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United States

Gene patents survive in the United States… for now

The mid-Summer 2011 ruling by the US Court of Appeals for the Federal Circuit in *Association for Molecular Pathology v United States Patent and Trademark Office* (commonly referred to as '*Myriad*') has helped to calm some of the ripples in the biotech industry created by the district court's ruling the previous year. In a split decision (two to one), the appellate court panel determined that isolated genes were not "products of nature" and thus could be patented. However, the majority of the method claims directed to ways to use genes were rejected.

The rock was first tossed into the biotech pond in March 2010, when the US District Court for the Southern District of New York issued a 156-page opinion holding that without more, the purification of a natural product (in this case, human BRCA1 and BRCA2 genes) could not transform it into patentable subject matter. The judge relied on Supreme Court precedent, including the oft-cited *Diamond v Chakrabarty*, to determine that the appropriate test was whether the invention had "markedly different characteristics" from the natural product (ie, had a new or distinctive form, quality or property). The court then examined the isolated DNA for the BRCA1 and BRCA2 genes as claimed in the patents, and held that it was unpatentable as it was not markedly different from native DNA as it exists in the human body.

The suit was brought by the American Civil Liberties Union (ACLU) and the Public Patent Foundation, a not-for-profit organisation, on behalf of numerous medical professionals and others. They asserted that several patents on two human genes associated with breast and ovarian cancer (BRCA1 and BRCA2) were unconstitutional and invalid. The plaintiffs included medical professionals, patent holders and an assortment of healthcare organisations, including the Association for Molecular Pathology, the American College of Medical Genetics, the American Society for Clinical Pathology, the College of American Pathologists, Breast Cancer Action and the Boston Women's Health Book Collective. Defendants included Myriad Genetics and the University of Utah Research Foundation, which exclusively license or own the patents in question, and the US Patent and Trademark Office (USPTO). The circumstances indicated that this was a case that the plaintiffs intended to pursue as an attack on gene patents in general.

BRCA patents

The plaintiffs chose a sympathetic vehicle to challenge the patentability of human genes. More than 40,000 women a year die from breast cancer in the United States and about one in eight US women will develop it at some point. Mutations in the BRCA1 and BRCA2 genes are associated with an increased risk of breast cancer, as well as ovarian cancer. Myriad Genetics owns the patents and is the only laboratory in the United States where diagnostic testing can be performed. The patents prevent others from testing these genes or developing alternative tests, which makes it impossible for women to use other tests or obtain an outside second opinion about test results. Moreover, the tests are expensive —Myriad charges over $3,000 for the tests, which places them out of the reach of many.

The plaintiffs included a number of sympathetic individuals, including patients and medical professionals. Based on court pleadings, one patient was unable to obtain a second opinion on her test, while another could not get Medicaid to pay for her test. Another patient submitted a blood sample to Myriad that her insurance company had informed her it would pay for, but allegedly Myriad would not accept that particular insurance coverage.

The suit attacked both the patentability of human genetic sequences and at least some form of diagnostic method claims. With regard to the first, it asserted that the BRCA1 and BRCA2 genes, and their naturally occurring mutations, are natural phenomena, products

of nature and manifestations of laws of nature, and thus are not patentable subject matter under 35 USC § 101. With regard to the second, it asserted that claims for any method of looking for naturally occurring mutations in human genes that do not specify a particular method of analysis are invalid due to indefiniteness under 35 USC § 101, as well as being directed to an unpatentable abstract mental process.

Standing

One of the initial hurdles was the procedural question of standing. None of the plaintiffs had individually been sued for infringement by Myriad, although several asserted that they had received 'cease and desist' letters and had a reasonable fear of being sued. The case was a declaratory judgment action and thus at least one plaintiff had to meet the constitutional requirement of standing.

In fact, the defendants had initially moved to dismiss all the claims for lack of standing, but the district court denied the request, finding that there was standing. The issue was raised again on appeal and the appellate panel affirmed that at least one plaintiff did have standing. While the question is likely to remain an issue if the case continues through the appellate process, it is secondary to the primary issue of patentability.

Patentability of isolated genes

There was no question that isolated human genes fall within the broad category of patentable subject matter as 'composition of matter'. The issue was whether they fall within the judicially created exception that excludes 'products of nature' from patent eligibility.

As a first step, the appellate panel agreed with the lower court's determination that the Supreme Court's decision in *Diamond v Chakrabarty* established the proper framework. In *Chakrabarty* the court had determined that genetically engineered bacteria modified to break down crude oil were patentable subject matter because the patent claims were directed to "a non-naturally occurring manufacture or composition of matter—a product of human ingenuity 'having a distinctive name, character [and] use'". More specifically, the key is whether the patent claims cover something that human intervention has given "markedly different" or "distinctive" characteristics.

Applying this test, the appellate panel held that the isolated DNAs were patentable because isolated DNAs are "markedly different" from native DNAs in the human body. Isolated DNA is not simply purified DNA. Instead, human intervention in cleaving or synthesising a portion of the native DNA imparts a distinctive chemical identity to the resulting isolated DNA. In nature, DNAs are covalently bonded to other materials (the covalent bond is the defining boundary between one molecule and another). When cleaved, an isolated DNA molecule is now a distinct chemical entity. Similarly, complementary DNA sequences (cDNA) also are patentable, as they are even more markedly different from native DNA.

The nomenclature used may be of importance, as prior cases had referred to unpatentable natural substances being merely 'purified' or 'isolated'. The appellate panel clearly distinguished between isolated DNA and purified DNA. Purification, the court said, makes pure what was the same material, but was previously impure. A natural substance is not purified by being isolated. On the conceptual spectrum of manipulation for determining patentability, isolating a substance falls further towards the patentability end than purifying that substance. Of course, this should depend on what "isolating a substance" actually requires in the way of manipulation. For DNA, isolation requires cleaving the covalent bond, thereby creating a distinct chemical entity (in the eyes of the appellate panel, at least).

A possible concern was the panel's apparent deference to USPTO policy. It observed that the USPTO had issued gene patents for almost 30 years, and stated that if gene patents should be excluded from the broad scope of Section 101 patentable subject matter "contrary to the settled expectation of the inventing community, the decision must come not from the courts, but from Congress". Interpreted broadly, this appears to give the USPTO law-making authority that it does not possess and may be a weak point on further appeal.

Interestingly, the federal government had filed a brief that went against the longstanding USPTO policy cited by the court. The government had argued for application of a 'magic microscope' test – that is, if an imaginary microscope could focus in on and observe the claimed DNA molecule as it exists in nature (ie, in the human body), then the claim would be unpatentable. In fact, on this basis the government argued that the claimed isolated BRCA1 and BRCA2 sequences were not patent eligible as they exist in the human body. The appellate panel rejected this argument.

Method claims not patentable

The challenged method claims did not fare as well as the isolated DNA claims. The appellate court upheld the district court's finding that five of the six challenged

claims did not meet the current 'machine or transformation' test applied to method claims in the United States. The machine or transformation test requires a claimed process or method to be tied to a particular machine or apparatus, or to transform a particular article into a different state or thing. There were several variations of method claims (eg, a claim directed towards comparing two gene sequences to see whether any differences exist). The appellate court held that the Myriad patent claims were directed to "abstract mental processes" and did not describe a specific method of transforming material.

The method claim that did survive was a method for screening potential cancer therapeutics via changes in cell growth rates. The appellate panel found that the claim included a transformative step in 'growing' host cells transformed with an altered BRCA1 gene, as well as a step involving physical manipulation of the cells. These steps were central to the purpose of the claimed process and thus the machine or transformation test was satisfied.

Next round

An inordinate amount of attention has been paid to the decisions, and undoubtedly this will continue until there is a final resolution.

The plaintiff's request for a re-hearing by the appellate panel was denied. The plaintiffs have stated that they will ask the Supreme Court will be asked to hear the case. The odds for this happening appear to be good, based on the Supreme Court's continuing interest in questions of patentable subject matter. As there appears to be little dispute about the applicability of the *Chakrabarty* test, the focus is likely to be technical — that is, are isolated DNA fragments truly "markedly different" from native DNA?

It should be borne in mind that only some of the claims in the Myriad patents were challenged and thus potentially at risk. Claims directed to a kit for detecting mutations in the BRCA1 gene, for example, were unchallenged. Thus, even if all of the challenged claims are rejected on further appeal, the Myriad patents themselves will survive, albeit with a few holes where certain claims used to be. It should also be noted that the oldest of the Myriad patents will begin to expire in a couple of years, possibly even before this case is finally resolved.

So, what should a biotech company do in the meantime? Patents will still need to be filed and prosecuted; and the delay in obtaining a patent is already so long that no company will want to put its patent programme on hold, even if it could.

The best approach is to assume that the 'markedly different' characteristic test will continue to apply. Applicants will still be able to get patents directed to genetic material, but will have to show that their claimed invention has markedly different characteristics from native DNA. Thus, any patent application of this sort should include some claims that at least arguably cross over the markedly different characteristics line. Of course, broader pre-*Myriad* claims should be included to maximise possible protection should the line between patentable and unpatentable subject matter ultimately be drawn closer to the natural product. However, this approach increases the likelihood that at least some of the claims in a resulting patent would survive a subject-matter challenge.

Flexibility is key. If a final determination is made during the pendency of the application, claims may be amended or cancelled as appropriate. If a patent has already issued, at least some of the claims will pass challenge. Alternatively, reissue may be an option. In addition, continuation practice is recommended. This allows a patent owner to respond to not only changes in the market, but also to changes or modifications in the law, such as have been seen in *In re Bilski* and as are likely to be seen on appeal in *Myriad*.

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