

ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Noninvasive Prenatal Testing for Trisomies 21, 18, and 13, Sex Chromosome Aneuploidies, and Microdeletions: A Health Technology Assessment

KEY MESSAGES

What Is This Health Technology Assessment About?

Anyone who is pregnant has a small chance of having a baby with a chromosomal anomaly. A chromosomal anomaly is a change in the usual structure or number of chromosomes that carry genetic information. Prenatal screening tests check whether a fetus (an unborn baby) has a chromosomal anomaly. Traditional prenatal screening uses a blood test and ultrasound to determine a fetus's risk of certain chromosomal anomalies. More recently, a new screening method called noninvasive prenatal testing has been introduced. It is a blood test that checks the fetus's DNA found in the mother's blood.

At the time of writing this report, noninvasive prenatal testing is publicly funded for people whose pregnancy is at high risk for a chromosomal anomaly (for example, pregnant people over age 40, or those who have had a previous pregnancy with a chromosomal anomaly). Pregnant people at average risk must pay out of pocket if they want the test.

This health technology assessment evaluates how accurate and useful noninvasive prenatal testing is for detecting several chromosomal anomalies in the average-risk or general population, and whether it is good value for money. It also explores the preferences and values of pregnant people, their families, and the parents of children affected by the conditions that noninvasive prenatal testing screens for.

What Did This Health Technology Assessment Find?

Noninvasive prenatal testing was effective for screening in average-risk pregnant people. It was more accurate than traditional prenatal screening, and it decreased the number of diagnostic tests (for example, amniocentesis) performed.

When used as a follow-up screening test after traditional prenatal screening, noninvasive prenatal testing detected more affected fetuses and slightly lowered the overall costs of prenatal screening compared with not using it. But when it was used as the first screening test (that is, instead of traditional prenatal screening), it increased costs substantially.

People who had undergone noninvasive prenatal testing talked about its benefits (more accurate results, no risk to the fetus). However, they raised concerns about the quality of the information people are given for decision-making when the result of testing is positive for a chromosomal anomaly. They also raised ethical concerns about prenatal screening more generally.

HEALTH TECHNOLOGY ASSESSMENT AT HEALTH QUALITY ONTARIO

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The statements, conclusions, and views expressed in this report do not necessarily represent the views of the consulted experts.

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ABSTRACT

Background

Pregnant people have a risk of carrying a fetus affected by a chromosomal anomaly. Prenatal screening is offered to pregnant people to assess their risk. Noninvasive prenatal testing (NIPT) has been introduced clinically, which uses the presence of circulating cell-free fetal DNA in the maternal blood to quantify the risk of a chromosomal anomaly. At the time of writing, NIPT is publicly funded in Ontario for pregnancies at high risk of a chromosomal anomaly.

Methods

We completed a health technology assessment, which included an evaluation of clinical benefits and harms, value for money, budget impact, and patient preferences related to NIPT. We performed a systematic literature search for studies on NIPT for trisomies 21, 18, and 13, sex chromosome aneuploidies, and microdeletions in the average-risk or general population. We evaluated the cost-effectiveness of traditional prenatal screening, NIPT as a second-tier test (performed after traditional prenatal screening), and NIPT as a first-tier test (performed instead of traditional prenatal screening). We also conducted a budget impact analysis to estimate the additional costs of funding first-tier NIPT. We interviewed people who had lived experience with NIPT and people living with the conditions NIPT screens for, or their families.

Results

The pooled clinical sensitivity of NIPT in the average-risk or general population was 99.5% (95% confidence interval [CI] 81.8%–99.9%) for trisomy 21, 93.1% (95% CI 75.9%–98.3%) for trisomy 18, and 92.7% (95% CI 81.6%–99.9%) for trisomy 13. The clinical specificity for any trisomy was 99.9% (95% CI 99.8%–99.9%). Compared with traditional prenatal screening, NIPT was more accurate in detecting trisomies 21, 18, and 13, and decreased the need for diagnostic testing. We found limited evidence on NIPT for sex chromosome aneuploidies or microdeletions in the average-risk or general population. Positive NIPT results should be confirmed by diagnostic testing.

Compared with traditional prenatal screening, second-tier NIPT detected more affected fetuses, substantially reduced the number of diagnostic tests performed, and slightly reduced the total cost of prenatal screening. Compared with second-tier NIPT, first-tier NIPT detected more affected cases, but also led to more diagnostic tests and additional budget of \$35 million per year for average-risk pregnant people in Ontario.

People who had undergone NIPT were largely supportive of the test and the benefits of earlier, more accurate results. However, many discussed the need for improved pre- and post-test counselling and raised concerns about the quality of the information they received from health care providers about the conditions NIPT can screen for.

Conclusions

NIPT is an effective and safe prenatal screening method for trisomies 21, 18, and 13 in the average-risk or general population. Compared with traditional prenatal screening, second-tier NIPT improved the overall performance of prenatal screening and slightly decreased costs. Compared with second-tier NIPT, first-tier NIPT detected more chromosomal anomalies, but resulted in a considerable increase in the total budget. Interviewees were generally positive about NIPT, but they raised concerns about the lack of good informed-choice conversations with primary care providers and the quality of the information they received from health care providers about chromosomal anomalies.

TABLE OF CONTENTS

LIST OF TABLES	8
LIST OF FIGURES	9
OBJECTIVE	10
BACKGROUND	10
Health Condition	10
<i>Chromosomal Aneuploidies</i>	10
<i>Microdeletions</i>	11
Prenatal Screening Options	12
Health Technology Under Review	13
Regulatory Information	14
Ontario, Canadian, and International Context	14
<i>Ontario Context</i>	14
<i>Canadian Context</i>	16
<i>International Context</i>	16
Values and Preferences	16
Guidelines	17
Systematic Reviews	17
Terminology	17
CLINICAL EVIDENCE	18
Research Questions	18
Methods	18
<i>Clinical Literature Search</i>	18
<i>Literature Screening</i>	18
<i>Inclusion Criteria</i>	18
<i>Exclusion Criteria</i>	19
<i>Outcomes of Interest</i>	19
<i>Data Extraction</i>	19
<i>Statistical Analysis</i>	19
<i>Critical Appraisal of Evidence</i>	20
<i>Expert Consultation</i>	20
Results	20
<i>Literature Search</i>	20
<i>Characteristics of Included Primary Studies</i>	22
<i>NIPT Accuracy</i>	26
<i>NIPT Clinical and Personal Utility</i>	31
Discussion	33
<i>NIPT Accuracy</i>	33
<i>NIPT Clinical and Personal Utility</i>	34
<i>Ongoing Studies</i>	35
Conclusions	35
ECONOMIC EVIDENCE	36
Research Question	36

Methods.....	36
<i>Economic Literature Search</i>	36
<i>Literature Screening</i>	36
<i>Inclusion Criteria</i>	36
<i>Exclusion Criteria</i>	36
<i>Outcomes of Interest</i>	37
<i>Data Extraction</i>	37
<i>Study Applicability</i>	37
Results	37
<i>Literature Search</i>	37
<i>Review of Included Economic Studies</i>	39
<i>Applicability of the Included Studies</i>	46
Discussion	46
Conclusions.....	46
PRIMARY ECONOMIC EVALUATION	47
Research Question	47
Methods.....	47
<i>Type of Analysis</i>	47
<i>Target Population</i>	48
<i>Perspective</i>	48
<i>Interventions</i>	48
<i>Discounting and Time Horizon</i>	49
<i>Main Assumptions</i>	49
<i>Model Structure</i>	50
<i>Clinical Outcome Parameters</i>	57
<i>Cost Parameters</i>	63
<i>Analysis</i>	65
Results	67
<i>Reference Case Analysis</i>	67
<i>Scenario Analyses</i>	70
<i>Sensitivity Analysis</i>	80
Discussion	83
<i>Measure of Effectiveness</i>	83
<i>Sex Chromosome Aneuploidies and Microdeletion Syndromes</i>	84
<i>Real-World Performance of Screening Tests</i>	84
<i>Prenatal Screening in Twin Pregnancies</i>	84
<i>Cost of Live Births Affected by Chromosomal Anomalies</i>	84
<i>Health Costs Not Included in the Economic Analysis</i>	85
<i>Study Strengths</i>	85
<i>Study Limitations</i>	85
Conclusions.....	85
BUDGET IMPACT ANALYSIS	86
Research Question	86
Methods.....	86

<i>Analytic Framework</i>	86
<i>Target Population</i>	86
<i>Current and New Screening Scenarios</i>	88
<i>Resource and Costs</i>	88
<i>Analysis</i>	89
<i>Expert Consultation</i>	89
Results	90
<i>Reference Case</i>	90
<i>Scenario Analysis</i>	90
Discussion	92
Conclusions.....	92
PATIENT PREFERENCES AND VALUES	93
Objective	93
Background	93
Methods.....	93
<i>Engagement Plan</i>	93
<i>Outreach Methods</i>	94
<i>Approach</i>	95
<i>Data Extraction and Analysis</i>	95
Results	95
<i>Lived Experience With NIPT</i>	95
<i>Perceived Benefits of NIPT</i>	97
<i>Concerns About NIPT</i>	99
<i>Quality of Information: Support for Informed Decision-Making</i>	102
<i>Ethical Concerns About NIPT</i>	104
<i>Lived Experience With the Conditions Screened For</i>	105
Discussion	106
Conclusions.....	107
CONCLUSIONS OF THE HEALTH TECHNOLOGY ASSESSMENT	108
ABBREVIATIONS	109
GLOSSARY	109
APPENDICES.....	111
Appendix 1: Funding Status of Noninvasive Prenatal Testing in Canada	111
Appendix 2: Guideline Recommendations.....	113
Appendix 3: Systematic Reviews	125
Appendix 4: Literature Search Strategies	126
<i>Clinical Evidence Search</i>	126
<i>Economic Evidence Search</i>	133
<i>Grey Literature Search</i>	141
Appendix 5: Critical Appraisal of Clinical Evidence	142
Appendix 6: Ongoing Studies of Noninvasive Prenatal Testing	145
Appendix 7: Results of Applicability Checklists for Studies Included in the Economic Literature Review	146
Appendix 8: Acceptance Rate for Further Testing After a Positive Screening Result	147
Appendix 9: Letter of Information	148

Appendix 10: Interview Guide 149

REFERENCES150

LIST OF TABLES

Table 1: Common Autosomal and Sex Chromosome Aneuploidies and Microdeletion Syndromes	11
Table 2: Traditional Prenatal Screening and Diagnostic Options Available in Ontario	12
Table 3: Characteristics of Panorama and Harmony Noninvasive Prenatal Tests	15
Table 4: Characteristics of Included Studies on NIPT Accuracy or Clinical Utility	23
Table 5: Characteristics of Included Studies on Health Care Professionals' Understanding of NIPT	25
Table 6: NIPT Accuracy for Trisomies 21, 18, and 13 Versus Traditional Prenatal Screening ...	28
Table 7: NIPT Failure Rate.....	30
Table 8: Health Care Providers' Understanding of NIPT	32
Table 9: Results of Economic Literature Review—Summary.....	41
Table 10: Calculated Approximate Cost and Effectiveness Per 10,000 Pregnant People From Included Studies.....	44
Table 11: Prenatal Screening Pathways for Pregnant People, Summary	49
Table 12: Estimated Prevalence of Chromosomal Anomalies at 12 Weeks of Pregnancy	58
Table 13: Risk of Pregnancy Loss.....	59
Table 14: Accuracy of Prenatal Screening Tests, Reference Case	61
Table 15: Additional Clinical Parameters.....	62
Table 16: Cost Parameters	64
Table 17: Additional Model Inputs Used in the Scenario Analyses	66
Table 18: Reference Case Analysis Results, Costs and Effectiveness for Three Prenatal Screening Strategies ^a	68
Table 19: Reference Case Analysis Results, Cost and Effectiveness Per 10,000 Average-Risk Pregnant People.....	69
Table 20: Reference Case Analysis Results, Incremental Cost, Incremental Effectiveness, and Incremental Cost per Case Detected.....	69
Table 21: Scenario Analysis Results, Inclusion of Sex Chromosome Aneuploidies and 22q11.2 Deletion in First-Tier NIPT	71
Table 22: Scenario Analysis Results, Increased Uptake of First-Tier NIPT	73
Table 23: Scenario Analysis Results, Results From a Cochrane Systematic Review on NIPT Test Accuracy.....	75
Table 24: Scenario Analysis Results, A Lower Trisomy 21 Risk Cutoff for Traditional Prenatal Screening in Second-Tier NIPT	77
Table 25: Scenario Analysis Results, A Subgroup of Pregnant People 35 to 39 Years Old ^a	79
Table 26: Sensitivity Analysis Results, Prenatal Screening Strategies	81
Table 27: Expected Target Population for Prenatal Screening in Ontario	88
Table 28: Total Newborns and Multiple-Gestation Pregnancies in Ontario, 2011/12–2015/16...88	
Table 29: Average Costs for First-Tier and Second-Tier NIPT Per 10,000 Pregnant People89	
Table 30: Budget Impact Analysis Results, Reference Case.....	90
Table 31: Budget Impact Analysis Results, Scenario Analyses	91
Table A1: Funding Status of Noninvasive Prenatal Testing in Canada.....	111
Table A2: Guideline Recommendations for Noninvasive Prenatal Testing	113
Table A3: Systematic Reviews on NIPT in the Average-Risk or General Population	125
Table A4: Risk of Bias ^a Among Diagnostic Accuracy Studies (QUADAS-2 Tool)	142
Table A5: Risk of Bias ^a Among Nonrandomized Trials (ROBINS-I Tool)	143
Table A6: GRADE Evidence Profile for Noninvasive Prenatal Testing	144
Table A7: Ongoing Studies of Noninvasive Prenatal Testing.....	145
Table A8: Assessment of the Applicability of Studies on the Cost-Effectiveness of NIPT	146
Table A9: Acceptance Rate for Further Testing After a Positive Screening Result	147

LIST OF FIGURES

Figure 1: PRISMA Flow Diagram—Clinical Search Strategy	21
Figure 2: NIPT Accuracy for Trisomy 21.....	26
Figure 3: NIPT Accuracy for Trisomy 18.....	26
Figure 4: NIPT Accuracy for Trisomy 13.....	27
Figure 5: PRISMA Flow Diagram—Economic Search Strategy	38
Figure 6: Cost-Effectiveness Analysis, Simplified Process	50
Figure 7: Simplified Pathway, Natural Course of Pregnancy	51
Figure 8: Simplified Pathway, Diagnostic Testing.....	52
Figure 9: Simplified Pathway, Traditional Prenatal Screening Without NIPT	53
Figure 10: Simplified Pathway, Second-Tier NIPT.....	54
Figure 11: Simplified Pathway, First-Tier NIPT.....	56
Figure 12: Estimating the Target Population	87

OBJECTIVE

This health technology assessment looked at the test accuracy, clinical utility, cost-effectiveness, budget impact, and patient experiences of noninvasive prenatal testing (NIPT) for trisomies 21, 18, and 13, sex chromosome aneuploidies, and microdeletions.

This health technology assessment has been registered in PROSPERO, the international prospective register of systematic reviews (CRD42018086261), available at <https://www.crd.york.ac.uk/PROSPERO>.

BACKGROUND

Health Condition

Chromosomes consist of DNA and proteins and carry genetic information in the cells of living organisms. In humans, the correct number of chromosomes is 22 pairs of autosomes (chromosomes that are common to all humans, regardless of sex), plus a 23rd pair of chromosomes that determines biological sex (XX for females and XY for males).

Anyone who is pregnant has a small chance of having a baby with a chromosomal anomaly. Anomalies can include an incorrect number of chromosome copies (called chromosomal aneuploidies), and small missing pieces from chromosomes (called microdeletions). Table 1 lists the most common autosomal and sex chromosome aneuploidies and microdeletion syndromes.

Chromosomal Aneuploidies

Chromosomal aneuploidies are errors in cell division that lead to trisomies (an extra, or third, copy of a chromosome) or monosomies (a lack of a copy of a chromosome).

Trisomies can occur as a result of:

- Nondisjunction (chromosomes do not properly separate in the egg or sperm)
- Translocation (part of a chromosome becomes attached to another during formation of the egg or sperm)
- Mosaicism (an error in cell division during early development of the embryo, resulting in aneuploidy in some cells, but not all)
- Inheritance from a carrier parent

Monosomies occur when a chromosome is partially or completely lost; they can also be mosaic.

The risk of autosomal aneuploidies increases with maternal age. These aneuploidies lead to genetic conditions that are associated with different levels of intellectual disability, developmental delay, dysmorphic features (i.e., differences in body structure), and impairments in body systems. In most cases, they also lead to a shorter life expectancy and increased risk of death. Affected fetuses may also have a higher risk of dying before they are born.

People typically have two sex chromosomes in each cell: females have XX and males have XY. Sex chromosome aneuploidies result from an incorrect number of X and/or Y chromosomes and result in phenotypic variability (i.e., differences in observable characteristics). Sex chromosome aneuploidies are not related to maternal age, except for X chromosome nondisjunction errors, which increase with maternal age. Some people with sex chromosome aneuploidies show few

to no symptoms or signs and may never be diagnosed, leading to underdiagnosis and lower prevalence estimates for these conditions.

Microdeletions

Microdeletion syndromes occur when a small piece of a chromosome is deleted. Chromosomal deletions that involve more than 5 million base pairs (bases are the chemical building blocks of DNA; base pairs are two complementary bases that help connect two complementary strands of DNA) are usually visible under a microscope, but in the case of microdeletions, the changes in genetic material are too small (usually 1 to 3 million base pairs) to be seen without higher-resolution cytogenetic methods. The exact size and location of a clinically relevant microdeletion may vary, but usually a specific critical region is involved. Most phenotypic effects are due to the absence of a few critical genes, or in some cases, a single gene.

The risk of microdeletions is not related to maternal age. Microdeletions can be inherited, occur randomly during formation of the egg or sperm cells, or occur early in fetal development. Microdeletion syndromes are clinically recognized, and have distinct physical, behavioural, and mental characteristics. Similar to sex chromosome aneuploidies, microdeletion syndromes result in phenotypic variability depending on the location and length of the microdeletion.

Table 1: Common Autosomal and Sex Chromosome Aneuploidies and Microdeletion Syndromes

Condition	Common Name(s)	Estimated Prevalence in Newborns
Autosomal Chromosome Aneuploidies		
Trisomy 21	Down syndrome	• 1 in 800 newborns • Most common autosomal chromosome aneuploidy among live births • Frequency is strongly dependent on maternal age
Trisomy 18	Edwards syndrome	• 1 in 5,000 newborns • More common in fetuses that do not survive to term • Frequency increases with maternal age
Trisomy 13	Patau syndrome	• 1 in 16,000 newborns • Frequency increases with maternal age
Sex Chromosome Aneuploidies		
Monosomy X (45, X)	Turner syndrome	• 1 in 2,000–2,500 newborn females • More common in fetuses that do not survive to term
XXY syndrome (47, XXY)	Klinefelter syndrome	• 1 in 500–1,000 newborn males • Most common sex chromosome aneuploidy • Variants are much rarer (e.g., XXXY, XXXXY, XYY, XX male), occurring in 1 in 50,000 or fewer newborn males
Triple X syndrome (47, XXX)	Trisomy X	• 1 in 1,000 newborn females
XYY syndrome (47, XYY)	Jacob's syndrome	• 1 in 1,000 newborn males
Microdeletion Syndromes		
15q11–q13 deletion (loss of function of active genes in regions on chromosome 15)	Prader-Willi syndrome	• 1 in 10,000–30,000 newborns
15q11–q13 deletion (loss of function of gene <i>UBE3A</i> on chromosome 15)	Angelman syndrome	• 1 in 12,000–20,000 newborns
22q11.2 deletion syndrome	DiGeorge syndrome	• 1 in 4,000 newborns
5p deletion syndrome	Cri-du-chat syndrome	• 1 in 20,000–50,000 newborns
1p36 deletion syndrome	Monosomy 1p36	• 1 in 5,000–10,000 newborns

Source: Adapted from the U.S. National Library of Medicine Genetics Home Reference.¹

Prenatal Screening Options

At the time of writing this report, screening for trisomy 21 and 18 is publicly funded in Ontario and available for all pregnant people through either enhanced first-trimester screening (eFTS) or maternal serum screening (MSS, also called quadruple screening; Table 2). The province has phased out previously offered screening options, including first-trimester screening (FTS), integrated prenatal screening (IPS), and serum integrated screening (SIPS).

To generate an overall risk result for trisomy 21 or 18, eFTS and MSS may use a combination of maternal age, ultrasound measurements, and serum biomarkers. The sensitivity of eFTS for trisomy 21 ranges from 85% to 90% (specificity, 94% to 97%).² The sensitivity of MSS for trisomy 21 in the second trimester is 75% to 85% (specificity, 90% to 95%).^{3,4} The sensitivity and false-positive rates for trisomy 21 or 18 may differ slightly depending on the risk cutoff used (the threshold used to determine whether screening tests results are positive [high risk for a chromosomal anomaly] or negative [low risk for a chromosomal anomaly]).

Trisomy 13, sex chromosome aneuploidies, and microdeletion syndromes cannot be detected using the serum biomarkers that are part of traditional prenatal screening. However, because chromosomal anomalies usually lead to anatomical malformations, some may be detected during the 18- to 22-week fetal anatomical ultrasound that is part of standard obstetric care.

Table 2: Traditional Prenatal Screening and Diagnostic Options Available in Ontario

Option	Components	Timing, weeks	Comments
Traditional Prenatal Screening Before 14 Weeks (First Trimester)			
eFTS	One blood test Screens for trisomy 21 and trisomy 18, but <i>not</i> open neural tube defects NT ultrasound	11–13	- Results available in the first trimester after blood is taken (earliest results) - CVS for confirmatory diagnostic testing - Not available in all areas of Ontario
Traditional Prenatal Screening After 14 Weeks (Second Trimester)			
MSS (or quadruple screening)	One blood test Screens for trisomy 21, trisomy 18, and open neural tube defects NT ultrasound is integrated into the test, if available	14–20	- Results available in second trimester - Amniocentesis for confirmatory diagnostic testing
Diagnostic Tests			
CVS	—	11–13	—
Amniocentesis	—	Preferably 15–22	—

Abbreviations: CVS, chorionic villus sampling; eFTS, enhanced first-trimester screening; MSS, maternal serum screening; NT, nuchal translucency. Source: Adapted from *Prenatal Screening Ontario and Trillium Health Partners*.²⁻⁴

Results from prenatal screening cannot be used to diagnose a condition; they provide information about how likely a fetus is to have a chromosomal anomaly. To confirm that the fetus does have a chromosomal anomaly, diagnostic testing (chorionic villus sampling or amniocentesis) is needed. However, many pregnant people are uncomfortable with diagnostic testing because it is invasive, and because it is associated with physical discomfort and the risk (about 1% or less) of procedure-related pregnancy loss.⁵

Health Technology Under Review

In 2011, NIPT became clinically available in the United States and Hong Kong and changed the traditional prenatal screening paradigm. It offers earlier screening than traditional prenatal options, and if used early enough in pregnancy, can avoid the potential harms of invasive diagnostic testing.

Noninvasive prenatal testing is a DNA test of maternal blood that screens pregnancies for common chromosomal anomalies. It uses a blood sample to assess fragments of cell-free fetal DNA that are circulating in the maternal blood. The cell-free DNA in maternal blood consists of approximately 10% DNA from the placenta (so-called “fetal” DNA) and 90% DNA from maternal cells.⁶ Testing can be done as early as 9 to 10 weeks in pregnancy, but it can also be performed up to birth.^{7,8} The results of the test are usually available within 10 days (includes processing and shipment time).^{7,8}

There are two main methods of NIPT. In massively parallel shotgun sequencing (MPSS), short stretches of randomly selected plasma DNA from both the mother and fetus are sequenced. Because the sequence of the entire genome is known, the chromosomal origin of each DNA fragment can be determined, and any small proportional increase in chromosomal fragments due to aneuploidies can be detected. In targeted massively parallel sequencing (TMPS), preselected DNA fragments from chromosomes of interest and a set of reference chromosomes are examined and quantified, instead of looking at all chromosomes.

An adequate amount of cell-free fetal DNA in the maternal blood (fetal fraction) is essential to obtain accurate test results. Many laboratories require a fetal fraction of at least 4% for a reportable result.⁹ Fetal fraction typically increases with advancing gestational age. A failed test (i.e., a “no call” result) can also occur (1% to 8% chance), usually for one of three reasons: issues with blood collection or transportation, low fetal fraction, or assay (analytical test) failure.⁹ When results are not reported, indeterminate, or uninterpretable, it is recommended that the person repeat the test. If the test fails a second time, additional counselling and diagnostic testing are recommended because of an increased risk of aneuploidy.⁹

Different versions of NIPT may report cell-free DNA test results in different ways. Some report risk as “positive” or “negative,” while others use “>99%” as high-risk and “<1/10,000” as average-risk.⁹

Factors that influence NIPT accuracy and discordant or failed results include low fetal fraction, maternal body weight, fetal or maternal mosaicism, a vanishing twin (a fetus in a multiple-gestation pregnancy dies in utero and is partially or completely absorbed by the other fetus, placenta, or mother), or a maternal malignancy.¹⁰⁻¹²

Because NIPT is a maternal blood test, there is no risk of procedure-related pregnancy loss, similar to traditional prenatal screening. A negative NIPT result can allow pregnant people to avoid invasive diagnostic testing, which does carry a small risk of procedure-related pregnancy loss. As with any screening test, the potential disadvantages of NIPT include false-positive and false-negative results, although these rates are typically lower than with traditional prenatal screening (eFTS and MSS). Because NIPT is not a 100% accurate test, downstream harms can occur from subsequent diagnostic testing, which may either confirm or refute positive NIPT results. Negative NIPT results are typically not confirmed. According to clinical practice, a positive result from NIPT should be confirmed by diagnostic testing, such as amniocentesis or chorionic villus sampling, before any irrevocable action is taken.

Noninvasive prenatal testing can be used as a first-tier test (i.e., first screening test done) or as a second-tier test (i.e., test is done after positive results from traditional prenatal screening and before diagnostic testing). However, it is not a comprehensive prenatal testing option. Ultrasound and other serum biomarkers that are part of traditional prenatal screening can detect conditions such as neural tube defects, other fetal structural abnormalities, and placental dysfunction.

Regulatory Information

Noninvasive prenatal testing does not require Health Canada or United States Food and Drug Administration approval, because it is a laboratory-developed test. However, in the United States, certification of the performing laboratory is required under Clinical Laboratory Improvement Amendments regulations to ensure the quality and validity of the test.¹³

Ontario, Canadian, and International Context

Ontario Context

In 2017, 14,217 NIPT tests were performed in Ontario, and 67.5% of those were publicly funded for high-risk pregnant people (9,593 tests; Better Outcomes Registry and Network [BORN] Ontario, March 22, 2018). Noninvasive prenatal testing is publicly funded for pregnant people at high risk for chromosome 21, 18, and 13, and sex chromosome aneuploidies in Ontario under two categories (testing for microdeletions is private-pay only). Any physician may order publicly funded NIPT for people in Category I. Category II is for situations in which additional specialist consultation is necessary to determine whether NIPT is warranted, and to provide appropriate pre- and post-test counselling. Testing for people in Category II must be ordered by a geneticist or maternal–fetal medicine specialist. People must meet any one of the following criteria in either category to be eligible to receive NIPT as a publicly funded test.¹⁴

- Category I (can be ordered by any physician)
 - Maternal age ≥ 40 years at time of delivery
 - Positive maternal serum screen result
 - Nuchal translucency ≥ 3.5 mm on ultrasound
 - Previous pregnancy with a chromosome anomaly
- Category II (must be ordered by a genetics or maternal–fetal medicine specialist)
 - Fetal congenital anomalies identified on ultrasound that are suggestive of trisomy 21, 18, or 13
 - Risk of aneuploidy for trisomies 21, 18, and 13 other than positive maternal multiple marker screen
 - If maternal age is < 40 years at expected date of delivery, must have at least one other risk factor noted
 - Risk of aneuploidy can be calculated by including any combination of risk indicators, including soft markers, biochemistry, maternal age, etc.
 - NIPT for sex chromosome determination for at least one of the following:
 - Risk of sex-limited disorder
 - Ultrasound findings suggestive of a sex chromosome aneuploidy
 - Ultrasound findings suggestive of a disorder of sex determination

At the time of writing this report, only two tests are available for publicly funded NIPT in Ontario: Panorama and Harmony. LifeLabs Genetics offers Natera's Panorama Prenatal Test. Dynacare offers Ariosa Diagnostics' (owned by Hoffmann-La Roche) Harmony test (Table 3).

Table 3: Characteristics of Panorama and Harmony Noninvasive Prenatal Tests

Test Characteristic	Panorama Prenatal Test	Harmony Prenatal Test
Manufacturer	Natera	Ariosa Diagnostics (Roche)
Laboratory availability	LifeLabs	Dynacare
Pregnancy population	Can be performed in consanguineous couples or people who have received a bone marrow transplant Should not be performed in twin pregnancies	Can be performed in twin pregnancies, consanguineous couples, and singleton pregnancies conceived by in vitro fertilization, including egg-donor and surrogate pregnancies Should not be performed in people who have received a bone marrow or organ transplant, or in people who have metastatic cancer
Analysis method	Targeted massively parallel sequencing Single nucleotide polymorphism	Targeted massively parallel sequencing
Sensitivity reported by manufacturer	Trisomy 21: >99.9% Trisomy 18: 96.4% Trisomy 13: >99% Monosomy X: 92.9% 22q11.2 deletion syndrome: 95.7% Microdeletion extended panel (1p36 deletion, 15q11–q13 deletions [Angelman syndrome and Prader-Willi syndrome], 5p deletion): 93.8% to >99%	Trisomy 21: >99% Trisomy 18: 97.4% Trisomy 13: 93.8%
False-positive rate reported by manufacturer ^a	Trisomy 21: 0% Trisomy 18: <0.1% Trisomy 13: 0% Monosomy X: <0.1% Each microdeletion syndrome: <1%	Trisomy 21: <0.1% Trisomy 18: <0.1% Trisomy 13: <0.1%
Test timing	As early as 9 weeks of pregnancy	As early as 10 weeks of pregnancy
Time to result	Within 10 days	Within 10 business days
Out-of-pocket test cost ^b	Trisomies 21, 18, and 13, and sex chromosome aneuploidies: \$550 Plus 22q11.2 deletion: additional \$195 Plus microdeletion extended panel: additional \$245	Trisomies 21, 18, and 13, and sex chromosome aneuploidies: \$495 Plus 22q11.2 deletion: additional \$175

^aSystematic reviews suggest a higher false-positive rate than those reported by the manufacturers.^{15–18} The false-positive rate is also not equivalent to the positive predictive value, which is defined as the probability of a true positive given a positive test result.

^bOut-of-pocket test cost as of April 2018.

Sources: Natera and Roche websites.^{7,8}

Each laboratory offers a special requisition form for ministry-funded NIPT, which must be completed by a physician to be eligible. Average-risk patients (patients who do not meet the ministry's eligibility criteria) must pay out of pocket for either test. Both tests offer detection of fetal aneuploidies for chromosomes 21, 18, and 13, and the sex chromosomes (with sex determination as an option at no additional cost). Natera's Panorama test offers testing for a panel of five microdeletions (22q11.2 deletion, 1p36 deletion, 15q11–q13 deletions [Angelman syndrome and Prader-Willi syndrome], and 5p deletion). In June 2017, Roche announced the addition of 22q11.2 deletion testing as an option for the Harmony test.¹⁹

Noninvasive prenatal testing is publicly funded only for pregnant people at high risk for fetal anomalies, so cost is one of the main barriers to accessing the test for people at average risk. Because NIPT can be performed earlier than any other traditional prenatal screening option (for which the earliest is currently 11 weeks), earlier access to results can allow parents more time to prepare (e.g., to look after an affected child) and to make other decisions about the pregnancy.²⁰ People who pay out of pocket for NIPT may also make subsequent use of public health care resources such as physician visits, genetic counselling, confirmatory diagnostic testing, and other prenatal services, leading to preferential earlier access to related prenatal services.²⁰

Canadian Context

In Canada, five provinces have confirmed public funding for NIPT: Ontario, British Columbia, Manitoba, Prince Edward Island, and Quebec. Quebec's decision to fund NIPT for high-risk pregnant people was announced in early 2018.²¹ Appendix 1 lists the responses received from the provincial and territorial ministry representatives about public funding of NIPT as of 2017. According to a 2016 environmental scan, Alberta, Saskatchewan, Newfoundland and Labrador, and the Northwest Territories have submitted requests for their governments to consider publicly funding NIPT.²²

International Context

In the United States, most pregnant people at high risk for fetal aneuploidy are covered for NIPT by commercial and/or public insurance plans. Some insurance companies, including Blue Cross Blue Shield and Cigna, have expanded their coverage to all pregnant people, although the patient typically still bears a portion of the cost.²³

In January 2016, the United Kingdom National Screening Committee recommended an evaluative implementation of NIPT to assess its impact on the existing National Health System Fetal Anomaly Screening Program.²⁴ The proposed change was to offer NIPT to pregnant people at higher risk following traditional prenatal screening (risk score $\geq 1/150$ for trisomy 21; combined risk score $\geq 1/150$ for trisomies 18 and 13). The committee recommended screening with NIPT for high-risk pregnant people because of the high accuracy of NIPT and the potential to avoid diagnostic testing.

In Europe, a number of countries (Denmark, France, the Netherlands, and Switzerland) fund NIPT as a second-tier (contingent) test.¹⁶ At the time of writing, Belgium is the only country to publicly fund NIPT as a first-tier test (Roche Diagnostics, October 23, 2017; Natera, December 13, 2017). Any physician can order NIPT in Belgium, although it is reimbursed only from 12 weeks' gestation onward.^{25,26}

Values and Preferences

In general, pregnant people have supported NIPT as a positive development in prenatal care.^{27,28} In studies from the Netherlands, the United Kingdom, and the United States, pregnant people have said that they prefer NIPT over traditional prenatal screening or diagnostic testing because of its accuracy, early timing, ease of testing, safety, and comprehensive information.^{27,29-32} People who had NIPT expressed satisfaction with the test and low decisional regret.^{32,33}

The values and preferences of pregnant people may be different from those of health care providers. For example, in Canada, pregnant people placed greater value on test safety and the

comprehensiveness of information, while health care providers placed greater value on accuracy and the timing of the results.³⁴

Concerns have also been raised about informed decision-making and consent. Because NIPT is a convenient blood test, its importance and impact may not be accurately conveyed to patients to allow for proper informed consent (i.e., “routinization” of NIPT).²⁸ There is also concern that the ease of testing may lead to increased pressure to test, and to terminate affected pregnancies, possibly leading to stigma and discrimination against people with disabilities and their families, as well as the belief that fetuses with chromosomal anomalies should be screened out of the population (i.e., eugenic social attitudes).^{28,30,35} Another concern is using NIPT to screen for even more genetic conditions with variable phenotype without having adequate informed-choice conversations with pregnant people and their families.”

Guidelines

Numerous guidelines have provided recommendations on the use of NIPT from different disciplines, such as gynecology and obstetrics, medical genetics, and genetic counselling (Appendix 2). The Society of Obstetricians and Gynaecologists of Canada and the Canadian College of Medical Geneticists published an update in 2017 on prenatal screening for fetal aneuploidy, which notes that NIPT is a highly effective screening test for trisomies 21, 18, and 13, and should be offered as a possible screening option where available in Canada (or with the understanding that it may not be publicly funded).³⁶

Some guidelines acknowledge that NIPT is an effective screening strategy as a second-tier test, but many have commented on the lack of data for NIPT as a first-tier test in the general population. None of the guidelines recommend NIPT as a first-tier screening test for sex chromosome aneuploidies or microdeletion syndromes. Other common themes in the guideline recommendations include the importance of patient choice for prenatal screening or testing, obtaining informed consent, and appropriate counselling on prenatal testing and the possible test results. A guideline on best ethical practices for clinicians who provide NIPT, and for manufacturers who offer NIPT, was published in 2013.³⁷

Systematic Reviews

A number of systematic reviews and meta-analyses have been conducted on the accuracy of NIPT for trisomies 21, 18, and 13, and sex chromosome aneuploidies, but most have focused on the high-risk population, where much of the published literature exists.³⁸⁻⁴² Only a few have performed analyses for the average-risk or general population (see Appendix 3 for a summary).¹⁵⁻¹⁸ These systematic reviews differed in their definitions of the general pregnancy population, and some focused only on trisomies 21, 18, and 13, while others also included sex chromosome aneuploidies.

We found no systematic reviews that included test accuracy for microdeletion syndromes, and none that specifically examined the clinical utility of NIPT. As well, we did not find a health technology assessment that addressed all of our research questions. Because the systematic reviews did not fit our specific purpose in this health technology assessment, and no other fully relevant health technology was found, we undertook our own review of primary studies.

Terminology

In this health technology assessment, *average risk* and *high risk* refer to pregnancies at average or high risk for a chromosomal anomaly (not risk of pregnancy complications).

CLINICAL EVIDENCE

Research Questions

1. What is the diagnostic accuracy and clinical and personal utility of noninvasive prenatal testing (NIPT) for trisomies 21, 18, and 13, sex chromosome aneuploidies, and microdeletions in the average-risk or general population?
2. What is the comparative accuracy between different NIPT methods in the average-risk or general population?
3. What is health care providers' understanding of NIPT?

Methods

We developed the research questions in consultation with health care providers, clinical experts, and other health system stakeholders.

Clinical Literature Search

We performed a literature search on September 11, 2017, to retrieve studies published from January 1, 2007, to the search date. We used the Ovid interface in the following databases: MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Health Technology Assessment, and National Health Service Economic Evaluation Database (NHS EED). We used the EBSCOhost interface to search the Cumulative Index to Nursing & Allied Health Literature (CINAHL).

Medical librarians developed the search strategy using controlled vocabulary (i.e., Medical Subject Headings) and relevant keywords. The final search strategy was peer-reviewed using the PRESS Checklist.⁴³ We created database auto-alerts in MEDLINE, Embase, and CINAHL and monitored them until April 2018.

We performed targeted grey literature searching of health technology assessment agency sites and clinical trial registries. See Appendix 4 for literature search strategies, including all search terms.

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using DistillerSR management software, and then obtained the full text of studies that appeared eligible for the review according to the inclusion criteria. The author then examined the full-text articles and selected studies that were eligible for inclusion. We also examined reference lists for any additional relevant studies not identified through the search.

Inclusion Criteria

- English-language full-text publications
- Studies published between January 1, 2007, and September 11, 2017
- Randomized controlled trials, cohort studies, or case-control studies
- Comparative and noncomparative diagnostic accuracy studies and clinical utility studies on NIPT for the average-risk or general population
- Comparative diagnostic accuracy studies of two different methods of NIPT in the average-risk or general population
- Studies on health care providers' understanding of NIPT

Exclusion Criteria

- Studies including mixed-risk pregnant people (i.e., mixed average-risk and high-risk that were not representative of a general population)
- Systematic reviews, meta-analyses, editorials, case reports, conference abstracts, or commentaries
- Animal and in vitro studies
- Studies where outcomes of interest could not be extracted (e.g., incomplete 2 × 2 table for test accuracy)

Outcomes of Interest

- NIPT accuracy
 - Sensitivity and specificity
 - Positive predictive value (i.e., the probability that someone with a positive test result truly has an affected fetus), negative predictive value (i.e., the probability that someone with a negative test result truly does not have an affected fetus)
 - Test failures and inconclusive results, and associated true results
- NIPT clinical utility
 - Reductions in diagnostic testing (diagnostic tests avoided)
 - Diagnostic-testing-related adverse events for the pregnant person or fetus
 - Differences in pregnancy outcomes
 - Test turnaround time
 - Uptake rate of NIPT (percentage of people who choose to receive NIPT)
 - Health care providers' understanding of NIPT
- NIPT personal utility
 - Differences in pregnant people's pregnancy decision-making
 - Maternal or parental psychological effects (e.g., depression, anxiety)
 - Maternal/parental education and satisfaction

Data Extraction

We extracted relevant data on study characteristics and risk-of-bias items using a data form to collect information about the following:

- Study characteristics (e.g., study primary author, year, country, source of funding, study sponsors)
- Methods (e.g., study design, inclusion/exclusion criteria, patient characteristics, length of follow-up; details on the index test, comparator, and reference standard)
- Outcomes (e.g., outcomes measured, number of participants for each outcome, outcome definition, time points at which the outcome was assessed, covariates considered, loss to follow-up, and associated reasons)

We contacted authors of the studies to provide clarification as needed.

Statistical Analysis

We conducted statistical analyses for test accuracy using Stata version 13 (Stata Statistical Software, StataCorp, College Station, Texas). We used a bivariate random-effects model to pool study sensitivities and specificities and their corresponding 95% confidence intervals. If the model failed to converge, we used two univariate random-effects models, as recommended by

Takwoingi et al.⁴⁴ We created forest plots for NIPT accuracy using Review Manager version 5.3.⁴⁵ Where meta-analysis was not appropriate because of clinical or statistical heterogeneity, we undertook a narrative synthesis of the results.

Critical Appraisal of Evidence

We assessed risk of bias for NIPT accuracy using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool (Appendix 5).⁴⁶ For studies that reported patient clinical utility outcomes, we used the Cochrane Risk of Bias tool⁴⁷ for randomized controlled trials and the Risk of Bias in Non-randomized Studies—of Interventions (ROBINS-I) tool for nonrandomized studies.⁴⁸

We evaluated the quality of the body of evidence for each outcome according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Handbook.⁴⁹ The body of evidence was assessed based on the following considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The quality score reflects our assessment of the reliability of the evidence.

Expert Consultation

We solicited expert feedback on NIPT. The consultation included experts in medical genetics, fetal medicine, primary care, genetic counselling, prenatal health care services, laboratory medicine, methodology, and industry. The role of the expert advisers was to help define the scope and research question, contextualize the evidence, review the draft report, and provide advice on NIPT and its use in Ontario.

Results

Literature Search

The literature search yielded 2,059 citations published between January 1, 2007, and September 11, 2017, after removing duplicates. We identified nine citations through other sources: eight from the grey literature during the literature search, and one from experts after the search date.

Eight studies on test accuracy and clinical utility met the inclusion criteria. Another seven survey studies on health care providers' understanding of NIPT were found. We included the additional study identified after the search date.

We found no studies on the accuracy or utility of NIPT for microdeletions or on the comparative diagnostic accuracy of NIPT methods in the average-risk or general pregnant population. We found no studies that reported on clinical outcomes for affected infants for any of the chromosomal anomalies of interest, diagnostic-testing-related adverse events for the pregnant person or fetus, or differences in the psychological effects of NIPT for the average-risk or general population.

Figure 1 presents the flow diagram for the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).

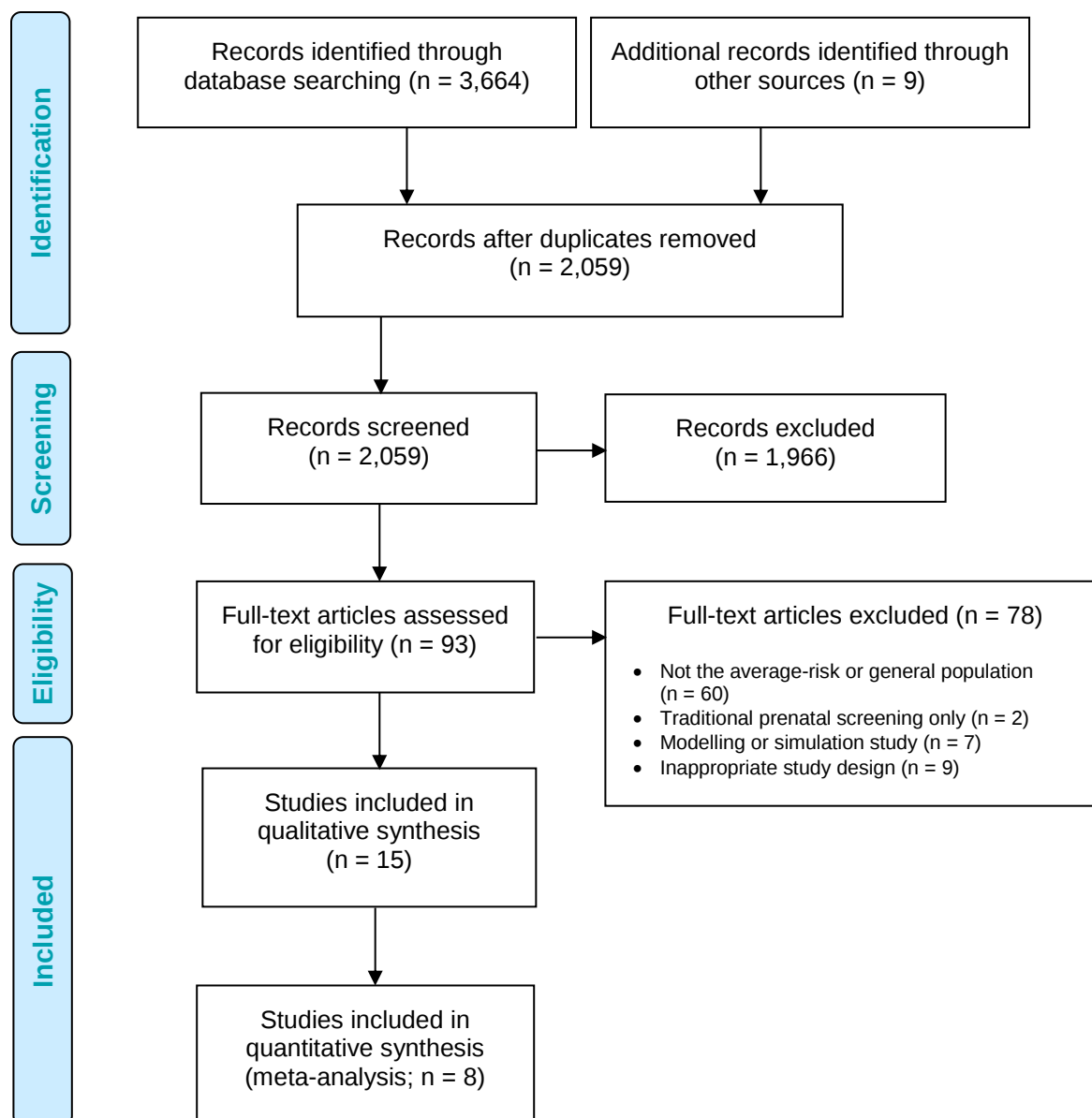


Figure 1: PRISMA Flow Diagram—Clinical Search Strategy

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
 Source: Adapted from Moher et al.⁵⁰

Characteristics of Included Primary Studies

Tables 4 and 5 summarize the characteristics of the included primary studies. We found eight test accuracy studies,⁵¹⁻⁵⁸ five^{51,53,55,57,58} of which were comparative and included a traditional prenatal screening option. However, the type of traditional prenatal screening varied across studies, as did the cutoffs to categorize results as high-risk or average-risk. Only one study assessed maternal satisfaction and education.⁵⁶ Another seven explored health care providers' understanding of NIPT.⁵⁹⁻⁶⁵

The test accuracy studies included pregnant people of different gestational ages. Song et al⁵⁸ followed pregnant people < 35 years of age. Six studies followed a general unselected population (without a priori risk).^{51-55,57} Palomaki et al⁵⁶ included a general pregnancy primary screening population, but a small number of participants were considered to be high-risk. The authors noted that this composition would reflect a routinely screened general population.

Versions of NIPT varied between studies, with most using the Harmony test. Two studies included NIPT versions that are not available in Canada: the Verifi prenatal test and a version of the Illumina platform.^{51,58} The reference standard for all test accuracy studies included karyotyping from diagnostic testing (chorionic villus sampling or amniocentesis). Negative screening results were followed up by neonate examination, cord blood, or the birth medical record.

Two of the test accuracy studies were funded by industry.^{51,55} An additional four accuracy studies involved industry funds (in most cases for the cost of the NIPT testing and result analysis), but stated that industry was not involved in conducting the study.^{52-54,56}

Among the test accuracy studies, risk of bias was often high because of concerns relating to patient selection and flow and timing. Studies were often unclear about the method of patient enrolment (e.g., whether enrolment was random or consecutive), and did not always include all patients in the analyses. The full risk-of-bias assessment can be found in Appendix 5.

We found seven studies evaluating health care providers' knowledge of NIPT.⁵⁹⁻⁶⁵ All studies were cross-sectional surveys and were conducted in the United States, except for one study that was from New Zealand.⁶⁰ All studies evaluated the knowledge of obstetricians, gynecologists, or maternal–fetal medicine specialists.

Table 4: Characteristics of Included Studies on NIPT Accuracy or Clinical Utility

Author, Year, Country	N	Study Design	Inclusion Criteria	Conditions Tested	NIPT Method, Index Test	Reference Standard(s)	Study Funding
Comparative Studies							
Bianchi et al, 2014, ⁵¹ United States	2,052	Prospective, comparative	Pregnant people ≥ 18 years old, ≥ 8 weeks' gestation Exclusion: people who had diagnostic testing within 2 weeks prior to enrolment, or had only NT ultrasound	Trisomies 21, 18, and 13	Verifi test, MPSS	Fetal karyotype Neonate examination Birth medical record	Illumina, Inc.
Langlois et al, 2017, ⁵³ Canada	1,165	Prospective, comparative	Pregnant people ≥ 19 years old, singleton pregnancy, < 14 weeks' gestation	Trisomies 21, 18, and 13	Harmony test, TMPS	Fetal karyotype Neonate examination Birth medical record	Genome Canada, Quebec, British Columbia, and Alberta Quebec ministry Ariosa Diagnostics (arms' length)
Norton et al, 2015, ⁵⁵ International	18,955	Prospective, comparative	Pregnant people ≥ 18 years old, 10–14 weeks' gestation Exclusion: people who had a pregnancy loss, or chose to terminate with confirmatory diagnostic testing	Trisomies 21, 18, and 13, other aneuploidies	Harmony test, TMPS	Fetal karyotype Neonate examination Birth medical record	Ariosa Diagnostics Perinatal Quality Foundation
Quezada et al, 2015, ⁵⁷ United Kingdom	2,905	Prospective, comparative	Pregnant people 10–11 weeks' gestation, singleton pregnancy, who had combined test	Trisomies 21, 18, and 13	Harmony test, TMPS	Fetal karyotype	Fetal Medicine Foundation
Song et al, 2013, ⁵⁸ China	1,916	Prospective, comparative	Pregnant people < 35 years old, singleton pregnancies No a priori risk of aneuploidy and undergoing routine prenatal screening	Trisomies 21, 18, and 13, sex chromosome aneuploidies	Illumina HiSeq platform, MPSS	Fetal karyotype Cord blood Birth medical record	Chinese National Key Technology Research and Development Program

Author, Year, Country	N	Study Design	Inclusion Criteria	Conditions Tested	NIPT Method, Index Test	Reference Standard(s)	Study Funding
Noncomparative Studies							
del Mar Gil et al, 2014, ⁵² United Kingdom	207	Retrospective, noncomparative	Pregnant people without a priori risk, undergoing first-trimester screening, twin pregnancies, 11–13 weeks' gestation	Trisomies 21, 18, and 13	Harmony test, TMPS	Fetal karyotype	Fetal Medicine Foundation Ariosa Diagnostics (provided test and analysis only)
Nicolaides et al, 2012, ⁵⁴ United Kingdom	2,230	Retrospective, noncomparative	Pregnant people 11–13.9 weeks' gestation, singleton pregnancy, archived sample ≥ 2 mL	Trisomies 21 and 18	Harmony test, TMPS	Fetal karyotype Neonate examination	Fetal Medicine Foundation Ariosa Diagnostics (provided test and analysis only)
Palomaki et al, 2017, ⁵⁶ United States	2,691	Prospective, noncomparative	Pregnant people ≥ 10 weeks' gestation, satisfy inclusion criteria for Panorama test	Trisomies 21, 18, and 13, monosomy X	Panorama test, TMPS	Fetal karyotype Newborn karyotype and examination	Natera, Inc. (no involvement)

Abbreviations: MPSS, massively parallel shotgun sequencing; NIPT, noninvasive prenatal testing; NT, nuchal translucency; TMPS, targeted massively parallel sequencing.

Table 5: Characteristics of Included Studies on Health Care Professionals' Understanding of NIPT

Author, Year, Country	N	Response Rate	Survey Method	Health Care Providers	Study Funding
Brewer et al, 2016, ⁵⁹ United States	103	20.6%	Online survey sent to health care providers within a database for qualitative and quantitative research	Obstetricians	Ariosa Diagnostics
Filoché et al, 2017, ⁶⁰ New Zealand	134	32%	Online survey sent to New Zealand–based Royal Australian and New Zealand Committee of Obstetricians and Gynaecologists members	Obstetricians and gynecologists	Lotteries Health Research—Te Tahua Rangahau Hauoratanga
Haymon et al, 2014, ⁶¹ United States	278	18.5%	Online survey sent to database of maternal–fetal medicine specialists	Maternal–fetal medicine specialists	Northwestern University Genetic Counseling Graduate Program, Center for Genetic Medicine of the Feinberg School of Medicine
Mayes et al, 2016, ⁶² United States	985	78%	Survey of physicians in the obstetrical department at University of Texas Graduate School of Biomedical Science	Obstetricians and gynecologists	Not reported
Musci et al, 2013, ⁶³ United States	101	11.2%	Online survey sent to database of 900 obstetrician-gynecologists	Obstetricians and gynecologists	Ariosa Diagnostics
Sayres et al, 2011, ⁶⁴ United States	62	34%	Paper survey distributed at continuing education course on obstetrics and gynecology	Obstetricians and gynecologists	Center for Integrating Ethics and Genetics Research grant
Swaney et al, 2016, ⁶⁵ United States	160	42.3%	Online survey to database of United States maternal–fetal medicine fellows who are members of the Society of Maternal-Fetal Medicine	Maternal–fetal medicine fellows	None

Abbreviation: NIPT, noninvasive prenatal testing.

NIPT Accuracy

NIPT Accuracy for Trisomies 21, 18, and 13

NIPT accuracy was evaluated in 8 studies (Figures 2, 3, and 4).⁵¹⁻⁵⁸ Sensitivity ranged from 90% to 100% for trisomy 21, 90% to 100% for trisomy 18, and 40% to 100% for trisomy 13.

Sensitivity was most consistent for trisomy 21; ranges in sensitivity for trisomies 18 and 13 were more variable across studies. Because of the low prevalence of the three conditions, sensitivity was greatly influenced by the number of (rare) false negatives. Specificity for any of the three trisomies remained high at $\geq 99.9\%$, indicating the ability of NIPT to accurately identify pregnant people who have an unaffected fetus. The reference standards used in the studies included fetal karyotype, neonate examination, cord blood, and birth records.

The pooled sensitivities for NIPT were 99.5% (95% confidence interval [CI], 81.8%–99.9%) for trisomy 21, 93.1% (95% CI, 75.9%–98.3%) for trisomy 18, and 92.7% (95% CI, 81.6%–99.9%) for trisomy 13. The pooled specificity for all three trisomies was 99.9% (95% CI, 99.8%–100%).

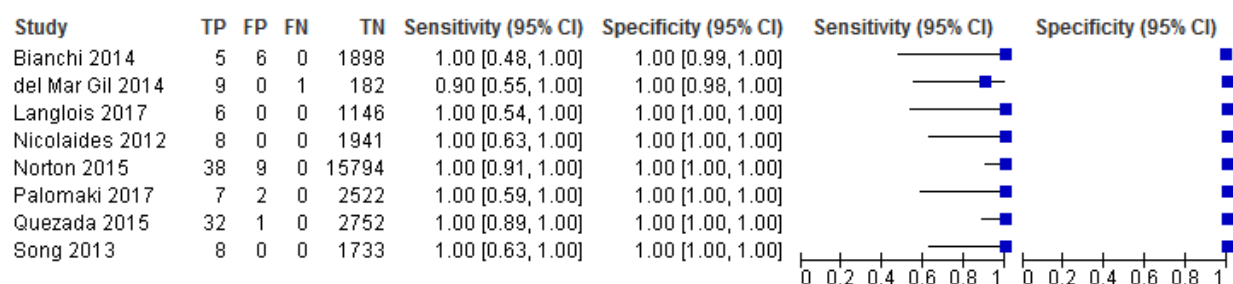


Figure 2: NIPT Accuracy for Trisomy 21

Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; NIPT, noninvasive prenatal testing; TN, true negative; TP, true positive.

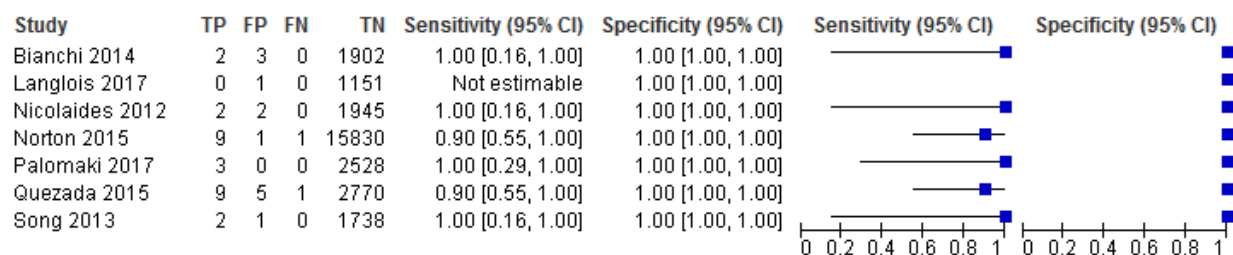
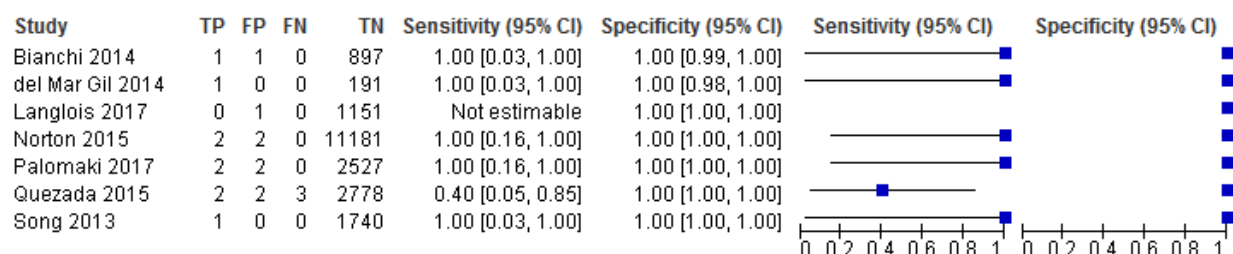


Figure 3: NIPT Accuracy for Trisomy 18

Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; NIPT, noninvasive prenatal testing; TN, true negative; TP, true positive.

**Figure 4: NIPT Accuracy for Trisomy 13**

Abbreviations: CI, confidence interval; FN, false negative; FP, false positive; NIPT, noninvasive prenatal testing; TN, true negative; TP, true positive.

While diagnostic accuracy studies generally start at high GRADE, we downgraded the evidence in the risk of bias domain for trisomies 21, 18, and 13 because of concerns with patient selection and flow and timing in most studies. Many of the studies did not specify whether patients were consecutively or randomly enrolled, or did not include all patients in the analysis. For trisomy 18 and 13, we further downgraded the GRADE because of imprecision.

The positive predictive value ranged from 45.5% to 100% for trisomy 21, 40% to 100% for trisomy 18, and 50% to 100% for trisomy 13 for the individual studies. The negative predictive value in all studies was 99.9% to 100% for all three trisomies.

NIPT Accuracy for Trisomies 21, 18, and 13 Versus Traditional Prenatal Screening

Five studies compared NIPT with traditional prenatal testing (Table 6).^{51,53,55,57,58} We did not pool the results because of differences in traditional prenatal testing options (e.g., different timing of screening and serum biomarkers) and thresholds used. Risk thresholds for positive results with traditional prenatal screening were variable in two studies, determined by either individual laboratories⁵¹ or provincial programs.⁵³ The other two studies had predetermined thresholds: 1:270 for all conditions in Song et al.⁵⁸ and 1:270 for trisomy 21 and 1:150 for trisomies 18 and 13 in Norton et al.⁵⁵ However, despite these differences in traditional prenatal screening, NIPT was more accurate (improved specificity, and in almost all studies, also higher sensitivity) than traditional prenatal screening in detecting trisomies 21, 18, and 13 in all studies. Song et al.⁵⁸ did not report separate accuracy results for trisomy 21, 18, or 13, instead reporting a combined result. The reference standards used were fetal karyotype, cord blood, or birth medical record.

Table 6: NIPT Accuracy for Trisomies 21, 18, and 13 Versus Traditional Prenatal Screening

Author, Year	Traditional Prenatal Screening Method	Traditional Trisomy 21 (95% CI)	NIPT Trisomy 21 (95% CI)	Traditional Trisomy 18 (95% CI)	NIPT Trisomy 18 (95% CI)	Traditional Trisomy 13 (95% CI)	NIPT Trisomy 13 (95% CI)
Bianchi et al, 2014 ⁵¹	First-trimester PAPP-A and total hCG or β -hCG Second-trimester α -fetoprotein, hCG, unconjugated estriol, inhibin-A, with or without NT	Sensitivity: 100% (29.2%–100%) FPR: 3.6% (2.8%–4.6%)	Sensitivity: 100% (47.8%–100%) FPR: 0.3% (0.1%–0.7%)	Sensitivity: 100% (2.5%–100%) FPR: 0.6% (0.1%–0.3%)	Sensitivity: 100% (15.8%–100%) FPR: 0.2% (0%–0.4%)	Not reported	Sensitivity: 100% (20.7%–100%) FPR: 0.2% (0.1%–0.5%)
Langlois et al, 2017 ⁵³	First-trimester PAPP-A, free β -hCG, NT First-trimester PAPP-A, second-trimester α -fetoprotein, hCG, unconjugated estriol, inhibin-A, with or without NT	Sensitivity: 83% (36%–99%) FPR: 5.4% (4.2%–6.9%)	Sensitivity: 100% (54%–100%) FPR: 0% (0%–0.3%)	Not reported	Not reported	Not reported	Not reported
Norton et al, 2015 ⁵⁵	PAPP-A, total hCG or β -hCG, NT	Sensitivity: 78.9% (62.7%–90.4%) FPR: 5.4% (5.1%–5.8%)	Sensitivity: 100% (90.7%–100%) FPR: 0.06% (0.03%–0.11%)	Sensitivity: 80.0% (44.4%–97.5%) FPR: 0% (0%–0.1%)	Sensitivity: 90% (55.5%–99.7%) FPR: 0.3% (0.2%–0.4%)	Sensitivity: 50% (1.2%–98.7%) FPR: 0.3% (0.2%–0.4%)	Sensitivity: 100% (15.8%–100%) FPR: 0% (0%–0.1%)
Quezada et al, 2015 ⁵⁷	PAPP-A, β -hCG, fetal crown–rump length, NT	Sensitivity: 100% (93%–100%) FPR: 4% (4%–5%)	Sensitivity: 100% (89.3%–100%) FPR: 0.1% (0%–0.2%)	Sensitivity: 100% (93%–100%) FPR: 4% (4%–5%)	Sensitivity: 90% (59.6%–98.2%) FPR: 0.2% (0.1%–0.4%)	Sensitivity: 100% (93%–100%) FPR: 4% (4%–5%)	Sensitivity: 40% (11.8%–76.9%) FPR: 0.1% (0%–0.1%)
Song et al, 2013 ⁵⁸	Second-trimester α -fetoprotein, free β -hCG, unconjugated estriol	Sensitivity: 55% (23%–83%) ^a FPR: 14% (12%–16%)	Sensitivity: 100% (59.8%–100%) FPR: 0% (0%–0.3%)	Sensitivity: 55% (23%–83%) ^a FPR: 14% (12%–16%)	Sensitivity: 100% (19.8%–100%) FPR: 0.1% (0.1%–0.4%)	Sensitivity: 55% (23%–83%) ^a FPR: 14% (12%–16%)	Sensitivity: 100% (5.5%–100%) FPR: 0% (0%–0.3%)

Abbreviations: CI, confidence interval; FPR, false-positive rate; hCG, human chorionic gonadotropin; NIPT, noninvasive prenatal testing; NT, nuchal translucency; PAPP-A, pregnancy-associated plasma protein A.

^aCombined test accuracy for trisomy 21, 18, and 13.

NIPT Accuracy for Sex Chromosome Aneuploidies

One study evaluated the accuracy of NIPT for monosomy X and XXY syndrome in addition to trisomies 21, 18, and 13.⁵⁸ For monosomy X, sensitivity was 50% (95% CI, 9.2%–90.8%) and the false-positive rate was 0% (95% CI, 0%–0.1%).⁵⁸ For XXY syndrome, the false-positive rate was 0.1% (95% CI, 0.1%–0.4%), but sensitivity could not be determined because no true XXY syndrome cases were detected in the study population.⁵⁸

The authors also compared the combined performance of NIPT for trisomies 21, 18, and 13, and sex chromosome aneuploidies versus traditional prenatal screening. They found that NIPT performed substantially better than traditional prenatal testing, with a sensitivity of 86.7% (95% CI, 58.4%–97.7%) and a false-positive rate of 0.1% (95% CI, 0.1%–0.5%) for NIPT, compared with a sensitivity of 40.0% (95% CI, 17.5%–67.1%) and a false-positive rate of 14.1% (95% CI, 12.5%–15.8%) for traditional prenatal screening.⁵⁸

NIPT Accuracy for Microdeletions

We found no studies that investigated the accuracy or utility of NIPT for the microdeletions of interest in the average-risk or general pregnant population.

NIPT Failure Rate

Seven studies reported NIPT test failures (Table 7).^{51,53–58} Failures for the initial NIPT test performed ranged from 0.9% to 5.6% among the studies; low fetal fraction was one of the most common reasons for failure. Among studies that performed a second NIPT test, the success rate ranged from 45% to 77%.^{53,56,57} Palomaki et al⁵⁶ noted higher failure rates among samples collected at 10 weeks compared to samples collected at 11 to 21 weeks (relative risk, 2.5%; 95% CI, 1.3%–4.5%; $P = .007$). Maternal weight was often associated with test failure in studies. As well, DNA failures were confirmed to be strongly associated with maternal weight ≥ 80 kg (relative risk, 11.4; 95% CI, 6.3–21; $P < .001$).⁵⁶ Langlois et al⁵³ similarly noted that maternal weight was ≥ 70 kg in 8 of 11 people who failed the initial NIPT test. In Norton et al,⁵⁵ the median maternal weight in people with a low fetal fraction was 93.7 kg, compared with 65.8 kg in people with a successful NIPT result ($P < .001$).

Table 7: NIPT Failure Rate

Author, Year	Initial NIPT Test	Repeat NIPT Test	True Status Among Failures
Bianchi et al, 2014 ⁵¹	0.9% (18/1,970) 50% (9/18) during cell-free DNA extraction 50% (9/18) during sequencing - No clear reason for failures	None	Not reported
Langlois et al, 2017 ⁵³	0.9% (11/1,165) 90.9% (10/11) low fetal fraction 9.1% (1/11) unusually high variance in cell-free DNA count	Repeat NIPT test: 45.5% (5/11) success	3/11 triploidy 3/11 normal
Nicolaides et al, 2012 ⁵⁴	4.9% (100/2,049) 46.0% (46/100) low fetal fraction 54.0% (54/100) assay failure	None	Not reported
Norton et al, 2015 ⁵⁵	3.0% (488/16,329) 39.3% (192/488) low fetal fraction 17.0% (83/488) fetal fraction could not be measured 43.6% (213/488) high assay variance or failure	None	13/488 aneuploidy
Palomaki et al, 2017 ⁵⁶	5.6% (150/2,681) 93.3% (140/150) complete test failure 6.7% (10/150) partial test failure	Repeat NIPT test: 76.5% (65/85) success	0 trisomy 21, 18, or 13
Quezada et al, 2015 ⁵⁷	4.2% (123/2,905) 30.9% (38/123) low fetal fraction 12.2% (15/123) assay failure 0.8% (1/123) sample not received by laboratory	Repeat NIPT test: 62.7% (69/110) success	49/54 normal 2/54 trisomy 21 3/54 pregnancy loss with no karyotype
Song et al, 2013 ⁵⁸	3.8% (73/1,916) 65.8% (48/73) failed DNA quality control 34.2% (25/73) failed sequencing quality control	None	Not reported

Abbreviation: NIPT, noninvasive prenatal testing.

NIPT Clinical and Personal Utility

Reductions in Diagnostic Testing

Two studies reported on the potential for reductions in diagnostic testing if NIPT was used as a first-tier screening test.^{51,53} Bianchi et al⁵¹ noted a potential 89% reduction in the number of diagnostic tests performed if everyone with a false positive result underwent diagnostic testing (9 false positives in the NIPT group and 80 in the traditional prenatal screening group). Langlois et al⁵³ noted that up to 62 diagnostic tests could have been avoided if NIPT had been used as a primary screen. The total diagnostic testing rate was 2% in the study cohort, but could have been as high as 6.8% based on traditional prenatal screening and ultrasound examination.⁵³

Test Turnaround Time

Three studies (United States, United Kingdom, and China) reported on the test turnaround time for NIPT.⁵⁶⁻⁵⁸ In Quezada et al,⁵⁷ the median interval between blood sampling and receipt of results was 9 days (range 5–20 days); 98% of results were available within 14 days of sampling. In Song et al,⁵⁸ the study design methods called for a test turnaround time of 10 working days. Palomaki et al⁵⁶ reported a median turnaround time of 10 days; 95% of results were returned within 15 days.

Understanding of Health Care Providers

Seven studies evaluated health care providers' understanding and knowledge of NIPT (Table 8).⁵⁹⁻⁶⁵

The most common misconception among responses was that NIPT was a diagnostic test, not a screening test. Other gaps in knowledge were related to the possible limitations of NIPT in twin pregnancies, and the availability of expanded NIPT testing for microdeletion syndromes. Health care providers' confidence in offering NIPT to their patients was often related to their understanding and previous experience with the test.

Five of the seven surveys focused on the understanding of obstetricians and/or gynecologists.^{59,60,62-64} The varying study dates (from 2011 when NIPT was first introduced clinically, to 2017) and the geographic context (primarily the United States) made it difficult to generalize the results.

Table 8: Health Care Providers' Understanding of NIPT

Author, Year, Country	Health Care Providers	Understanding of NIPT
Brewer et al, 2016, ⁵⁹ United States	Obstetricians	85.4% said that NIPT was a screening test for fetal aneuploidy; 14.6% said that it was a diagnostic test 40.8% said they would recommend diagnostic testing for fetal aneuploidy for all 23 chromosomes; 46.6% said they would recommend NIPT 92.2% agreed that the sensitivity of NIPT is better than traditional prenatal screening for trisomy 21 81.5% agreed that NIPT performs well, regardless of age or risk, and should be offered as a screening option for any pregnant person, regardless of age or risk status
Filoché et al, 2017, ⁶⁰ New Zealand	Obstetricians	35.2% felt "very confident" in offering NIPT for fetal aneuploidy; 40.6% felt "quite confident" 30.7% felt "very confident" in explaining positive predictive value 23.6% felt "very confident" in explaining fetal fraction
Haymon et al, 2013, ⁶¹ United States	Maternal–fetal medicine specialists	86.7% said that NIPT is being offered as a screening test in their practice; 13.3% said that NIPT was being offered as a diagnostic test 91.1% felt confident with knowledge of NIPT
Mayes et al, 2016, ⁶² United States	Obstetricians	75% were aware of expanded NIPT options (testing for additional trisomies and microdeletion syndromes) 50% told patients that the accuracy of the expanded testing option is 99% to 100%; 25% said 90% to 98% 34% who did not order expanded NIPT would feel at least somewhat comfortable explaining the testing to patients; 83% of those who did order expanded NIPT would feel at least somewhat comfortable 14% who did not order expanded NIPT identified it as a diagnostic test; 33% who did order expanded NIPT identified it as a diagnostic test 41% who felt comfortable explaining expanded NIPT agreed that its clinical utility and validity has been established; only 7% who were not comfortable explaining expanded NIPT agreed that its clinical utility and validity has been established
Musci et al, 2013, ⁶³ United States	Obstetricians	32% already included NIPT in their practice; 22% were familiar with the published literature but had not yet ordered tests 39% had heard of the technology, but were less familiar with the data; 8% had never heard of NIPT
Sayres et al, 2011, ⁶⁴ United States	Mainly obstetricians, but also nurses and nurse–midwives	85% reported a low level of knowledge about NIPT
Swaney et al, 2016, ⁶⁵ United States	Maternal–fetal medicine fellows	97.4% agreed that NIPT is screening test, not a diagnostic test 42.1% knew that the test was available for twins but could not identify which twin was carrying the aneuploidy; 48.2% were unaware of the possible use of NIPT in twins 81.9% knew that NIPT could be offered after 10 weeks' gestation; 13.8% thought it could be offered at any time 63% were comfortable ordering NIPT without further education; 23% would not independently order the test based on their current knowledge level

Abbreviation: NIPT, noninvasive prenatal testing.

Maternal Education

Only one study⁵⁶ addressed aspects of maternal education for NIPT. In a survey of the general pregnant population, 15% incorrectly thought NIPT identified all genetic anomalies—not only trisomy 21. Furthermore, 13% thought that a negative NIPT result ruled out trisomy 21, and 21% thought NIPT could confirm whether a fetus was affected with trisomy 21. Because NIPT is a screening test, false positives and negatives can still occur; confirmation must still be made with diagnostic testing.

Maternal Satisfaction

Maternal satisfaction was also evaluated in one study.⁵⁶ Among a general population of pregnant people, 93% were satisfied with undergoing NIPT, and thought that their decision was “good” or “great” (rating average 4.2 out of 5).

Discussion

NIPT Accuracy

We conducted a systematic review of primary studies because we found no health technology assessment or systematic review that addressed all of our research questions. Two recently published systematic reviews relevant to our research questions^{15,16} were ongoing when we ran our literature search, and were published only part way into our review process. However, our findings for test accuracy were similar to those of the recently and previously published systematic reviews for the average-risk or general unselected population.¹⁵⁻¹⁸ Our data showed that NIPT had high accuracy for trisomy 21 and lower accuracy for trisomies 18 and 13. However, NIPT accuracy was still higher than that of traditional prenatal screening for trisomies 21, 18, and 13.

One of the systematic reviews published during our review process was a Cochrane review on NIPT test accuracy.⁶⁶ The review included 65 studies in total, but only five were conducted in a general unselected population, all of which we also included in our review. The Cochrane authors also found 18 studies in the mixed-risk group, but we excluded most of these from our review because results were reported for the entire mixed-risk group, and did not focus solely on the average-risk or general population.

Our findings showed sensitivity and specificity for NIPT that were lower than those reported by the manufacturers.^{7,8} This could have been because the majority of evidence around test accuracy is for the high-risk population, which has higher test sensitivity for trisomies 21, 18, and 13.¹⁵⁻¹⁸ As well, although the specificity of NIPT was high for trisomies 21, 18, and 13, the positive predictive value was variable, ranging from as low as 40% to as high as 100% in the included studies. Positive predictive value is affected by the prevalence of a condition, and NIPT was sensitive to slight changes in the number of true positives and/or false positives, because the prevalence of the conditions screened for is low.

The literature on NIPT for sex chromosome aneuploidies in the average-risk or general population is sparse, as noted by other authors.¹⁵ Previous systematic reviews in the high-risk population found that the accuracy of NIPT for sex chromosome aneuploidies was lower than that for trisomies 21, 18, and 13.^{38,40} Gil et al³⁸ found a sensitivity of 95.8% (95% CI, 83.6%–100%) and a false-positive rate of 0.14% (95% CI, 0.05%–0.38%) for monosomy X in the high-risk population. Similarly, a systematic review by Mackie et al⁴⁰ found a sensitivity of 92.9%

(95% CI, 74.1%–98.4%) and a false-positive rate of 0.01% (95% CI, 0%–0.01%) for monosomy X in the high-risk population.

Because of the limited number of studies in the meta-analysis, it was not possible to adequately assess how NIPT method, gestational age, or fetal fraction affected test accuracy. However, most NIPT was performed using the TMPS approach and the Harmony test. We included any NIPT test version in our review, but the accuracy results from other NIPT versions (e.g., Verifi or other lab-developed tests) may not be fully generalizable to Ontario, given that only the Harmony and Panorama tests are widely available.

Our review accepted different types of reference standards for test accuracy, and the included studies used a range of these. In addition to fetal karyotype from diagnostic testing, clinical phenotype was also accepted (e.g., neonate examination, birth record). The latter may not be as accurate, given the potential for phenotypic variability in affected fetuses. However, given that the focus of the review was the average-risk or general population, it would not have been appropriate for the only reference standard to be diagnostic testing, as it is for a high-risk population.

The true number of affected fetuses may also have been underreported. Fetuses affected by a chromosomal anomaly are likely to be at increased risk of spontaneous pregnancy loss,⁹ something that was not always captured in the included studies. As well, some studies excluded patients in the analysis if the initial NIPT test led to a failed result, and/or did not adequately report the true status of fetuses that failed NIPT to examine possible chromosomal reasons for test failure. However, the included studies found that the most common reason for test failure was low fetal fraction (i.e., below the minimum amount required to assess patient risk), a measure that was often strongly correlated with high maternal body weight.^{53,55,56}

Clinical validation studies of diagnostic accuracy for microdeletions are difficult to perform because of the very low prevalence of microdeletions. We found no studies for microdeletion test accuracy among the average-risk or general population. There are accuracy studies in the high-risk population, but they were excluded from this review. Alternative study designs have used archived samples or artificial mixtures to estimate test accuracy, and sensitivity has ranged widely, from 60% to >99%.⁶⁷ Test performance also depends on deletion size: 3 million base pairs is the approximate lower limit for detection.⁶⁸ Because microdeletion syndromes can have deletions that are shorter in length, NIPT may not capture all syndromes that are clinically relevant. Similarly, NIPT may inadvertently capture “variants of unknown significance” (chromosomal anomalies without clear clinical manifestations).⁶⁹ The relative rarity of microdeletion syndromes, combined with test performance, could mean that the actual false-positive rate of a microdeletion panel could exceed 1%.⁶⁸ Combined with testing for other chromosomal aneuploidies, the false-positive rate would be even higher, because of the additive effect of false positives. Given that the literature on microdeletion testing is sparse, clinical guidelines do not support routine testing for microdeletions with NIPT.

NIPT Clinical and Personal Utility

Studies of clinical utility for the average-risk or general population are lacking. We identified only one study that focused on aspects of personal utility (i.e., maternal education and satisfaction).⁵⁶ However, in high-risk populations, people have shown high satisfaction and low decisional regret with NIPT.^{32,33}

We also assessed the published literature on health care providers' understanding of NIPT. The studies we found were surveys, primarily in the United States obstetrician population. Because of the cross-sectional nature of the surveys and the varying publication dates, it was difficult to draw conclusions about health care providers' current understanding of NIPT, particularly for the Canadian context. Nevertheless, a common gap in knowledge noted in the published studies was the misconception that NIPT is a diagnostic test rather than a screening test.^{59,61,62,65} Some health care providers were also unaware that NIPT is available for use in twin pregnancies and for testing certain microdeletion syndromes.

It has been noted in patient preferences literature that pregnant people want to understand the conditions being screened for, and often look to their health care provider for this information.⁷⁰ Thus, ongoing education and training for health care professionals is essential to establish and maintain their understanding of NIPT, particularly as new indications emerge and additional conditions are tested for.

Ongoing Studies

We searched ClinicalTrials.gov for relevant ongoing studies of NIPT in the average-risk or general pregnant population. We also searched the World Health Organization International Clinical Trials Registry platform for ongoing studies.

We found seven potentially relevant ongoing studies (Appendix 6). Two recruited only participants from the average-risk population, three included both average-risk and high-risk participants, one recruited from the general population, and one did not specify risk. We found no studies on the accuracy of NIPT for microdeletions in the average-risk or general population, but one of the ongoing studies has set out to determine NIPT performance for 22q11.2 microdeletion syndrome in the general population.

We searched PROSPERO for ongoing systematic reviews, but found no relevant reviews.

Conclusions

The pooled sensitivity of NIPT was 99.5% (95% CI, 81.8%–99.9%) for trisomy 21, 93.1% (95% CI, 75.9%–98.3%) for trisomy 18, and 92.7% (95% CI, 81.6%–99.9%) for trisomy 13 (GRADE: low to moderate). The specificity for any trisomy was 99.9% (95% CI, 99.8%–100%; GRADE: moderate).

The accuracy of NIPT was higher than that of traditional prenatal testing (GRADE: low to moderate) and decreased the number of diagnostic tests performed (GRADE: moderate).

Evidence for the use of NIPT in the average-risk or general population for sex chromosome aneuploidies was limited. We found no studies on the accuracy or clinical utility of NIPT for microdeletion syndromes in the average-risk or general population.

Although NIPT is a screening test, health care providers may misinterpret it to be a diagnostic test. Positive NIPT results should be confirmed by diagnostic testing.

ECONOMIC EVIDENCE

Research Question

What are the findings of the published evidence on the cost-effectiveness of first-tier or second-tier noninvasive prenatal testing (NIPT) for trisomies 21, 18, and 13, sex chromosome aneuploidies, and microdeletions in average-risk or general population?

Methods

Economic Literature Search

We performed an economic literature search on September 14, 2017, for studies published from January 1, 2007, to the search date. To retrieve relevant studies, we developed a search using the clinical search strategy with an economic filter applied.

We created database auto-alerts in MEDLINE, Embase, and CINAHL and monitored them for the duration of the health technology assessment. We performed a targeted grey literature search of health technology assessment agency websites, clinical trial registries, Tufts Cost-Effectiveness Analysis Registry and the Hospital for Sick Children Toronto's Paediatric Economic Database Evaluation (PEDE). See the Clinical Evidence literature search section above for further details on methods used. See Appendix 4 for the literature search strategies, including all search terms.

Literature Screening

A systematic review of NIPT economic evaluations by Nshimyumukiza et al⁷¹ captured relevant literature published between January 1, 2009, and December 31, 2015. We have summarized the findings of its included studies in this review. We then included studies published after January 1, 2016, in our review.⁷¹

A single reviewer reviewed titles and abstracts, and, for those studies likely to meet the eligibility criteria, we obtained full-text articles and performed further assessment for eligibility.

Inclusion Criteria

- English-language full-text publications
- Studies comparing traditional prenatal screening with NIPT for trisomies 21, 18, or 13, sex chromosome aneuploidies, or microdeletions in pregnant people at average risk for chromosomal anomalies
- Studies published between January 1, 2016, and September 14, 2017
- Cost–utility analyses, cost-effectiveness analyses, or cost–benefit analyses

Exclusion Criteria

- Studies on cost analyses (e.g., no clinical outcomes)
- Studies focusing on pregnancies at high risk for chromosomal anomalies
- Studies from countries with economic levels (e.g., gross domestic product per capita) and health care systems (e.g., China, Turkey) considerably different from Canada's
- Abstracts, letters, commentaries, and editorials

Outcomes of Interest

- Total cost of different prenatal screening strategies
- Number of affected cases identified (or detection rate)
- Number of diagnostic tests (or number of diagnostic tests per diagnosis), including chorionic villus sampling or amniocentesis
- False-positive rate
- Incremental cost-effectiveness ratio (ICER; i.e., incremental cost per additional affected case identified)

Data Extraction

A single reviewer conducted the preliminary data extraction, applying the inclusion criteria. We extracted relevant data on the following:

- Source (e.g., first author, country, year of publication)
- Population, perspective, and time horizon
- Interventions and comparators (e.g., different prenatal screening strategies)
- Outcomes (e.g., health outcomes, costs, conclusions of economic evaluations)

We contacted authors of the studies to provide clarification as needed.

Study Applicability

We determined the usefulness of each identified study for decision-making by applying a modified applicability checklist for economic evaluations that was originally developed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom. The original checklist is used to inform development of clinical guidelines by NICE.⁷² We retained questions from the NICE checklist related to study applicability and modified the wording of the questions to remove references to guidelines and to make it Ontario-specific. A summary of the number of studies judged to be directly applicable, partially applicable, or not applicable to the research question is presented (Appendix 7).

Results

Literature Search

The literature search yielded 311 citations published between January 1, 2007, and September 14, 2017, after removing duplicates. Our literature search found a relevant economic systematic review that searched the literature up to 2016.⁷¹ For this reason, we limited studies to those published after January 1, 2016, to capture the updated economic evidence (i.e., studies published after the end search date of the published systematic review).⁷¹ We excluded a total of 305 articles based on information in the title and abstract, as well as the year of publication. We then obtained the full texts of six potentially relevant articles for further assessment. Figure 5 presents the flow diagram for the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).⁵⁰

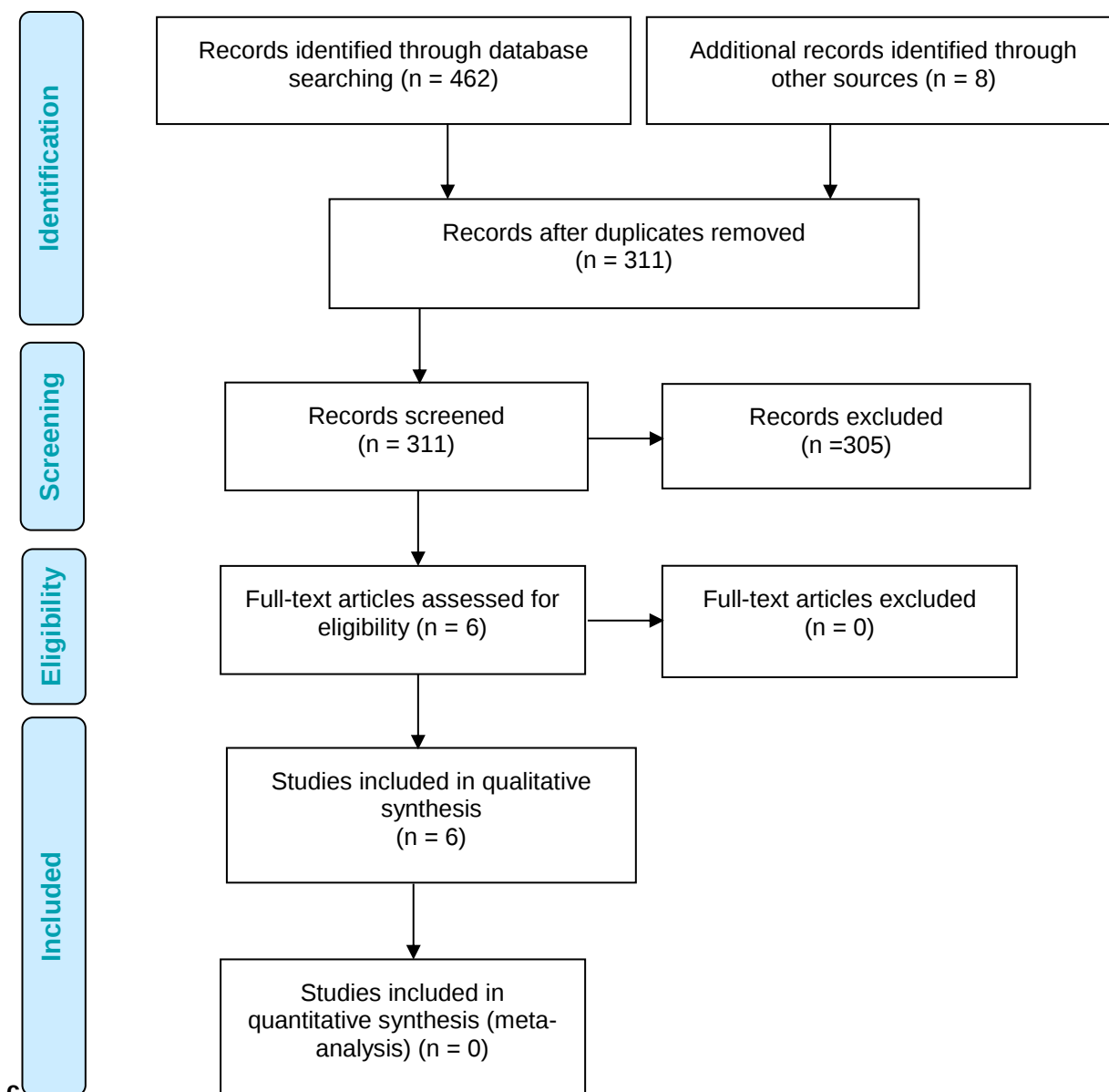


Figure 5: PRISMA Flow Diagram—Economic Search Strategy

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
 Source: Adapted from Moher et al.⁵⁰

Six economic evaluations published between January 1, 2016, and our search date met the inclusion criteria.⁷³⁻⁷⁸ We have also summarized the economic evidence before 2016 based on the systematic review by Nshimyumukiza et al.⁷¹

Review of Included Economic Studies

We included six studies, two of which were from Canada.^{73,74} The remaining four studies were from the United Kingdom,⁷⁷ the United States,⁷⁸ Italy,⁷⁶ and Australia.⁷⁵ Three studies^{73,74,76} included strategies for first-tier NIPT (i.e., first screening test done) and second-tier NIPT (i.e., test is done after positive results from traditional prenatal screening and before diagnostic testing); two studies^{75,77} included second-tier NIPT only. Only one study⁷⁸ compared first-tier NIPT with traditional prenatal screening. In three of the included studies,⁷⁴⁻⁷⁶ the target population was pregnant people who had accepted prenatal screening; the other three studies^{73,77,78} included all pregnant people, with a screening uptake rate (percentage of people who choose to receive prenatal screening) of 66% to 70%.

In all six studies, the main economic outcome was the total cost required to implement each prenatal screening option, and the target cohort was all pregnant people. The total required budget included the costs of traditional prenatal screening, NIPT, and diagnostic testing. In five studies,⁷³⁻⁷⁷ the time horizon was the duration of pregnancy; one study⁷⁸ used a lifetime horizon and reported direct medical costs and indirect costs for trisomy births. Most of the studies conducted various analyses by exploring different NIPT implementation strategies,^{73,74} risk cutoffs,^{75,77} traditional prenatal screening options,^{73,74,77} or prices of NIPT.^{74,78} We have reported the most relevant results (e.g., strategies including enhanced first-trimester screening and maternal serum screening, which are performed in Ontario) in Table 9. We have summarized the first-tier and second-tier NIPT findings for the six studies below.

Five studies⁷³⁻⁷⁷ included second-tier NIPT. Compared to traditional prenatal screening, second-tier NIPT led to a substantial reduction in the number of subsequent confirmatory diagnostic tests. However, the performance of second-tier NIPT in identifying affected fetuses differed among studies. When using a lower risk cutoff for positive test results than that used for traditional prenatal screening (e.g., 1:1,000 for traditional prenatal screening for trisomy 21), second-tier NIPT had a higher detection rate.⁷⁵⁻⁷⁷ When using the same risk cutoff and the same acceptance rate for further testing (with NIPT or diagnostic testing) as for traditional screening, second-tier NIPT had a lower detection rate than traditional screening.⁷³ However, when second-tier NIPT substantially increased the acceptance rate for further testing, it led to increased detection of affected fetuses.⁷⁹ These studies also showed that second-tier NIPT and traditional prenatal screening incurred similar total costs. The cost and performance (e.g., number of affected cases identified and diagnostic tests avoided) of second-tier NIPT were affected by the unit price of NIPT and the risk cutoff for further testing.

Four studies^{73,74,76,78} evaluated first-tier NIPT. In one study, compared with traditional prenatal screening, first-tier NIPT identified more affected fetuses at a substantially increased cost when excluding the lifetime cost of trisomy births. Using a low-risk cutoff (e.g., 1:1,000) for second-tier NIPT, the performance of first-tier and second-tier NIPT was similar.^{74,76}

The diagnostic pathway for people with a failed NIPT (e.g., an inconclusive test result) affected the number of diagnostic tests for first-tier NIPT.^{74,76} If people with inconclusive results did not receive diagnostic testing, the number of diagnostic tests performed would be substantially lower.

All studies reported clinical outcomes and costs for the entire cohort, and the cohort size varied between studies. Most studies did not report an ICER (i.e., incremental cost per additional affected case identified). To compare the clinical and economic outcomes of studies with different cohort sizes, we calculated the cost and main effectiveness measures for a

standardized unit (per 10,000 pregnant people), as well as the ICER for first-tier and second-tier NIPT (see Table 10). These calculated results are based on reported study data and have not been verified by the study authors, so the findings should be interpreted with caution. In general, even after standardizing the cohort size, we still found considerable differences in cost, number of cases detected, number of diagnostic tests performed, and incremental cost per additional case identified, both for NIPT as a second-tier test versus traditional prenatal screening, and for first-tier NIPT versus second-tier NIPT.

To our knowledge, there are no thresholds to assess cost-effectiveness using incremental cost per case detected or number of diagnostic tests avoided. The main factors that affected the ICER included target population (entire pregnant population versus pregnant people who accepted prenatal screening), chromosomal aneuploidies (trisomies 21, 18, and 13, versus only trisomy 21), prenatal screening pathway (e.g., diagnostic testing or no diagnostic testing directly after NIPT test failure), diagnostic testing acceptance rate, test performance for traditional prenatal screening and NIPT, cost of NIPT, and other cost components included in the analyses.

Despite the differences between studies, the conclusions for second-tier NIPT were consistent. Compared with traditional prenatal screening, second-tier NIPT can improve the overall performance of prenatal screening without a significant increase in total budget.⁷³⁻⁷⁷ Compared with traditional prenatal screening, first-tier NIPT would improve overall performance, but with a substantial increase to the total budget.^{73,74,76}

Economic Evidence Prior to January 1, 2016

The systematic review by Nshimyumukiza et al⁷¹ included 16 studies: eight from the United States, two from Canada, two from Australia, and one each from Belgium, the Netherlands, Sweden, and the United Kingdom. All studies were published between 2012 and 2015. The review authors concluded that the general quality of these studies was “fair.” Of the 16 studies, 10 focused on prenatal screening for trisomy 21; four included trisomies 21, 18, and 13; one included trisomies 21, 18, and 13, and monosomy X; and one included all detectable chromosomal abnormalities. The authors of these studies generally concluded that second-tier NIPT was cost-effective at the current NIPT test price (approximately \$400 to \$1,796 USD, purchasing power parity in 2015), but that first-tier NIPT was not cost-effective in most of the studies. Important factors affecting cost-effectiveness included the price of NIPT, the risk cutoff for positive test results for traditional prenatal screening, and the uptake rate of prenatal screening.

Table 9: Results of Economic Literature Review—Summary

Author, Year, Country	Study Design ^a and Perspective	Population/ Target Fetal Aneuploidies	Intervention/ Comparator ^b	Results		
				Health Outcomes ^c	Costs ^d	Conclusions ^e
Nshimyumukiza et al, 2018, ⁷³ Canada	- Type of economic analysis: cost-effectiveness analysis - Study design: decision-analytic model - Perspective: public payer - Time horizon: duration of pregnancy	- Pregnancies in Quebec (6% per year of 1,879,872 people 15–49 years old) with an uptake of 70% - Trisomies 21, 18, and 13	- FTS (risk cutoff 1:300 for trisomy 21) - MSS (risk cutoff 1:300 for trisomy 21) - FTS + NIPT - MSS + NIPT - Universal NIPT <i>Note: the authors included 13 screening strategies; we have reported the 5 most relevant to this review</i>	Cases identified, n (trisomy 21; trisomies 18 and 13): - FTS: 281 (184; 97) - MSS: 240 (173; 67) - FTS + NIPT: 251 (163; 88) - MSS + NIPT: 210 (155; 55) - Universal NIPT: 314 (216; 98) Diagnostic tests, n: - FTS: 2,659 - MSS: 3,146 - FTS + NIPT: 292 - MSS + NIPT: 253 - Universal NIPT: 539	CAD; fiscal year 2014/15 Cost of NIPT: \$795 - FTS: \$16.9 M - MSS: \$11.9 M - FTS + NIPT: \$15.0 M - MSS + NIPT: \$10.4 M - Universal NIPT: \$66.6 M	Compared with FTS, first-tier NIPT would cost \$1.5 M to detect 1 additional case of trisomy 21 Compared with traditional prenatal screening, NIPT as a second-tier test for high-risk pregnant people was likely to be cost-effective
Huang et al, 2017, ⁷⁴ Canada	- Type of economic analysis: cost-effectiveness analysis - Study design: decision-analytic model - Perspective: public payer - Time horizon: duration of pregnancy	- Cohort of 97,385 pregnancies screened annually in Ontario (total annual pregnancies 142,376) - Trisomy 21	- IPS (risk cutoff 1:200) - FTS (risk cutoff 1:1,500) + NIPT - eFTS (risk cutoff 1:1,000) + NIPT - Universal NIPT(a): 100% of those with NIPT test failures would have diagnostic testing - Universal NIPT(b): 0% of those with NIPT test failures would have diagnostic testing	Cases identified, n: - IPS: 135 - FTS + NIPT: 238 - eFTS + NIPT: 238 - Universal NIPT(a): 251 - Universal NIPT(b): 243 Diagnostic tests, n: - IPS: 3,190 - FTS + NIPT: 813 - eFTS + NIPT: 563 - Universal NIPT(a): 3,259 - Universal NIPT(b): 338 False-positive rate, %: - IPS: 3.30 - FTS + NIPT: 0.59 - eFTS + NIPT: 0.33 - Universal NIPT(a): 3.09 - Universal NIPT(b): 0.10	CAD; costing year not reported Cost of NIPT: \$550 - IPS: \$17.3 M - FTS + NIPT: \$21.8 M - eFTS + NIPT: \$18.6 M - Universal NIPT(a): \$59.4 M - Universal NIPT(b): \$54.1 M Cost of NIPT: \$400 - IPS: \$17.3 M - FTS + NIPT: \$19.0 M - eFTS + NIPT: \$17.0 M - Universal NIPT(a): \$44.8 M - Universal NIPT(b): \$39.6 M Cost of NIPT: \$200 - IPS: \$17.3 M - FTS + NIPT: \$15.2 M - eFTS + NIPT: \$14.8 M - Universal NIPT(a): \$25.3 M - Universal NIPT(b): \$20.1 M	eFTS with second-tier NIPT provided performance similar to that of universal NIPT at a substantially lower cost

Author, Year, Country	Study Design ^a and Perspective	Population/ Target Fetal Aneuploidies	Intervention/ Comparator ^b	Results		
				Health Outcomes ^c	Costs ^d	Conclusions ^e
Maxwell et al, 2017, ⁷⁵ Australia	- Type of economic analysis: cost-effectiveness analysis - Study design: decision-analytic model - Perspective: public payer - Time horizon: duration of pregnancy	- Cohort of 300,000 screened pregnancies representing the approximate number of live births annually in Australia - Trisomy 21	- FTS (risk cutoff 1:300) - FTS + NIPT (risk cutoff 1:300 for NIPT, 1:5 for diagnostic testing) - FTS + NIPT (risk cutoff 1:1,000 for NIPT, 1:10 for diagnostic testing) <i>Note: this article included 25 second-tier NIPT models. We have reported results from 2 models and the traditional prenatal screening model</i>	Detection rate, %: - FTS: 82.0 - FTS + NIPT (risk cutoff 1:300): 81.3 - FTS + NIPT (risk cutoff 1:1,000): 90.1 Diagnostic tests per diagnosis, n: - FTS: 14.18 - FTS + NIPT (risk cutoff 1:300): 1.7 - FTS + NIPT (risk cutoff 1:1,000): 2.03	Australian dollars; 2014 Cost of NIPT: \$400 - FTS: \$38.2 M - FTS + NIPT (risk cutoff, 1:300): \$36.0 M - FTS + NIPT (risk cutoff, 1:1,000): \$42.9 M	Compared with FTS, second-tier NIPT models using more sensitive risk cutoffs improved the detection rate for trisomy 21, reduced procedure-related pregnancy loss and could be provided at a lower cost per diagnosis
Colosi et al, 2017, ⁷⁶ Italy	- Type of economic analysis: cost-effectiveness analysis - Study design: decision-analytic model - Perspective: health care sector - Time horizon: duration of pregnancy	- Singleton pregnancies in Tuscany, Italy: 20,831 people - Trisomies 21, 18, and 13	- FTS (risk cutoff 1:250) - FTS + NIPT without nasal bone evaluation (risk cutoff 1:10–1:1,000 for NIPT, 1:10 for diagnostic testing) - FTS + NIPT with nasal bone evaluation (risk cutoff 1:10–1:1,000 for NIPT, 1:10 for diagnostic testing) - Universal NIPT	Detection rate, %: - FTS: 94.92 - FTS + NIPT without nasal bone evaluation: 97.82 - FTS + NIPT with nasal bone evaluation: 97.82 - Universal NIPT: 97.82 <i>Note: no breakdown on detection rate of trisomies 21, 18, or 13</i> Diagnostic tests, n: - FTS: 1,313 - FTS + NIPT without nasal bone evaluation: 339 - FTS + NIPT with nasal bone evaluation: 285 - Universal NIPT: 760 (positive NIPT results and NIPT test failures received diagnostic testing) False-positive rate, %: - FTS: 5.63 - FTS + NIPT and without nasal bone evaluation: 0.85 - FTS + NIPT and nasal bone evaluation: 0.85 - Universal NIPT: 0.43	Euro; cost year not reported Cost of NIPT: 260 € - FTS: €2.4 M - FTS + NIPT without nasal bone evaluation: €2.8 M - FTS + NIPT with nasal bone evaluation: €2.3 M - Universal NIPT: €5.8 M	Second-tier NIPT could be a cost-efficient and feasible first-trimester screening test for aneuploidies in the public health system

Author, Year, Country	Study Design ^a and Perspective	Population/ Target Fetal Aneuploidies	Intervention/ Comparator ^b	Results		
				Health Outcomes ^c	Costs ^d	Conclusions ^e
Chitty et al, 2016, ⁷⁷ United Kingdom	- Type of economic analysis: cost-effectiveness analysis - Study design: decision-analytic model - Perspective: United Kingdom National Screening Committee - Time horizon: duration of pregnancy	- Cohort of 698,500 pregnancies, based on annual live births in England and Wales and an uptake rate of 66% - Trisomy 21	- Traditional prenatal screening—FTS (86.9%) and MSS (13.1%; risk cutoff 1:150) - FTS/MSS + NIPT(a): pregnant people can have diagnostic testing directly without NIPT first (risk cutoff 1:150) - FTS/MSS + NIPT(b): pregnant people cannot have diagnostic testing directly (risk cutoff 1:150) - Note: this article also reported results at risk cutoffs of 1:500 and 1:1,000	Cases identified, n: - FTS/MSS: 577 - FTS/MSS + NIPT(a): 688 - FTS/MSS + NIPT(b): 556 - Note: We have presented the number of positive findings confirmed by diagnostic testing Diagnostic tests, n: - FTS/MSS: 5,743 - FTS/MSS + NIPT(a): 2,375 - FTS/MSS + NIPT(b): 615	GBP; 2012/13 Cost of NIPT: £250 - FTS/MSS: \$17.0 M - FTS/MSS + NIPT(a): \$17.0 M - FTS/MSS + NIPT(b): \$16.4 M	Second-tier NIPT improved the overall performance of prenatal screening without increasing costs
Fairbrother et al, 2016, ⁷⁸ United States	- Type of economic analysis: cost-effectiveness analysis - Study design: decision-analytic model - Perspective: societal^f - Time horizon: lifetime	- General pregnancy population based on annual live births in the United States (4,000,000) and an uptake rate of 70% - Trisomies 21, 18 and 13	- FTS - Universal NIPT	Total cases identified, n (trisomy 21; trisomy 18; trisomy 13): - FTS: 7,799 (4,768; 2,356; 674) - Universal NIPT: 8,993 (5,544; 2,710; 738) Diagnostic tests, n: - FTS: 147,311 - Universal NIPT: 17,303	USD; 2014 - FTS: \$3.88 B - Universal NIPT: when the NIPT unit cost was \$453 or less, NIPT resulted in cost savings over FTS - Discounting not reported	First-tier NIPT resulted in more trisomy cases detected than FTS, and was more economical at a NIPT unit cost of \$453

Abbreviations: B, billion; eFTS, enhanced first-trimester screening; FTS, first-trimester screening; ICER, incremental cost-effectiveness ratio; IPS, integrated prenatal screening; MSS, maternal serum screening (also known as quadruple screening); M, million; NIPT, noninvasive prenatal testing; NT, nuchal translucency.

^aThe included studies used different terms (e.g., cost-effectiveness analysis⁷³ and cost analysis^{74,75}) in their titles. Since all included studies reported both health outcomes and costs, we used the term “cost-effectiveness analysis” in this review. Moreover, some studies can be categorized as cost-consequence studies, since they did not report cost per case detected or incremental cost per case detected.

^bThe intervention and comparator refer to NIPT strategies (i.e., first-tier or second-tier NIPT). When studies included numerous strategies, we reported the results from the strategies most relevant to this review:

- FTS, IPS, eFTS and MSS: traditional prenatal screening without NIPT
- FTS/IPS/eFTS/MSS + NIPT: second-tier NIPT
- Universal NIPT: first-tier NIPT

^cPublished studies presented various health outcomes. We reported three health outcomes: the number of trisomy cases identified (or detection rate), the number of invasive diagnostic tests (or invasive diagnostic tests per diagnosis), and false-positive rate. We kept the original measures (e.g., the number of case identified or the detection rate) reported in these studies. *Invasive diagnostic tests* refers to amniocentesis or chorionic villus sampling.

^dThe costs refer to the total costs of implementing each screening strategy for the entire hypothetical cohort, including the cost of traditional prenatal screening, NIPT, and diagnostic testing.

^eWe summarized the conclusions from authors in each economic evaluation. We did not calculate the ICER (incremental cost per case detected or diagnostic test avoided) if it was not reported in the study.

^fAuthors did not clearly state the perspective. Because this study included both direct medical costs and indirect costs for a given trisomy birth, we assumed that the study was conducted from a societal perspective with a lifetime horizon.

Table 10: Calculated Approximate Cost and Effectiveness Per 10,000 Pregnant People From Included Studies

Name, Year, Location	Intervention/Comparator	Approximated Cost and Effectiveness per 10,000 Pregnant People		
		Health Outcomes	Costs	ICER (Incremental Cost Per Additional Case Identified)
Nshimyumukiza et al, 2018, ⁷³ Canada	• FTS (risk cutoff 1:300 for trisomy 21) • MSS (risk cutoff 1:300 for trisomy 21) • FTS + NIPT • MSS + NIPT • Universal NIPT	Total trisomy 21, 18, and 13 cases identified, n: • FTS: 24.9 • MSS: 21.3 • FTS + NIPT: 22.3 • MSS + NIPT: 18.6 • Universal NIPT: 27.8 Diagnostic tests, n: • FTS: 235.7 • MSS: 278.9 • FTS + NIPT: 25.9 • MSS + NIPT: 22.4 • Universal NIPT: 47.8	CAD; fiscal year 2014/15 Cost of NIPT: \$795 per test • FTS: \$1.5 M • MSS: \$1.1 M • FTS + NIPT: \$1.3 M • MSS + NIPT: \$0.9 M • Universal NIPT: \$5.9 M	Second-tier NIPT vs. traditional prenatal screening: • FTS + NIPT vs. FTS: FTS + NIPT was less effective and less costly, so we did not calculate an ICER^b • MSS + NIPT vs. MSS: MSS + NIPT was less effective and less costly, so we did not calculate an ICER^b First-tier vs. second-tier NIPT: • Universal NIPT vs. FTS + NIPT: \$819,048 • Universal NIPT vs. MSS + NIPT: \$540,385
Huang et al, 2017, ⁷⁴ Canada	• IPS (risk cutoff 1:200) • FTS (risk cutoff 1:1,500) + NIPT • eFTS (risk cutoff 1:1,000) + NIPT • Universal NIPT(a): 100% of those with NIPT test failures would have diagnostic testing • Universal NIPT(b): 0% of those with NIPT test failures would have diagnostic testing	Trisomy 21 cases identified, n: • IPS: 13.9 • FTS + NIPT: 24.4 • eFTS + NIPT: 24.4 • Universal NIPT(a): 25.8 • Universal NIPT(b): 25.0 Diagnostic tests, n: • IPS: 327.6 • FTS + NIPT: 83.5 • eFTS + NIPT: 57.8 • Universal NIPT(a): 334.7 • Universal NIPT(b): 34.7	CAD; costing year not reported Cost of NIPT: \$400 per test • IPS: \$1.8 M • FTS + NIPT: \$2.0 M • eFTS + NIPT: \$1.7 M • Universal NIPT(a): \$4.6 M • Universal NIPT(b): \$4.1 M	Second-tier NIPT vs. traditional prenatal screening: • FTS + NIPT vs. IPS: \$16,505 • eFTS + NIPT vs. IPS: dominant First-tier vs. second-tier NIPT: • Universal NIPT(b) vs. FTS + NIPT: \$4.12 M • Universal NIPT(b) vs. eFTS + NIPT: \$4.52 M
Maxwell et al, 2017, ⁷⁵ Australia	• FTS (risk cutoff 1:300) • FTS + NIPT (risk cutoff 1:300 for NIPT and 1:5 for diagnostic testing) • FTS + NIPT (risk cutoff 1:1,000 for NIPT and 1:10 for diagnostic testing)	Trisomy 21 cases identified, n^a: • NA Diagnostic tests^a: • NA	Australian dollars; 2014 Cost of NIPT: \$400 per test • FTS: \$1.3 M • FTS + NIPT (risk cutoff 1:300): \$1.2 M • FTS + NIPT (risk cutoff 1:1,000): \$1.4 M	NA

Name, Year, Location	Intervention/Comparator	Approximated Cost and Effectiveness per 10,000 Pregnant People		
		Health Outcomes	Costs	ICER (Incremental Cost Per Additional Case Identified)
Colosi et al, 2017, ⁷⁶ Italy	• FTS (risk cutoff 1:250) • FTS + NIPT and without nasal bone evaluation • FTS + NIPT and with nasal bone evaluation • Universal NIPT	Trisomy 21 cases identified, n ^a : • NA Diagnostic tests, n: • FTS: 630.3 • FTS + NIPT without nasal bone evaluation: 162.7 • FTS + NIPT with nasal bone evaluation: 136.8 • Universal NIPT: 364.8 (both positive NIPT results and NIPT test failures received diagnostic testing)	Euros; cost year not reported Cost of NIPT: €260 per test • FTS: €1.2 M • FTS + NIPT without nasal bone evaluation: €1.3 M • FTS + NIPT with nasal bone evaluation: €1.1 M • Universal NIPT: €2.8 M	NA
Chitty et al, 2016, ⁷⁷ United Kingdom	• Traditional prenatal screening: FTS (86.9%) and MSS (13.1%) • FTS/MSS + NIPT(a): people can have diagnostic testing directly without NIPT first (risk cutoff 1:150) • FTS/MSS + NIPT(b): people cannot have diagnostic testing directly (risk cutoff, 1:150)	Trisomy 21 cases identified, n: • FTS/MSS: 8.3 • FTS/MSS + NIPT(a): 9.8 • FTS/MSS + NIPT(b): 8.0 Diagnostic tests, n: • FTS/MSS: 82.2 • FTS/MSS + NIPT(a): 34 • FTS/MSS + NIPT(b): 8.8	GBP; 2012/13 Cost of NIPT: £250 per test • FTS/MSS: \$0.24 M • FTS/MSS + NIPT(a): \$0.24 M • FTS/MSS + NIPT(b): \$0.23 M	Second-tier NIPT • FTS/MSS + NIPT(a) vs. FTS/MSS: FTS/MSS + NIPT(a) dominated FTS/MSS with greater effectiveness and equal cost • FTS/MSS + NIPT(b) vs. FTS/MSS: FTS/MSS + NIPT(b) was less effective and less costly, so we did not calculate an ICER^b
Fairbrother et al 2016, ⁷⁸ United States	• FTS • Universal NIPT	Trisomy 21, 18, and 13 cases identified, n: • FTS: 19.5 • Universal NIPT: 22.5 Diagnostic tests, n: • FTS: 368.3 • Universal NIPT: 43.3	USD; 2014 No explicit cost for NIPT in analysis • FTS: \$9.7 M • Universal NIPT^a: When the NIPT unit cost was \$453 or less, NIPT resulted in cost savings compared with FTS	NA

Abbreviations: eFTS, enhanced first-trimester screening; FTS, first-trimester screening; ICER, incremental cost-effectiveness ratio (incremental cost per additional case detected); IPS, integrated prenatal screening; MSS, maternal serum screening (also known as quadruple screening); M, million; NA, not applicable; NIPT, noninvasive prenatal testing.

Note: These calculated results are based on the reported study data and have not been verified by study authors; the findings should be interpreted with caution.

^aIt was not straightforward to obtain an accurate estimate of these parameters, so we did not calculate this value.

^bWhen both the incremental cost and incremental effectiveness have negative values, there is a positive ICER. However, its interpretation is opposite from a positive ICER because of a positive incremental cost and incremental effectiveness. To avoid confusion, we did not present these calculated ICERs.

Applicability of the Included Studies

The results of the applicability checklist for the included studies are presented in Appendix 7. One study from the United States⁷⁸ was not applicable, but the other five studies were partially applicable to the research question.⁷³⁻⁷⁷ Two studies conducted in Canada were relevant for the Ontario setting,^{73,74} but both studies included all pregnant people, while our target population was average-risk pregnant people. Thus, their results were not directly applicable to our research question.

Discussion

A number of economic evaluations of NIPT have been published over the past few years. The main economic results of these studies were the total budget required in the jurisdiction for each screening strategy, not the average cost per pregnant person. The studies also often reported the number of affected fetuses detected and the number of diagnostic tests performed as clinical outcomes; they did not report commonly used measures in health economic evaluations (e.g., quality-adjusted life-years). Because there are no explicit thresholds for assessing the cost-effectiveness or cost per additional affected fetus detected, the authors did not use ICERs to assess the cost-effectiveness of NIPT. However, the conclusions of these economic evaluations were consistent overall. Second-tier NIPT might be cost-effective, because it may improve performance (e.g., by using a lower risk cutoff and increasing the rate of further testing after positive results from traditional prenatal screening) compared with traditional prenatal screening and without increasing the total budget. In contrast, first-tier NIPT would increase the total screening budget substantially.

The two Canadian studies included pregnant people at various risk levels in Quebec⁷³ and Ontario.⁷⁴ However, our population of focus was average-risk pregnant people, because NIPT is already publicly funded for high-risk pregnant people in Ontario. In addition, some of the traditional prenatal screening options included (e.g., integrated prenatal screening and first-trimester screening) have been phased out and are no longer performed in Ontario. Enhanced first-trimester screening and maternal serum screening are now the only traditional prenatal screening options performed in Ontario. Because the previous Canadian economic evaluations did not focus on our target population, we decided to conduct a primary economic evaluation of NIPT for average-risk pregnant people.

Conclusions

The systematic review identified six studies published between January 1, 2016, and September 14, 2017, that evaluated the economic implications of first-tier and second-tier NIPT. The studies showed that compared with traditional prenatal screening, second-tier NIPT might improve the detection rate and reduce the number of diagnostic tests performed without a significant increase to the total prenatal screening budget. Compared with traditional prenatal screening, first-tier NIPT improved the overall performance of prenatal screening but at a substantial increase in total cost. Two Canadian studies were partially applicable to the Ontario context.

PRIMARY ECONOMIC EVALUATION

The clinical evidence review showed that in comparative test accuracy studies, noninvasive prenatal testing (NIPT) performed better than traditional prenatal screening and decreased the number of diagnostic tests required. However, the NIPT test is more expensive than traditional prenatal screening. The economic evidence review found a number of studies that evaluated the clinical and economic outcomes of implementing NIPT, including two recently published studies for trisomy 21 from Ontario and Quebec,^{73,74} but these two economic evaluations did not distinguish between average-risk and high-risk populations in their findings. This was important because in addition to risk differences for chromosomal anomalies, high-risk and average-risk pregnant people in Ontario follow different clinical pathways and have different reimbursement policies. In Ontario, NIPT is publicly funded as a first-tier test for people at high risk of having a chromosomal anomaly, including pregnant people who are 40 years of age or older at the time of delivery. For pregnant people at average risk, including people less than 40 years old, NIPT is funded as a second-tier test (i.e., only after positive results from traditional prenatal screening and before diagnostic testing). Finally, we were interested in the economic implications of using NIPT for detecting chromosomal anomalies other than trisomy 21, including trisomy 13 and 18, sex chromosome aneuploidies, and microdeletion syndromes. For these reasons, we conducted a primary economic evaluation to investigate the cost-effectiveness of NIPT for chromosomal anomalies of interest for average-risk pregnant people in Ontario.

Research Question

What is the cost-effectiveness of three prenatal screening strategies for average-risk pregnant people in the context of the Ontario Ministry of Health and Long-Term Care: traditional prenatal screening (i.e., without NIPT); NIPT as a second-tier test (i.e., contingent NIPT, following positive results from traditional prenatal screening); and NIPT as a first-tier test (i.e., primary screening)?

Methods

The information presented in this report follows the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards Statement.⁸⁰

Type of Analysis

We conducted a cost-effectiveness analysis comparing three prenatal screening strategies (or screening pathways) in Ontario. We used the following clinical outcomes to measure clinical effectiveness:

- Number of cases detected of the chromosomal anomalies of interest (i.e., identified by the screening test and confirmed by subsequent diagnostic testing)
- Number of diagnostic tests performed (chorionic villus sampling or amniocentesis)
- Number of pregnancy losses related to diagnostic testing
- Number of live births with the chromosomal anomalies of interest

We considered the number of cases detected as the primary clinical outcome. Positive results from screening must have been confirmed by diagnostic testing to count as a detected case. If diagnostic testing was declined, we considered the case undetected.

Target Population

The study population was pregnant people less than 40 years of age at the time of delivery, with a singleton pregnancy of gestational age 10 to 20 weeks, and without a previous pregnancy that had a chromosomal anomaly. According to data from Ontario's Better Outcomes Registry and Network (BORN), 95.8% of pregnant people are less than 40 years old at the time of delivery.⁸¹ Assuming that a very small proportion of people have a previous pregnancy with a chromosomal anomaly, our target population would cover approximately 95% of pregnant people with a singleton pregnancy. We estimated the annual number of average-risk pregnant people to be 142,000 to 148,000 in the next 5 years. Details of the process for population estimation can be found in the budget impact analysis.

Perspective

We conducted this analysis from the perspective of the Ontario Ministry of Health and Long-Term Care.

Interventions

Noninvasive prenatal testing can be used as a first-tier or second-tier test. We included three strategies in our reference case: traditional prenatal screening without NIPT, NIPT used as a second-tier test, and NIPT used as a first-tier test. It has been suggested that NIPT could be used as a third-tier test (i.e., as a replacement for diagnostic testing), but this is not a clinically recommended pathway and is not currently part of clinical practice in Ontario, so we excluded this strategy from our analysis.

The Ontario Ministry of Health and Long-Term Care has recently announced plans to reform prenatal screening. Laboratories have phased out first-trimester screening, integrated prenatal screening, and serum integrated prenatal screening, and switched to enhanced first-trimester screening (eFTS). Maternal serum screening (MSS, or quadruple screening) in the second trimester is still important for people who miss screening in the first trimester. Therefore, in this economic evaluation we focused on the traditional prenatal screening strategies of eFTS for people who present in the first trimester and MSS for people who present in the second trimester.

We based the proportions of pregnant people who undergo eFTS (90%) or MSS (10%) on recent data from BORN. We incorporated the proportion of pregnant people who undergo NIPT as a second-tier test into the eFTS and MSS pathways. As a first-tier test, NIPT may be performed along with nuchal translucency ultrasound when pregnant people are screened in the first trimester.

Overall, we investigated six screening options as part of three strategies. Table 11 describes the prenatal screening pathways.

Table 11: Prenatal Screening Pathways for Pregnant People, Summary

Strategy	Screening Test	Second Test ^a	Third Test ^b
Strategy 1: Traditional Prenatal Screening Without NIPT			
First trimester ^c	eFTS ^d	CVS (70%) or amniocentesis (30%)	NA
Second trimester ^e	MSS ^f	Amniocentesis (100%)	NA
Strategy 2: Second-Tier NIPT			
First trimester ^c	eFTS ^d	NIPT or amniocentesis for very high-risk pregnancies ^g	Amniocentesis ^h
Second trimester ^e	MSS ^f	NIPT or amniocentesis for very high-risk pregnancies ^g	Amniocentesis ^h
Strategy 3: First-Tier NIPT			
First trimester ^c	NIPT + NT ultrasound	CVS (70%) or amniocentesis (30%)	Not applicable
Second trimester ^e	NIPT	Amniocentesis	Not applicable

Abbreviations: CVS, chorionic villus sampling; eFTS, enhanced first-trimester screening; MSS, maternal serum screening (also known as quadruple screening); NA, not applicable; NIPT, noninvasive prenatal testing; NT, nuchal translucency.

^aCVS and amniocentesis are diagnostic tests for confirming the results of a positive first test. Second-tier NIPT is still a screening test.

^bAmniocentesis is for confirming the results of a positive NIPT test.

^c90% of people who receive prenatal screening.

^deFTS consists of a single blood test, which includes pregnancy-associated plasma protein A, free β -human chorionic gonadotrophin, placental growth factor, and α -fetoprotein. As well, eFTS includes NT ultrasound.

^e10% of people who receive prenatal screening.

^fMSS (quadruple screening) consists of a single blood test, which includes α -fetoprotein, unconjugated oestriol, free β -human chorionic gonadotrophin, and inhibin-A.

^gPeople who have a trisomy 21 risk > 1/10 or nuchal translucency $\geq$ 3.5 mm.

^hOnly for people who had second-tier NIPT.

Discounting and Time Horizon

We did not include pregnancy-related outcomes or costs incurred beyond birth. Therefore, the time horizon was the duration of a full-term pregnancy (12 weeks' gestation to term); discounting was not applicable.

Main Assumptions

To simplify the model, we assumed the following:

- Pregnant people who declined prenatal screening followed the natural course of pregnancy. Fetuses affected by chromosomal anomalies were at a risk of spontaneous pregnancy loss because of these anomalies. Unaffected fetuses also had a small risk of spontaneous pregnancy loss (background risk unrelated to chromosomal anomalies).
- Pregnant people who declined diagnostic testing (chorionic villus sampling or amniocentesis) after positive results from traditional prenatal screening or NIPT followed the natural course of pregnancy.
- The sensitivity and specificity of confirmatory diagnostic testing (chorionic villus sampling or amniocentesis) were 100% for all chromosomal anomalies of interest. Diagnostic testing was associated with a small risk of procedure-related pregnancy loss.
- Traditional prenatal serum screening (eFTS and MSS) screens for only trisomy 21 and 18, but some cases of trisomy 13 could be detected incidentally during diagnostic testing (i.e., some might undergo diagnostic testing because of false-positive results for trisomy 21 or 18 from traditional prenatal screening).
- The fetal anatomical ultrasound at 18 to 20 weeks would be performed in all screening pathways, but was not included because it is a part of standard obstetric care. The results of the ultrasound would not affect the risk score for the fetus.

Model Structure

The process for the cost-effectiveness analysis is outlined in Figure 6. We simulated 5,000 cohorts (i.e., outer loop to capture parameter uncertainty), each with 142,000 to 148,000 average-risk pregnant people with singleton pregnancies at 12 weeks' gestation (i.e., inner loop to incorporate individual variability). We randomly assigned each fetus a risk level for the chromosomal anomaly of interest (trisomies 21, 18, and 13, sex chromosome aneuploidies, or microdeletions) using a distribution. Through microsimulation, each fetus obtained a latent ("true") chromosomal anomaly status (i.e., had or did not have a chromosomal anomaly) based on maternal-age-specific risk. The hypothetical cohort then went through each of the three screening strategies. We simulated screening results (true positive, false negative, false positive, and true negative) for each condition of interest in each pregnant person, based on the accuracy of the tests performed (detection rate and false-positive rate) and true disease classifications. Then, we simulated other clinical parameters and events (e.g., diagnostic testing and spontaneous pregnancy loss). We assigned costs related to the clinical events. Finally, we summarized the average results from the 5,000 iterations (i.e., total cost, number of cases detected, incremental cost per case detected) and calculated 95% credible intervals for cost and effectiveness results. Additional details of each prenatal screening strategy can be found in Figures 7 to 11.

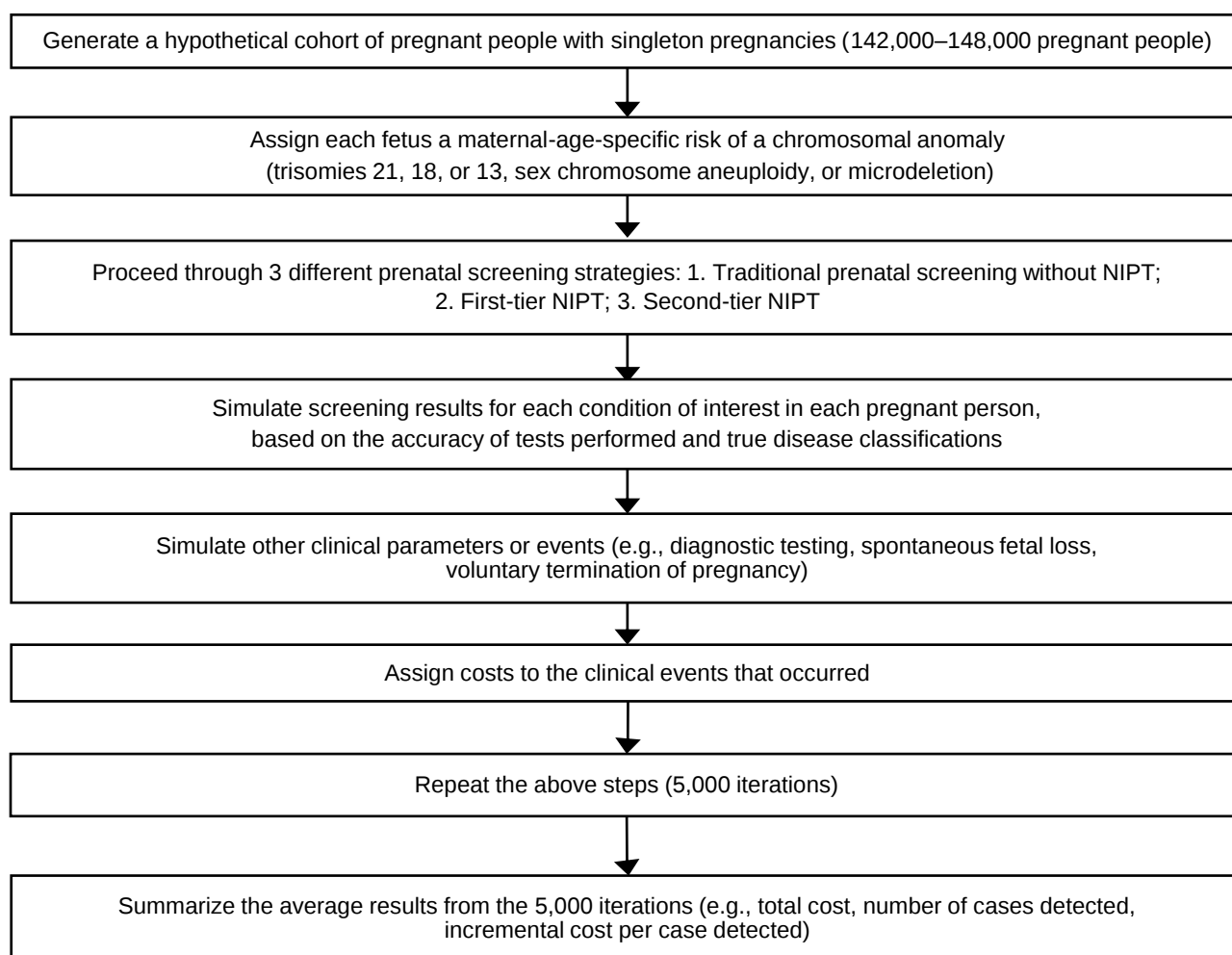


Figure 6: Cost-Effectiveness Analysis, Simplified Process

Two of the strategies (traditional prenatal screening without NIPT and second-tier NIPT) included two different initial prenatal screening options (eFTS and MSS). For simplicity, we did not differentiate between the clinical pathways for these initial prenatal screening options, but we did incorporate their different screening performance (i.e., detection rate and false-positive rate) into the model, along with the confirmatory diagnostic test that would be performed (chorionic villus sampling or amniocentesis).

The clinical pathways for each of the three screening strategies are briefly described below, along with the pathways for the natural course of pregnancy (e.g., for people who choose to decline prenatal screening) and diagnostic testing (to confirm positive test results).

Natural Course of Pregnancy

Pregnant people with an unaffected fetus will give birth to an unaffected newborn, but they have a small risk of spontaneous pregnancy loss (Figure 7). Pregnant people with an affected fetus will give birth to an affected newborn or experience spontaneous pregnancy loss. For simplicity, we did not present spontaneous pregnancy loss for unaffected fetuses in any of the models, because this pathway did not include our clinical and economic outcomes of interest, and the number of pregnancy losses for unaffected fetuses was similar for all pathways.

We also modelled the risk of spontaneous loss of affected and unaffected fetuses between 12 and 18 weeks' gestation. Given the considerable risk of spontaneous pregnancy loss as a result of chromosomal anomalies, the prevalence of trisomies 21, 18, and 13 in the second trimester was lower than in the first trimester (see the clinical evidence review for details).

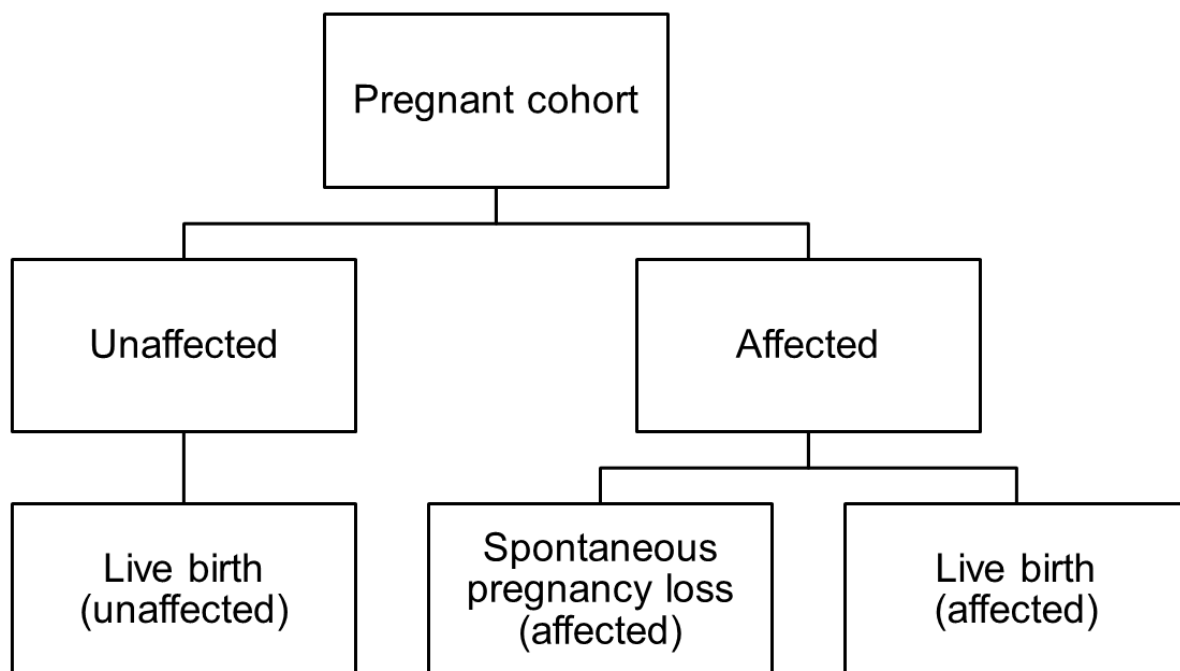


Figure 7: Simplified Pathway, Natural Course of Pregnancy

Diagnostic Testing

People who choose to undergo diagnostic testing with chorionic villus sampling or amniocentesis have a risk of procedure-related pregnancy loss, regardless of whether the fetus is affected or unaffected by a chromosomal anomaly (Figure 8). Pregnant people with an unaffected fetus may give birth to an unaffected newborn, while people with an affected fetus may choose voluntary termination of pregnancy, experience spontaneous pregnancy loss, or give birth to an affected newborn.

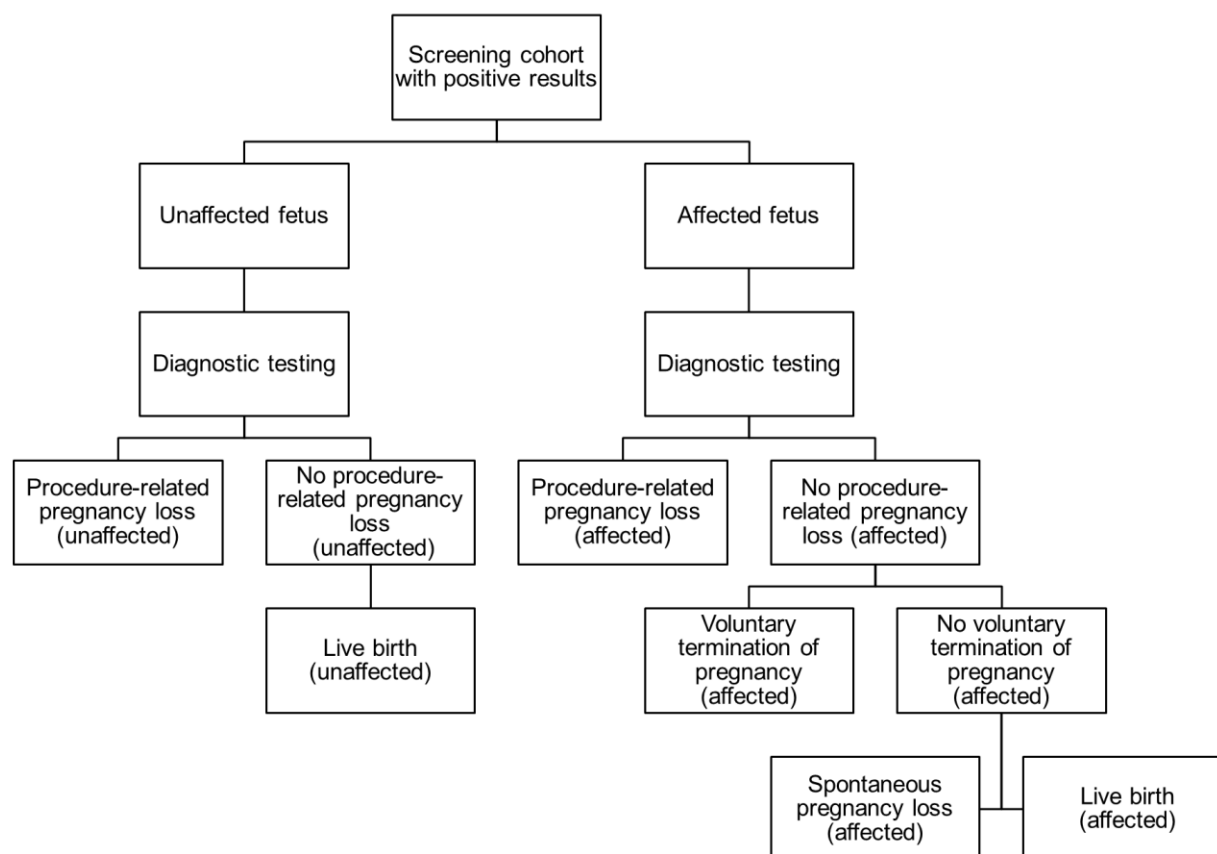


Figure 8: Simplified Pathway, Diagnostic Testing

Traditional Prenatal Screening Without NIPT

Figure 9 shows the clinical pathway for traditional prenatal screening without NIPT. Pregnant people who choose to decline prenatal screening follow the natural course of pregnancy pathway (Figure 7). If they choose traditional prenatal screening and the results are positive, they can choose to undergo confirmatory diagnostic testing (Figure 8). If they choose to decline diagnostic testing, they will follow the natural course of pregnancy (similar to those who decline prenatal screening). If the results are negative, there is no further testing.

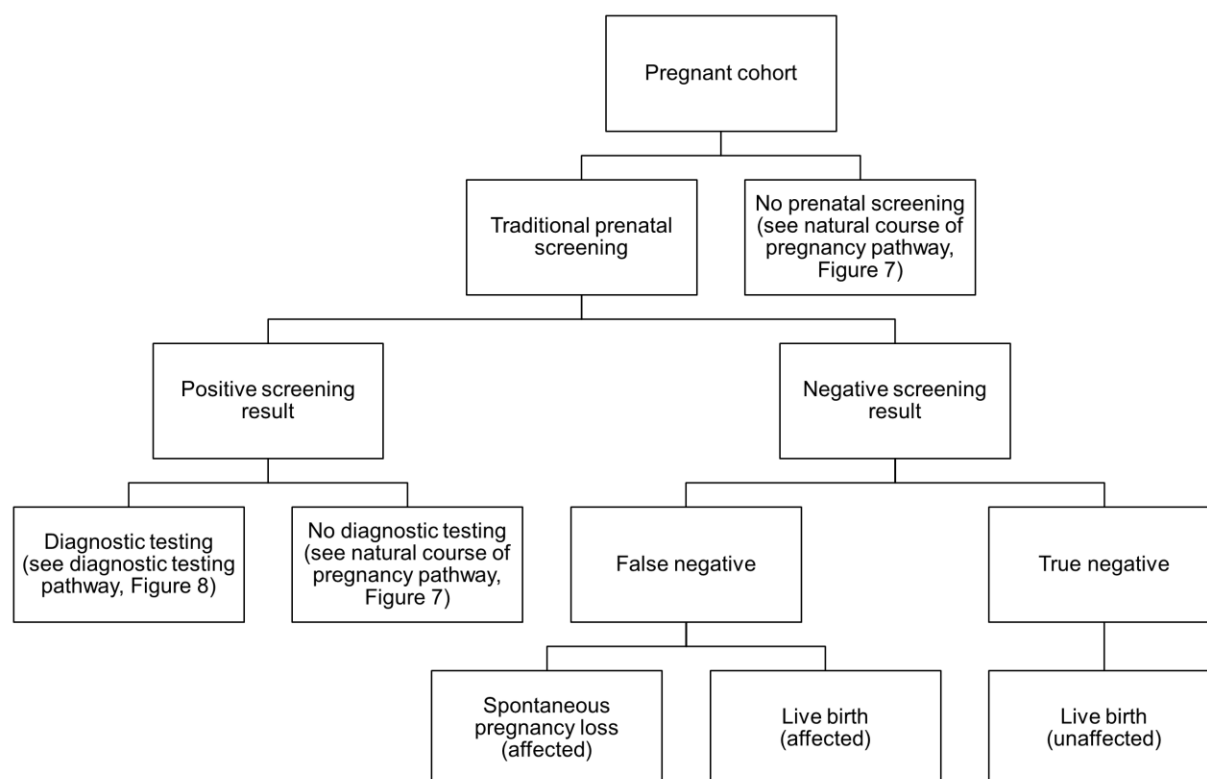


Figure 9: Simplified Pathway, Traditional Prenatal Screening Without NIPT

Abbreviation: NIPT, noninvasive prenatal testing

Second-Tier NIPT

Figure 10 shows the clinical pathway for second-tier NIPT. In general, this screening strategy reflects current practice in Ontario for people at average risk for a chromosomal anomaly. Pregnant people who decline prenatal screening follow the natural course of pregnancy (Figure 7). A small group (about 0.6%; BORN data) of very high-risk people (defined as a risk of trisomy 21 greater than 1/10 from traditional prenatal screening or nuchal translucency ≥ 3.5 mm) undergo diagnostic testing directly without NIPT. For those remaining, second-tier NIPT is performed following positive results from traditional prenatal screening and before diagnostic testing. If NIPT results are positive, people can choose to proceed to diagnostic testing (Figure 8). If NIPT results are negative, no further testing is conducted. If second-tier NIPT fails (once or twice), people are offered diagnostic testing. Test failure can occur for different reasons, such as inconclusive test results or test assay issues.

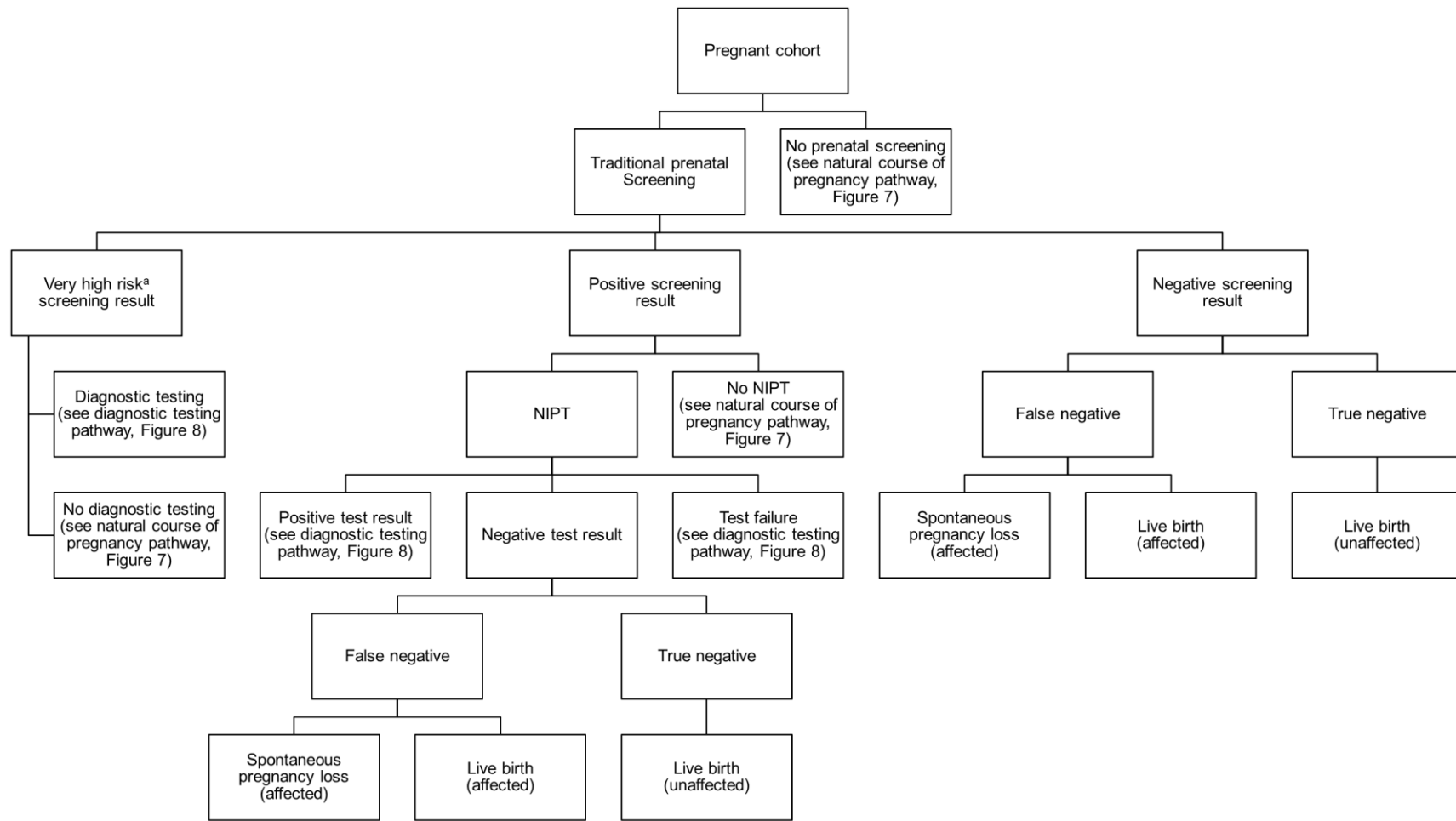


Figure 10: Simplified Pathway, Second-Tier NIPT

Abbreviation: NIPT, noninvasive prenatal testing

^aPregnant people who have a trisomy 21 risk > 1/10 or nuchal translucency ≥ 3.5 mm.

First-Tier NIPT

Figure 11 shows the clinical pathway for first-tier NIPT. Pregnant people who decline prenatal screening follow the natural course of pregnancy (Figure 7). If NIPT test results are positive, people may choose diagnostic testing (Figure 8). If people decline diagnostic testing, they will follow the natural course of pregnancy (similar to those who decline prenatal screening). If NIPT results are negative, no further testing is conducted. If first-tier NIPT fails (either once or twice), pregnant people are offered MSS if screening was performed in the first trimester, or diagnostic testing if screening was performed in the second trimester.

For first-tier NIPT, we assumed that pregnant people would have a nuchal translucency ultrasound if they were screened in the first trimester. Therefore, this strategy would see the same proportion (i.e., 90%) of pregnant people undergoing nuchal translucency ultrasound as traditional prenatal screening and second-tier NIPT. Nuchal translucency ultrasound is not used only to detect chromosomal anomalies (e.g., it is also used to detect cardiac disease and gastrointestinal malformations), but we focused only on its use for chromosomal anomalies. For simplicity, we included the cost of nuchal translucency ultrasound for pregnant people who may receive it, but we did not incorporate the potential effect of the results on screening or diagnosis pathways.

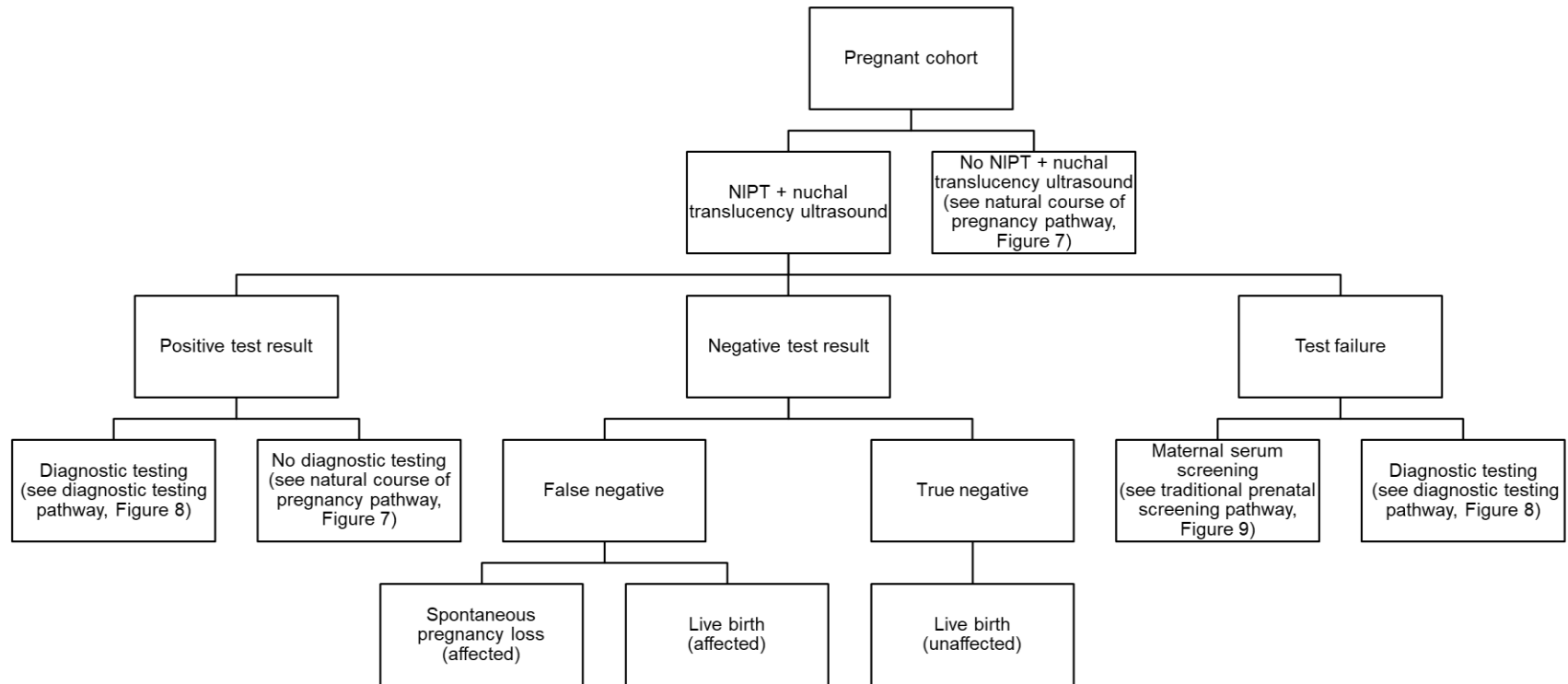


Figure 11: Simplified Pathway, First-Tier NIPT

Abbreviation: NIPT, noninvasive prenatal testing

Clinical Outcome Parameters

Ontario's Better Outcomes Registry and Network (BORN) collects data on pregnancy, prenatal screening, diagnostic testing, births, and newborns. We requested data from BORN for the key model inputs for pregnant people who were less than 40 years old at the estimated date of delivery, including screening uptake rate; test performance for eFTS, MSS, and NIPT for trisomy 21; uptake rate for further testing after positive screening results; and the proportion of pregnant people at very high risk for a chromosomal anomaly. We used BORN data from 2012 to 2016 to obtain the number of average-risk pregnant people who were less than 40 years of age at the estimated date of delivery, had singleton pregnancies, and did not have a previous pregnancy with a chromosomal anomaly.

We also used Ontario data from other sources when possible. When Ontario data were unavailable or inappropriate, we used data from published Canadian and international studies. The model inputs are provided below.

Prevalence of Chromosomal Anomalies and Risk of Pregnancy Loss

Based on the distribution of maternal age at the estimated date of delivery in Ontario,⁸¹ we assigned a maternal age to each simulated pregnant person. We did not use local data to estimate the prevalence of chromosomal anomalies, because local prenatal data linkages were incomplete and ongoing.⁸² Based on estimated maternal-age-specific live birth prevalence (in the absence of prenatal diagnosis) from the United Kingdom,⁸³ and the spontaneous pregnancy loss rate, we calculated the prevalence of trisomies 21, 18, and 13 in viable fetuses at 12 weeks' gestation (first trimester), with an adjustment for spontaneous pregnancy loss because of the chromosomal anomaly. Thus, live birth prevalence (excluding voluntary termination of pregnancy) was approximately equal to the prevalence of viable fetuses at a given time minus spontaneous pregnancy loss at the same time point:

$$\text{Live birth prevalence}^a = \text{prevalence of viable fetuses} \times (1 - \text{spontaneous pregnancy loss rate}^b)$$

^aLive birth prevalence of a chromosomal anomaly in the absence of prenatal diagnosis and voluntary termination of pregnancy.

^bSpontaneous pregnancy loss rate from 12 weeks (first trimester) to term for a given chromosomal anomaly.

Then:

$$\text{Prevalence of viable fetuses} = \text{live birth prevalence} \div (1 - \text{spontaneous pregnancy loss rate})$$

Studies from the United Kingdom have estimated spontaneous pregnancy loss rates from 12 weeks to term of 43% (95% confidence interval [CI], 31%–54%) for trisomy 21,⁸⁴ 72% (95% CI, 61%–81%) for trisomy 18,⁸⁵ and 49% (95% CI, 29%–73%) for trisomy 13⁸⁵ when estimating live birth prevalence.⁸³ We used the same spontaneous pregnancy loss rates to estimate the prevalence of trisomies 21, 18, and 13 at 12 weeks' gestation. We obtained the distribution of maternal age groups from 2014–2016 BORN data.⁸¹ Using the formula above, we calculated the maternal-age-specific prevalence of trisomies 21, 18, and 13 at 12 weeks' gestation, and have summarized the results in Table 12.

Table 12: Estimated Prevalence of Chromosomal Anomalies at 12 Weeks of Pregnancy

Chromosomal Anomaly	N (95% CrI) per 10,000 Pregnant People, First Trimester (12 weeks)	N (95% CrI) per 10,000 Pregnant People, Second Trimester (18 weeks)	Sources
Autosomal Trisomies (Overall and by Maternal Age)			
Trisomy 21 (overall) ^a	23.9 (18.9–30.6)	18.1 (14.2–23.1)	BORN, 2016; Savva et al, 2010; Morris et al, 1999 ^{81,83,84}
< 20 years old	11.8 (2.9–24.2)	8.9 (2.2–18.3)	
20–24 years old	12.1 (7.1–18.6)	9.1 (5.4–14.0)	
25–29 years old	13.4 (9.2–18.5)	10.1 (6.9–13.9)	
30–34 years old	19.8 (14.7–25.8)	15.0 (11.1–19.5)	
35–39 years old	55.2 (41.9–72.6)	41.7 (31.6–54.8)	
Trisomy 18 (overall) ^a	8.4 (5.4–12.7)	6.9 (4.4–10.4)	BORN, 2016; Savva et al, 2010; Morris et al, 2008 ^{81,83,85}
< 20 years old	4.0 (0–12.2)	3.2 (0–10.0)	
20–24 years old	4.1 (1.2–7.9)	3.3 (1.0–6.5)	
25–29 years old	4.5 (2.2–7.7)	3.7 (1.8–6.3)	
30–34 years old	6.5 (3.7–10.4)	5.3 (3.1–8.5)	
35–39 years old	20.8 (12.7–32.0)	17.0 (10.4–26.1)	
Trisomy 13 (overall) ^a	3.0 (1.7–5.1)	2.7 (1.5–4.6)	BORN, 2016; Savva et al, 2010; Morris et al, 2008 ^{81,83,85}
< 20 years old	1.5 (0–6.1)	1.3 (0–5.5)	
20–24 years old	1.5 (0–4.1)	1.3 (0–3.7)	
25–29 years old	1.7 (0.5–3.4)	1.5 (0.4–3.1)	
30–34 years old	2.4 (1.1–4.5)	2.2 (1.0–4.1)	
35–39 years old	7.1 (3.5–12.8)	6.4 (3.1–11.5)	
Expected Sex Chromosome Aneuploidies ^b			
Monosomy X (45,X)	13.0 per 10,000 female fetuses	NA	Viuff et al, 2015; Gravholt et al, 1996 ^{86,87}
Triple X syndrome	10.0 per 10,000 female fetuses	NA	Viuff et al, 2015; Tartaglia et al, 2010 ^{86,88}
XXY syndrome (47,XXY)	15.3 per 10,000 male fetuses	NA	Bojesen et al, 2003 ⁸⁹
XYY syndrome	10.0 per 10,000 male fetuses	NA	Viuff et al, 2015; Stockholm et al, 2012 ^{86,90}
Detected Sex Chromosome Aneuploidies ^b			
Monosomy X (45,X)	6.28 per 10,000 female fetuses	NA	European Registry ⁹¹
Triple X syndrome	1.6 per 10,000 female fetuses	NA	Viuff et al, 2015; Tartaglia et al, 2010 ^{86,88}
XXY syndrome (47,XXY)	1.94 per 10,000 male fetuses	NA	European Registry ⁹¹
XYY syndrome	0.5 per 10,000 male fetuses	NA	Viuff et al, 2015; Stockholm et al, 2012 ^{86,90}
Microdeletion Syndromes			
22q11.2 deletion syndrome	10.0	NA	McDonald-McGinn et al, 2015 ⁹²

Abbreviations: BORN, Better Outcomes Registry and Network; CrI: credible interval; NA, not applicable.

^aOverall prevalence for pregnant people < 40 years old. Age distribution is based on BORN data from 2014 to 2016.⁸¹

^bThe expected prevalence can be thought of as the “true” prevalence based on screening and subsequent confirmatory diagnostic testing. Because of the possible underdiagnosis and underreporting of sex chromosome aneuploidies, the expected prevalence is higher than the detected prevalence.

Because about 10% of pregnant people receive prenatal screening only in the second trimester, we also estimated the prevalence of chromosomal anomalies during the second trimester. We estimated the risk of spontaneous pregnancy loss between 12 and 18 weeks as a result of trisomy 21, 18, or 13 using the probabilities of spontaneous pregnancy loss from the first trimester to term, and from the second trimester to term. We also estimated the background risk of spontaneous pregnancy loss between 12 and 18 weeks for unaffected fetuses to be approximately 2%,⁹³ much lower than for affected fetuses. Therefore, the prevalence of chromosomal anomalies in the second trimester would be lower than that in the first trimester. Furthermore, people may decide to voluntarily terminate a pregnancy if the fetus is confirmed to be affected. The risk of pregnancy loss is presented in Table 13.

Table 13: Risk of Pregnancy Loss

Chromosomal Anomaly	Mean; Distribution (alpha; beta)	Sources
Spontaneous Pregnancy Loss Between 12 Weeks (First Trimester) and Term		
Trisomy 21	43%; beta (30.2; 40.0)	Morris et al, 1999 ⁸⁴
Trisomy 18	72%; beta (55.0; 21.4)	Morris et al, 2008 ⁸⁵
Trisomy 13	49%; beta (9.2; 9.6)	Morris et al, 2008 ⁸⁵
Spontaneous Pregnancy Loss Between 18 Weeks (Second Trimester) and Term		
Trisomy 21	23%; calculated	Morris et al, 1999 ⁸⁴
Trisomy 18	65%; calculated	Morris et al, 2008 ⁸⁵
Trisomy 13	42%; calculated	Morris et al, 2008 ⁸⁵
Spontaneous Pregnancy Loss Between 12 Weeks (First Trimester) and 18 Weeks (Second Trimester)		
Trisomy 21	26%; calculated	Morris et al, 1999 ⁸⁴
Trisomy 18	20%; calculated	Morris et al, 2008 ⁸⁵
Trisomy 13	12%; calculated	Morris et al, 2008 ⁸⁵
Spontaneous Pregnancy Loss Between Diagnostic Testing (CVS or Amniocentesis) and Term		
Monosomy X (45,X)	40%; beta (8; 12)	Iyer et al, 2012 ⁹⁴
Triple X syndrome	3% ^a ; fixed	Estimate based on Tartaglia et al, 2010; Hook et al, 1983 ^{88,95}
XXY syndrome (47,XXY)	4%; fixed	Bojesen et al, 2003; Hook et al 1983 ^{89,95}
XYY syndrome	3% ^a ; fixed	Hook et al, 1983 ⁹⁵
22q11.2 deletion syndrome	62%; fixed	Estimate based on Hook et al, 1983 ⁹⁵
Voluntary Termination of Pregnancy for a Confirmed Affected Fetus		
Trisomy 21	74.6%; beta (2,033; 691)	Natoli et al, 2012 ⁹⁶
Trisomy 18	74.6%; beta (2,033; 691)	Estimate
Trisomy 13	74.6%; beta (2,033; 691)	Estimate
Sex chromosome aneuploidy	68%; beta (115; 54)	Christian et al, 2000 ⁹⁷
22q11.2 deletion syndrome	68%; beta (115; 54)	Estimate
Diagnostic-Procedure-Related Pregnancy Loss		
Amniocentesis	0.11%; fixed	Akolekar et al, 2015 ⁵
Chorionic villus sampling	0.22%; fixed	Akolekar et al, 2015 ⁵
Background Risk of Spontaneous Pregnancy Loss for Unaffected Fetuses		
From 12 weeks (first trimester) to term	3%; fixed	Ammon et al, 2012; Wyatt et al, 2005 ^{93,98}
From 18 weeks (second trimester) to term	1%; fixed	Ammon et al, 2012; Wyatt et al, 2005 ^{93,98}
From 12 weeks (first trimester) to 18 weeks (second trimester)	2%; fixed	Ammon et al, 2012; Wyatt et al, 2005 ^{93,98}

^aWe assumed that the risk of spontaneous pregnancy loss for affected fetuses was greater than or equal to that of the unaffected fetus: 3%.

We also included sex chromosome aneuploidies and microdeletion syndromes in the scenario analysis (Tables 12 and 13). Prevalence data for sex chromosome aneuploidies and microdeletion syndromes are sparse. As well, because phenotypes vary widely for these conditions, they may be underdiagnosed. We included four sex chromosome aneuploidies (monosomy X, XXY syndrome, triple X syndrome, XYY syndrome), and the most prevalent microdeletion syndrome, 22q11.2 deletion syndrome. Unlike the autosomal trisomies, we accounted for the fact that sex chromosome aneuploidies and microdeletions occur independently of maternal age. We also assumed a sex ratio (male vs. female) of 1:1 for fetuses. Sex chromosome aneuploidies were conditional on fetal sex (i.e., monosomy X and triple X syndrome affected only female fetuses, and XXY syndrome and XYY syndrome affected only male fetuses). Because of the lack of literature, we could not distinguish between the prevalence of sex chromosome aneuploidies and microdeletions in the first and second trimester.

Accuracy of Prenatal Screening Tests

The accuracy of prenatal screening tests is presented in Table 14. Data from BORN showed a NIPT detection rate of 98.5% and a false-positive rate of 1.9% for trisomy 21 (note: BORN's data collection is ongoing and not all data for confirmatory diagnostic testing are available. The detection rate reflects confirmed affected cases). The false-positive rate for NIPT from preliminary local data was much higher than that found in the clinical evidence review and published meta-analyses (about 0.1%).^{18,66} A Cochrane review found that the combined NIPT false-positive rate for trisomies 21, 18, and 13 was approximately 0.1%.⁶⁶ We used various NIPT false-positive rates in the sensitivity analyses. For first-tier NIPT, we estimated test performance for trisomies 18 and 13 based on our clinical evidence review of the average-risk or general population. For second-tier NIPT, we based NIPT test performance for trisomies 18 and 13 on a meta-analysis of select high-risk pregnant people from the Cochrane review (from studies that used the targeted massively parallel sequencing method).⁶⁶

We included sex chromosome aneuploidies and microdeletions in the scenario analysis. We based the performance of NIPT for sex chromosome aneuploidies on the Cochrane review, which focused on a high-risk population.⁶⁶ Published data on NIPT test performance for microdeletion syndromes are sparse, but a case-control study showed a sensitivity of 90%, and nine out of 10 fetuses affected by the 22q11.2 deletion were identified.⁹⁹ However, test accuracy studies with a case-control design may overestimate test performance, and may not represent an average-risk or general population.¹⁰⁰ Negative NIPT results for microdeletions have seldom been further investigated in test accuracy studies, so potential false-negative results are often missed. For this reason, the sensitivity of NIPT for microdeletion syndromes in cohort studies has been rarely reported. However, most studies have shown a very low false-positive rate for NIPT for the 22q11.2 deletion.^{99,101} We used a fixed false-positive rate of 0.1%^{99,101} and varied the NIPT sensitivity for 22q11.2 deletion (90%, 75%, and 50%; see Table 17, below).

We did not distinguish between the reasons for NIPT test failure at initial testing and repeat testing, because there is no additional cost to repeat the NIPT in Ontario.

Table 14: Accuracy of Prenatal Screening Tests, Reference Case

Screening Option	Mean; Distribution (Parameter 1; Parameter 2)		Sources
	Detection Rate	False-Positive Rate	
NIPT			
Trisomy 21	98.5%; beta (197; 3) in first-tier and second-tier NIPT	2%; beta (160; 7,840) ^a	BORN data
Trisomy 18	93.1%; beta (27; 2) in first-tier NIPT	NA	Clinical evidence review
	98.2%; beta (110; 2) in second-tier NIPT	NA	Badeau et al, 2017 ⁶⁶
Trisomy 13	75%; beta (9; 3) in first-tier NIPT	NA	Clinical evidence review
	100%; fixed in second-tier NIPT	NA	Badeau et al, 2017 ⁶⁶
Failure rate at first and/or second blood draw	2% uniform (0.01, 0.03)	NA	Clinical evidence review
eFTS			
Trisomy 21 (risk cutoff: 1/400)	91.2%; beta (125; 12)	5.0%; beta (34; 650)	Huang et al, 2015 ¹⁰²
Trisomy 18	72.9%; beta (35; 13)	Extra 0.2% ^b ; fixed	Okun and Dougan, 2017; Huang et al 2018 ^{82,103}
MSS (quadruple screening)			
Trisomy 21 (risk cutoff: 1/200)	65.4%; beta (39.2; 20.8)	3.5%; beta (1,038; 28,962)	BORN data
Trisomy 18	52.8%; beta (66; 59)	0.15%; beta (647, 423123)	Summers et al, 2003 ¹⁰⁴

Abbreviation: BORN, Better Outcomes Registry and Network; eFTS, enhanced first-trimester screening; MSS, maternal serum screening (also known as quadruple screening); NA, not applicable; NIPT, noninvasive prenatal testing.

Note: The accuracy of traditional prenatal screening is based on multiple serum biomarker testing and may or may not include nuchal translucency ultrasound (depending on the prenatal screening option).

^aCombined false-positive rate: according to BORN data, the false-positive rate of NIPT for trisomy 21 was 1.9%. We estimated that the combined false-positive rate for trisomies 21, 18, and 13 was 2%. Note: BORN data collection is currently ongoing and data is incomplete. We addressed potential data issues by using a lower false-positive rate in the sensitivity analysis.

^bThe combined false-positive rate for trisomies 21 and 18 was the false-positive rate of trisomy 21 plus 0.2% for trisomy 18.

Screening Uptake Rate

In Ontario from 2014 to 2016, the uptake of prenatal screening was approximately 68% in people who were less than 40 years of age at their estimated date of delivery (BORN data). In the reference scenario, we assumed that all three strategies had the same uptake rate of 68%. However, we assumed that for first-tier NIPT, the uptake rate may have been higher. Therefore, in the scenario analyses we kept the uptake rate of 68% for traditional prenatal screening and second-tier NIPT, but increased it for first-tier NIPT to 80%, 90%, and 100% (Table 15).

Table 15: Additional Clinical Parameters

Parameter	Mean; Distribution (Parameter 1; Parameter 2)	Sources
Hypothetical cohort size of target population	145,000; uniform (142,000; 148,000)	Calculated
Uptake rate for prenatal screening		
Traditional prenatal screening	68%; fixed	BORN data
Second-tier NIPT	68%; fixed	BORN data
First-tier NIPT	68%; fixed	BORN data
Pregnant people who accept prenatal screening		
Screening in the first trimester	90%; fixed	BORN data
Screening in the second trimester	10%; fixed	BORN data
Accept further testing after a positive result		
Traditional prenatal screening	60%; fixed	Huang et al, 2017; Okun et al, 2014 ^{74,105}
Second-tier NIPT	76%; fixed	BORN data
Diagnostic testing after positive results from traditional prenatal screening and NIPT	95%; fixed	Estimate
First-tier NIPT	85%; fixed	Estimate
Very-high-risk population ^a	0.6%; fixed	BORN data

Abbreviation: NIPT, noninvasive prenatal testing.

^aVery high risk was defined as pregnant people with a trisomy 21 risk > 1/10 or nuchal translucency ≥ 3.5 mm. In the second-tier NIPT strategy, these people would receive diagnostic testing directly instead of second-tier NIPT.

Further Testing After Positive Results From Traditional Prenatal Screening and/or NIPT

Based on an earlier Ontario study, we estimated that 60% of pregnant people with positive results from traditional prenatal screening would accept diagnostic testing.^{74,105} Based on BORN data, we estimated that 76% of pregnant people with positive results from traditional prenatal screening would accept second-tier NIPT. The rate of acceptance of further testing after receiving positive results from traditional prenatal screening substantially increased after the NIPT was implemented in Denmark,¹⁰⁶ the United Kingdom,¹⁰⁷ the Netherlands,¹⁰⁸ and the United States¹⁰⁹ (see Table A9). Therefore, we used a higher acceptance rate (i.e., 85% and 95%) for further testing for second-tier NIPT in a sensitivity analysis. We assumed that if both traditional prenatal screening and NIPT results were positive, 95% of people would choose diagnostic testing.

In the reference case, we estimated that 85% of pregnant people with positive results from first-tier NIPT would accept diagnostic testing. In the sensitivity analysis, we also explored diagnostic testing acceptance rates of 90% and 95% after first-tier NIPT.

Cost Parameters

Cost parameters are presented in Table 16. Based on the Ontario *Schedule of Benefits*,¹¹⁰ the Ontario Case Costing Initiative database,¹¹¹ consultation with experts, and published Canadian economic studies, we identified cost parameters related to each screening strategy. Costs are reported in 2017 Canadian dollars.

We included an initial general assessment cost for all pregnant people in all three strategies. For the proportion of pregnant people who accepted prenatal screening, we included the costs of screening. We assumed that pregnant people with positive results from traditional prenatal screening or NIPT would have a post-test counselling visit, regardless of their decision to continue with diagnostic testing. If they decided to undergo diagnostic testing, there were associated physician fees. Those with a confirmed affected fetus would have another physician visit to discuss next steps.

The ministry-funded cost of NIPT is \$390 per test. For pregnant people who choose NIPT (first-tier or second-tier), we included the cost of genetic counselling for trisomies 21, 18, and 13: \$74.70 for a positive NIPT result and \$37.65 for a negative NIPT result. We also assumed that about 90% of people would have the nuchal translucency ultrasound. Therefore, the total screening cost for first-tier NIPT was approximately \$480 per person. We assumed an additional counselling unit for sex chromosome aneuploidies and 22q11.2 deletion, because genetic counselling may take longer for these conditions.

Most cost parameters (e.g., from the *Schedule of Benefits*) are either fixed in Ontario, or have a small standard error because of large sample sizes, such as the cost of termination of pregnancy from the Ontario Case Costing Initiative database.¹¹¹ We assumed that costs followed normal distributions, and assigned a standard error of 10% of the mean in the probabilistic analyses to capture potential uncertainty in the estimates (e.g., varying the future cost of NIPT).

We included costs related to spontaneous pregnancy loss for affected fetuses or because of diagnostic testing, but did not include the cost of spontaneous pregnancy loss for unaffected fetuses.

Table 16: Cost Parameters

Parameter	Cost, \$	Sources
Prenatal screening		
eFTS ^a	124.50	Expert opinion
MSS ^b	186.75	Expert opinion
NIPT ^c		
Trisomies 21, 18, and 13, and sex chromosome aneuploidies	390	Ministry of Health and Long-Term Care
Inclusion of 22q11.2 deletion	Extra 195 (Panorama)	LifeLabs Genetics ¹¹²
NT ultrasound (for 90% people for first-tier NIPT)	59.85	Ontario Schedule of Benefits ¹¹³
General assessment physician visit (e.g., to introduce prenatal screening)	77.20	Ontario Schedule of Benefits ¹¹³
Genetic counselling for trisomies 21, 18, and 13		
Positive NIPT result	74.70	Ontario Schedule of Benefits ¹¹³
Negative NIPT result	37.65	Ontario Schedule of Benefits ¹¹³
Additional counselling for sex chromosome aneuploidies and/or 22q11.2 deletion	74.70	Ontario Schedule of Benefits ¹¹³
Amniocentesis (total)	586	
Physician	102	Ontario Schedule of Benefits ¹¹³
Laboratory expenses, labour, and reagents	484	Lilley et al, 2017 ¹¹⁴
Chorionic villus sampling (total)	1,003	
Physician	153	Ontario Schedule of Benefits ¹¹³
Laboratory expenses, labour, and reagents	850	Lilley et al, 2017 ¹¹⁴
Post-test physician visit for pregnant people with positive screening test results (any strategy)	74.70	Ontario Schedule of Benefits ¹¹³
Physician visit for pregnant people with a confirmed affected fetus	161.15	Ontario Schedule of Benefits ¹¹³
Voluntary termination of pregnancy (total)	1,308	
Surgeon and anesthesiologist	204	Ontario Schedule of Benefits ¹¹³
Termination of pregnancy	1,104	Ontario Case Costing Initiative ¹¹⁵
Spontaneous pregnancy loss or diagnostic testing procedure-related pregnancy loss (total)	658	
Surgeon and anesthesiologist	204	Ontario Schedule of Benefits ¹¹³
Ambulatory care	454	Ontario Case Costing Initiative ¹¹⁵

Abbreviations: eFTS, enhanced first-trimester screening; MSS, maternal serum screening (also known as quadruple screening); NIPT, noninvasive prenatal testing; NT, nuchal translucency.

^aeFTS includes pregnancy-associated plasma protein A, free β -human chorionic gonadotrophin, placental growth factor, α -fetoprotein, and NT ultrasound.

^bMSS (quadruple screening) includes α -fetoprotein, unconjugated estriol, free β -human chorionic gonadotrophin, and inhibin-A.

^cIf NIPT fails for any reason, there are no additional costs for a repeat test. If the repeat (second) NIPT test also fails, there are no refunds for unsuccessful tests.

Analysis

Using the models and parameters above, we estimated the total annual health care costs and effectiveness of traditional prenatal screening without NIPT, second-tier NIPT, and first-tier NIPT for a hypothetical cohort of pregnant people with singleton pregnancies in Ontario. In the reference case, we presented the cost-effectiveness results in a standardized unit, per 10,000 pregnant people. We conducted a reference case analysis using probabilistic analysis by assigning probability distributions to model parameters. The probabilistic analysis can capture parameter uncertainty and individual variability.

We also conducted the following scenario analyses to examine the cost-effectiveness of adopting NIPT (see Table 17 for the additional parameter estimates used in the analyses):

- Inclusion of sex chromosome aneuploidies (i.e., trisomies 21, 18, and 13 + sex chromosome aneuploidies) in first-tier NIPT
- Inclusion of both sex chromosome aneuploidies and microdeletion syndromes (i.e., trisomies 21, 18, and 13 + sex chromosome aneuploidies + microdeletions) in first-tier NIPT
- Increased uptake of first-tier NIPT (80%, 90%, and 100%)
- Results from a recent Cochrane systematic review⁶⁶ on NIPT test accuracy
- A lower trisomy 21 risk cutoff (of positive results for traditional prenatal screening) in second-tier NIPT; and increasing the acceptance rate of further testing (after a positive result from traditional prenatal screening) from 76% to 90% for second-tier NIPT
- A subgroup of pregnant people 35 to 39 years old at time of delivery (pregnant people at higher risk of chromosomal anomalies, but who do not meet the currently defined threshold of high-risk based on age [i.e., ≥ 40 years old])

Table 17: Additional Model Inputs Used in the Scenario Analyses

Screening Option	Mean; Distribution (Alpha; Beta)		Sources
	Detection Rate	False-Positive Rate	
Inclusion of Sex Chromosome Aneuploidies and/or Microdeletions			
Sex chromosome aneuploidies	93.8%; beta (90; 6)	0.4%; beta (4; 964)	Badeau et al, 2017 ⁶⁶
22q11.2 deletion	90% or 75% or 50%; fixed	0.1%; fixed	Ravi et al, 2018; Martin et al, 2018 ^{99,101}
NIPT Performance Based on Cochrane Review ^a			
Trisomy 21	99.2%; beta (87.3; 0.7) in first-tier NIPT	0.1%; beta (20; 19,980) ^b in first-tier NIPT	Badeau et al, 2017 ⁶⁶
	99.2%; beta (244; 2) in second-tier NIPT	0.1%; beta (4; 3,996) ^a in second-tier NIPT	Badeau et al, 2017 ⁶⁶
Trisomy 18	90.9%; beta (20; 2) in first-tier NIPT	NA	Badeau et al, 2017 ⁶⁶
	98.2%; beta (110; 2) in second-tier NIPT	NA	Badeau et al, 2017 ⁶⁶
Trisomy 13	62.5%; beta (5; 3) in first-tier NIPT	NA	Badeau et al, 2017 ⁶⁶
	100%; fixed in second-tier NIPT	NA	Badeau et al, 2017 ⁶⁶
Lower Trisomy 21 Risk Cutoff for Second-Tier NIPT			
eFTS ^b (risk cutoff: 1/1,000)	94.8%; beta (129.9; 7.1)	10.5% ^b ; beta (71.8; 612.2)	Huang et al, 2015 ¹⁰²
MSS (risk cutoff: 1/700)	80.8%; beta (48.5; 11.5)	10.1%; beta (3024; 26,976)	BORN data
Lower Trisomy 21 Risk Cutoff and Higher Acceptance of Further Testing for Second-Tier NIPT			
Higher acceptance rate after positive results from traditional prenatal screening	90%	—	Estimate

Abbreviations: eFTS, enhanced first-trimester screening; MSS, maternal serum screening (also known as quadruple screening); NA, not applicable; NIPT, noninvasive prenatal testing.

^aTest failures (for any reason) were excluded in estimating the performance of NIPT.⁶⁶

^bCombined false-positive rate for trisomies 21, 18, and 13.

We also conducted sensitivity analyses (e.g., changing from the mean to other fixed values for the input variables) to assess the impact of key variables on the total budget and effectiveness of each screening strategy, and the incremental cost-effectiveness ratio.

We ran 5,000 iterations for the reference case and 1,000 iterations for each of the scenario and sensitivity analyses. We reported the total cost and effectiveness of the target cohort, rather than the cost and effectiveness per target individual. For the reference case, we calculated the cost-effectiveness results in a standardized unit, per 10,000 people, to make the results comparable with earlier publications. The results are expressed as means (95% credible interval [CrI], i.e., 2.5th and 97.5th percentiles from the Monte Carlo simulation). We conducted all analyses using SAS version 9.4 (SAS Institute, Cary, North Carolina).

Results

Reference Case Analysis

The main cost and effectiveness outcomes of the three reference case strategies are summarized in Table 18. We have also reported costs and effectiveness for a standardized cohort size of 10,000 people in Table 19. We have presented the incremental cost, incremental effectiveness, and incremental cost per additional affected case detected for second-tier NIPT versus traditional prenatal screening, and for first-tier versus second-tier NIPT in Table 20.

The mean cohort size of the target population was 145,022 (95% CrI, 142,160–147,856) in 5,000 simulations. This reflected the approximate number of annual singleton pregnancies in Ontario over next 5 years. Of these, 88,754 (95% CrI, 86,972–90,541) and 9,657 (95% CrI, 9,373–9,944) people received prenatal screening in the first and second trimester, respectively. The remaining 46,611 (95% CrI, 45,586–47,627) had no prenatal screening. The total number of fetuses with any trisomy was 512 (95% CrI, 424–623). The total numbers of fetuses with trisomy 21, 18, or 13 were 347 (95% CrI, 275–440), 121 (95% CrI, 80–181), and 44 (95% CrI, 24–75), respectively.

Second-tier NIPT dominated traditional prenatal screening. Compared with traditional prenatal screening, second-tier NIPT detected more affected fetuses, substantially reduced the number of diagnostic tests performed, and slightly reduced the total screening budget.

Compared with second-tier NIPT, first-tier NIPT was associated with 84 (95% CrI, 54–117) additional affected fetuses detected, 1,407 (95% CrI, 1,128–1,696) additional diagnostic tests performed, and an additional cost of \$35 million (95% CrI, \$27 million–\$42 million).

Table 18: Reference Case Analysis Results, Costs and Effectiveness for Three Prenatal Screening Strategies^a

Strategy	Total Costs (95% CrI), \$	Cases Detected (95% CrI), n	Diagnostic Tests Performed (95% CrI), n	Diagnostic-Procedure-Related Pregnancy Losses (95% CrI), n	Affected Live Births (95% CrI), n
Traditional prenatal screening	27,487,017 (24,140,385–30,815,491)	All: 158 (123–202) Trisomy 21: 123 (92–161) Trisomy 18: 35 (19–55) Trisomy 13: 1 (0–3)	3,110 (2,297–4,040)	6 (1–12)	All: 189 (162–216) Trisomy 21: 142 (119–166) Trisomy 18: 26 (17–36) Trisomy 13: 21 (12–30)
eFTS	21,120,295 (18,338,516–23,895,779)	149 (116–190)	2,893 (2,078–3,820)	6 (1–11)	97 (78–116)
MSS	2,719,663 (2,326,295–3,111,197)	9 (3–16)	218 (186–250)	0 (0–1)	12 (6–20)
No screening	3,647,059 (2,950,378–4,341,750)	0	0	0	80 (63–98)
Second-tier NIPT	26,656,979 (23,423,892–29,934,127)	All: 188 (148–238) Trisomy 21: 147 (112–193) Trisomy 18: 41 (23–65) Trisomy 13: 0 (0–1)	718 (634–814)	1 (0–3)	All: 177 (151–204) Trisomy 21: 132 (109–155) Trisomy 18: 24 (15–35) Trisomy 13: 21 (12–30)
eFTS + NIPT	20,283,588 (17,612,370–22,963,994)	178 (139–226)	678 (596–769)	1 (0–3)	86 (68–105)
MSS + NIPT	2,726,332 (2,330,961–3,116,509)	11 (4–18)	40 (28–54)	0 (0–1)	12 (5–19)
No screening	3,647,059 (2,950,378–4,341,750)	0	0	0	80 (63–98)
First-tier NIPT	61,292,985 (53,532,496–69,178,382)	All: 273 (219–337) Trisomy 21: 191 (148–245) Trisomy 18: 63 (38–97) Trisomy 13: 18 (7–35)	2,125 (1,837–2,427)	4 (0–8)	All: 147 (123–171) Trisomy 21: 112 (91–134) Trisomy 18: 20 (11–29) Trisomy 13: 14 (7–23)
First trimester	52,509,033 (45,522,346–59,513,228)	251 (202–313)	1,780 (1,537–2,035)	3 (0–7)	60 (46–77)
Second trimester	5,136,893 (4,375,162–5,895,052)	22 (12–32)	346 (253–442)	0 (0–2)	7 (2–12)
No screening	3,647,059 (2,950,378–4,341,750)	0	0	0	80 (63–98)

Abbreviations: CrI, credible interval; eFTS, enhanced first-trimester screening; MSS, maternal serum screening (also known as quadruple screening); NIPT, noninvasive prenatal testing.

Note: Numbers may appear inexact due to rounding. The prevalence of chromosomal anomalies in the second trimester was lower than in the first trimester because of a risk of spontaneous pregnancy loss between the first and second trimester.

^aMean cohort size: 145,022 pregnant people.

Table 19: Reference Case Analysis Results, Cost and Effectiveness Per 10,000 Average-Risk Pregnant People

Strategy	Total Costs, \$	Cases Detected, n	Diagnostic Tests Performed, n	Diagnostic-Procedure-Related Pregnancy Losses, n	Affected Live Births, n
Traditional prenatal screening	1,895,372	10.9	214.5	0.4	13.0
Second-tier NIPT	1,838,137	13.0	49.5	0.1	12.2
First-tier NIPT	4,226,468	18.8	146.6	0.3	10.1

Abbreviation: NIPT, noninvasive prenatal testing.

Table 20: Reference Case Analysis Results, Incremental Cost, Incremental Effectiveness, and Incremental Cost per Case Detected

Comparison	Incremental Costs (95% CrI), \$	Additional Cases Detected (95% CrI), n	Difference in Diagnostic Tests (95% CrI), n	Difference in Diagnostic-Procedure-Related Pregnancy Losses (95% CrI), n	Difference in Affected Live Births (95% CrI), n	Incremental Cost Per Case Detected, \$
Second-tier NIPT vs. traditional prenatal screening	-830,038 (-1,502,076 to -266,284)	30 (6–56)	-2,392 (-3,275 to -1,612)	-5 (-11 to 0)	-11 (-34 to 12)	Dominant
First-tier vs. second-tier NIPT	34,636,006 (27,131,648– 42,272,116)	84 (54–117)	1,407 (1,128– 1,696)	3 (-1 to 7)	-31 (-53 to -8)	411,274

Abbreviations: CrI, credible interval; NIPT, noninvasive prenatal testing.

Note: Numbers may appear inexact due to rounding.

Scenario Analyses

Inclusion of Sex Chromosome Aneuploidies and 22q11.2 Deletion in First-Tier NIPT

The results for first-tier NIPT including screening for sex chromosome aneuploidies, with or without the 22q11.2 deletion, are presented in Table 21.

When first-tier NIPT included trisomies 21, 18, and 13, and sex chromosome aneuploidies, the total cost increased to \$69 million (95% CrI, \$61 million–\$77 million) using either the expected or detected sex chromosome aneuploidy prevalence (the detected prevalence is much lower than the expected prevalence). Although there are no additional costs associated with testing for sex chromosome aneuploidies in NIPT, more genetic counselling would be needed (additional \$74.70). On average, 185 cases of sex chromosome aneuploidies would be detected using expected detected sex chromosome aneuploidy prevalence, and 40 cases would be detected using the expected prevalence.

When first-tier NIPT included trisomies 21, 18, and 13, sex chromosome aneuploidies, and 1 microdeletion syndrome (22q11.2 deletion), the total cost increased to \$89 million (95% CrI, \$77 million–\$101 million). Including the 22q11.2 deletion would involve an additional \$195 for the test and an additional \$74.70 for more genetic counselling. First-tier NIPT would detect 74, 62, and 42 cases of 22q11.2 deletion at detection rates of 90%, 75%, and 50%, respectively.

Table 21: Scenario Analysis Results, Inclusion of Sex Chromosome Aneuploidies and 22q11.2 Deletion in First-Tier NIPT

Scenario	Total Cost (95% CrI), \$	Cases Detected (95% CrI), n	Diagnostic Tests Performed (95% CrI), n	Diagnostic- Procedure-Related Pregnancy Losses (95% CrI), n	Affected Live Births (95% CrI), n	Incremental Cost Per Case Detected, vs. Second-Tier NIPT, ^a \$
Trisomies and Sex Chromosome Aneuploidies						
Trisomies 21, 18, and 13, and sex chromosome aneuploidies (expected prevalence)	69,137,967 (60,606,739–77,198,825)	All: 456 (396–530) Trisomies 21, 18, 13: 272 (218–335) SCA: 185 (156–215)	2,696 (2,290–3,203)	5 (1–10)	All: 339 (302–382) Trisomies 21, 18, and 13: 147 (123–171) SCA: 192 (163–227)	158,623
Trisomies 21, 18, and 13, and sex chromosome aneuploidies (detected prevalence)	68,994,511 (60,901,341–76,637,397)	All: 313 (258–378) Trisomies 21, 18, 13: 273 (219–340) SCA: 40 (27–52)	2,501 (2,098–2,957)	4 (1–9)	All: 181 (154–211) Trisomies 21, 18, and 13: 146 (122–172) SCA: 35 (22–49)	339,908
Trisomies and Sex Chromosome Aneuploidies and 22q11.2 Deletion						
Trisomies 21, 18, and 13, sex chromosome aneuploidies (expected prevalence) and 22q11.2 deletion (90% detection rate)	88,748,952 (77,081,835–100,742,353)	All: 531 (468–603) Trisomies 21, 18, 13: 273 (220–334) SCA: 185 (156–215) 22Q: 74 (57–93)	2,801 (2,392–3,307)	5 (1–10)	All: 374 (329–420) Trisomies 21, 18, 13: 146 (121–173) SCA: 193 (159–227) 22Q: 36 (24–48)	181,381
Trisomies 21, 18, and 13, sex chromosome aneuploidies (expected prevalence) and 22q11.2 deletion (75% detection rate)	88,806,163 (76,749,356–100,783,584)	All: 520 (456–596) Trisomies 21, 18, 13: 273 (225–337) SCA: 186 (157–216) 22Q: 62 (46–77)	2,791 (2,381–3,303)	5 (1–9)	All: 378 (333–424) Trisomies 21, 18, 13: 147 (124–170) SCA: 193 (158–227) 22Q: 39 (27–51)	187,534
Trisomies 21, 18, and 13, sex chromosome aneuploidies (expected prevalence) and 22q11.2 deletion (50% detection rate)	88,711,674 (76,501,667–100,834,662)	All: 499 (432–572) Trisomies 21, 18, 13: 273 (218–339) SCA: 185 (157–213) 22Q: 42 (30–55)	2,769 (2,379–3,273)	5 (1–9)	All: 383 (340–427) Trisomies 21, 18, 13: 146 (123–171) SCA: 192 (161–224) 22Q: 44 (32–58)	199,667

Abbreviations: 22Q, 22q11.2 deletion; CrI, credible interval; DR, detection rate; NIPT, noninvasive prenatal testing; SCA, sex chromosome aneuploidies.

Note: Numbers may appear inexact due to rounding.

^aWe compared first-tier NIPT (including sex chromosome aneuploidies and 22q11.2 deletion) with second-tier NIPT. The cost and effectiveness of first-tier NIPT (including sex chromosome aneuploidies and 22q11.2 deletion) were based on simulations from the scenario analysis, but the cost and effectiveness of second-tier NIPT were based on the results of the reference case analysis. See Table 18 (reference case) for cost and effectiveness outcomes for second-tier NIPT.

Increased Uptake of First-Tier NIPT

Increasing the uptake of first-tier NIPT led to increased total costs and a greater number of affected fetuses detected (Table 22) compared to the reference case. The incremental cost-effectiveness of first-tier NIPT improved with an increase in uptake rate.

Table 22: Scenario Analysis Results, Increased Uptake of First-Tier NIPT

Uptake of First-Tier NIPT	Total Costs (95% CrI), \$	Cases Detected (95% CrI), n	Diagnostic Tests Performed (95% CrI), n	Diagnostic-Procedure-Related Pregnancy Losses (95% CrI), n	Affected Live Births (95% CrI), n	Incremental Cost Per Case Detected, vs. Second-Tier NIPT, ^a \$
80%	70,132,717 (60,705,461–79,300,267)	All: 321 (263–400) Trisomy 21: 224 (176–286) Trisomy 18: 75 (45–116) Trisomy 13: 22 (9–42)	2,497 (2,154–2,859)	4 (1–9)	All: 129 (105–155) Trisomy 21: 98 (78–120) Trisomy 18: 18 (10–26) Trisomy 13: 13 (6–21)	327,247
90%	77,488,657 (67,296,999–87,898,000)	All: 362 (296–451) Trisomy 21: 253 (197–321) Trisomy 18: 84 (53–129) Trisomy 13: 24 (10–46)	2,807 (2,443–3,187)	5 (1–9)	All: 114 (92–136) Trisomy 21: 86 (68–104) Trisomy 18: 15 (8–24) Trisomy 13: 12 (5–20)	293,134
100%	84,473,692 (72,615,687–96,107,514)	All: 400 (326–495) Trisomy 21: 280 (220–360) Trisomy 18: 93 (58–141) Trisomy 13: 27 (12–52)	3,124 (2,708–3,563)	6 (2–11)	All: 98 (79–120) Trisomy 21: 74 (57–93) Trisomy 18: 14 (7–21) Trisomy 13: 11 (5–19)	273,187

Abbreviations: CrI, credible interval; NIPT, noninvasive prenatal screening.

Note: Numbers may appear inexact due to rounding.

^aSee Table 18 (reference case) for cost and effectiveness outcomes for second-tier NIPT.

Results From a Cochrane Systematic Review on NIPT Test Accuracy

In general, the detection rates of trisomy 21, 18, and 13 from BORN data and our clinical evidence review were similar to those found in the Cochrane review.⁶⁶ However, the number of NIPT false positives from the BORN data was much higher than that from the Cochrane review (2% versus 0.1%). When we used the test accuracy results from the Cochrane review in our model, the number of diagnostic tests performed for first-tier NIPT was substantially reduced, from 2,125 in the reference case to 572 (95% CrI, 442–710). As a result, the total cost of first-tier NIPT also decreased. In contrast, using the Cochrane review results had only a marginal effect on the second-tier NIPT results (Table 23).

Table 23: Scenario Analysis Results, Results From a Cochrane Systematic Review on NIPT Test Accuracy

Strategy	Total Costs (95% CrI), \$	Cases Detected (95% CrI), n	Diagnostic Tests Performed (95% CrI), n	Diagnostic- Procedure-Related Pregnancy Losses (95% CrI), n	Affected Live Births (95% CrI), n	Incremental Cost Per Case Detected, vs. Second-Tier NIPT, \$
Second-tier NIPT	26,649,544 (23,187,889– 29,795,150)	All: 189 (148–236) Trisomy 21: 148 (112–195) Trisomy 18: 41 (23–64) Trisomy 13: 0 (0–1)	659 (584–742)	1 (0–3)	All: 177 (150–204) Trisomy 21: 132 (109–155) Trisomy 18: 25 (15–35) Trisomy 13: 21 (12–31)	—
First-tier NIPT	59,674,614 (51,919,853– 67,932,570)	All: 269 (215–331) Trisomy 21: 192 (150–246) Trisomy 18: 62 (37–94) Trisomy 13: 15 (5–31)	572 (442–710)	1 (0–3)	All: 148 (124–173) Trisomy 21: 112 (91–134) Trisomy 18: 20 (12–30) Trisomy 13: 15 (8–24)	412,010

Abbreviations: CrI, credible interval; NIPT, noninvasive prenatal testing.

Note: Numbers may appear inexact due to rounding.

A Lower Trisomy 21 Risk Cutoff for Traditional Prenatal Screening in Second-Tier NIPT

We used a trisomy 21 risk cutoff of 1:700 (compared with 1:400 for eFTS and 1:200 for MSS in the reference case) to determine positive results for traditional prenatal screening (i.e., false-positive rate around 10% for trisomy 21) in second-tier NIPT. A risk cutoff is a threshold used to determine whether screening results are positive (high risk for a chromosomal anomaly) or negative (low risk for a chromosomal anomaly). A risk cutoff of 1:700 means that the screening test results are described as “positive” if they show that a fetus’s chance of having a chromosomal anomaly is 1 in 700 or higher. With this cutoff, the detection rate increased compared with the reference case (eFTS, 94.8% versus 91.2%; MSS, 80.8% versus 65.4%), and an additional seven cases of trisomy 21 were detected (Table 24). Compared with second-tier NIPT in the reference case, the volumes of NIPT and diagnostic testing, as well as the total screening cost, also increased. We did not consider a potential increase in detection of trisomies 18 and 13 when using a lower cutoff for trisomy 21.

We also conducted analyses for second-tier NIPT using a lower trisomy 21 risk cutoff of 1:700 in combination with a higher acceptance rate for further testing (90%) after positive results from traditional prenatal screening. Compared with second-tier NIPT in the reference case, this scenario detected an additional 43 affected fetuses. However, the detection of affected fetuses using second-tier NIPT was still less than that using first-tier NIPT.

Table 24: Scenario Analysis Results, A Lower Trisomy 21 Risk Cutoff for Traditional Prenatal Screening in Second-Tier NIPT

Scenario	Total Costs (95% CrI), \$	Cases Detected (95% CrI), n	Diagnostic Tests Performed (95% CrI), n	Diagnostic- Procedure- Related Pregnancy Losses (95% CrI), n	Affected Live Births (95% CrI), n	Incremental Cost Per Case Detected, First- Tier vs. Second- Tier NIPT, \$
Acceptance of further testing after a positive result from traditional prenatal screening: 76% (same as reference case)	28,949,494 (25,455,144–32,548,127)	All: 195 (153–247) Trisomy 21: 154 (117–202) Trisomy 18: 41 (23–65) Trisomy 13: 0 (0–2)	908 (782–1,047)	1 (0–3)	All: 174 (148–201) Trisomy 21: 129 (106–152) Trisomy 18: 24 (15–35) Trisomy 13: 21 (13–31)	415,702
Acceptance of further testing after a positive result from traditional prenatal screening: 90%	29,488,926 (25,937,229–32,769,117)	All: 231 (181–288) Trisomy 21: 182 (140–234) Trisomy 18: 49 (27–76) Trisomy 13: 0 (0–2)	1,055 (920–1,210)	1 (0–4)	All: 161 (135–188) Trisomy 21: 117 (94–140) Trisomy 18: 23 (13–34) Trisomy 13: 21 (12–31)	758,384

Abbreviations: CrI, credible interval; N, number; NIPT, noninvasive prenatal screening.

Note: Numbers may appear inexact due to rounding.

^aIncremental cost per case detected for first-tier NIPT (see Table 18 for reference case results) versus second-tier NIPT (the present scenario).

A Subgroup of Pregnant People 35 to 39 Years Old

Results for the scenario analysis assessing a subgroup of pregnant people aged 35 to 39 years are presented in Table 25. According to our simulations, this subgroup accounted for approximately 20% of average-risk pregnant people who were less than 40 years old. This subgroup had 237 (95% CrI, 190–295) affected fetuses, accounting for about 46% of the affected fetuses in the entire average-risk cohort. Compared with second-tier NIPT, first-tier NIPT led to an additional cost of \$6.8 million (95% CrI, \$5.4 million–8.5 million) for this cohort of 28,563 pregnant people. The incremental cost per affected case detected of first-tier versus second-tier NIPT was \$173,680, lower than that for the entire reference case cohort (\$411,274).

Primary Economic Evaluation

August 2018

Table 25: Scenario Analysis Results, A Subgroup of Pregnant People 35 to 39 Years Old^a

Strategy	Total Costs (95% CrI), \$	Cases Detected (95% CrI), n	Diagnostic Tests Performed (95% CrI), n	Diagnostic-Procedure-Related Pregnancy Losses (95% CrI), n	Affected Live Births (95% CrI), n	Incremental Cost Per Case Detected, vs. Second-Tier NIPT, \$
Traditional prenatal screening	5,540,080 (4,888,764–6,164,005)	All: 73 (52–98) Trisomy 21: 56 (38–77) Trisomy 18: 17 (7–29) Trisomy 13: 0 (0–2)	653 (482–841)	1 (0–4)	All: 87 (69–107) Trisomy 21: 65 (49–82) Trisomy 18: 12 (6–20) Trisomy 13: 10 (4–16)	—
Second-tier NIPT	5,398,917 (4,744,893–6,045,225)	All: 87 (64–114) Trisomy 21: 67 (46–91) Trisomy 18: 20 (10–33) Trisomy 13: 0 (0–1)	191 (159–225)	0 (0–1)	All: 82 (65–100) Trisomy 21: 60 (46–76) Trisomy 18: 12 (6–19) Trisomy 13: 10 (4–17)	—
First-tier NIPT	12,257,869 (10,619,425–13,982,271)	All: 126 (98–162) Trisomy 21: 87 (64–117) Trisomy 18: 31 (17–50) Trisomy 13: 9 (2–18)	490 (423–564)	1 (0–3)	All: 68 (52–85) Trisomy 21: 51 (38–67) Trisomy 18: 10 (4–16) Trisomy 13: 7 (2–13)	173,680

Abbreviations: CrI, credible interval; NIPT, noninvasive prenatal testing.

Note: Numbers may appear inexact due to rounding.

^aAverage cohort size: 28,563 pregnant people.

Sensitivity Analysis

Table 26 shows the results of the sensitivity analyses. We examined several factors that could affect the costs and effectiveness of different screening strategies: NIPT price, NIPT false-positive rate, higher trisomy prevalence, acceptance rate for further testing, and higher NIPT failure rate.

The price of NIPT affected the total screening costs of first-tier NIPT, but it had minimal impact on the costs for second-tier NIPT. When the NIPT false-positive rate was lower (e.g., 0.5% or 1%), the number of diagnostic tests for first-tier NIPT decreased substantially, and the total cost of screening for this strategy was also reduced. When the prevalence of trisomies increased (e.g., due to the increasing maternal age at date of delivery), the number of affected cases detected also increased. When a greater proportion of people with positive results from initial screening accepted further testing (for first-tier or second-tier NIPT), the number of affected cases detected also increased.

Table 26: Sensitivity Analysis Results, Prenatal Screening Strategies

Variable	Strategy	Total Costs (95% CrI), \$	Cases Detected (95% CrI), n	Diagnostic Tests Performed (95% CrI), n	Incremental Cost Per Case Detected, First-Tier vs. Second-Tier NIPT, \$
NIPT Price					
\$200	Second-tier NIPT	26,084,204 (22,798,602–29,280,686)	NA ^a	NA ^a	—
	First-tier NIPT	42,750,076 (38,190,790–47,735,425)	NA ^a	NA ^a	198,236
\$300	Second-tier NIPT	26,412,508 (22,909,454–29,548,072)	NA ^a	NA ^a	—
	First-tier NIPT	52,333,813 (45,555,192–58,487,874)	NA ^a	NA ^a	309,106
\$500	Second-tier NIPT	27,119,609 (23,728,181–30,263,419)	NA ^a	NA ^a	—
	First-tier NIPT	72,141,215 (62,179,210–82,628,259)	NA ^a	NA ^a	535,404
\$600	Second-tier NIPT	27,460,478 (24,118,240–30,805,287)	NA ^a	NA ^a	—
	First-tier NIPT	81,849,048 (70,303,593–93,705,152)	NA ^a	NA ^a	647,421
NIPT False-Positive Rate					
0.1%	Second-tier NIPT	26,654,498 (23,246,365–29,967,176)	NA ^a	659 (582–746)	—
	First-tier NIPT	59,789,622 (51,478,080–68,306,686)	NA ^a	571 (444–699)	394,997
0.5%	Second-tier NIPT	26,715,288 (23,418,883–29,980,976)	NA ^a	672 (599–757)	—
	First-tier NIPT	59,991,375 (51,792,152–68,305,006)	NA ^a	901 (766–1,036)	396,309
1%	Second-tier NIPT	26,725,446 (23,407,759–29,910,452)	NA ^a	687 (608–773)	—
	First-tier NIPT	60,395,928 (52,277,838–68,913,184)	NA ^a	1,308 (1,178–1,445)	403,157

Trisomy Prevalence					
10% lower prevalence of trisomies 21, 18 and 13 than the reference case	Second-tier NIPT	26,637,545 (23,471,426–30,144,412)	169 (130–211)	702 (623–796)	—
	First-tier NIPT	61,228,599 (53,246,695–69,691,743)	245 (194–301)	2,108 (1,821–2,406)	456,702
20% higher prevalence of trisomies 21, 18, and 13 than the reference case	Second-tier NIPT	26,757,004 (23,432,884–29,950,239)	225 (179–282)	754 (671–857)	—
	First-tier NIPT	61,468,969 (53,499,592–69,764,090)	326 (260–399)	2,177 (1,900–2,492)	342,973
Acceptance Rate for Further Testing					
After positive NIPT results, first-tier NIPT: 90%	First-tier NIPT	61,461,986 (53,728,139–69,621,998)	288 (232–358)	2,242 (1,936–2,554)	347,947 ^b
After positive NIPT results, first-tier NIPT: 95%	First-tier NIPT	61,526,572 (53,679,534–69,414,722)	305 (244–374)	2,368 (2,049–2,719)	299,771 ^b
After positive results from traditional prenatal screening, second-tier NIPT: 85%	Second-tier NIPT	26,910,157 (23,520,315–30,207,872)	210 (166–267)	804 (711–916)	546,804 ^c
After positive results from traditional prenatal screening, second-tier NIPT: 95%	Second-tier NIPT	27,163,740 (23,753,183–30,751,347)	234 (188–298)	898 (800–1,008)	891,252 ^c
NIPT Failure Rate					
4% ^d	Second-tier NIPT	26,774,569 (23,364,183–30,097,831)	188 (147–236)	783 (687–880)	—
	First-tier NIPT	61,567,714 (53,390,895–70,139,842)	270 (216–330)	2,310 (2,046–2,588)	426,967
Cost of Post-Test Physician Visits for Pregnant People With Positive Screening Results for All Strategies					
\$33.7	Second-tier NIPT	26,475,773 (23,201,201–29,875,843)	NA ^a	NA ^a	—
	First-tier NIPT	61,197,204 (52,937,184–69,348,009)	NA ^a	NA ^a	413,414

Abbreviations: CrI, credible interval, NIPT, noninvasive prenatal testing.

Note: Numbers may appear inexact due to rounding.

^aThis analysis did not affect the results of this outcome, which was same as that reported in Table 18 (reference case).^bThe cost and effectiveness of second-tier NIPT was based on the reference case results.^cThe cost and effectiveness of first-tier NIPT was based on the reference case results.^dThere was no additional cost for a repeat NIPT test.

Discussion

Our economic evaluation showed that second-tier NIPT performed better than traditional screening—increasing the number of detected fetuses and decreasing the number of diagnostic tests performed. The main reason for the higher detection rate was increased acceptance of further testing after positive screening results with second-tier NIPT. The total cost of second-tier NIPT was slightly lower than that of traditional prenatal screening, mainly because of the reduced volume of diagnostic testing. In general, these findings were consistent with a recently published study by Huang et al⁷⁴ using Ontario data and Ontario-specific costs.

Compared with second-tier NIPT, first-tier NIPT detected more affected fetuses, but at a significantly increased total cost. According to the study by Huang et al, detection rates for trisomy 21 with first-tier or second-tier NIPT could be very close if a lower risk cutoff was used to define positive results in traditional prenatal screening for second-tier NIPT.⁷⁴

There were some other differences between our evaluation and the study by Huang et al. We included trisomies 21, 18, and 13, and used different acceptance rates for further testing after a positive NIPT result (85% for first-tier NIPT and 76% for second-tier NIPT).⁵⁵ Therefore, some of the additional affected cases identified by first-tier NIPT occurred not only because of the higher detection rate of NIPT, but also because of expected higher uptake of diagnostic testing. In contrast, the study by Huang et al. focused only on trisomy 21 and assumed that 100% of pregnant people with positive screening results would accept further testing for both first-tier and second-tier NIPT.⁷⁴ Furthermore, our economic evaluation included all average-risk pregnant people who accepted (68%) or declined (32%) prenatal screening. The study by Huang et al included only pregnant people who accepted prenatal screening.⁷⁴

In this study, the main factors affecting the costs and effectiveness of the different prenatal screening strategies were the uptake rate of prenatal screening, the acceptance rate of further testing after positive screening results, test accuracy, and the prices of both traditional prenatal screening and NIPT.

We discuss other findings from our economic evaluation below.

Measure of Effectiveness

Canadian economic evaluation guidelines recommend using quality-adjusted life-years (QALYs) as the primary measure of effectiveness whenever possible.¹¹⁶ However, QALYs were not a feasible measure for this evaluation. Detection of an affected fetus may lead a pregnant person to terminate the affected pregnancy. The “effectiveness” of these two outcomes (i.e., newborn affected with a chromosomal anomaly versus termination of pregnancy) cannot be readily compared using a measure such as the life-year or QALY. There is also no consensus in the literature about whether to include only pregnant people in economic evaluations, or to include pregnant people, their partners, and their newborns. Furthermore, because of a paucity of published studies assessing health utilities related to terminating a pregnancy, health utilities related to having (or not having) a child with a chromosomal anomaly, and the duration of psychological effects related to clinical outcomes, it is difficult to reliably estimate QALYs for pregnant people and newborns. For this reason, we did not conduct a cost–utility analysis.

As well, we did not include psychological outcomes in our economic evaluation. The two most relevant psychological outcomes are anxiety and depression related to either a positive test result or a pregnancy loss (i.e., spontaneous pregnancy loss, procedure-related pregnancy loss,

or voluntary termination). A Canadian study concluded that prenatal screening did not cause serious psychological harm to pregnant people in Ontario.¹¹⁷ However, there are psychological outcomes associated with the termination of pregnancy, and likely psychological effects for pregnant people who choose to continue with an affected pregnancy. It was therefore difficult to justify how to appropriately incorporate psychological outcomes in our model.

Sex Chromosome Aneuploidies and Microdeletion Syndromes

In addition to trisomies 21, 18, and 13, we included four common sex chromosome aneuploidies and 22q11.2 deletion syndrome in the scenario analyses. At present, reliable prevalence data for these conditions are sparse. In addition, the accuracy of NIPT for these conditions in the average-risk or general population has not been well investigated. Therefore, the results of these analyses were less robust and should be interpreted with caution.

Real-World Performance of Screening Tests

We based detection rates and false-positive rates for NIPT and MSS on local Ontario data. Data collection is still ongoing, so findings on test performance are still preliminary. We addressed these data-quality issues in the scenario analyses. Clinical trials often recruit homogeneous populations by setting rigid inclusion and exclusion criteria; real-world data likely includes more heterogeneous cohorts that better reflect the actual population. In addition, the chromosomal anomalies of interest are relatively rare, so one or two affected cases can greatly affect detection rates; it is not surprising that greater variation in test performance may be observed in real-world data.

Prenatal Screening in Twin Pregnancies

In Ontario, approximately 3% of infants are from a multiple-gestation pregnancy (4,730 from 147,244 pregnancies in 2015–2016),⁸¹ and the majority of multiple-gestation pregnancies involve twins. We did not include twin pregnancies in our analyses because the published data on eFTS and MSS performance for twins is sparse. One review¹⁸ found lower detection rates with NIPT in twins compared with singleton pregnancies (9%, 28%, and 22% lower for trisomies 21, 18, and 13, respectively), but another systematic review¹¹⁸ reported very high pooled NIPT accuracy for twin pregnancies (99% [95% CI, 92%–100%] for trisomy 21 and 85% [95% CI, 55%–98%] for trisomy 18). Furthermore, the clinical pathway for screening twin pregnancies is more complex. Because of these uncertainties in the model inputs, we did not conduct an analysis for twins.

Cost of Live Births Affected by Chromosomal Anomalies

We did estimate the number of live births affected by the chromosomal anomalies of interest. However, we did not estimate the long-term costs of managing these conditions because of ethical considerations related to valuing the lives of people with these chromosomal anomalies, and to comparing those costs to the consequences of pregnancy termination.

Health Costs Not Included in the Economic Analysis

We did not include the following costs in the economic analysis, because it was difficult to accurately estimate them, and because they would have had a minimal impact on our analyses:

- We did not include additional follow-up costs for those who received a positive screening result but declined confirmatory diagnostic testing; still, this population may receive additional follow-up visits or interventions based on their positive screening result
- We did not consider the additional use of health care resources for a second blood draw for NIPT. We assumed that there would be no additional test cost because a second draw for NIPT is currently covered for a pregnant person if the first draw fails
- In the case of first-tier NIPT, MSS would be performed only for pregnant people with a failed NIPT test result. In this situation, the cost of MSS would likely be higher because of the low volume of tests performed

Study Strengths

Our study had the following strengths:

- Our key parameters, main model assumptions, and screening pathways reflected the current prenatal screening context in Ontario and were verified by clinical experts
- We obtained local Ontario data to estimate several important parameters in the model, including NIPT test accuracy for trisomy 21 and the uptake of prenatal screening
- We evaluated the effect of including NIPT for additional chromosomal anomalies (i.e., sex chromosome aneuploidies and microdeletions). Previous economic evaluations have focused on the use of NIPT for only trisomies 21, 18, and 13

Study Limitations

The following limitations should be noted when interpreting the findings of this analysis:

- First-tier NIPT has not been adopted in most developed countries; therefore, we did not find high-quality evidence for input parameters related to this screening strategy
- The reality of prenatal screening is more complex than our current model. However, our model includes the most common screening pathways that affect most pregnant people
- We found no high-quality evidence for input parameters related to sex chromosome aneuploidies and microdeletions; results should be interpreted with caution
- Data collection by BORN is ongoing; results using this preliminary data should be interpreted with caution

Conclusions

Compared with traditional prenatal screening, NIPT as a second-tier test improved overall prenatal screening performance by detecting more affected fetuses and substantially reducing the number of diagnostic tests performed, with decreased costs. Compared with second-tier NIPT, first-tier NIPT could detect more affected fetuses, but would increase total prenatal screening costs considerably.

BUDGET IMPACT ANALYSIS

Research Question

What is the potential budget impact for the Ontario Ministry of Health and Long-Term Care of publicly funding first-tier noninvasive prenatal testing (NIPT) for average-risk pregnant people with singleton pregnancies?

Methods

Analytic Framework

We estimated the budget impact of NIPT as the cost difference between two scenarios: second-tier NIPT (the current scenario) and first-tier NIPT (the new scenario). We focused on average-risk pregnant people with singleton pregnancies in our analysis.

When risk classification is determined at the initial stage of screening (i.e., before prenatal screening), pregnant people aged 40 years or older at date of delivery and pregnant people who have had a previous pregnancy with a chromosomal anomaly are considered high-risk; NIPT is already publicly funded for this population, according to the current Ontario funding policy. Thus, we have limited our scope to the average-risk population: pregnant people less than 40 years old and who have had no previous pregnancy with a chromosomal anomaly. Because the published literature on the performance of NIPT and traditional prenatal screening in twin pregnancies is limited, we did not include twins in our analysis. The clinical pathway for twin pregnancies is also more complex, and the funding policy for twin pregnancies is not the same as for singleton pregnancies.

We conducted a reference case analysis and scenario analyses. Our reference case analysis represents the analysis with the most likely set of input parameters and model assumptions. Our scenario analyses explored how the results are affected by varying input parameters and model assumptions.

Target Population

The target population was average-risk pregnant people with a singleton pregnancy who chose prenatal screening. The process for estimating the target population is outlined in Figure 12, and expected target populations for years 1 to 5 (i.e., 2017/18 to 2021/22) are presented in Table 27. The total number of newborns has increased slightly in recent years, from 140,999 in 2011/12 to 147,244 in 2015/16 (Table 28).¹¹⁹ Assuming that this trend continues (1% increase per year), the projected number of newborns would be 150,204 in year 1 (2017/18) and 156,303 in year 5 (2021/22; Table 27). In addition, the number of newborns from multiple-gestation pregnancies decreased slightly from 2012/13 to 2014/15, but was stable in 2014/15 and 2015/16 (Table 28).⁸¹ We assumed that the total newborns per year from multiple-gestation pregnancies over the next 5 years would be same as that in 2015/16. We then approximated the total number of people with singleton pregnancies.

According to data for 2014–2016 from the Better Outcomes Registry and Network (BORN), 4.2% of people were aged 40 years or older at time they delivered.⁸¹ Assuming that a very small proportion of pregnant people had a previous pregnancy with a chromosomal anomaly, approximately 95% of people would fall into the average-risk category. Including a background risk of 3% of spontaneous pregnancy loss between 12 weeks (first trimester) and full term,^{93,98} we estimated that the number of average-risk people with a singleton pregnancy in

the first trimester would be approximately equal to the estimated number of average-risk people multiplied by 1.03 (e.g., $138,200 \times 1.03 = 142,346$ in year 1).

Prenatal screening is voluntary, and pregnant people may choose to accept or decline it. The uptake rate is approximately 68% among average-risk pregnant people in Ontario (BORN data). Assuming that uptake is constant over the next 5 years, we estimated that about 96,602 and 100,653 pregnant people would accept prenatal screening in years 1 and 5, respectively.

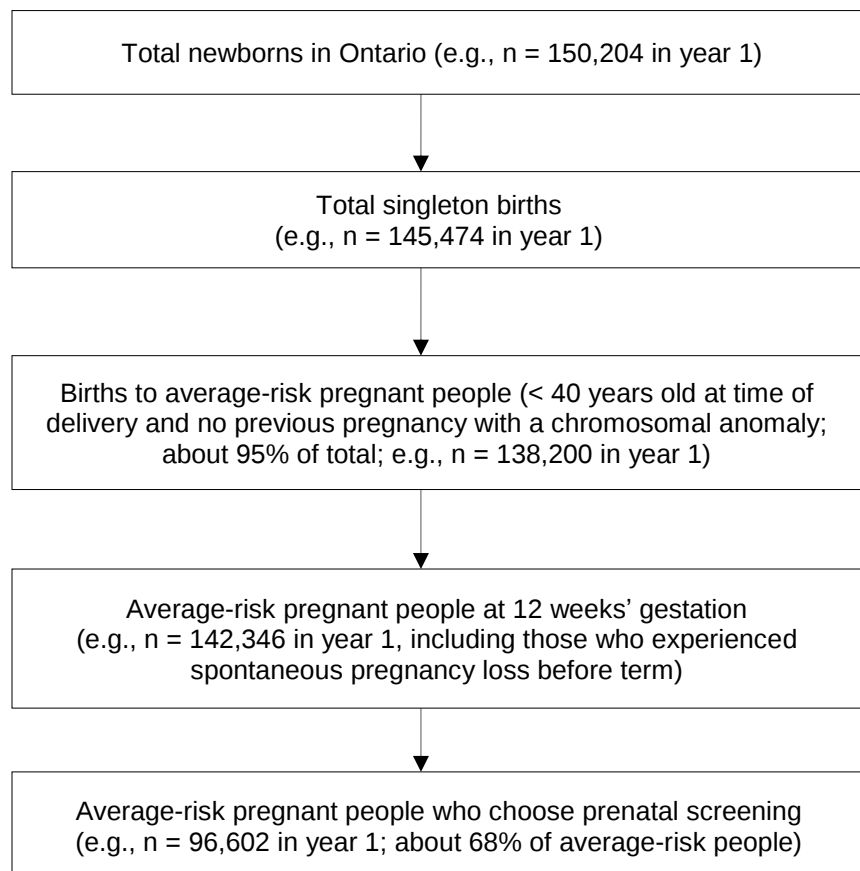


Figure 12: Estimating the Target Population

Table 27: Expected Target Population for Prenatal Screening in Ontario

Population	Year 1	Year 2	Year 3	Year 4	Year 5
Total newborns	150,204	151,706	153,223	154,755	156,303
Newborns from a multiple-gestation pregnancy	4,730	4,730	4,730	4,730	4,730
Total singleton births	145,474	146,976	148,493	150,025	151,573
Births to average-risk pregnant people ^a	138,200	139,627	141,068	142,524	143,994
Average-risk pregnant people at 12 weeks' gestation ^b	142,346	143,816	145,300	146,800	148,314
Average-risk pregnant people who choose prenatal screening ^c	96,602	97,600	98,607	99,625	100,653
First trimester (90%)	87,116	88,016	88,924	89,842	90,769
Second trimester (10%)	9,486	9,584	9,683	9,783	9,884

Note: Some numbers may appear inexact due to rounding.

^aAccording to data for 2014–2016 from the Better Outcomes Registry and Network (BORN), 4.2% of people were ≥ 40 years old at time they delivered.⁸¹ Assuming that a very small proportion of pregnant people had a previous pregnancy with a chromosomal anomaly, approximately 95% of people would fall into the average-risk category.

^bAssuming a spontaneous pregnancy loss background risk of 3% between 12 weeks (first trimester) and term,^{93,98} we estimated that the number of average-risk people with a singleton pregnancy during the first trimester would be approximately equal to the estimated number of average-risk people multiplied by 1.03 (e.g., 138,200 × 1.03 = 142,346 in year 1).

^cThe uptake rate for prenatal screening is approximately 68% among average-risk pregnant people in Ontario (BORN data).

Table 28: Total Newborns and Multiple-Gestation Pregnancies in Ontario, 2011/12–2015/16

	2011/12	2012/13	2013/14	2014/15	2015/16	Sources
Total newborns	140,999	142,367	144,051	145,513	147,244	Statistics Canada ¹¹⁹
Newborns from a multiple-gestation pregnancy	NA	5,263	5,185	4,784	4,730	BORN ⁸¹ (2014–2016)

Abbreviations: BORN, Better Outcomes Registry and Network.

Current and New Screening Scenarios

In Ontario, NIPT is publicly funded only as a second-tier test for our target population (i.e., pregnant people less than 40 years old at time of delivery, with a singleton pregnancy, without a previous pregnancy with a chromosomal anomaly) for trisomies 21, 18, and 13, and for sex chromosome aneuploidies (the current scenario). The new screening scenario is first-tier NIPT for trisomies 21, 18, and 13.

Resource and Costs

Based on results from the primary economic evaluation, we estimated the health care costs of first-tier and second-tier NIPT for average-risk pregnant people, using uniform uptake rates and including additional chromosomal anomalies. We translated the health care costs for each strategy in the reference case and various scenario analyses into a standardized cohort size (per 10,000 pregnant people; Table 29). The scenario analyses are described in the primary economic evaluation. Costs included physician fees, prenatal screening, genetic counselling, diagnostic testing, and the costs related to termination of pregnancy. All costs are reported in 2017 Canadian dollars. Additional details on the included cost components can be found in the primary economic analysis.

Table 29: Average Costs for First-Tier and Second-Tier NIPT Per 10,000 Pregnant People

Analysis	First-Tier NIPT, \$	Second-Tier NIPT, \$
Reference case ^a	4,226,461	1,838,133
Scenario Analyses		
Increased uptake of first-tier NIPT		
80%	4,836,005	1,838,133
90%	5,343,235	1,838,133
100%	5,824,888	1,838,133
Inclusion of sex chromosome aneuploidies in first-tier NIPT	4,767,412 ^a	1,838,133
Inclusion of sex chromosome aneuploidies and 22q11.2 deletion in first-tier NIPT	6,117,118 ^b	1,838,133
Varying price of NIPT		
\$200	2,947,834	1,798,638
\$300	3,608,681	1,821,276
\$500	4,974,501	1,870,034
Funding first-tier NIPT for pregnant people 35–39 years old	4,291,520	1,890,179

Abbreviation: NIPT, noninvasive prenatal testing.

Note: Some numbers may appear inexact due to rounding. All costs are in 2017 Canadian dollars.

^aPrice of NIPT is \$390.

^aCosts were based on the expected prevalence of sex chromosome aneuploidies and trisomies 21, 18, and 13.

^bCosts were based on an NIPT detection rate of 50% for 22q11.2 deletion.

Analysis

We calculated the budget impact as the cost difference between the new scenario (first-tier NIPT) and the current scenario (second-tier NIPT) for average-risk pregnant people. We calculated the total cost for each scenario using the average cost per pregnant person multiplied by the number of pregnant people per year. We also calculated the total net budget impact over 5 years.

In addition to the reference case, we conducted the following scenario analyses (Table 29):

- Increased uptake of first-tier NIPT
- Inclusion of sex chromosome aneuploidies in first-tier NIPT
- Inclusion of sex chromosome aneuploidies and 22q11.2 deletion in first-tier NIPT
- Varying price of NIPT
- Funding first-tier NIPT for pregnant people 35 to 39 years old

We conducted the budget impact analysis using Excel 2013 (Microsoft, Redmond, Washington).

Expert Consultation

We solicited expert feedback on NIPT. The consultation included experts in medical genetics, fetal medicine, primary care, genetic counselling, prenatal health care services, laboratory medicine, methodology, and industry. The role of the expert advisers was to help define the scope and research question, contextualize the evidence, review the draft report, and provide advice on NIPT and its use in Ontario.

Results

Reference Case

Table 30 presents the projected total costs of first-tier and second-tier NIPT, as well as the expected net budget impact. In the reference case analysis, first-tier NIPT would lead to an annual budget increase of \$34 million to \$35 million per year over the next 5 years.

Table 30: Budget Impact Analysis Results, Reference Case

Strategy	Cost, \$				
	Year 1	Year 2	Year 3	Year 4	Year 5
Second-tier NIPT	26,165,094	26,435,300	26,708,079	26,983,799	27,262,093
First-tier NIPT	60,161,984	60,783,274	61,410,481	62,044,450	62,684,336
Net budget impact	33,996,890	34,347,974	34,702,402	35,060,651	35,422,243

Abbreviation: NIPT, noninvasive prenatal testing.

Note: Some numbers may appear inexact due to rounding. All costs are in 2017 Canadian dollars.

Scenario Analysis

Table 31 presents the results of the scenario analyses. If uptake of first-tier NIPT increased, it would lead to a greater budget impact. If first-tier NIPT screening included trisomies 21, 18, and 13, and sex chromosome aneuploidies, the annual budget increase would be \$42 million to \$43 million per year. If the price of NIPT decreased, the net budget impact would decrease accordingly. If first-tier NIPT were funded for pregnant people 35 to 39 years old, the annual budget increase would be \$7 million per year.

Table 31: Budget Impact Analysis Results, Scenario Analyses

		Cost, \$				
Scenario	Strategy	Year 1	Year 2	Year 3	Year 4	Year 5
Increased Uptake of First-Tier NIPT ^a						
80%	First-tier NIPT	68,838,602	69,549,495	70,267,158	70,992,559	71,724,730
Net budget impact	–	42,673,507	43,114,195	43,559,079	44,008,760	44,462,637
90%	First-tier NIPT	76,058,807	76,844,263	77,637,199	78,438,684	79,247,650
Net budget impact	–	49,893,713	50,408,963	50,929,120	51,454,885	51,985,557
100%	First-tier NIPT	82,914,952	83,771,210	84,635,624	85,509,357	86,391,245
Net budget impact	–	56,749,857	57,335,910	57,927,545	58,525,558	59,129,153
Inclusion of Sex Chromosome Aneuploidies in First-Tier NIPT ^a						
Inclusion of sex chromosome aneuploidies	First-tier NIPT	67,862,207	68,563,017	69,270,501	69,985,613	70,707,399
Net budget impact	–	41,697,113	42,127,717	42,562,422	43,001,814	43,445,307
Inclusion of Sex Chromosome Aneuploidies and 22q11.2 Deletion in First-Tier NIPT ^a						
Inclusion of sex chromosome aneuploidies and 22q11.2 deletion	First-tier NIPT	87,074,733	87,973,950	88,881,730	89,799,298	90,725,429
Net budget impact	–	60,909,639	61,538,649	62,173,651	62,815,499	63,463,337
Varying Price of NIPT						
\$200	Second-tier NIPT	25,602,889	25,867,288	26,134,206	26,404,002	26,676,316
	First-tier NIPT	41,961,236	42,394,567	42,832,026	43,274,201	43,720,503
Net budget impact	—	16,358,347	16,527,279	16,697,820	16,870,199	17,044,187
\$300	Second-tier NIPT	25,925,135	26,192,862	26,463,139	26,736,331	27,012,072
	First-tier NIPT	51,368,130	51,898,606	52,434,134	52,975,436	53,521,791
Net budget impact	—	25,442,995	25,705,744	25,970,995	26,239,106	26,509,719
\$500	Second-tier NIPT	26,619,188	26,894,083	27,171,596	27,452,101	27,735,224
	First-tier NIPT	70,810,038	71,541,290	72,279,506	73,025,681	73,778,821
Net budget impact	—	44,190,851	44,647,207	45,107,910	45,573,580	46,043,597
Funding First-Tier NIPT for Pregnant People 35–39 Years Old ^b						
Funding for pregnant people 35–39 years old	Second-tier NIPT	5,299,305	5,353,931	5,409,313	5,465,073	5,521,401
	First-tier NIPT	12,031,706	12,155,731	12,281,472	12,408,072	12,535,960
Net budget impact	—	6,732,401	6,801,800	6,872,159	6,942,999	7,014,559

Abbreviation: NIPT, noninvasive prenatal testing.

Note: Some numbers may appear inexact due to rounding. All costs are in 2017 Canadian dollars.

^aThis scenario did not affect the cost of second-tier NIPT. We estimated the net budget impact using the cost of first-tier NIPT in this scenario minus the total cost of second-tier NIPT in the reference case.

^bThis subgroup accounted for about 20% of average-risk pregnant people < 40 years old. Assuming that the proportion of pregnant people in this age group would be constant over the next 5 years, we estimated that the target population in this subgroup would be 28,036 in year 1, 28,325 in year 2, 28,618 in year 3, 28,913 in year 4, and 29,211 in year 5.

Discussion

Funding first-tier NIPT could lead to a budget increase of approximately \$35 million per year, based on the current price of NIPT (\$390 per test). When we included the costs for genetic counselling and nuchal translucency ultrasound, approximately \$90 in additional costs were associated with first-tier NIPT. This total cost for NIPT (approximately \$480 [\$390 + \$90] per person) is much higher than that of eFTS (\$124.50) or maternal serum screening (\$186.75). If the price of NIPT decreased to \$200 per test, the budget impact for first-tier NIPT would decrease to approximately \$17 million per year.

It is likely that the uptake rate of prenatal screening would increase if NIPT were used as a first-tier test. If the uptake rate increased, first-tier NIPT would lead to a higher budget increase (e.g., an additional \$57 million to \$59 million at an uptake rate of 100%). Finally, if screening for sex chromosome aneuploidies and/or microdeletion syndromes were included in first-tier NIPT, the net budget impact would also increase considerably.

Conclusions

Noninvasive prenatal testing is currently used as a second-tier test in average-risk pregnancies in Ontario. If it were used as a first-tier test instead, it would lead to an annual budget increase of approximately \$35 million per year.

PATIENT PREFERENCES AND VALUES

Objective

The objective of this analysis was to explore the underlying values, needs, preferences, and priorities of those who have lived experience with noninvasive prenatal testing (NIPT).

Background

The patient preferences and values section explores the lived experience of a person with a health condition, including the impact the condition and its treatment has on the patient, the patient's family or other caregivers, and the patient's personal environment. Patient, Caregiver, and Public Engagement intends to increase awareness and build appreciation for the needs, priorities, and preferences of the individual at the centre of a treatment program. The insights provide an in-depth picture of lived experience through an intimate look at the values that underpin the experience.

Lived experience is a unique source of evidence about the personal impact of a health condition and how that condition is managed, including what it is like to navigate the health care system with that condition, and how technologies may or may not make a difference in people's lives. Information shared from lived experience can also identify gaps or limitations in published research (for example, outcome measures that do not reflect what is important to those with lived experience).¹²⁰⁻¹²² Additionally, lived experience can provide information or perspectives on the ethical and social values implications of technologies and treatments.

Because the needs, priorities, preferences, and values of those with lived experience in Ontario are not often adequately explored by published literature, Health Quality Ontario makes an effort to reach out to, and directly speak with, people who are affected by this technology, including those who may have experience with the intervention in question.

This health technology assessment will affect two distinct populations: pregnant people who would like to access prenatal screening, and people living with the conditions that NIPT screens for. Noninvasive prenatal testing may be important to people who would like access to less invasive prenatal screening earlier in their pregnancy. It may also be important to help alleviate anxieties about a pregnancy or help people make decisions about the next steps of testing for a definitive diagnosis.

Recognizing this, we looked to engage with people who represented a variety of perspectives and experiences. The potential effects of implementing or not implementing NIPT more broadly in Ontario may affect people with a diverse range of lived experiences.

Methods

Engagement Plan

Engagement as a concept captures a range of efforts used to involve the public and patients in various domains and stages of health technology assessment decision-making.¹²³ Rowe and Frewer outline three types of engagement: communication, consultation, and participation.¹²⁴ Communication describes a one-way transfer of information from the sponsor to the individual, while participation involves the sponsor and individual collaborating through real-time dialogue. The engagement approach for this health technology assessment was consultation, defined as the seeking out and soliciting of information (for example, experiential input) by the public,

patients, and caregivers who are affected by the technology or intervention in question.¹²⁵ Within this typology, the engagement design focused on interview methodology to examine the lived experience of patients, caregivers, and families, including those who have undergone the intervention.

We selected the qualitative interview as an appropriate consultation methodology because it allowed Health Quality Ontario staff to explore the meaning of central themes in the lived experience of the participants. The main task in interviewing is to understand the meaning of what participants say.¹²⁶ Interviews are particularly useful for getting the story behind a participant's experiences, which was the aim of this portion of the health technology assessment. The sensitive nature of exploring quality-of-life issues supports the use of interviews for this project.

Outreach Methods

For this project we connected with the Ontario Prenatal Screening Program, the Better Outcomes Registry and Network (BORN), the Provincial Council for Child and Maternal Health, the Association of Ontario Midwives, support groups such as Pregnancy and Infant Loss, the Down Syndrome Association of Ontario (local chapters and the provincial organization), the Foundation for Prader-Willi Research Canada, Support Organization for Trisomy 18, 13 and Related Disorders (an international organization; there is no related Canada- or Ontario-specific organization), the Turner Syndrome Society and the Klinefelter Syndrome Association of Canada. We also recruited through social media on a dozen Facebook parent groups representing communities across the province.

Inclusion Criteria

We sought to speak with Ontario residents who had had a pregnancy affected by one of the conditions screened for and who may or may not have used NIPT. We also sought to speak with people living with the conditions NIPT screens for, or with their parents or family members. Participants were not required to have experience with NIPT. We sought broad geographic, cultural, and socioeconomic representations to identify possible equity issues in accessing NIPT.

Exclusion Criteria

We did not set specific exclusion criteria.

Participants

From the population of pregnant people potentially affected by NIPT, we interviewed:

- 7 people who had had false-positive results with traditional prenatal screening and went on to have NIPT
- 2 people who experienced barriers to accessing NIPT
- 5 people whose pregnancies were affected by Down syndrome, Edwards syndrome, Patau syndrome, or Turner syndrome, and who experienced pregnancy loss or infant loss, or who terminated the pregnancy.

From the population living with conditions that NIPT screens for, we interviewed:

- 16 parents of children with Down syndrome
- 2 parents of children with sex chromosome disorders
- 5 adult women with Turner syndrome
- 2 parents of children with Prader-Willi syndrome

Overall, 18 of 39 participants had used NIPT: 13 had accessed it as a second-tier screening test, and 5 had accessed it as a first-tier screening test, either out of pocket or covered by the Ontario Health Insurance Plan because they met the funding criteria.

Approach

At the outset of the interview, we explained the purpose of the health technology assessment, the risks from participation, and how we would protect participants' personal health information. We explained this context verbally and through a call for participation (see Appendix 9). Interviews were recorded and transcribed with participants' consent.

Interviews lasted approximately 20 to 60 minutes. They were semi-structured and consisted of a series of open-ended questions. Questions were based on a list developed by the Health Technology Assessment International Interest Group on Patient and Citizen Involvement in Health Technology Assessment.¹²⁷ Questions focused on the impact of living with one of the conditions screened for, or of parenting a child with one of the conditions screened for, as applicable; the impact of having access or not having access to NIPT; the impact of the timing of access to NIPT; the experience of going through both traditional prenatal screening and/or NIPT as applicable; and participant perceptions of the benefits or limitations of NIPT. See Appendix 10 for our patient interview guide.

Data Extraction and Analysis

We used a modified version of grounded theory methodology to analyze transcripts of participant interviews. Grounded theory follows an iterative process of eliciting, documenting, and analyzing responses while simultaneously collecting and analyzing data using a constant comparative approach.^{128,129} This allowed us to organize and compare information on experiences across participants. Staff coded transcripts and compared themes using NVivo (QSR International, Doncaster, Victoria, Australia), a qualitative software program that enabled identification and interpretation of patterns in the interview data. The themes we identified helped us highlight the impact of NIPT, as well as different aspects of the prenatal screening experience.

Results

Lived Experience With NIPT

Access

The review of the qualitative literature on NIPT¹³⁰ that is a companion to this report revealed that access to NIPT and timing of NIPT were important considerations for people, and this rang true for the people we spoke with as well. People articulated their frustration that the test can be used as early as 9 to 10 weeks of pregnancy, but that their pathway to the screen was not as straightforward as that. Many participants noted that people who would like to access NIPT currently must pay out of pocket if they do not qualify as "high risk" under the Ontario Health Insurance Plan.

Awareness of Self-Pay Option

Several participants said that they had not known that NIPT was an option for them, even if they had to pay for it:

NIPT has never been presented to me—ever—in any of my previous pregnancies as an option that I could have paid for. I now know that there is an option that I can pay—I believe it is \$500, or maybe \$750.

One parent of a child with Down syndrome said that not enough people knew about NIPT as an option:

I think more knowledge of it [NIPT], definitely. People don't understand that it's out there. And I think a lot of people are blindsided by a diagnosis of Down syndrome at delivery, because they're not really aware of how beneficial it is to have this information ahead of time. I'm a big believer that having that information ahead of time really made a world of difference for my family.

Second-Tier Screen

Participants who received false-positive results from traditional screening expressed their frustration and stress knowing that if NIPT had been the first prenatal screening test they underwent, they would likely have gone through less emotional turmoil:

Having this other test available that has these fairly high chances of ... false positives, it does put a lot of people through a lot of stress. If there's a test that's more accurate that is also noninvasive, that it's just blood work, why wouldn't they have the more accurate test available?

If the NIPT test had been available for me from the beginning. I wouldn't have to go through this gruelling process that took weeks and weeks.

Timing of NIPT

Many participants talked about the anxiety and emotional distress of getting a positive result from traditional prenatal screening and having to decide between invasive testing and NIPT, based on the timing of the screening and the accuracy of the results. An example of how this pathway can play out for people is highlighted in the following example: a participant shared the many stages of screening she went through to finally confirm a diagnosis of trisomy 18, a condition in which her baby was unlikely to survive after birth. She had traditional prenatal screening, ultrasounds, NIPT and an amniocentesis. The entire process took many weeks, and by the time she was able to access a medical termination, she was 22 weeks' pregnant.

I think that they should actually do that [NIPT] at 10 weeks, to be completely honest, because you're not at that point where you're so attached. I had already sent out invitations for my baby shower for her. At 10 weeks, it's still obviously hard, but I think it's not as traumatic. I was 5 months pregnant, and the baby was moving, and I was forced to sit there and just wait.

Cost to the System

Delays in accessing publicly funded screening was very frustrating for many people we spoke with, and is well-documented in Ontario-specific research.¹³¹ Several participants who went through traditional screening, followed by NIPT and invasive testing, remarked on the stress they experienced, as well as the cost to the system:

Just taking my personal feelings out of it and looking at it from a system perspective, it would have saved the system a lot of money, in my case, if we had done the NIPT screening at 11 weeks. Because what ended up happening was that I went under a full anaesthetic for a D&C [dilation and curettage] and it was in an emergency operating room—not to mention the CVS [chorionic villus sampling] is expensive; I'd imagine more expensive than the NIPT. There were numerous OB [obstetrician] appointments, there were ultrasounds with specialists ... I required a lot of treatment that could have been avoided with a simple blood test. Not to mention the risk of miscarriage with CVS. When you're in the position I was in, you're already uncomfortable that your baby's not healthy, and to have to make a choice to put them at increased risk [with invasive testing] is really difficult.

Perceived Benefits of NIPT

The majority of participants, representing a wide range of perspectives and experiences, said that NIPT was a great option because it was more accurate than traditional screening, but because it is noninvasive they were less concerned about safety and potential miscarriage than with CVS or amniocentesis. This was articulated by participants who would opt to end a pregnancy and by participants who knew that they would continue a pregnancy regardless of the diagnosis.

Accurate and Noninvasive

As has been noted in the qualitative companion to this report,¹³⁰ the fact that NIPT is noninvasive, can be done early in pregnancy, and is more accurate than traditional prenatal screening makes it very appealing to people who would choose prenatal screening. Participants said that the lower frequency of false positives made it a more desirable screening tool. Many participants preferred being able to access information to support pregnancy decision-making without having to move straight to invasive diagnostic testing. In particular, people who would not have opted to end a pregnancy for any reason could confidently prepare for the birth of a child with a disability without putting their pregnancy at risk.

Many parents of children with Down syndrome who received their positive result from NIPT felt grateful for the information. They appreciated that NIPT wasn't a risk to the pregnancy, and that they could have more accurate information than with traditional prenatal screening. A mother who chose to continue a pregnancy after a positive result for trisomy 18 felt grateful that she and her husband could have the information from NIPT without putting an already at-risk pregnancy at further risk.

We both knew we didn't want to terminate, which is why I turned down the [amniocentesis], because I didn't want to risk terminating the pregnancy even through a miscarriage; I've been through those, and they were horrible. So for me, the NIPT was strictly to confirm the diagnosis, to be able to prepare for

what was coming. I think NIPT is a good tool and a good confirmation for those diagnoses, so that you know and you can research what's coming rather than being surprised at birth.

Access to Information

People with children who had one of the conditions screened for noted that having the information allowed them time to prepare for the birth and educate themselves about their baby's condition. This information also allowed them to access extra medical care for their baby, such as additional ultrasounds and a fetal echocardiogram. They also appreciated having the information so that they could prepare for a baby with a disability by reaching out to support groups, finding other parents in their community who had experience with the condition, and deciding about where to give birth. They were able to read about their baby's condition, talk to clinicians, and share information with family and friends.

Because we knew we weren't going to terminate, we liked the idea of the NIPT, because it still gave us 99% positive without doing anything that we felt was too invasive or too risky. Because we could prepare ourselves, that was the greatest thing for us. We were so OK with everything by the time our daughter arrived. I mean, her birth was pretty typical, because everybody knew she had Down syndrome, nobody had to come in and give us bad news. Finding out at birth would be very difficult because we had basically 6 months of time knowing that she was going to be born with Down syndrome to research Down syndrome, to research what supports were available, to get all that in place as much as we could before she was born, whereas if you find out at birth not only are you a new parent with a new baby, you all of a sudden have all these other things to consider at once, and it's hard enough caring for an infant.

Some participants who had children with Down syndrome were offered the test with subsequent pregnancies and said that it was beneficial to have the information ahead of time so they could prepare for another child with special needs.

A mother of an adult daughter with Down syndrome said that as much information as possible should be provided in terms of screening, testing, and diagnosis. Based on her experience and because it is often women who take on a disproportionate load of caregiving she felt that expectant parents, should be given the opportunity to make informed decisions about an affected pregnancy.

I would want them to have as many facts about everything as they could possibly have. I think it would be helpful for people. My experience taught me that the mother, no matter what kind of situation you're in always is the person who bears the greatest load for caregiving. I don't care how wonderful your family is, in our society it's the woman who does the most and is responsible ultimately even into old age. So first of all, I would like to say if they're making this decision, it's the mother who should call all the shots, because it's the mother who is going to be getting all of the results of her decisions. She is going to mostly bear the brunt. Government promises I have found are not reliable.

For parents expecting a child with a sex chromosome condition, access to this information during pregnancy can lead to earlier intervention with recommended treatments and lead to better health outcomes.

From a growth-hormone standpoint, it's starting to be given earlier and earlier, so I think that that's helping patients with Turner syndrome gain a higher average height. That's one of the benefits of earlier diagnosis. Also, being able to test for other complications and monitor for heart issues is probably one of the biggest advantages [of NIPT].

Preparation for Potential Pregnancy Loss

Another benefit of using NIPT for information is that it can let pregnant people understand if their pregnancy is at risk of miscarriage and can help them prepare for potential loss. A participant with Turner syndrome said:

Because there's such a high miscarriage rate in Turner syndrome, it [NIPT] helps to track the reason why the baby was miscarried. So, from a medical standpoint, I see why this would be very important. I don't know, at a patient level, how that affects mothers emotionally. I guess they get a diagnosis and they can prepare for the worst, should the worst happen.

Concerns About NIPT

Routinization of Screening

A number of participants said that it was often taken for granted by health care providers that people want screening, thereby limiting informed choice and decision-making.

I am somebody who does respect choice, but choice that is informed, right? And for me, this is not an area where people are being fully informed before being asked to make a choice.

Many participants who had received traditional prenatal screening noted that in hindsight it felt routine, just something you did as part of pregnancy care, without being fully aware of the potential consequences.

Well, we didn't really think about it. The prenatal screening was just something you did because everybody did it. We didn't even really think about it until we had the positive screen come back.

As screening such as NIPT becomes more widespread, early in pregnancy and part of the standard of care for pregnant people, there may be increasing expectations of “opt-out” rather than “opt-in” screening.

I was never asked if I wanted to do screening; they just did it. They did not give me a choice. And it was my first pregnancy. I didn't know. I thought this was what everybody gets.

Honestly, it was one of those things where they hand you the requisition, you go and do it, and I never really thought anything of it. People mentioned nuchal fold and Down syndrome and that, but I didn't really pay any attention, because you never really think, “That's going to be me.”

It is important to note that not everyone decides to do screening, and several participants noted that they wanted this choice to be respected. A parent of a toddler with Down syndrome said that she didn't want to do testing or screening of any kind in pregnancy, because of how it would shape her view of her child and her experience of pregnancy.

A lot of people say the advantage [of NIPT] is so that they can prepare, but I really fall into the camp of, I want my hopes and dreams for my child to not be consumed during my pregnancy with what they're not going to be able to do. Disadvantages [of NIPT] are people not having the right information before they take the test, and then potentially just spending their whole pregnancy learning about all the things their child is not going to do when that's not the whole story, and that's not at all what the life of it is.

Another participant shared that she had declined prenatal screening, and she wasn't aware she was being screened when she presented for a nuchal translucency ultrasound, having been told by her doctor, "It's an opportunity for you to see the baby." We heard from participants who initially opted out of screening but then something came up during the pregnancy that led them to do testing, even if they didn't want that information at first.

I did not want to do any testing. You know—the triple screen or whatever is offered early on in your pregnancy—so I didn't do it, and it was at my 21-week scan, the anatomical scan, that they noticed some soft markers for Down syndrome, and that's when I kind of was led down the path of genetic testing ... leading ultimately to an amniocentesis. Certainly, what was being portrayed to me was: "You've got to find this out, because this could be a bad thing," right?

There were also concerns—particularly from parents of children with the disabilities screened for—that the routinization of prenatal screening would extend to NIPT if it were implemented more broadly across the province, and that people would not feel that they could opt out, or would not understand that this simple blood test early in pregnancy could have a significant effect on their pregnancy experience.

It's almost like parents are being faced with two decisions: one to have the testing done, and then second, what does this then mean for your pregnancy?

Understanding Options: Pre- and Post-screening Counselling

At times it was evident that some participants did not always have all the information they needed about what NIPT can screen for or about the accuracy and limitations of NIPT. Some common misperceptions were shared by a couple of participants who incorrectly perceived that NIPT could screen for autism and that NIPT is more accurate than diagnostic testing.

I was told that Down syndrome and autism were the primary sort of catches that NIPT was responsible for.

It's more accurate than the CVS. That was how they described it to me at that prenatal screening clinic. Like its 99.9% where the CVS was—it was a little bit less, actually.

Some participants were concerned that NIPT could falsely reassure people, leading them to believe that their baby had no health issues, even though the screening looks for only a few possible conditions.

I feel like people take the test and they're like, "If it comes back negative, then all of my fears about my child are clear." They're not focusing enough on the fact that it doesn't test for everything.

Participants weren't always given the opportunity for an informed-choice discussion with their health care provider about whether they wanted to do screening and what they would do with the information. Some of the stories we heard pointed to a lack of awareness and education about the conditions screened for, as well as how people might get on a path of screening and testing, perhaps without enough information, and this demonstrated how the implementation of prenatal screening and testing affects people's choices. When people do not understand the full implications of screening and diagnostic testing, they may make choices they would not otherwise make.

We should've sat down before having the CVS, looking back. We should've sat down and we should've talked about, "OK. Well, what do we want to do if this baby does have Turner syndrome? And what is Turner syndrome?" because we didn't even know at that point, before doing the CVS. And if it was, "We want to carry on with the pregnancy," well, maybe we don't want to risk having the CVS. I think when you're in this situation, you go to the hospital, they say there might be something wrong with your baby. You have NIPT, and they kind of brush over some of the things that it might be, but you don't go into any detail, because there's too many options, you know? So then you get your result back from the NIPT and it's like, "OK. We're looking at Turner syndrome. And if you want a CVS, then we need to do it tomorrow, because we're running out of time." And as a pregnant lady, you feel this panic, like, "Oh, my goodness. I need to do things now. I don't want to wait another two or three weeks till I can have an amnio, because what happens if I do decide to terminate the pregnancy? This baby's going to be growing bigger ..."

The impact of the experience of screening can change people's experience of pregnancy, from an exciting time to a time of anxiety and concern. One participant said that after she went through traditional screening and NIPT only to find out that her pregnancy was unaffected by any of the conditions screened for, the experience stayed with her and her partner, to the point that it was affecting their decision-making about where to give birth; they were no longer considering home birth:

After this experience, he's still really freaking out for the chances of me having any issues, so he wants me to give birth at the hospital. So, it does change your view of your pregnancy and your labour, because you're so scared.

The need for information—about screening and testing, and about what information NIPT can provide—was highlighted in many of the stories people shared with us. Participants sometimes felt the urgency of continuing down a pathway for invasive testing because their pregnancy was progressing. Sometimes they felt pressured to seek a definitive diagnosis before they had all the information, even about what condition they might be presented with. One mother said that the

notion of screening itself was something people have a negative association with—the idea that if they are screening for it, it must be bad.

You're going to screen for it, then this is something bad, just like we screen for all kinds of things: prostate cancer, breast cancer, and all kinds of stuff. So if you're going to screen for these three [trisomies 13, 18, 21] or anything else, then obviously this is bad for me. And that's my sticking point. This is a philosophical thing, I guess. You know, I have three children. I know exactly who their parents are, and they are three very different individuals. You don't know ahead of time what the future may bring. You have your parenting skills, you have all kinds of things, but there are issues that people come with that you have no idea.

Another shared that in our culture “if something is different, then it's wrong and it's not good for us.” Other parents worried about people being persuaded to do invasive testing.

I was in the genetic clinic. They have this system where they cattle you in with like 10 or 20 other families in a really small room. And then they explain to you the different stages of the testing. Afterwards, I reflected on it. This is social coercion. Because they put you in a room with all these other families, and they minimize the risk for amniocentesis. They don't talk a lot about the false positives, and they really minimize, just brushed over, the risks for amniocentesis. I'm imagining somebody with English as a second language or isn't as educated or wants to follow the doctor. So here you are sitting in a room, 10 or 20 other people, and this nurse or whoever it was, sitting there saying, “OK, so this is the next step. You do this. And then this is the next step if it comes positive.” And everybody was like, “OK, OK, OK.” And I'm saying, “Whoa, whoa, whoa, wait a minute. Like, where are your other options here?”

Quality of Information: Support for Informed Decision-Making

For many parents of children with the conditions screened for, as well as women with Turner syndrome, up-to-date information presented in a balanced and empathetic way was something they saw as essential to accompany prenatal screening and diagnosis. If there was one thing that nearly all participants were unanimous about, it was the importance of access to good information to support decision-making. Many parents of children with the conditions screened for articulated negative experiences with physicians, nurses and genetic counsellors. They talked about being given one-sided or out-of-date information about their child's condition.

There's the testing and all that, but it's how doctors or genetic counsellors give you the results, and then what kind of information prospective parents are given about a chromosomal condition. That's what makes it. It's not the test itself, it's the information you're getting, and that's where we're trying to help in our community is to try to make sure that new parents get accurate information and they can make a decision that's really well-informed. Access to accurate—not outdated, not stereotypical—information and doctors who deliver the diagnosis in a way that isn't leading is crucial. Especially if it's going to be available widespread, the testing. I think the test is great. The information delivery needs to be worked on.

So, I'm fully in support of early testing, better testing. I think it really does give you all of your options. I hope that along with that comes more education on things like Down syndrome, because a lot of people just aren't aware of how not scary it is in the end. I'm a big believer that you should have all the information at the ready. That's in today's age your right as a parent.

One point that several participants made was the importance of being supported in making decisions that were right for them. The mother who received a diagnosis of trisomy 18 but decided to continue the pregnancy shared this experience:

The genetic counsellor, to be totally honest, really pushed for us to terminate. She kept telling us that we didn't understand how bad this was going to be. She told us that, you know, babies with trisomy 18 are considered incompatible with life. And she showed us pictures of babies with trisomy 18 and prepared us for a completely different lifestyle. We were told numerous times that we weren't listening to them, we weren't taking in what they were telling us, we weren't prepared for what was coming. We knew life expectancy was 48 hours to 2 weeks, and that was if he was full-term. So we had many doctors try to suggest we terminate. Many doctors hinted that we didn't understand the depth, the severity. I work as an educational assistant with children with all kinds of disabilities, so I kept saying, "I do get it," and they kept saying, "No, you're not listening." And I said, "I am listening, but you know, this is our choice." We saw numerous doctors who felt we were making the wrong decision, but in the end it was our decision to make, and so we did.

In conditions such as Turner syndrome, participants who had lived experience with the condition said that early diagnosis prenatally or in infancy is important for long-term outcomes, but that it is equally important that accurate and up-to-date information is shared with expectant parents.

In terms of things that wouldn't be beneficial, it's not necessarily with the testing, I would say, but with how it is disclosed and handled after it's done. I know with a lot of those disorders there still tends to be some misinformation within the medical community, especially with Turner syndrome. Physicians tend to either not know much about it, or present the worst-case scenario in some cases, and there still are some physicians who will recommend termination if they find out that there's a fetus diagnosed with Turner syndrome.

Another parent said that she fully supported NIPT and thought that the information it could provide was important.

I'm for it. I absolutely am. The more knowledge the better, and like I said, the most important thing is not the test, it's the information, and how it's delivered, and making sure that parents have access to accurate, up-to-date, current information, because I think we all have our understanding of what Down syndrome is in our minds, and I have to say our understanding before our daughter was completely based on old information and biases, and what you see on TV etc., and it's not reality. I don't know how you break through that. It's a long process, and we're still working on it, but it's something that needs to change, and I think that this testing available widespread is cause for a great dialogue, but I just hope that the government sees that having this test

open also indicates the need for educating and giving doctors the tools they need to deliver the diagnosis in the right way. I think that's really important to make sure they go hand in hand.

Ethical Concerns About NIPT

A number of participants, particularly parents of children with the conditions screened for, brought up some of the larger ethical and societal issues around prenatal screening, which at a macro level can be seen as screening out genetic conditions or disabilities in society—a devaluing of certain kinds of lives—but at a micro level is about a pregnant person's right to make choices that are best for their family. Many parents of children with Down syndrome wanted to bring up these issues, and their fears about how their children are viewed in a society in which many choose to end an affected pregnancy. As certain conditions are screened for and some pregnancies terminated, some participants expressed concern that there will be fewer and fewer people with those conditions in society, and that those pregnancies would be expected to be terminated and fewer supportive resources made available.

I think the testing itself is great, but I might not be the majority of opinions, because I know a lot of people in the community worry that if this screening is more readily available, it means there will be less people born with Down syndrome, and for them that's not a good thing, or it makes you feel kind of sad, because it's like people saying that your child shouldn't be born, or something like that.

A participant whose son was born before NIPT was available noted:

This kind of noninvasive testing wasn't available when I was pregnant. What caught my attention for this, although I appreciate the benefits of testing, it also worries me in the way that I don't feel people are always given a very balanced view of what it's like to have a child who has a disability, and that really, really worries me when it comes to making this testing a lot easier.

This was why many wanted to ensure that people had access to good information in pregnancy, and to share their stories about the joys of having a child with Down syndrome in their family. Participants wanted pregnant people to have as much information as possible to make truly informed decisions about their pregnancies, as well as access to support for their choices. One mother of a child with Down syndrome noted that the government should offer choices to pregnant people in terms of screening and access to termination, but should also provide support and options to people who continue an affected pregnancy—to not judge that family as a burden on the system, but to support a society that truly considers people with disabilities to be citizens. Parents of children with Down syndrome also expressed fears that their children would grow up without other children like them. They spoke of news stories about countries like Iceland, which have virtually eliminated Down syndrome:

I'm OK if more funding goes into it. I'm not OK if it's not hand in hand with more appropriate education for the people that are going to deliver the news. I just really want there to be more positive conversations around what a life with Down syndrome actually looks like, or what a life for anybody with a disability looks like ... There just needs to be a larger story about it, or a larger conversation about what it actually means.

Parents of children with Down syndrome shared their concerns about the potential negative effects of widespread screening on the social treatment of their children and others with the conditions screened for. They expressed concern that the rapid uptake of NIPT into the provincial health care system without public discourse and a deeper exploration of societal values will negatively affect people living with disabilities and their families. This was a big concern for some participants: is good information enough in a society that doesn't always value and support people with disabilities and their families?

This is the thing I wonder. If you offer the screening, but at the same time you offer good information, is that enough for people to make truly informed choices when they're living in a world that still thinks of diversity the way that it does?

Lived Experience With the Conditions Screened For

Parents of children born with one of the conditions screened for with NIPT wanted this report to reflect the meaning and significance of their children's lives. There was no doubt that parenting a child with a disability could be challenging:

The other thing I guess I would want people to know is that my life with my daughter with Down syndrome has been wonderful in many ways. It was crushingly difficult, but it's been stunningly beneficial to me as well, in ways that I hadn't anticipated. So, my experience—although very taxing and still is—has made me a happier person, ultimately. I would want people to understand that.

At the same time, it could be challenging for some parents to express the negative aspects of their experience, because they were so often advocating for their children and trying to represent a positive view of disability to their friends, family, and the greater public.

You know what? No, life is not always rosy, it totally sucks sometimes, but that's OK, too. I don't understand why people think that a life is always rosy, right? There is going to be hardship, and there are going to be things that aren't the best, but that's part of life. I have to hesitate on what I share on social media or to people that are not very close to me, because, you know, I don't want there to be an unfavourable view of her or her life.

A mother of an adult daughter with Down syndrome said:

I paid a heavy price financially to get her to the stage where she was able to go off to school and just be OK, and go home, and then go off to work. It was a huge, huge investment of time. I took 12 years off, not working, to support her, and then when it became time for my retirement, I had to work longer than most of my peers to get my full pension, because I hadn't been able to work full-time. And those last few years were very hard on me. So it was a sacrifice that I made at the time, which you have to think about. You don't think about what your life is going to be like when you retire when you're in your 20s, but the decisions I made then directly impacted everything that happened to me after. I guess that's the most important thing I think I've learned.

Participants also expressed their desire to share that “a diagnosis in utero cannot predict a life.” Many parents of children with Down syndrome wanted to say that their children with Down syndrome brought joy and challenges, just as their other children did.

And you know we're only like 3 years into this journey—our little girl turns 3 next month—but it has been like an amazing gift that we would never have chosen for ourselves. And it's so funny—I remember when I was pregnant I was reading this about other people who had like kids with Down syndrome, and they're like, “I wouldn't change it if I could,” and I'm like, “Really? Seriously?” And I still don't know that I could say that, but I'm getting to the point where I understand why, I really do, and it's almost like you have to live that experience to realize the benefits that having someone with Down syndrome in your life brings, and it's really hard to explain that to someone who hasn't been there. But you don't even get there if you don't have somebody in your life.

Sex chromosome conditions such as Turner syndrome and Klinefelter syndrome can have relatively minor effects on people's lives. What is the effect of screening on people with these conditions, and on the way they are viewed by society? We spoke to 5 women with Turner syndrome who ranged in age from their early twenties to their mid-sixties. Some were diagnosed soon after birth, while others weren't diagnosed until later in childhood. We also spoke with 2 mothers of children with Turner syndrome. Participants with Turner syndrome shared what they wanted people to understand:

Turner's girls can live a healthy, happy, productive life, and there's no reason to end a pregnancy. I mean I know that a lot of parents have a lot of questions when they get a diagnosis with that, and I don't blame them, and that's where the medical world needs to be informed enough to help them understand what exactly Turner's means.

One parent commented on the unpredictability of life, and that a better understanding of the ways disability can affect everyone is important:

I think we forget that at one time or another we'll all be disabled. You know, as we get older ... we will rely on other people to do different things. We should truly consider that disability can affect us at any time. I want people to understand that disability is a sector in life we can all become members of, as we age, or without having been born into it.

Discussion

Patient engagement surrounding the topic of noninvasive prenatal screening was robust. We were able to interview many people with a wide range of experiences related to prenatal screening.

People who had accessed NIPT were able to discuss their experience with the screening and were often able to compare it to previous pregnancies with traditional screening. Those interviewed were, for the most part, supportive of NIPT and the benefits of the earlier, more accurate results it can provide. However, while most people interviewed were positively inclined toward NIPT, many—particularly from the disability community—identified concerns or challenges related to the screening. These concerns were largely about pre- and post-test

counselling, and the information offered by health care providers. They were concerned that some health care providers offer biased, out-of-date information. Another concern for some participants was the potential for inaccurate results with the rarer conditions screened for.

We did not discuss the particular benefits of specific NIPT tests as part of patient engagement for this topic.

Conclusions

Participants were largely positive about NIPT. They perceived that it could provide important information about pregnancies—earlier and with more accuracy. Many participants highlighted that NIPT is currently only offered as a second-tier screen after traditional prenatal screening for people considered average-risk. They felt that this process caused them undue stress and anxiety and led to a definitive diagnosis too late in pregnancy.

A notable concern for many participants was the lack of good informed-choice conversations with their primary care providers about the benefits of screening, the limitations of screening, and what the pregnant person might do with the information provided. Many participants brought up ethical concerns with NIPT and broadened access to more accurate prenatal screening, the quality of information provided when people received a positive result, the lack of support in society for raising children with disabilities and the potential stigma associated with knowingly choosing to raise a child with one of the conditions screened for.

CONCLUSIONS OF THE HEALTH TECHNOLOGY ASSESSMENT

The clinical sensitivity of NIPT was 99.5% (95% confidence interval [CI] 81.8%–99.9%) for trisomy 21, 93.1% (95% CI 75.9%–98.3%) for trisomy 18, and 92.7% (95% CI 81.6%–99.9%) for trisomy 13 (GRADE: low to moderate). The specificity for any trisomy was 99.9% (GRADE: moderate). The accuracy of NIPT was higher than that of traditional prenatal testing (GRADE: low to moderate) and decreased the number of diagnostic tests performed (GRADE: moderate). However, evidence for the use of NIPT in the average-risk or general population for sex chromosome aneuploidies was limited. We found no studies on the accuracy or clinical utility of NIPT for microdeletion syndromes in the average-risk or general population. As well, NIPT should not be considered a diagnostic test; positive results should be confirmed by diagnostic testing.

Compared with traditional prenatal screening, NIPT as a second-tier test detected more affected fetuses and substantially reduced the number of diagnostic tests performed, with decreased costs. Compared with second-tier NIPT, first-tier NIPT could detect an additional 84 fetuses with chromosomal anomalies, but it would lead to an annual budget increase of approximately \$35 million per year.

Participants in this health technology assessment were largely positive about NIPT. They perceived that screening could provide important information about their pregnancy—earlier and with more accuracy. However, many participants noted that because NIPT is currently offered only as a second-tier screen, they experienced undue stress and anxiety and felt they received a definitive diagnosis too late in pregnancy. A notable concern for many participants was the lack of informed-choice conversations with their primary care providers about the benefits of screening, the limitations of screening, and what pregnant people might do with the information provided. Participants spoke of the complexities of the larger ethical and societal issues around prenatal screening, which at a macro level can be seen as screening out genetic conditions or disabilities in society—a devaluing of certain kinds of lives—but at a micro level is about a pregnant person's right to make choices that are best for their family.

ABBREVIATIONS

BORN	Better Outcomes Registry and Network
CI	Confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CrI	Credible interval
eFTS	Enhanced first-trimester screening
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
ICER	Incremental cost-effectiveness ratio
MPSS	Massively parallel shotgun sequencing
MSS	Maternal serum screening (also known as quadruple screening)
NICE	National Institute for Health and Care Excellence
NIPT	Noninvasive prenatal testing
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
TMPS	Targeted massively parallel sequencing

GLOSSARY

Amniocentesis	A procedure performed during pregnancy in which a needle is used to withdraw a small amount of fluid from the sac around the fetus. It is used to diagnose certain genetic anomalies.
Aneuploidy	An incorrect number of chromosomes.
Chorionic villus sampling	A procedure performed during pregnancy in which a small number of cells is taken from the placenta and tested. It is used to diagnose certain genetic anomalies.
Chromosomal anomaly	Having an incorrect number of chromosomes, or a change in the structure of a chromosome.
Fetal fraction	The percentage of cell-free DNA present in a pregnant person's blood that is from the fetus.
Incremental cost-effectiveness ratio (ICER)	Determines a “unit of benefit” for an intervention by dividing the incremental cost by the incremental effectiveness. The incremental cost is the difference between the cost of the treatment under study and an alternative treatment. The effectiveness is usually measured as years of life or as “quality-adjusted life-years.”
Microdeletion	Loss of a tiny piece of a chromosome that is too small to be easily seen by a microscope.
Monosomy	The presence of one copy of a chromosome rather than two.

Nuchal translucency	A collection of fluid under the skin at the back of a fetus's neck early in pregnancy. Nuchal translucency ultrasound screening is done during pregnancy to see if a fetus is likely to have Down syndrome (trisomy 21) or another anomaly, since many babies with Down syndrome or other anomalies have more of this fluid than babies without genetic anomalies.
Phenotype	The observable characteristics (e.g., appearance, development, behaviour) resulting from a person's genetic profile (their genotype).
Trisomy	The presence of three copies of a chromosome rather than two; trisomy is the most common aneuploidy.

APPENDICES

Appendix 1: Funding Status of Noninvasive Prenatal Testing in Canada

Table A1: Funding Status of Noninvasive Prenatal Testing in Canada

Province or Territory	Public Funding	Eligibility Criteria/Notes
Nova Scotia	No	None
Prince Edward Island	Yes ^a	Funded based on the following criteria^a: • Positive early combined screen of $\geq 1/50$ (NT + early maternal serum testing) • Second-trimester positive screen (age, second-trimester maternal serum test, SIPS, or IPS) + genetic sonogram by maternal–fetal specialist and overall risk $> 1/304$) (No official response received from provincial ministry representative)
New Brunswick	No ^a	Rarely funded or even available (there are no private laboratories in the province)^a (No official response received from provincial ministry representative)
Newfoundland and Labrador	No	Currently not funded, but there has been some recent consideration for funding in the high-risk population
Quebec	Yes	Announced funding for high-risk pregnant people in early 2018. Previously, Harmony, Panorama, or MaterniT21 PLUS were available at private clinics
Ontario	Yes	Funded for people who meet one of the following criteria: • Category I ○ ≥ 40 years of age at time of delivery ○ Positive serum screen result ○ NT ≥ 3.5 mm ○ Previous pregnancy with a chromosome anomaly • Category II ○ Fetal congenital anomalies identified on ultrasound that are suggestive of trisomy 21, 18, or 13 ○ Risk of aneuploidy for trisomies 21, 18, and 13 other than that of positive maternal multiple marker screen ○ < 40 years old at expected date of delivery (must have at least one other risk factor noted) ○ Risk of aneuploidy can be calculated by including any combination of risk indicators, including soft markers, biochemistry, maternal age, etc. ○ NIPT for sex chromosome determination for at least one of the following: • Risk of sex-limited disorder • Ultrasound findings suggestive of a sex chromosome aneuploidy • Ultrasound findings suggestive of a disorder of sex determination Funding is available for NIPT analysis for trisomies 21, 18, and 13 and sex chromosome aneuploidies. Microdeletion testing is not funded

Manitoba	Yes ^a	Funded for people who meet one of the following criteria^a: • Either biological parent with a previous aneuploidy pregnancy (trisomy 21, 18, or 13) • Either biological parent is a carrier of a balanced Robertsonian translocation (involving chromosome 21 or 13) • Female carrier of a severe X-linked genetic disorder or has a child with a severe X-linked disorder for which prenatal detection would be considered (for fetal sexing) • Positive maternal serum screen for trisomy 21 or 18 in people who are HIV- or hepatitis-positive (surface-antigen-positive or E-antigen-positive) with detectable viral loads Manitoba also serves some Ontario patients and counsels them according to Ontario criteria^a (No official response received from provincial ministry representative)
Saskatchewan	No	None
Alberta	No ^a	(No official response received from provincial ministry representative)
British Columbia	Yes	Funded for people who meet one of the following criteria: • Positive screen result from IPS, SIPS, or quadruple screening • Previous trisomy 21, 18, or 13 pregnancy • Risk of Down syndrome > 1 in 300 based on results of screening and ultrasound marker(s) of aneuploidy Funding is available for NIPT analysis for trisomies 21, 18, and 13, and sex chromosome aneuploidy. Microdeletion testing is not funded Harmony test (available through Dynacare laboratories) is the only publicly funded test available for NIPT (i.e., Panorama is not publicly funded)
Yukon	Yes ^a	Funded based on the same criteria as British Columbia (No official response received from territorial ministry representative)
Northwest Territories	No	None
Nunavut	No ^a	Funded under the same criteria as the jurisdiction that the pregnant individual is seen in^a (No official response received from territorial ministry representative)

Abbreviations: IPS, integrated prenatal screening; NIPT, noninvasive prenatal testing; NT, nuchal translucency; SIPS, serum integrated prenatal screening.

^aAccording to a 2016 Canadian environmental scan on NIPT.²²

Appendices

Appendix 2: Guideline Recommendations

Table A2: Guideline Recommendations for Noninvasive Prenatal Testing

Author, Year	Recommendation Excerpts
Canadian Guideline	
Society of Obstetricians and Gynaecologists of Canada, Canadian College of Medical Geneticists, 2017 ³⁶	- A discussion of the risks, benefits, and alternatives of the various prenatal diagnoses and screening options, including the option of no testing, should be undertaken with all patients prior to any prenatal screening. Following this counselling, patients should be offered (1) no aneuploidy screening, (2) standard prenatal screening based on locally offered paradigms, (3) ultrasound-guided invasive testing when appropriate indications are present, or (4) maternal plasma cell-free DNA screening where available, with the understanding that it may not be provincially funded [Quality of evidence: II-2, Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group. Classification of recommendation: B, There is fair evidence to recommend the clinical preventive action] - Regardless of aneuploidy screening choice, all women should be offered a fetal ultrasound (optimally between 11 and 14 weeks) to confirm viability, gestational age, number of fetuses, chorionicity in multiples, early anatomic assessment, and nuchal translucency (NT) evaluation where available. The NT measurement for aneuploidy risk estimation (combined with maternal serum) should not be performed if cell-free DNA screening has been used. Every effort should be made to improve access to high-quality first-trimester ultrasound for all Canadian women. In areas where NT assessment is not available, a first-trimester dating ultrasound improves the accuracy of maternal serum screening and the management of pregnancy [Quality of evidence: II-1, Evidence from well-designed controlled trials without randomization. Classification of recommendation: A, There is good evidence to recommend the clinical preventive action] Women who are considering undergoing maternal plasma cell-free DNA (cfDNA) screening should be informed that: - It is a highly effective screening test for the common fetal trisomies (21, 18, 13), performed after 10 weeks' gestation. [Quality of evidence assessment, II-1, Evidence from well-designed controlled trials without randomization. Classification of recommendations: A, There is good evidence to recommend the clinical preventive action] - There is a possibility of a failed test (no result available), false-negative or positive fetal result, and an unexpected fetal or maternal result. [Quality of evidence assessment, II-1, Evidence from well-designed controlled trials without randomization. Classification of recommendations: A, There is good evidence to recommend the clinical preventive action] - All positive cfDNA screening results should be confirmed with invasive fetal diagnostic testing prior to any irrevocable decision (II-1B). Classification of recommendation: B, There is fair evidence to recommend the clinical preventive action] - Management decisions, including termination of pregnancy, require diagnostic testing and should not be based on maternal plasma cfDNA results alone, because it is not a diagnostic test [Quality of evidence: II-2, Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group. Classification of recommendation: B, There is fair evidence to recommend the clinical preventive action] - If a fetal structural abnormality is identified in a woman, regardless of previous screening test results, the woman should undergo genetic counselling and be offered invasive diagnostic testing with rapid aneuploidy detection and reflex to microarray analysis if rapid aneuploidy detection is normal or inconclusive. [Quality of evidence: II-2, Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group. Classification of recommendation: B, There is fair evidence to recommend the clinical preventive action]

- Although cfDNA screening for aneuploidy in twin pregnancy is available, there is less validation data than for a singleton pregnancy and it should be undertaken with caution. [Quality of evidence: II-2, Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group. Classification of recommendation: C, The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making]
- Routine cfDNA screening for fetal microdeletions is not currently recommended. [Quality of evidence: II-2, Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group. Classification of recommendation: B, There is fair evidence to recommend the clinical preventive action]

International Guidelines

American College of Medical Genetics and Genomics, 2016¹³²

For implementation of NIPS into practice, ACMG recommends:

- Providing up-to-date, balanced, and accurate information early in gestation to optimize patient decision-making, independent of the screening approach used
- Laboratories work with public health officials, policymakers, and private payers to make NIPS, including the pre- and post-test education and counseling, accessible to all pregnant women
- Allowing patients to select *diagnostic* or *screening* approaches for the detection of fetal aneuploidy and/or genomic changes that are consistent with their personal goals and preferences
- Informing all pregnant women that diagnostic testing (CVS or amniocentesis) is an option for the detection of chromosome abnormalities and clinically significant CNVs

For average- and low-risk women, ACMG recommends:

- Informing all pregnant women that NIPS is the most sensitive screening option for traditionally screened aneuploidies (i.e., Patau, Edwards, and Down syndromes)
- Referring patients to a trained genetics professional when an increased risk of aneuploidy is reported after NIPS
- Offering diagnostic testing when a positive screening test result is reported after NIPS
- Providing accurate, balanced, up-to-date information, at an appropriate literacy level when a fetus is diagnosed with a chromosomal or genomic variation in an effort to educate prospective parents about the condition of concern. These materials should reflect the medical and psychosocial implications of the diagnosis
- Laboratories should provide readily visible and clearly stated DR, SPEC, PPV, and NPV for conditions being screened, in pretest marketing materials, and when reporting laboratory results to assist patients and providers in making decisions and interpreting results
- Laboratories should not offer screening for Patau, Edwards, and Down syndromes if they cannot report DR, SPEC, and PPV for these conditions

For autosomal aneuploidies other than Patau, Edwards, and Down syndrome, ACMG does *not* recommend:

- NIPS to screen for autosomal aneuploidies other than those involving chromosomes 13, 18, and 21

For sex chromosome aneuploidies, ACMG recommends:

- Informing all pregnant women, as part of pretest counseling for NIPS, of the availability of the expanded use of screening for sex chromosome aneuploidies

-
- Providers should make efforts to deter patients from selecting sex chromosome aneuploidy screening for the sole purpose of biologic sex identification in the absence of a clinical indication for this information
 - Informing patients about the causes and increased possibilities of false-positive results for sex chromosome aneuploidies as part of pretest counseling and screening for these conditions. Patients should also be informed of the potential for results of conditions that, once confirmed, may have a variable prognosis (e.g., Turner syndrome) before consenting to screening for sex chromosome aneuploidies
 - Referring patients to a trained genetics professional when an increased risk of sex chromosome aneuploidy is reported after NIPS
 - Offering diagnostic testing when a positive screening test result is reported after screening for sex chromosome aneuploidies
 - Providing accurate, balanced, up-to-date information and materials at an appropriate literacy level when a fetus is diagnosed with a sex chromosome aneuploidy in an effort to educate prospective parents about the specific condition. These materials should reflect medical and psychosocial implications for the diagnosis
 - Laboratories include easily recognizable and highly visible DR, SPEC, PPV, and NPV for each sex chromosome aneuploidy when reporting results to assist patients and providers in making decisions and interpreting results
 - Laboratories should not offer screening for sex chromosome aneuploidies if they cannot report DR, SPEC, PPV, and NPV for these conditions

For CNV, ACMG recommends:

- Informing all pregnant women of the *availability* of the expanded use of NIPS to screen for clinically relevant CNVs when the following conditions can also be met:
 - Obstetric care providers should discuss with their patients the desire for prenatal screening as opposed to diagnostic testing (i.e., CVS or amniocentesis)
 - Obstetric care providers should discuss with their patients the desire for maximum fetal genomic information through prenatal screening
 - Obstetric care providers should inform their patients of the higher likelihood of false-positive and false-negative results for these conditions as compared to results obtained when NIPS is limited to common aneuploidy screening
 - Obstetric care providers should inform their patients of the potential for results of conditions that, once confirmed, may have an uncertain prognosis
 - Referring patients to a trained genetics professional when NIPS identifies a CNV
 - Offering diagnostic testing (CVS or amniocentesis) with chromosomal microarray when NIPS identifies a CNV
 - Providing accurate, balanced, up-to-date information at an appropriate literacy level when a fetus is diagnosed with a CNV in an effort to educate prospective parents about the condition of concern. These materials should reflect the medical and psychosocial implications of the diagnosis
 - Laboratory requisitions and pretest counseling information should specify the DR, SPEC, PPV, and NPV of each CNV screened. This material should state whether PPV and NPV are modeled or derived from clinical utility studies (natural population or sample with known prevalence)
 - Laboratories include easily recognizable and highly visible DR, SPEC, PPV, and NPV for each CNV screened when reporting laboratory results to assist patients and providers in making decisions and interpreting results. Reports should state whether PPV and NPV are
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	modelled or derived from clinical utility studies (natural population or sample with known prevalence). When laboratories cannot report specific DR, SPEC, PPV, and NPV, screening for those CNVs should not be performed by that laboratory For CNV, ACMG does <i>not</i> recommend: • In pregnancies with multiple gestations and/or donor oocytes, testing laboratories should be contacted regarding the validity of NIPS before it is offered to the patient as a screening option
American College of Obstetricians and Gynecologists, Society for Maternal–Fetal Medicine, 2016 ¹³³	The following recommendations and conclusions are based on good and consistent scientific evidence (Level A): • Women who have a negative screening test result should not be offered additional screening tests for aneuploidy because this will increase their potential for a false-positive test result • Because cell-free DNA is a screening test with the potential for false-positive and false-negative results, such testing should not be used as a substitute for diagnostic testing • All women with a positive cell-free DNA test result should have a diagnostic procedure before any irreversible action, such as pregnancy termination, is taken • Women whose cell-free DNA screening test results are not reported, are indeterminate, or are uninterpretable (a no call test result) should receive further genetic counselling and be offered comprehensive ultrasound evaluation and diagnostic testing because of an increased risk of aneuploidy • Women with a positive screening test result for fetal aneuploidy should be offered further detailed counselling and testing The following recommendations and conclusions are based on limited or inconsistent scientific evidence (Level B): • Cell-free DNA screening tests for microdeletions have not been validated clinically and are not recommended at this time • Patients who conceive after preimplantation genetic screening for aneuploidy should be offered aneuploidy screening and diagnosis during their pregnancy • No method of aneuploidy screening is as accurate in twin gestations as it is in singleton pregnancies. Because data generally are unavailable for higher-order multifetal gestations, analyte screening for fetal aneuploidy should be limited to singleton and twin pregnancies The following recommendations and conclusions are based primarily on consensus and expert opinion (Level C): • Screening for aneuploidy should be an informed patient choice, with an underlying foundation of shared decision-making that fits the patient's clinical circumstances, values, interests, and goals • Aneuploidy screening or diagnostic testing should be discussed and offered to all women early in pregnancy, ideally at the first prenatal visit • All women should be offered the option of aneuploidy screening or diagnostic testing for fetal genetic disorders, regardless of maternal age • If an isolated ultrasonographic marker for aneuploidy is detected, the patient should be offered aneuploidy screening if it was not offered previously • Some women who receive a positive test result from traditional screening may prefer to have cell-free DNA screening rather than undergo definitive testing. This approach may delay definitive diagnosis and management and may fail to identify some fetuses with aneuploidy

	• Parallel or simultaneous testing with multiple screening methodologies for aneuploidy is not cost-effective and should not be performed • In multifetal gestations, if fetal demise or an anomaly is identified in one fetus, serum-based aneuploidy screening should be discouraged. There is a significant risk of an inaccurate test result in these circumstances
American College of Obstetricians and Gynecologists, Society for Maternal-Fetal Medicine, 2015 ¹³⁴	• Given the performance of conventional screening methods, the limitations of cell-free DNA screening performance, and the limited data on cost-effectiveness in the low-risk obstetric population, conventional screening methods remain the most appropriate choice for first-line screening for most women in the general obstetric population • Although any patient may choose cell-free DNA analysis as a screening strategy for common aneuploidies regardless of their risk status, the patient choosing this testing should understand the limitations and benefits of this screening paradigm in the context of alternative screening and diagnostic options • Given the potential for inaccurate results and to understand the type of trisomy for recurrence-risk counselling, a diagnostic test should be recommended for a patient who has a positive cell-free DNA test result • Parallel or simultaneous testing with multiple screening methodologies for aneuploidy is not cost-effective and should not be performed • Management decisions, including termination of the pregnancy, should not be based on the results of the cell-free DNA screening alone • Women whose results are not reported, indeterminate, or uninterpretable (a “no call” test result) from cell-free DNA screening should receive further genetic counselling and be offered comprehensive ultrasound evaluation and diagnostic testing because of an increased risk of aneuploidy • Routine cell-free DNA screening for microdeletion syndromes should not be performed • Cell-free DNA screening is not recommended for women with multiple gestations • Patients should be counselled that a negative cell-free DNA test results does not ensure an unaffected pregnancy • Cell-free DNA screening does not assess risk of fetal anomalies such as neural tube defects or ventral wall defects; patients who are undergoing cell-free DNA screening should be offered maternal serum alpha-fetoprotein screening or ultrasound evaluation for risk assessment • Patients may decline all screening or diagnostic testing for aneuploidy
Society for Maternal-Fetal Medicine, 2015 ¹³⁵	• Optimal candidates for routine cfDNA aneuploidy screening are women with [Level 1B recommendation: strong recommendation, moderate quality of evidence]: ○ Maternal age ≥ 35 years at delivery ○ Fetal ultrasound finding that indicates an increased risk of aneuploidy, specifically for trisomies 13, 18, or 21 ○ History of previous pregnancy with a trisomy detectable by cfDNA screening (trisomies 13, 18, or 21) ○ Positive screening results for aneuploidy that include a first-trimester, sequential, integrated, or quadruple screen ○ Parental balanced Robertsonian translocation with increased risk of fetal trisomy 13 or 21 • Routine screening for microdeletions with cfDNA is not recommended [Level 1B recommendation: strong recommendation, moderate quality of evidence] • For women who desire comprehensive testing for chromosomal disorders, diagnostic testing should be offered [Level 1B recommendation: strong recommendation, moderate quality of evidence]

- For women who undergo cfDNA aneuploidy screening, maternal serum alpha-fetoprotein, and/or second-trimester anatomy ultrasound scan should also be performed [Best practice recommendation]
- Formal genetic counseling by maternal–fetal medicine subspecialist, geneticist, or genetic counselor after a positive cfDNA test is recommended [Best practice recommendation]
- Chorionic villous sampling or amniocentesis should be offered after a positive cfDNA screen to confirm the diagnosis [Best practice recommendation]
- Traditional aneuploidy screening and cfDNA aneuploidy screening should not be performed at the same time [Best practice recommendation]

After a failed cfDNA test, genetic counseling should be performed that includes offering diagnostic testing (chorionic villous sampling or amniocentesis) and repeat cfDNA screening [Best practice recommendation]

Society for
Maternal–Fetal
Medicine,
2017¹³⁶

- In women who have already received a negative cfDNA screen, ultrasound at 11–14 weeks of gestation solely for the purpose of NT measurement is not recommended (GRADE 1B: strong recommendation, moderate-quality evidence)
- Diagnostic testing should not be recommended to patients solely for the indication of an isolated soft marker in the setting of a negative cfDNA screen (GRADE 1B: strong recommendation, moderate-quality evidence)
- In women with an isolated soft marker that has no other clinical implications (i.e., choroid plexus cyst or echogenic intracardiac focus) and a negative cfDNA screen, we recommend describing the finding as not clinically significant or as a normal variant (GRADE 2B: weak recommendation, moderate-quality evidence)
- In women with an isolated soft marker without other clinical implications (i.e., choroid plexus cyst or echogenic intracardiac focus) and a negative first- or second-trimester screening result, we recommend describing the finding as not clinically significant or as a normal variant (GRADE 2B: weak recommendation, moderate-quality evidence)
- We recommend that all women in whom a structural abnormality is identified by ultrasound be offered diagnostic testing with chromosomal microarray (GRADE 1A: strong recommendation, high-quality evidence)
- Routine screening for microdeletions with cfDNA is not recommended (GRADE 1B: strong recommendation, moderate-quality evidence)

National
Society of
Genetic
Counselors,
2013¹³⁷

- NSGC recognizes NIPT as an option for aneuploidy assessment in pregnancy: Peer-reviewed data currently supports NIPT only as a screening tool for select populations. While NIPT has proven effective in detecting fetuses with aneuploidy, in light of potential false-positive results, NIPT results should not be considered diagnostic, and any abnormal results should be confirmed through a conventional prenatal diagnostic procedure, such as chorionic villus sampling or amniocentesis
- NSGC does not currently support NIPT as a routine, first-tier aneuploidy screening test in low-risk populations: To date, these technologies have been validated primarily in pregnancies considered to be at an increased risk for fetal aneuploidy, based on maternal age, family history, or positive serum and/or sonographic screening tests or in pregnancies in which invasive testing is being performed, which is not truly representative of an average-risk population
- Although one study has suggested that NIPT in screening for trisomy 21 and trisomy 18 in an average-risk population would be effective, further studies are needed before NIPT can replace current aneuploidy screening programs
- Clinical studies show that MPS effectively detects fetal trisomy 21, trisomy 13, trisomy 18, and monosomy X and that DANSR effectively detects trisomy 21, trisomy 18, and trisomy 13. NIPT has not yet been proven efficacious in detecting other chromosomal abnormalities

or single-gene disorders. NSGC recommends that pretest counselling for NIPT include information about the disorders that it may detect, its limitations in detecting these conditions, and its unproven role in detecting other conditions

- Pre- and post-NIPT genetic counselling: As with any prenatal testing, patients must have accurate, up-to-date information regarding the test, the possible results, and the available follow-up in order to make an informed choice when considering NIPT. Given NIPT's vastly superior sensitivity and specificity compared to other available aneuploidy screening—such as, first-trimester nuchal translucency and/or biochemical screening and second-trimester quad screening—it is imperative that patients understand the significant implications of a positive result prior to undergoing NIPT. NSGC recognizes that, due to limited resources, it may not be feasible for all women seeking NIPT to receive pretest counselling from a genetic counsellor. But a qualified healthcare provider should provide nondirective pretest counselling for all women considering NIPT. NSGC recommends that any patient with abnormal NIPT results should receive genetic counselling with a certified genetic counsellor and be given the option of conventional confirmatory diagnostic testing
- NSGC recommends that patients who have other factors suggestive of a chromosome abnormality should receive genetic counselling and have the option of conventional confirmatory diagnostic testing, regardless of NIPT results: Because NIPT does not screen for all chromosomal or genetic conditions, it does not replace standard risk assessment and prenatal diagnosis. Indications for genetic counselling, regardless of NIPT results, include the presence of ultrasound abnormalities, family or personal history of a chromosome anomaly, and a history of recurrent pregnancy loss. Patients who are of advanced maternal age and/or have had a positive screening test may also benefit from detailed genetic counselling, regardless of NIPT results. In addition, patients who have an increased risk for genetic conditions that are beyond NIPT's scope should receive genetic counselling to discuss appropriate testing options
- Future considerations: NIPT's landscape is rapidly changing. Additional companies are currently administering studies to validate their laboratory-developed tests for NIPT, and are expected to launch competing tests in the near future. NIPT will likely expand to include additional chromosomal abnormalities and/or microarray analysis as future studies support the clinical validity of such results. Studies to assess clinical validity in the general population (e.g. average-risk women) are currently underway. As the sensitivity and specificity in the general population are better established, NIPT has the potential to function with the sensitivity and specificity similar to currently available diagnostic tests. Single-gene testing will also be possible, as this is an area of ongoing research. As this technology evolves, NSGC will reassess its recommendations to reflect these changes

Human Genetics Society of Australia, Royal Australian and New Zealand College of Obstetricians and Gynaecologists, 2016¹³⁸

- Accurate dating, confirmation of viability and determination of the number of embryos by ultrasound is recommended prior to cfDNA testing (Consensus-based recommendation)
- cfDNA based screening for fetal aneuploidy is not diagnostic. The chance of having an affected fetus following a cfDNA result reported as high-risk (i.e., the positive predictive value, PPV) may be < 50%, depending on the specific chromosome involved and the background risk of the woman. Confirmatory diagnostic testing is strongly recommended after an abnormal cfDNA result (Consensus-based recommendation)
- If a woman has received a cfDNA reported as normal/low-risk, an additional calculation for aneuploidy (e.g. by combined first-trimester or second-trimester serum screening) is not recommended as this will increase the false-positive rate without substantially improving the detection rate (Consensus-based recommendation)
- The presence of a fetal structural anomaly remains an important indication for invasive prenatal testing, even in the presence of a prior cfDNA result reported as normal/low risk (Consensus-based recommendation)
- Pretest counselling should include informed decision-making regarding testing for fetal sex and sex chromosome aneuploidy. Women should be given the choice to opt out of receiving this information (Consensus-based recommendation)

European Society of

- NIPT offers improved accuracy when testing for common autosomal aneuploidies compared with existing tests such as cFIS. However, a positive NIPT result should not be regarded as a final diagnosis: false positives occur for a variety of reasons (including that the DNA

Appendices

Human Genetics, American Society of Human Genetics, 2015 ¹³⁹	sequenced is both maternal and fetal in origin, and that the fetal fraction derives from the placenta as well as the developing fetus). Thus women should be advised to have a positive result confirmed through diagnostic testing, preferably by amniocentesis, if they are considering a possible termination of pregnancy • The better test performance, including lower invasive testing rate of NIPT-based screening should not lead to lower standards for pretest information and counselling. This is especially important in the light of the aim of providing pregnant women with meaningful options for reproductive choice. There should be specific attention paid to the information needs of women from other linguistic and cultural backgrounds or who are less health literate • If NIPT is offered for a specific set of conditions (e.g., trisomies 21, 18 and 13), it may not be reasonably possible to avoid additional findings, such as other chromosomal anomalies or large scale insertions or deletions. As part of pretest information, women and couples should be made aware of the possibility of such additional findings and the range of their implications. There should be a clear policy for dealing with such findings, as much as possible also taking account of pregnant women's wishes with regard to receiving or not receiving specific information • Expanding NIPT-based prenatal screening to also report on sex-chromosomal abnormalities and microdeletions not only raises ethical concerns related to information and counseling challenges but also risks reversing the important reduction in invasive testing achieved with implementation of NIPT for aneuploidy, and is therefore currently not recommended • Emerging opportunities for combining prenatal screening for fetal abnormalities with screening aimed at prevention may undermine adequate counseling by sending mixed messages. The objective of any prenatal screening activity should be made explicit and, as far as possible, forms of prenatal screening with different aims should be presented separately. If not physically possible, this separation should at least be made conceptually when providing the relevant information • In countries where prenatal screening for fetal abnormalities is offered as a public health program, governments and public health authorities should adopt an active role to ensure the responsible introduction of NIPT as a second or first-tier screening test for Down syndrome and other common autosomal aneuploidies. This entails ensuring quality control also extending to the non-laboratory aspects of NIPT-based prenatal screening (information, counseling), education of professionals, systematic evaluation of all aspects of the screening program, as well as promoting equity of access for all pregnant women within the confines of the available budget, and setting up a governance structure for responsible further innovation in prenatal screening • Different scenarios for NIPT-based screening for common autosomal aneuploidies are possible, including NIPT as an alternative first-tier option. The inevitable trade-offs underlying those scenarios should not just be regarded as a matter of screening technology and health economics; the question is also how these trade-offs enable or impede meaningful reproductive choices and how they affect both the balance of benefits and burdens for pregnant women and their partners, and the screening goals and values acceptable to society • In order to adequately evaluate prenatal screening practices, there is a need to further develop and validate measures of informed choice as well as interventions aimed at enabling informed choices. The transition to NIPT-based prenatal screening presents an opportunity to fill this gap in knowledge • In the light of sequencing technologies becoming better and cheaper, there is an acute need for a proactive professional and societal debate about what the future scope of prenatal screening for fetal abnormalities should be. As argued in this document, there are strong ethical reasons for not expanding the scope of prenatal screening beyond serious congenital and childhood disorders • The scenario in which prenatal screening would open up possibilities for fetal therapy in addition to autonomous reproductive choice raises fundamental questions about the relation between reproductive autonomy and parental responsibility that require an in-depth proactive ethical analysis
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Schmid et al, 2015¹⁴⁰ (Supported by: Austrian Society of Obstetrics and Gynecology, Austrian Society of Ultrasound in Medicine, Austrian Society of Pre- and Perinatal Medicine, Austrian Society of Human Genetics, German Society of Ultrasound in Medicine, Fetal Medicine Foundation of Germany, Swiss Society of Ultrasound in Medicine)	• cfDNA testing should be offered only after, or in conjunction with, a qualified ultrasound and following appropriate counseling about the nature, scope and significance of the test • cfDNA tests are screening tests. A high-risk cfDNA testing result should always be confirmed by an invasive diagnostic test (chorionic villous sampling, amniocentesis), before a clinical consequence is drawn from the findings • cfDNA testing can be used as secondary screening test for trisomy 21 (Down syndrome) for the reduction of invasive procedures after a high or intermediate-risk result from first trimester combined test (1 in 1,000 or > 1: 500 [FMF-D]). It should be noted that, even when cfDNA testing is used as a secondary screening, invasive diagnostic testing (chorionic villous sampling, amniocentesis) is still the method of choice when the adjusted risk for trisomy 21 after the combined test is > 1:10 or the fetal nuchal translucency thickness is > 3.5mm or a fetal malformation is present • cfDNA tests can also be used as a primary screening method for fetal trisomy 21 in pregnant women of every age and risk group • In general, it should be noted that the performance of cfDNA screening for trisomy 18 (Edwards syndrome) and trisomy 13 (Patau syndrome) is lower than that for trisomy 21 • Based on the available evidence the use of cfDNA tests to screen for aneuploidy of sex chromosomes and microdeletion syndromes can currently not be recommended without reservation
Polish Gynecological Society, Polish Human Genetics Society, 2017¹⁴¹	• NIPT should not replace first-trimester screening based on fetal ultrasound scan and biochemical testing of maternal blood. NIPT should be ordered by a physician who has experience in obstetrics, perinatology or clinical genetics • NIPT should be performed between the 10th and 15th week of pregnancy • NIPT is not recommended for low-risk pregnancies with a risk less than 1:1000 as indicated by integrated tests (ultrasound + biochemical testing of maternal blood) • NIPT should be offered to pregnant women with a risk of fetal chromosomal aberration from 1:100 to 1:1000 • If the risk is higher than 1:100, invasive prenatal diagnosis should be offered • When fetal congenital anomalies are diagnosed based on ultrasound but the NIPT results are correct, the patient must be referred to a genetics specialist for further diagnostics and genetic counselling • NIPT is not recommended for multiple pregnancies (triplets and higher)

	• Before NIPT ultrasound scan should be performed to assess the number of fetuses and the gestational age • NIPT should not replace fetal ultrasound examination. Ultrasound scan has to be performed following the guidelines of the Ultrasound Section of the Polish Gynaecological Society • When NIPT results could not be obtained (up to 5%) the NIPT test may be repeated or invasive diagnostics has to be offered • NIPT and invasive diagnostics should not be performed at the same time • When NIPT shows high risk of chromosomal aberration amniocentesis is indicated as a method of invasive diagnostics • When NIPT estimates high risk of fetal chromosomal aberration the patient has to be consulted by clinical geneticist or specialist in perinatology • Pregnancy cannot be terminated based only on NIPT result • NIPT results should be signed by a specialist in medical laboratory diagnostics
International Society for Prenatal Diagnosis, 2015 ¹⁴²	• High sensitivities and specificities are potentially achievable with cfDNA screening for some fetal aneuploidies, notably trisomy 21 • Definitive diagnosis of Down syndrome and other fetal chromosome abnormalities can only be achieved through testing on cells obtained by amniocentesis or CVS • The use of maternal age alone to assess fetal Down syndrome risk in pregnant women is not recommended • A combination of ultrasound NT measurement and maternal serum markers in the first trimester should be available to women who want an early risk assessment and for whom cfDNA screening cannot be provided • A four-marker serum test should be available to women who first attend for their prenatal care after 13 weeks 6 days of pregnancy and where cfDNA screening cannot be provided • Protocols that combine first-trimester and second-trimester conventional markers are valid • Second-trimester ultrasound can be a useful adjunct to conventional aneuploidy screening protocols • When cfDNA screening is extended to microdeletion and microduplication syndromes or rare trisomies, the testing should be limited to clinically significant disorders or well-defined severe conditions. There should be defined estimates for the DRs, FPRs, and information about the clinical significance of a positive test for each disorder being screened
International Society of Ultrasound in Obstetrics and Gynecology, 2017 ¹⁴³	• All women should be offered a first-trimester ultrasound scan according to ISUOG guidelines, regardless of their intention to undergo cfDNA testing ○ If the woman has had a negative cfDNA test result, nuchal translucency (NT) thickness should still be measured and reported as a raw value and centile. The management of increased NT with a normal cfDNA test result is currently based on local guidelines. However, it is not necessary to compute first-trimester risk estimates for trisomies 21, 18 and 13 based on NT measurements and maternal biochemistry in a woman known to have a normal cfDNA result. Accordingly, soft markers for trisomy 21 should not be assessed in women with a normal cfDNA test result due to their high false-positive rate and poor positive predictive value ○ If the woman has not had a cfDNA test, pretest counseling is essential. Various options regarding screening or testing for trisomy 21 and, to a lesser extent, trisomies 18 and 13 should be explained clearly, including information on the expected test performance, potential adverse effects, and pros and cons of each option. Following a normal first-trimester scan, as defined by ISUOG guidelines, three options might be considered for women who wish to have further risk assessment:

1. Screening strategies based on individual risk calculated from maternal age and NT measurement and/or maternal serum markers and/or other ultrasound markers in the first trimester (defined by the conventional crown–rump length range of 45–84 mm). Following such screening, women can be offered a choice, according to their calculated individual risk, of having no further testing, cfDNA testing or invasive testing. Cutoffs, defining two (low/high-risk) or three (low/intermediate/high risk) groups, should be defined on a local/national basis and will be affected by public health priorities and available resources. Offering cfDNA testing should always be balanced with the potential and risk of conventional karyotyping, with or without microarray analysis, following invasive sampling. More importantly, the role of cfDNA testing as an alternative to standard invasive testing in women considered to be at very high risk after combined screening ($>1:10$) but with no ultrasound anomaly should be evaluated in prospective studies. Expert opinion currently suggests that cfDNA testing should not replace routinely invasive testing in this group, based on the fact that, in this population, only 70% of the chromosomal abnormalities are trisomy 21, 18 or 13, and that chromosomal microarray analysis, if offered, is able to detect a large number of additional anomalies
 2. cfDNA testing as a first-line screening test. Most current guidelines endorse cfDNA testing only for high- or intermediate-risk populations, for which comprehensive data exist. Experience in low-risk populations is increasing, apparently confirming the high detection rates published for high-risk populations. However, testing in low-risk women may impact on the quality of both pretest counselling and subsequent ultrasound screening. In particular, cfDNA testing should not replace first-trimester ultrasound and should not be offered when an ultrasound anomaly or markedly increased NT is detected. Using cfDNA in low-risk patients might be endorsed as a widely available option only when more data emerge and cfDNA costs decrease
 3. Invasive testing based on a woman's preference or background risk (maternal age, previous history, fetal ultrasound anomaly) with no further individual risk calculation. An invasive test might be discussed in light of the recently reported reduction in the risk of invasive procedures as well as the increase in cytogenetic resolution provided by microarray techniques. However, the cost of this option is not usually covered by most national insurance policies and it should not be recommended beyond the context of clinical trials and until sufficient peer-reviewed data and validation studies have been published
- cfDNA test results should always be interpreted and explained individually in relation to the a priori risk and the fetal fraction
 - In the presence of a fetal structural anomaly, the indications for fetal karyotyping and/or microarray testing should not be modified by a previously normal cfDNA test result
 - In the case of a failed cfDNA test, the patient should be informed about the increased risk of anomalies as well as alternative screening and testing strategies
 - cfDNA testing is not diagnostic, and confirmatory invasive testing is required in the presence of an abnormal result. Whenever there is discordance between an abnormal cfDNA test result and a normal ultrasound examination, amniocentesis rather than chorionic villus sampling should be performed
 - Accuracy of cfDNA testing in twin pregnancies should be investigated further
 - Variations in cfDNA test performance by different providers should be investigated further
 - It is becoming technically feasible to test non-invasively, not only for trisomies but also for other genetic syndromes. Both healthcare providers and women should be clearly aware of the tests being performed and of their performance, as having multiple tests increases the overall false-positive rate and failure rate. The detection rate for microdeletions has yet to be established and most national guidelines currently do not support testing for microdeletions on cfDNA. Screening for microdeletions also raises complex issues regarding pretest and post-test counseling
 - Prospective, publicly funded studies assessing the cost-effectiveness of various screening strategies should be performed as a matter of urgency

Allyse et al,
2013³⁷

Best ethical practices for clinicians

Medical providers offering noninvasive prenatal testing should:

- Offer all women the opportunity to receive reliable, medically relevant prenatal tests that have demonstrated safety and effectiveness in their demographic
- Where possible, work with third party payors to help all patients access noninvasive prenatal testing, if medically appropriate
- Structure the informed consent process so that it is comprehensive, interactive and sensitive to the need to understand the subjective experience of disease and disability
- Ensure that patients are offered genetic counseling both before and after testing
- Give patients clear opportunities to decline testing, both in general and for specific disorders, and never pressure patients to undergo testing
- Encourage patients to make clear choices about which results they wish to receive, including paternity and sex testing, before testing is undergone

Best ethical practices for commercial test providers

Companies offering noninvasive prenatal testing should:

- Offer testing only through licensed clinicians and not directly to consumers
- Seek oversight to validate the safety and effectiveness of genetic tests from relevant regulatory agencies
- Do their best to comply with national and international regulations and laws regarding the results that can legally be returned to patients
- Implement proficiency testing procedures verified independently by a third party to ensure analytic validity. Set transparent standards for data interpretation and error rates
- Require verification of comprehensive informed consent from clinicians before testing is conducted. Companies may wish to provide clinicians with appropriate informed consent forms in order to facilitate this process
- Obtain written consent for the storage of samples and genetic data and any research conducted using samples or test results. Samples should not be used for research without explicit consent separate from consent obtained to use samples for clinical purposes, and samples destroyed after clinical testing unless specific consent for future use has been obtained
- Provide the capacity to return selected results based on the wishes of the patient
- Provide genetic counseling resources to assist clinicians in facilitating the informed consent process
- Design marketing and advertising materials to promote values-based decision-making and avoid advocating for specific actions on the basis of test results

Abbreviations: ACMG, American College of Medical Genetics and Genomics; cfDNA, cell-free DNA; cFVS, combined first-trimester testing; CNV, copy-number variant; CVS, chorionic villus sampling; DR, detection rate; DANSR, Digital Analysis for Selected Regions; FPR, false-positive rate; ISUOG, International Society of Ultrasound in Obstetrics and Gynecology; MPS, massively parallel sequencing; NIPS, noninvasive prenatal screening; NIPT, noninvasive prenatal testing; NSGC, National Society of Genetic Counselors; NPV, negative predictive value; PPV, positive predictive value; NT, nuchal translucency; SPEC, specificity.

Note: Guideline statements and recommendations are verbatim.

Appendices

Appendix 3: Systematic Reviews

Table A3: Systematic Reviews on NIPT in the Average-Risk or General Population

Author, Year	Search Period	Databases	Included Studies	Results
Taylor-Phillips et al, 2016 ¹⁸	1997 to Feb 9, 2015 (auto-alerts until April 1, 2015)	PubMed, Medline, Embase, Cochrane Library Trial registries: ClinicalTrials.gov, WHO ICTRP	6 studies in general population	- Trisomy 21: sensitivity 95.9%, specificity 99.9%, PPV 82% - Trisomy 18: sensitivity 86.5%, specificity 99.8%, PPV 37% - Trisomy 13: sensitivity 77.5%, specificity 99.9%, PPV 49%
Iwarsson et al, 2017 ¹⁷	To Apr 2, 2015	PubMed, Embase, Cochrane Library	6 studies for average risk of trisomy 21 5 studies for average risk of trisomy 18 5 studies for average risk of trisomy 13	- Trisomy 21: sensitivity 99.3% (95% CI, 95.5%–99.9%), specificity 99.9% (95% CI, 99.8%–99.9%), GRADE moderate - Pooled sensitivity and specificity for trisomy 18 and 13 were not calculated because of the low number of studies
Badeau et al, 2017 ¹⁵	January 2007 to July 12, 2016	Medline, Embase, Web of Science, Cochrane Register of Diagnostic Test Accuracy Studies, Cochrane Library, ClinicalTrials.gov, European Clinical Trials Register, WHO ICTRP, National Technical Information Service, OpenGrey, National Guideline Clearing House	5 studies in general unselected pregnant population	- TMPS sensitivity: - Trisomy 21: 99.2% (95% CI, 78.2%–100%) - Trisomy 18: 90.9% (95% CI, 70.0%–97.7%) - Trisomy 13: 65.1% (95% CI, 9.16%–97.2%) - TMPS specificity for trisomies 21, 18, and 13: >99.9% - Sex chromosome aneuploidies: unable to perform meta-analysis because of limited data
Varela-Lema et al, 2017 ¹⁶	Inception to February/March 2017	Centre for Reviews and Dissemination, Cochrane Library Plus, Medline, Embase, Web of Science	8 studies in general population	Trisomy 21: sensitivity 99.3% (95% CI, 97.8%–99.8%), specificity 99.9% (95% CI, 99.8%–99.9%) Trisomy 18: sensitivity 97.4% (95% CI, 94.4%–98.8%), specificity 99.9% (95% CI, 99.87%–99.97%) Trisomy 13: sensitivity 98.8% (95% CI, 1.41%–100%), specificity 99.9% (95% CI, 99.94%–99.97%)

Abbreviations: CI, confidence interval; NIPT, noninvasive prenatal testing; PPV, positive predictive value; TMPS, targeted massively parallel sequencing; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform.

Appendix 4: Literature Search Strategies

Clinical Evidence Search

Search date: September 11, 2017

Databases searched: Ovid MEDLINE, Embase, CINAHL, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, CRD Health Technology Assessment Database, and NHS Economic Evaluation Database

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <August 2017>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to September 7, 2017>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2017 Week 37>, All Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

-
- 1 exp Aneuploidy/ (72175)
Annotation: Sub-terms under Aneuploidy/ include Trisomy/ and Chromosome Deletion/
 - 2 aneuploid*.ti,ab,kf. (43746)
 - 3 (trisom* or chromosom* triplicat*).ti,ab,kf. (41658)
 - 4 Chromosome Disorders/ (24985)
 - 5 ((chromosom* or subchromosom* or sub-chromosom*) adj (disorder* or anomal* or abnormal*)).ti,ab,kf. (46333)
 - 6 exp Chromosome Duplication/ (17855)
Annotation: Scope note:An aberration in which an extra chromosome or a chromosomal segment is made
Subterms:
Tetrasomy/ (The possession of four chromosomes of any one type in an otherwise diploid cell.)
Trisomy/
 - 7 Chromosomes, Human, Pair 13/ (8168)
 - 8 (chromosome* 13 or chromosome* thirteen or patau* or bartholin-patau* or T13).ti,ab,kf. (9488)
 - 9 Chromosomes, Human, Pair 18/ (8817)
 - 10 (chromosome* 18 or chromosome* eighteen or edward* syndrome* or T18).ti,ab,kf. (6226)
 - 11 Chromosomes, Human, Pair 21/ (9778)
 - 12 Down Syndrome/ (53600)
 - 13 (chromosome* 21 or chromosome* twenty-one or chromosome* twentyone or down* syndrome* or T21).ti,ab,kf. (50915)
 - 14 Chromosomes, Human, X/ (23292)
 - 15 Chromosomes, Human, Y/ (17885)
 - 16 exp Sex Chromosome Disorders/ (69290)
 - 17 (((x or y) adj chromosom*) or male sex chromosom* or female sex chromosom*).ti,ab,kf. (61635)
 - 18 Turner syndrome/ (17279)
 - 19 (45 x or turner* syndrome* or bonnevill-ullrich or monosom* x or ullrich-turner*).ti,ab,kf. (21326)
 - 20 Klinefelter syndrome/ (8401)
 - 21 (xxy or klinefelter* syndrome*).ti,ab,kf. (8330)
 - 22 XYY Karyotype/ (884)

- 23 (xyy or jacob* syndrome* or yy syndrome*).ti,ab,kf. (2427)
- 24 (xxx or triple-x or triplo-x*).ti,ab,kf. (3572)
- 25 (micro-deletion* or microdeletion* or (copy number adj variant*) or (chromosom* adj deletion*) or (partial adj monosom*)).ti,ab,kf. (22337)
- 26 1p36*.ti,ab,kf. (3788)
- 27 DiGeorge Syndrome/ (4568)
- 28 (digeorge* or di george* or CATCH22 or 22q11* or velocardiofacial or velo-cardio-facial or VCFS or cayler cardiofacial syndrome* or conotruncal anomaly face syndrome* or CTAF or sedlackova syndrome* or shprintzen syndrome* or takao syndrome*).ti,ab,kf. (11931)
- 29 Prader-Willi Syndrome/ (7648)
- 30 (prader-willi* or labhart-willi* or prader-labhart-willi* or prader* syndrome* or royer* syndrome* or PWS or PLW or PLWS).ti,ab,kf. (9960)
- 31 Angelman Syndrome/ (2915)
- 32 (angelman* or happy puppet* or 15q11*).ti,ab,kf. (5712)
- 33 Williams Syndrome/ (3656)
- 34 (((supravalvar or hypercalcemia-supravalvar) adj aortic stenosis) or williams* syndrome* or beuren* syndrome* or 7q11*).ti,ab,kf. (5631)
- 35 22q11 Deletion Syndrome/ (742)
- 36 22q11*.ti,ab,kf. (8233)
- 37 Cri-du-Chat Syndrome/ (1372)
- 38 (cri-du-chat or crying cat or cat cry or ((5p or 5q) adj2 (syndrome* or monosom*))).ti,ab,kf. (2593)
- 39 or/1-38 (382292)
- 40 Sequence Analysis, DNA/ (305481)
- 41 ((DNA or parallel or next-generation or shotgun or target*) adj sequenc*).ti,ab,kf. (255174)
- 42 (MPSS or NGS or CSS or TMPS).ti,ab,kf. (36772)
- 43 High-Throughput Nucleotide Sequencing/ (28228)
- 44 ((high throughput adj2 (analys#s or sequenc*)) or single nucleotide polymorphism* or SNP or SNPs).ti,ab,kf. (255638)
- 45 or/40-44 (745097)
- 46 Genetic Testing/ (61686)
- 47 ((genetic* or gene*1 or genome*1 or genomic*) adj2 (test or tests or testing or diagnos#s or screen*)).ti,ab,kf. (134466)
- 48 or/46-47 (173089)
- 49 (noninvasive* or non-invasive*).ti,ab,kf. (394139)
- 50 48 and 49 (2231)
- 51 45 or 50 (746958)
- 52 Prenatal Diagnosis/ (88789)
- 53 ((antenatal or ante-natal or intrauterine or intra-uterine or prenatal or pre-natal) adj2 (test or tests or testing or diagnos#s or detect* or screen*)).ti,ab,kf. (75086)
- 54 (maternal adj2 (plasm* or blood)).ti,ab,kf. (28418)
- 55 or/52-54 (145986)
- 56 51 and 55 (4879)
- 57 (((f?etal or f?etus* or free-f?etal or placenta*) adj2 dna) or cell-free dna).ti,ab,kf. (9774)
- 58 (cff DNA or cffDNA or cf DNA or cfDNA or f DNA or fDNA or ff DNA or ffDNA).ti,ab,kf. (3746)
- 59 ((noninvasive* or non-invasive*) adj5 (prenatal or f?etal or f?etus*) adj (test or tests or testing or diagnos#s or detect* or screen*)).ti,ab,kf. (3888)
- 60 (NIPT or NIPD or NIDT or gNIPT or NIPS).ti,ab,kf. (2880)
- 61 or/56-60 (17100)
- 62 39 and 61 (4887)

- 63 exp Animals/ not Humans/ (14739671)
- 64 62 not 63 (3258)
- 65 Case Reports/ or Comment.pt. or Editorial.pt. or Letter.pt. or Congresses.pt. (4954736)
- 66 64 not 65 (2964)
- 67 limit 66 to english language [Limit not valid in CDSR; records were retained] (2713)
- 68 67 use ppez,coch,cctr,clhta,cleed (1498)
- 69 exp aneuploidy/ (72175)
- 70 aneuploid*.tw,kw. (44692)
- 71 trisomy/ (21627)
- 72 (trisom* or chromosom* triplicat*).tw,kw. (42442)
- 73 chromosome disorder/ (28876)
- 74 ((chromosom* or subchromosom* or sub-chromosom*) adj (disorder* or anomal* or abnormal*)).tw,kw. (46385)
- 75 chromosome duplication/ (5471)
- 76 trisomy 13/ (2267)
- 77 (chromosome* 13 or chromosome* thirteen or patau* or bartholin-patau* or T13).tw,kw. (9592)
- 78 trisomy 18/ (3144)
- 79 Edwards syndrome/ (463)
- 80 (chromosome* 18 or chromosome* eighteen or edward* syndrome* or T18).tw,kw. (6334)
- 81 trisomy 21/ (30940)
- 82 Down syndrome/ (53600)
- 83 (chromosome* 21 or chromosome* twenty-one or chromosome* twentyone or down* syndrome* or T21).tw,kw. (51741)
- 84 X chromosome/ (38452)
- 85 Y chromosome/ (21567)
- 86 exp sex chromosome aberration/ (15516)
- 87 (((x or y) adj chromosom*) or male sex chromosom* or female sex chromosom*).tw,kw. (62294)
- 88 Turner syndrome/ (17279)
- 89 (45 x or turner* syndrome* or bonnevill-ullrich or monosom* x or ullrich-turner*).tw,kw. (21502)
- 90 exp Klinefelter syndrome/ (8508)
- 91 (xxy or klinefelter* syndrome*).tw,kw. (8405)
- 92 karyotype 47,XYY/ (529)
- 93 (xyy or jacob* syndrome* or yy syndrome*).tw,kw. (2455)
- 94 47,XXX syndrome/ (54)
- 95 (xxx or triple-x or triplo-x*).tw,kw. (3598)
- 96 chromosome deletion/ (40585)
- 97 (micro-deletion* or microdeletion* or (copy number adj variant*) or (chromosom* adj deletion*) or (partial adj monosom*)).tw,kw. (22975)
- 98 1p36*.tw,kw. (3799)
- 99 DiGeorge syndrome/ (4568)
- 100 (digeorge* or di george* or CATCH22 or 22q11* or velocardiofacial or velo-cardio-facial or VCFS or cayler cardiofacial syndrome* or conotruncal anomaly face syndrome* or CTAF or sedlackova syndrome* or shprintzen syndrome* or takao syndrome*).tw,kw. (12043)
- 101 Prader Willi syndrome/ (7648)
- 102 (prader-willi* or labhart-willi* or prader-labhart-willi* or prader* syndrome* or royer* syndrome* or PWS or PLW or PLWS).tw,kw. (10100)
- 103 happy puppet syndrome/ (3489)
- 104 (angelman* or happy puppet* or 15q11*).tw,kw. (5816)

- 105 Williams Beuren syndrome/ (4505)
- 106 (((supravalvar or hypercalcemia-supravalvar) adj aortic stenosis) or williams* syndrome* or beuren* syndrome* or 7q11*).tw,kw. (5693)
- 107 chromosome deletion 22q11/ (1205)
- 108 22q11*.tw,kw. (8320)
- 109 cat cry syndrome/ (1420)
- 110 (cri-du-chat or crying cat or cat cry or ((5p or 5q) adj2 (syndrome* or monosom*))).tw,kw. (2634)
- 111 or/69-110 (392560)
- 112 dna sequence/ (623128)
- 113 next generation sequencing/ (23023)
- 114 ((DNA or parallel or next-generation or shotgun or target*) adj sequenc*).tw,kw,dv. (257559)
- 115 (MPSS or NGS or CSS or TMPS).tw,kw,dv. (37286)
- 116 high throughput sequencing/ (15438)
- 117 ((high throughput adj2 (analys#s or sequenc*)) or single nucleotide polymorphism* or SNP or SNPs).tw,kw,dv. (261185)
- 118 or/112-117 (1044893)
- 119 genetic screening/ (99427)
- 120 ((genetic* or gene*1 or genome*1 or genomic*) adj2 (test or tests or testing or diagnos#s or screen*)).tw,kw,dv. (137097)
- 121 or/119-120 (195072)
- 122 non invasive procedure/ (22579)
- 123 (noninvasive* or non-invasive*).tw,kw,dv. (397409)
- 124 or/122-123 (401063)
- 125 121 and 124 (2555)
- 126 118 or 125 (1047024)
- 127 prenatal diagnosis/ (88789)
- 128 ((antenatal or ante-natal or intrauterine or intra-uterine or prenatal or pre-natal) adj2 (test or tests or testing or diagnos#s or detect* or screen*)).tw,kw,dv. (78643)
- 129 maternal plasma/ (3085)
- 130 (maternal adj2 (plasm* or blood)).tw,kw,dv. (28664)
- 131 or/127-130 (147990)
- 132 126 and 131 (5826)
- 133 (((f?etal or f?etus* or free-f?etal or placenta*) adj2 dna) or cell-free dna).tw,kw,dv. (9994)
- 134 (cff DNA or cffDNA or cf DNA or cfDNA or f DNA or fDNA or ff DNA or ffDNA).tw,kw,dv. (3786)
- 135 ((noninvasive* or non-invasive*) adj5 (prenatal or pre-natal or f?etal or f?etus*) adj (test or tests or testing or diagnos#s or detect* or screen*)).tw,kw,dv. (4002)
- 136 (NIPT or NIPD or NIDT or gNIPT or NIPS).tw,kw,dv. (2948)
- 137 or/132-136 (18162)
- 138 111 and 137 (5130)
- 139 (exp animal/ or nonhuman/) not exp human/ (10421029)
- 140 138 not 139 (5084)
- 141 Case Report/ or Comment/ or Editorial/ or Letter/ or conference abstract.pt. (9439143)
- 142 140 not 141 (3647)
- 143 limit 142 to english language [Limit not valid in CDSR; records were retained] (3309)
- 144 143 use emez (1775)
- 145 68 or 144 (3273)
- 146 limit 145 to yr="2007 -Current" (2613)
- 147 146 use ppez (1148)

148 146 use emez (1424)
 149 146 use cctr (25)
 150 146 use coch (1)
 151 146 use clhta (6)
 152 146 use cleed (9)
 153 remove duplicates from 146 (1605)

CINAHL

#	Query	Results
S1	(MH "Chromosome Aberrations+")	1,656
S2	aneuploid*	1,492
S3	(trisom* or chromosom* triplicat*)	1,480
S4	(MH "Chromosome Disorders")	3,823
S5	((chromosom* or subchromosom* or sub-chromosom*) N1 (disorder* or anomal* or abnormal*))	4,891
S6	(MH "Trisomy 13")	62
S7	(chromosome* 13 or chromosome* thirteen or patau* or bartholin-patau* or T13)	459
S8	(MH "Trisomy 18")	75
S9	(chromosome* 18 or chromosome* eighteen or edward* syndrome* or T18)	311
S10	(MH "Down Syndrome")	5,566
S11	(chromosome* 21 or chromosome* twenty-one or chromosome* twentyone or down* syndrome* or T21)	7,008
S12	((x or y) N1 chromosom*) or male sex chromosom* or female sex chromosom*)	673
S13	(MH "Turner's Syndrome")	483
S14	(45 x or turner* syndrome* or bonnevill-ullrich or monosom* x or ullrich-turner*)	868
S15	(MH "Klinefelter's Syndrome")	236
S16	(xxy or klinefelter* syndrome*)	332
S17	(MH "XYY Syndrome")	5
S18	(xxy or jacob* syndrome* or yy syndrome*)	66
S19	(xxx or triple-x or triplo-x*)	183,845

S20	(micro-deletion* or microdeletion* or (copy number N1 variant*) or (chromosom* N1 deletion*) or (partial N1 monosom*))	729
S21	1p36*	693
S22	(MH "DiGeorge Syndrome")	237
S23	(digeorge* or di george* or CATCH22 or 22q11* or velocardiofacial or velo-cardio-facial or VCFS or cayler cardiofacial syndrome* or conotruncal anomaly face syndrome* or CTAF or sedlackova syndrome* or shprintzen syndrome* or takao syndrome*)	863
S24	(MH "Prader-Willi Syndrome")	539
S25	(prader-willi* or labhart-willi* or prader-labhart-willi* or prader* syndrome* or royer* syndrome* or PWS or PLW or PLWS)	823
S26	(MH "Angelman Syndrome")	154
S27	(angelman* or happy puppet* or 15q11*)	264
S28	(MH "Williams Syndrome")	424
S29	((supravalvar or hypercalcemia-supravalvar) N1 aortic stenosis) or williams* syndrome* or beuren* syndrome* or 7q11*)	558
S30	(MH "22q11 Deletion Syndrome+")	297
S31	22q11*	438
S32	(MH "Cri-Du-Chat Syndrome")	84
S33	(cri-du-chat or crying cat or cat cry or ((5p or 5q) N2 (syndrome* or monosom*)))	858
S34	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33	201,252
S35	(MH "Sequence Analysis+")	12,935
S36	((DNA or parallel or next-generation or shotgun or target*) N1 sequenc*)	3,714
S37	(MPSS or NGS or CSS or TMPS)	1,678
S38	((high throughput N2 (analys#s or sequenc*)) or single nucleotide polymorphism* or SNP or SNPs)	8,017
S39	S35 OR S36 OR S37 OR S38	23,341
S40	(MH "Genetic Screening")	9,414

S41	((genetic* or gene or genes or genome* or genomic*) N2 (test or tests or testing or diagnos#s or screen*))	14,372
S42	S40 OR S41	14,372
S43	(MH "Noninvasive Procedures")	1,777
S44	(noninvasive* or non-invasive*)	22,509
S45	S43 OR S44	22,509
S46	S42 AND S45	294
S47	S39 OR S46	23,575
S48	(MH "Prenatal Diagnosis")	6,277
S49	((antenatal or ante-natal or intrauterine or intra-uterine or prenatal or pre-natal) N2 (test or tests or testing or diagnos#s or detect* or screen*))	9,738
S50	(maternal N2 (plasm* or blood))	1,823
S51	S48 OR S49 OR S50	11,233
S52	S47 AND S51	546
S53	((f?etal or f?etus* or free-f?etal or placenta*) N2 dna) or cell-free dna)	5,146
S54	(cff DNA or cffDNA or cf DNA or cfDNA or f DNA or fDNA or ff DNA or ffdNA)	311
S55	((noninvasive* or non-invasive*) N5 (prenatal or pre-natal or f?etal or f?etus*) N1 (test or tests or testing or diagnos#s or detect* or screen*))	1,084
S56	(NIPT or NIPD or NIDT or gNIPT or NIPS)	409
S57	S52 OR S53 OR S54 OR S55 OR S56	6,493
S58	S34 AND S57	1,247
S59	PT Case Study or Commentary or Editorial or Letter or Proceedings	403,814
S60	S58 not S59	1,181
S61	Limiters - Published Date: 20070101-20171231	1,055
S62	Narrow by Language: - english	1,051

Economic Evidence Search

Search date: September 14, 2017

Databases searched: Ovid MEDLINE, Embase, CINAHL, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, CRD Health Technology Assessment Database, and NHS Economic Evaluation Database

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <August 2017>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to September 13, 2017>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2017 Week 37>, All Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

-
- 1 exp Aneuploidy/ (72195)
Annotation: Sub-terms under Aneuploidy/ include Trisomy/ and Chromosome Deletion/
 - 2 aneuploid*.ti,ab,kf. (43738)
 - 3 (trisom* or chromosom* triplicat*).ti,ab,kf. (41658)
 - 4 Chromosome Disorders/ (24987)
 - 5 ((chromosom* or subchromosom* or sub-chromosom*) adj (disorder* or anomal* or abnormal*)).ti,ab,kf. (46325)
 - 6 exp Chromosome Duplication/ (17858)
Annotation: Scope note:An aberration in which an extra chromosome or a chromosomal segment is made
Subterms:
Tetrasomy/ (The possession of four chromosomes of any one type in an otherwise diploid cell.)
Trisomy/
 - 7 Chromosomes, Human, Pair 13/ (8171)
 - 8 (chromosome* 13 or chromosome* thirteen or patau* or bartholin-patau* or T13).ti,ab,kf. (9486)
 - 9 Chromosomes, Human, Pair 18/ (8819)
 - 10 (chromosome* 18 or chromosome* eighteen or edward* syndrome* or T18).ti,ab,kf. (6226)
 - 11 Chromosomes, Human, Pair 21/ (9778)
 - 12 Down Syndrome/ (53611)
 - 13 (chromosome* 21 or chromosome* twenty-one or chromosome* twentyone or down* syndrome* or T21).ti,ab,kf. (50915)
 - 14 Chromosomes, Human, X/ (23294)
 - 15 Chromosomes, Human, Y/ (17887)
 - 16 exp Sex Chromosome Disorders/ (69295)
 - 17 (((x or y) adj chromosom*) or male sex chromosom* or female sex chromosom*).ti,ab,kf. (61627)
 - 18 Turner syndrome/ (17283)
 - 19 (45 x or turner* syndrome* or bonnevill-ullrich or monosom* x or ullrich-turner*).ti,ab,kf. (21325)
 - 20 Klinefelter syndrome/ (8401)
 - 21 (xxy or klinefelter* syndrome*).ti,ab,kf. (8332)
 - 22 XYY Karyotype/ (884)
 - 23 (xyy or jacob* syndrome* or yy syndrome*).ti,ab,kf. (2428)
 - 24 (xxx or triple-x or triplo-x*).ti,ab,kf. (3572)

- 25 (micro-deletion* or microdeletion* or (copy number adj variant*) or (chromosom* adj deletion*) or (partial adj monosom*)).ti,ab,kf. (22332)
- 26 1p36*.ti,ab,kf. (3789)
- 27 DiGeorge Syndrome/ (4568)
- 28 (digeorge* or di george* or CATCH22 or 22q11* or velocardiofacial or velo-cardio-facial or VCFS or cayler cardiofacial syndrome* or conotruncal anomaly face syndrome* or CTAF or sedlackova syndrome* or shprintzen syndrome* or takao syndrome*).ti,ab,kf. (11932)
- 29 Prader-Willi Syndrome/ (7649)
- 30 (prader-willi* or labhart-willi* or prader-labhart-willi* or prader* syndrome* or royer* syndrome* or PWS or PLW or PLWS).ti,ab,kf. (9960)
- 31 Angelman Syndrome/ (2915)
- 32 (angelman* or happy puppet* or 15q11*).ti,ab,kf. (5715)
- 33 Williams Syndrome/ (3656)
- 34 (((supravalvar or hypercalcemia-supravalvar) adj aortic stenosis) or williams* syndrome* or beuren* syndrome* or 7q11*).ti,ab,kf. (5628)
- 35 22q11 Deletion Syndrome/ (742)
- 36 22q11*.ti,ab,kf. (8233)
- 37 Cri-du-Chat Syndrome/ (1372)
- 38 (cri-du-chat or crying cat or cat cry or ((5p or 5q) adj2 (syndrome* or monosom*))).ti,ab,kf. (2593)
- 39 or/1-38 (382280)
- 40 Sequence Analysis, DNA/ (305684)
- 41 ((DNA or parallel or next-generation or shotgun or target*) adj sequenc*).ti,ab,kf. (255120)
- 42 (MPSS or NGS or CSS or TMPS).ti,ab,kf. (36771)
- 43 High-Throughput Nucleotide Sequencing/ (28412)
- 44 ((high throughput adj2 (analys#s or sequenc*)) or single nucleotide polymorphism* or SNP or SNPs).ti,ab,kf. (255606)
- 45 or/40-44 (745279)
- 46 Genetic Testing/ (61722)
- 47 ((genetic* or gene*1 or genome*1 or genomic*) adj2 (test or tests or testing or diagnos#s or screen*)).ti,ab,kf. (134472)
- 48 or/46-47 (173107)
- 49 (noninvasive* or non-invasive*).ti,ab,kf. (394165)
- 50 48 and 49 (2232)
- 51 45 or 50 (747141)
- 52 Prenatal Diagnosis/ (88801)
- 53 ((antenatal or ante-natal or intrauterine or intra-uterine or prenatal or pre-natal) adj2 (test or tests or testing or diagnos#s or detect* or screen*)).ti,ab,kf. (75088)
- 54 (maternal adj2 (plasm* or blood)).ti,ab,kf. (28413)
- 55 or/52-54 (145987)
- 56 51 and 55 (4879)
- 57 (((f?etal or f?etus* or free-f?etal or placenta*) adj2 dna) or cell-free dna).ti,ab,kf. (9771)
- 58 (cff DNA or cffDNA or cf DNA or cfDNA or f DNA or fDNA or ff DNA or ffDNA).ti,ab,kf. (3747)
- 59 ((noninvasive* or non-invasive*) adj5 (prenatal or f?etal or f?etus*) adj (test or tests or testing or diagnos#s or detect* or screen*)).ti,ab,kf. (3885)
- 60 (NIPT or NIPD or NIDT or gNIPT or NIPS).ti,ab,kf. (2878)
- 61 or/56-60 (17096)
- 62 39 and 61 (4885)
- 63 economics/ (254063)

- 64 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (784912)
- 65 economics.fs. (408693)
- 66 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmaco-economic* or pharmaco-economic*).ti,ab,kf. (775112)
- 67 exp "costs and cost analysis"/ (549308)
- 68 (cost or costs or costing or costly).ti. (238182)
- 69 cost effective*.ti,ab,kf. (277495)
- 70 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*).ab. (180176)
- 71 models, economic/ (11024)
- 72 markov chains/ or monte carlo method/ (72818)
- 73 (decision adj1 (tree* or analy* or model*).ti,ab,kf. (35829)
- 74 (markov or markow or monte carlo).ti,ab,kf. (114677)
- 75 quality-adjusted life years/ (33915)
- 76 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (58350)
- 77 ((adjusted adj (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (94568)
- 78 or/63-77 (2320493)
- 79 62 and 78 (434)
- 80 79 use ppez,coch,cctr,clhta (142)
- 81 62 use cleed (10)
- 82 or/80-81 (152)
- 83 limit 82 to english language [Limit not valid in CDSR; records were retained] (140)
- 84 exp aneuploidy/ (72195)
- 85 aneuploid*.tw,kw. (44685)
- 86 trisomy/ (21629)
- 87 (trisom* or chromosom* triplicat*).tw,kw. (42441)
- 88 chromosome disorder/ (28878)
- 89 ((chromosom* or subchromosom* or sub-chromosom*) adj (disorder* or anomal* or abnormal*).tw,kw. (46380)
- 90 chromosome duplication/ (5472)
- 91 trisomy 13/ (2267)
- 92 (chromosome* 13 or chromosome* thirteen or patau* or bartholin-patau* or T13).tw,kw. (9590)
- 93 trisomy 18/ (3144)
- 94 Edwards syndrome/ (463)
- 95 (chromosome* 18 or chromosome* eighteen or edward* syndrome* or T18).tw,kw. (6334)
- 96 trisomy 21/ (30951)
- 97 Down syndrome/ (53611)
- 98 (chromosome* 21 or chromosome* twenty-one or chromosome* twentyone or down* syndrome* or T21).tw,kw. (51741)
- 99 X chromosome/ (38453)
- 100 Y chromosome/ (21567)
- 101 exp sex chromosome aberration/ (15517)
- 102 (((x or y) adj chromosom*) or male sex chromosom* or female sex chromosom*).tw,kw. (62286)
- 103 Turner syndrome/ (17283)
- 104 (45 x or turner* syndrome* or bonnevie-ullrich or monosom* x or ullrich-turner*).tw,kw. (21501)
- 105 exp Klinefelter syndrome/ (8508)

- 106 (xxy or klinefelter* syndrome*).tw,kw. (8407)
- 107 karyotype 47,XY/ (529)
- 108 (xxy or jacob* syndrome* or yy syndrome*).tw,kw. (2456)
- 109 47,XXX syndrome/ (54)
- 110 (xxx or triple-x or triplo-x*).tw,kw. (3598)
- 111 chromosome deletion/ (40591)
- 112 (micro-deletion* or microdeletion* or (copy number adj variant*) or (chromosom* adj deletion*) or (partial adj monosom*)).tw,kw. (22970)
- 113 1p36*.tw,kw. (3800)
- 114 DiGeorge syndrome/ (4568)
- 115 (digeorge* or di george* or CATCH22 or 22q11* or velocardiofacial or velo-cardio-facial or VCFS or cayler cardiofacial syndrome* or conotruncal anomaly face syndrome* or CTAF or sedlackova syndrome* or shprintzen syndrome* or takao syndrome*).tw,kw. (12044)
- 116 Prader Willi syndrome/ (7649)
- 117 (prader-willi* or labhart-willi* or prader-labhart-willi* or prader* syndrome* or royer* syndrome* or PWS or PLW or PLWS).tw,kw. (10100)
- 118 happy puppet syndrome/ (3489)
- 119 (angelman* or happy puppet* or 15q11*).tw,kw. (5819)
- 120 Williams Beuren syndrome/ (4505)
- 121 (((supravalvar or hypercalcemia-supravalvar) adj aortic stenosis) or williams* syndrome* or beuren* syndrome* or 7q11*).tw,kw. (5690)
- 122 chromosome deletion 22q11/ (1205)
- 123 22q11*.tw,kw. (8320)
- 124 cat cry syndrome/ (1420)
- 125 (cri-du-chat or crying cat or cat cry or ((5p or 5q) adj2 (syndrome* or monosom*)).tw,kw. (2634)
- 126 or/84-125 (392546)
- 127 dna sequence/ (623222)
- 128 next generation sequencing/ (23023)
- 129 ((DNA or parallel or next-generation or shotgun or target*) adj sequenc*).tw,kw,dv. (257498)
- 130 (MPSS or NGS or CSS or TMPS).tw,kw,dv. (37282)
- 131 high throughput sequencing/ (15438)
- 132 ((high throughput adj2 (analys#s or sequenc*)) or single nucleotide polymorphism* or SNP or SNPs).tw,kw,dv. (261153)
- 133 or/127-132 (1044877)
- 134 genetic screening/ (99463)
- 135 ((genetic* or gene*1 or genome*1 or genomic*) adj2 (test or tests or testing or diagnos#s or screen*)).tw,kw,dv. (137099)
- 136 or/134-135 (195087)
- 137 non invasive procedure/ (22579)
- 138 (noninvasive* or non-invasive*).tw,kw,dv. (397434)
- 139 or/137-138 (401088)
- 140 136 and 139 (2555)
- 141 133 or 140 (1047008)
- 142 prenatal diagnosis/ (88801)
- 143 ((antenatal or ante-natal or intrauterine or intra-uterine or prenatal or pre-natal) adj2 (test or tests or testing or diagnos#s or detect* or screen*)).tw,kw,dv. (78640)
- 144 maternal plasma/ (3085)
- 145 (maternal adj2 (plasm* or blood)).tw,kw,dv. (28659)
- 146 or/142-145 (147987)

147 141 and 146 (5825)
 148 (((f?etal or f?etus* or free-f?etal or placenta*) adj2 dna) or cell-free dna).tw,kw,dv. (9991)
 149 (cff DNA or cffDNA or cf DNA or cfDNA or f DNA or fDNA or ff DNA or ffDNA).tw,kw,dv. (3787)
 150 ((noninvasive* or non-invasive*) adj5 (prenatal or pre-natal or f?etal or f?etus*) adj (test or tests or testing or diagnos#s or detect* or screen*)).tw,kw,dv. (3998)
 151 (NIPT or NIPD or NIDT or gNIPT or NIPS).tw,kw,dv. (2946)
 152 or/147-151 (18157)
 153 126 and 152 (5127)
 154 Economics/ (254063)
 155 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (128271)
 156 Economic Aspect/ or exp Economic Evaluation/ (421883)
 157 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw. (799420)
 158 exp "Cost"/ (549308)
 159 (cost or costs or costing or costly).ti. (238182)
 160 cost effective*.tw,kw. (288324)
 161 (cost* adj2 (util* or efficac* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab. (181289)
 162 Monte Carlo Method/ (58993)
 163 (decision adj1 (tree* or analy* or model*)).tw,kw. (39527)
 164 (markov or markow or monte carlo).tw,kw. (119639)
 165 Quality-Adjusted Life Years/ (33915)
 166 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw. (62103)
 167 ((adjusted adj (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw. (113787)
 168 or/154-167 (1964482)
 169 153 and 168 (412)
 170 169 use emez (274)
 171 limit 170 to english language [Limit not valid in CDSR; records were retained] (265)
 172 83 or 171 (405)
 173 limit 172 to yr="2007 -Current" (384)
 174 173 use ppez (118)
 175 173 use emez (253)
 176 173 use coch (0)
 177 173 use cctr (3)
 178 173 use clhta (1)
 179 173 use cleed (9)
 180 remove duplicates from 173 (281)

CINAHL

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S45	S43 OR S44	22,526
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S50	(maternal N2 (plasm* or blood))	1,823

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S55	((noninvasive* or non-invasive*) N5 (prenatal or pre-natal or f?etal or f?etus*) N1 (test or tests or testing or diagnos#s or detect* or screen*))	1,084
S56	(NIPT or NIPD or NIDT or gNIPT or NIPS)	409
S57	S52 OR S53 OR S54 OR S55 OR S56	6,495
S58	S34 AND S57	1,248
S59	(MH "Economics")	11,409
S60	(MH "Economic Aspects of Illness")	6,976
S61	(MH "Economic Value of Life")	524
S62	MH "Economics, Dental"	110
S63	MH "Economics, Pharmaceutical"	1,801
S64	MW "ec"	145,411
S65	(econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*)	224,154
S66	(MH "Costs and Cost Analysis+")	87,576
S67	TI cost*	41,334
S68	(cost effective*)	30,213
S69	AB (cost* N2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*))	20,956
S70	(decision N1 (tree* or analy* or model*))	5,470
S71	(markov or markow or monte carlo)	3,627
S72	(MH "Quality-Adjusted Life Years")	2,874
S73	(QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs)	6,879
S74	((adjusted N1 (quality or life)) or (willing* N2 pay) or sensitivity analys?s)	12,813

S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S75 S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74	300,110
S76 S58 AND S75	84
S77 Limiters - Published Date: 20070101-20171231	78
S78 Narrow by Language: - english	78

Grey Literature Search

Search Dates: August 25–30, 2017

Websites searched: HTA Database Canadian Repository, Alberta Health Technologies Decision Process reviews, Canadian Agency for Drugs and Technologies in Health (CADTH), Institut national d'excellence en santé et en services sociaux (INESSS), Institute of Health Economics (IHE), McGill University Health Centre Health Technology Assessment Unit, National Institute for Health and Care Excellence (NICE), Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Australian Government Medical Services Advisory Committee, Centers for Medicare & Medicaid Services Technology Assessments, Institute for Clinical and Economic Review, Ireland Health Information and Quality Authority Health Technology Assessments, Washington State Health Care Authority Health Technology Reviews, clinicaltrials.gov, Tufts Cost Effectiveness Analysis Registry, Sick Kids' Paediatric Economic Database Evaluation (PEDE)

Keywords: noninvasive, non-invasive, prenatal, fetus, fetal, faetus, faetal, cell-free DNA, aneuploidy, aneuploidies, trisomy, trisomies, chromosome triplication, chromosomal triplication, micro-deletion, microdeletion, copy number variant, NIPT, NIPD, NIDT, gNIPT, NIPS

Results

- HTA = 8
- Trials = 41 (not counted in PRISMA flow diagram)

Appendices

Appendix 5: Critical Appraisal of Clinical Evidence

Table A4: Risk of Bias^a Among Diagnostic Accuracy Studies (QUADAS-2 Tool)

Author, Year	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Bianchi et al, 2014 ⁵¹	High ^b	Low	Low	High ^c	High ^d	Low	Low
del Mar Gil et al, 2014 ⁵²	Unclear ^e	Low	Low	High ^c	Low	Low	Low
Langlois et al, 2017 ⁵³	High ^b	Low	Low	Low	Low	Low	Low
Nicolaides et al, 2012 ⁵⁴	High ^b	Low	Low	High ^c	Low	Low	Low
Norton et al, 2015 ⁵⁵	High ^b	Low	Low	High ^c	Low	Low	Low
Palomaki et al, 2017 ⁵⁶	High ^b	Low	Low	High ^c	Low	Low	Low
Quezada et al, 2015 ⁵⁷	High ^b	Low	Unclear ^f	High ^c	Low	Low	Low
Song et al, 2013 ⁵⁸	High ^b	Low	Low	High ^c	Low	Low	Low

Abbreviation: NIPT, noninvasive prenatal testing; QUADAS-2; Quality Assessment of Diagnostic Accuracy Studies.

^aPossible risk of bias levels: low, high, unclear.

^bDid not avoid inappropriate exclusions or had unclear consecutive or random enrolment of patients.

^cInappropriate interval between NIPT and reference standard. Some studies missing or excluded patients in analysis.

^dApplicability concerns because of inappropriate patient exclusions.

^eUnclear patient enrolment and study exclusions.

^fUnclear whether reference standard was interpreted without knowledge of NIPT results.

Table A5: Risk of Bias^a Among Nonrandomized Trials (ROBINS-I Tool)

Author, Year	Preintervention		At Intervention		Postintervention		
	Confounding	Study Participation Selection	Classification of Interventions	Deviations From Intended Intervention	Missing Data	Measurement of Outcomes	Selection of Reported Results
Bianchi et al, 2014 ⁵¹	Low	Moderate ^a	Low	Low	Moderate ^b	Low	Low
Langlois et al, 2017 ⁵³	Low	Moderate ^a	Low	Low	Low	Low	Low
Palomaki et al, 2017 ⁵⁶	Low	Moderate ^a	Low	Low	Moderate ^b	Serious ^c	Moderate ^d
Quezada et al, 2015 ⁵⁷	Low	Moderate ^a	Low	Low	Moderate ^b	Moderate ^e	Low
Song et al, 2013 ⁵⁸	Low	Moderate ^a	Low	Low	Low	Moderate ^e	Low

Abbreviation: ROBINS-I, Risk of Bias in Non-randomized Studies—of Interventions.

^aPossible risk of bias levels: low, moderate, serious, critical, and no information.

^bDid not avoid inappropriate exclusions or had unclear consecutive or random enrolment of patients.

^cMissing data for some patients who did not have a successful noninvasive prenatal testing result.

^dLimited information regarding how clinical utility was measured among patients. Did not use a validated measurement tool.

^eNot all patients were included in the analysis.

^fLimited information regarding how clinical utility was measured among patients.

Table A6: GRADE Evidence Profile for Noninvasive Prenatal Testing

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
NIPT Accuracy							
Trisomy 21, sensitivity (8 test accuracy studies ^a)	Serious limitations (–1) ^b	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Trisomy 21, specificity (8 test accuracy studies ^a)	Serious limitations (–1) ^b	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Trisomy 18, sensitivity (7 test accuracy studies ^a)	Serious limitations (–1) ^b	No serious limitations	No serious limitations	Serious limitations (–1) ^c	Undetected	None	⊕⊕ Low
Trisomy 18, specificity (7 test accuracy studies ^a)	Serious limitations (–1) ^b	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Trisomy 13, sensitivity (7 test accuracy studies ^a)	Serious limitations (–1) ^b	No serious limitations	No serious limitations	Serious limitations (–1) ^c	Undetected	None	⊕⊕ Low
Trisomy 13, specificity (7 test accuracy studies ^a)	Serious limitations (–1) ^b	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Test failure rate (7 observational studies)	Serious limitations (–1) ^b	Serious limitations (–1) ^d	No serious limitations	No serious limitations	Undetected	None	⊕ Very Low
NIPT Clinical Utility							
Reduction in diagnostic testing (2 observational studies)	Serious limitations (–1) ^b	No serious limitations	No serious limitations	No serious limitations	Undetected	+2 for large magnitude of effect	⊕⊕⊕ Moderate
Test turnaround time (3 observational studies)	Serious limitations (–1) ^b	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕ Very Low
Understanding of health care providers (7 observational studies)	Serious limitations (–1) ^e	Very serious limitations (–2) ^f	No serious limitations	Very serious limitations (–2) ^f	Undetected	None	⊕ Very Low
NIPT Personal Utility							
Maternal education (1 observational study)	Serious limitations (–1) ^b	No serious limitations	No serious limitations	Very serious limitations (–2) ^g	Undetected	None	⊕ Very Low
Maternal satisfaction (1 observational study)	Serious limitations (–1) ^b	No serious limitations	No serious limitations	Very serious limitations (–2) ^g	Undetected	None	⊕ Very Low

Abbreviation: Grading of Recommendations, Assessment, Development and Evaluation.

Note: Publication bias cannot be adequately assessed for test accuracy, unless there are known studies that cannot be accessed.

^aTest accuracy studies start at high GRADE.^bRisk of bias concerns regarding patient selection and flow and timing among studies. Not all patients were included in analyses, some of which were likely at higher risk of chromosomal anomalies.^cWide confidence intervals because of low prevalence of conditions and very low number of false negatives that highly influenced test sensitivity.^dDifferences in NIPT testing platform and algorithms may have affected the cutoff for low fetal fraction, affecting the failure rate.^eNot a validated method of assessing satisfaction or education.^fLow response rate among some studies. Convenience sampling of health care providers. Response bias.^gDifferences in geographical location, education, and regional practice patterns impact providers' education. Different survey design and questions (non-validated) used to assess provider understanding. Broad range of understanding is covered within studies.

Appendices

Appendix 6: Ongoing Studies of Noninvasive Prenatal Testing

Table A7: Ongoing Studies of Noninvasive Prenatal Testing

Registry	ID	Population	Country	Official Title	Condition(s)	Sponsor
ClinicalTrials.gov	NCT02424474	Average-risk	France	Fetal aneuploidies screening (21,18, and 13) by cell-free fetal DNA analysis	Trisomies 21, 18, 13	Assistance Publique—Hôpitaux de Paris
Australian New Zealand Clinical Trials Registry	ACTRN12617001587392	Average-risk	Australia	Prenatal screening for aneuploidy in the Australian public hospital system: a noninvasive prenatal screening test (NIPT) feasibility study	Trisomies 21, 18, 13 Monosomy X	Nepean Hospital
ClinicalTrials.gov	NCT02787486	Average-risk and high-risk	United States	A clinical study to evaluate the relative clinical sensitivity, specificity, and performance of a laboratory-developed test as a screening test for fetal chromosomal aneuploidy, infectious and other diseases, and RhD genotyping in the general population of pregnant people	Trisomies 21, 18, 13 Sex chromosome aneuploidies	Progenity, Inc.
ClinicalTrials.gov	NCT03200041	Average-risk and high-risk	United Kingdom	Clinical evaluation of the IONA test for noninvasive prenatal screening in twin pregnancies	Trisomies 21, 18, 13	Premaittha Health
Chinese Clinical Trial Registry	ChiCTR-DDD-17013213	Average-risk and high-risk	China	The value of noninvasive prenatal testing in pregnancies of Hebei province: a prospective multi-center study	Trisomies 21, 18, 13	Second Hospital of Hebei Medical University
ClinicalTrials.gov	NCT02381457	General pregnant population	United States	SNP-based microdeletion and aneuploidy registry	Trisomies 21, 18, 13 Sex chromosome aneuploidies Microdeletion syndromes	Natera, Inc.
UMIN Clinical Trials Registry	UMIN000023935	Pregnant people (risk not specified)	Japan	Analysis of state-trait anxiety in clients of noninvasive prenatal testing: an investigation to improve the quality of genetic counselling	Not specified	Niigata University Hospital

Abbreviation: RhD, rhesus D antigen; SNP, single nucleotide polymorphism.

Appendix 7: Results of Applicability Checklists for Studies Included in the Economic Literature Review

Table A8: Assessment of the Applicability of Studies on the Cost-Effectiveness of NIPT

Objective: To assess the cost-effectiveness of NIPT					
Author, Year	Is the study population similar to the question?	Are the interventions similar to the question?	Is the health care system in which the study was conducted sufficiently similar to the current Ontario context?	Were the perspectives clearly stated and what were they?	Are estimates of relative treatment effect from the best available source?
Nshimyumukiza et al, 2018 ⁷³	Partially	Partially	Yes (Quebec, Canada)	Yes; public payer	Yes
Huang et al, 2017 ⁷⁴	Partially	Yes	Yes (Ontario, Canada)	Yes; public payer	Yes
Maxwell et al, 2017 ⁷⁵	Partially	Partially	Yes (Australia)	Yes; public payer	Yes
Colosi et al 2017 ⁷⁶	Partially	Partially	Yes (Italy)	Yes; health care perspective	NA
Chitty et al, 2016 ⁷⁷	Partially	Partially	Yes (United Kingdom)	Yes; United Kingdom National Screening Committee	Yes
Fairbrother et al 2016 ⁷⁸	Partially	Partially	No (United States)	No	Yes

Author, Year	Are all future costs and outcomes discounted? (If yes, at what rate?)	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?	Overall judgment (directly applicable/partially applicable/not applicable)
Nshimyumukiza et al, 2018 ⁷³	NA	No	No	Partially applicable
Huang et al, 2017 ⁷⁴	NA	No	No	Partially applicable
Maxwell et al, 2017 ⁷⁵	NA	No	No	Partially applicable
Colosi et al 2017 ⁷⁶	NA	No	No	Partially applicable
Chitty et al, 2016 ⁷⁷	NA	No	No	Partially applicable
Fairbrother et al 2016 ⁷⁸	Unclear	No	Unclear	Not applicable

Note: Response options for all items were “yes,” “partially,” “no,” “unclear,” and “NA” (not applicable).

Appendix 8: Acceptance Rate for Further Testing After a Positive Screening Result

Table A9: Acceptance Rate for Further Testing After a Positive Screening Result

Country ^a	Risk Cutoff	Before Implementation of NIPT	After Implementation of NIPT ^b
Canada	Combined risk of trisomy 21, $\geq 1:200$	60% ⁷⁴	90%
Denmark ¹⁰⁶	Combined risk of trisomy 21, $\geq 1:300$	74%	97%
United Kingdom ¹⁰⁷	Risk of trisomy 21 or trisomies 18/13, $\geq 1:100$	66%	98%
Netherlands ¹⁰⁸	Combined risk of trisomies 21, 18, or 13, $\geq 1:200$	50%	$\geq 86\%$ ^c
United States ¹⁰⁹	NA	53%	79%

Abbreviations: NA, not available; NIPT, noninvasive prenatal testing.

^aNot based on national statistics, but regional studies.

^bAny further testing, NIPT and/or chorionic villus sampling or amniocentesis.

^cThis study showed that 86% of people (1,211 out of 1,413) with a risk of trisomy 21 $\geq 1:200$ received NIPT, but the status of further testing for the remaining 202 people was unclear.

Appendix 9: Letter of Information



CALL FOR PARTICIPATION REVIEW OF NON-INVASIVE PRENATAL TESTING

WHAT IS THE OPPORTUNITY?

Health Quality Ontario is currently reviewing **Noninvasive Prenatal Testing (NIPT)**. The purpose is to understand whether this screening test should be more broadly funded in Ontario. An important part of this review is to make sure a variety of perspectives and experiences are taken into account.

WHO ARE WE LOOKING FOR?

We are looking to speak to people with any of the following perspectives and experiences:

- People who accessed NIPT during a pregnancy and received a positive screening result
- People who received a false-positive or false-negative result from NIPT
- People who didn't access NIPT in pregnancy but would have liked to
- People with other personal experience relevant to NIPT who have views to share

At this time we are also seeking to speak with parents of children who have or had a condition screened for with NIPT—you do not need to have experience with NIPT to participate. We will ask you about your experience with an affected pregnancy and/or having an infant or child with this condition and your thoughts on public funding of a new prenatal test.

- Trisomy 13, 18 and 21
- Prader Willi syndrome, Angelman syndrome, 1p36 deletion syndrome, Cri-du-chat syndrome or Jacob's syndrome
- Klinefelter syndrome or triple X syndrome

WHY GET INVOLVED?

This review will result in a recommendation to the Ministry of Health and Long-Term Care about the public funding of Non-Invasive Prenatal Testing. The views, values, and experiences of people affected by this technology are a really important source of information that will help with the development of a recommendation.

If you are interested in participating, please click

here: <http://www.surveygizmo.com/s3/4026453/NIPT-Health-Technology-Assessment>

WHAT DO WE NEED FROM YOU?

- 20-60 minutes of your time for a phone interview (or online survey if that is your preference)
- Willingness to share your story

We are hoping to conduct interviews through the end of **February 2018**. If you are interested in sharing your story or have any questions about this opportunity, please don't hesitate to reach out.

Appendix 10: Interview Guide

Intro

Explain HQO purpose, HTA process, privacy and confidentiality

Background context of prenatal screening in Ontario

Why are you interested in participating? (to guide direction of conversation)

Prenatal testing/screening decision-making

Can you tell me about your experience with prenatal screening?

What options are/were available to you?

Cost/inconveniences?

Were there any issues related to access to NIPT or other prenatal screening?

Was it difficult to weigh up potential benefits and risks when deciding to do prenatal screening or not? For NIPT?

What factors influenced those decisions?

Role of family in decision-making?

Role of Physician? Midwife? Genetics counsellor?

If you were given information about screening, how easy or difficult was it to understand?

Previous pregnancies?

Other sources of information (Internet)?

Lived experience

Emotional impact: Anxiety? Experience of waiting for results? Waiting to do invasive testing?

Receiving a diagnosis? Termination of pregnancy?

Lived experience (for people with a condition screened for or parents of children with a condition screened for)

As policy makers are considering making available a new test which will allow pregnant people to find out whether their pregnancy is affected by certain conditions, what would you want them to know about what it's like to parent a child with _____?

Impact on parent/family if child has one of the conditions screened for (or impact on individual if it is an adult with the condition answering the questions).

For everyone

What you think are the advantages and disadvantages of using NIPT for prenatal screening?

What do you think about increasing access to NIPT for any pregnant person in Ontario who wants it?

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About Health Quality Ontario

Health Quality Ontario is the provincial advisor on the quality of health care, providing advice to specific health sectors, the system at large, and the Minister of Health and Long-Term Care on **how to make health care better for patients and health care providers**.

Health Quality Ontario has a legislative mandate to:

- Report to the public on how the health care system is performing,
- Find the best evidence of what works,
- Translate this evidence into concrete standards and tools that health care providers and organizations can put into practice to support ongoing quality improvement.

Health Quality Ontario is governed by its own 12-member Board of Directors with representation from the medical and nursing professions, patients, and other segments of health care. It is committed to supporting the development of a quality health care system based on six fundamental dimensions: efficiency, timeliness, safety, effectiveness, patient-centredness and equity.

In everything it does, Health Quality Ontario works with doctors, nurses, other health care providers, patients and families to support higher quality care across the system. Health Quality Ontario also works with partner organizations across the province to encourage the spread of innovative and proven programs to save money, eliminate redundancy and improve care.

Ways Health Quality Ontario improves health care quality include:

- The spread of practical tools for doctors, nurses, other health care providers and patients to improve care at the front lines.
- Tools for patients that help them manage their care, such as an initiative to help patients after leaving hospital.
- Rapid access to addiction medicine clinics in communities across Ontario.
- Confidential, voluntary information for family physicians about their practice, along with concrete suggestions on how to improve the care they provide.
- Innovative quality improvement programs across health sectors – including hospitals, primary care, long-term care and mental health and addictions – that spread proven programs that save money, eliminate redundancy and improve care.
- Easily accessible and understandable information for patients and health care providers about wait times for tests, specialists and surgical care.
- A yearly report tabled in the legislature on the health of Ontario's health system, shining a light on what is working and where the system must improve.
- Health technology assessments which include recommendations for or against public funding of health care technologies or services, and by an independent group of patients, health care providers and other experts. These are rigorous reviews that analyze the evidence and look at benefits, harms, value for money, and affordability.
- Helping hospitals, long-term care homes, primary care and home care organizations establish and meet their quality improvement goals through their annual quality improvement plans.
- Using the power of innovative digital tools to improve care at the front lines.

- Quality standards that set out for clinicians and patients what the evidence defines as quality care for important health conditions such as opioid use and dementia, and for which are unwarranted variations in care.
- Actively involving patients and families who are users of the health care system – bringing their perspective into the work that we do and providing tools for health care providers and patients to effectively partner to improve health care quality.

The intent at Health Quality Ontario is to harness the energy and attention of the health care system by focusing on changes needed to make things better for patients and health care providers, and on pragmatic solutions based on the evidence. The organization's mandate is to continuously improve the quality of health care in Ontario while always listening to the voices of physicians, nurses, other health care providers, and patients themselves – to fuel confidence, transparency, and accountability.

For more information: www.hqontario.ca

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