

## CASE 1

### Deciding Value for Money: Improving Prenatal Genetic Screening in Ontario

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#### BACKGROUND

The Ministry of Health and Long-Term Care (MOHLTC) has supported prenatal genetic screening in Ontario since 1993, publically funding an array of screening options. In February 2013, a new screening option became available in Ontario. This technology, known as non-invasive prenatal testing (NIPT), promises improved accuracy and safety and is currently only available to those willing to independently pay for the test (Okun, Teitelbaum, Huang, Dewa, & Hoch, 2014). With increasing public interest in the technology and wanting to maintain a centralized, standardized, high quality provincial screening program, the Ministry has recognized the need for an urgent response on the use of NIPT within the public system. In March 2014, the Ministry appointed a Prenatal Genetic Screening Group (PGSG) to advise on current screening practices and make recommendations for an improved prenatal genetic screening program in Ontario. As part of the group's work, the Ministry has requested an economic evaluation, examining the costs and performance outcomes associated with NIPT and its introduction into the public system.

#### INTRODUCTION TO PRENATAL GENETIC SCREENING

Prenatal genetic screening for fetal chromosomal abnormalities began in the mid-1960s. At this time the screening involved offering women who were considered of advanced maternal age (>35 years of age at expected date of delivery) an invasive test called an amniocentesis. This test carried with it a small risk of fetal loss (0.01% to 0.5%). The age 35 was chosen as it was the determined point where the risk of fetal loss related to screening was less than the chance of identifying a significant fetal chromosomal condition (Prenatal Screening Ontario, 2014). Since this time, great advances in prenatal genetic technology have been made, lessening the need for invasive testing and subsequently reducing the number of fetal losses due to complications. Today, prenatal genetic screening consists of minimally invasive procedures such as blood work and ultrasounds and has become a routine part of publicly funded prenatal care for all women in Ontario.

Women may choose to have screening done if they wish to learn more about their pregnancy, want to gather the best information and prepare for their newborn and the delivery, or want the opportunity to terminate a pregnancy if a diagnosis is made. Prenatal genetic screening does not screen for all chromosomal abnormalities nor does it provide a definitive diagnosis. Women who receive a positive screen are given the option of further diagnostic testing. This consists of either chorionic villus sampling (CVS) or amniocentesis. Both procedures carry a small risk of fetal loss (1% and 0.01% to 0.5% respectively; Prenatal Screening Ontario, 2014).

With the discovery of cell-free fetal DNA (cffDNA) in maternal blood, a new form of screening has evolved. This screening is referred to as non-invasive prenatal testing (NIPT) and offers an improved detection rate (DR) and fewer false positives. This test has the potential to further reduce the number of invasive tests performed, subsequently reducing the number of fetal losses due to complications (Langois & Brock, 2013).

### **FETAL CHROMOSOMAL CONDITIONS**

Typically, individuals have 46 chromosomes or 23 pairs of chromosomes in each cell of their body. This is the result of proper chromosome alignment during the creation of an egg or a sperm. If the chromosomes do not properly align during this process, too few or too many chromosomes can result. This is referred to as aneuploidy and once this occurs the chromosome imbalance will be in every cell and cannot be treated. The cause of this misalignment is unknown; however, it is known that it occurs more often as women age. The misbalance of chromosomes can lead to development and growth challenges in the fetus, often resulting in spontaneous miscarriage (Prenatal Screening Ontario, 2014). The incidence of any fetal chromosomal condition is approximately 1 in 160 live births, with the majority of these being aneuploidies (Canadian Agency for Drugs and Technologies in Health, 2014). The most common fetal aneuploidies include Trisomy 21 (Down syndrome) and Trisomy 18 (Edward syndrome). Prenatal genetic screening assesses the chance of carrying a fetus with one of these conditions, along with assessing for open neural tube defects (ONTDs) and other structural chromosomal conditions.

#### **Down syndrome (Trisomy 21)**

Down syndrome is the most common aneuploidy, occurring in about 1 in 1000 births in Ontario (Prenatal Screening Ontario, 2014). This rate varies with age, being more common as women age. The common characteristic shared by those with Down syndrome is extra genetic material associated with chromosome 21. The effects associated with the extra genetic material are highly variable among individuals. Individuals with Down syndrome may be predisposed to certain medical and learning-style challenges. Common medical conditions associated with Down syndrome include heart, stomach, thyroid, hearing, and vision problems. Each individual with Down syndrome is different and there is no way to predict the level of disability during pregnancy. There is no cure for Down syndrome, but early intervention and medical management can improve the common conditions associated with it (Canadian Down Syndrome Society, 2009).

#### **Edward syndrome (Trisomy 18)**

Edward syndrome is less common than Down syndrome, occurring in about 1 in 6,000 births. This condition also varies with age, being more common as women age. Individuals with Edward syndrome have extra genetic material associated with chromosome 18 and are predisposed to serious congenital malformations. Of the pregnancies diagnosed, 95% will result in a miscarriage and of the babies born, 95% will die within the first year of life (Prenatal Screening Ontario, 2014).

#### **Open Neural Tube Defects (ONTDs)**

ONTDs occur when the spine or brain does not develop properly during the first trimester. During this time the neural tube folds together; if complete closure or folding of the tube does not occur, an opening remains. Depending on the location of this opening, the type and severity of ONTD varies. An opening lower in the spine is called spina bifida, which can lead to physical and intellectual disabilities. An opening higher in the spine is called anencephaly, which is considered incompatible

with life. The incidence of ONTDs in Canada is 1 in 2,000 births (Prenatal Screening Ontario, 2014).

### CURRENT SCREENING SYSTEM

Clinical practice guidelines indicate that all pregnant women in Canada should be offered the option of prenatal genetic screening. This should be done through an informed counseling process, where non-directive information is provided and client decisions are respected (Chitayat, Langois, & Wilson, 2011). In Ontario, four different screening tests are available, three if the client presents before 14 weeks gestation and one if the client presents after 14 weeks (Prenatal Screening Ontario, 2014). All options involve the measurement of maternal serum biomarkers through a maternal blood sample. This may be accompanied by a second maternal serum sample and/or a nuchal translucency (NT) ultrasound.<sup>1</sup> The level of accuracy of each test varies, with each screen carrying a different detection rate (DR) and false positive rate (FPR). Screens that have a higher DR (proportion of those with the condition with a screen positive result) and a lower FPR (proportion of those without the condition with a screen positive result) are considered superior. The Society of Obstetricians and Gynecologists Canada (SOGC) recommends that the minimum standard of any prenatal screen for Down syndrome offered in Canada should be a DR of 75% and a FPR no greater than 3-5% (Chitayat et. al., 2011). The overall accuracy of the four tests currently offered in Ontario ranges from a DR of 75% - 90% and a FPR of 2% - 10% (Prenatal Screening Ontario, 2014; see Exhibit 1).

The current available screening options that may be offered and are publically funded include:

- **Integrated Prenatal Genetic Screening (IPS):** Has the highest DR and lowest FPR. It involves two maternal serum samples, one in the first trimester (before 14 weeks gestation) and one in the second trimester (after 14 weeks gestation). It also involves an NT ultrasound. Due to its superior accuracy, the majority of women in Ontario undergo this screen (Okun et al., 2014).
- **First Trimester Screening (FTS):** This screen provides the earliest results (first trimester). It involves one maternal serum sample and a NT ultrasound. It has a lower DR and higher FPR than IPS.
- **Serum Integrated Prenatal Screening (SIPS):** This test requires two maternal serum samples, one in the first trimester and one in the second. Few women (2%) in Ontario undergo this screen (Okun et al., 2014), as it does not involve NT ultrasound. This test is mainly used in geographical areas where first trimester ultrasound is not available (Chitayat et. al., 2011).
- **Maternal Serum Screen (Quad screening):** This is a second trimester screen (only screen offered to those over 14 weeks gestation) that involves taking one maternal serum sample. This screen has the highest FPR.

Overall, the uptake rate of screening in Ontario is estimated to be 67% (Okun et al., 2014). The type of screen offered and chosen may depend on geographical location, gestational age, and provider and client preference. In addition to one of the above screens, all pregnant women should be offered a detailed second trimester ultrasound (between 18 and 20 weeks gestation). This ultrasound screens for anatomic abnormalities, including ONTDs, and can be used to modify the known chance of aneuploidy established by prior screening (Chitayat et. al., 2011).

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<sup>1</sup> NT ultrasound is done between 11 and 13 weeks gestation. It measures the thickness of tissue on the back of the fetus's neck, which can be indicative of certain chromosomal conditions. Its use is recommended by the International Society of Prenatal Diagnosis; however, its use depends on geographical location, as some areas within the province do not have access to first trimester scanning expertise.

If a client receives a screen positive on any of these tests, it indicates that the chance of a fetal chromosomal condition or ONTD is higher than the specified cut-off. It does not necessarily mean that the fetus has one of these conditions. The majority of screen positives will be false positives (meaning the fetus does not actually have the condition); however, there is no way of knowing this until the baby is born or diagnostic testing is performed (Prenatal Screening Ontario, 2014). It is estimated that approximately 60% of screen positive women and 1.2% of screen negative women will choose to undergo diagnostic testing (Okun et al., 2014).

### **Diagnostic Testing**

Diagnostic tests are invasive tests that are highly accurate at detecting fetal chromosomal conditions. Clinical practice guidelines indicate that clients who have a screen positive may be eligible for diagnostic testing if they are 35 years of age or older, have a family history of genetic chromosomal conditions, conceived through IVF with intracytoplasmic sperm injection, or have certain ultrasound findings (Prenatal Screening Ontario, 2014; Ministry of Health and Long Term Care, 2012). Two forms of testing exist: amniocentesis and CVS. CVS involves the removal of placental cells in order to analyze fetal genetic material. This procedure is performed between 11 and 13 weeks gestation. It carries a fetal loss risk of 1% and does not test for ONTDs (Prenatal Screening Ontario, 2014). The majority of women do not receive screening results in time for CVS and therefore their only option is amniocentesis (Okun et al., 2014). Amniocentesis is performed between 15 and 22 weeks gestation and involves the removal of amniotic fluid to analyze fetal genetic material. This test carries a slightly lower fetal loss risk (0.01% - 0.5%, Prenatal Screening Ontario, 2014); however, because the procedure occurs at a later gestational age, women may experience increased anxiety and may be at higher risk of complications if choosing to terminate (Vanstone, King, deVrijier, & Nisker, 2014).

## **NEW DEVELOPMENTS IN PRENATAL GENETIC SCREENING**

Advances in technology have led to the development of a new type of prenatal genetic screening. This technology is known as non-invasive prenatal testing (NIPT) and offers the promise of improved accuracy and safety<sup>2</sup> in the screening of Down syndrome. Just like current screening approaches, NIPT involves the analysis of a maternal blood sample. However, instead of analyzing maternal biomarkers (as current approaches do), NIPT analyzes fetal DNA found in maternal blood. This DNA is known as cell-free fetal DNA (cffDNA) and it makes up 10-20% of the maternal plasma (Langois & Brock, 2013). With advanced technology, this DNA can be sequenced and analyzed for certain fetal chromosomal conditions. cffDNA can be detected and analyzed throughout pregnancy, starting as early as ten weeks gestation. Results are generally received within ten days (Vanstone et. al., 2014), opening the window to earlier diagnostic testing (CVS).

Several clinical studies have been published assessing the use of NIPT for the detection of fetal chromosomal conditions. The majority of these studies have focused on the detection of Down syndrome among women with an increased chance of fetal chromosomal conditions. The results of these studies have been consistent, reporting a DR rate reaching 100% and a FPR of <1% (see Exhibit 2; Langois & Brock, 2013). Studies examining the effectiveness of NIPT for the detection of other common fetal chromosomal conditions have also been carried out, with similar results being reported for Trisomy 18 (see Exhibit 3; Langois & Brock, 2013). Overall,

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<sup>2</sup> With improved accuracy, specifically a reduced false positive rate, it is expected that fewer women will undergo unnecessary invasive testing, which is associated with fetal loss.

published results suggest NIPT to be a more accurate screening approach (than the current) for common fetal aneuploidies in high-chance populations (Langois & Brock, 2013; Vanstone et. al., 2014). Studies investigating the applicability of these results in average-chance populations are currently underway (Vanstone et. al., 2014). The largest published study to date, with a cohort of 2049 women, reported a DR of 100% and a FPR of <0.1% for Down syndrome and Trisomy 18 (Nicolaidis, Syngelaki, Ashoor, Birdir, & Touzet, 2012). This suggests the test may be universally appropriate.<sup>3</sup>

As with current screening approaches, although the chance is much lower, the chance of receiving a false positive exists. Because of this, NIPT remains a screening tool and does not replace invasive testing for diagnosis. Those who would consider termination based on a diagnosis are still advised to undergo CVS or amniocentesis for confirmation (Langois & Brock, 2013). In certain situations, women may have to undergo a repeat test due to initial test failure. This can happen in up to 6% of tests (Children's Hospital of Eastern Ontario, 2014), often as a result of poor quality control measures or low fetal fraction (less than 4% cfDNA in maternal blood; Vanstone, et. al., 2014). Low fetal fraction may be a result of early gestation (fetal fraction increases as gestational age increases) or maternal obesity. Other identified limitations of the test include unclear results with multiple gestation pregnancies or chromosomal mosaicism.<sup>4</sup>

### CURRENT INTEGRATION IN ONTARIO

In light of the evidence, the SOGC recommends NIPT be offered to women as a second tier screening option (Langois & Brock, 2013). This means that NIPT should be offered to individuals whose pregnancies have been identified as high-chance (on the basis of current screening modalities) and who wish to continue testing, but avoid invasive testing. Similar recommendations have come from other professional bodies, including the American College of Obstetricians and Gynecologists (American Congress of Obstetricians and Gynecologists, 2012), the National Society of Genetic Counselors (National Society of Genetic Counselors, 2012), and the International Society of Prenatal Diagnosis (Children's Hospital of Eastern Ontario, 2014). Although NIPT is currently an available option to this population of women in Canada, it is expensive, costing more than \$800, and for the most part is only accessible to those who can afford to pay for it (Okun et al., 2014).

In Ontario, the MOHLTC has recently begun supporting the use of NIPT in certain circumstances. These circumstances are limited and are based on specific indications.<sup>5</sup> Eligible providers (genetics or maternal fetal medicine specialists) who believe their client meets the criteria can submit an application for funding to the Ministry.<sup>6</sup> Women who do not qualify for NIPT funding and who wish to have the test must find a provider who is willing to facilitate the process (with blood samples being sent to the U.S. for analysis) and pay out-of-pocket for the service.

### CURRENT CHALLENGES

Jenny Black, Maternal Fetal Medicine Specialist and chair of the PGSG, has experienced applying to the MOHLTC on behalf of clients for funding of NIPT. Receiving variable responses

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<sup>3</sup> The majority of studies use the gold standard of comparing the detection rate of Down syndrome by NIPT with the detection rate by diagnostic testing.

<sup>4</sup> Mosaicism is a condition in which cells within an individual have a different genetic makeup.

<sup>5</sup> Funding eligibility indications may include, in a singleton pregnancy, any one of the following: screen positive result, women > 40 years of age at expected date of delivery, NT > 3.5 mm, pregnancy history or previous child with aneuploidy. Other indications may include: anomalies identified on ultrasound and/or other risk factors (MOHLTC, 2014).

<sup>6</sup> Approval from the ministry must be received prior to receiving the services (MOHLTC, 2014).

from the MOHLTC and having few applications approved, Jenny has not been satisfied with the current process. Discussing her challenges with colleagues, Jenny heard her frustrations being echoed. Following the annual Ontario conference on new developments in prenatal genetics, Jenny met with providers (midwives, family physicians, and genetic counselors) from across the province to discuss their experience with NIPT. From the meeting, Jenny realized that confusion regarding the appropriate use and funding of NIPT in Ontario was strong. Inconsistencies in practice were common, with some providers offering the test to all clients (mainly out of liability concern), while others were just learning of the new technology and had not been offering it at all.

Jenny suspected that much of the confusion and variability in practice was attributable to the rapid emergence of this new technology through the private market. Wanting to support the ministry's vision of a centralized, standardized, high quality screening program for Ontario (Okun et al., 2014), Jenny knew changes to the current system would need to be made. She also knew that the changes would need to be cost-effective, as resources were scarce within the publicly funded system.

### **ECONOMIC EVALUATION<sup>7</sup> OF NIPT INTEGRATION OPTIONS (OKUN et. al., 2014)**

Different scenarios have been proposed for which the Ministry could introduce NIPT into the public system. This includes NIPT as a second-tier contingency screen or NIPT as the primary screen. These scenarios are compared to the current system, where NIPT remains mainly within the private market. Three algorithms (see Exhibit 4) are presented, demonstrating the screening pathway of each scenario. Numbers informing the algorithms and evaluation were retrieved from the provincial Better Outcomes Registry Network (BORN) (fiscal year 2012-2013) and the five Ontario regional laboratories. This includes data on test performance and cost, number of total pregnancies, expected number of cases of Down syndrome, uptake of screening and diagnostic testing, and pregnancy loss rate due to diagnostic testing (see Exhibit 5).

Within each scenario the system performance and costs are analyzed (see Exhibit 6). The performance outcomes analyzed include the total number of cases of Down syndrome detected, the total number of invasive tests (amniocentesis) performed, and the total number of fetal losses (false positive cases) related to invasive testing. The cost outcomes include the total cost of the screening program (up to and including prenatal diagnosis of Down syndrome), the cost per woman screened, and the cost per case of Down syndrome detected.

Overall assumptions within the evaluation include:

- Diagnostic testing may be directly offered to women identified as high-chance for fetal chromosomal conditions;
- Diagnostic testing following primary screening is amniocentesis whereas NIPT is accompanied with a first trimester ultrasound;
- Where contingent NIPT screening follows FTS as the primary screen<sup>8</sup> it is assumed that 100% of those who receive a screen positive after FTS will undergo NIPT and 100% of those who receive a positive result after NIPT will undergo amniocentesis; and

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<sup>7</sup> Information informing this section was retrieved from the economic evaluation conducted by Okun et. al., (2014). This is a recent 2014 Ontario study, with its quality being validated within a critical appraisal by the Canadian Agency for Drugs and Technologies in Health.

<sup>8</sup> FTS is the only screening option that provides results within the first trimester. Using this screen as the primary screen ensures NIPT (if warranted) can be performed within a reasonable time. FTS has a DR of up to 85% and FPR of up to 9%. The high FPR is not of concern as screen positives will be screened with NIPT prior to diagnostic testing. The lower DR however means that fewer cases of Down syndrome may be detected than if IPS were used.

- A provincial lead centre will be established to monitor and evaluate NIPT and therefore an operating cost of \$1,044,000 is added to the scenarios that include publicly funded NIPT.

### 1. NIPT as a Commercial Test

NIPT would remain in the private market, with companies promoting its use directly to the public and providers. Two different models were used to demonstrate this scenario (models 1-2 in Exhibit 6), with one using current FTS/IPS screening modalities and one using FTS as the only screening modality. Based on the evaluation of these models, the total screening costs to the system would range from \$17,353,789-\$17,580,080, with the cost per woman screened being \$179-\$182, and the cost per case of Down syndrome diagnosed being \$112,919-\$114,391. The performance of this scenario includes 3,211-4,247 invasive procedures being performed, 154 cases of Down syndrome being detected, and 31-41 procedure-related fetal losses occurring.

### 2. NIPT as a Contingency Test (second-tier screening)

The use of NIPT as a contingent test would mean it is only offered to individuals based on certain criteria. In this evaluation, NIPT is only offered to women who receive a screen positive following FTS. Five different contingent NIPT models were created (models 4-8 in Exhibit 6). These models depict possible alternatives and are based on the assumption that as technology becomes safer and more accurate the rate of uptake will be higher, the accuracy of FTS will improve with continued research and quality assurance, and the cost of NIPT will decrease over time. Taking the different models into consideration, it is estimated that the total cost of screening to the system will range from \$17,353,081 to \$21,372,742, with the cost per woman screened being \$179-\$208, and the cost per case of Down syndrome diagnosed being \$68,530-\$71,474. The performance of this scenario includes 293-1,358 invasive procedures being performed, 253-337 cases of Down syndrome being detected, and 0-13 procedure-related fetal losses occurring.

### 3. NIPT as the Primary Testing Method

In this scenario (model 3 in Exhibit 6), NIPT would replace the current primary screening options and would be offered to all pregnant women. This scenario is estimated to cost the system a total of \$85,146,250 with the cost per woman screened being \$879, and the cost per case of Down syndrome diagnosed being \$286,428. The performance of this scenario includes 394 invasive procedures being performed, 297 cases of Down syndrome being detected, and 1 procedure-related fetal loss occurring.

## RECOMMENDATION

Based on the evaluation, the introduction of NIPT into the public system would result in more cases of Down syndrome being detected, fewer invasive tests being performed, and fewer related pregnancy losses. However these benefits would come with an increased cost to the healthcare system. NIPT as a primary test (which evidence does not yet fully support, but may relatively soon) significantly increases the cost to the system, costing four to five times more than the current system. NIPT as a contingency test is a more feasible option, costing slightly more than the current system, yet deriving similar benefits to that of the primary approach.

Taking the economic evaluation into consideration, along with other relevant decision-making elements, Jenny, together with the PGSG, needs to make recommendations to the MOHLTC for an improved prenatal genetic screening program in Ontario.

**EXHIBIT 1**  
**Current Prenatal Genetic Screening Options in Ontario**

Tests	Down syndrome DR	Down syndrome FPR	Comments
<b>Integrated Prenatal Screening (IPS)</b> <i>First Trimester (11-13<sup>+6/7</sup> wks)</i> - ↑NT – by registered sonographer - maternal serum: ↓PAPP-A <i>Second Trimester (15-20<sup>+6/7</sup> wks)</i> - maternal serum: ↓AFP, ↑hCG, ↓uE3	85-90%	2-4%	- Results available in 2 <sup>nd</sup> trimester after blood taken - Diagnostic test after counselling for screen positive = amniocentesis
<b>Serum Integrated Prenatal Screening (SIPS)</b> <i>First Trimester (11-13<sup>+6/7</sup> wks)</i> - maternal serum: ↓PAPP-A <i>Second Trimester (15-20<sup>+6/7</sup> wks)</i> - maternal serum: ↓AFP, ↑hCG, ↓uE3, ↑DIA	80-90%	2-7%	- Results available in 2 <sup>nd</sup> trimester after blood taken - Diagnostic test after counselling for screen positive = amniocentesis - Is available in most places where NT ultrasound is not available
<b>(* First Trimester Combined Screening (FTS))</b> <i>First Trimester (11-13<sup>+6/7</sup> wks)</i> - ↑NT – by registered sonographer - maternal serum: ↓PAPP-A, ↑fbhCG	78-85%	3-9%	- Results available in 1 <sup>st</sup> trimester after blood taken – usually end of 1 <sup>st</sup> trimester, earliest results - CVS for diagnostic testing - <b>Does not screen for NTD*</b>

(\* First trimester screening is not available in all areas of Ontario

\* NTDs (open neural tube defects) can be screened for by MS-AFP and/or ultrasound at 18-20 weeks

DR: detection rate – also known as sensitivity, is the probability that a fetus affected with Down syndrome will be detected by the prenatal test

FPR: false positive rate – the proportion of women with unaffected pregnancies who have positive results

↑: increased value

↓: decreased value

Test	Down syndrome DR	Down syndrome FPR	Comments
<b>Maternal Serum Screen (Quadruple Screening – MSS)</b> <i>Second Trimester (15-20<sup>+6/7</sup> wks)</i> - maternal serum: ↓AFP, ↑hCG, ↓uE3, ↓DIA	75-85%	5-10%	- Results available in 2 <sup>nd</sup> trimester - Amniocentesis for diagnostic testing

Source: Prenatal Screening Ontario, 2014b.

EXHIBIT 2

Published Studies Examining the Use of NIPT for the Detection of Down Syndrome

Table 2. Results of validation studies for non-invasive detection of fetal trisomy 21

Study	Number samples tested	Failure rate*	Sequencing approach	Detection rate	False-positive rate
Chiu et al. 2011 <sup>8</sup>	764	1.4%	8-plex shotgun	79.1% (68/86)	1.1%
	232	N/A	2-plex shotgun	100% (86/86)	2.1%
Palomaki et al. 2011 <sup>9</sup>	1696	0.8%	4-plex shotgun	98.6% (209/212) 95% CI 95.9 to 99.7	0.2% 95% CI <0.1 to 0.6
Ehrich et al. 2011 <sup>10</sup>	467	3.9%	4-plex shotgun	100% (39/39) 95% CI 89 to 100	0.2% 95% CI 0.1 to 1.5
Lau et al. 2011 <sup>11</sup>	108	0	12-plex shotgun	100% (11/11)	0
Sehnert et al. 2012 <sup>12</sup>	47	0	1-plex shotgun	100% (13/13)	0
Sparks et al. 2012 <sup>13</sup>	167	0†	96-plex selective	100% (36/36)	0.8%
Ashoor et al. 2012 <sup>14</sup>	400	0.75%	96-plex selective	100% (50/50)	0
Bianchi et al. 2012 <sup>15</sup>	532	3%	6-plex	100% (89/89) 95% CI 95.9 to 100	0
Norton et al. 2012 <sup>16</sup>	3228	4.5%	96-plex selective	100% (81/81) 95% CI 95.5 to 100	0.03% 35% CI 0.002 to 0.2

\*Percentage of samples that did not meet quality control requirements for the sequencing so that no results could be obtained.

†5% failure in their training set.

N/A: not applicable – only samples that passed original sequencing quality control were retested within the 2-plex.

Source: Langois & Brock, 2013 (by permission of The Society of Obstetricians and Gynaecologists of Canada).

**EXHIBIT 3**

**Published Studies Examining the Use of NIPT for the Detection of Trisomy 18**

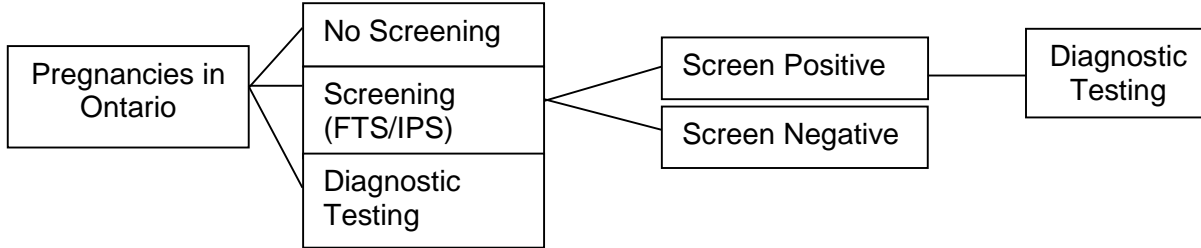
**Table 3. Results of validation studies for non-invasive detection of fetal trisomy**

Study	Sequencing approach	Trisomy 18 detection rate	Trisomy 18 false-positive rate
Lau et al. 2011 <sup>11</sup>	12-plex shotgun	90% (9/10)	0
Sehnert et al. 2012 <sup>12</sup>	1-plex shotgun	100% (8/8)	0
Sparks et al. 2012 <sup>13</sup>	96-plex selective	100% (8/8)	0.8%
Ashoor et al. 2012 <sup>14</sup>	96-plex selective	98% (49/50)	0
Bianchi et al. 2012 <sup>15</sup>	6-plex	97.2% (35/36)	0
Norton et al. 2012 <sup>15</sup>	96-plex selective	97.4% (37/38)	0.07%
Palomaki et al. 2012 <sup>15</sup>	4-plex shotgun	100% (59/59)	0.28%

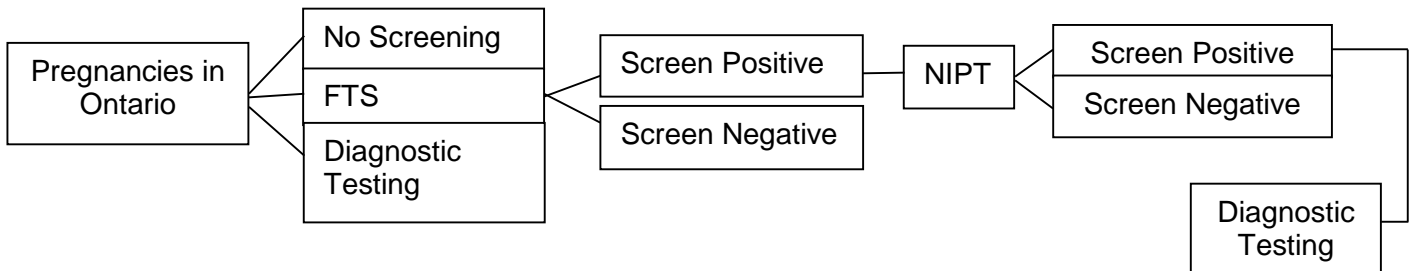
Source: Langois & Brock, 2013 (by permission of The Society of Obstetricians and Gynaecologists of Canada).

**EXHIBIT 4**  
**Algorithms of Screening Pathways**

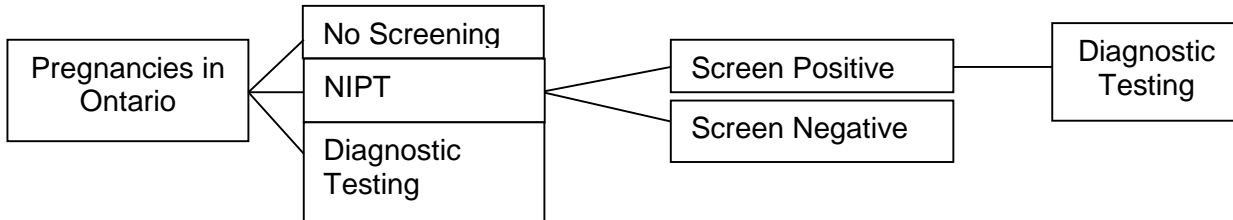
1. Current model



2. Contingent model



3. Primary model



Source: Adapted from Okun et. al., 2014.

**EXHIBIT 5**  
**Evaluation Assumptions**

Table 1 **Background conditions and assumptions for various scenarios of prenatal screening for Down syndrome in Ontario**

Conditions/ assumptions	Current system, No cffDNA (1)	FTS, No cffDNA (2)	Primary cffDNA DS screen (3)	Contingent cffDNA				
				Current FTS performance (4)	Cost recovery (5)	Improved DR (6)	Higher uptake (7)	Optimized FTS (8)
# total pregnancies	144 570	144 570	144 570	144 570	144 570	144 570	144 570	144 570
Expected number of cases of DS	448	448	448	448	448	448	448	448
Uptake of prenatal screening	67%	67%	67%	67%	67%	67%	80%	80%
Number of screened pregnancies	96 862	96 862	96 862	96 862	96 862	96 862	115 656	115 656
Detection rate of IPS/FTS	85%	85%	99%	85%	85%	95%	85%	95%
Positive rate	3.6%	5.4%	0.1%	5.4%	5.4%	11.2%	5.4%	11.2%
Rate of diagnostic testing among screen-positive women	60%	60%	100%	100%	100%	100%	100%	100%
Rate of diagnostic testing among screen-negative or no screening group	1.2%	1.2%	0%	1.2%	1.2%	0%	1.2%	0%
Pregnancy loss rate due to amniocentesis (ref RCT)	1%	1%	1%	1%	1%	1%	1%	1%
Cost of cffDNA test (ref)	—	—	\$795	\$795	\$744	\$795	\$795	\$600

cffDNA, cell-free fetal DNA; FTS, first trimester screening; DS, Down syndrome; DR, detection rate; IPS, integrated prenatal screening.

Source: Okun et. al., 2014 (by permission of John Wiley and Sons and Copyright Clearance Center).

**EXHIBIT 6**  
**Evaluation Outcomes: Models 1-3**

Table 2 Performance and cost outcomes with different modeled scenarios of prenatal screening for Down syndrome in Ontario

Outcomes	Current system, No cffDNA (1)	FTS, No cffDNA (2)	Primary cffDNA DS screen (3) <sup>a</sup>
# amniocentesis performed	3211 <sup>b</sup>	4247 <sup>b</sup>	394 <sup>c</sup>
# prenatal cases of DS detected prenatally	154	154	297
# amniocenteses related losses of non-DS affected pregnancies	31	41	1
Total program cost	\$17 353 789	\$17 580 080	\$85 146 250
Cost/woman screened	\$179	\$182	\$879
Cost/prenatally diagnosed pregnancy with DS	\$112 919	\$114 391	\$286 428
Cost/additional prenatally diagnosed pregnancy with DS	—	—	\$472 139

cffDNA, cell-free DNA; FTS, first trimester screening; DS, Down syndrome.  
<sup>a</sup>Includes cost of first trimester ultrasound.  
<sup>b</sup>Assumes 1.2% of screen-negative women continue to request amniocentesis.  
<sup>c</sup>Assumes only contingent screen-positive women undergo amniocentesis

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**EXHIBIT 7**  
**Evaluation Outcomes: Models 4-8**

Table 3 Performance and cost outcomes with different cell-free fetal DNA contingent modeled scenarios

Outcomes	Contingent cffDNA with current FTS performance (4)	Contingent cffDNA with Cost recovery (5)	Contingent cffDNA with Improved DR (6)	Contingent cffDNA with Higher uptake (7)	Contingent cffDNA with Optimized FTS (8)
# amniocentesis performed	1358 <sup>a</sup>	1358 <sup>a</sup>	293 <sup>b</sup>	1621 <sup>a</sup>	350 <sup>b</sup>
# prenatal cases of DS detected prenatally	253	253	282	302	337
# amniocenteses related losses of non-DS affected pregnancies	11	11	0	13	0
Total program cost	\$17 619 839	\$17 353 081	\$20 184 795	\$20 836 046	\$21 372 742
Cost/woman screened	\$182	\$179	\$208	\$180	\$185
Cost/prenatally diagnosed pregnancy with DS	\$69 583	\$68 530	\$71 474	\$68 913	\$63 383
Cost/additional prenatally diagnosed pregnancy with DS	\$2673	\$0	\$21 933	\$23 423	\$21 900

cffDNA, cell-free DNA; FTS, first trimester screening; DS, Down syndrome.

<sup>a</sup>Assumes 1.2% of screen-negative women continue to request amniocentesis.

<sup>b</sup>Assumes only contingent screen-positive women undergo amniocentesis.

Source: Okun et. al., 2014 (by permission of John Wiley and Sons and Copyright Clearance Center).

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## INSTRUCTOR GUIDANCE

### Deciding Value for Money: Improving Prenatal Genetic Screening in Ontario

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#### BACKGROUND

Since 1993, the Ontario Ministry of Health and Long-Term Care (MOHLTC) has financed prenatal genetic screening through its provincial health insurance plan. In 2013, a new technology became available. Non-invasive prenatal testing (NIPT) promises improved accuracy and screening safety at a higher cost than other screening tests. Since 2013, pregnant women in Ontario have been paying for the test themselves. In March 2014, the Ministry appointed a Prenatal Genetic Screening Group (PGSG), to make recommendations on making NIPT available through the provincial health insurance plan. The Ministry requested an economic evaluation, appraising the value of NIPT.

#### OBJECTIVES

1. Understand the role of economic evaluation in health policy decision-making
2. Critically appraise the quality of an economic evaluation and evaluate its applicability
3. Interpret economic evaluations and use the results to inform policy recommendations
4. Discuss the challenges of interpreting cost-effectiveness analysis as compared to cost-utility analysis
5. Consider broader social, political, and ethical concerns such as equity, quality assurance, allocative efficiency, and appropriate use of screening in making health policy decisions

#### DISCUSSION QUESTIONS

1. How should scarce resources be allocated within a publically funded healthcare system?
2. What type of economic evaluation was performed (cost-minimization, cost-effectiveness, cost-utility, cost-benefit)?
3. How would you appraise the quality of the economic evaluation? Is it adequate for use in policy decision-making?
4. What are the challenges associated with using the cost per case of Down syndrome diagnosed as a measure of value for money? Are there additional analyses you would recommend?
5. What recommendations would you make about NIPT screening based on the results of economic evaluation?
6. Are there important factors not addressed by the economic evaluation?
7. Should the ministry allocate resources to supporting parents of children with Down syndrome?

#### KEYWORDS

Economic evaluation; cost-effectiveness analysis; genetic screening; Down syndrome.