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INSIGHT: The Latest in Patenting Diagnostic Methods

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ABSTRACT

U.S. courts and the U.S. Patent and Trademark Office have been wrestling with the fundamental question of what is and is not eligible subject matter for a patent in the United States. 35 U.S.C. § 101 serves as the statutory threshold for eligibility, but various Supreme Court decisions in the past decade have severely limited patentable subject matter. Under the *Mayo*/*Alice* framework, courts first ask if the subject matter of an invention is directed to ineligible subject matter; if so, courts then look for an application that transforms the invention into patent eligible subject matter.

The Court of Appeals for the Federal Circuit has recently taken a broad interpretive view of *Mayo*/*Alice* as it relates to diagnostic method patents. This year, the Federal Circuit has signaled a willingness to find valid diagnostic method claims that recite a practical application of diagnostic test results in addition to ineligible, *Mayo*-like diagnostic observations. In *Vanda Pharma v. West-Ward Pharma* (2018)), the claims at issue are directed to an *application* of the results of diagnostic testing. Shortly following *Vanda*, the USPTO released guidance suggesting diagnostic method patents may be salvaged by including ''apply it'' language to diagnostic results.

Here, we explore the evolving law of § 101 eligibility of diagnostic method claims in light of *Vanda*. We also highlight indicia that congressional action on subject matter eligibility may be forthcoming.

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One striking aspect of patent law is the widespread confusion over what actually is a patentable invention. 35 U.S.C. § 101 defines subject matter eligibility: ''Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.''

Unfortunately, the seemingly straightforward language of § 101 has been complicated by legal interpretation and ''judicially recognized exceptions.'' These judicial exceptions prevent certain classes of subject matter from satisfying § 101: abstract ideas, laws of nature, and natural phenomena.

The judicial exceptions to subject matter eligibility often muddy the waters, particularly with regard to the eligibility of methods of diagnosing disease. Are methods of diagnosis merely observations of ''natural phenomena'' in the human body? And are these disease states or diagnostic markers ''laws of nature''?

The Backdrop of Supreme Court Precedent In *Mayo Collaborative Services v. Prometheus Laboratories, Inc.* (2012) the Supreme Court unanimously held that diagnostic method claims directed to a correlation between a drug metabolite and dosing needs are unpatentable. Because a patient's unique metabolic response to a drug is nevertheless a natural process, claims directed at observing this response in conventional ways are ineligible subject matter under *Mayo*.

The following year, the Supreme Court held in *Association for Molecular Pathology v. Myriad Genetics, Inc.* (2013) that naturally-occurring DNA removed from the body by conventional methods is unpatentable as a diagnostic marker for breast cancer susceptibility. However, cDNA synthesized using a naturally-occurring mRNA template is patent eligible. Whereas cDNA synthesis can be accomplished through conventional means, and the relevant mRNA templates are naturally-occurring, the synthetic cDNA product itself

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is a composition of matter not found in nature and thus directed to patentable subject matter.

In 2014, the Supreme Court again ruled unanimously in *Alice Corp. v. CLS Bank International* that ineligible subject matter—in this case, the abstract idea of an escrow arrangement—is not transformed into patent eligible subject matter merely because the process is implemented in some generic way, such as on a computer network. Since then, the district courts and Federal Circuit have been bound by the *Mayo/Alice* framework: (1) Is an invention directed to ineligible subject matter? (2) If so, is there some inventive concept about the elements of the claim that transforms the invention into something more than ineligible subject matter?

Setting the Stage for *Vanda* at the Federal Circuit In *Ariosa Diagnostics, Inc. v. Sequenom, Inc.* (2015), the patent at issue described a method of isolating cell-free fetal DNA (cffDNA) from maternal blood samples, and determining from a paternal DNA fraction certain genetic characteristics, such as biological sex. The steps of isolating, amplifying, and sequencing paternal cffDNA are known and routine. What was unknown prior to this invention, however, was the discovery that cffDNA circulated in maternal blood and could in fact be used as a safe option for fetal genetic testing.

Following the *Mayo/Alice* two-step test, the Federal Circuit concluded the claims were invalid. Like in *Myriad*, the invention was directed at the natural phenomenon of naturally-occurring DNA capable of being sequenced for genetic purposes. Despite the new and useful *discovery* of this diagnostic marker, there was a failure in the second *Mayo/Alice* step to transform the *method* into something more than a mere application of ineligible subject matter.

This distinction is critical in understanding the current state of review of diagnostic method claims at the Federal Circuit. *Myriad* instructs that it is not enough to merely identify and isolate naturally occurring DNA sequences. *Ariosa* indicates that even new and useful discoveries of natural phenomena are not transformed into eligible subject matter when the actual method claimed is a mere application of routine and conventional laboratory techniques.

Following a clear showing of dissatisfaction with *Mayo* in *Ariosa*, the Federal Circuit in 2016 began to push back. In *Rapid Litigation Management Ltd. v. CellzDirect, Inc.* (2016), another question of natural law arose. The contested claims were directed at a specific freeze-thaw preparation of hepatocytes which allowed the cells to retain viability.

The district court held the patent invalid as being directed to a law of nature: that hepatocytes are in fact capable of surviving multiple freeze-thaw cycles. On appeal, the Federal Circuit vacated and remanded the district court decision, stating the claims were not directed to a patent ineligible judicial exception. The invention was characterized as a new method to preserve hepatocytes, which was previously difficult to do. This distinguished *CellzDirect* from *Myriad*, but also from *Ariosa*, wherein claims which were technically in method form were nevertheless directed at patent ineligible cffDNA itself.

CellzDirect highlights the importance of careful claims draftsmanship. Had the claims been directed to the newly discovered freeze-thaw resistance of hepatocyte cells themselves, or directed a practitioner to apply a series of routine and conventional techniques to exploit the freeze-thaw resistance of hepatocytes, the claims may similarly have been invalid, following *Ariosa*. It is precisely because of the new and useful ''innovative method'' of hepatocyte preparation that the claims were held not to be directed at patent ineligible subject matter.

***Vanda:* Hope for Diagnostic Method Innovators** Perhaps the most instructive Federal Circuit decision to date relating to subject matter eligibility of diagnostic method patents is the recent April 2018 decision in *Vanda Pharma v. West-Ward Pharma* (2018). Contrary to *Ariosa*, this case opened the door for § 101 validity of a patent directed to the *application* of diagnostic results, even in conventional and routine ways. The following representative claim from U.S. Patent No. 8,586,610 describes a method of genotyping a patient, then administering an amount of iloperidone based on that genotype:

''A method for treating a patient with iloperidone, wherein the patient is suffering from schizophrenia, the method comprising the steps of: determining whether the patient is a CYP2D6 poor metabolizer by: obtaining or having obtained a biological sample from the patient; and performing or having performed a genotyping assay on the biological sample to determine if the patient has a CYP2D6 poor metabolizer genotype; and if the patient has a CYP2D6 poor metabolizer genotype, then internally administering iloperidone to the patient in an amount of 12 mg/day or less, and if the patient does not have a CYP2D6 poor metabolizer genotype, then internally administering iloperidone to the patient in an amount that is greater than 12 mg/day, up to 24 mg/day, wherein a risk of QTc prolongation for a patient having a CYP2D6 poor metabolizer genotype is lower following the internal administration of 12 mg/day or less than it would be if the iloperidone were administered in an amount of greater than 12 mg/day, up to 24 mg/day.''

The district court held the patent not invalid and infringed and the Federal Circuit affirmed. Critical for the Federal Circuit was the way the claims were drafted: to administer specific dosages of a drug based on what is arguably a law of nature. The claims here are not directed at the law of nature itself (a genetic variant resulting in a difference in iloperidone metabolism), but rather the administration of a drug based on genetic diagnosis, with the aim of using the drug in a safer way. Had the claims in *Vanda* only highlighted the discovery of a differential metabolic response to iloperidone in CYP2D6 genotype individuals, without directing a specific treatment decision, the case would arguably have been indistinguishable from *Mayo*. The *Vanda* court stated: ''At bottom, the claims here are directed to a specific method of treatment for specific patients using a specific compound at specific doses to achieve a specific outcome. They are different from Mayo. They recite more than the natural relationship between CYP2D6 metabolizer genotype and the risk of QTc prolongation. Instead, they recite a method of treating patients based on this relationship that makes iloperidone safer by lowering the risk of QTc prolongation. Accordingly, the claims are patent eligible.''

And citing *CellzDirect*, the Federal Circuit again asserted that method claims premised on a law of nature are in fact directed at the method and not the law of nature itself. In *CellzDirect*, by carefully drafting the

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claims to a method of cell preparation rather than a feature of the cells themselves, patent owner escaped *Mayo* ineligibility. The *Vanda* court stated: ''[In *Cellz-Direct*, w]e explained that '[t]he end result of the . . . claims is not simply an observation or detection of the ability of hepatocytes to survive multiple freeze-thaw cycles. Rather, the claims [were] directed to a new and useful method of preserving hepatocyte cells.' [ ] We further emphasized that 'the natural ability of the subject matter to *undergo* the process does not make the claim ''directed to'' that natural ability.' [ ] Otherwise, claims directed to actually 'treating cancer with chemotherapy' or 'treating headaches with aspirin' would be patent ineligible.''

While this is encouraging news for patentees, not everyone on the Federal Circuit agrees with the *Vanda* decision. In her dissent, Chief Judge Prost seemed unconvinced this kind of strategic draftsmanship was effective in evading *Mayo*: ''While the claims here do not solely state a law of nature, they do no more than simply direct the relevant audience to apply it.''

USPTO Guidance Following *Vanda* On June 7, 2018, the USPTO publicly issued guidance to the Patent Examining Corps, in light of *Vanda*. Most importantly, the USPTO wrote that '' '[m]ethod of treatment' claims that practically apply natural relationships should be considered **patent eligible**'', and ''it is not necessary for 'method of treatment' claims that practically apply natural relationships to include nonroutine or unconventional steps to be considered **patent eligible** under 35 U.S.C. § 101.'' That last bit of guidance distinguishes *Vanda* from *Ariosa*, where routine and conventional methods of isolating, amplifying, and sequencing DNA prevented § 101 eligibility under *Mayo*/*Alice*.

The USPTO memo highlights the importance of determining § 101 eligibility of claims as a whole, and not based on the eligibility of individual steps in isolation: ''the Federal Circuit evaluated the claims as a whole, including the arguably conventional genotyping and treatment steps, when determining that the claim was not 'directed to' the recited natural relationship between the patient's genotype and the risk of QTc prolongation.'' *Vanda*, therefore, seems to stand for the proposition that diagnostic method claims reworked as ''method of treatment'' claims are likely patent eligible subject matter, even if the diagnostic method or application of the results of a diagnostic test are routine and conventional.

Possible Future Developments and Takeaways As seen in *Ariosa*, the Federal Circuit has repeatedly demonstrated frustration with *Mayo*, and has suggested Congress take action. In a recent concurrence in denial of a rehearing *en banc* in *Berkheimer v. HP Inc.* (2018), Judge Lourie wrote ''I believe the law needs clarification by higher authority, perhaps by Congress, to work its way out of what so many in the innovation field consider are § 101 problems.''

There may soon be congressional action on § 101 subject matter eligibility. Several groups are clamoring for clarification as to the requirements for patentability, and Congress has been made aware of this need. On April 18, 2018, newly-minted USPTO Director Iancu spoke to the Senate Judiciary Committee about, among other things, patent eligibility. When asked about the current state of patent eligibility case law and medical diagnostics, Iancu warned that Supreme Court case law risks harming innovation. He expressed a willingness of the USPTO to work with the Committee to draft suitable legislation to clarify subject matter eligibility under 35 U.S.C. § 101.

While the future of patent eligibility is unclear, recent case law and the USPTO have provided guidance for drafting claims that protect diagnostic method inventions. It is tempting to read these cases as suggesting one should include in diagnostic method claims a step wherein there is a practical application of the information gained during diagnostic steps, such as actual administration of a drug. Moreover, diagnostic methods can be reworked as methods of treatment using results from diagnostic steps even if the techniques used are conventional or routine. However, practitioners need to balance obtaining a patent that is valid under § 101, but difficult to enforce in an infringement action. As described in detail elsewhere, *Vanda* convinced the Federal Circuit of inducement of infringement by establishing that West-Ward's proposed product label itself recommends or encourages infringing acts. While it may be difficult to enforce method of treatment patent claims in a *direct* infringement suit, it may be easier to follow *Vanda's* lead and establish that a product label *induces* infringement. Patentees should carefully evaluate how and when to mimic the proposed product label language in patent application claims.

It is unclear if courts will continue to handle diagnostic method claims along the lines of *Vanda*. For now, we can only hope that Congress will step in to clarify subject matter eligibility and protect innovators in the diagnostic method space.

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