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# Ariosa Diagnostics, Inc. v. Sequenom, Inc. – Another Diagnostic Patent Meets its End

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On Friday, June 12, 2015, the Federal Circuit issued its decision in *Ariosa Diagnostics, Inc. v. Sequenom, Inc.* (Fed. Cir. 2015) finding that the claims of U.S. Patent No. 6,258,540 (the '540 patent) did not meet the patent-eligibility requirements of 35 U.S.C. §101.

## *The '540 patent*

The '540 patent claims certain methods of using cell-free fetal DNA (cffDNA). In 1996, the inventors, Doctors Dennis Lo and James Wainscoat, discovered cffDNA in material plasma and serum. Traditionally, this portion of maternal blood samples was discarded by researchers as medical waste. As a result, the inventors developed a method for detecting a small fraction of paternally inherited cffDNA in maternal plasma or serum to determine certain fetal characteristics, such as gender. The method was commercialized by Sequenom as the MaterniT21 test. An advantage provided by the test is that it created an alternative for prenatal diagnosis of fetal DNA that avoided the risks of widely-used techniques that took samples from the fetus or placenta.

In addition to claiming methods of using cffDNA, the '540 patent also provides for making a diagnosis of certain fetal characteristics based on the detection of paternally inherited cffDNA. According to the specification, a pregnant woman carrying a fetus with certain genetic defects has more cffDNA in her blood than a woman with a normal fetus.

Claims 1, 24 and 25 of the '540 patent recite:

> 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 a nucleated 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.

The remaining claims describe how the method of detection occurs or how it can be used. For example, claim 2, which depends from claim 1, recites amplification by polymerase chain reaction (PCR). Claim 4, which also depends from claim 1, recites detection by a sequence specific probe.

## *District Court Proceedings*

Ariosa Diagnostics, Inc. (Ariosa) and Natera, Inc. (Natera) make and sell alternative non-invasive tests that compete with Sequenom's MaterniT21 test. Specifically, Ariosa sells the Harmony Test, a non-invasive test used for prenatal diagnosis of certain fetal characteristics, and Natera sells the Non-Invasive Paternity Test, which is used to confirm the paternity or non-paternity of a gestating fetus from genetic information in fetal DNA available in the blood of a pregnant female.

In response to letters threatening claims of infringement, from December 2011 through early 2012, Ariosa and Natera each filed separate declaratory judgment actions against Sequenom alleging non-infringement of the '540 patent. Sequenom counterclaimed alleging infringement. Sequenom filed a motion seeking an preliminary injunction to enjoin Ariosa from selling the Harmony Prenatal test. In July 2012, the district court denied the motion finding that there was a substantial question over whether the subject matter of the asserted claims was directed to eligible subject matter. Sequenom appealed to the Federal Circuit.

In August 2013, the Federal Circuit vacated and remanded the case, holding that the district court erred in certain respects not relevant to this appeal. Additionally, the Court did not offer any opinion regarding the subject matter eligibility of the asserted claims.

After remand, the parties filed cross motions for summary judgment regarding invalidity under 35 U.S.C. §101. The district court found that the '540 patent was directed to the natural phenomenon of paternally inherited cffDNA and that the claims did not add enough to the natural phenomenon to make the claims patent eligible under §101. According to the district court, at the time of the filing of the '540 patent in 1997, the steps of amplifying and detecting were well-understood, routine, or conventional. Thus, the district court concluded that the '540 patent was not directed to patentable subject matter finding that the only "inventive concept of the processes of the '540 patent is to apply

those well-understood, routine processes to paternally inherited cffDNA, a natural phenomenon". Additionally, the district court also found that the claimed processes posed a risk of preempting a natural phenomenon. Sequenom appealed.

## *Federal Circuit Decision*

The Federal Circuit began its decision by setting forth the two-prong patent-eligibility test (citing *Mayo Collaborative Services v. Prometheus Laboratories, Inc.* (March 2012)). The first prong is to determine whether the claims at issue are directed to a patent-ineligible concept. If answered in the affirmative, the second prong is to determine whether the elements of each claim, both individually and as an ordered combination, recite additional elements that transform the nature of the claim into a patent-eligible invention that amounts to significantly more than the ineligible concept itself.

Regarding the first prong, the Federal Circuit noted that the claims of the '540 patent were method claims, which generally constitute eligible subject matter. However, upon further inspection, the Court further noted that the claims were directed to a multistep method that began with cffDNA taken from a maternal plasma or serum sample. cffDNA was naturally occurring and circulated freely in the blood stream of a pregnant woman. As a result, the existence of cffDNA in maternal blood was a natural phenomena. The Court further noted that the method ended with paternally inherited cffDNA, which was also a natural phenomena. Therefore, because the method began and ended with a natural phenomenon, the Federal Circuit held that the claims were directed to naturally occurring matter. The Court stated that the specification supported its conclusion. For example, column 1, lines 50-51 states: "[i]t has now been discovered that foetal DNA is detectable in maternal serum or plasma samples", column 13, line 11-13 states: "[t]hese observations indicate that maternal plasma/serum DNA may be a useful source of material for the non-invasive prenatal diagnosis of certain genetic disorders," and column 16, lines 12-14 states: "[t]he most important observation in this study is the very high concentration of foetal DNA in maternal plasma and serum".

Regarding the second prong, the Federal Circuit concluded that the practice of the method claims did not result in an inventive concept that transformed the natural phenomena of cffDNA into a patentable invention. Specifically, the Court stated that for process claims that encompass natural phenomenon, the process steps must recite additional features that are new and useful. According to the Court:

> "The method at issue here amounts to a general instruction to doctors to apply routine, conventional techniques when seeking to detect cffDNA. Because the method steps were well-understood, conventional and routine, the method of detecting paternally inherited cffDNA is not new and useful. The only subject matter new and useful as of the date of the application was the discovery of the presence of cffDNA in maternal plasma or serum."

With respect to the preparation and amplification steps, the Court noted that the specification confirmed that in 1997 that these steps were well-understood, routine, conventional activities performed by doctors. Additionally, Sequenom's expert testified that PCR and other methodologies for amplifying DNA were well known in 1997. The Court further found that the detecting steps were also similarly well-understood, routine and conventional.

Regarding the dependent claims, the Court found that these claims were broad examples of how to

detect cffDNA in maternal plasma. The Court noted that these claims were focused on the use of the natural phenomenon in combination with well-understood, routine and conventional activity.

The Court concluded stating

> "Thus in this case, appending routine conventional steps to a natural phenomenon, specified at a high level of generality, is not enough to supply an inventive concept. Where claims of a method patent are directed to an application that starts and ends with a naturally occurring phenomenon, the patent fails to disclose patent eligible subject matter if the methods themselves are conventional, routine and well understood applications in the art."

Regarding preemption, Sequenom argued that there were numerous other uses of cffDNA aside from those claimed in the '540 patent and as a result, the '540 patent did not preempt all uses of cffDNA. The Federal Circuit disagreed. The Court noted that while preemption might signal patent ineligible subject matter, the absence of complete preemption did not demonstrate patent eligibility. Specifically, in this case, the Court noted that Sequenom's attempts to limit the breadth of the breadth of the claims by showing alternative uses of cffDNA outside the scope of the claims did not change the conclusion that the claims were directed to patent ineligible subject matter.

At the end of the opinion, the Court addressed Sequenom's arguments that before the '540 patent that "no one" was using plasma or serum of pregnant mothers to amplify and detect paternally-inherited cffDNA. Moreover, Sequenom noted that the 1997 Lancet publication of the inventors had been cited over a thousand times and that the claimed method utilized the man-made tools of biotechnology in a new way that revolutionized prenatal care. The Court agreed but noted, citing to *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.* (June 2013), that just because a discovery is groundbreaking, innovative or brilliant does not by itself satisfy §101. The Court stated:

> "While Drs. Lo and Wainscoat's discovery regarding cffDNA may have been a significant contribution to the medical field, that alone does not make it patentable. We do not disagree that detecting cffDNA in maternal plasma or serum that before was discarded as waste material is a positive and valuable contribution to science. But even such valuable and contributions can fall short of statutory patentable subject matter, as it does here".



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