Growth and Implementation of Noninvasive Prenatal Genetic Testing

ABSTRACT

Noninvasive prenatal genetic testing (NIPT) accounts for a large proportion of spending on genetic testing. The rapid growth of this market is due to new cell-free DNA detection methods along with a need for less invasive, safer methods for fetal genetic testing. Currently, NIPT is used to detect a variety of chromosomal and sub-chromosomal aberrations. While, NIPT has some limitations, obvious advantages of NIPT has led to swift adoption of the testing globally.

INTRODUCTION

Traditionally, definitive diagnosis of fetal genetic disorders involved invasive prenatal tests, such as amniocentesis and chorionic villus sampling (CVS).[1] Amniocentesis is typically performed between 15 and 20 weeks gestation and involves ultrasound guided insertion of a 20- or 22-gauge needle into amniotic fluid.[2] CVS involves collection of placental tissue and may be performed through the abdomen or the cervix at 10-13 weeks gestation.[2] Both tests carry a risk of miscarriage.[3] Women often struggle with the decision surrounding invasive testing, weighing the risk of pregnancy loss against the desire for diagnosis.[4-6]

A recent shift toward noninvasive methods for prenatal testing has aimed to reduce the risk of miscarriage while still determining the fetal risk for genetic disorders.[7] Generally, NIPT is safer for the mother and fetus, can be conducted as early as ten weeks gestation, and is very accurate (99% sensitivity and 99.5% specificity for Down Syndrome).[6-7]

The discovery of cell-free fetal DNA (cffDNA) in maternal plasma along with advances in molecular diagnostics and next-generation sequencing (NGS) technology have led to new screening methods for fetal chromosomal abnormalities. These noninvasive prenatal tests are now widely used in clinical practice.[7] In fact, analyses of genetic testing databases showed that NIPT and prenatal carrier screenings accounted for the highest percentage of genetic testing spending between 2014 and 2016.[8]

CELL-FREE FETAL DNA METHODS AND NIPT APPLICATIONS

In 1997, Lo *et al*. described the detection of cffDNA in maternal plasma.[9] Cell-free fetal DNA is released into the mother's bloodstream during apoptosis (programmed cell death) of trophoblasts (placental cells). Per volume of blood, the concentration of cffDNA is nearly 25 times higher than the concentration of fetal DNA extracted from blood cells. Thus, using cffDNA makes any testing easier and less time consuming.[10] At 11 to 13 weeks of gestation, the concentration of cffDNA is between 7.8 and 13.0%, making noninvasive analysis of aneuploidy (presence of an abnormal number of chromosomes) possible after 10 weeks of gestation.[11]

NIPT is primarily used to detect Down syndrome, trisomy 18, trisomy 13, and extra or missing copies of the X- and Y-chromosome.[12] While cffDNA-based NIPT is primarily used for detection of aneuploidy, cffDNA analysis combined with next-generation sequencing (NGS) technology, is now being used to detect sub-chromosomal aberrations or disorders caused by deleted or duplicated sections of a chromosome.[7,12] These approaches are based on low-coverage whole genome sequencing of DNA derived from maternal plasma.[13]

NIPT LIMITATIONS

As a screening test, NIPT can estimate the risk of certain genetic conditions and is highly accurate for detection of common fetal chromosomal aneuploidies.[7, 14] However, it is important to note that NIPT is not diagnostic and confirmation of any abnormal results may require invasive testing.[7]

Additionally, NIPT capability can be affected by the fraction of cffDNA in the mother's bloodstream. Studies have shown that ratio of cffDNA to maternal cell-free DNA decreases with increasing maternal weight.[15] Therefore, NIPT is likely to be less informative in obese patients.[16]

Some studies have investigated NIPT for detection of sub-chromosomal copy number variants, such as microdeletions using whole-genome sequencing of plasma DNA. However, since the prevalence of syndromes associated with microdeletions is low and interpretation of such data is complicated,[17] the American College of Obstetricians and Gynecologists does not currently recommend routine cffDNA screening for microdeletions.[18] However, detection of microdeletions may be possible in the future through advances in single-cell genomics. One study reported successful isolation and detection of copy number abnormalities using low coverage NGS of individual fetal nucleated red blood cells.[19]

IMPLEMENTATION OF NIPT IN CLINICAL SETTINGS

Adoption of cffDNA-based NIPT has been rapid due to its many benefits over invasive methods.[7] NIPT for detection of chromosomal aneuploidies using cffDNA were first introduced to clinical practice in Hong Kong in 2011 and commercially launched in the U.S. later that same year.[20-22] Due to commercialization, NIPT quickly spread to markets around the world.[22] By 2015, NIPT was available in 60 countries across six continents.[23] Because of its previously mentioned advantages, NIPT has become a standard procedure for all pregnant women in the Netherlands.[24] Evaluation of implementation of NIPT in national health services is being conducted in the UK,[25-26] Canada,[27] and Germany.[24,28]

In a survey of 49 clinicians from 46 countries, the majority reported that NIPT was available and offered in their practice.[29] However, test prices ranged from $350 to $2900 in 2015, which limited widespread use of NIPT for some clinicians.[28] Nonetheless, the overall clinical uptake of NIPT in the U.S. is high has led to a decrease in invasive prenatal procedures.[7,23]

CONCLUSIONS

Improved safety for mother and fetus combined with rapid, accurate results for fetal chromosomal disorders have prompted rapid growth and use of NIPT in recent years. While cffDNA-based methods have some limitations, NIPT is already becoming standard procedure in several countries and the NIPT market continues to expand. Although NIPT will not completely replace invasive procedures, experts believe that NIPT will evolve from screening to a final diagnostic test in the future. Advances in NGS and fetal DNA and cell methods will likely expand the type of genetic disorders detectable by NIPT in the near future.

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