

Noninvasive Fetal Aneuploidy Detection for Trisomy 21, 13, and 18 ^[1]

By: Possehl, Cassidy Keywords: [Noninvasive fetal aneuploidy detection](#) ^[2]

Noninvasive fetal [aneuploidy](#) ^[3] detection technology allows for the detection of fetal genetic conditions, specifically having three chromosomes, a condition called [aneuploidy](#) ^[3], by analyzing a simple blood sample from the pregnant woman. Dennis Lo and Rossa Chiu researched methods of detection of aneuploidies in the early twenty-first century. Their research has been specifically applied to three trisomies, trisomy twenty-one known as Down syndrome, trisomy eighteen known as [Edwards Syndrome](#) ^[4], and trisomy thirteen known as Patau Syndrome. Prior to the ability to detect fetal DNA in a pregnant woman's blood, physicians performed amniocentesis or chorionic villus sampling, two techniques that increase the risk of spontaneous [abortion](#) ^[5]. Noninvasive detection of trisomy twenty-one, eighteen, and thirteen technology allows for a more accurate and safer detection of those conditions than methods available before.

As fetal [genome](#) ^[6] screening became an efficient and widely-used process, scientists researched trisomy twenty-one, eighteen, and thirteen because these trisomies occurred more frequently in comparison to other trisomies. Trisomy twenty-one, known as Down syndrome, is one of the most common [birth defects](#) ^[7], occurring in twenty two of every ten thousand live births. It can lead to intellectual as well as physical developmental delays. Trisomy eighteen, known as Edwards' syndrome, is seen in five out of every ten thousand live births. Many developmental defects are associated with Edwards syndrome, including heart and cranial underdevelopment. Trisomy thirteen, known as Patau Syndrome, is seen in two out of every ten thousand live births. An [aneuploidy](#) ^[3] in the thirteenth chromosome has severe developmental consequences such as brain and spinal cord abnormalities, cleft palate, as well as heart and eye defects.

Before scientists found that a pregnant woman's blood contains cell-free fetal DNA, DNA that is circulating outside of a fetal body cell, physicians conducted diagnostic tests like amniocentesis and chorionic villus sampling to analyze fetal genomes. [Amniocentesis](#) ^[8] is a method that collects fetal DNA using a needle to draw amniotic fluid through the pregnant woman's abdomen. Chorionic villus sampling is a procedure where a specialized catheter is inserted into the abdomen or into the [vagina](#) ^[9] and through the [cervix](#) ^[10] of the pregnant woman to gain access to placental tissue that contains fetal DNA. In both techniques fetal DNA is then isolated from the pregnant woman's DNA and tested for genetic abnormalities. Both amniocentesis and chorionic villus sampling pose significant health risks to both the pregnant woman and the [fetus](#) ^[11] due to the possibility of amniotic fluid leakage and infections that can lead to spontaneous [abortion](#) ^[5] or stillbirth. Lo and Chiu developed an early detection method for fetal DNA, allowing researchers to obtain the same genetic information from fetuses without posing such significant health risks.

In 1997 Lo and his colleagues isolated cell free fetal DNA from a maternal blood sample for the first time at John Radcliffe Hospital at the [University of Oxford](#) ^[12] in Oxford, England. They presented the results in the paper, "Presence of Fetal DNA in Maternal Plasma and Serum," which showed that fetal DNA could be isolated from blood drawn from the pregnant woman. The research team isolated the fetal DNA from the maternal DNA that circulates normally in the blood, as well as other cells and liquids. They then replicated the fetal DNA that was isolated using a technique called polymerase chain reaction to create copies of the small pieces of fetal DNA to sequence the full [genome](#) ^[6]. The discovery that the entire fetal [genome](#) ^[6] could be accessed without using amniocentesis or chorionic villus sampling allowed researchers to avoid putting the pregnant woman and [fetus](#) ^[11] at significant risk for genetic screening.

Lo and his colleagues isolated only fetal DNA with the Y-chromosome, which is male specific, because that allowed them to discern between maternal DNA and fetal DNA. They also looked at the sex of the [fetus](#) ^[11], which relates to the presence or absence of a Y chromosome.

To address restrictions related to the fact that they could easily detect the fetus' DNA only if the [fetus](#) ^[11] was a male, Lo and Stephen Chim, a scientist at the Chinese University of Hong Kong, Hong Kong, China and colleagues searched for other ways to distinguish maternal DNA from fetal DNA. In 2008 the team published a paper titled, "Systemic Search for Placental DNA-Methylation Markers on Chromosome 21: Toward a Maternal Plasma-Based Epigenetic Test for Fetal Trisomy." In their paper the authors described a new method to distinguish fetal DNA from maternal DNA based on a pattern in fetal placental red blood cells that was different from adult maternal DNA. The team identified a gene on chromosome twenty-one called SERPINB5 in fetal

DNA that had fewer carbon and hydrogen molecules attached compared to the adult DNA in which the gene had many carbon and hydrogen molecules. The difference in number of carbon and hydrogen molecules on the gene allowed geneticists to separate fetal DNA from maternal DNA without looking for the presence of the Y chromosome, which previously did not allow for female fetus^[11] DNA to be isolated. That pattern of carbons and hydrogen attached to the DNA molecules also allowed geneticists to differentiate between maternal and fetal DNA without looking for a specific sex trait in the fetal DNA that the pregnant woman did not carry. Researchers then looked at larger gene issues, such as aneuploidies, rather than only single gene issues.

Chim and colleagues continued to research the difference in DNA to identify pieces on chromosome twenty-one that had the highest difference in methylation between the fetal and maternal DNA. They identified the two areas on the chromosome that had the biggest difference in methylation and created two markers. Each marker allowed scientists to detect fetal DNA from maternal plasma. Those markers allowed researchers to find fetal DNA even when mixed with maternal DNA in the pregnant woman's blood. Researchers used markers as a new method for fetal DNA identification to identify genetic abnormalities.

Geneticists replicated the fetal DNA after isolating it from the maternal blood to produce enough quantity to test. They used an amplification technique called polymerase chain reaction or PCR, which consists of a sequence of steps heating and cooling DNA with other enzymes to replicate the original DNA sample many times over. The PCR technique of amplifying fetal DNA increased the rate of detection of the trisomies. However, the PCR technique contributed to an issue of false positives in the genetic tests.

Researchers continued to study fetal DNA detection methods to address the issues with PCR in its applicability to fetal genomic testing. In 2002 Bernhard Zimmerman, an obstetrician from Switzerland, and his team analyzed fetal DNA to identify trisomy using a comparative analysis technique. The researchers used the relative amounts of chromosomes to identify when too many chromosomes were present in the genome^[6]. For aneuploidies, fetal samples with three chromosomes measured higher than the normal level of fetal chromosomes of just two. Such a technique is called relative chromosome dosage analysis or RCD and it allows researchers to measure a difference in the amount of chromosomes in fetal samples with trisomy twenty-one. Zimmerman and his team also created and used a new type of digital PCR that sped up the process to make it more efficient.

The opportunity to analyze the extracted fetal DNA in a faster and more efficient way led to further research into the different applications of the new technology. In 2007 Lo and a team of researchers used Zimmerman's digital PCR technique to detect trisomy 21 for the first time. They published the results of that research in "Digital PCR for the Molecular Detection of Fetal Chromosomal Aneuploidy," which showed two things using the digital PCR method. First, they reestablished Zimmerman and team's research that a reliable diagnosis of trisomy twenty-one can be assessed from a technique that identifies an abnormality in the ratio of alleles. Second, they found that analyzing the overrepresentation, or over dosage, of a particular gene can lead to an aneuploidy^[3] diagnosis. Therefore, if there is one gene of interest on the chromosome, a signal for two of those genes^[13] is normal and a signal for three means the fetus^[11] has a trisomy. Lo and colleagues advanced fetal genetic screening by making it more efficient through digitalized PCR and using gene ratio information to diagnose trisomies.

As fetal DNA isolation from maternal serum became a popular research topic in obstetrics, scientists researched how to make general genome^[6] sequencing more efficient as well. Next Generation Sequencing or NGS, also known as massively parallel sequencing, lowers the cost of genome^[6] sequencing and also reveals more information about the genome^[6]. The process amplifies the sample DNA quickly to create a significant amount of DNA to test and analyze. Also, rather than analyzing individual genomes to identify possible genetic abnormalities, NGS compares the test genomes to a large database of references to identify irregularities that are more significant than the normal differences seen between individuals. The change in the amplification as well as the analysis technique have made NGS a much more efficient process than original DNA sequencing and analysis, which has reduced cost and made genetic testing more available to the general public.

Noninvasive fetal diagnostic techniques have evolved from that the early work of Lo and his team to become efficient and tools of testing a mother's blood for information about the fetus' genome^[6]. High-risk fetal DNA collection techniques like amniocentesis and chorionic villus sampling are becoming less common methods to detect for genetic abnormalities, reducing the risk for pregnant women and their fetuses.

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[sampling](#) ^[35] [New Hyde Park \(N.Y.\)](#) ^[36] [University College \(University of Oxford\)](#) ^[37] [John Radcliffe Hospital](#) ^[38] [Polymerase Chain Reaction](#) ^[39] [Trisomy 18](#) ^[40] [Trisomy 13 syndrome](#) ^[41]

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