The future of prenatal molecular diagnostics: impact of the changing patent landscape

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Recent developments in US patent law will provide both challenges and opportunities for creating effective intellectual property and commercialization strategies for prenatal molecular diagnostic methods and may ultimately influence provider and patient access to certain tests.

In *Mayo v. Prometheus* [1], the US Supreme Court addressed the legal standards for patent-eligible subject matter under 35 USC §101, with important implications for patents directed to diagnostic methods.

In general terms, the patents-in-suit [101,102] claimed methods of optimizing the therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder by: administering a drug to a subject; and determining levels of drug metabolite(s), wherein the assayed metabolite levels are compared with predetermined levels to determine whether there is a need to increase or decrease the amount of drug administered.

Under US patent law, certain subject matter is not eligible for patenting. Such patent-ineligible subject matter includes laws of nature, natural phenomena and abstract ideas. According to the Court, the relationship between the concentration of metabolites in the blood and the likelihood that a drug dosage would be effective constitutes a patent-ineligible ‘law of nature’.

The Court then looked to see whether the claims additionally included an “inventive concept”, particularly one that is not a “well-understood, routine, conventional activity”, which would transform “unpatentable natural laws into patent-eligible applications of those laws”. Finding none, the Court held that the claims of the patents ‘effectively claim the underlying laws of nature themselves’ and are thus invalid.

In its decision in *AMP v. Myriad* [2], the Supreme Court addressed the issue of patent-eligible subject matter for composition of matter claims directed to isolated nucleic acid molecules. Reversing years of US patent policy, the Court held that isolated (genomic) DNA segments are not patent-eligible, finding them to be products of nature. In contrast, cDNA were held to be patent-eligible subject matter, since such molecules are not naturally occurring.

While the *Myriad* Supreme Court did not address diagnostic method claims, its decision impacts the validity of claims directed to isolated DNA molecules used in diagnosis. What may be of even greater concern is that, in view of the Court's efforts to delineate what constitutes a 'product of nature' in the biotechnology context, its decision in *Myriad* may call into question the patentability of other isolated

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biomolecules, such as polypeptides. This could negatively affect the validity of claims to certain molecules used as biomarkers.

In *PerkinElmer, Inc. v. Intema Ltd.* [3], the US Court of Appeals for the Federal Circuit ('Federal Circuit') held that patent [103] claims to a prenatal test for Down's syndrome were invalid as being directed to patent-ineligible subject matter. Although a non-precedential opinion, this case may be instructive as to how prenatal diagnostic method claims may be analyzed in US courts and examined at the USPTO in the wake of *Mayo*.

In simplified terms, the claims were directed to a method of determining whether a pregnant woman is at an increased risk of having a fetus with Down's syndrome, comprising the steps of measuring the level of one or more screening markers from the first trimester of pregnancy; measuring the level of one or more screening markers from the second trimester of pregnancy; and determining the risk of Down's syndrome by comparing the measured levels of both the first screening marker(s) and the second screening marker(s) with observed relative frequency distributions of marker levels in Down's syndrome pregnancies and in unaffected pregnancies.

In reaching its decision, the court applied the *Mayo* analysis, first analyzing the method claims to determine whether they contained patent-ineligible subject matter. In doing so, the court looked to the Federal Circuit decision [4] in *Myriad* regarding diagnostic method claims that were found to be patent-ineligible as drawn to abstract mental processes. In *PerkinElmer*, the step of 'determining' risk was found to require no action beyond 'comparing' statistical information, which was a patent-ineligible mental process. In addition, the court stated that the relationship between screening marker levels and the risk of fetal Down's syndrome constituted a patent-ineligible law of nature.

Finding that the claims recited both mental processes and natural laws, the court then determined whether additional aspects of the method "added enough to the statements of ineligible subject matter to direct the claims, not to the ineligible concepts themselves, but to [patent-eligible] applications of those concepts".

Addressing the 'measuring' steps, the court found these to use known methods to assay screening markers, thus failing to render the claims patent-eligible. Regarding the 'determining' step, the statistical information relied upon in this step did not make the claim patent-eligible because it was considered to be "well-understood, conventional information".

Notably, the court pointed out that the claims contained no requirement for anyone to act on the calculated risk. Finding that no aspect of the method

converted ineligible concepts into a patentable application of those concepts, the court held that the claims are not patent-eligible under §101.

The analysis in *PerkinElmer* indicates that the addition of a step requiring a further action, such as a treatment step, may convert a patent-ineligible diagnostic method claim into one that is patentable. Patent practitioners, however, may have concerns about the potential difficulty of enforcing method claims that could be subject to 'divided' or 'joint' infringement, in which two or more entities perform different steps of a method.

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For example, to show induced infringement under 35 USC §271(b), it is required that each step of a method claim be performed (direct infringement). Under the prior 'single-entity rule' [5], inducement could only be found if the underlying direct infringement had been committed by a single party. This sometimes led to a bizarre result in which an inducer could avoid liability by dividing method steps among entities; for example, by performing some of the steps itself.

More recently, however, in its 2012 decision in *Akamai* [6], the Federal Circuit found induced infringement when the method steps were performed by multiple entities. This ruling may make it easier to enforce diagnostic method claims having steps that may be performed by multiple actors.

How should one draft valid claims to a prenatal molecular diagnostic method? The following is a simplified outline of such a claim.

A method for diagnosing/determining a condition/risk level in a subject comprising the following:

- Assaying a sample for a biomarker;
- Comparing the results with a 'standard' value;
- Making a diagnosis/determination of the condition/risk, and;
- Implementing the diagnosis/determination (e.g., treatment).

If the relationship between the biomarker and the condition/risk is already appreciated, this relationship will likely be considered to be a patent-ineligible law of nature. This may be true not only if the relationship is relatively simple (e.g., in *Mayo*), but also if it is expressed by a complex algorithm or determined by sophisticated statistical analysis (e.g., in *PerkinElmer*).

If a novel assay method or biomarker is specified in the claim, this may provide the required ‘inventive concept’ to render the first three steps above patentable. If not, the addition of a further step specifying a practical implementation such as a treatment may transform otherwise patent-ineligible subject matter into a patentable application of that subject matter.

It is worth noting that, while the addition of a treatment step may render an otherwise patent-ineligible diagnostic method claim patentable in the USA, in a number of countries, methods of medical treatment are themselves considered patent-ineligible. In such jurisdictions, structuring the claim as an *in vitro* diagnostic method might, in fact, be necessary for patentability. Thus, a variety of approaches, including drafting claims of varying scope and in multiple formats, should be considered when designing a global patenting strategy.

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The prognosis for patenting prenatal molecular diagnostic methods presents a mixed bag. The bad news is that it has become more difficult to patent molecular diagnostic methods under *Mayo* and *Myriad*, and their progeny. In view of the heightened scrutiny to be applied at the USPTO as well as by US courts regarding patent-eligible subject matter, the patenting of diagnostic methods will require carefully crafted claims. The good news is that, under *Akamai*, it may

be easier to enforce diagnostic method claims having steps performed by multiple entities.

In view of the general requirement that patent applicants disclose their invention to the public before any patent is granted, in some cases there may be a shift away from a strategy focused on patenting toward a service provider model that includes trade secret protection. Under such a model, patient samples may be tested in-house, and certain biomarkers and/or diagnostic algorithms may be maintained as trade secrets. If such a strategy is contemplated, it should be implemented early, while the diagnostic markers and methods are being developed and before patent applications are filed and/or published.

What does this mean for the future of prenatal molecular diagnostics? Uncertainty concerning the validity of existing patents and the potential difficulty of obtaining new patents may shape different intellectual property strategies for various stakeholders. Such uncertainty may also affect licensing and acquisition strategies, financing and, ultimately, the availability in the market for some prenatal diagnostic tests.

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