An Unclear Diagnosis

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What constitutes patentable subject matter? The tension between the broad language of 35 U.S.C. Section 101 and the limitations of its scope by the courts is playing out in the context of patent eligibility of process claims. For claims directed to diagnostics and other aspects of personalized medicine, the issue has been framed in terms of pre-emption; do the claims impermissibly seek to monopolize a law of nature?

In 2008, the Federal Circuit in *In re Bilski,* 545 F.3d 943 (Fed. Cir. 2008) re-examined the requirements for determining patent eligibility of process claims under Section 101. Although the patent at issue in *Bilski* is directed to a business method, the decision has far-reaching effects that impact medical diagnostics and personalized medicine patents.

Justice Stephen Breyer's dissent in *Laboratory Corporation of America Holdings v. Metabolite Laboratories Inc.,* 548 U.S. 124 (2006) argues that a popular type of medical diagnostic claim is unpatentable subject matter under Section 101. The dissent questioned the proper scope of protection for method claims that rely on correlating biological phenomenon to reach diagnostic conclusions. In *Labcorp.*, the patented technology was based on the inventors' discovery of an inverse correlation between the amino acid, homocysteine and certain vitamin deficiencies. The claim at issue broadly recited a method of diagnosing a vitamin deficiency by measuring (by any means) the level of homocysteine, and correlating an elevated level with certain vitamin deficiencies. In his dissent, Breyer set out his reasoning for finding the claim invalid as in improper attempt to claim a law of nature. In short, he argued, that the claim pre-empts all beneficial uses of the natural physiological relationship between homocysteine and certain vitamin deficiencies.

The Federal Circuit's decision in *Bilski* picks up this thread and advances a "machine-or-transformation" test for determining the patent eligibility of process claims under Section 101. Under this test, a claim is patent eligible if it is tied to a particular machine or apparatus, or it transforms a particular article into a different state or thing. Certain criteria must be met under either branch. First, use of the specific machine or transformation of an article must convey meaningful limits on the claim's scope to impart patent eligibility. Second, the involvement of the machine or transformation must be central to the claim's purpose and not merely insignificant extra-solution activity.

This test may sometimes meaningfully discriminate between claims that improperly attempt to claim a "law of nature" (because they pre-empt all practical uses of a natural phenomenon) and those that do not. Depending on how "insignificant extra-solution activity" (such as, e.g., data gathering) is interpreted, this test may exclude under Section 101, claims that arguably do not pre-empt, and not exclude claims that do. Thus, for many biotechnology cases, application of the "machine-or-transformation" test articulated by *Bilski* as the exclusive test for patent-eligible subject matter provides a coarse tool for discriminating claims that improperly claim laws of nature from those that do not._

Under the machine-or-transformation test the claims for inhibiting gene expression considered in *Ariad v. Lilly,* 560 F.3d 1366 (Fed. Cir. 2009) could be considered patentable subject matter because they involve a transformation, *i.e.,* a reduction of a transcription factor (NF-κB) activity by reducing binding of the transcription factor to DNA sequences found in genes transcriptionally-regulated by the transcription factor. The claim is not limited to the use of any particular compound or agent for reducing transcription factor activity. In this instance, the claim passes the *Bilski* test, even though it pre-empts

all uses of the basic biological fact that NF-κB is a transcription factor that regulates the expression of certain genes. Although these claims arguably pass muster under *Bilski*, they were easily invalidated by the Federal Circuit under the written description requirement of 35 U.S.C. Section 112, as the specification failed to demonstrate that the inventors were in possession of any specific compound that could be used to practice the method.

On the other hand, the method claims in *Classen Immunotherapies Inc. v. Biogen IDEC, et al.*, 381 F.Supp. 2d 452 (D. Md. 2005), fail the machine-or-transformation test. The claims in *Classen* recite methods for determining optimal immunization schedules based on comparing incidence of immune-mediated disorders in treatment groups subjected to different schedules. Similar to *Bilski*, whose claims were not limited to any specific transactions, *Classen's* claims are not limited to any specific vaccine or vaccination schedule. The patent does not claim any specific technique or technical method of testing vaccine safety and is but a general inquiry into whether the proposed correlation even exists. As the Federal Circuit recently concluded the machine-or-transformation test invalidates *Classen's* claims.

It is unclear, however, what impact the machine-or-transformation has on the patentability of claims directed to biological phenomena that exists only as a result of human intervention. Such is the issue in *Prometheus v. Mayo*, No. 04-cv-1200, 2008 U.S. Dist. LEXIS 25062 (S.D. Cal. March 28, 2008), where the district court, citing Breyer's dissent in *LabCorp*., found the claims covering the correlation between the level of drug metabolite in the blood with effective therapeutic treatment the result of a natural body process. Under the machine-or-transformation test, the *Prometheus* claims arguably constitute patentable subject matter because they recite injecting a drug and measuring the drug metabolite, a transformation in the underlying subject matter. The input is a thiopurine drug, however what is being "determined" is not the level of thiopurine drug but its metabolite in the body. Additional questions remain as to whether *Prometheus'* "injecting" and "determining" steps are construed to be insignificant extra solution activities that reduce this claim to the *LabCorp*. "assay and correlate" format now considered ineligible subject matter under *Bilski*.

Certain personalized medicine diagnostic technologies (*e.g.*, in vitro diagnostic multi-analyte index assays) use data obtained from patient samples as inputs that are mathematically combined using an interpretive function to generate a single score based on a quantitative predictive model. The score reflects the weighted contribution of a defined set of biomarkers and is useful for diagnosing disease, monitoring disease progression or predicting drug response or adverse effects.

Several arguments can be advanced to demonstrate that claims directed to multi-analyte index assays do not trigger the pre-emption concerns raised by the now disfavored *LabCorp*. assay and correlate style claims. First, such claims do not pre-empt all uses of the biomarker set, but instead typically are directed to a single, well-defined use. Use of the same set of biomarkers with a different interpretive function for a different use is not foreclosed. Second, different sets of biomarkers often can be used to generate essentially equivalent result. Thus, these claims do not foreclose use of different biomarker sets for diagnosing disease, monitoring disease progression or predicting drug response or adverse effects.

Despite these differences, claims directed to multi-analyte index assays are subject to Section 101 challenges under the *Bilski* machine-or-transformation test. As for the first distinction, *Bilski* suggests that field of use restrictions may not cure Section 101 deficiencies in claims that do not recite a machine-or-transformation. The decision is silent as to the second distinction.

What is certain is that the machine-or-transformation test raises serious questions as to the ability of diagnostic and personalized medicine companies to protect the technologies behind the products they create. The advancement of these sectors is better served by patent laws that articulate appropriate tests for patentable subject matter that do not exclude their contributions. The Supreme Court recently granted

certiorari in *Bilski*. As several amici have pointed out, Section 101 is a blunt instrument ill-suited for discriminating patentable from non-patentable subject matter in emerging technologies. There are multiple alternative statutes that can be used to carry out more nuanced patentability evaluations of method claims. Should it broadly construe Section 101, the Court will minimize the likelihood that the *Bilski* machine-or-transformation test slows innovation in valuable emerging technologies such as personalized medicine.

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