BRCA1 polypeptide. Thus, claim 5 would cover not only the isolated BRCA1 gene in each of its numerous molecular variations, but also any sub-sequence of those molecules, including portions that fall in the undefined range of those molecules denoted 'vvvvvvvvvvvv.'"

Infringement issues

From the enforcement standpoint what did Myirad lose by their excursion to the Supreme Court?

It is submitted it was the intention of the Supreme Court that any loss should be only marginal, as evidenced by the interventions of the Justices during oral argument, because incentives had to be preserved to undertake the work and make the investments required to bring such products to market. Justice Kagan in particular recognised that it was not sufficient to leave innovation to scientists who wanted Nobel prizes.

For BRCA1 clinical testing Myriad carries out a full sequence determination in both forward and reverse directions of approximately 5,400 base pairs comprising 22 coding exons and approximately 750 adjacent base pairs in the non-coding intervening sequences (introns). The non-coding intronic regions that are sequenced do not extend more than 20 base pairs proximal to the 5' end and 10 base pairs distal to the 3' end of each exon. In their so-called BRACAnalysis Rearrangement Test (BART) all coding exons of BRCA1/BRCA2, limited flanking intron regions and their respective promoters are examined for evidence of deletions and duplications by either quantitative endpoint PCR analysis or microarray comparative genomic hybridization analysis (microarray-CGH). Single site analysis is also carried out.

Their test method involves extracting and purifying DNA from peripheral blood samples or buccal mouthwash samples. For sequence analysis aliquots of patient DNA are each subjected to polymerase chain reaction (PCR) amplification. The amplified products are each directly sequenced in forward and reverse directions using fluorescent dye-labelled sequencing primers. Chromatographic tracings of each amplicon are analyzed by a proprietary computer-based review followed by visual inspection and confirmation. Genetic variants are detected by comparison with a consensus wild-type sequence constructed for each gene.

The above explanation, taken from Myriad's technical specification, casts doubt on whether BRAC testing either needs or involves actual isolation as single continuous sequences of either full length BRCA1 and BRCA2 genes or corresponding full length cDNA. If not, then at least claims 1 and 2 of the '282 patent were of little importance from the legal infringement, as opposed to public relations, standpoint. Enforcement of claims 5 and 6 would be problematic having regard to the interpretation of Judge Bryson in the CAFC, for which an effective counter-arguments would be difficult to create. It therefore appears, adopting a comment of Justice Sotomayor in oral argument, that much of the dispute was, as between the parties, an argument about nothing.

Comment

Both in the US and Europe lack of novelty is often treated as a pedantic and literal-minded objection. For that reason, putting the relevant skilled person and his or her perceptions at the centre of the enquiry represents a potentially fruitful innovation.

However, courts minded to embark on judicial legislation should follow the Hippocratic injunction: *primum non nocere* (first do no harm). Legal disputes arise between particular parties within a particular factual matrix and in a particular timeframe. Rules that are expressed more broadly than needed to dispose of the facts of a case foreseeably have unintended consequences, especially in a rapidly developing field such as biotechnology where a rule providing a just solution in the context of the technology of 1995 and in a specific research field may be inappropriate or even damaging today or in the future in other research fields. When expressed by a superior court they also put at risk necessary step-by-step development of the law by inferior courts.

Scenarios where a blanket rule could work injustice are not difficult to identify. For example, owing to evolutionary selection pressure bacterial genes are intron-free and may be only a few thousand bp in length, similar to the cDNA in Prometheus, readily amplified by PCR and readily manipulable. Many such genes when isolated have industrial utility, and an inability to claim them could prove an embarrassment. Suppose DNA is isolated from a newly identified thermophilic bacterium encoding for a new form of the enzyme β-amylase of improved activity and stability, the sequence being insertable into the genomes of other microorganisms to permit improved industrial use. Should such a sequence be denied patentability? In another example, many researchers extract genomic DNA from one plant and put it in another to produce a plant that e.g. needs less water to grow. A DNA sequence imparting drought-tolerance is highly valuable, especially if it can be incorporated into a wide range of plants. It is debatable whether claiming the corresponding cDNA provides adequate protection. Once the cDNA has been disclosed, third parties can easily get the genomic DNA and use it instead, the manipulation of large sequences of DNA with current technology being relatively easy. A blanket exclusion of claims to natural DNA of these kinds threatens to inhibit patenting and drive researchers towards trade secret protection, thereby inhibiting the free and full disclosure of technical information which is one of the prime objectives of the patent system.

A conservative approach to *Myriad* demands that its ratio decidendi should be correctly understood rather than gold-plated, and that wording in the decision providing limits that are workable and consistent with existing authority should be identified. The question before the Court was whether a naturally occurring segment of DNA becomes patent-eligible by virtue of its isolation from the rest of the genome, and the answer is that simple isolation is not enough. It is submitted that the word "*simply*" in the final paragraph of the opinion is an important qualification deliberately introduced with future problems in mind. For example, it is widely accepted both in the US and

elsewhere that isolation of a product of nature in a form that has new and valuable properties is patentable, the relevant authorities in the US being *Parke-Davis & Co. v. H.K. Mulford Co*., 189 F. 95, 103 (C.C.S.D.N.Y. 1911) and *Merck & Co. v. Olin Mathieson Chem. Corp*., 253 F.2d 156, 161-64 (4th Cir. 1958). In *Mayo v Prometheus* (2012) the Supreme Court made it clear that it was not the intention to change the rules relating to new drugs, and arguably the qualification *simply* implicitly preserves those existing rules. On the same reasoning, the above mentioned amylase gene provides more than a simple substrate for analysis but instead enables industrial processes of improved utility. The water-resistance gene again is not there simply as a substrate but instead is a tool by which new drought-resistant plants can be created. Arguably new and unexpected properties of this kind, possibly in DNA that has in fact been isolated and fully sequenced, should avoid the rule and give rise to patent-eligibility.

The USPTO reacted to *Myriad* on the day that the decision was handed down with a bright line rule for the Patent Examining Corps that they should now reject product claims drawn solely to naturally occurring nucleic acids or fragments thereof, whether isolated or not, as being ineligible subject matter under 35 U.S.C. § 101. It is submitted that a short delay giving time for more considered analysis might have been wiser, and it is hoped that the promised more comprehensive guidance will explain that the exclusion is not quite so straightforward as at first sight appears.