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The Practical Lessons Of Myriad

Law360, New York (September 04, 2012, 11:56 AM ET) -- On Aug. 16, the U.S. Court of Appeals for the Federal Circuit issued what may be the final decision in the prominent case of Association for Molecular Pathology v. Myriad Genetics Inc., No. 2010-1406 (Fed. Cir. Aug. 16, 2012). The decision is the culmination of a focused effort to reverse the policy of the U.S. Patent and Trademark Office that isolated polynucleotide molecules ("IPMs") are eligible for patenting under 35 U.S.C. § 101 (a policy that has been tacitly followed by the courts). As many commentators have observed, this effort has failed. The majority of the three-judge panel held that IPMs are like any other chemical and are patent-eligible under 35 U.S.C. § 101.

Myriad Genetics is the exclusive licensee of patents claiming isolated DNA molecules and methods that are key to detecting mutations in the BRCA1 and BRCA2 genes (collectively "BRCA genes"). Certain mutations in the BRCA genes lead to greatly increased risk of breast and ovarian cancer. The presence of these mutations is so predictive of breast cancer that prophylactic mastectomy is recommended for women who test positive. It is uncontested that the patented test has saved countless lives.

However, the test is relatively expensive, and some insurance companies refuse to cover it. Although Myriad Genetics has offered at-cost (and in some cases below-cost) testing to low income individuals, patient and physician groups have still voiced aggravation that the test is not generally available at low cost. This made Myriad Genetics an easy target for those opposed to the patenting of genetic tests. A group of such plaintiffs filed a declaratory judgment motion against Myriad, the University of Utah (partial owner of some of the patents at issue), and the USPTO, the central argument of which was that DNA in every form should be held noneligible for patenting.

An aspect of the case that has been less focused upon, but of nearly equal importance, involves the question of the validity of two claims to methods of detecting alterations in the BRCA genes. The claims each recited only one active step. One recited "analyzing" a BRCA gene from a sample, and the other recited "comparing" a BRCA gene from a tumor sample from a patient to a BRCA gene from a nontumor sample from the same patient. The Federal Circuit found both claims noneligible for patenting under 35 U.S.C. § 101.

This conclusion was reached, not because the claims involved DNA, but because the steps of "analyzing" and "comparing" were considered to be abstract mental steps. After the U.S. Supreme Court's recent decision in Mayo Collaborative Services v. Prometheus Laboratories Inc., No. 10-1150 (S.Ct. Mar. 20, 2012) that 35 U.S.C. § 101 requires a claim reciting a diagnostically relevant correlation include something "other than what is well-understood, routine, conventional activity, previously engaged in by those in the field" (slip op. at 13), the Federal Circuit's holding in this regard was not particularly surprising.

Debate rages as to whether the Federal Circuit applied the proper legal precedent in the most logical fashion in reaching its decision. However, little has been written as to how efforts to patent genetic tests

should adapt to the Myriad decision (assuming it is not altered upon further review).

There are clear ways that intellectual property strategy regarding genetic testing should be modified to capitalize on some aspects of the Myriad decision and to mitigate the difficulties caused by other aspects. Despite the decision that IPMs remain patentable, patenting genetic tests will be more difficult in the future due to the recent expansion of the "mental step" exception to patent-eligible subject matter. This is especially true when the test involves a genetic marker that was previously known to exist, but which is discovered to have a new diagnostic use.

The clearest aspect of the Myriad decision is that IPMs are patent-eligible under 35 U.S.C. § 101. Thus, one useful way to react to the decision is to rely more heavily on claims covering IPMs and less heavily on generalized method claims. A claim to an IPM, if carefully drafted, can protect the right to use nearly every approach to genetic analysis and testing, such as the use of oligonucleotide probes, the use of oligonucleotide primers in PCR, and the synthesis of the IPM or its compliment (as occurs in nearly every DNA-sequencing technique).

Like any invention, IPMs are only patentable if they are novel and nonobvious. The shorter the claimed sequence, the greater the likelihood that the sequence is already present in the prior art. As a result, practitioners realize that a claim to a longer sequence is generally less likely to be anticipated. On the other hand, the longer the claimed sequence, the easier it is for an infringer to avoid infringing the claim simply by using a truncated version of the claimed sequence. This has always created a tension in drafting claims to IPMs: The claimed sequence must be short enough to claim all useful versions of the IPM, but long enough to be novel.

Before the Myriad and Prometheus decisions, IPM claims often relied on homology ranges and claims to fragments of a certain size. In genetic testing, such claims were only adequate if accompanied by more generalized claims covering methods of testing. Because Myriad and Prometheus have created new requirements that claims to diagnostic methods recite particular physical steps, it will not always be possible to rely on diagnostic method claims to provide protection where IPM claims fail to do so. Consequently, those interested in protecting genetic tests should now be particularly rigorous in drafting IPM claims.

Conventionally IPMs are claimed as specific sequences, sequences that encode a specific polypeptide, sequences within a certain homology range of a reference sequence, or a fragment of any of the above. For the purposes of protecting genetic tests, claims directed to fragments are by far the most valuable. Genetic tests frequently employ oligonucleotide probes that complement a short sequence present in the genetic marker. They also frequently employ short primer sequences and involve the synthesis of a fragment of the marker or its complement.

One approach to effectively claim fragments is to identify all possible fragments in the marker (and flanking the marker, for the purposes of protecting PCR primers) that are not in the prior art. The search may be constrained by the minimum practical length for a probe, primer, etc. The complete set of novel fragments may be submitted as a mega-table or can be more simply disclosed as regions between set positions in the sequence of the genetic marker. IPMs that are complementary to the fragments should also be claimed. This approach, although laborious, provides a precise method of claiming fragments that are unique to the marker, without relying on ranges of size or homology that are of uncertain value in actually protecting the genetic test.

Such a thorough approach may become impractical when the goal is to protect any set of primers useful in amplifying the marker, because such primers may be found far from the marker itself. Fortunately, the actual use of such primers would result in the synthesis of fragments of the marker itself (if not the

entire marker), which should be protected by carefully crafted fragment claims as described above.

After the Myriad and Prometheus decisions claims can still be written for methods of using IPMs in genetic testing. These opinions seem to allow claims directed to methods such as hybridizing a probe to a template, amplifying a target using a given set of primers, and artificially synthesizing a given IPM (all of which are useful in genetic testing). Another approach is to claim the process of amplifying the target marker comprising polymerizing the complement of a unique fragment of the marker. Assuming that the probe, primers and synthesized IPM are independently patentable, methods of using them should also be patentable.

What if a genetic test is developed when it is learned that a previously known sequence has a new use as a genetic marker? This creates a more difficult situation under the Myriad decision. If the marker is a new mutation in a previously known gene, then the IPM comprising the mutated sequence should be patentable. However, if the marker was already known, then a claim directed to an IPM comprising the marker will be anticipated. A claim directed to an IPM consisting of a fragment of the marker that was not known as specifically useful might be patentable, although it is certain to raise questions of obviousness under 35 U.S.C. § 103. If the fragment is particularly useful in genetic testing (due to relative high efficiency of binding, for example), then it may overcome a patent examiner's presumption of obviousness.

However, a claim that is limited to a fragment (as opposed to a claim that covers an IPM that comprises the fragment) provides little patent protection, because it is relatively easily to design a longer fragment with similar utility. Such a limited claim could provide effective protection if using the fragment in the genetic test requires premarketing approval by the U.S. Food and Drug Administration. In such a situation an imitator who wishes to avoid infringing the patent by varying the design of the primer might need to independently seek FDA approval for the new primer, which can be a serious impediment to market entry.

At this point in time, review of the panel's decision is still available in the form of reconsideration (by the panel or en banc) and writ of certiorari. Even absent such review, the Myriad decision leaves open the possibility that, in the future, a subset of IPMs could be ruled noneligible for patenting. Of the three judges on the panel, Judges Kimberly Moore and Alan Lourie agreed that IPMs are patent-eligible, and Judge William Bryson (the only member of the panel with no training in science or engineering) opined that they are not.

However, Judge Moore's concurrence was based on troubling logic. Judge Moore wrote that short IPMs are patent-eligible because they have utility beyond that of naturally occurring DNA, but that longer IPMs lack such utility.[1] Judge Moore therefore decided that the patentability of long IPMs should be preserved only because holding otherwise would upset the long-standing expectations of the public due to the USPTO's policy of granting patents for long IPMs.

Judge Moore's concurrence reads as if she would reverse her position on long IPMs if the USPTO reversed its position on the patent eligibility of IPMs. Such a reversal by the USPTO is not out of the question. There appears to be a schism in the executive branch regarding the patent eligibility of IPMs. The brief submitted by the U.S. Department of Justice in Myriad asked the court to decide that DNA is generally patent-eligible, but that IPMs that contain identical sequences to naturally occurring sequences are not patent-eligible.

It has been widely noted that this brief did not bear the signature of any lawyers from the USPTO (typically when the DOJ submits a brief on behalf of another agency, counsel from that agency co-author the brief and co-sign the brief). Is there a dispute between the DOJ and the USPTO regarding this

question, which might eventually lead to a change in the policy of the USPTO on which Judge Moore relies?

In summary, the Myriad decision signals a need for increased rigor in claiming IPMs to protect genetic tests. If care is taken in claiming IPMs, then this decision should not prevent inventors from obtaining patent protection for genetic tests when the genetic marker was previously unknown. If a genetic test has been invented that is a new diagnostic use of a known sequence, then the Myriad decision and its doctrinal parent Prometheus will complicate procurement of patent protection. Whether these complications will be sufficient to discourage the commercial development of genetic tests involving new uses of known markers has yet to be seen.

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[1] Of course, her factual conclusion is wrong. Although she correctly notes that long IPMs cannot be practically used as probes and primers, she misses the fact that long IPMs are used for other purposes, such as the insertion of transgenes into genetically modified organisms.
