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How Sequenom Lost Patent Protection For Fetal DNA Test

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In Ariosa Diagnostics Inc. v. Sequenom Inc., 788 F.3d 1371 (Fed. Cir. 2015), Federal Circuit Judge Richard Linn spoke effusively about a groundbreaking invention useful in noninvasive prenatal testing that "effectuated a practical result and benefit not previously attained" and that was "deserving of patent protection." He wrote this in an opinion concurring that the invention was ineligible for patent protection — that claims in Sequenom's U.S. Patent No. 6,258,540 were invalid under 35 USC §101.[1] Who is responsible for such a seemingly anomalous result?

The Patent Statute

The Constitution empowers Congress to award inventors with patents "[t]o promote the Progress of Science and useful Arts." Congress broadly defined the types of inventions eligible for patent protection in 35 USC §101: "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," so long as other requirements of the patent statute are met. Sequenom's patent claims were directed to a "new and useful process," satisfying the literal requirement of the statute. Congress' broadly worded statute is not responsible for the anomalous result.

The Supreme Court's Pronouncements of Judicially Ineligible Subject Matter

Understanding the fate of Sequenom's patent requires an understanding of the U.S. Supreme Court's interpretation of §101. Instead of performing its customary role of interpreting statutes, the court has created "judicial exceptions" to §101. "The Court's precedents provide three specific exceptions to §101's broad patent-eligibility principles: laws of nature, physical phenomena, and abstract ideas." Bilski v. Kappos (2010). In Bilski, the court acknowledged that "these exceptions are not required by the statutory text."

In trying to grapple with controversial "business method" patents, the Bilski court refused to accept a relatively bright-line test, known as the "Machine-or-Transformation test"[2] ("MOT test") as being a definitive test for distinguishing patent-eligible processes from the three judicial exceptions. The Bilski court rejected the MOT test as potentially being too restrictive — imposing limits on eligible processes not justifiable by the plain language of §101. "This Court has more than once cautioned that courts should not read into the patent laws limitations and conditions which the legislature has not expressed."

The Supreme Court revisited patent eligibility in Mayo Collaborative Services v. Prometheus Laboratories (2012), a case involving a medical process invention of administering a drug dose and measuring a drug metabolite in the body to determine if the dose was safe and effective. Although the court quoted §101 in Mayo, the court devoted its entire legal analysis to construing the court's own exceptions to the statute, "in light of the Court's precedents."

The Federal Circuit had concluded that Prometheus' claims were eligible because they satisfied the MOT test, which Bilski had indicated was still a "useful and important clue" to patent-eligibility. The Mayo court interpreted Bilski differently. Because the MOT test was no longer the definitive test for patent-eligibility, a claim's satisfaction of the test did not necessarily mean that claim was patent-eligible. Thus, Mayo imparted a new spin on Bilski, where the court had suggested that failing the MOT test did not definitively render a claim ineligible. After Mayo, the court's "law of nature" exclusion trumped the MOT test, and claims involving a law of nature needed something more to be eligible.

The Mayo court also expanded the scope of "natural law." Whereas traditional "natural laws" were human attempts to characterize the natural world (e.g., Einstein's famous E=mc2), Prometheus' "laws of nature" involved human activity and synthetic drugs: "relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a … drug will prove ineffective or cause harm."

The court revisited §101 in Association for Molecular Pathology v. Myriad Genetics (2013). Again, the court quoted §101, but devoted the entirety of its analysis to construing the court's judicial exceptions. The court concluded that Myriad's patent claims directed to isolated human DNA were not directed to a "new and useful … composition of matter," but were instead directed to ineligible "naturally occurring phenomena," thus expanding the judicial exceptions to exclude some compositions of matter from patent eligibility under §101.

The court rendered its most recent subject matter eligibility decision in Alice Corp. v. CLS Bank International (2014). The pattern begun in Mayo and Myriad of pro forma quotation of statute, but legal analysis focusing only on the court's exceptions, continued. In Alice, the court discerned an eligibility "framework" from Mayo:

In Mayo … we set forth a framework for distinguishing patents that claim laws of nature, natural phenomena, and abstract ideas from those that claim patent-eligible applications of those concepts. First, we determine whether the claims at issue are directed to one of those patent-ineligible concepts. … If so, we then ask, "[w]hat else is there in the claims before us?" … To answer that question, we consider the elements of each claim both individually and "as an ordered combination" to determine whether the additional elements "transform the nature of the claim" into a patent-eligible application. ... We have described step two of this analysis as a search for an "inventive concept" — i.e., an element or combination of elements that is "sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the [ineligible concept] itself."

Using this "framework," the court concluded that claims to Alice's computer-implemented scheme for mitigating settlement risk in a financial transaction were invalid.

Thus, in 2010 the court in Bilski construed §101 and cautioned that courts should not read into the patent laws limitations and conditions (e.g., passage of the MOT test) which the legislature has not expressed. In 2012, the court had essentially stopped construing §101, and was instead construing its

own precedents for guidance about applying the nuances of its "judicial exceptions" to §101 to the particular fact scenario in Mayo. In 2014, the court had generalized from Mayo an eligibility "framework" that the legislature never expressed. The Supreme Court's "judicial exceptions" doctrine and recent pattern of invalidating patents represents a major contributing factor to the invalidation of Sequenom's patent claims.

The Federal Circuit's Sequenom Decision

Even if Bilski, Mayo, Myriad and Alice represent an expanding cloud of judicially ineligible subject matter, these decisions did not mandate that the Federal Circuit invalidate Sequenom's fetal DNA testing patent.

First, the Myriad decision was distinguishable, because Sequenom's patent claims were not directed to isolated human fetal DNA ("cffDNA"), but rather, to methods of using the DNA. (The Myriad court had made clear that its Myriad opinion was not disparaging method-of-using claims.) Nonetheless, the Federal Circuit blurred this distinction between statutory categories and accepted Ariosa's characterization that the method claims of Sequenom's patents were "directed to the natural phenomenon of paternally inherited cffDNA."

Second, the circuit court elevated the Mayo/Alice "framework" over substance, by refusing to give weight to evidence presented by the patentee that the patent did not preempt other scientists from using cffDNA. Indeed, Sequenom had presented evidence in district court that "numerous other uses of cffDNA" existed that were not preempted by the claims of its patent. The Federal Circuit acknowledged that "[t]he Supreme Court has made clear that the principle of preemption is the basis for the judicial exceptions to patentability." Nonetheless, instead of remanding the litigation to the district court, with instructions to weigh the parties' competing evidence on the issue of preemption, the Federal Circuit concluded that "questions of preemption are inherent in and resolved by the [Mayo/Alice] §101 analysis. … While preemption may signal patent ineligible subject matter, the absence of complete preemption does not demonstrate patent eligibility. … Where a patent's claims are deemed only to disclose patent ineligible subject matter under the Mayo framework, … preemption concerns are fully addressed and made moot."

Given that the Supreme Court's justification for its judicial exceptions is concern about preemption, it is difficult to understand why direct evidence adduced at the trial court on the issue of preemption would be deemed irrelevant. And given the Supreme Courts aversion (expressed in Bilski) to using a single test to evaluate judicial exceptions to §101, it is difficult to understand why the Mayo/Alice "framework" should be considered the authoritative test for evaluating preemption. This is particularly true in the context of a "composition of matter" judicial exception, because the Supreme Court has not yet applied its "framework" to this category of judicial exception.

Third, the Federal Circuit's implementation of the Mayo/Alice "framework" is subject to criticism. For instance, the circuit court concluded that Sequenom's claims "are directed to a multistep method that starts with cffDNA taken from a sample of maternal plasma or serum." In actuality, the claims start with maternal serum or plasma, which had numerous medical uses before the Sequenom inventors disovered small amounts of cffDNA in it. (Sequenom's claims do not preempt all uses of maternal serum or plasma.) The circuit court also said that the method "ends with paternally inherited cffDNA, which is also a natural phenomenon." In actuality, the methods end with detecting the paternally inherited fetal DNA in the sample, or amplifying that nucleic acid. "Detecting" and "amplifying" are human actions, not natural phenomena.

Having made these dubious characterizations of Sequenom's claims, the Federal Circuit concluded that the claims failed the first part of the Mayo/Alice test: "The method therefore begins and end with a natural phenomenon. Thus, the claims are directed to matter that is naturally occurring." The court then concluded that the individual steps used to amplify and detect the cffDNA were routine and conventional and "specified at a high level of generality," and the claims failed the second element of the test as well, and were invalid.

On Aug. 13, Sequenom petitioned the Federal Circuit for rehearing en banc, giving the circuit court another opportunity to consider whether Supreme Court precedent necessitates invalidation of the patent.

The U.S. Patent and Trademark Office and the Patentee

Even with the Federal Circuit's expansive application of the Mayo/Alice test, and refusal to consider evidence of preemption, different prosecution or litigation tactics might have preserved a patent on Sequenom's invention.

The existing patent teaches that maternal plasma contains both maternal and fetal DNA. How did the inventors discern the minor fraction of paternally inherited fetal DNA from the intermingled, larger fraction of maternal DNA? The Sequenom patent teaches that a scientist can screen the serum sample for Y-chromosome DNA (which can only be attributable to male fetal DNA, never maternal DNA). Alternatively, the patent teaches that one can first genotype the father and mother (e.g., using a panel of genetic markers of interest), then screen the DNA in the maternal plasma for markers that are present in the father, but absent from the mother.

During examination of the patent application that matured into Sequenom's patent, the PTO did not require Sequenom to specify (in Sequenom's broadest claims) that the detection or analysis of paternally inherited nucleic acid be performed using Y-chromosome markers; or performed with other markers, determined through parental testing, to be present in the father's DNA but not the mothers. Nor did the PTO require the addition of steps that involved paternal and maternal genetic testing in combination with fetal DNA analysis. Some limitations of this nature were found in narrower claims 5-7 (involving detection of sequence from the Y-chromosome) and claim 11 (Rhesus D genotyping in a Rhesus D-negative mother) of Sequenom's patent.[3]

It is interesting to speculate whether Sequenom could have argued more explicitly and persuasively for the eligibility of these narrower claims, involving screening for particular paternal sequences in maternal serum, and achieved a different result. Each of these claims requires a particular genetic analysis that, arguably, was not conventionally performed on maternal serum or plasma at the time of the invention.

Likewise, it is interesting to speculate whether Sequenom could have prevailed had the Patent Office required Sequenom to insert in its broadest claims one or more method steps or reagents by which the paternally inherited fetal DNA is amplified or detected from a fluid that contained more maternal DNA than paternally inherited DNA. Sequenom's broadest claims specify amplification of paternally inherited nucleic acid, for example, but do not state how. The Federal Circuit concluded that only well-known, routine, and conventional activity was required.

In summary, even though Sequenom's claims specify amplifying the paternally inherited DNA in serum/plasma from a mother's serum, and the Federal Circuit understood that Sequenom's method

"effectuated a practical result and benefit not previously obtained," the Federal Circuit was unable to discern from the patent, or from the patentee, the details of the claimed method that were unconventional, compared to genetic amplifications and detections that others had done before. For this disconnect, the PTO or the patentee bear some responsibility.

Congress

In 1952, Congress broadly defined the categories of patent-eligible subject matter in 35 USC §101, but Congress has stood silent while the Supreme Court chisels away at these broad categories through "judicial exceptions." If Congress is troubled by the fact that the courts have been striking down patents on inventions that are deserving of patent protection, then Congress can intervene through legislation, to try to clarify what inventions are patent-eligible, and to limit the scope of the "judicial exceptions." If Congress fails to do so, more patents "deserving of patent protection" may meet the same fate as Sequenom's.

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[1] Exemplary claims 1, 24 and 25 of Sequencom's '540 patent specify:

1. A method for detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which method comprises
amplifying a paternally inherited nucleic acid from the serum or plasma sample and
detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample.

24. A method for detecting a paternally inherited nucleic acid on a maternal blood sample, which method comprises:
removing all or substantially all nucleated and anucleated cell populations from the blood sample,
amplifying a paternally inherited nucleic acid from the remaining fluid and subjecting the amplified nucleic acid to a test for the Paternally inherited fetal nucleic acid.

25. A method for performing a prenatal diagnosis on a maternal blood sample, which method comprises obtaining a non-cellular fraction of the blood sample
amplifying a paternally inherited nucleic acid from the non-cellular fraction
and performing nucleic acid analysis on the amplified nucleic acid to detect paternally inherited fetal nucleic acid.

[2] Under the "machine-or-transformation" test, "[a] claimed process is surely patent-eligible under § 101 if: (1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing." Id. (quoting In re Bilski, 545 F.3d 943, 959-60 and n. 19 (Fed. Cir. 2008)).

[3] Claim 11 was not at issue in the proceedings.