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Genetics Education Canada: Knowledge Organization
Centre d'éducation en génétique canadien: Connaissances organisées
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NON-INVASIVE PRENATAL TESTING

Highly sensitive and specific non-invasive prenatal screening for common chromosome differences available in the first trimester. *Updated Jan 2023*

WHAT IS NIPT?

Prenatal screening using cell-free DNA (cfDNA), also known as Non-Invasive Prenatal Testing (NIPT), is a test to prenatally detect Down syndrome and other common chromosome differences (aneuploidies). This test assesses fragments of cfDNA derived from the placenta that are circulating in maternal blood to determine if there is an increased chance that the fetus has an aneuploidy.

WHEN TO CONSIDER OFFERING NIPT?

Evidence supports screening by NIPT in a pregnancy determined to be at increased risk for a common aneuploidy. (e.g. age 40 or older at the time of birth, positive prenatal screening result, ultrasound finding suggestive of chromosome difference such as nuchal transluscency 3.5mm or greater, multiple soft markers).

BENEFITS OF NIPT

- Increased accuracy: Higher detection rate, higher positive predictive value, lower false positive rate compared to conventional prenatal genetic screening.
- Earlier timing: Screening by NIPT is a single blood test that is available as early as 9-10 weeks. Results are available within 1-2 week.

LIMITATIONS OF NIPT

- NIPT is **not** a diagnostic test: No irrevocable obstetrical decisions should be made without confirmatory diagnostic testing
- No result: This may occur in up to 6% of cases but may be resolved following a repeat blood test.
- NIPT does not screen for all possible conditions e.g. congenital anomalies, single gene conditions are not screened for.
- Incidental findings: Some companies will report high risk of sex chromosome differences even if fetal sex is not selected. Maternal conditions (e.g. mosaic aneuploidy) may also be detected and reported.

SEX CHROMOSOME DIFFERENCES

- Prenatal determination of fetal sex is only clinically indicated when a male fetus is at risk for an X-linked condition or for a female fetus affected by congenital adrenal hyperplasia, thus at risk of virilisation.
- If fetal sex is not selected on a test requisition, a company may still report a high risk of sex chromosome difference if detected.
- Sex chromosome differences involve an extra or missing X or Y chromosome in whole or in part.
- Examples are Turner syndrome (45,X), and sex chromosome trisomies (e.g. Klinefelter syndrome (47, XXY), Triple X syndrome (47, XXX) and Jacobs syndrome (47, XYY)).
- The combined prevalence is about 1 in 500.
- Clinical presentation is highly variable.

RESULTS

NEGATIVE/LOW RISK

- This is reassuring
- Recommend first trimester ultrasound (11 to 14 weeks gestation) and a second trimester ultrasound (18 to 22 weeks gestation)
- Consider referral for genetic and/or maternal fetal medicine consultation depending on the reason for NIPT
  - e.g. for an ultrasound finding of an NT ≥ 3.5mm and a negative NIPT, a detailed ultrasound, fetal echocardiogram and additional genetic investigations would be offered

POSITIVE/HIGH RISK

- **No irrevocable obstetrical decisions should be made in pregnancies with abnormal NIPT results without confirmatory diagnostic testing** (CVS or amniocentesis) as false positive results do occur.
- Offer genetic counselling and confirmation by diagnostic testing should be offered.
- The positive predictive value (PPV) is not 100% for any condition in any population
- Consider the PPV of the result for your patient for the condition screened positive.

NO RESULT/UNINTERPRETABLE

- This may occur in up to about 6% of cases. The laboratory will usually request a second blood sample repeating the test at no extra cost. In 50-60% a result will then be available.
- Possible reasons for test failure are (1) blood collection and/or transportation issues, (2) technical issues e.g. a poor sample or quality assessment failure, and, most often (3) low fetal fraction (amount of fetal cfDNA relative to mother's) which is influenced by factors such as early gestational age, high maternal BMI, IVF or fetal aneuploidy.
- When contemplating repeating the blood test, consider whether a delay in results/no result and possible further delay to diagnostic testing is important.
- If the NIPT result is still not interpretable following repeat blood draw, test failure may be due to low fetal fraction, which is associated with an increased aneuploidy risk (~5%). Consider genetic counselling where diagnostic testing and ultrasound may be offered.

ADDITIONAL SCREENING BY NIPT

- Currently no national or international organizations support routine clinical implementation of additional screening by NIPT.
- The clinical utility and sensitivity have not been demonstrated.
- Examples are microdeletion and microduplication syndromes, rare trisomies (e.g. trisomy 15 or 16), and structural anomalies.

MICRODELETIONS AND MICRODUPLICATIONS

- Microdeletion and microduplication syndromes are **rare** genetic conditions, occurring in about 1 in 5,000 to 1 in 50,000 pregnancies caused by very tiny extra or missing pieces of a chromosome.
- The imbalance of genetic information may have developmental and health implications.
- The most common example is 22q11.2 or DiGeorge syndrome.

PRIVATE PAY NIPT

- When public health care funding is not available, paying out of pocket may be an option.
- Cost and access vary by company, test selection and geographic location.
- GEC-KO does not endorse one company.
- Consider talking to your local prenatal genetic counsellor about what is available near you. See www.geneticseducation.ca > Clinics
- When ordering NIPT as a private pay option you may wish to discuss with a company representative some of the considerations below.

(1) Support: Is there direct support available by a board-certified genetic counsellor, before and after testing?
(2) Process: (a) How and where is blood drawn? (b) Ideal gestational age for blood draw? (Some companies offer blood draw as early as 9 weeks but this may not be ideal, for example, if the patient has a high BMI the fetal fraction may be too low.) (c) Is an ultrasound required?[Note that ultrasound is recommended to confirm gestational age, confirm viability and to exclude multiples]
(3) Cost: (a) Are there added costs for blood draw, genetic counselling support? (b) Are additional testing options at extra cost
(4) Exclusion criteria: (a) Is this test validated in all pregnancies? i.e. pregnancy achieved by *in vitro* fertilization, with egg donor, by surrogate, multiples, vanishing twin, consanguineous couple, pregnant person with high BMI
(5) Privacy: (a) Does the patient's sample leave the province and/or country? How is the patient's data protected? Data sharing policies?

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References and more at www.geneticseducation.ca

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