

# Israeli Society of Medical Genetics NIPT Committee Opinion 072013: Non-Invasive Prenatal Testing of Cell-Free DNA in Maternal Plasma for Detection of Fetal Aneuploidy

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## Key Words

Aneuploidy · Trisomy 21 · Cell-free fetal DNA · Non-invasive prenatal testing · Down syndrome screening tests

## Abstract

Non-invasive prenatal testing (NIPT) of cell-free fetal DNA in maternal plasma is a novel approach, designed for detecting common aneuploidies in the fetus. The Israeli Society of Medical Geneticists (ISMG) supports its use according to the guidelines stated herein. The clinical data collected thus far indicate that NIPT is highly sensitive in detecting trisomies 21 and 18, and fairly sensitive in detecting trisomy 13 and sex chromosome aneuploidies. Because false-positive results may occur, an abnormal result must be validated by invasive prenatal testing. At this juncture, NIPT does not replace existing prenatal screening tests for Down syndrome, as these are relatively inexpensive and cost-effective. Nonetheless, NIPT may be offered to women considered to be at high risk for fetal chromosomal abnormalities as early as 10 weeks of ges-

tation. The ISMG states that NIPT should be an informed patient choice, and that pretest counseling regarding the limitations of NIPT is warranted. Women at high risk for genetic disorders not detected by NIPT should be referred for genetic counseling. A normal test result may be conveyed by a relevant healthcare provider, while an abnormal result should be discussed during a formal genetic consultation session.

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## Introduction

Non-invasive prenatal testing (NIPT) of cell-free fetal DNA (cffDNA) in maternal plasma is a new screening test, designed for detection of common aneuploidies in the fetus. The Israeli Society of Medical Geneticists (ISMG) supports the use of this test according to the guidelines stated herein.

## What Is NIPT Based On?

In the process of cell proliferation and apoptosis, short fragments of DNA are released into the plasma. During pregnancy, cfDNA is also released into the maternal circulation. From 10 weeks of gestation, cfDNA comprises 2–20% of the total DNA in maternal plasma [1]. In normal pregnancies, there is a relatively constant ratio of cfDNA derived from each chromosome. In case of fetal aneuploidy however, the proportion of cfDNA fragments deriving from the abnormal chromosome deviates from the expected ratio. For example, in cases of fetal trisomy 21, there is an excess of cfDNA fragments from chromosome 21.

NIPT is based on the ability to identify alterations in the expected ratios of fragments derived from each chromosome. Several methods have been described for detecting such abnormalities, and to date, performance characteristics of the available methods are comparable [2]. Thus, the ISMG does not favor the use of any specific method.

The clinical data from numerous studies indicate that NIPT is highly sensitive in detecting trisomy 21 (98.6–100%), trisomy 18 (>97%), and fairly sensitive in detecting trisomy 13 (>80%) [3–6]. Most studies focus on women determined to be at high risk for these chromosomal anomalies. The tests are highly specific (specificity of 97.9–100% for all the above-mentioned anomalies). Most of the commercial tests available allow identification of sex chromosome abnormalities, such as Klinefelter and Turner syndromes. Despite high test performance, NIPT is still considered a screening test and not a diagnostic test. Therefore, positive results must be validated by invasive prenatal testing (chorionic villi sampling or amniocentesis) [7].

## Can NIPT Replace Current Screening Tests for Down Syndrome?

Current prenatal screening tests for Down syndrome (first-trimester fetal sonography for nuchal translucency, first- and second-trimester maternal serum biochemical markers, and second-trimester anatomical scan) are relatively inexpensive and cost-effective. Thus, currently there is no intent to replace these tests with NIPT. However, it may be advantageous to integrate NIPT with the current screening modalities as part of the screening program for fetal aneuploidy in Israel. This option must be carefully explored before implementation.

## To Whom Should NIPT Be Offered?

NIPT should be considered for women at high risk for fetal chromosomal abnormalities, in singleton pregnancies, from 10 weeks of gestation. The following categories are considered high risk:

- Maternal age of 35 years or above at the time of conception.
- Sonographic ‘soft markers’ of chromosomal anomaly (such as intracardiac echogenic foci, mild pyelectasis, etc.).
- Personal or familial history of a chromosomal anomaly detectable by NIPT.
- Abnormal Down syndrome screening result (first or second trimester).
- A parent carrier of a Robertsonian translocation involving chromosomes 13 or 21.

## Pretest Counseling

Use of NIPT should be an informed patient choice. Pretest counseling regarding the advantages and limitations of NIPT is warranted. Women at high risk for genetic disorders not detected by NIPT should be referred to genetic counseling, in line with the regulations of the Israeli Health Ministry [8]. Informed consent must include all details outlined in online supplementary data ([www.karger.com/doi/10.1159/000360420](http://www.karger.com/doi/10.1159/000360420)).

## Posttest Counseling

### *Normal Test Result*

May be delivered by one of the following healthcare providers (as stipulated by Israeli Law) [9]: a medical geneticist, a clinical geneticist, a genetic counselor, or a board-certified obstetrician. Counseling should re-emphasize the limitations of the testing (described in online suppl. data). New information relevant to the pregnancy (occurring after NIPT was performed) must be addressed accordingly.

### *Abnormal Test Result*

Should be delivered during formal genetic consultation. Abnormal results should be confirmed by invasive prenatal testing (CVS or amniocentesis).

Due to the emerging clinical and scientific advances in this field, this statement should be reviewed within a year.

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