Perinatal Services BC
Provincial Health Services Authority

BC Prenatal Genetic Screening Program

First tier NIPS: Considerations for Providers When Selecting Conditions to Include.

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Self-pay NIPS (also known as NIPT) is being presented to pregnant individuals when discussing all screening options for Down syndrome. When considering NIPS as a first tier screen for women who are **not at increased risk of a chromosomal abnormality** (outside of their age related risk), it is critical that maternity care providers discuss the different options available, in terms of the conditions being screened for by these tests, and the potential benefits and harms of testing for more than the common trisomies. In order to achieve informed consent when considering screening for an array of conditions, both patients and providers should be familiar with the conditions being tested as well as the chance of false positive and false negative results and the likelihood that a positive screen will be a true positive (PPV).

1. **Clinical conditions that can be screened for include:**
   - Trisomies 21, 18 and 13 (NIPS was first developed to screen for these)
   - Sex chromosome aneuploidies, conditions that can have a very mild presentation or no clinical impact.
   - Microdeletion syndromes, conditions that have significant clinical impact but are rare.
   - Rare autosomal trisomies, conditions that are rare and when detected can be confined to the placenta and not be present in the fetus.

2. **Conditions included with various NIPS available tests differ as does the cost of these tests**.
   - A summary of the NIPS tests for the common trisomies available in BC are included in the table with details of conditions tested as a default or as options.

Tests	Trisomy 13, 18, 21	Sex Chromosome Aneuploidy	Microdeletion 22q11.2	Microdeletion panel	Rare Autosomal Trisomies
Harmony (Dynacare)	Default	Optional	Optional	N/A	N/A
Invitae (Invitae)	Default	Optional	Optional	Optional	Optional
MaterniT21 Plus (Dynacare)	Default	Optional	Included in microdeletion panel (ESS)[1]	Optional (ESS)	Included with microdeletion panel (ESS)
Panorama (LifeLabs)	Default	Default	Optional	Optional	N/A

3. **NIPS is a screening test:**
   - A result showing a very high risk for any of the conditions tested can be a false positive.
   - When screening for the common trisomies, the chance that a high risk result is a true positive (affected pregnancy) varies between 25-90% depending on maternal age and the trisomy involved (lower chance of a true positive with trisomy 13 and 18).
   - **Patients with a positive NIPS result should be offered an invasive diagnostic procedure (CVS or amnio) to make a definite diagnosis.**

[1] ESS = Extended sequencing series: 7 microdeletion syndrome and two rare trisomies (trisomy 22, trisomy 16)

4. Performance of NIPS for the different conditions is variable:
    - NIPS is less effective at screening for sex chromosomal aneuploidy and microdeletions as compared to screening for the common trisomies.
    - Detection rate: The test is better at detecting the common trisomies than any microdeletion (i.e. NIPS is more likely to produce false negative results for microdeletions than for the common trisomies).
    - Positive Predictive Value: A high risk result for the common trisomies is more likely to predict an affected pregnancy compared to a high risk result for Turner syndrome or the microdeletion syndromes. For example, a 30 year old woman with a high risk result for:
        - Trisomy 21 has a **60%** chance that her baby has the condition.
        - 45,X has a **25%** chance that her baby has the condition.
        - 22q11.2 microdeletion has a **20%** chance that her baby has the condition.
        - Prader-Willi syndrome has a **5%** chance that her baby has the condition.

5. **Screening for more conditions results in an increase in false positive screens:**
    - Screening for only trisomies 13, 18, and 21 will have a positive rate of around 0.3%. When adding sex chromosomal aneuploidy and microdeletion panels the positive rate will be 1%.
    - The chance that the positive screens for 45,X or microdeletion syndromes are true positives is low (25% or less), so by testing for these conditions, we are increasing the number of false positive screens.

6. **Recommendations by national/international societies (SOGC, ISPD):**
    - NIPS is a highly effective screen for the common trisomies (21, 18 and 13) and should be offered as a first tier screening. (Society of Obstetricians and Gynecologists of Canada, International Society for Prenatal Diagnosis)
    - When women are offered cfDNA screening for fetal sex chromosome abnormalities, they should be informed that testing for fetal sex chromosomes could involve potential discovery of both fetal and maternal sex chromosome abnormalities, including those that may be of minor, or no, clinical significance. (International Society for Prenatal Diagnosis)
    - **Routine NIPS for fetal microdeletions is not currently recommended (Society of Obstetricians and Gynecologists of Canada).**
    - **Routine NIPS for fetal microdeletions and rare autosomal trisomies is not currently recommended (International Society for Prenatal Diagnosis).**

It is important for pregnant individuals to be informed that even if a pregnancy has screening for all the conditions offered by NIPS, and the result is low risk, there will remain a chance of having a baby with a genetic condition or congenital abnormality. Adding the microdeletion panel does not significantly reduce this chance given it represents a small number of all the genetic syndromes.

The Prenatal Genetic Screening Program endorses the recommendation of the SOGC and ISPD and recommends against screening for the microdeletion syndromes and rare autosomal trisomies.

References:

Audibert F, De Bie I, Johnson JA, et al. No. 348-Joint SOGC-CCMG Guideline: Update on Prenatal Screening for Fetal Aneuploidy, Fetal Anomalies, and Adverse Pregnancy Outcomes. J Obstet Gynaecol Can. 2017 Sep;39(9):805-817.

Hui L, Ellis K, Mayen D, et al. Position statement form the International Society for Prenatal Diagnosis on the use of non invasive prenatal detection of fetal chromosomal conditions in singleton pregnancies. Prenat Diagn. 2023; 43:814-828.