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Prenatal Genetic Screening in Ontario

Updated: October 2022

About This Slide Deck

- The slide deck was created as a resource for providers in the prenatal community about the current state of prenatal genetic screening in Ontario.
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What is Prenatal Screening Ontario?

- Prenatal Screening Ontario (PSO) was launched in 2018 to coordinate prenatal screening services in Ontario.
- PSO is housed within the province's maternal, newborn and child registry, the Better Outcomes Registry and Network (BORN) Ontario.
- BORN is a prescribed registry established in Ontario under the Personal Health Information Protection Act, for the purpose of facilitating and/or improving the provision of health care in our province, with a vision for the best possible beginnings for lifelong health.

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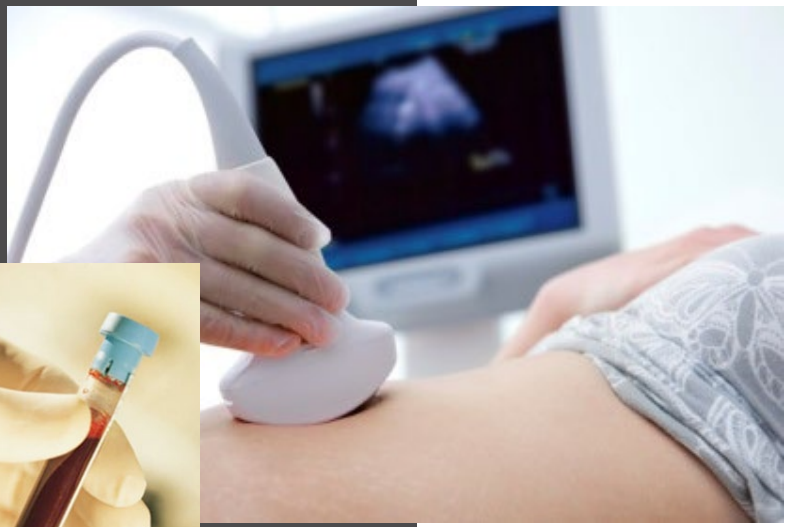
Prenatal Screening Ontario Mandate



- Enhance **access** to high quality prenatal screening for all pregnant individuals in Ontario.
- Provide the **education** supports, information, and transparency needed for health care providers and pregnant individuals and their families to make informed decisions.
- Undertake ongoing **quality assurance and system performance** evaluation to support all components of the system in functioning effectively and meeting established standards.
- Facilitate the **incorporation of evolving technologies** or screening options, supporting evidence-based integration.
- Support the ongoing **alignment** of screening service provision.

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PSO:
Prenatal Screening Resource for Providers and Pregnant Individuals

- Read about testing options, results and obtain requisitions and tools to support the discussion between you and pregnant individuals.
- Contact one of the on-call genetic counsellors to answer questions about prenatal screening.
- Request educational webinars for your team targeted to your needs.

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PSO:
Prenatal Screening Resource For Sonographers

- Nuchal Translucency Quality Assurance (NTQA) program was implemented in 2019 to support sonographers in their NT practice.
- Without participation in such a program, measurement quality deteriorates over time.
- Sonographers can access how their NT performance compares to the Fetal Medicine Foundation standards, and can obtain support and updates on NTQA activities.

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Slide Deck Content Overview

- Overview of prenatal genetic screening options
  - Multiple Marker Screening
  - Non-Invasive Prenatal Testing
- Offering prenatal genetic screening
- Arranging prenatal genetic screening
- How to discuss prenatal genetic screening results
- When to consider a referral for genetic counselling
- Take-home messages

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Overview of Prenatal Genetic Screening

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Prenatal Genetic Screening Options

Multiple Marker Screening (MMS)

OHIP-funded for all and includes: enhanced First Trimester Screening (eFTS), Second Trimester Screening (STS), Nuchal Translucency (NT) + Second Trimester Screening (STS).

Non-Invasive Prenatal Testing (NIPT)

OHIP-funded when at least one of specific criteria is met. Private-pay NIPT is available for pregnant individuals who do not meet criteria.

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What is Prenatal Genetic Screening?

- Prenatal genetic screening is a type of testing that should be offered to all pregnant individuals in Ontario, regardless of age.
- It is a non-invasive way to determine the chance to have a pregnancy with trisomy 21, trisomy 18, and sometimes other chromosome differences.
- This chance is assessed by collecting pregnancy information through ultrasound and/or bloodwork from the pregnant individual.
- Screening tests are not diagnostic and only a diagnostic test like chorionic villus sampling or amniocentesis can give definitive answers regarding these chromosome differences.

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Multiple Marker Screening

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Multiple Marker Screening Overview

Factors	eFTS	STS
Timing (gestation)	11 weeks and 2 days to 13 weeks and 3 days	14 weeks 0 days to 20 weeks 6 days
Screened chromosome differences	• Trisomy 21 • Trisomy 18	• Trisomy 21 • Trisomy 18
Screening components	• Age of pregnant person (+ clinical information) • Nuchal translucency • hCG, PAPP-A, MS-AFP, +/- PIGF[1]	• Age of pregnant person (+ clinical information) • MS-AFP[2], uE3, DIA, hCG
Screening cut-off	Trisomy 21: 1/350 Trisomy 18: 1/200	Trisomy 21: 1/350 Trisomy 18: 1/200
Turn around time	5 business days	5 business days

[1] PIGF is incorporated as part of eFTS at North York General and Credit Valley Hospitals, and not Mount Sinai Hospital

[2] MS-AFP is no longer used to screen for open neural tube defects, except when there is no access to good detailed anatomy ultrasound

DIA = Inhibin-A
eFTS = enhanced First Trimester Screening
hCG = free beta Human Chorionic Gonadotropin
MS-AFP = Maternal Serum Alpha-feto-protein
PAPP-A = Placenta-Associated Plasma Protein A
PIGF = Placenta Growth Factor
STS = Second Trimester Screening
uE3 = unconjugated Estriol

Multiple Marker Screening Performance

Trisomy 21

Screening test	DR % (95% CI)	FPR % (95% CI)
eFTS	89.02 (86.68, 91.08)	6.34 (6.25, 6.43)
STS	86.79Θ (74.66, 94.52)	7.88Θ (7.56,8.22)

Trisomy 18

Screening test	DR % (95% CI)	FPR % (95% CI)
eFTS	84.98 (79.73, 89.31)	0.26 (0.24, 0.26)
STS	S (33.38, 88.18)*	0.58 (0.49, 0.68)

Notes:

1. Data were extracted from the BORN Information System (BIS) on 1 Feb, 2022, using cytogenetic testing data with results reported up to June 30, 2021. Note that data submission to the BIS is both voluntary and open to updates and amendments. This table represents a snapshot of the BIS on the date of data extraction.
2. The cohort timeline was defined by infant estimated date of delivery (EDD): 01-Sep-2016 to 03-31-2021.
3. Θ = The cut-off of STS was changed on 1 April 2020 from 1 in 200 to 1 in 350. These performance metrics have been calculated with the current cut-off of 1 in 350 applied to the entire cohort to provide a stable estimate of the performance expected for this screen.
4. S = point estimate suppressed when confidence interval >20%.
5. * = performance data have a confidence interval greater than 20%. These performance metrics were calculated using small cell sizes from the available Multiple Marker Screening (MMS) and cytogenetic data in the BIS and are subject to change as more data are collected. Please interpret these data with caution.
6. Only singleton pregnancies were included in this analysis.
7. Only pregnancies with a valid MMS result and cytogenetic result were included in this analysis. Outcome data were supplemented using clinical examination data from the BIS for negative results for T21, and T18 when cytogenetic results were missing.
8. "eFTS" includes both "4-marker eFTS" and "5-marker eFTS".

DR = Detection Rate
eFTS = enhanced First Trimester Screening
FPR = False Positive Rate
STS = Second Trimester Screening

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Which Multiple Marker Screening Modality Should I Offer?

eFTS is the preferred multiple marker screening modality given earlier results and the benefits of 11-14 week (NT) ultrasound beyond screening for the common aneuploidies.

When NT ultrasound is not available, or individual presents after 14 weeks gestation, STS can be done in the second trimester.

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Special Scenario

Vanishing Twins

- Vanishing twin = pregnancy that started as twins with subsequent loss of fetal heart activity or loss of the embryo in one of the pregnancy sacs.
- Cannot offer eFTS or NIPT, due to the potential interference of hormones or residual DNA from demised twin.
- Preferred screening method:
  - Nuchal Translucency ultrasound + Second Trimester Screening (STS).
  - Blood work for STS to be done at least 8 weeks post demise.
- Offer STS on its own if NT ultrasound is not available.

What About Screening for Open Neural Tube Defects?

"The primary screening test for detection of fetal structural abnormalities including neural tube defects is a second trimester anatomical ultrasound with detailed fetal cranial and spinal imaging assessment"

"Second trimester serum alpha fetoprotein screening to rule out open neural tube defects is no longer necessary unless there is a barrier to good quality ultrasound examination."

Reference: Joint SOGC-CCMG Clinical Practice Guideline. J Obstet Gynaecol Can 2017

Maternal serum alpha-fetoprotein (MS-AFP) is no longer used to routinely screen for open neural tube defects

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Non-Invasive Prenatal Testing (NIPT)

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NIPT – How It Works

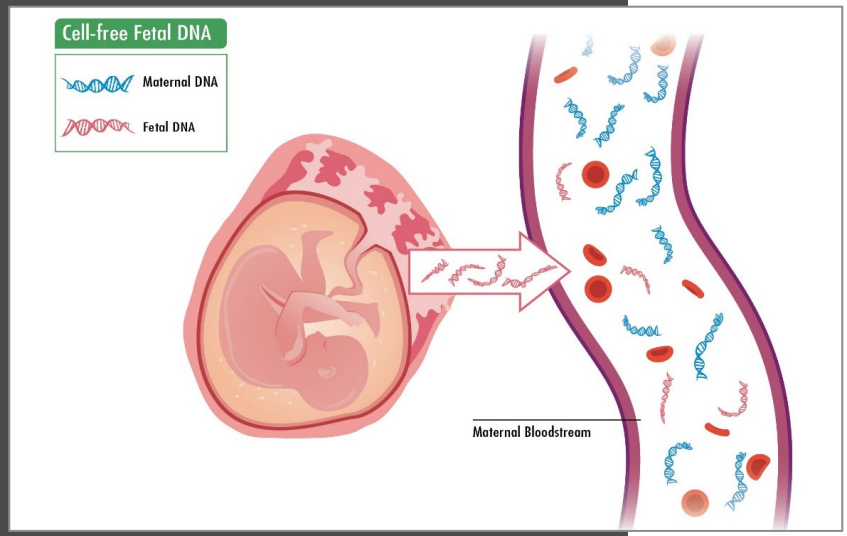

Illustration adapted from Genetic Counseling Aids, 7th Edition, Copyright 2020, permission for use granted by Greenwood Genetic Center

- Non-Invasive Prenatal Testing (NIPT) analyzes cell-free DNA from plasma of pregnant individual after 9 or 10 weeks gestation.
- The plasma contains cfDNA from the pregnant individual and the placenta.
- A fetal chromosomal aneuploidy is suspected when the amount (percentage) of cfDNA fragments from a particular chromosome differs from the expected amount.

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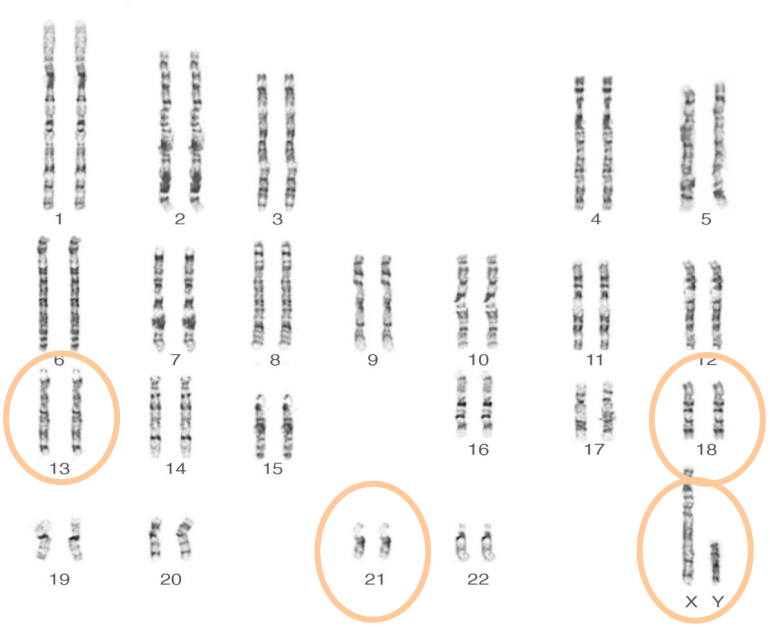

Illustration adapted from Genetic Counseling Aids, 7th Edition, Copyright 2020, permission for use granted by Greenwood Genetic Center

What Does NIPT Screen For?

- Trisomy 21
- Trisomy 18
- Trisomy 13
- Triploidy (LifeLabs)
- +/- Sex Chromosome Differences

Screening for additional chromosome differences (e.g. microdeletion syndromes) is possible but this testing is not funded by MOH and not recommended Canadian and international guidelines.

Reference: Joint SOGC-CCMG Clinical Practice Guideline. J Obstet Gynaecol Can 2017

NIPT = Non-Invasive Prenatal Testing

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NIPT Performance

Chromosome Difference	DR % (95% CI)	FPR % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Trisomy 21	99.49 (98.82, 99.84)	0.07 (0.05, 0.09)	95.76 (94.24, 96.97)	99.99 (99.97,100.00)
Trisomy 18	95.96 (92.48, 98.14)	0.03 (0.02, 0.05)	93.69 (89.45, 96.60)	99.98 (99.96,99.99)
Trisomy 13	92.11 (83.60, 97.05)	0.04 (0.03, 0.06)	73.49 (62.66, 82.58)	99.99 (99.97,100.00)

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DR (Detection Rate) = probability that a fetus with a chromosome difference will get a high risk screening result
FPR (False Positive Rate) = probability that that a fetus that does not have the chromosome difference will get a high risk screening result
PPV (Positive Predictive Value) = probability that a fetus with a high risk screening result truly has the chromosome difference
NPV (Negative Predictive Value) = probability that a fetus with a low risk screening result truly does not have the chromosome difference

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Multiple Marker Screening Versus NIPT

Trisomy 21

Screening test	DR % (95% CI)	FPR % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
eFTS	89.02 (86.68, 91.08)	6.34 (6.25, 6.43)	3.70 (3.44, 3.98)	99.97 (99.96, 99.97)
STS	86.79θ (74.66, 94.52)	7.88θ (7.56,8.22)	2.23 (1.64, 2.96)	99.95 (99.91, 99.97)
NIPT	99.49 (98.82, 99.84)	0.07 (0.05, 0.09)	95.76 (94.24, 96.97)	99.99 (99.97,100.00)

DR = Detection Rate
FPR = False Positive Rate
PPV = Positive Predictive Value
NPV = Negative Predictive Value

Notes:

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3. Only singleton pregnancies were included in this analysis.
4. θ = The cut-off of STS was changed on 1 April 2020 from 1 in 200 to 1 in 350. These performance metrics have been calculated with the current cut-off of 1 in 350 applied to the entire cohort to provide a stable estimate of the performance expected for this screen.
5. Only pregnancies with a valid MMS / NIPT result and cytogenetic result were included in this analysis. Outcome data were supplemented using clinical examination data from the BIS for negative results for T21, T18 and T13 when cytogenetic results were missing.
6. "eFTS" includes both "4-marker eFTS" and "5-marker eFTS".

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“High Risk” NIPT Result

What it means

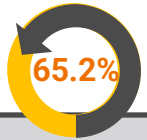
There is a significant chance the fetus has the condition. The specific probability (Positive Predictive Value) depends on the NIPT performance for the chromosome difference, and how frequently the chromosome difference occurs in the screened population

- e.g. A “high risk” result for trisomy 21 in a high risk population (e.g. advanced maternal age, positive multiple marker screen, ultrasound abnormalities) is more likely to be a true result than in a low risk population

NIPT = Non-Invasive Prenatal Testing

Next steps

Offer referral for genetic counselling. Options include invasive diagnostic testing and ultrasound.



65.2% of Ontario pregnancies with a “high risk” NIPT result for trisomy 21 had follow up prenatal diagnosis

Pregnancy management and/or delivery recommendations can be impacted even if prenatal diagnosis is not pursued.

Reference: Dougan, S et al (2021): DOI: https://doi.org/10.1503/cmaj.202456

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“Low Risk” NIPT Result

What it means

The chance that a low risk result for trisomy 21, trisomy 18 or trisomy 13 is a true result is generally >99.9%.

Next steps

Routine care if no other pregnancy concerns.

NIPT = Non-Invasive Prenatal Testing

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“No Call / Failed NIPT Result

- Current literature reports a failure / “no call” rate of 1-8%.
- A low fetal fraction is the main cause for a failed NIPT.
- There are many biological factors linked to a low fetal fraction that are unrelated to the fetal chromosomes, such as:
  - Early gestational age
  - High Body Mass Index (BMI)
  - In vitro fertilization (IVF) conception
  - Multiple gestation pregnancy

NIPT = Non-Invasive prenatal Testing

A low fetal fraction is associated with a higher likelihood of fetal aneuploidy ranging from 2.7% to 23.3% across studies

Reference: Hui, L., Bianchi, D. W. (2019) Fetal fraction and noninvasive prenatal testing: What clinicians need to know. *Pren Diag* **40(2)**:155-163

A pregnant person's options will depend on gestational age, presence of singleton versus twin gestation, other risk factors for aneuploidy, genetics/MFM referral guidelines, and preference of the individual.

Possible options after failed NIPT:

- Repeat blood draw: depending on the reason, a second draw may or may not help resolve the issue. The NIPT report and the lab genetic counsellor can provide further guidance with regards to the likelihood a repeat blood draw would yield a result.
- Alternative screening test (eFTS or STS).
- 18-22 week (detailed anatomy) ultrasound.
- Referral for genetic counselling, to include a discussion about diagnostic testing.

No Call/Failed NIPT Result

Next Steps

Reference: Hui, L., Bianchi, D. W. (2019) Fetal fraction and noninvasive prenatal testing: What clinicians need to know. *Pren Diag* **40(2)**:155-163

eFTS = enhanced First Trimester Screening
STS = Second Trimester Screening
NIPT = Non-Invasive Prenatal Testing

OHIP-Funded NIPT

- NIPT is funded by the Ministry of Health in the following circumstances:
  - All twin pregnancies
  - Singleton pregnancies when there is an increased probability for trisomy 21, trisomy 18, trisomy 13, a sex chromosome difference, or a disorder of sex determination
- Offered through two provincial labs:
  - LifeLabs® (Panorama NIPT)
  - Dynacare® (Harmony Prenatal Test)

NIPT = Non-Invasive prenatal Testing

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Category 1 Criteria

Eligibility for OHIP-funded NIPT

- a positive prenatal screening result from Multiple Marker Screening (MMS) for this pregnancy.
- the maternal age will be 40 years or older at the expected date of delivery.
    - In the context of in-vitro fertilization, the maternal age is guided by the age at egg retrieval (whether own egg or donor egg).
- the nuchal translucency (NT) measurement is ≥3.5 mm[2].
- there is a personal history of a previous pregnancy or child with trisomy 21, 18 or 13.
- there is a viable twin pregnancy.

[2]NT ≥3.5mm - increased NT is known to be associated with an increased chance for aneuploidy, microarray abnormalities, single gene disorders and cardiac abnormalities. Genetic counselling referral is recommended.

NIPT = Non-Invasive prenatal Testing
NT = Nuchal Translucency

In these situation, NIPT can be ordered by any physician or nurse pracitioner for singletons and twin pregnancies

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Category 2 Criteria

Eligibility for OHIP-funded NIPT

- there are findings on ultrasound which are associated with an increased chance for trisomy 21, trisomy 18 or trisomy 13.
- there is a chance for a sex-linked genetic condition.
- the ultrasound shows findings suggestive of a sex chromosome difference.
- the ultrasound shows findings suggestive of a disorder of sex determination.

NIPT = Non-Invasive prenatal Testing

In these situations, NIPT must be ordered by genetics or maternal fetal medicine specialist

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Prenatal Screening for Multiple Gestation Pregnancies

Type of Pregnancy	NT	eFTS	STS	NIPT
Singletons (including IVF)	Yes	Yes	Yes	Yes (OHIP-funded / private–pay)
Twins	Yes	No	No	Yes (OHIP-funded)
Higher Order Multiples (e.g. triplets, quadruplets)	Yes	No	No	No

NIPT for Twins

- Can use either Panorama NIPT or Harmony Prenatal Test for most twin pregancies.
- Panorama NIPT includes zygosity testing
- Use Harmony Prenatal Test (not Panorama NIPT) for twins conceived through *in vitro* fertilization (IVF) using donor egg and/or gestational carrier.

eFTS = enhanced First Trimester Screening
NIPT = Non-Invasive Prenatal Testing
STS = Second Trimester Screening

Reference: International Society for Prenatal Diagnosis Position Statement: cell free (cf)DNA screening for Down syndrome in multiple pregnancies (2020)

What are Sex Chromosome Differences?

- Refer to a variation from the typical number of sex chromosomes (e.g. 45,X; 47,XXY; 47,XXX).
- Incidence: 1/500 – 1/1000.
- Wide variation in symptoms and severity.
- Features include:
  - Tall or short stature
  - Infertility
  - Delayed puberty
  - Hypotonia
  - Learning and social difficulties
  - Anxiety and other psychiatric challenges.

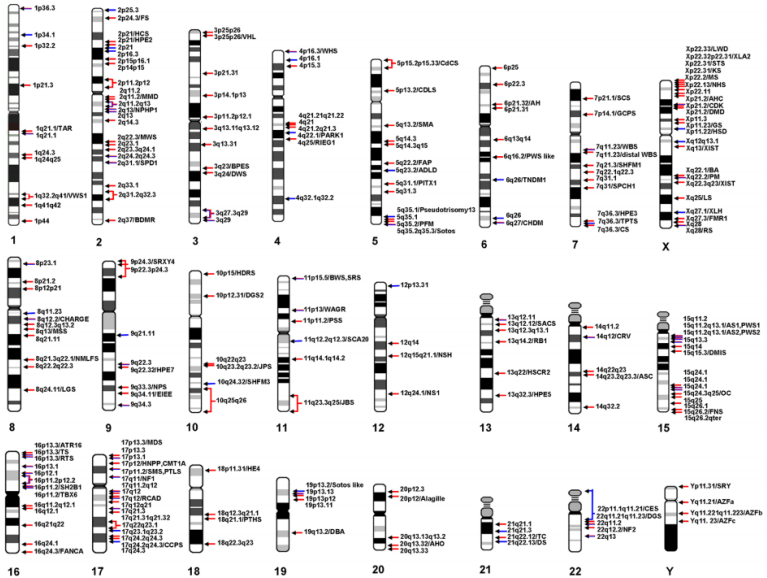
NIPT for Sex Chromosome Differences

- The NIPT performance for sex chromosome differences is lower than for trisomy 21, 18, 13 (including a lower detection rate and positive predictive value).
- If diagnostic testing is done following a “high risk” NIPT result, amniocentesis is preferred over CVS.
    - CVS samples placental tissue, so the result from CVS can be wrong for the same reason NIPT can be wrong: confined placental mosaicism.
- The choice to not screen for sex chromosome differences is available through Harmony Prenatal Test (as an opt-in choice) and Panorama NIPT (as an opt-out choice).

Reference: Joint SOGC-CCMG Clinical Practice Guideline. J Obstet Gynaecol Can 2017

Pregnant individuals need to balance the need to know with the risk for potentially unnecessary procedures, unnecessary anxiety, stressful decision-making given the relatively milder presentation.

What are Microdeletion and Microduplication Syndromes?



Red arrows indicate reported microdeletions, blue arrows microduplications, and mixed red/blue arrows reciprocal microduplication and microdeletion regions.

Illustration from “Microdeletion and microduplication syndromes” by A. Weise et al., 2012, Journal of Histochemistry and Cytochemistry 60(5) 346-358.

- Refer to conditions caused by submicroscopic deletions or duplications in specific chromosome regions.
- Individually rare but collectively occur in 1-1.5% of the population.
- The incidence is independent of the pregnancy individual’s age.
- Generally not inherited .
- Highly variable presentation, ranging from normal to severe.
- Can be diagnosed prenatally by microarray analysis through procedures such as chorionic villus sampling or amniocentesis.

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NIPT for Microdeletion Syndromes

- NIPT companies often include the option of screening for one or a few of the hundreds of microdeletions that can occur.
- There are limited data related to the clinical utility of screening for microdeletion syndromes in the general obstetric population, largely due to the rarity of these individual conditions.
- The screening and diagnosis of microdeletion syndromes is complicated by the variable presentation of these conditions.
- Due to the low prevalence of these individual microdeletions, most “high risk” results are expected to be false positives.
    - This has the potential to result in an increase in unnecessary patient anxiety, referrals to genetics centres and invasive fetal procedures.

NIPT = Non-Invasive Prenatal Testing

Most professional societies[1] do not recommend cfDNA screening for microdeletion syndromes.

[1] American College of Obstetricians and Gynecologists, and the Society of Obstetricians, Human Genetics Society of Australasia (HGSA), European Society of Human Genetics (ESHG) / American Society of Human Genetics (ASHG) and Gynaecologists of Canada (SOGC) / Canadian College of Medical Geneticists (CCMG)

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Benefits of NIPT

- Superior performance for trisomy 21 and trisomy 18, compared to multiple marker screening (eFTS and STS).
- Screens for more chromosome differences compared to multiple marker screening.
- Offered earlier than multiple marker screening leading to
  - Earlier diagnostic test options or other follow up investigations.
  - Earlier reassurance.
  - Earlier management options.
- Decreased diagnostic procedures, and therefore decrease in procedure-related losses.

eFTS = enhanced First Trimester Screening
STS = Second Trimester Screening
NIPT = Non-Invasive Prenatal Testing

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Limitations of NIPT

- NIPT is a screening test.
  - Only diagnostic testing (e.g. chorionic villus sampling/amniocentesis) can provide a “yes” or “no” answer.
- NIPT only screens for trisomy 21, 18, 13 and sex chromosome differences.
  - Not able to give information about other genetic conditions or structural defects.
- No call / failed result is possible with NIPT, and is only a rare occurrence with multiple marker screening.
  - A failed NIPT may significantly delay diagnosis.

NIPT = Non-Invasive Prenatal Testing

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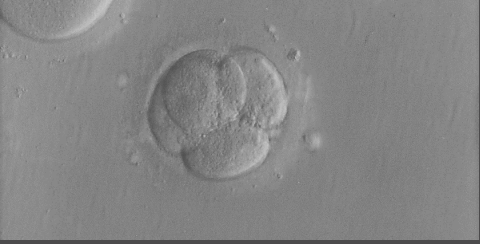

Prenatal Testing after IVF with PGT-A

- Pre-implantation Genetic Testing for Aneuploidy (PGT-A) is a screening test for aneuploidy performed on embryos during the in vitro fertilization (IVF) process.
- PGT-A has high sensitivity and specificity.
- Euploid embryo transfer after PGT-A
  - eFTS/STS are not recommended
  - NIPT for common aneuploidies can be considered following thorough genetic counselling.
- Mosaic embryo transfer after PGT-A
  - Genetic counselling is strongly recommended for individuals considering transfer of a mosaic embryo.
  - Diagnostic testing is always recommended after such transfer.

Reference: Committee Opinion No 406: prenatal testing after IVF with preimplantation genetic testing for aneuploidy. J Obstet Gynaecol Can 2020

eFTS = enhanced First Trimester Screening
STS = Second Trimester Screening
NIPT = Non-Invasive Prenatal Testing

Offering Prenatal Genetic Screening

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No. 348-Joint SOGC-CCMG Guideline

Update on Prenatal Screening for Fetal Aneuploidy, Fetal Anomalies, and Adverse Pregnancy Outcomes

- Discussion of risks, benefits and alternatives of the various prenatal diagnosis and screening options, including option of no testing should be undertaken with **all** patients prior to any prenatal screening.
- Patients should be offered:
  - No aneuploidy screening.
  - Standard prenatal screening based on locally offered paradigms.
  - Invasive testing when appropriate indications are present.
  - Maternal plasma cell-free DNA screening where available, with the understanding that it my not be provincially funded (II-B).

Reference: Joint SOGC-CCMG Clinical Practice Guideline. J Obstet Gynaecol Can 2017

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Determining Factors for What Options You Offer

Gestational age, singleton vs multiple gestation pregnancy, presence of “vanishing twin”, history of IVF with PGT-A, other screening tests in current pregnancy, additional risk factors for aneuploidy, etc

IVF = In Vitro Fertilization
PGT-A = Preimplantation Genetic Testing for Aneuploidy

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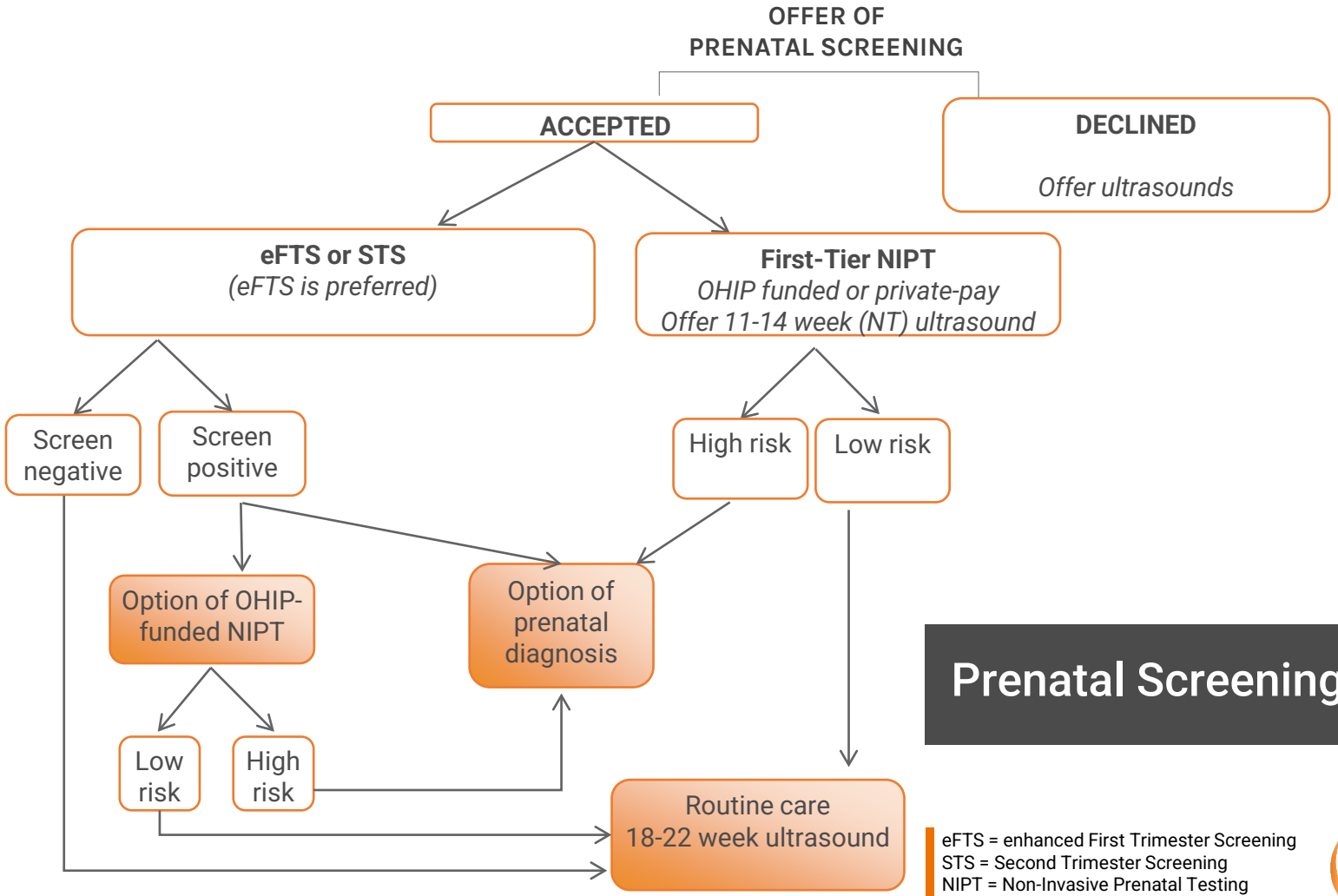

Prenatal Screening Model

eFTS = enhanced First Trimester Screening
STS = Second Trimester Screening
NIPT = Non-Invasive Prenatal Testing

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Screening After First-Tier NIPT

If NIPT is Done

Do not offer eFTS or STS

- A positive screen after a “low risk” NIPT can be confusing.
- Universal screening for adverse pregnancy outcomes using maternal serum markers is not recommended.

Do offer 11-14 week (NT) Ultrasound

An increased NT has been associated with conditions beyond the common aneuploidies: other chromosome differences, single gene disorders, structural abnormalities.

eFTS = enhanced First Trimester Screening
NIPT = Non-Invasive Prenatal Testing
NT = Nuchal Translucency
STS = Second Trimester Screening

Reference: Joint SOGC-CCMG Clinical Practice Guideline. J Obstet Gynaecol Can 2017

How to Offer Prenatal Screening

- Every person, irrespective of age, has a chance for having a pregnancy with trisomy 21, 18 and 13.
- Prenatal genetic screening is a personal choice and the person's decision about screening should not affect their care.
- Prenatal genetic screening is not diagnostic and does not test for "everything":
  - A negative (or low risk) screening result does not guarantee the birth of a baby without that chromosome difference or other genetic and non-genetic health concerns.
  - A positive (or high risk) screening result does not mean the pregnancy has the chromosome difference. It means that the chance is increased above the accepted cut-off, and further testing would be offered.
- Consider using sensitive language (e.g. "probability" or "chance" instead of "risk", avoid using the term "abnormality")

An adapted pdf version of this slide is available on the PSO Website ("How to Offer Prenatal Genetic Screening"): www.prenatalscreeningontario.ca.

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Counselling Framework

Explore values and attitudes

- Can explore how screening may or may not be helpful for the individual.
- Can provide reasons why people may accept or decline screening to help with decision making.

INFORMED CHOICE

Provide information

- Explore purpose of prenatal screening, that it is non-invasive and optional.
- Provide balanced information on the clinical features of screened chromosome differences.
- Compare tests in terms of: components, timing, performance, eligibility for OHIP coverage, private-pay cost, turn around time, possible results and implications.

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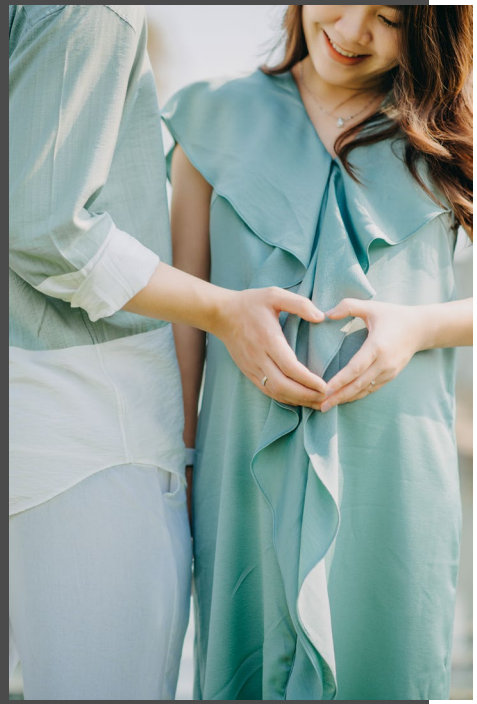
Explore How Screening May or May Not be Helpful



- How important is it for you to know if your baby has an increased chance of having a chromosome difference?
- If your screen result is positive, how likely are you to consider additional testing?
- How useful would it be for you to know about a chromosome difference before your baby's birth in order to prepare?
- What are your thoughts about continuing or ending your pregnancy if your baby has a chromosome difference?
- How would knowing/not knowing affect you emotionally throughout the pregnancy?

An adapted pdf version of this slide is available on the PSO Website ("How to Offer Prenatal Genetic Screening"): www.prenatalscreeningontario.ca.

Reasons for Choosing Prenatal Genetic Screening

- Gain knowledge about the health of the pregnancy.
- Seek “low risk” result for reassurance.
- A “high risk” result may help to emotionally prepare for a baby with special needs, or allow time to consider an adoption plan.
- Improve health outcomes - a “high risk” result for a chromosome difference may lead to changes in pregnancy management and delivery.
- A “high risk” result may lead to interruption of pregnancy if the chromosome difference is confirmed.

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Reasons for Declining Prenatal Genetic Screening

- Would not consider interruption of pregnancy.
- Avoid having to make difficult decisions about the pregnancy.
- Avoid possibility of a false positive result and unnecessary worry.
- The risk for having a chromosome difference is perceived to be low.
- Difficult access to prenatal screening (e.g. NT ultrasound or NIPT blood work).

NT = Nuchal Translucency
NIPT = Non-Invasive Prenatal Testing

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Arranging Prenatal Genetic Screening

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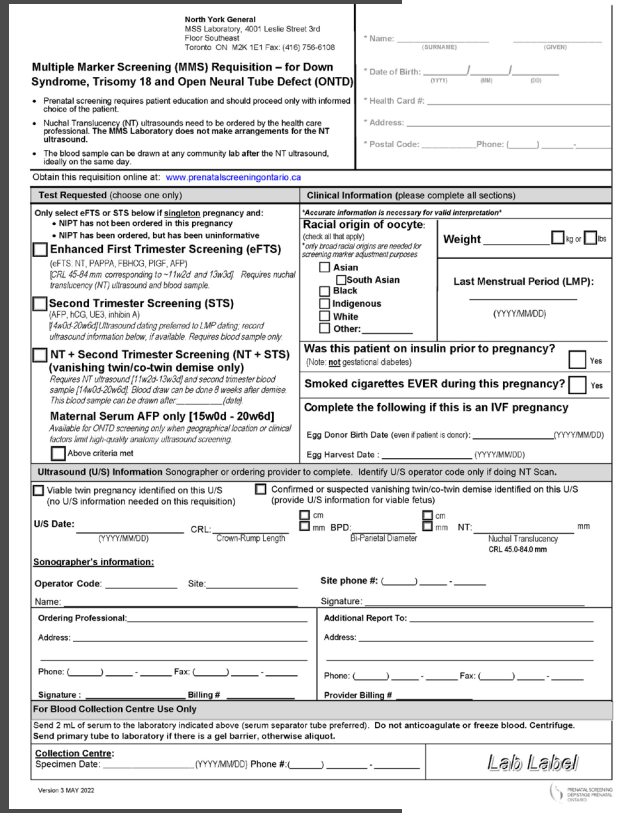
How To Arrange Multiple Marker Screening



North York General
MSS Laboratory, 4001 Leslie Street 3rd Floor Southeast
Toronto ON M2K 1E1 Fax: (416) 756-6108

Multiple Marker Screening (MMS) Requisition – for Down Syndrome, Trisomy 18 and Open Neural Tube Defect (ONTD)

- Prenatal screening requires patient education and should proceed only with informed choice of the patient.
- Nuchal Translucency (NT) ultrasounds need to be ordered by the health care professional. The MMS Laboratory does not make arrangements for the NT ultrasound.
- The blood sample can be drawn at any community lab after the NT ultrasound, ideally on the same day.

* Name: _____ (SURNAME) _____ (GIVEN)
* Date of Birth: ____/____/____ (YYYY) (MM) (DD)
* Health Card #: _____
* Address: _____
* Postal Code: _____ Phone: (____) _____-_____

Obtain this requisition online at: www.prenatalscreeningontario.ca

Test Requested (choose one only)

Only select eFTS or STS below if singleton pregnancy and:
- NIPT has not been ordered in this pregnancy
- NIPT has been ordered, but has been uninformative

☐ **Enhanced First Trimester Screening (eFTS)**
(eFTS: NT, PAPPA, FBHCG, PlGF, AFP)
[CRL 45-84 mm corresponding to ~11w2d and 13w3d]. Requires nuchal translucency (NT) ultrasound and blood sample.

☐ **Second Trimester Screening (STS)**
(AFP, hCG, UE3, inhibin A)
[14w0d-20w6d].Ultrasound dating preferred to LMP dating; record ultrasound information below, if available. Requires blood sample only.

☐ **NT + Second Trimester Screening (NT + STS) (vanishing twin/co-twin demise only)**
Requires IVF ultrasound [11w2d-13w3d] and second trimester blood sample [14w0d-20w6d]. Blood draw can be done 8 weeks after demise. This blood sample can be drawn after:_____(date).

Maternal Serum AFP only [15w0d - 20w6d]
Available for ONTD screening only when geographical location or clinical factors limit high-quality anatomy ultrasound screening.
☐ Above criteria met

Clinical Information (please complete all sections)

Accurate information is necessary for valid interpretation

Racial origin of oocyte: (check all that apply)
** only broad racial origins are needed for screening marker adjustment purposes*
☐ Asian
☐ South Asian
☐ Black
☐ Indigenous
☐ White
☐ Other:_____

Weight _____ ☐ kg or ☐ lbs

Last Menstrual Period (LMP): _____ (YYYY/MM/DD)

Was this patient on insulin prior to pregnancy? (Note: not gestational diabetes) ☐ Yes

Smoked cigarettes EVER during this pregnancy? ☐ Yes

Complete the following if this is an IVF pregnancy
Egg Donor Birth Date (even if patient is donor): _____(YYYY/MM/DD)
Egg Harvest Date : _____ (YYYY/MM/DD)

Ultrasound (U/S) Information Sonographer or ordering provider to complete. Identify U/S operator code only if doing NT Scan.

☐ Viable twin pregnancy identified on this U/S (no U/S information needed on this requisition)
☐ Confirmed or suspected vanishing twin/co-twin demise identified on this U/S (provide U/S information for viable fetus)

U/S Date: _____ (YYYY/MM/DD) CRL: ☐ cm ☐ mm _____ Crown-Rump Length BPD: ☐ cm ☐ mm _____ Bi-Parietal Diameter NT: _____ mm Nuchal Translucency CRL 45.0-84.0 mm

Sonographer's information:
Operator Code: _____ Site:_____ **Site phone #:** (____) ____-____
Name: _____ Signature: _____

Ordering Professional:_____
Address: _____
_____
Phone: (____) ____-____ Fax: (____) ____-____
Signature : _____ **Billing #** _____

Additional Report To: _____
Address: _____
_____
Phone: (____) ____-____ Fax: (____) ____-____
Provider Billing # _____

For Blood Collection Centre Use Only
Send 2 mL of serum to the laboratory indicated above (serum separator tube preferred). **Do not anticoagulate or freeze blood. Centrifuge. Send primary tube to laboratory if there is a gel barrier, otherwise aliquot.**

Collection Centre:
Specimen Date: _____ (YYYY/MM/DD) Phone #:(____) _____-_____

Lab Label

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Prenatal Screening Ontario website houses:

- MMS Requisitions for the three provincial labs (Trillium Health Partners – Credit Valley Hospital, North York General Hospital and Mount Sinai Hospital) – last updated May 2022.
- Catchment areas for the three MMS laboratories to help identify the appropriate requisition based on your location.
- Guides for how to order eFTS, STS and NT + STS.

eFTS = enhanced First Trimester Screening
NT = Nuchal Translucency
STS = Second Trimester Screening

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How to Arrange Non-Invasive Prenatal Testing

STEP 1 Discussion with Pregnant Individual	STEP 2 Provide Requisition	STEP 3 Blood Draw	STEP 4 Results
Provide information, and explore patient values and attitudes	NIPT is available through Dynacare® and LifeLabs®. Ensure the appropriate requisition is used (private-pay vs OHIP-funded)	SOGC guidelines recommend blood draw >10 weeks to decrease the chance of a failed result	7-10 business days

Prenatal Screening Ontario website only houses OHIP-funded NIPT requisitions. Private-pay requisitions can be located on the commercial labs' websites.

NIPT = Non-Invasive Prenatal Testing

Reference: Joint SOGC-CCMG Clinical Practice Guideline. J Obstet Gynaecol Can 2017

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How to Discuss Prenatal Genetic Screening Results

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How to Discuss Multiple Marker Screening Results (eFTS / STS)

Screen Negative Result

- Explanation of probability can be provided in different ways (e.g. ratio, percentage).
- A negative screen result is reassuring but does not guarantee the birth of a baby without health concerns.
- A negative screen result would typically not prompt the offer of diagnostic testing (CVS or amniocentesis), in the absence of additional risk factors.

Screen Positive Result

- Explanation of probability can be provided in different ways.
- A positive screen result does not mean the pregnancy has the chromosome difference. It means that the chance is increased above the accepted cut-off.
- The pregnant person can choose between NIPT, diagnostic testing or no further prenatal testing.
- Only diagnostic testing (CVS or amniocentesis) can provide definitive information prenatally.

CVS = Chorionic Villus Sampling
eFTS = enhanced First Trimester Screening
STS = Second Trimester Screening

An adapted pdf version of this slide is available on the PSO Website ("How to Discuss Prenatal Screening Results – eFTS / STS"): www.prenatalscreeningontario.ca.

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How to Discuss Non-Invasive Prenatal Testing Results

Low Risk Result

- Typically means the chance for trisomy 21, 18, 13 is <1:10,000.
- A low risk result is reassuring and would not typically prompt the offer of diagnostic testing (CVS, amniocentesis), but this depends on the indication for testing.
- A low risk result does not guarantee the birth of a baby without any health concerns.

High Risk Result

- Typically means the chance for trisomy 21, 18, 13 is significantly increased.
- The chance that a high risk screen result truly represents a pregnancy with that chromosome difference varies by chromosome and the pregnant person's risk prior to the screen.
- Offer a referral for genetic counselling.
- NIPT is a screening test – only diagnostic testing can provide definitive information prenatally

No call/Failed Result

- There are different reasons why NIPT fails.
- It can mean an increased chance for a chromosome difference.
- Repeating a blood draw may or may not be recommended by the lab depending on the reason the test failed.
- If a redraw is done, it yields a result in most cases.
- Can offer: repeat blood draw, alternative screen, detailed anatomy ultrasound and a referral for genetic counselling, as appropriate.

CVS = Chorionic Villus Sampling
NIPT = Non-Invasive Prenatal Testing

An adapted pdf version of this slide is available on the PSO Website ("How to Discuss Prenatal Screening Results - NIPT"): www.prenatalscreeningontario.ca.

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Referral to Genetics Clinic

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When to Consider a Referral to Genetics / MFM

- NT measurement is increased (3.5 mm or above).
- NIPT result is “high risk”, the NIPT fails (usually after two attempts) or there is an atypical NIPT result.
- Ultrasound anomalies or certain soft markers.
- Personal or family history of genetic conditions, intellectual disability or birth defects why may impact the pregnancy.
- Pregnant individual is considering prenatal diagnostic testing.
- In some cases, “screen positive” results from multiple marker screening.

NT = Nuchal Translucency
NIPT = Non-Invasive Prenatal Testing

Genetic clinics vary in their referral criteria. You may consider contacting your local genetics centre to obtain more centre-specific guidance.

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Take-Home Messages

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Take-Home Messages (part 1)

- Prenatal genetic screening is useful for all, not just those of advanced reproductive age.
  - “All pregnant women in Canada, regardless of age, should be offered, through an informed counselling process, the option of a prenatal screening test for the most common fetal aneuploidies (II-A)”.
- Screening is not diagnostic.
  - Definitive information can be obtained through a prenatal diagnostic test, such as chorionic villus sampling or amniocentesis.
- Nuchal translucency ultrasound is useful beyond screening for aneuploidy.
  - “Where available with documented expertise, the first trimester ultrasound (11 to 14 weeks’ gestation) offers many advantages including accurate dating, determination of twin chronicity, early detection of major structural abnormalities and aneuploidy screening (II-A)”.

Reference: Joint SOGC-CCMG Clinical Practice Guideline. J Obstet Gynaecol Can 2017

Take-Home Messages (part 2)

- Screening can still be useful if the pregnant individual would not consider interrupting a pregnancy.
  - E.g. emotional preparation and prenatal/postnatal management
- More is not always better.
  - Initiating a multiple marker screen (eFTS/STS) after a low risk NIPT can be confusing as it can result in conflicting results. A 11-14 week (NT) ultrasound alone should be offered.
  - Screening for microdeletion syndromes is not currently recommended.
- For further information or counselling regarding prenatal genetic screening, contact Prenatal Screening Ontario and/or your local genetics centre.

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NIPT = Non-Invasive Prenatal Testing
NT = Nuchal Translucency
STS = Second Trimester Screening

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PSO has on-call genetic counsellors to answer questions about prenatal screening

Mon - Fri / 9 am - 3 pm

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