The first available Non – Invasive prenatal test in the U.S. – Sequenom's MaterniT21™

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Sequenom's story begins in 1996, when a pair of doctors noted that there were trace amounts of cell - free fetal DNA in the plasma of expectant mothers. That kind of fetal DNA exists in the blood of the fetus, and till then it was accessible only by invasive methods, such as amniocentesis, that created risks of miscarriage. The doctors created a test that could extract cell – free fetal DNA form maternal plasma and determine a baby's sex and risk of genetic disorders like Down syndrome, without the need for invasive procedures. This was considered as a **breakthrough** achievement and the idea was patented the following year. The test is now sold by Sequenom as MaterniT21.

Sequenom took the exclusive license of U.S. Patent No. 6.258.540 on 1997, which claims methods of using cell free fetal DNA (cffDNA) circulating in maternal plasma (cell free blood) to diagnose fetal abnormalities. The basic claim is:

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 (1) amplifying a paternally inherited nucleic acid from the serum or plasma sample and (2) detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample. (1)
The claim has two simple steps: first amplifying (by polymerase chain reaction, PCR) and then detecting the paternally inherited DNA from the plasma sample. The technology for amplifying and detecting DNA was already well known and generally used to detect DNA, thus it could not be considered as inventive or having an inventive step. There was a problem however, of how to ascertain which DNA in the sample was that of the fetus and which was the mother's. The scientists focused on the genetic fragments containing paternally inherited sequences the mother did not share but had travelled from the fetal blood into the maternal blood through placenta. This observation was the important point of the patent "invention". (2)

After Sequenom lunched its test on the market on October 2011, four other companies began to market similar tests and cut prices. Sequenom send letters to Arioza Diagnostics, Inc., Natera, Inc. and Diagnostics Center, Inc., threatening each of them with patent infringement suits. Ariosa (and co-declaratory judgment plaintiffs Natera Inc. and Diagnostic Center, Inc.) filed a declaratory judgment action against Sequenom stating that it did not violate the patent. In other words Ariosa Diagnostics said the fetal test was not novel enough to deserve a patent. (3)

On July 2012, the District Court had held that the claims of the patent were directed toward a **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 the law. The District Court stated that the steps of amplifying and detecting were "well-understood, routine, or conventional activity in 1997, when the application … was filed." The Court held that the patent was not directed to patentable subject matter because "the only inventive component of the processes is to apply those well-understood, routine processes to paternally inherited cffDNA, a natural phenomenon". (4)

Taking its turn, the Federal Circuit, provided an opinion through which it appreciated that the inventors had found cell-free fetal DNA (cffDNA) in maternal plasma or

serum "*that other researchers had previously discarded as medical waste*". Then the majority of the three – judge panel concluded that the claims were not patent eligible because "*cffDNA was a natural phenomenon or product and the manipulative steps to determine the prenatal condition were routine*". The patent failed the two – step test that the Supreme Court developed in Mayo case (Mayo v. Prometheus, 2012) for determining whether a method patent impermissibly claims a natural law or phenomenon:

(1) Is claim directed to natural material? If so,
(2) Do the additional steps add "significantly more" to the invention?

The invention failed the "inventive step" (step 2) test.

The decision of the Federal Circuit was considered as a controversial decision. Scientists predicted that companies and investors will be less likely to fund expensive research for fear of having patents invalidated by the courts. Start-ups and giants across the life sciences (biotech industries), including Pfizer and Novartis expressed fears that after this decision it will be extremely difficult to obtain effective patent protection for diagnostic methods, involving genetic amplification and detection.

In December 2015, the Federal Circuit denied a motion for *en banc* rehearing, with several members of the court filing opinions urging Supreme Court review. (5) Several judges who concurred in the denial wrote separately that they disagreed with the sweep of the Supreme Court's *Mayo* decision that had compelled the result.

On March 21, 2016, Sequenom filed a certiorari petition. The petition raises the following question (Sequenom petition No. 15 / http://ipwatchdog.com/Sequenom-Cert-Petition.pdf):
"Whether a novel method is patent-eligible where:
(1) A researcher is the first to discover a natural phenomenon; (2) that unique knowledge motivates him to apply a new combination of known techniques to that discovery; and (3) he thereby achieves a previously impossible result without pre-empting other uses of the discovery?"

On June 27, 2016, Supreme Court of U.S. denied Sequenom's petition for a writ of certiorari. (6)

The European equivalent to the U.S. Patent No. 6.258.540 ('540 patent), i.e., European Publication No. EP 0994963 ("the '963 patent"), contained similar claims to the '540 patent. The '963 patent was examined by the EPO Appeal Board in December 2011 and was **found to contain an inventive step** (see EPO Case Number T 0146/07- 3.3.08). Patent eligibility of the claims were not at issue, as the discussion of inventive step was limited **to non-obviousness over the prior art**. The '963 patent was ultimately maintained with amendments. These is very strange taking into account that **Article 53(c) EPC appears to specifically exclude diagnostic methods from patentability altogether**.

If I were a Committee member of a Patent Office, clearly I would have decided that the claims followed the particular Non – invasive prenatal test **are not patent eligible.** First of all the method is based on a discovery (cffDNA travelling from the fetal blood into maternal blood, through placenta) and not on an invention. The application of already known methods of DNA amplification and sequencing on maternal plasma cannot be considered as an inventive step. We are not dealing with something novel however we cannot deny that there is an industrial applicability of the method and the research team has mixed its labour for the development of that test. But according to my judgement this is not enough for giving IP rights to that method. The researchers offered to the society a great service, but this does not

mean that they deserve exclusive rights for the product. I believe that IP rights must be given in cases where researchers find ways to modify “naturally occurring” genetic material into “something new”, in order to isolate and detect it, when developing for example predictive tests.

References

(1) https://patents.google.com/patent/US6258540 (accessed on 09-05-2018)
(2) https://en.wikipedia.org/wiki/Ariosa_v._Sequenom (accessed on 08-05-2018)
(3) https://www.statnews.com/2016/06/27/supreme-court-biotech-patents/ (accessed on 08-05-2018)
(4) http://www.krameramado.com/blog/ariosa-diagnostics-inc-v-sequenom-inc-end-genetic-diagnostic-method-patents (accessed on 09-05-2018)
(5) Dennis Crouch, *Federal Circuit Reluctantly Affirms Ariosa v. Sequenom and Denies En Banc Rehearing*, PATENTLY-O Dec. 23, 2015
(6) https://www.supremecourt.gov/orders/courtorders/062716zor_4fbi.pdf (accessed on 08-05-2018)