

Personalized Medicine Patents at Risk: Tips for Battling *Prometheus* and *Myriad* to Obtain Claims to Diagnostics

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Imagine a scenario where a pharmaceutical company discovers that a discarded drug candidate, perhaps initially dropped from the pipeline after mediocre clinical results, is surprisingly effective in a small subset of patients. These responders all have a particular genetic profile. The pharmaceutical company seeks a partnership with a diagnostics company to develop a test to identify the responders. But the diagnostics company is concerned about protecting its investment because patent counsel asserts that the diagnostic test will no longer be patentable in the United States. Its counsel says that claims to diagnosing disease X by detecting genetic marker Y are prohibited from patent protection under 35 U.S.C. § 101, based on a recent U.S. Supreme Court decision that found similar claims were an unpatentable law of nature. Is counsel correct? Are all diagnostic methods for detecting correlations between genetic profiles and treatments unpatentable in the United States? While counsel is validly concerned, certain claims to diagnostic correlations are still obtainable by applying a few claim drafting techniques.

Recent court decisions have necessitated a change in the way personalized medicine inventions are protected in the United States. For example, previously patentable subject matter represented by the hypothetical claim above may no longer be patentable. In *Mayo v. Prometheus*,¹ the U.S. Supreme Court found that claims reciting methods for detecting a correlation between a metabolite and the likelihood of responding to a drug, without “more,” are not patentable. Similarly, in *Association for Molecular Pathology v. U.S. Patent & Trademark Office and Myriad Genetics (“Myriad”)*,² the Court of Appeals for the Federal Circuit (“the Federal Circuit”) found certain method claims ineligible because they were drawn to mental processes. In *Myriad*, one stricken method claim was directed to screening for cancer-predisposing mutations with no further non-mental steps,³ while another was directed to a method comprising the single step of comparing a gene sequence to a control to identify a certain mutation.⁴ And recently, the Federal Circuit invalidated a patent having personalized medicine claims based on the precedent in *Prometheus* and *Myriad*.⁵ These cases will certainly impact how patent practitioners should draft claims to personalized medicine inventions.

What Is Personalized Medicine?

According to the U.S. President's Council on Advisors on Science and Technology, "Personalized Medicine" refers to the tailoring of medical treatment to the individual characteristics of each patient." Personalized medicine enables health care workers to "classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventative or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not."⁶ In the near future, prescribing the same treatment to all patients with the same disease will seem archaic. Companion diagnostic tests will predict whether a particular therapy is suitable. They may also evaluate a treatment in progress and provide information for tailoring dosages or therapies mid-treatment.

Thanks to improved genetic sequencing techniques and biomarker prediction, personalized medicine has already taken a greater role in patients' treatment decisions. For example, the U.S. Food and Drug Administration (FDA) now lists 119 approved drugs that include information about pharmacogenomic markers in their labels. But will advances in personalized medicine be hampered by the changing landscape of U.S. patent law?

Recent Developments in U.S. Courts Have Upset Settled Assumptions About Certain Types of Personalized Medicine Claims

A. Mayo v. Prometheus, Myriad, and Classen

The Supreme Court recently took an interest in two cases that have particular relevance to personalized medicine. The first, *Mayo v. Prometheus*, concerned a patented method for determining the ideal dosage of thiopurine drugs in treating autoimmune diseases. The inventors discovered that the drug was most effective when the concentration of a particular metabolite in a blood sample fell within a narrow window. The patent recited method claims using a fairly typical series of steps: administer the drug, determine the level of the metabolite, and if it falls outside of the window, the next dose should be decreased or increased for optimal effectiveness. Importantly, the claim did not require the actual administration of the next dose, only a "wherein" clause that stated that levels within a certain range "indicate[] a need to increase the amount of said drug subsequently administered"⁷

In March 2012, the Supreme Court found this claim unpatentable because the relationship between the metabolite concentration and the optimized dosage was a patent-ineligible "law of nature." They reasoned that more was necessary to transform the relationship into a patent-eligible application of a natural law. The case raised many uncertainties about how this expanded concept of a "law of nature" will play out in practice as others attempt to patent diagnostic methods relying on correlations between a reporter compound or gene product and some physiological condition.

In one of the first *Prometheus*-like cases to be considered after the Supreme Court opinion, the Federal Circuit invalidated a diagnostic claim as being directed to patent-ineligible subject matter. The nonprecedential decision in *PerkinElmer v. Intema*⁸ may forecast how other diagnostic claims

will be treated in U.S. courts and the Patent Office. Intema's patent included claims to methods for determining the risk of fetal Down's syndrome. Roughly, the methods recited the steps of measuring a first-trimester screening marker, a second-trimester screening marker, and determining the risk of Down's syndrome by comparing the measured marker levels with an empirical frequency distribution of the appropriate marker levels in affected and unaffected pregnancies. Neither marker was specifically claimed in the representative claims, and the marker levels were measured by "assaying a sample" and/or measuring the marker from an ultrasound scan. As was the case in *Prometheus*, the claims in *PerkinElmer* did not require any action to be taken after determining the correlation.

The Federal Circuit characterized the determining step as a mental process (like aspects of the claims in *Myriad*), and the relationship between screening marker levels and the risk of Down's syndrome as a law of nature. It made a broad statement about the bounds of a law of nature that would be shocking in the absence of the Supreme Court's remarkable *Prometheus* decision: "That an increased risk of fetal Down's syndrome produces certain analytical results is a natural process, an eternal truth that 'exists in principle apart from any human action.'"⁹ The Court noted that measurements and comparisons would be made using routine and conventional activity. In this case, the Federal Circuit found that the claims as a whole did not sufficiently convert the mental comparison step and natural law into a patent-eligible application.

The Court next distinguished these claims from the claims in *Classen Immunotherapies v. Biogen IDEC*,¹⁰ in which certain patent-eligible claims involved a "further act" that moved an abstract scientific principle to a specific application. *Classen* predates the Supreme Court's opinion in *Prometheus*, but was not clearly modified by it—*Classen* stands for the principle that by adding a physical administration step, an abstract diagnostic test becomes an application, and the Federal Circuit indeed referenced that rationale in the *PerkinElmer* opinion. The claims in *Classen* were directed to methods of immunizing a mammalian subject, comprising a screening step that effectively comprised mental steps, followed by an immunization step in which the subject was physically immunized according to the result of the screen. The Federal Circuit held that the addition of this concrete, physical step "moves [a claim] through the coarse filter of § 101 . . . from [abstract scientific] principle to application."¹¹

Thus, while *Prometheus* and *Myriad* have limited the scope of certain diagnostic method claims that were previously believed patentable, all hope is not lost. If the method of measuring the level of the biomarker is novel (for instance, a novel antibody is used), or if the claim includes the additional step of administering the treatment to the patient if the biomarker is greater or less than a standard, then the claim will likely be patentable. There are also other techniques that just may save the day or your patent.

B. The Compound Claims in *Myriad*

The *Myriad* case also involved compound claims, directed to naturally occurring mutations in the *BRCA* genes, which when detected provide information regarding the likelihood of having or

getting breast cancer. The disputed compound claims include claims to isolated DNA sequences encoding the BRCA1 protein, corresponding isolated cDNA, and isolated DNA fragments that map to a gene encoding the BRCA1 protein. In November 2012, the Supreme Court granted certiorari to determine whether the isolated DNA claims in Myriad are patentable, and in April 2013, the Supreme Court will hear oral arguments.

The Federal Circuit has twice found Myriad's compound claims patentable (first on appeal from the district court decision, and again on remand from the Supreme Court). Following past precedent, the Federal Circuit found that an isolated nucleic acid molecule is fundamentally different from that same sequence integrated into the chromosome, and thus the isolated BRCA1 gene claimed by Myriad is patent-eligible and not merely a product of nature. But not all judges agreed. Certain members of the panel argued that purification of a naturally occurring element is generally insufficient to confer patent eligibility. And another judge argued that her decision was influenced by a reluctance to upset settled expectations of patentability of genes.

Thus, this year the Supreme Court will make yet another foray into the field of personalized medicine, and in doing so, may create law that invalidates thousands of patents relating to isolated DNA sequences. For example, the Court could find that claims to isolated, naturally occurring DNA sequences are ineligible for patenting, regardless of their novelty or nonobviousness. It may also find the DNA probe claims (directed to fragments of the gene of at least 15 nucleotides) cover patent-ineligible products of nature. Such a finding, combined with the holding in *Prometheus*, may preclude many previously patentable claims in the field of diagnostics and personalized medicine. Keep in mind, however, that depending on the scope of the decision, the Myriad case may not have as severe an impact on future patents as it may initially appear, since most, if not all, human genes have now been cloned and publically disclosed.

Time to Review the Strategy for Obtaining Claims to Personalized Medicine-Related Technologies

Both the *Prometheus* and *Myriad* decisions affect the legal concept of subject-matter eligibility, governed under United States law by 35 U.S.C. § 101. This initial test for patent eligibility has historically been very broad, because to obtain a patent, the claimed material must still meet the secondary hurdles of novelty and nonobviousness, as well as certain requirements intended to ensure that a patent applicant has sufficiently demonstrated possession of the invention and has disclosed enough to enable others to make and use the invention. These recent decisions, however, have generally narrowed the scope of the first screen for patent eligibility.

Nevertheless, these cases are not without clues for how to protect many personalized medicine technologies. For instance, using the guidance of these decisions, the U.S. Patent and Trademark Office (USPTO) has released guidelines outlining the examination approach for method claims after *Prometheus*.¹² The guidelines set forth a three-step test for determining patent eligibility under § 101: (1) determine whether the claim is directed to a process (i.e., a method claim); (2) determine whether the claim focuses on a natural principle; and (3) determine whether the claim includes additional

elements or a combination of elements that integrate the natural principle into the claimed invention such that the natural principle is practically applied. Step 3 asks whether the claim is more than simply a law of nature plus instruction to apply it. If the answer is yes, the USPTO will likely reject the claim. The guidelines also include examples of patent eligible and ineligible claims.

It seems clear that diagnostic method claims in the United States relating to correlations between genomic sequences or biomarkers and an outcome will now require more for patent protection. For example, diagnostic method claims that use known proteins to identify responders will not be patent eligible unless they include some additional step that is more than an instruction to apply the natural law. Consider the following hypothetical claims:

A. Unconventional Reagents or Methods

Hypothetical 1: A method for diagnosing X in a patient by analyzing a patient sample for the presence or absence of protein A, wherein the patient is diagnosed with X if A is detected.

Even if A has never been associated with disease X, hypothetical claim 1 will likely fail to satisfy § 101 since the fact that the presence of A correlates with X is a law of nature, and there are no additional elements or steps to convert the law of nature into an application of that natural law.

The Supreme Court disapproved of the claims in *Prometheus* in part because “[p]urely conventional or obvious pre-solution activity is normally not sufficient to transform an unpatentable law of nature into a patent-eligible application of such a law.”¹³ Thus if the analyzing step relies upon a novel and nonobvious technique or reagent (e.g., a novel detection agent), the claim will likely transition to a patent-eligible application of a law of nature. Consider hypotheticals 2 and 3, both of which will likely transform hypothetical 1 into patent eligible subject matter.

Hypothetical 2: A method for diagnosing X in a patient by analyzing a patient sample for the presence or absence of protein A, wherein the protein is detected using novel antibody B, and wherein the patient is diagnosed with X if A is detected.

In Hypothetical 2, adding the limitation that the protein is detected by a novel and nonobvious reagent will certainly satisfy the requirement of § 101 post *Prometheus* and *Myriad*. Consider Hypothetical 3, which will also likely convert hypothetical 1 to a patent eligible claim.

Hypothetical 3: A method for diagnosing X in a patient by analyzing a patient sample for the presence or absence of protein A, wherein the protein is analyzed using a new (novel and nonobvious) type of ELISA assay, and wherein the patient is diagnosed with X if A is detected.

While both hypotheticals 2 and 3 are likely now patent eligible under § 101, the scope has been compromised.

B. Combinations of Markers

While the Supreme Court’s position on the patent-eligibility of a method relying on a single reporter is relatively clear, whether the new requirement of introducing “unconventional” or “nonobvious” elements may be met by claiming a novel or unexpected combination of known markers is not. Consider Hypothetical 4, and assume that the proteins C, D, and E are known, but this particular combination has never before been associated with disease or outcome X:

Hypothetical 4: A method for diagnosing X in a patient by analyzing a patient sample for the presence or absence of proteins C, D, and E, wherein the patient is diagnosed with X if C, D, and E are detected.

It is unclear, but possible, that a court would find that Hypothetical 4 claims a natural law in that it is directed to the correlation between a particular combination of markers and a disease state. This type of interpretation may have severe consequences for the nascent but rapidly developing personalized medicine industry. Yet it may be possible to argue that such a discovery is still patent-eligible by reframing the component that a court might characterize as a natural law. Consider Hypothetical 5:

Hypothetical 5: A method for diagnosing X in a patient by analyzing a patient sample for the presence or absence of cell type F by measuring the presence or absence of proteins C, D, and E, wherein the patient is diagnosed with X if cell type F is detected.

In this claim, the novel combination of markers for identifying outcome X is positioned as a novel technique for measuring the presence of a particular cell type that is associated with outcome X. Thus here, the claim focuses on the correlation between cell type F and outcome X, and detecting the combination of biomarkers C, D, and E is a novel and nonobvious technique for applying the natural law.

C. Administration Steps

If the invention does not rely upon a novel technique or reagent, the applicant can look to *Classen*, in which the Federal Circuit provided guidance on how to transform an unpatentable abstract principle into a patent-eligible application. As discussed above, *Classen*’s rationale was referenced in the recent *PerkinElmer* nonprecedential opinion, where a claim that did not require a physical dosing step was deemed patent-ineligible subject matter. According to *Classen*, a claim relating to a natural law can become patent eligible where an “administering” step is provided. Importantly, though, in this type of claim, the infringement is likely divided (diagnostic and therapeutic actions included in the same claim but likely not performed by the same infringer). One way to avoid divided infringement is to add a step relating to ordering or requesting the result of the biomarker measurement.¹⁴

Consider the following hypothetical.

Hypothetical 6: A method for diagnosing and treating X in a patient comprising: analyzing a patient sample for the presence or absence of protein A, wherein the patient is diagnosed with X if A is detected; and administering treatment Y to the diagnosed patient.

According to Classen, this claim satisfies § 101 since the administration step effectively takes the claim from a natural law to an application of a natural law.

Finally, consider the following hypothetical claim, which arguably satisfies § 101, and may avoid concerns over divided infringement.

Hypothetical 7: A method for treating X in a patient comprising: requesting a test providing the results of an analysis to determine whether the patient expresses protein A and administering treatment Y to the patient if the patient expresses A.

D. “Man-Made” Samples

Yet another option for carving out patent-eligible subject matter from the discovery of natural correlations may be the inclusion of a “man-made” sample. For example, if a claim includes binding a DNA probe to a biological sample and such a sample with the bound probe would not otherwise exist in nature, the existence of a “man-made” sample may also impart patent eligibility. Consider the following hypothetical, which relates to antibody detection of a biomarker in the blood.

Hypothetical 8: A method for diagnosing cancer in a human subject, wherein the cancer is characterized by the presence of X biomarker comprising:

- i) obtaining a biological sample from the subject;
- ii) applying a monoclonal antibody specific for X biomarker to the sample (note that the antibody does not need to be novel or nonobvious), wherein presence of the biomarker creates an antibody-biomarker complex;
- iii) applying a detection agent that detects the antibody-biomarker complex; and
- iv) diagnosing cancer where the detection agent of step iii) is detected.

This hypothetical may be considered to satisfy § 101 since the claim requires the creation of a non-natural intermediate—an antibody-biomarker complex. This complex does not exist in nature, and thus the claim should be patent eligible.

Conclusion

The U.S. Supreme Court in *Prometheus*, and the Federal Circuit in *Myriad*, have elevated the requirements for what constitutes a permissible application of a natural law in a manner that effectively targets the field of personalized medicine. While this may be problematic and limit the

options for patenting personalized-medicine-based diagnostic methods, some creative claim drafting can still save the day.

¹ 132 S. Ct. 1289 (2012).

² 689 F.3d 1303 (Fed. Cir. 2012).

³ Id. at 1309-10.

⁴ Id. at 1310.

⁵ *PerkinElmer v. Intema*, No. 2011-1577, 2012 U.S. App. LEXIS 23845 (Fed. Cir. Nov. 20, 2012).

⁶ Priorities for Personalized Medicine, President's Council of Advisors on Science and Technology, September 2008 at p.1,
http://www.whitehouse.gov/files/documents/ostp/PCAST/pcast_report_v2.pdf.

⁷ 132 S. Ct. at 1295.

⁸ No. 2011-1577, 2012 U.S. App. LEXIS 23845 (Fed. Cir. Nov. 20, 2012).

⁹ Id. at *14.

¹⁰ 659 F.3d 1057 (Fed. Cir. 2011).

¹¹ Id. at 1068.

¹² 2012 Interim Procedure for Subject Matter Eligibility Analysis of Process Claims Involving Laws of Nature, United States Patent and Trademark Office, July 3, 2012,
http://www.uspto.gov/patents/law/exam/2012_interim_guidance.pdf.

¹³ 132 S. Ct. at 1298 (internal quotes removed).

¹⁴ Applicants should be mindful of divided infringement concerns with method claims. Under current law, a party can assert an induced infringement claim under 35 U.S.C. § 271(b) even where more than one entity is induced to perform the steps of the method. *Akamai Technologies v. Limelight Networks* and *McKesson Technologies v. Epic Systems Corp.*, 692 F.3d 1301 (Fed. Cir. 2012) (en banc). But this decision was far from unanimous. Further, a direct infringement claim requires that a single party performs each of the steps of the method.

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