Bloomberg BNA

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The author provides approaches and strategies for obtaining patent protection for diagnostic inventions after the Federal Circuit's *Sequenom* decision.

Protection of Diagnostic Inventions After *Ariosa v. Sequenom*

By Friedrich B. Laub

The past three years have seen dramatic changes in U.S. life science and biotechnology patent law. Particularly notable in this regard are the Supreme Court's *Prometheus*[1] and *Myriad*[2] decisions, in which the Court began to define the boundaries of what should and should not be considered patent eligible subject matter under 35 U.S.C. § 101.

While *Prometheus* and *Myriad* drew widespread attention, their ultimate impact on the life sciences was unclear at the time because the two decisions were largely viewed as limited to their relatively narrow sets of facts.

Initially, patent practitioners and stake holders held out hope that the U.S. Patent and Trademark Office and the U.S. Court of Appeals for the Federal Circuit would soon more clearly define the applicability and scope of *Prometheus* and *Myriad*. This hope, however, was soon abandoned.

For example, on March 4, 2014, the PTO issued the ''Guidance for Determining Subject Matter Eligibility of Claims Reciting or Involving Laws of Nature, Natural Phenomena, & Natural Products.'' While the PTO Guidance greatly expanded the holdings of *Prometheus* and *Myriad* to any claim involving a law of nature, a natural phenomenon or a natural product, it raised more questions than it answered. As a result, the PTO had to supplement its Guidance less than nine months later.

While this update was helpful to a certain extent in explaining how the PTO intended to determine patentability of unnatural combinations of natural products in view of *Myriad*, it was less helpful regarding the patentability of diagnostic methods. In fact, the updated PTO Guidance was virtually silent in this regard.

Finally, the PTO provided another update of its Guidance on July 30, 2015, entitled ''July 2015 Update: Subject Matter Eligibility,'' which is available to the public on the PTO's web site. This update does not provide any new insight regarding how the PTO will handle diagnostic method claims; it only states that ''Examples in the biotechnology area, especially diagnostic and other method claims directed to laws of nature and natural phenomena, are . . . [evolving] in light of recent judicial developments.''

Continuing uncertainty regarding the scope of IP protection available for inventions related to medical diagnoses has potentially significant ramifications. The U.S. medical diagnostics industry is expanding rapidly and projected to grow, by some accounts, to a volume of about $30 billion by the end of 2018. Furthermore, the

[1] *Mayo Collaborative Servs. v. Prometheus Labs. Inc.*, 132 S. Ct. 1289, 2012 BL 66018, 101 U.S.P.Q.2d 1961 (2012) (83 PTCJ 727, 3/23/12).

[2] *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2013 BL 155804, 106 U.S.P.Q.2d 1972 (2013) (86 PTCJ 332, 6/14/13).

Friedrich B. Laub, Ph.D., is an associate at Kenyon & Kenyon LLP. Laub's practice focuses primarily on patent prosecution, opinion writing and due diligence work in connection with biotechnological, chemical and pharmaceutical inventions. He can be reached at (212) 908-6222 or flaub@kenyon.com.

medical diagnostics industry relies heavily on patent protection since the underlying inventions can often not be protected sufficiently by other means, for example as trade secrets.

Thus, lack of a clear path leading to proper patent protection is likely to reduce investment into new and innovative technologies for medical diagnosis and could stifle development of this vitally important area of industry.

Sequenom

The recent case of *Ariosa Diagnostics v. Sequenom*[3] represented an opportunity for the Federal Circuit to clarify the Supreme Court's analysis in *Prometheus*. Unfortunately, the Federal Circuit apparently ignored this opportunity and chose to make this area of law even more uncertain.

Sequenom arose from a dispute about the infringement of U.S. Patent No. 6,258,540, entitled ''Non-Invasive Prenatal Diagnosis.'' The '540 patent is based on the inventors' recognition that cell-free fetal DNA (cffDNA) is contained in the plasma and serum of pregnant women, usually discarded as medical waste.

The '540 patent has essentially two types of claims. The first set of claims is, arguably, directed to the detection of the discovered phenomenon itself and recites ''[a] method for detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female.'' The second set of claims, by contrast, is not directed to the phenomenon itself. Rather, it is directed to a method of prenatal genetic diagnosis which is novel because it is noninvasive. Claims 21 and 22 below exemplify this second category of claims[4]:

> 21. A method of performing a prenatal diagnosis, which method comprises the steps of:
>
> (i) providing a maternal blood sample;
>
> (ii) separating the sample into a cellular and a non-cellular fraction;
>
> (iii) detecting the presence of a nucleic acid of foetal origin in the non-cellular fraction according to the method of claim 1;
>
> (iv) providing a diagnosis based on the presence and/or quantity and/or sequence of the foetal nucleic acid.
>
> 22. The method according to claim 21, wherein the non-cellular fraction as used in step (iii) is a plasma fraction.

While the discovery of cffDNA facilitates this new method set forth in claims 21 and 22, it is not its focus. However, on summary judgment, the U.S. District Court for the Northern District of California found both types of claims to be invalid under 35 U.S.C. § 101 as not directed to patent eligible subject matter. Contrary to the expectations of many patent practitioners, the Federal Circuit affirmed the lower court on appeal.

Applying the analytical framework provided by *Prometheus*, the Federal Circuit reasoned that the claims of the '540 patent are nothing more than the detection of a natural phenomenon, i.e., the presence of cffDNA in maternal plasma and serum, in combination with well-understood, routine, and conventional activity, e.g., detecting the cffDNA by polymerase chain reaction (PCR). The Court found its decision to be supported by language in the summary of the invention section stating that ''[i]t has now been discovered that foetal DNA is detectable in maternal serum or plasma samples.''[5]

Difference between *Prometheus* and *Sequenom*

The *Sequenom* decision makes it clear that the Federal Circuit saw little substantive difference between the claims in *Prometheus* and those at issue in *Sequenom* because in both cases the claims were allegedly nothing more than a combination of a natural phenomenon and thoroughly conventional techniques. What the Federal Circuit apparently overlooked, or at least not fully considered, was that the inventions underlying *Prometheus* and *Sequenom* are in fact quite different.

In *Prometheus*, the natural phenomenon was the correlation between the effectiveness of a thiopurine drug and the concentration of its 6-thioguanine metabolite. Essentially, the claims at issue in *Prometheus* only required detecting the metabolite, by any means, and then concluding whether the drug dosage regimen should be modified.

In *Sequenom*, the natural phenomenon was the presence of cffDNA in maternal plasma and serum. At its core, the invention in this case, however, is not simply the recognition of this phenomenon and its detection by thoroughly conventional techniques. Rather, the invention is the practical *application* of the observation that cffDNA is present in maternal plasma and serum, leading to the development of the claimed neonatal genetic testing method that is non-invasive. Such a method did not exist before the '540 patent was filed because the prior art only taught (1) genetic testing methods that were invasive rather than non-invasive, and (2) non-invasive tests that relied on biochemistry rather than genetics.

The invention of the '540 patent represents a milestone in prenatal care because it allows prenatal genetic testing that does not rely on amniocentesis or chorionic villus sampling. These two approaches had been the predominant methods for genetic prenatal testing, but are unfortunately invasive in nature and carry a small yet distinct risk of harming the fetus and/or leading to a miscarriage, apart from being much more costly and inconvenient for the patient.

While the '540 patent includes claims directed to the *use* of cffDNA in maternal plasma and serum as the basis for a new approach to prenatal genetic testing, the patent also has claims seemingly directed to the detection of this cffDNA (i.e., detection of the ''phenomenon''). Thus the '540 patent and its claims are not as well drafted with respect to the requirements under Section 101 as they should have been in the post-*Prometheus* world. However, the patentees can hardly be faulted for not having anticipated the radical changes in U.S. patent law that occurred more than 15 years after the '540 patent had originally been drafted.

The Federal Circuit, on the other hand, should have looked beneath the surface of the '540 patent and realized, and addressed, that this patent is fundamentally different at its core from the patent at issue in *Pro-*

[3] *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 115 U.S.P.Q.2d 1152 (Fed. Cir. 2015) (90 PTCJ 2385, 6/19/15).

[4] Claims 1, 2, 4, 5, 8, 19-22, 24, and 25 of the '540 patent were asserted in this litigation.

[5] The '540 patent has been subject of an inter partes review proceeding at the PTO, which is beyond the scope of this article.

   ISSN 0148-7965

metheus. At least those claims of the '540 patent directed to methods for performing prenatal diagnosis on maternal blood samples should have been found patent eligible under Section 101 because they clearly pass the first step of the *Prometheus* test, i.e., they are not directed to a patent ineligible concept itself, but only based on it.[6]

Significance of *Sequenom*

The *Sequenom* decision significantly broadens the scope of the Supreme Court's ruling in *Prometheus* because it holds that not only claims clearly directed to natural phenomena are patent ineligible, but also claims that only apply or make use of natural phenomena. Inventions are often derived from the combination of known elements in a new manner. Or they are derived from known subject matter modified by the addition of new elements that are, directly or indirectly, based on a law of nature, whether the law of nature is fully understood and recognized as such or not. The latter is particularly true for the medical diagnostics field, where inventions (e.g., novel biomarkers and the use thereof) are not necessarily directed to naturally occurring relationships, but apply them.

It is noteworthy in this regard that even the PTO acknowledged in the December 2014 update of its Guidance that, at some level, a law of nature underlies almost any invention: ''Courts [should] tread carefully in scrutinizing claims [reciting a law of nature, a natural phenomenon, or an abstract idea] because at some level all inventions embody, use, reflect, rest upon, or apply a law of nature, natural phenomenon, or abstract idea.'' Citing the Supreme Court in *Alice Corp.*,[7] the PTO then went on to state that ''[a]n invention is not rendered ineligible for patent simply because it involves an abstract concept . . . [and a]pplications of such concepts 'to a new and useful end,' remain eligible for patent protection.''

Thus, the types and number of inventions potentially excluded from patent protection based on *Sequenom's* expansive view of what is patent ineligible subject matter is potentially vast. It is unclear at the time this article is being drafted whether *Sequenom* will be appealed to the Supreme Court, whether the Court might grant *certiorari*, and what the Court might decide if it does. Furthermore, it is uncertain at this point what if any legislative action might be taken by Congress to bring more clarity to the issue of patent protection in the area of medical diagnostics.

Thus, it is critical for patent practitioners and stake holders to develop strategies that mitigate the potential consequence of the *Sequenom* decision.

Enforcement of Diagnostic Claims

In *Prometheus*, the Supreme Court seemed to suggest that the diagnostic claims at issue might have been patent eligible had they additionally recited a specific and novel treatment regimen. As a result, adding such a step to a diagnostic method was considered by many to be the most promising and relatively straight-forward way of obtaining patent protections for diagnostic inventions.[8] However, this approach could be shortsighted.

While it is important to consider adding certain limitations to diagnostic claims in view of *Sequenom*, it is equally important to recognize that patent claims need to be enforceable to have any commercial value. To prove infringement of a patent claim under §§ 271(a) and (b), the patentee must generally prove that the alleged infringer performed each and every step of the claim, or induced another party to do so. While the Federal Circuit in *Akamai* initially held that at least inducement to infringe does not require direct infringement by one single party, the Supreme Court disagreed, holding that inducement to infringe will be found only where one party performs all the claimed steps.[9]

Accordingly, any strategy for obtaining patent protection for diagnostic methods must take enforceability of the claims into consideration. This usually means that claims should be obtained that cover the activities of only one party.

In the medical diagnostics field, the main players are the hospitals and physicians on the one side and the diagnostic testing companies on the other. Since patent stakeholders, typically diagnostic testing companies in this context, tend to avoid suing potential customers, i.e., hospitals and doctors, or because the latter are immune from liability under Section 287(c), competing diagnostic testing companies are the primary target of any infringement litigation in this technology area. Thus, patent claims in these circumstances should not cover activities usually only undertaken by hospitals and doctors, e.g., obtaining medical specimens from patients, articulating diagnoses and administering or prescribe the resulting drug treatment regimens. Rather, to be enforceable against competing diagnostic companies, such claims should only cover the analysis of medical specimens and diagnostic testing.

While, as mentioned, stakeholders generally avoid suing healthcare providers for patent infringement directly, they might nevertheless sue third parties under Section 271(b) for inducing such infringement. This situation might arise, for example, where a commercial competitor does not conduct any diagnostic testing itself, but sells test kits to health care providers. Patent claims meant to be enforced in this type of situation should only recite activities conducted by healthcare providers. Different from the hypothetical set forth above, a claim potentially useful in this context might recite not only that the diagnostic test is performed on the specimen, but also that the specimen is obtained from the patient, that a diagnosis is articulated based on

[6] Judge Linn, in his concurrence, does address the difference between *Prometheus* and *Sequenom*, stating the following: ''Unlike in *Mayo*, the '540 patent claims a new method that should be patent eligible. While the instructions in the claims at issue in *Mayo* had been widely used by doctors—they had been measuring metabolites and recalculating dosages based on toxicity/inefficacy limits for years—here, the amplification and detection of cffDNA had never before been done.'' However, Judge Linn ultimately felt ''bound by the sweeping language of the test set out in . . . *Mayo*.''

[7] *Alice Corp. Pty Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2014 BL 170103, 110 U.S.P.Q.2d 1976 (2014) (88 PTCJ 513, 6/20/14).

[8] *See also Classen Immunotherapies v. Biogen IDEC*, 659 F.3d 1057, 100 U.S.P.Q.2d 1492 (Fed. Cir. 2011) (82 PTCJ 650, 9/16/11).

[9] *Limelight Networks, Inc. v. Akamai Techs, Inc.*, 134 S. Ct. 2111, 2014 BL 151636, 110 U.S.P.Q.2d 1681 (2014) (88 PTCJ 371, 6/6/14).

the test result and that a drug is then administered or prescribed by the physician based on the diagnosis.

Obtaining Diagnostic Claims in View of *Sequenom*

The *Sequenom* decision significantly broadens the scope of the Supreme Court's ruling in *Prometheus*. As set forth below, strategies exist to mitigate the negative impact of *Sequenom*, at least to a certain extent.

However, most of these approaches go beyond just using differently structured patent claims and might affect the earliest stages of research and development. Patent stakeholders should understand that while patent protection for diagnostic methods is still possible, the process of obtaining it has probably become more difficult, lengthy and costly, and might result in a diminished scope of protection. In view of the general uncertainly *Sequenom* (and *Prometheus*) have created regarding the patentability of diagnostic method claims, it is advisable to file patent applications that support as many different aspects of the invention and claim types as possible.

Trade secrets and proprietary information

Trade secret protection is exactly the opposite of patent protection in the sense that protection is achieved by non-disclosure. By contrast, patent law mandates the full disclosure of the invention to the public in return for a limited monopoly, i.e., a patent. Both types of protection have their advantages and disadvantages, depending on the particular circumstances, and might also work in tandem since they are complementary. A good example of the use of trade secret-based protection for diagnostic inventions is provided by the strategy chosen by Myriad Genetics.

Until recently, Myriad relied primarily on patents to protect its methods of diagnosing predispositions to breast and certain other types of cancer. However, on June 13, 2013, in a unanimous decision, the Supreme Court invalidated Myriad's claims to isolated genes, and subsequently other patent claims were struck down by other courts. Additional Myriad patents are scheduled to expire in the near future.

In response, Myriad seems to have shifted from patent to trade secret law to protect its inventions.[10] Specifically, the company tries to obtain a competitive edge by relying on its proprietary database of gene variants to provide faster and higher quality service, or at least by claiming to do so.

The database of gene variants was established over the last 20 years when Myriad still received protection from its extensive patent portfolio and had no real commercial competitor. This approach seems to be quite successful in the sense that other testing companies operating in the same space as Myriad are not likely to be able to establish such a database themselves in the near term.

It should be noted that Myriad's business model relies on its ability to maintain its proprietary database as a trade secret. At the moment, the FDA does not require Myriad, or similarly situated companies, to disclose all the data and algorithms it uses for its analysis. That, however, could change in response to demand by the public and other stakeholders (e.g., the health insurance industry) to make testing data publicly available for the benefit of all patients and researchers generally.[11] Moreover, the FDA seems to attempt to regulate so-called ''laboratory-developed tests'' used in-house by companies offering diagnostic services like Myriad in the same way it currently regulates diagnostic kits sold to third parties. What this means in terms of Myriad's and other testing companies' ability to protect their IP via a trade secret route remains to be seen.

Myriad appears to be the first diagnostic company that utilizes trade secret law on a large scale, instead of patents. It is not unlikely, however, that others might follow. The diagnostics industry becomes more and more intertwined with the personal medicine field, which often requires numerous bio-markers and an analysis that is significantly more complex than the one-marker approach that until recently predominated. While it is clear that trade secret law can provide protection where patents are unavailable, creating information that qualifies as a trade secret and results in a competitive advantage will take time and investment. Ideally, the groundwork for such a non-patent approach to invention protection should therefore be established early on during research and development.

Detect a novel or at least unobvious molecule, single nucleotide polymorphism (SNP), target epitope of a known molecule, detection agent or the like

Another approach to hedge against the likely effects of *Sequenom* is the development of diagnostic tests that additionally rely on a novel or at least unobvious molecule, single nucleotide polymorphism (SNP), target epitope of a known molecule, detection agent, or the like, as long as any of these do not simply represent the ''natural phenomenon'' itself. In *Prometheus* and *Sequenom*, the claims found to be directed to patent ineligible subject matter unfortunately did not require any of such features. The principal detriment of this approach is that it might be relatively easy for competitors to design around patent claims requiring such limitation.

Thus, any attempt to obtain protection against market competitors using the route described here might necessitate studies determining whether potential design-arounds are commercially feasible. It might well be that such studies reveal that particular molecules, epitopes, SNPs or antibodies provide significantly better results than others (for known or unknown reasons). More specifically, it could turn out that a specific epitope of a viral protein can be particularly well detected immunologically because it is particularly exposed under typical ELISA (enzyme-linked immunosorbent assay) conditions. In such a case, the risk of a market competitor gaining an edge by circumventing the patent claims may be relatively small. Research and development regarding ideally critical, unobvious targets and detection reagents for the diagnostic test at issue will take time and resources, and should therefore be initiated early in any research and development program.

[10] *See, e.g.*, Eleonore Pauwels, ''Our Genes, Their Secrets,'' New York Times, June 18, 2013.

[11] *See, e.g.*, Cook-Deegan *et al.*, Eur. J. Hum. Genet. 2013 Jun;21(6):585-8.

   ISSN 0148-7965

Test for a novel combination of markers

The burgeoning field of personalized medicine will require multi-marker tests, or even whole genome and/or proteome analyses, which might necessitate the use of a unique combination of biomarkers. Although this is not assured, such combinations could make diagnostic claims directed to this subject matter patent eligible (*see, e.g.*, U.S. Patent No. 8,465,923).

It might also be useful in this context to preempt any argument by the PTO or the courts that the markers used are simply part of a naturally occurring phenomenon. This might be achieved by clearly characterizing the marker combination as part of a *method* to detect something else, for example the presence of certain cell types or the activation of certain signaling pathways, based on which a diagnosis or other medical conclusion could then be drawn.

Use of specific assay parameters

The claims at issue in *Sequenom* were not found to be patent eligible although at least some were directed to non-invasive diagnostic testing based on the recognition that maternal plasma or serum could be used as source material, as explained above. One possible way of obtaining patent protection for inventions of this type might be to pursue claims that additionally require chemical or mechanical reaction conditions that are necessary yet unobvious in view of the particular biological source material.

For example, one could envision claims that require the presence of certain buffer types or salt conditions that are particularly suitable for the extraction of nucleic acids or proteins form a particular tissue type. Or a claim might be possible that additionally recites limitations reflecting a way of eliminating a specific background signal during ELISA detection of markers derived from a particular tissue source. It goes without saying that research and development regarding ideally critical, unobvious assay conditions will take time and resources, and should therefore be initiated way ahead of the envisioned patent filing date.

Patent protection for diagnostic technologies abroad

Patent regimes in countries other than the U.S. generally do not have provisions comparable to Section 101 as currently interpreted, and therefore tend to be much less restrictive in terms patent eligibility for diagnostic claims. One recent development that exemplifies the lower bar abroad is the recent decision by the Australian High Court, ruling that *purified* DNA is still patent eligible in Australia. Thus, the above described approaches for obtaining claims directed to diagnostic technologies have much less relevance in foreign countries.

However, particularly in situations where large international patent estates are being created, it is imperative that the filing, disclosure and claim strategies are as coherent as possible. This usually means that the above discussed approaches should be implemented across all jurisdictions in which patent protection is sought for a particular invention, at least as long as the U.S. is among them. Typically, this can be accomplished in a straight forward manner by first filing a Patent Cooperation Treaty application and later allowing this application to enter the individual countries where patent protection is desired.

It should also be kept in mind that several foreign jurisdictions exclude from patentability treatment or diagnostic claims that include steps involving the human body (including the European Patent Office and Japan). While such claims are not *per se* excluded from patentability in the U.S., they should also be avoided here to circumvent the problem of divided infringement, as explained above.

Conclusion

In summary, the Federal Circuit's decision in *Sequenom* appears to broaden the scope and applicability of *Prometheus*. While approaches and strategies exist to mitigate the impact of *Sequenom*, obtaining patent protection for diagnostic inventions will likely become more difficult, lengthy and costly, and may ultimately result in a diminished scope of protection available for such inventions.