Myriad: picking up the pieces

The US Supreme Court in a landmark decision held that a DNA molecule is potentially eligible for patenting in the US if its sequence does not occur in nature, but is not patent-eligible if its sequence is identical to a naturally occurring DNA sequence. Janis Fraser looks at the major issues in the case.

With a stroke of the pen, the decision in *Association for Molecular Pathology v Myriad Genetics, Inc* effectively invalidates what are expected to be many thousands of issued US patent claims that encompass DNAs or nucleic acids broadly defined in terms of the protein they encode, and that attempt to distinguish over naturally occurring genomic DNA solely by requiring that the claimed DNA/nucleic acid be 'isolated'.

However, to the relief of many in the biotechnology industry, most claims limited to cDNAs ('complementary' DNAs)—particularly those cDNAs that are derived from vertebrate genes—should survive. The scramble is on for patentees to identify which of their DNA/nucleic acid claims remain viable after this groundbreaking decision, and whether those claims are adequate to cover important commercial products.

The *Myriad* case began in 2009 when the American Civil Liberties Union and the Public Patent Foundation, acting on behalf of a motley group of researchers, doctors, patients and medical institutions, filed suit against Myriad Genetics, Inc, seeking a declaratory judgment that Myriad's patents claiming two isolated genes associated with breast cancer, BRCA1 and BRCA2, were invalid. The plaintiffs originally targeted several categories of claims, including not only composition claims drawn to DNAs but also method claims drawn to various uses of those DNAs.

The trial court held that all of the challenged claims were invalid under 35 USC § 101 because they encompassed subject matter that did not qualify as eligible for patenting. Myriad appealed to the Court of Appeals of the Federal Circuit (CAFC). After the CAFC's first holding in Myriad's favour was vacated and remanded back to the CAFC by the Supreme Court, the CAFC ultimately held that Myriad's composition claims and screening assay claims were patent-eligible. The Supreme Court then granted the plaintiffs' request to consider the question of whether human genes are patent-eligible subject matter. Though the question presented to the Supreme Court was worded in terms of 'human genes', the impact of the decision does not appear to be limited to 'human' sequences nor to 'genes' *per se*, but instead broadly encompasses any DNA with a nucleotide sequence identical to any portion of a naturally occurring genomic sequence.

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The court explicitly considered the patent-eligibility of two categories of DNA that were separately claimed by Myriad. The first category of DNA was claimed as an 'isolated' DNA encoding BRCA1 or BRCA2 (which broadly encompasses both genomic and cDNA as well as degenerate variants of both), or a portion of such an isolated DNA at least 15 nucleotides in length. The CAFC had relied on the 'isolated' limitation as adequately distinguishing these DNAs from the BRCA1 and BRCA2 genes as they occur naturally in the genome, reasoning that an 'isolated' DNA by definition differs from non-isolated DNA in that 'isolated' DNA lacks covalent bonds linking its two ends to the rest of the chromosomal DNA. The CAFC also observed that isolating the DNA by breaking those two bonds is a significant change because it makes the DNA useful in ways that DNA present in the chromosome is not.

The Supreme Court disagreed with the CAFC's conclusions, holding that characterising the DNA as 'isolated' is insufficient to distinguish it from DNA present in a natural chromosome. The court stated that "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."

The court dismissed Myriad's argument that the US Patent and Trademark Office's (USPTO's) past practice of awarding such 'isolated DNA' claims is entitled to deference, pointing to the fact that the US Justice Department's *amicus* brief submitted on behalf of the US took the contrary position that the 'isolated DNA' claims should not be eligible for patenting and that no deference should be given to the USPTO's longstanding practice.

The second category of DNA considered by the court was cDNA. The court characterised Myriad's claimed BRCA1 and BRCA2 cDNAs as 'synthetically created' cDNA that contains the same protein-coding information found in a segment of naturally occurring genomic DNA, but omits intervening non-coding DNA sequences (introns) that are present

Case: *Association for Molecular Pathology et al v Myriad Genetics Inc. et al*

Court: US Supreme Court, Washington DC

Judge: Authored by Justice Thomas

Decision: Isolated DNA is not patent eligible

Organisation: Myriad Genetics Inc

Founded: 1991

Headquarters: Salt Lake City, Utah, US

Business: Molecular diagnostics

2012 revenue: $496 million

Organisation: Association for Molecular Pathology

Founded: 1995

Headquarters: Bethesda, Maryland, US

Business: Not-for-profit industry advocacy group

in the naturally occurring genomic DNA. Given that the nucleotide sequences of the BRCA1 and BRCA2 cDNAs are not found in nature, the court was satisfied that these cDNAs are patent-eligible.

However, the court went on to highlight an important exception to this cDNA holding: if a particular natural gene has no intervening introns, so has no sequence that is removed when creating cDNA, the resulting cDNA "may be indistinguishable from natural DNA". The unstated implication of that statement is that the latter type of cDNA, and presumably any other DNA that is 'indistinguishable from natural DNA', would not pass muster under §101. This calls into question the validity of claims encompassing, for example, DNA probes or primers with sequences that match sequences imbedded in the genome of any organism. It also appears to invalidate most claims drawn to bacterial cDNAs, since bacterial genes only rarely have any introns.

Finally, the opinion makes it clear that certain topics are specifically not implicated by the decision: for example, methods of manipulating genes, methods involving application of knowledge about the gene sequences, and DNA in which the order of the naturally occurring nucleotides has been altered. According to the court, "We merely hold that genes and the information they encode are not patent eligible under §101 simply because they have been isolated from the surrounding genetic material." This does not mean the court has endorsed the patent-eligibility of the other categories of inventions, but rather it has simply left that question for another day and another case.

Of significant concern in the wake of the *Myriad* decision are claims drawn to other types of biological substances that are identical to naturally occurring substances, including proteins, antibodies, and antibiotics, as well as microorganisms and other cells isolated from nature. These important categories of invention were not addressed by the court, which appears to be oblivious to the potentially far-reaching and devastating implications of its decision.

The full impact of this decision will take years to be fully realised. Savvy patentees will now study their issued DNA claims to determine which seem likely to have been undermined by this decision, and whether those patents contain backup claims that adequately protect their commercially important inventions even if the broader claims can no longer be relied upon. One can expect to see a spike in the number of reissue requests filed at the USPTO, as frantic patentees attempt to salvage their affected claims by requesting the claims be reissued in a narrower form that excludes genomic sequences. Where the commercialised product is a cDNA produced from an intronless gene, the patentee may be forced to rely on claims limited to vectors, transfected cells, and methods of using the cDNA or cells, or to cDNA with an artificial label or heterologous promoter attached.

Claims drawn to DNA probes or primers derived from genomic sequence should survive if they specify an attached label or solid substrate/microarray or some other feature (other than simply 'isolated') that unambiguously distinguishes them from what occurs naturally in the cell.

Since at least some other major industrialised nations do not have a similar prohibition patenting 'isolated' DNAs with naturally occurring sequences, we may see flight of some highly affected sectors of the biotechnology industry to other regions (such as Europe) with friendlier patent laws. The court left such policy considerations to Congress. ■

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