Patenting Personalized Medicine Inventions after *Myriad*

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The Federal Circuit's recent decision in *Assoc. for Mol. Pathology v. USPTO* (2010-1406) (informally referred to as the *Myriad* decision), provides some clarity to entrepreneurs and scientists working in the personalized medicine industry. The Court overturned the district court decision and confirmed that isolated DNA molecules are patent eligible subject matter as they "have a distinctive chemical identity and nature – from molecules that exist in nature." Slip opinion at 41. The Court did not limit patent eligibility to cDNA as had been suggested by the U.S. Government in its *amicus* brief. Judge Moore's concurrence highlights an important policy further supporting the majority decision. The settled expectations of the biotechnology industry should not be taken lightly and deserve deference. Concurring-in-part slip opinion at 21. Nevertheless, the Court found some of the disputed method claims patent eligible and some not. The claims that included only steps of analyzing and comparing DNA sequences were found not to be patent eligible whereas the claim that included steps of growing cells and determining their growth rate were patent eligible.

For those in the personalized medicine industry, the news that isolated DNA molecules remain patent eligible is good news. Although, as genetic sequence data proliferates, we can anticipate a time in the not-too-distant future when new genetic variations will be found less often. In the post-genomic age, claims to isolated nucleic acid compositions having a defined sequence or polymorphism will become increasingly rare.. Personalized medicine's greatest innovations lie in teasing out the powers of sequence polymorphisms and marker panel expression levels to predict disease likelihood, severity, activity, or therapy response. In the absence of composition claims, these innovations find patent protection through method claims.

The *Myriad* decision provides guidance to the types of method claims that are patent eligible. The patent-eligible method claim (claim 20 of U.S. Pat. No. 5,747,282) included steps directed to growing cells and determining or comparing growth rates. The Court found the steps of growing the cells and the comparing of the growth rates to be transformative and "central to the purpose of the claimed process." Slip opinion 53. As we'll discuss later in the article, including such steps in a method claim can later create problems associated with their enforcement. The patent-ineligible method claims in the *Myriad* case (including claim 1 of U.S. Pat. No. 5,709,999 and claim 1 of U.S. Pat. No. 5,710,001) only included steps directed to comparing or analyzing sequences. The Court found these steps could "be accomplished by mere inspection alone" and thus are "directed to the abstract mental process of comparing two nucleotide sequences." Slip opinion at 52-53.

The Court looked to its own prior decision in *Prometheus Laboratories, Inc. v Mayo Collaborative Services* (628 F.3d 1347 (Fed. Cir. 2010)) in making these eligibility determinations. In *Prometheus*, the claims at issue were directed to methods of optimizing therapy for specific drugs (6-mercaptopurine and azathiopurine) by determining whether specific metabolite levels were above or below a threshold. Levels exceeding the threshold indicate that dosing should be adjusted downward, and vice versa. All claims recite determining the level of metabolite. Some claims also recite administering the drug prior to the determining step. For those claims including a drug administering step, the Court stated, "[t]he transformation is of the human body and of its components following the administration of a specific class of drugs and the various chemical and physical changes of the drugs' metabolites that enable their concentrations to be determined. We thus have no need to separately determine whether the claims also satisfy the machine prong of the test." Slip opinion at 16. As for claims that did not include "administering" the Court found the metabolite determining step "necessarily involves transformation." Quoting a Prometheus expert, the Court noted that" 'at the end of the process, the human blood sample is no longer human blood; human tissue is no longer human tissue.' " Slip opinion at 18.

Pre-emption analysis provides another useful framework for evaluating patent-eligibility of method claims in the personalized medicine space. Note that the *Prometheus* claims are directed to a specific drug used to treat a specific disease, and the monitoring of a specific threshold of a specific metabolite to indicate the need to adjust dose up or down. Such a claim does not pre-empt all uses of the basic biological fact that drugs work best when their concentration is within a therapeutic window, or that drugs are metabolized to other compounds whose concentrations can be determined.

The Court's analysis of Myriad claim 20 of the '282 Patent illustrates such an inquiry. Claim 20 is directed to a method for screening potential cancer therapeutics via changes in cell growth rates. As mentioned previously, it includes the steps of growing cells, determining their growth rates and then comparing their growth rates. In addition to finding that the steps of growing the cells and determining their growth rates were transformative and "central to the purpose of the claimed process," the Court also assessed whether the claim was attempting to claim the scientific principle that decreased growth rate of cells after treatment with a substance indicates that the substance inhibits cell growth. The Court found that this claim did not claim a scientific principle because, "The claim does not cover all cells, all compounds, or all methods of determining the therapeutic effect of a compound. Rather, it is tied to specific host cells transformed with specific genes and grown in the presence of absence of a specific type of therapeutic." The Court quoted its own decision in *Prometheus* where they determined that the claims at issue in *Prometheus* "do not preempt all uses of the natural correlations; they utilize them in a series of specific steps." Slip opinion at 54. The invalidated method claims in *Myriad* pose the question as to whether claims broadly covering the basic relationship between particular polymorphisms and disease risk pre-empt all use of basic biological fact that certain BRCA1/2 polymorphisms are correlated with ovarian and breast cancer risk. The public policy in favor of a robust, domestic personalized medicine industry is best served by drawing the eligibility line in a way that includes claims drawn to particular polymorphisms used to analyze particular disease risks, activities, or responses. Such claims do not pre-empt all use of the biological law that genes impact disease, or even that genetic information about BRCA1/2 can be used to predict cancer risk. The U.S. Supreme Court has granted *cert* in *Prometheus* and the case will be heard in the next term.

The preemption analysis can be extended to other types of personalized medicine claims. Claims directed to multianalyte index assays, analyze expression of multiple biomarkers using a predictive model to determine diagnose disease or determine an individual's disease risk. Claims can be drawn in a manner that does not preempt the basic biological fact that biomarker levels are correlated with disease state. For example, claims that are drafted to address a particular condition and recite particular biomarkers, do not preempt all uses of this basic biological fact because in general, many independent sets of biomarkers can be used to arrive at a particular prediction. Thus, other biomarkers are still available for others to use in creating their own diagnostic kits. Additionally, because the use of the biomarkers is tied in the claim to a particular condition, the recited biomarkers can still be used freely in other diagnostic methods.

The Court did not apply the preemption analysis in determining that claim 1 of the '999 Patent and claim 1 of the '001 Patent were not patent eligible. Instead, the Court looked to the verbs used in the steps of these claims, "analyzing" and "comparing," and found the steps to be "only abstract mental processes." Slip opinion at 49-50. However, using the preemption analysis, these claims would be patent eligible. There is a natural correlation between a person's genetic makeup and cancer. Claim 1 of the '999 Patent however is directed to determining whether the sample BRCA1 gene being analyzed has one of a group of enumerated alterations. There could be other alterations to that gene or to other genes that also correlate to an increased risk of breast or ovarian cancer. Claim 1 of the '001 Patent is directed to determining a difference between the BRCA1 gene in a patient's tumor sample to the BRCA1 gene in a non-tumor sample from the patient. This claim presents a closer call under preemption analysis because it is not limited to particular polymorphisms, but rather broadly covers all use of the biological fact that BRCA1 polymorphisms can predict cancer risk. In

considering the *Prometheus* case, the Supreme Court has the opportunity to provide clarity on the use of the preemption analysis that could lead to a different result on the patent eligibility for claims such as those invalidated in the *Myriad* decision.

This analysis can also be applied to the claims at issue in *Classen Immunotherapies, Inc. v. Biogen Idec, et al.*, a case whose decision is due from the Federal Circuit any day now. Classen's claim 1 is to a method of determining whether an immunization schedule affects the incidence or severity of chronic-immune-mediated disorders. The claim is however not limited to a particular immunogen, class of immunogens, disorder, class of disorders or marker or class of markers. Thus, there is a reasonable argument that the Classen claim preempts all uses of the natural correlation between immunizations and immune-mediated disorders. The Court may determine that these claims are not patent eligible under preemption analysis. We note as an aside that the Machine or Transformation test would lead to a different result, since surely a subject is transformed upon immunization.

In drafting a method claim that is patent eligible, a new issue can be created if the various steps of the method claim are performed by more than one party. A step such as determining the presence or absence of a particular SNP in a patient sample can be performed by a contract lab while the diagnosis of what that SNP means for a patient will be made by the patient's physician. In the near future, many patients will carry extensive genetic information as part of their electronic medical record. Such information can be generated by a company specializing in low cost sequencing, while the analysis can be carried out by a separate company focused on diagnostic test development. Under these facts, determining whether a patient has a particular mutation is separate from understanding its diagnostic implications.

In either scenario, there is the problem of divided infringement. Currently, in order to find infringement of a method claim, one party must do all of the steps of the asserted method or if more than one party performs the steps of a claimed method, one party must be exercising "control or direction" over the entire process. (*BMC Resources, Inc. v. Paymentech, L.P.* 498 F.3d 1373, 1380-81 (Fed. Cir. 2007)) Additional guidance is coming from the Court when it rehears *McKesson Technologies Inc. v. Epic Systems Corp.* and *Akamai Technologies, Inc. v Limelight Networks, Inc. en banc* next session. In the panel decisions for those cases, now vacated, the Court had articulated a very strict standard for finding that one party controls or directs the process. In granting the request for rehearing *en banc*, it is possible the Court is considering softening that very strict standard but it is less likely that the original standard that one party directs or controls the process will be changed. In *MuniAuction, Inc. v. Thomson Corporation*, the Court stated that one party directs or controls the entire process if that party would be vicariously liable for the actions of the second party doing the method steps that the first party is not actually doing. (532 F.3d 1318, 1330 (Fed. Cir. 2008)) Thus, it is prudent to write method claims that include steps that are only performed by a single party – such as the party actually making a diagnosis.

The Federal Circuit's expected *Classen* decision and the upcoming *Prometheus* Supreme Court decision will hopefully bring even more clarity for the personalized medicine community. We suggest that preemption analysis provides a way to draw the 101 subject matter line for method claims in a way that preserves settled expectations and promotes a robust, domestic personalized medicine industry without unduly impeding either basic research or the ability of the personalized medicine industry to bring products to market.

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