Alberta STE Report

First and second trimester prenatal screening update

August 2014

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Alberta STE Report: Policy-driven Health Technology Assessment reports that include an analysis of the social and system demographics (S), technological effects and effectiveness (T) and economic implications (E) of adopting a health technology. The reports are written under contract with the Alberta Health Technologies Decision Process and contextualized for use in Alberta. This report includes an assessment of the T and E.

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The views expressed in this report are of the Institute of Health Economics.

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Declared Competing Interest of Authors

Competing interest is considered to be financial interest of non-financial interest, either direct or indirect, that would affect the research contained in this report or create a situation in which a person's judgement could be unduly influenced by a secondary interest such as personal advancement.

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Executive Summary

Technology Section

Objective

Three primary research questions are investigated in this update:

1. What are the safety, screening accuracy, therapeutic efficacy, and patient outcome efficacy of first trimester Quad (1T-Quad) +/- NT and NIPT screening for fetal trisomies?
2. What is the overall quality of the evidence with respect to key outcomes for this algorithm?
3. What gaps exist in the evidence with respect to these outcomes for this algorithm?

Methods

An IHE information specialist searched MEDLINE (including in-process), EMBASE, CINAHL, Web of Science, and Scopus from 2008 to 14 January 2014. Also searched were HTA agency websites, clinical trials registries and Google. Reference lists of the retrieved reports were also scanned for relevant publications. Two reviewers screened the retrieved citations. Two reviewers assessed the full text of potentially relevant studies independently, using the following inclusion criteria.

Inclusion criteria

Population: women in their first trimester of pregnancy.

Intervention: first trimester quadruple serum screening with or without nuchal translucency (NT) screening, followed by non-invasive (cff-DNA) prenatal testing.

Comparator: for screening accuracy studies, the ideal reference standard is karyotype based on samples obtained from chorionic villi sampling or on samples obtained via autopsy; however, clinical examination upon birth will also be used as a reference standard, which would be appropriate for those pregnancies considered at low risk of chromosomal anomaly. For assessment of therapeutic and patient outcome effectiveness, suitable reference standards are usual care or other risk assessment protocols for a risk assessment within the same trimester, for example, first trimester combined.

Outcome: study provides:

- sufficient quantitative data to complete contingency tables for the calculation of test sensitivity and specificity;
- quantitative data on safety;
- quantitative data on therapeutic efficacy; and
- quantitative or qualitative data on patient (maternal or fetal) outcomes.

Design: prospective or retrospective cross-sectional screening accuracy or comparative design (randomized or non-randomized).

Setting: studies included in the review must have been conducted in countries that have developed market economies, as defined by the United Nations.

Exclusion criteria

Studies were excluded if they met at least one of the following criteria:

- were published in a language other than English
- did not evaluate the algorithm of interest
- did not contain sufficient primary data
- did not evaluate the algorithm within the context of a screening program (for example, simulation or modeling studies)

One reviewer abstracted data from the published reports of primary studies according to predetermined data extraction forms. Two reviewers appraised the methodological quality of selected systematic reviews independently, using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS 2) checklist. Characteristics of the included studies were summarized narratively and in tables. Quality assessment results were summarized narratively by checklist domain. No statistical analyses were conducted. Assessment of the quality of the body of evidence for outcomes with quantitative data was assessed according to the following domains:

- potential for bias due to design and conduct of studies
- directness of outcome
- precision of effect estimate
- consistency of results (if more than one study)

Results

No studies were identified that met the inclusion criteria.

Conclusion

No empirical studies have evaluated the accuracy and effectiveness of the 1T-Quad +/- NT + NIPT algorithm for prenatal screening of fetal trisomies. Good evidence exists for the screening accuracy of NIPT using the massive parallel sequencing techniques (either shotgun or targeted approaches) as a second-tier screen for women whose pregnancies are considered high-risk for fetal trisomy based on an existing first or second trimester screen. The results of two modeling studies suggest that the use of 1T-Quad with contingent use of NT may be an appropriate and useful alternative to the first trimester combined screen for jurisdictions with limited resources for NT; however, uncertainty remains regarding its actual performance within the context of a screening program. Little empirical work has been done to assess how the information provided by these screens influences clinical decision-making or the decisions made by women regarding the management of their pregnancies. A large, multicentre, Genome Canada-funded study is currently evaluating the use of NIPT and the 1T-Quad +/- NT algorithm for prenatal screening of fetal trisomies. The results of this trial will likely provide robust evidence about the accuracy and effectiveness of this algorithm, in addition to answering questions about potential social and ethical issues.

Economics Section

Objective

Research Questions

The primary research question being posed is: how do recent alternative first and second trimester screening (FASTS) options compare to those specified in the Alberta Health policy directive of 12 December 2012 in terms of cost-effectiveness and budget impact? The FASTS options are as follows:

Screening Option	Markers/Tests
When NT services are available	
Serum Integrated Prenatal Screening (SIPS) (AH directive)	PAPP-A in first trimester, AFP, uE3, hCG and inhibin A in second trimester
Combined (AH directive)	NT, hCG, and PAPP-A
First trimester quadruple serum screening with NT and NIPT (1TQuad_NT+NIPT)	Free β-hCG, PAPP-A, PlGF, AFP, NT. Positives receive NIPT
NIPT alone	NIPT
SIPS+NIPT	PAPP-A in first trimester, AFP, uE3, hCG, and inhibin A in second trimester; positives receive NIPT
Combined+NIPT	NT, hCG, and PAPP-A; positives receive NIPT
When NT services are unavailable	
SIPS	PAPP-A in first trimester, AFP, uE3, hCG, and inhibin A in second trimester
1TQuad with a detection rate of 0.85 and NIPT ($1TQuad_{0.85}$ +NIPT)	Free β-hCG, PAPP-A, PlGF, AFP; positives receive NIPT
1TQuad with a detection rate of 0.90 and NIPT ($1TQuad_{0.90}$ +NIPT)	Free β-hCG, PAPP-A, PlGF, AFP; positives receive NIPT
1TQuad with a detection rate of 0.95 and NIPT ($1TQuad_{0.95}$ +NIPT)	Free β-hCG, PAPP-A, PlGF, AFP; positives receive NIPT
NIPT alone	NIPT
SIPS+NIPT	PAPP-A in first trimester, AFP, uE3, hCG, and inhibin A in second trimester; positives receive NIPT

Methods

An Alberta-based cost-effectiveness and budget impact model was developed to address the research questions. The analysis adopted a payer perspective and considered direct medical service costs to the Alberta health system, including costs of physician, outpatient, and laboratory services, but excluding abortions. The time horizon for the analysis considered costs from initial screen to final diagnosis. Cost components included costs and services associated with genetic counseling, GP visits, invasive diagnosis tests, prenatal tests, and induction of labour, including physician, outpatient, and laboratory services.

Test performance was derived from available published evidence and the AHS FASTS advisory group report. Epidemiological, health service utilization, and cost data were derived primarily from Alberta administrative databases.

Results

NT Availability	Measure of Effectiveness	Time Preferences for Test Results	Most Cost-Effective Option
Available	Cases detected	Include SIPS as an option	SIPS
Available	Correctly diagnosed pregnancies	Include SIPS as an option	SIPS+NIPT
Available	Cases detected	Exclude SIPS as an option	1TQuad_NT+NIPT
Available	Correctly diagnosed pregnancies	Exclude SIPS as an option	1TQuad_NT+NIPT
Unavailable	Cases detected	Include SIPS as an option	SIPS
Unavailable	Correctly diagnosed pregnancies	Include SIPS as an option	SIPS+NIPT
Unavailable	Cases detected	Exclude SIPS as an option	$1TQuad_{0.85}$+NIPT
Unavailable	Correctly diagnosed pregnancies	Exclude SIPS as an option	$1TQuad_{0.85}$+NIPT

Conclusion

Arguments of efficiency favour a definition of effectiveness that better captures the total value of a screening option, particularly in light of an already constrained health system. When effectiveness is defined as the number of correctly diagnosed pregnancies, SIPS+NIPT is the option that likely provides the best value for money. If we exclude options employing SIPS and focus on those that provide their results in the first trimester of pregnancy, then 1TQuad_NT+NIPT (when NT services are available—refer to main body for possible alternative) and $1TQuad_{0.85}$+NIPT (when NT services are not available) are the most cost-effective FASTS option. The cost impact of establishing a systematic, province-wide screening program with increased coverage of pregnancies will result in net budget increases to physician, outpatient, and laboratory services.

Note that the conclusions are dependent on whether the screening performance characteristics used to populate the economic model are valid and reflect what would be observed in an actual screening population (refer to the T-section).

Abbreviations

All abbreviations that have been used in this report are listed here unless the abbreviation is well known, has been used only once, or has been used only in tables or appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

1T-Quad	first trimester quadruple marker serum screen
95% CI	95% confidence interval
ACASS	Alberta congenital anomalies surveillance
AFP	alpha-fetoprotein
AHS	Alberta Health Services
β-hCG	beta-human chorionic gonadotropin
BIA	budget impact analysis
CCASS	Canadian congenital anomalies surveillance system
CE	cost-effectiveness
CEA	cost-effectiveness analysis
CIHI	Canadian Institute for Health Information
CLIA	Clinical Laboratory Improvement Amendment
CLS	Calgary Laboratory Services
CVS	chorionic villus sampling
DIA	dimeric inhibin-a
DR	detection rate
DS	Down syndrome
FASTS	first and second trimester screening
FN	false negative
FP	false positive
FPR	false positive rate
FT	first trimester
FTS	first trimester combined screening
ß-hCG	beta-human chorionic gonadotropin
hCG	human chorionic gonadotropin
ICER	incremental cost-effectiveness ratio
Inhibin-A	dimeric inhibin-a
IPS	integrated prenatal screening

ND	not described
NIPT	non-invasive prenatal testing
NT	nuchal translucency
NTD	neural tube defects
ONTD	open neural tube defects
PAPP-A	pregnancy-associated plasma protein-a
PlGF	placental growth factor
PPV	positive predictive value
PSA	probabilistic sensitivity analysis
SIPS	serum integrated prenatal screening
SOGC	Society of Obstetricians and Gynecologists of Canada
ST	second trimester
T21	trisomy 21
T18	trisomy 18
T13	trisomy 13
uE3	unconjugated estriol
WTP	willingness to pay
+ve	positive
-ve	negative

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SECTION ONE: Technology Effectiveness and Safety

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Background and Context

Background

The Society of Obstetricians and Gynecologists of Canada (SOGC)[1] recommends that all pregnant women in Canada, regardless of maternal age, be offered a prenatal risk assessment for the most common clinically significant fetal aneuploidies in addition to a second trimester ultrasound for dating, growth, and screening for other congenital conditions. The SOGC guidelines indicate that invasive prenatal diagnosis (that is, amniocentesis or chorionic villus sampling [CVS]) should be limited to women who screen above a set risk cut-off level on first and second trimester screening tests (FASTS). The SOGC guidelines do not recommend a specific screening strategy, suggesting instead that the resources available in a given geographic area govern implementation of any particular screening program.

In 2011, the Institute of Health Economics conducted a health technology assessment[2] of the first and second trimester risk assessments for trisomy 21, 18, and 13 (also referred to as, respectively, Down syndrome, Edwards syndrome, and Patau syndrome) available at that time to help Alberta Health determine the most appropriate screening algorithm for a provincial prenatal screening program. Recent developments in prenatal screening have led to consideration of two new risk assessments—first trimester quadruple serum (1T-Quad) and testing of cell-free fetal DNA in maternal plasma (cff-DNA), commonly referred to as non-invasive prenatal testing (NIPT)—as potential options for use within the Alberta healthcare system. The 1T-Quad risk assessment consists of four biochemical markers (PAPP-A, free ß-hCG, P1GF, and AFP) measured between 9 and 13^{+6} weeks. cff-DNA analyzes the cell-free fetal genetic material present in a pregnant woman's plasma in order to detect chromosomal anomalies. Although both tests involve a sample of maternal blood, NIPT analyzes the cell-free fetal DNA, whereas the 1T-Quad, like the combined and second trimester quadruple screens, analyzes biochemical markers present in the mother's blood that have been correlated with fetal status.

Currently, NIPT is available to women in Alberta who have an increased chance of: having a fetus affected by trisomies 21, 18, or 13 due to advanced maternal age (35 years or older); a "positive" early prenatal screen such as a first trimester screen or quadruple serum screen; having a previous pregnancy with a chromosomal condition; or abnormal ultrasound findings.

In the context of prenatal risk assessment, the 1T-Quad can be used contingently with nuchal translucency (NT) ultrasound to improve the sensitivity and specificity of the 1T-Quad. Based on the results of the 1T-Quad +/- NT risk assessment, women are referred to NIPT. Although NIPT is considered an option for women who wish to avoid invasive diagnostic testing, it is not considered a replacement for diagnostic testing, and CVS and amniocentesis remain diagnostic options for all women.

Advances in Non-invasive Prenatal Risk Assessment

Until recently, non-invasive screening for aneuploidy relied on measurement of either maternal serum analytes (such as those measured in the first trimester combined and the second trimester quadruple and integrated tests) and/or ultrasonography (nuchal translucency). More recent advances

in genomics and genomic technologies have resulted in the development of a non-invasive prenatal screening test (NIPT) using cell-free fetal DNA (cff-DNA) sequences isolated from a maternal blood sample.[3] Although most of the cell-free DNA circulating in the blood is maternal in origin, it is believed that a portion of cff-DNA in maternal blood corresponds to the fetus, called the "fetal fraction," and ranges from 3 to 20% of the total cff-DNA, with an average of about 10%.[4] The cff-DNA fragments are very short (typically 150 base pairs); however, the entire fetal genome is represented. Importantly, the cff-DNA is thought to be derived primarily from the placenta (not the fetus) and is cleared from the maternal blood within hours of childbirth.[5,6] Initially, the clinical utility of NIPT using the analysis of cff-DNA was established for fetal RhD genotyping and sex determination as an aid to risk assessment of X-chromosome-linked disorders.[4]

Next-generation sequencing platforms use highly sensitive assays to quantify millions of DNA fragments as early as the tenth week of pregnancy, and provide results in approximately one week.[6] Platforms differ according to whether the targets of sequencing are amplified regions throughout the genome, chromosome-specific regions, or single-nucleotide polymorphisms (SNP). By using statistical modelling, differences between maternal and fetal sequences and dosage differences in identical sequences or a reference chromosome can be determined and used for non-invasive screening for fetal aneuploidy. The main methods for sequencing the DNA fragments have been described well by Benn et al.[5] and Swanson et al.,[4] and are described briefly below.

Types of Non-invasive Prenatal Testing

Massive Parallel Shotgun Sequencing (MPSS) relies on the identification and counting of large numbers of the DNA fragments in the maternal plasma sample. Using massively parallel sequencing, millions of both fetal and maternal DNA fragments are sequenced simultaneously and, since the entire human genome is known, analysts can determine the chromosomal origin for each fragment.[5] The approach is referred to as "shotgun" because it relies on sequencing and counting all informative chromosome regions; "uninformative" fragments are those that cannot be mapped to a chromosome location. If fetal aneuploidy is present, there should be a relative excess or deficit for the chromosome in question. So, for example, if the fetus is affected with T21, a relative excess of fragments that map to chromosome 21 would be present. To be able to reliably detect the differences in frequency, large numbers of counts are required. Although it is possible to convert the calculated probability of difference between the frequencies into a patient-specific risk, most commercial tests present results as either a "positive" or "negative" result, based on predefined thresholds. To contain the costs of analyses, it is common to run multiple samples together, a practice referred to as "multiplexing."[5]

Targeted Massively Parallel Sequencing selects and amplifies only those chromosomal regions that are of interest (for example, chromosomes 21, 18, and 13) and assesses whether an excess or deficit of a given chromosome is present, based on the relative number of DNA fragment counts for that subset of chromosomes.[5] Because targeted approaches require less sequencing than the shotgun approaches, they typically costs less. The current commercial provider of this approach combines the result with maternal age to provide a patient-specific risk for trisomy 21, 18, and 13. In theory, results could also be combined with additional factors such as the results of other screening tests or a history of aneuploidy pregnancy.[5]

Single Nucleotide Polymorphism (SNP)-based approaches analyze variations in single nucleotides (A, T, C, or G) and calculate the likelihood that a fetus is euploid or aneuploidy.[5] Two main approaches have been developed and both approaches offer the advantage of providing not

only information on fetal status, but also information about parent of origin of aneuploidy, recombination, and inheritance of mutations.[5] The methods and data analyses used for SNP-based NIPT are considered substantially different from those used for shotgun and targeted MPS approaches.

Digital Polymerase Chain Reaction (PCR) is a technology that allows for the dilution, amplification, and counting of individual DNA fragments of interest. If reliable cff-DNA enrichment methods are developed, PCR offers a way to reduce sequencing costs.[5]

RNA-based testing identifies cell-free fetal RNA (cff-RNA) in maternal plasma. If, like cff-DNA, the cff-RNA carries polymorphisms that distinguish the fetal alleles, the presence of aneuploidy can be deduced. RNA-based methods are still in development, but, as additional RNAs are discovered, this approach may play an important role in NIPT.[5]

Commercially Available NIPT

Technologies for isolation and genetic analysis required for NIPT using cff-DNA have been patented or exclusively licensed to a small number of companies in the United States (US) and internationally.[6] Currently, four US-based companies—Sequenom, Verinata Health, Ariosa Diagnostics, and Natera—are marketing laboratory-developed tests that use a combination of polymerase chain reaction (PCR) and sequencing technologies and proprietary algorithms to analyze cff-DNA for chromosomal aneuploidies (see Table T.1). The tests are being used to detect the most common chromosomal trisomies, including T21, 18, and 13, and some are also used to detect common sex chromosome aneuploidies and fetal sex.

In the US, laboratory tests (that is, those like cff-DNA that are developed for in-house use by a single laboratory) are governed by the Clinical Laboratory Improvement Amendment (CLIA), a program under the Centers for Medicare and Medicaid Services, rather than by the Food and Drug Administration (FDA).[7] Under the terms of the Amendment, companies are required to demonstrate their test's accuracy, precision, sensitivity, and specificity; however, companies do not need to provide robust evidence about a test's clinical utility.[7] The College of American Pathologists (CAP) also provides an accreditation program for laboratories in the US. For DNA testing laboratories, CAP evaluates the techniques used by the labs and ensures the labs are complying with or exceeding national regulations (*www.cap.org*).

TABLE T.1: COMMERCIALLY AVAILABLE CFF-DNA TESTS IN THE UNITED STATES

	Sequenom	Verinata Health	Ariosa Diagnostics	Natera
Test	MaterniT21 Plus	Verifi	Harmony Prenatal	Panorama Prenatal
Platform	MPSS	MPSS	DANSR technology and targeted sequencing	SNP-based targeted aneuploidy testing
Conditions screened	Trisomies 13, 18, 21 and sex chromosome aneuploidies	Trisomies 13, 18, 21, sex chromosome aneuploidies, and fetal sex	Trisomies 13, 18, 21	Trisomies 13, 18, 21 and sex chromosome aneuploidies
Lab turnaround	8 to 10 days	8 to 10 days	8 to 10 days	15 days
US regulatory status	CAP accredited, CLIA certified	CAP accredited, CLIA certified	CAP accredited, CLIA certified	CAP accredited, CLIA certified

CAP — College of American Pathologists; CLIA – Clinical Laboratory Improvement Amendment; DANSR – digital analysis of selected regions; MPSS – massively parallel shotgun sequencing; SNP – single nucleotide polymorphism
Adapted from: Agarwal et al. 2013[6]

Availability in Canada

At the time of writing, NIPT is not formally organized through any institutional genetics programs; however, the Ontario Ministry of Health has recently decided to cover the cost of NIPT as part of its prenatal screening program (EAG communication). Outside of Ontario, women are able to seek referrals from physicians to have the tests done through private laboratories located in British Columbia and Quebec on a patient-pay basis (see Table T.2). Women who would like to have NIPT must pay for the test and have their blood sent to the US for testing by a physician/centre offering to facilitate NIPT. Eligibility criteria for the tests are company-specific. It should be noted that technologies and companies change rapidly in the field of genetics, so the tests may not always be available through the companies currently offering NIPT.

TABLE T.2: NIPT TESTS AVAILABLE IN CANADA

Province	Test	Laboratory	Cost
Ontario	Panorama	LifeLabs	Unavailable
	Verifi	Medcan Clinic	$995
	Harmony Prenatal	Gamma-Dynacare	$795
Quebec	Harmony Prenatal	GD Specialized Diagnostics (Division of Gamma-Dynacare)	$795
Alberta*	Unavailable	Unavailable	$795[†]
British Columbia	Panorama	LifeLabs and BCBiomedical Laboratories (Division of LifeLabs)	Unavailable

*The Early Risk Assessment Program website (*www.earlyriskassessment.com*) indicates that NIPT is offered in Alberta by a private company

[†]AHS FASTS Advisory Group recommendation

Clinical Practice Guidelines

Four North American professional societies (one Canadian[8] and three American[3,6,9]) and one international society,[10] have published position statements regarding the use of NIPT for the detection of fetal aneuploidy (trisomies 13, 18, 21). All five of the societies recommend that NIPT be offered to women as a follow-up test if they have had a positive result from an existing first trimester or second trimester screening test (for example, combined, sequential, or integrated screen, or a quadruple screen). The societies further recommend that NIPT not be seen as equivalent to current invasive diagnostic testing, and that positive NIPT results be confirmed using amniocentesis or CVS. Four of the societies explicitly recommend against the use of NIPT as a screen for fetal aneuploidy in average-risk pregnancies (a "first-tier" screen) due to the current lack of evidence for test performance in this group. See Appendix T.A for summaries of individual guideline recommendations.

First Trimester Quadruple Serum Screen (1T-Quad)

The 1T-Quad risk assessment consists of four biochemical markers: pregnancy-associated plasma protein (PAPP-A), free beta-human chorionic gonadotropin (ß-hCG), placental growth factor

(P1GF), and alpha-fetoprotein (AFP), measured between 9 and 13^{+6} weeks. Two of the markers, PAPP-A and ß-hCG (free and total), are already part of the first trimester combined screen. The addition of the other two biochemical markers, P1GF and AFP, offers the opportunity to increase the discriminatory power of the first trimester screen in the absence of NT measurement. However, the NT measurement can be used in conjunction with the 1T-Quad assessment to further increase the overall accuracy of the screen.

As mentioned above, because of the current lack of evidence supporting the use of NIPT with low- and average-risk pregnancies and the current relatively high cost of NIPT, professional bodies have recommended that NIPT be used as a second-tier test in order to provide further high-quality information to women prior to invasive testing. In addition, the need for high-quality NT for appropriate implementation of the first trimester combined test has raised concerns about the ability for jurisdictions that have a high proportion of rural and remote areas to provide this service.[11] The ability to combine the 1T-Quad, NT, and NIPT in a contingent manner offers a way to address the concern about resources for NT while still meeting recommendations regarding prenatal risk assessment.

Project Context

Alberta does not currently have a provincial screening program. Services for first trimester screening in the province are delivered through a variety of practice patterns without unified criteria. The current state of screening has been described previously.[2] Alberta Health Services (AHS) provides FASTS through the Edmonton Early Pregnancy Risk Assessment Program in Edmonton and the Early Prenatal Risk Assessment (ERA) Program in Calgary. Under both programs, women can access the first trimester combined test (PAPP-A, ß-hCG, and NT measurements) and the second trimester quadruple test. Both biochemical analysis and nuchal translucency ultrasound are performed in designated AHS facilities. In Alberta, approximately 35% of the province's 60,000 pregnancies annually undergo some form of prenatal screening for fetal aneuploidy: 50% receive a first trimester combined screen and 50% receive the second trimester quadruple test (FASTS Advisory Group). Nevertheless, the number of women accessing the programs and using the screening tests varies between zones. In Calgary, approximately 11,000 women receive a first trimester combined screen, while in Edmonton, approximately 3-4000 women receive the first trimester combined screen and about 8000 receive a second trimester quadruple screen (FASTS Advisory Group). As a result, concerns exist not only about providing consistent quality information to pregnant women, but also about equity of access.

Alberta Health (AH) has agreed that a provincial screening program is needed in order to bring the province into alignment with national guidelines and to ensure all pregnant women have equitable access to prenatal risk assessment. Given the rapid advances in prenatal risk assessment described above, it has been deemed crucial to include 1T-Quad +/- NT and NIPT in the health technology assessment to inform the development of a recommendation regarding a prenatal risk assessment program. As a result, AH has requested that the clinical effectiveness and cost-effectiveness of 1T-Quad +/- NT and NIPT be formally assessed.

Technological Effects and Effectiveness

Objective

The objective of the technology section of this report is to perform a systematic review and critical appraisal of the evidence available about the efficacy and safety of screening algorithms that

incorporate the first trimester quadruple serum screen with or without nuchal translucency (1T-Quad +/- NT) followed by cell-free fetal DNA in maternal plasma (cff-DNA), commonly referred to as non-invasive prenatal testing (NIPT), to determine the optimal screening test for use in pregnant women who wish to obtain a risk assessment for fetal trisomies.

Research Question

What is the role of 1T-Quad +/- NT and NIPT screening in Alberta in screening for fetal trisomies?

By addressing the research question, the T-section aimed to provide information to address the following policy considerations:

1. What are the safety, screening accuracy, therapeutic efficacy, and patient-outcome efficacy of 1T-Quad +/- NT and NIPT screening for fetal trisomies?
2. What is the overall quality of the evidence with respect to key outcomes?
3. What gaps exist in the evidence with respect to these outcomes?

Elements of Assessment

- Literature searches were conducted for primary studies that provide quantitative assessments of the safety, screening accuracy, and therapeutic efficacy (effect on healthcare provider decision-making regarding management) of 1T-Quad +/- NT and NIPT screening for fetal trisomies.
- Literature searches were conducted for primary studies that provide qualitative assessments of the potential benefits and harms of 1T-Quad +/- NT and NIPT screening for fetal trisomies with respect to patient-outcome efficacy.

Literature Search Strategy

An IHE information specialist searched MEDLINE (including in-process), EMBASE, CINAHL, Web of Science, Scopus, and various grey literature sources such as HTA agency websites, clinical trials registries, and Google. Reference lists of the retrieved reports were also scanned for relevant publications.

Study selection

Two reviewers screened the retrieved citations. Two reviewers assessed independently the full text of potentially relevant studies, using the following inclusion and exclusion criteria.

Inclusion criteria

- **Population:** women in their first trimester of pregnancy.
- **Intervention:** first trimester quadruple serum screening with or without nuchal translucency screening, followed by non-invasive (cfDNA) prenatal testing.
- **Comparator:** for screening accuracy studies, the ideal reference standard is karyotype based on samples obtained from chorionic villi sampling or on samples obtained via autopsy; however, clinical examination upon birth will also be used as a reference standard, which would be appropriate for those pregnancies considered at low-risk of chromosomal anomaly. For other effectiveness assessments, suitable reference standards are usual care or other risk assessment protocols for a risk assessment within the same trimester, for example, first trimester combined.

- **Outcome:** study provides sufficient quantitative data to complete contingency tables for the calculation of test sensitivity and specificity or quantitative data on safety *or* quantitative data on therapeutic efficacy *or* quantitative or qualitative data on patient (maternal or fetal) outcomes.
- **Design:** prospective or retrospective cross-sectional screening accuracy or comparative design (randomized or non-randomized).
- **Setting:** studies included in the review must have been conducted in countries with developed market economies, as defined by the United Nations. These countries include Australia, Canada, Japan, New Zealand, the United States, and European countries (*http://unpan1.un.org/intradoc/groups/public/documents/un/unpan008092.pdf*).

In the case of duplicate publications, the most recent or principal (that is, most comprehensive) version was included.

Exclusion criteria

Published reports that met a least one of the following criteria were excluded:

- published in a language other than English
- no primary data (for example, systematic or narrative reviews, commentaries, editorials, news reports)
- did not evaluate technologies in the context of a screening program (for example, simulation or modeling studies)
- did not evaluate 1T-Quad +/- NT and/or NIPT
- did not report sufficient quantitative data to complete contingency tables for the calculation of performance measures, or quantitative data on safety or therapeutic efficacy, or quantitative or qualitative data on patient outcomes.

Data extraction

One reviewer abstracted data from the published reports of primary studies according to predetermined data extraction forms and a second reviewer verified the abstracted data. The following general categories of data were abstracted: publication information, study population and setting characteristics, intervention characteristics and reference standards, results, and authors' conclusions.

Methodological quality assessment

Two reviewers appraised independently the methodological quality of selected systematic reviews, using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS 2) checklist.

Data synthesis

Characteristics of the included studies were summarized narratively and in tables. Quality assessment results were summarized narratively by checklist domain. No statistical analyses were conducted.

Quality assessment of the body of evidence

Assessment of the quality of the body of evidence for those outcomes with quantitative data was performed according to the following domains: potential for bias due to design and conduct of studies, directness of outcome, precision of effect estimate, and consistency of results.

External review

Members of the provincial Expert Advisory Group (EAG) assembled for this project reviewed the draft report.

Results

The literature search identified 3772 citations. After applying the screening and inclusion/exclusion criteria, no studies were identified that met the review criteria of assessing the use of 1T-Quad followed contingently by NT and NIPT.

Nevertheless, the search did identify two modeling studies that examined the use of the first trimester quadruple test, one of which also examined contingent NT,[11,12] and three systematic reviews[8,13,14] that have examined the use of NIPT for the detection of fetal aneuploidy.

Discussion

Although the specific algorithm of interest to Alberta Health, 1T-Quad +/- NT + NIPT, has not been empirically evaluated, the performance of the algorithm has been validated in two modeling studies, one performed in the UK[12] and one in Canada.[11] In addition, the Canadian study[11] modeled the performance of the addition of 1T-Quad +/- NT and the performance of NIPT as a second-tier screen for pregnant women considered at high risk for fetal trisomy based on the results of an 1T-Quad +/- NT screen. Hence, this single study provides the only information about the potential performance of the algorithm of interest to AH. NIPT on its own has been the focus of much recent research and has been subject to at least three systematic reviews.[8,13,14] Because the two studies and three reviews mentioned above are the primary sources of information about these potential screening tests, the studies and their results are summarized below and discussed. Also discussed are potential limitations of the available evidence and an ongoing Genome Canada-funded study of this technology.

1T-Quad

Donalson et al.[12] conducted a case-control and modeling study to evaluate the addition of PlGF and AFP to the first trimester combined test (NT, ß-hCG, and PAPP-A) for Down syndrome and a first trimester quadruple serum-only protocol using PlGF, AFP, ß-hCG, and PAPP-A. The researchers used stored serum samples from singleton pregnancies that had received a first trimester combined test (11^{+2} to 13^{+6} weeks). The samples included 92 Down syndrome cases and 522 unaffected controls collected in a UK hospital between 2009 and March 2012. Controls were matched with cases in a ratio of 6:1. Samples were tested blind to the pregnancy outcome. Screening performance of PlGF and AFP was based on multivariate Gaussian modeling with parameters based on distributions of the markers in the cases and controls. Assays were conducted using the 1235 AutoDELFIA system. The model parameters for the performance of the combined test were derived from a published meta-analysis and intervention studies that adjusted for viability bias (the bias that results from a failure to detect false negative cases due to fetal loss).

Researchers found that both PlGF and AFP concentration in controls increased in a linear fashion with increasing gestational age. In comparison, PlGF and AFP concentrations for Down syndrome cases were significantly lower. The results of modeling indicated that the addition of PlGF and AFP to the combined test increased the detection rate (sensitivity) by 5 to 8%, depending on the false positive rate (FPR), and reduced the FPR by 50%. Modeling the performance of the four serum markers (PlGF, AFP, ß-hCG, and PAPP-A) indicated that, if performed at 11 weeks, 1T-Quad would have a detection rate of 71% for an FPR of 5%. If the positive risk threshold is set so that 20% of women tested fall within the "high-risk" category, the detection rates for a 5% FPR would be 85, 83, and 80% at 11, 12, and 13 weeks' gestation, respectively.

The researchers concluded that if quality ultrasound is not available, the quadruple serum screen could be used instead of the combined screen, with a detection rate comparable to the second trimester quadruple serum screen if conducted at 11 weeks. However, the authors note that the model's predicted performance is only applicable in settings where an early ultrasound dating scan is performed, and also that performance would be reduced if the parameters were based on menstrual dates. Researchers also suggest that if the availability of quality NT were limited, the first trimester quadruple serum screen might be used in a contingent fashion, whereby those with the highest Down syndrome risk would be selected for NT.

Johnson et al.[11] conducted a case-control and modeling study to evaluate a serum-only four-marker (PlGF, AFP, ß-hCG, and PAPP-A) first trimester Down syndrome screen (1T-Quad) alone or contingently with NT or cff-DNA. Researchers used stored serum samples from singleton pregnancies (9 to 13^{+6} weeks) and NT measured between 11 and 13^{+6} weeks. The samples included 90 Down syndrome cases and 1607 unaffected controls collected in an early prenatal risk assessment program in Alberta, Canada, between March 2006 and December 2010. Controls were matched with cases in a ratio of not less than 9:1. Model parameters of the screening performance of the four serum markers were based on multivariate Gaussian modeling with normal median values for serum and NT derived from the controls, and performance parameters for cff-DNA derived from a published meta-analysis. PerkinElmer conducted the 1T-Quad using the AutoDELFIA assay.

The model-predicted detection rate for 1T-Quad for a fixed FPR of 5% was 74%. Using a contingent approach, whereby 10% of women with the highest risks from the 1T-Quad would be referred to NT and re-evaluated, resulted in detection rates of 84 and 81% at a 5 and 3% FPR, respectively. If, instead, 20% of women with the highest risks from the 1T-Quad were to receive NT and were re-evaluated, the resulting detection rates would be 89 and 87% at a 5 and 3% FPR, respectively. By comparison, the authors estimated the results for a combined test using the same samples would have a detection rate of 93% at a 5% FPR. If, instead of NT, those considered at high risk are referred to cff-DNA testing, the estimated detection rate is 83% for 10% referral, and a detection rate of 91% for 20% referral with FPRs of 0.02 and 0.04%, respectively.

The authors conclude that the 1T-Quad test can achieve a similar detection rate to a second trimester quadruple test. The 1T-Quad screen can be enhanced contingently by selecting 10 to 20% of women with the highest risks for NT ultrasound or cff-DNA. Incorporating cff-DNA contingently provides a novel way to integrate NIPT testing into clinical usage while respecting current SOGC guidelines regarding adequate test performance.

Non-invasive prenatal testing (NIPT)

Three systematic reviews[8,13,14] examined the use of NIPT (either cff-DNA or cff-RNA) analysis for the detection of trisomies 13, 18, and 21 (see Table T.3). Benn et al.[5] have also provided a detailed review of the evidence on the use and performance of NIPT; however, the methods for evidence collection and assessment were not described sufficiently to consider it a systematic review. No prospective trials have been conducted to evaluate the performance of NIPT as a screening test for women at high risk of fetal aneuploidy. None of the reviews considered the studies sufficiently similar to consider pooling the results.

TABLE T.3: STUDIES INCLUDED IN THE SYSTEMATIC REVIEWS

	Mersy 2013[13]	Langlois 2012[8]	Walsh 2012[14]
Test type			
DANSR	Ashoor 2012 Nicolaides 2012 Norton 2012 (NICE)	Ashoor 2012 Norton 2012 (NICE) Sparks 2012	Ashoor 2012 Norton 2012 (NICE) Sparks 2012
MeDiP	Papageorgiou 2011		
MPSS	Bianchi 2012 (MELISSA) Dan 2012 Chiu 2011 Ehrich 2011 Palomaki 2011/2012	Bianchi 2012 (MELISSA) Chiu 2011 Ehrich 2011 Lau 2011 Palomaki 2011 Sehnert 2011	Bianchi 2012 (MELISSA) Chiu 2011 Ehrich 2011 Palomaki 2011/2012 Sehnert 2011
qMSP UI	Lim 2011	---	---
qPCR	Jorgez 2007	---	---
SNP	Deng 2011 Dhallan 2007 Ghanta 2010 Lo 2007 Tsui 2010	---	---
Total studies included	16	9	8

Mersy et al.[13](researchers from The Netherlands) conducted a systematic review to determine the diagnostic accuracy of the molecular techniques for NIPT for the detection of trisomy 21 in a clinical setting. The authors searched for studies published between 1997 and 2012 and indexed in PubMed (search current to 15 December 2012) that have reported sensitivity and specificity. No search limits were used. Studies examining NIPT for other disorders were excluded. The authors assessed study quality using the QUADAS-2 tool and an a priori description of the "ideal study" on NIPT for trisomy 21. In addition to extracting the reported sensitivities and specificities, the authors calculated positive and negative predictive values for three risk categories:

- 1:200 (a prior risk of a 38-year-old pregnant woman and high-risk cut-off in The Netherlands)

- 1:380 (a prior risk of a 35-year-old pregnant woman based on prevalence estimates in the European population)
- 1:1500 (a prior risk of a 20-year-old pregnant woman)

The authors did not pool the results of individual studies because of heterogeneity among the molecular techniques and cut-off points used.

The authors included 16 studies published between 2007 and 2012 that applied six different molecular genetic techniques (MPSS, DANSR, MeDiP, qMSP, qPCR, and SNP) for NIPT for trisomy 21 (see Tables T.3 and T.4). Small cohorts (<25 T21 cases) were used in nine of the studies, and four studies included fewer than 10 cases (see Table T.4). Two of the studies (Dan 2012, Nicolaides 2012) examined the use of NIPT in low-risk pregnancies, with the remaining studies examining NIPT in pregnancies considered at high risk of fetal trisomy, though different definitions of "high risk of T21" were used. None of the studies were judged to be at low risk of bias or low concern regarding applicability across the four domains assessed. Most studies were considered to be at high risk of bias with respect to patient selection, flow, and timing (samples included in analysis), and applicability was a concern because of the broad range of gestational ages included or the late stage of pregnancy at which blood sampling was conducted.

Overall, reported sensitivity ranged from 58.8 to 100% and FPR ranged from 0 to 16.7%. The larger studies that employed MPSS or digital analysis of selected regions (DANSR) generally reported higher sensitivity, 98.6 to 100%, and lower false positive rates, 0 to 2%, than did the smaller studies using other techniques. One study (Nicolaides 2012) examined the performance of DANSR in a low-risk population. However, the authors comment that because this group had only a small number of T21 cases, the study does not provide a good estimation of test performance, particularly test sensitivity. Predictive values in the eight studies assessing shotgun or targeted approaches varied. Because of the low likelihood of T21 and good sensitivity, negative predictive values were high (100%); however, positive predictive values ranged widely for the three risk groups: 19.7 to 100% for a risk of 1:200, 11.4 to 100% for 1:380, and 3.1 to 100% for 1:1500.

The authors concluded that, although the results from NIPT studies are promising, the ideal NIPT study has not yet been performed in high-risk pregnancies. The sensitivity and specificity of NIPT of T21 are better than those of the current first trimester risk assessment. The authors considered the calculated positive predictive values to be very low, even in high-risk pregnancies, with the potential for positive screening results to be false in over 80% of cases. Before NIPT can be introduced as a screening test in a social insurance healthcare system, more evidence is needed from large prospective diagnostic accuracy studies in first trimester pregnancies. The authors also concluded that large prospective NIPT studies by massive parallel sequencing with and without pre-selection of chromosomes will provide more certainty about the predictive value of NIPT in the high-risk group.

Langlois et al.[8] conducted a systematic review of published studies on the use of cff-DNA in maternal plasma for the non-invasive diagnosis of T21, 18, and 13. The review formed the basis for a committee opinion statement from the Society of Obstetricians and Gynecologists of Canada on the use of cff-DNA for the detection of fetal aneuploidy. The authors searched PubMed for systematic reviews and experimental and observational studies published between 2006 and October 2012 inclusive. Grey literature was sought by searching HTA and HTA-related agency websites, clinical practice guideline collections, trial registries, and national and international medical specialty societies. The authors did not describe how methodological quality of individual studies was

assessed; the strength of the evidence and grade of recommendation was assessed using the Canadian Preventive Task Force evidence hierarchy and ranking system.

The review included nine studies (eight of which were included in the other reviews—see Tables T.3 and T.4). The majority of studies used a case-control design (selecting trisomy cases from a cohort and additional controls for analysis). Only studies that included maternal blood samples before invasive procedures were included. The authors did not pool the results of individual studies because of differences among the studies in methodology and sequencing analysis. Six of the studies examined an MPSS approach, and three examined the use of a targeted sequencing approach (DANSR). All nine studies examined cff-DNA for the detection of T21, seven studies examined the detection of T18, and three studies examined the detection of T13. All studies used amniocentesis or CVS to determine the true chromosomal status of the fetus. The number of T21 cases included in the studies ranged from 11 to 212. The detection rate for T21 was 100% in eight studies and 98.6% in one study; the false positive rate ranged from 0.03 to 2.1%. The number of T18 cases ranged from 8 to 59; sensitivity ranged from 90 to 100% and false positive rates (reported by three of the seven studies) ranged from 0.07 to 0.8%. The number of T13 cases ranged from two to 14; sensitivity ranged from 78.6 to 100% and false positive rates were 0 to 0.9%. The authors also reported failure rates for T21 testing ranging from 0.75 to 4.5%. Failure rates describe the percentage of samples that did not meet quality control requirements for the sequencing, with the result that no results could be obtained.

The authors noted that, although MPSS is less accurate at detecting T18 and T13 than it is for detecting T21, studies that examined the use of DANSR (Ashoor et al. 2012, Norton et al. 2012, Sparks et al. 2012, and Sehnert et al. 2011) or different sequencing analysis (Bianchi et al. 2012, Palomaki et al. 2012) reported detection rates approaching or equivalent to the detection rates for T21. The authors concluded that NIPT using MPSS has shown promising results in studies including women considered at high risk of carrying a fetus with T21, 18, or 13. Hence, NIPT should be an option as a second-level contingent screening test (after a positive result from currently used serum and ultrasound screening techniques) for women wishing to avoid invasive testing. In addition, further studies are needed to determine whether NIPT can be reliably used as a first-tier screening test in average-risk pregnancies.

Walsh and Goldberg[14] conducted a systematic review for the California Technology Assessment Forum (ctaf.org) to determine the diagnostic accuracy of the molecular techniques for NIPT of T21, 18, or 13 in a clinical setting. The authors searched Medline and Cochrane CENTRAL and DARE databases from inception to 31 August 2012 for published reports of studies that reported data on test sensitivity and specificity. The studies had to have been published in the English language. The assessment of the strength of recommendation used the California Technology Forum technology assessment criteria; however, the authors did not specify how the methodological quality of individual studies was assessed, or how the strength of the body of evidence was determined.

The assessment included eight studies, the majority of which used a case-control design (selecting trisomy cases from a cohort and additional controls for analysis) (see Tables T.3 and T.4). Five of the studies examined MPSS technology and three examined the DANSR technique. All eight studies examined cff-DNA for the detection of T21, six studies used it to detect T18, and two studies used it to detect T13. All studies used amniocentesis or CVS to determine the true chromosomal status of the fetus. The number of T21 cases ranged from 39 to 212. The sensitivity (or detection rate) ranged from 98.6 to 100% and the false positive rate ranged from 2.1 to 0.03%. For studies using cff-DNA

to detect T18, sensitivity ranged from 97 to 100% and false positive rates ranged from 0.07 to 0%. For the two studies using cff-DNA to detect T13, reported sensitivities were 78.6% and 91.7%; the false positive rate was 0.07% for the latter study. One large cohort study by Norton et al. was performed in multiple settings (reflective of real-world settings) in three different countries.

Most studies evaluated the use of cff-DNA screening in high-risk women; however, the authors note that a study that examined the use of cff-DNA for routine first trimester screening was published after the search cut-off date. This study, by Nicolaides et al., was included in the review by Mersy et al. The authors note that the unrepresentative prevalence of T21 and the small number of T21 and T18 cases, as well as limitations in the use of the reference standard and the calculation of risk scores for some pregnancies, limit the conclusions that can be drawn from the study regarding the performance of the test in average-risk women. The authors note that, other than this study, no studies have evaluated incorporating cff-DNA into prenatal clinical practice in a large cohort of average-risk women compared with the current standard of care. In addition, they remark that no studies have compared using cff-DNA as a primary screening test with the current standard of care. Nevertheless, the authors conclude that cff-DNA might have potential utility for average-risk women, and that this potential should be evaluated in future studies. The authors conclude that the scientific evidence for the use of cff-DNA screening for T21 and T18 in women whose pregnancies are considered to be at high risk for fetal aneuploidy indicates that cff-DNA screening is as beneficial as any of the established alternatives, and that improvements in screening performance are likely attainable outside the investigational setting. The screen has the potential to reduce the number of invasive diagnostic procedures, with their associated risks of fetal loss. Insufficient evidence is currently available upon which to base a judgment about the appropriateness of the routine use of cff-DNA in the screening of average-risk women.

TABLE T.4: CHARACTERISTICS OF STUDIES INCLUDED IN THE SYSTEMATIC REVIEWS (ORDERED BY TEST TYPE)

Author, year Study type Commercial test	Method and sequencing approach Trisomy targeted	Total no. samples No. abnormal karyotype	Detection rate (%)*	False positive rate (%)†	Inclusion criteria
Ashoor 2012 Nested case control Harmony Prenatal	DANSR 21, 18	400 50 (T21) 50 (T18)	T21: 100 T18: 98	T21: 0 T18: 0	Stored plasma High-risk women where risk for aneuploidy was >1:300
Nicolaides 2012 Retrospective Harmony Prenatal	DANSR 21	2049 8 (T21)	100 (95% CI 67.5–100)	0 (95% CI 0–0.2)	First trimester and undergoing combined test
Norton 2012 (NICE) Prospective cohort Harmony Prenatal	DANSR 21, 18	3228 81 (T21) 38 (T18)	T21: 100 (95% CI 95.5–100) T18: 97 (95% CI 86.5–99.9)	T21: 0.3 (95% CI 0.002–0.2) T18: 0.07 (95% CI 0.02–0.25)	At least 18 years of age; at least 10 weeks pregnant; singleton pregnancy; planning to undergo invasive procedure for any reason
Sparks 2012 Case-control Harmony Prenatal	DANSR 21, 18	338 36 (T21) 8 (T18)	T21: 100 T18: 100	T21: NR T18: NR	At least 18 years of age; at least 10 weeks pregnant; singleton pregnancy (subset of larger prospective group chosen based on ploidy status)
Papageorgiou 2011	MeDIP 21	40 14 (T21)	100 (95% CI 78.5–100)	0 (95% CI 0–12.9)	NR
Bianchi 2012 (MELISSA) Blinded prospective, multicenter with nested case-control Verifi	MPSS 21, 18, 13	532 89 (T21) 36 (T18) 14 (T13)	T21: 100 (95% CI 95.9–100) T18: 97.2 T13: 78.6	T21: NR T18: NR T13: NR	Women undergoing an invasive prenatal procedure: aged ≥38 years, positive screening test for aneuploidy or prior aneuploidy fetus
Chiu 2011 Prospective and case-control NR	MPSS 21	753 86 (T21)	100 (95% CI 95.7–100)	2.1 (95% CI 0.7–5.9)	Women with clinical indications for CVS or amniocentesis
Ehrich 2011 Case-control MaterniT21 Plus	MPSS 21	480 39 (T21)	100 (95% CI 89–100)	0.3	Advanced maternal age; positive screening test; personal or family history of DS

Lau 2011 Prospective NR	MPSS 21, 18, 13	108 11 (T21)	100	0	
Palomaki 2011/2012 Multicentre case-control MaterniT21 Plus	MPSS 21, 18, 13	1971 212 (T21) 59 (T18) 12 (T13)	T21: 98.6 (95% CI 95.9–99.7) T18: 100 T13: 91.7	T21: 0.2 T18: 0.28 T13: 0.97	High-risk for DS: maternal age, family history, or positive screening test
Sehnert 2011 Multicentre cross-sectional validation study Verifi	MPSS 21, 18	119 13 (T21) 8 (T18)	T21: 100 T18: 100	T21: NR T18: NR	Aged ≥18 years and pregnant
Lim 2011 NR	qMSP UI 21	108 18 (T21)	83.3 (95% CI 60.8–94.2)	94.4 (95% CI 0.024–0.124)	Later T21 detected by amniocentesis or CVS
Jorgez 2007 NR	qPCR 21	47 17 (T21)	58.8 (95% CI 36–78.4)	16.7 (95% CI 0.073–33.6)	NR
Deng 2011 NR	SNP (RNA) 21	121 24 (T21)	95.8 (95% CI 79.8–99.3)	0 (95% CI 0–4.2)	Unknown and high-risk pregnancies
Dhallan 2007 NR	SNP (DNA) 21	60 3 (T21)	66.7 (95% CI 20.8–93.9)	1.7 (95% CI 0.3–9.7)	8–38 weeks' gestational age
Ghanta 2010 NR	SNP (DNA) 21	40 7 (T21)	100 (95% CI 64.6–100)	0 (0–16.1)	Indication of CVS or amniocentesis
Lo 2007 NR	SNP (RNA) 21	67 10 (T21)	90 (95% CI 59.6–98.2)	3.5 (95% CI 1–11.9)	NR
Tsui 2010 NR	SNP (RNA) 21	153 4 (T21)	100 (95% CI 51–100)	10.3 (95% CI 4.8–20.8)	High-risk pregnancies

CI – confidence interval; CVS – chorionic villi sampling; DANSR – digital analysis of selected regions; DS – Down syndrome; NR – not reported; NICE – Non-invasive Chromosomal Evaluation; NS – not specified; MPSS – massively parallel signature sequencing; SNP – single nucleotide polymorphism

* If a review reported more than one specificity, for example because of different multiplexes, we reported the best result.

† For consistency, and if not provided, false-positive rates were calculated using reported specificity.

Although Mersy et al.[13]concluded that the ideal study to assess NIPT in high-risk pregnancies has yet to be conducted, the strongest evidence for the use of NIPT comes from the six studies included in all three reviews (Ashoor 2012, Bianchi 2012, Chiu 2011, Ehrich 2011, Palomaki 2011/2012, and Norton 2012) that included relatively large cohorts and examined the use of MPSS or DANSR in pregnancies considered at high risk of fetal trisomy. On the basis of these studies, Walsh et al. and Langlois et al. concluded that cff-DNA (using either a shotgun or targeted approach) would be an appropriate second-tier screen for women with an increased risk of having a fetus with T21. Nevertheless, guidelines[10] have stated explicitly that NIPT should be considered a test still under clinical development. Insufficient evidence is currently available to determine the potential role of the other NIPT approaches. Though Mersy et al. reviewed a larger number of trials than did the other reviews, an international panel of experts in prenatal diagnosis[10] likewise concluded that only those cff-DNA analyses based on massively parallel sequencing (either shotgun or targeted) have been sufficiently validated in trials to be considered analytically sound. Although professional groups agree about the validity and reliability of cff-DNA testing to screen for trisomies 21 and 18, they differ regarding the reliability of NIPT to screen for trisomy 13.[9,10]

Given the number of studies that have examined cff-DNA testing, statistical pooling of the results may have helped to provide a better estimate of the two approaches. However, two reviews[8,13] and one position statement[10] stated explicitly that direct comparison of the various clinical trials and approaches applied to studies of high-risk women is confounded by the criteria used to select cases, the depth of sequencing, adjustments for GC content of the sequences, the number of acceptable mismatches in sequences, and test failure criteria. Despite these limitations, Benn et al.[5] reported meta-analyzing the results of the seven studies included in Langlois et al. and Walsh et al. 2012 (all but Sehnert 2011 and Lau 2011), asserting that, methodological differences aside, the results from the seven studies are consistent with one another, and combining the individual study results gives the best estimate of detection rates and FPR for Down syndrome detection. The pooled result for the seven studies is an overall detection rate of 99.3% (95% CI 98.2 to 99.8) and an FPR of 0.16% (95% CI 0.08 to 0.31).[5] The results of six studies that examined the detection of T18 were pooled to provide an overall detection rate of 97.4% (95% CI 93.7 to 99) and an FPR of 0.15% (95% CI 0.07 to 0.31). The results of three studies that examined the detection of T13 were pooled to provide an overall detection rate of 78.9% (95% CI 65.9 to 91.9) and an FPR of 0.41% (95% CI 0.22 to 0.61). Nevertheless, even without a measure of heterogeneity such as the I^2 statistic,[15] which would likely be low given the similarity of the trial results, the reported precision of the likely effect reflected by the confidence intervals may be misleading. In general, meta-analysis is only conducted when a group of studies is considered to be sufficiently homogeneous in terms of the participants, interventions, comparators, and outcomes to provide a meaningful summary.[15] Without the benefit of a pooled estimate, decision-makers will have to rely on the results of individual studies, paying special attention to the results of studies that most closely reflect the population, intervention, and outcomes of interest for them. Canadian researchers have indicated that the Harmony prenatal test is, because of its cost, most likely to be the test adopted in Canadian jurisdictions.

The only available evidence on the 1T-Quad test, the 1T-Quad +/- NT, and the algorithm of 1T-Quad+/- NT + NIPT comes from two case-control studies that used multivariate modeling to estimate the performance of the screening tests and algorithm. As discussed below, the previous assessment of prenatal screening excluded modeling studies. In contrast, the evidence for the serum integrated screen (SIPS) comprised two large prospective cohort studies conducted in average-risk women in the UK and the USA. Detection rates were 88% with 95% confidence intervals of 62 to

98% and 77 to 95%. The FPR for both studies was 3% (95% CI 3 to 4). The evidence for the first trimester combined test and second trimester quadruple test comprised, respectively, 31 studies (14 of which were prospective) and seven cohort studies (five of which were prospective), providing good evidence for the use of these tests in prenatal screening programs.

The two studies[11,12] that have modeled the performance of 1T-Quad indicate that, on its own, this quadruple serum-only screen does not meet the minimum performance for a first trimester screen recommended by the SOGC. However, the minimal performance threshold recommended by the SOGC was presumably based on the assumption that those categorized as "high-risk" would then be offered invasive diagnosis as a next test. If, instead, a subsequent more sensitive and specific non-invasive test is available as a "second-tier" screen, the need to meet this suggested performance threshold no longer holds. Rather than being used on its own, the first screening test would be the first step in a series of non-invasive screens, and the risk thresholds would be adjusted in order to achieve the performance that allows the final result of the non-invasive screening pathway to detect cases effectively, while at the same time minimizing the risk of false positive results prior to the offer of invasive diagnostic testing. Importantly, in the absence of NIPT testing, even sending 20% of women with the highest risk from the 1T-Quad to receive NT (detection rate of 87% at a 3% FPR) does not match the performance of the first trimester combined test. By comparison, the authors estimated the results for a combined test using the same samples would have had a detection rate of 93% at a 5% FPR. Nonetheless, an added benefit of first trimester protocols that include both PAPP-A and PlGF, as is done in the 1T-Quad, is the ability to assess the risk of pre-eclampsia.[11]

The addition of NIPT has implications for implementation that will have an impact on resources. The results of a retrospective study[16] indicate that the adoption of NIPT as a follow-up test to serum screening in a prenatal diagnosis clinic in the US was associated with a decrease in the rate of invasive testing (CVS or amniocentesis) from 47.2 to 39.2% ($p = 0.012$) following a positive serum screen and an increase in the number of women accepting follow-up testing (NIPT). The NSGC[9] has stated that the need for and importance of comprehensive genetic counseling along with NIPT should not be underestimated. Provision of pre-test and post-test counseling is considered essential to a high-quality prenatal screening program and NIPT only increases the need for genetic counseling. Reproductive decisions should be made in the context of unbiased and comprehensive information, free from discrimination or coercion.[9] As such, it is important that women have accurate information not only about the screening tests which they are being offered and about how to interpret screening results, but that they also have accurate, unbiased information about the conditions for which they are being screened. A content analysis of the prenatal screening information provided to women in Canadian clinics suggests strongly that this aspect of counseling is not being met.[17] Studies in other countries with developed economies indicate a need to improve the quality of informed consent for multi-step prenatal genetic examinations.[18] Adequately addressing this deficiency is an important goal for the implementation of any program, but especially with NIPT. Because the test is highly specific, most women who receive a positive result will have essentially received a prenatal diagnosis of aneuploidy.[4] In addition, because of the promoted accuracy of the test, there is the risk that women may choose to forego invasive testing and choose whether to terminate the pregnancy or not on the basis of the NIPT screen result.

Limitations

The evidence available to support the use of NIPT for use in high-risk populations is similar in strength to that available for the use of the second trimester quadruple screen. Likewise, the studies

examining the first trimester combined test and the second trimester quadruple screen were considered too heterogeneous to warrant the pooling of individual study results. Only two relatively small modelling studies have assessed the 1T-Quad test and contingent NT. Both studies were clinical validation studies, that is, studies that test the quality of the screening test based on prior evidence (samples from known cases of fetal trisomy and unaffected fetuses). To be consistent with the previous FASTS assessment[2] this review sought to identify empirical studies and excluded modeling studies. Cuckle[19] has noted that multivariate Gaussian modeling is an established method for estimating the added value of additional markers and that modeling has been very successful in predicting the results for the second trimester double, triple, and quadruple screens. Nevertheless, just because the study results are based on a model, rather than a study of the test as it could be or has been used in practice, modeling studies are at best suggestive of the performance of a screening algorithm. The reason for this caution in accepting the results of a model to support full-scale implementation is because models do not capture the complexity of the system they attempt to model and, as a result, may not adequately reflect the performance of screening as it is used in practice. In contrast, NIPT has been subject to multiple, larger, prospective cohort studies to establish its performance.

In terms of the usefulness for decision-making (whether clinical or maternal), the most informative measures regarding test performance are a test's positive and negative predictive values (respectively, the probability that someone with a positive test result has the condition and someone with a negative screen results does not have the condition). The calculation of predictive values requires an accurate measure of the prevalence of the condition of interest within the study population. Case-control studies, just because the study populations are assembled with known cases, cannot provide this measure, so cannot be used to calculate these important measures. The published cohort studies on NIPT have rarely reported the positive and negative predictive values. Mersy et al.[13] calculated positive and negative predictive values for all studies included in their review. Negative predictive values ranged from 99 to 100% for all studies (high- and average-risk pregnancies). Positive predictive values, although generally high (93 to 100%), have been reported as low as 20% in high-risk pregnancies (cut-off of 1:200), indicating that a positive result, even in high-risk populations, may be false in 80% or more of cases.[13]

A major limitation of this report, and of all research on the prenatal screening tests discussed in the previous report,[2] is the paucity of research on the utility of the information provided by prenatal screening tests to facilitate women's decision-making regarding the management of their pregnancy (or, at the very least, their wish to receive invasive diagnostic testing). No clinical studies were identified that have examined 1T-Quad+/- NT or NIPT with respect to outcomes related to patient and physician decision-making or to maternal or fetal health. This lack of evidence represents a crucial gap in our understanding of the actual benefits and challenges of a prenatal screening program, and possible challenges in full-scale implementation using 1T-Quad, NT measurement, and NIPT. The American Journal of Bioethics is planning a special issue on NIPT (to be published in 2014). Topics to be addressed in the special issue include: patient and family experiences with regard to being offered or receiving the results of NIPT; perspectives of prenatal healthcare providers on offering NIPT, indications for NIPT, and quality and/or format of NIPT results; views of community representatives, religious experts, disability advocates, etc., concerning NIPT; international perspectives on NIPT; and content analyses of media reports and professional society recommendations discussing NIPT.

Ongoing Trials

The authors of three reviews and five professional guidelines all agree on the need for further large-scale studies to assess the performance of NIPT in average-risk populations. To help address some of the uncertainty regarding the performance and appropriate use of NIPT in average- and high-risk pregnancies, Genome Canada, together with genome centres in Quebec and British Columbia and other co-sponsors, have provided $10.5 million to fund the multisite Personalized Genomics for Prenatal Aneuploidy Using Maternal Blood (PEGASUS) study (clinical trials identifier NCT01925742). The project, which involves an interdisciplinary team of 27 researchers from 12 universities—eight in Canada, four in Europe—and five federal and provincial policy-makers in the healthcare field, will compare different non-invasive prenatal tests, alone and in combination with current prenatal screening approaches. The non-randomized study is designed to compare the effectiveness, costs, and social and ethical issues of the first trimester combined test, the 1T-Quad test, and both shotgun and targeted NIPT approaches to detect fetal aneuploidy (T21, 18, and 13) in 3600 high-risk and 2000 low-risk pregnant women. The results of the study are expected to be available in 2017.

The PEGASUS study will include an evaluation of Ariosa's Harmony Prenatal test, which researchers considered the one most likely to be adopted in the Canadian context due to its comparatively lower cost. The Harmony test uses a targeted massive parallel sequencing approach and has been evaluated in the studies by Ashoor et al., Norton et al., and Sparks et al. (see Table T.4). The detection rate for T21 in all three studies was 100% with FPRs ranging from 0.00 to 0.81%. Detection rates for T18 were similar, ranging from 97.4 to 100% and with FPRs ranging from 0.00 to 0.81%. None of the studies examined the detection of T13; however, the PEGASUS study will include screening for this condition.

The SOGC has recommended that acceptable first trimester screens have a minimum 75% DR and 3% FPR for trisomy 21.[1] Based on this minimum standard, the previous assessment[2] conducted by IHE considered the first trimester combined, full integrated, integrated–inhibin A, serum integrated, and sequential screens to be acceptable options. The guidelines also recommend that an acceptable second trimester screen have a minimum 75% DR and 5% FPR for trisomy 21. The results of this update agree with the SOGC in finding that the 1T-Quad screen meets the second trimester threshold (see Table T.5). Using NT contingently may allow the test to exceed the first trimester performance threshold. However, as noted above, without the need to maintain an FPR of 3 or 5%, a much higher false positive rate (for example, 20%) can be tolerated in order to achieve a detection rate that is comparable to or, possibly, exceeds that of the first trimester combined test. The second-tier non-invasive screen—NT, NIPT, or both—can then be used to reduce the FPR to 5% or less prior to invasive diagnostic testing. Because the DNA sequences derived from NIPT are derived from the placenta, the sequences may not reflect the true fetal karyotype and can result in false positive results due to confined placental mosaicism. Consequently, clinical researchers and guideline authors consistently emphasize the need to follow up positive NIPT results with diagnostic testing. Nevertheless, a non-invasive test that could achieve the performance of a standard invasive prenatal diagnostic test (that is, CVS) would have the potential to radically alter the landscape of prenatal risk assessment.

TABLE T.5: SCREENING TESTS FOR MEETING SOGC MINIMUM PERFORMANCE VALUES

Screening test	Meet SOGC Minimum Performance
Threshold of 75% DR and 3% FPR	• First trimester combined (NT and PAPP-A, hCG serum test) • Full integrated (NT, PAPP-A + quadruple screen) • Serum integrated (PAPP-A, hCG serum test + quadruple screen) • 1T-Quad + NT (10%) • 1T-Quad + NT (20%) • 1T-Quad + NIPT
Threshold of 75% DR and 5% FPR	Second trimester quadruple (AFP, hCG, uE3, inhibin-A serum test)

Conclusions

Current scientific evidence supports the use of cff-DNA (either "shotgun" or "targeted" approaches) for use as a "second-tier" prenatal risk assessment for those women whose pregnancies have been rated as "high-risk" based on a first trimester or second trimester risk assessment. The evidence for 1T-Quad +/- NT suggests this screen may be a reasonable option for jurisdictions that have insufficient resources for NT; however, uncertainty remains about its actual performance. Little empirical work has been done to assess how the information provided by these tests influences clinical decision-making or the decisions made by women regarding the management of their pregnancies. A large multicentre Canadian study (PEGASUS) is currently evaluating the use of cff-DNA and the 1T-Quad +/- NT algorithm for prenatal screening of fetal trisomies. The results of this trial will likely provide good evidence about the accuracy and effectiveness of this algorithm, in addition to answering questions about potential social and ethical issues.

Appendix T.A: Summary of Clinical Guidelines on NIPT

The *Society of Obstetricians and Gynecologists of Canada (SOGC)*[8] (Committee opinion released February 2013) recommends that NIPT using MPSS of cff-DNA to screen for trisomies 21, 18, and 13 be an option available to women in lieu of invasive diagnostic testing if the woman is considered at high risk of fetal trisomy 21, 18, or 13 based on the results from an available screening test or ultrasound. The committee also recommends that no irrevocable obstetrical decision should be made in pregnancies receiving a positive NIPT result without diagnostic testing (amniocentesis). Finally, the committee recommended that studies in average-risk pregnancies are required before NIPT is used in place of biochemical markers with or without NT ultrasound.

The *American College of Obstetricians and Gynecologists (ACOG)*[6] (Committee opinion released December 2012) recommends that women, regardless of maternal age, be offered prenatal assessment for aneuploidy either by screening or invasive diagnostic testing. The ACOG recommends that the option of cff-DNA testing be offered to women at increased risk of fetal aneuploidy, based on maternal age or other factors, as a primary screening test. In addition, ACOG recommends that cff-DNA screening can be used as a follow-up test for women with a positive first trimester or second trimester screening test result (after first trimester combined, sequential, or integrated screen, or a quadruple screen). The Committee recommends confirmation of positive NIPT results with amniocentesis or CVS because of false-positive NIPT results. Maternal serum alpha-fetoprotein (AFP) screening or ultrasonographic evaluation for open fetal defects should continue to be offered.

The *International Society for Prenatal Diagnosis (ISPD)*[10] (Committee opinion released April 2013) recommends that cff-DNA screening be available for women classified as high-risk by any one or a combination of existing screening tests (first trimester combined +NT, sequential, or integrated screen, or a quadruple screen, second trimester ultrasound). In addition, the ISPD recommends that cff-DNA screening can be considered for women who did not receive any other screening and who are considered to be at high risk on the basis of: maternal age; presence of an ultrasound abnormality suggestive of trisomy 21, 18, or 13; family history of chromosome abnormality that could result in full trisomy; history of previous pregnancy with trisomy 21, 18, or 13.

The *National Society of Genetic Counselors (NSGC)*[9] (Committee opinion released January 2013) recognizes NIPT as an option for aneuploidy assessment in pregnancies considered to be at a high risk for fetal aneuploidy based on maternal age, family history, or positive serum/sonographic screening tests. It counsels that NIPT should not be considered diagnostic and that abnormal results be confirmed through amniocentesis or CVS. The NSGC does not support the use of NIPT as a routine, first-tier screen in low-risk populations. In addition, because NIPT does not screen for all chromosomal or genetic conditions, it does not replace standard risk assessment and prenatal diagnosis.

The *American College of Medical Genetics and Genomics (ACMG)*[3] (Committee opinion released 2013) recommends that NIPT be considered a screening test to identify pregnancies at risk for common aneuploidies (trisomies 21, 18, 13); however, it does not specify a specific population, for example, high-risk pregnancies. The ACMG emphasizes that definitive diagnosis still requires invasive testing with CVS or amniocentesis. Furthermore, the ACMG recommends that NIPT not be used in lieu of first trimester ultrasound examination, which can be useful for accurate gestational dating, assessment of the nuchal translucency region to identify a fetus at increased risk for a chromosome abnormality, and multiple pregnancies.

Appendix T.B: Methods

Literature search strategy

An IHE information specialist searched the following sources for evidence:

- **Electronic databases:** MEDLINE (including in-process), EMBASE, CINAHL, Web of Science, Scopus, and various grey literature sources such as HTA agency websites, clinical trials registries, and Google
- **Reference lists** of the retrieved reports

Study selection

Two reviewers screened the retrieved citations for potentially relevant studies, based on the titles and abstracts. Citations were judged clearly not relevant if reviewers could determine from the title or abstract that the report was:

- not a primary study
- not on pregnant women
- not on NIPT or 1T-Quad as a screening test for fetal trisomy

Two reviewers independently assessed the relevance of the full text of the studies using the following inclusion and exclusion criteria:

Inclusion criteria

- **Population:** women in their first trimester of pregnancy.
- **Intervention:** first trimester quadruple serum screening with or without nuchal translucency screening, followed by non-invasive (cff-DNA) prenatal testing.
- **Comparator:** for screening accuracy studies, the ideal reference standard is karyotype based on samples obtained from chorionic villi sampling or on samples obtained via autopsy; however, clinical examination upon birth will also be used as a reference standard, which would be appropriate for those pregnancies considered at low risk of chromosomal anomaly. For other effectiveness assessments, suitable reference standards are usual care or other risk assessment protocols for a risk assessment within the same trimester, for example, first trimester combined.
- **Outcome:** study provides sufficient quantitative data to complete contingency tables for the calculation of test sensitivity and specificity or quantitative data on safety *or* quantitative data on therapeutic efficacy *or* quantitative or qualitative data on patient (maternal or fetal) outcomes.
- **Design:** prospective or retrospective cross-sectional screening accuracy or comparative design (randomized or non-randomized).
- **Setting:** studies included in the review must have been conducted in countries with developed market economies, as defined by the United Nations. These countries include Australia, Canada, Japan, New Zealand, the United States, and European countries (*http://unpan1.un.org/intradoc/groups/public/documents/un/unpan008092.pdf*).

In the case of duplicate publications, the most recent or principal (that is, most comprehensive) version was included.

Exclusion criteria

Excluded were reports that:

- were not published in English
- did not report primary data (for example, systematic or narrative reviews, commentaries, editorials, news reports)
- did not evaluate technologies in the context of a screening program (for example, simulation studies or clinical validation studies)
- did not evaluate 1T-Quad +/- NT and/or NIPT
- did not report sufficient quantitative data to complete contingency tables for the calculation of performance measures, quantitative data on safety or therapeutic efficacy, or quantitative or qualitative data on patient outcomes

Data extraction

One reviewer abstracted data from the published reports of primary studies according to predetermined data extraction forms. A second reviewer verified the abstracted data. The following general categories of data were abstracted: publication information, study population and setting characteristics, intervention characteristics and reference standards, results, and authors' conclusions.

Methodological quality assessment

Two reviewers assessed independently the methodological quality of selected systematic reviews using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS 2) checklist.

Data synthesis

Quality assessment results were summarized narratively by checklist domain. Characteristics of included studies were summarized narratively and in tabular form. No statistical analyses were conducted.

Quality assessment of the body of evidence

The quality of the body of evidence for those outcomes with quantitative data was assessed according to the following domains: potential for bias due to design and conduct of studies, directness of outcome, precision of effect estimate, and consistency of results.

External review

Members of the provincial Expert Advisory Group (EAG) assembled for this project reviewed this draft report.

Appendix T.C: Searches

Literature Search Summary: FASTS Update Search

The IHE Research Librarian conducted the literature search between 8 January 2014 and 15 January 2014. The search was limited to publications from 2000 onwards and to diagnostic accuracy studies. There were no language restrictions.

TABLE T.C.1: SEARCH STRATEGY

Database	Edition or date searched	Search Terms ††
Core Databases		
MEDLINE (includes in-process and other non-indexed citations) OVID Licensed Resource	8 January 2014	1 (pregnan* or fetal or prenatal or perinatal or antenatal or antepartum or maternal or ?trimester).sh,ti. 2 mass screening/ or genetic testing/ 3 1 and 2 4 prenatal diagnosis/ 5 (screen* or diagnos* or test or tests or testing or detect*).ti. 6 1 and 5 7 3 or 4 or 6 8 Chorionic Gonadotropin/ or Chorionic Gonadotropin, beta Subunit, Human/ 9 ((chorionic adj2 gonadotrop*) or hcg).mp. 10 8 or 9 11 alpha-Fetoproteins/ 12 (afp or alpha fetoprotein*).mp. 13 11 or 12 21721 14 exp Estriol/ 15 (UE3 or estriol).mp. 16 14 or 15 17 inhibin*.mp. 18 (quad or quadruple).mp. 19 10 and 13 and 16 and 17 20 18 or 19 21 Pregnancy Proteins/ 22 pregnancy protein*.mp. 23 21 or 22 24 (placenta* growth adj (factor* or hormone*)).mp. 25 (PlGF or hPGH).mp. 26 23 or 24 or 25 27 (free adj2 (DNA or nucleic acid)).tw. 28 cfDNA.tw. 29 ((non invasive or noninvasive) adj3 (testing or detect* or diagnos* or screen* or test or tests or evaluation or assessment)).tw. 30 (DNA adj3 sequencing).tw. 31 exp Sequence Analysis, DNA/ 32 exp High-Throughput Nucleotide Sequencing/

		33 NIPT.tw. 34 or/27-33 35 7 or 20 or 26 or 34 36 Aneuploidy/ 37 aneuploid*.tw. 38 ((down* or patau or edwards) adj syndrome).tw. 39 Down syndrome/ 40 Trisom*.tw. 41 Trisomy/ 42 congenital abnormalities/ 43 Chromosome Disorders/ 44 ((congenital or chromosom* or anatomic*) adj anomal*).tw. 45 ((chromosom* or anatomic*) adj abnormalit*).tw. 46 or/36-45 47 35 and 46 48 limit 47 to yr="2008 -Current" 49 limit 48 to animals 50 limit 48 to humans 51 49 not (49 and 50) 52 48 not 51 53 exp "Sensitivity and Specificity"/ 54 (sensitivity or specificity).tw. 55 Reference Values/ 56 false negative reactions/ or false positive reactions/ 57 ((detection adj2 rate*) or false positive* or false negative* or predictive value* or reference value* or performance or MoM or "multiples of the median" or screen positive* or accura* or reliab*).tw. 58 53 or 54 or 55 or 56 or 57 59 52 and 58 **(1127 results)**
Embase	8 January 2014	1 (pregnan* or fetal or prenatal or perinatal or antenatal or antepartum or maternal or ?trimester).sh,ti. 2 *mass screening/ or *genetic screening/ 3 1 and 2 4 *prenatal diagnosis/ or *prenatal screening/ 5 (screen* or diagnos* or test or tests or testing or detect*).ti. 6 1 and 5 7 3 or 4 or 6 8 *chorionic gonadotropin/ or *chorionic gonadotropin beta subunit/ 9 ((chorionic adj2 gonadotrop*) or hcg).mp. 10 8 or 9 11 *alpha fetoprotein/ 12 (afp or alpha fetoprotein*).mp. 13 11 or 12 14 *estriol/ 15 (UE3 or estriol).mp. 16 14 or 15

		17 inhibin*.mp. or *inhibin A/ 18 (quad or quadruple).mp. 19 10 and 13 and 16 and 17 20 18 or 19 21 *placenta protein/ or *placental growth factor/ 22 ((pregnancy or placenta) adj protein*).mp. 23 21 or 22 24 (placenta* growth adj (factor* or hormone*)).mp. 25 (PlGF or hPGH).mp. 26 23 or 24 or 25 27 (free adj2 (DNA or nucleic acid)).tw. 28 cfDNA.tw. 29 ((non invasive or noninvasive) adj3 (testing or detect* or diagnos* or screen* or test or tests or evaluation or assessment)).tw. 30 (DNA adj3 sequencing).tw. 31 *dna sequence/ 32 *high throughput sequencing/ 33 NIPT.tw. 34 or/27-33 35 7 or 20 or 26 or 34 36 *aneuploidy/ 37 aneuploid*.tw. 38 ((down* or patau or edwards) adj syndrome).tw. 39 *Down syndrome/ or *Edwards syndrome/ 40 Trisom*.tw. 41 exp *trisomy/ 42 *congenital disorder/ 43 *chromosome disorder/ 44 ((congenital or chromosom* or anatomic*) adj (disorder* or anomal*)).tw. 45 ((congenital or chromosom* or anatomic*) adj abnormalit*).tw. 46 or/36-45 47 35 and 46 48 limit 47 to yr="2008 -Current" 49 limit 48 to animals 50 limit 48 to humans 51 49 not (49 and 50) 52 48 not 51 **(3443 results)**
Cochrane Library	7 January 2014	1 (pregnan* or fetal or prenatal or perinatal or antenatal or antepartum or maternal or ?trimester).sh,ti. 2 *mass screening/ or *genetic screening/ 3 1 and 2 4 *prenatal diagnosis/ or *prenatal screening/ 5 (screen* or diagnos* or test or tests or testing or detect*).ti. 6 1 and 5 7 3 or 4 or 6 8 *chorionic gonadotropin/ or *chorionic gonadotropin beta subunit/

		9 ((chorionic adj2 gonadotrop*) or hcg).mp. 10 8 or 9 11 *alpha fetoprotein/ 12 (afp or alpha fetoprotein*).mp. 13 11 or 12 14 *estriol/ 15 (UE3 or estriol).mp. 16 14 or 15 17 inhibin*.mp. or *inhibin A/ 18 (quad or quadruple).mp. 19 10 and 13 and 16 and 17 20 18 or 19 21 *placenta protein/ or *placental growth factor/ 22 ((pregnancy or placenta) adj protein*).mp. 23 21 or 22 24 (placenta* growth adj (factor* or hormone*)).mp. 25 (PlGF or hPGH).mp. 26 23 or 24 or 25 27 (free adj2 (DNA or nucleic acid)).tw. 28 cfDNA.tw. 29 ((non invasive or noninvasive) adj3 (testing or detect* or diagnos* or screen* or test or tests or evaluation or assessment)).tw. 30 (DNA adj3 sequencing).tw. 31 *dna sequence/ 32 *high throughput sequencing/ 33 NIPT.tw. 34 or/27-33 35 7 or 20 or 26 or 34 36 *aneuploidy/ 37 aneuploid*.tw. 38 ((down* or patau or edwards) adj syndrome).tw. 39 *Down syndrome/ or *Edwards syndrome/ 40 Trisom*.tw. 41 exp *trisomy/ 42 *congenital disorder/ 43 *chromosome disorder/ 44 ((congenital or chromosom* or anatomic*) adj (disorder* or anomal*)).tw. 45 ((congenital or chromosom* or anatomic*) adj abnormalit*).tw. 46 or/36-45 47 35 and 46 48 limit 47 to yr="2008 -Current" 49 limit 48 to animals 50 limit 48 to humans 51 49 not (49 and 50) 52 48 not 51 53 "sensitivity and specificity"/ 54 (sensitivity or specificity).tw.

		55 reference value/ 56 ((detection adj2 rate*) or false positive* or false negative* or predictive value* or reference value* or performance or MoM or "multiples of the median" or screen positive* or accura* or reliab*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 57 false positive result/ or false negative result/ or laboratory diagnosis/ or diagnostic accuracy/ 58 diagnostic error/ 59 53 or 54 or 55 or 56 or 57 or 58 60 52 and 59 **(1588 results)**
Scopus		Your query: ((((((TITLE-ABS-KEY((afp OR alpha fetoprotein*)) AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal) AND PUBYEAR > 2007) AND (TITLE-ABS-KEY((ue3 OR estriol)) AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal) AND PUBYEAR > 2007) AND (TITLE-ABS-KEY(inhibin*) AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal) AND PUBYEAR > 2007) AND (TITLE-ABS-KEY(((chorionic W/2 gonadotrop*) OR hcg)) AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal) AND PUBYEAR > 2007)) OR (TITLE-ABS-KEY((quad OR quadruple)) AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal) AND PUBYEAR > 2007)) OR ((TITLE-ABS-KEY(pregnancy protein*) AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal) AND PUBYEAR > 2007) OR (TITLE-ABS-KEY((placenta* growth W/2 (factor* OR hormone*))) AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal) AND PUBYEAR > 2007) OR (TITLE-ABS-KEY(plgf OR hpgh) AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal) AND PUBYEAR > 2007)) OR ((TITLE-ABS-KEY((free W/2 dna) OR (free W/2 nucleic acid)) AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal) AND PUBYEAR > 2007) OR (TITLE-ABS-KEY((noninvasive) W/2 (testing OR detect* OR diagnos* OR screen* OR test OR tests OR evaluation OR assessment)) AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal) AND PUBYEAR > 2007) OR (TITLE-ABS-KEY(("non invasive") W/2 (testing OR detect* OR diagnos* OR screen* OR test OR tests OR evaluation OR assessment)) AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal) AND PUBYEAR > 2007) OR (TITLE-ABS-KEY(dna W/3 sequencing) AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal) AND PUBYEAR > 2007) OR (TITLE-ABS-KEY(nipt) AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal) AND PUBYEAR > 2007))) AND ((TITLE-ABS-KEY(aneuploid*) AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal) AND PUBYEAR > 2007) OR (TITLE-ABS-KEY(((down* OR patau OR edwards) W/1 syndrome)) AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal) AND PUBYEAR > 2007) OR (TITLE-ABS-KEY(trisom*) AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal) AND PUBYEAR > 2007) OR (TITLE-ABS-KEY(((congenital OR chromosom* OR anatomic*) W/1 anomal*)) AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal) AND PUBYEAR >

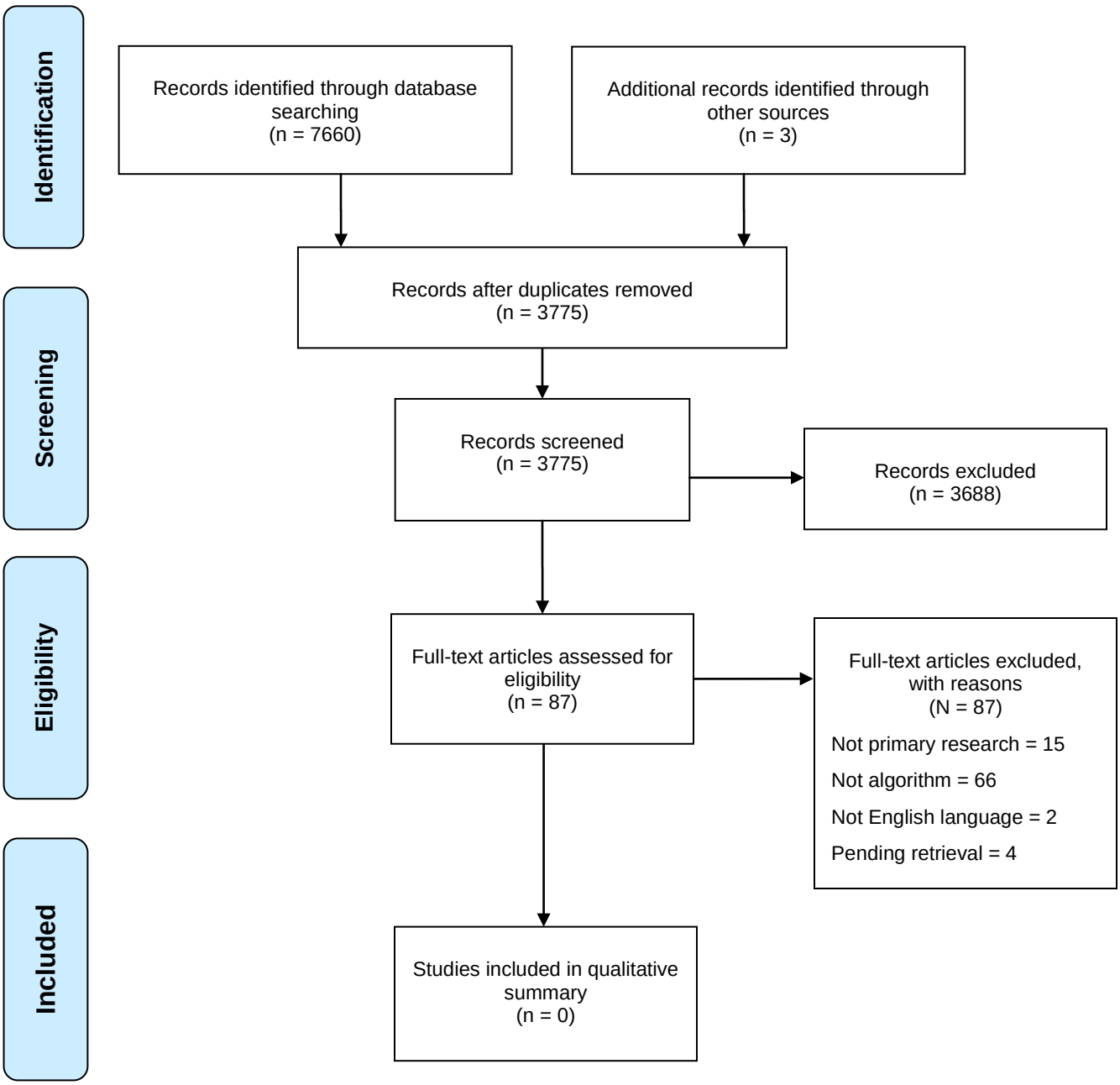
		2007))) OR (((TITLE-ABS-KEY((pregnan* OR fetal OR prenatal OR perinatal OR antenatal OR antepartum OR maternal OR ?trimester) .) AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal) AND PUBYEAR > 2007) AND (TITLE((screen* OR diagnos* OR test OR tests OR testing OR detect*)) AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal) AND PUBYEAR > 2007)) AND ((TITLE-ABS-KEY(aneuploid*) AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal) AND PUBYEAR > 2007) OR (TITLE-ABS-KEY(((down* OR patau OR edwards) W/1 syndrome)) AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal) AND PUBYEAR > 2007) OR (TITLE-ABS-KEY(trisom*) AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal) AND PUBYEAR > 2007) OR (TITLE-ABS-KEY(((congenital OR chromosom* OR anatomic*) W/1 anomal*)) AND SUBJAREA(mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal) AND PUBYEAR > 2007)))) AND (TITLE-ABS-KEY(sensitivity OR specificity OR reference value* OR false negative* OR false posit **(86 results)**
CINAHL	8 January 2014	S50 S47 AND S48 Limiters - Published Date: 20080101-20141231 S49 S47 AND S48 S48 ((detection N2 rate*) or false positive* or false negative* or predictive value* or reference value* or performance or MoM or "multiples of the median" or screen positive* or accura* or reliab* or sensitiv* or specific*) S47 S35 AND S46 S46 S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 S45 ((chromosom* or anatomic*) N1 abnormalit*) S44 ((congenital or chromosom* or anatomic*) N1 anomal*) S43 (MH "Chromosome Disorders+") S42 (MH "Congenital, Hereditary, and Neonatal Diseases and Abnormalities+") S41 MH "Trisomy 13") OR (MH "Trisomy 18") S40 Trisom* S39 (MH "Down Syndrome") S38 ((down* or patau or edwards) N1 syndrome) S37 aneuploid* S36 (MH "Aneuploidy") S35 S9 OR S22 OR S28 OR S34 S34 S29 OR S30 OR S31 OR S32 OR S33 S33 NIPT S32 (DNA N3 sequencing) S31 (non invasive or noninvasive) N3 (testing or detect* or diagnos* or screen* or test or tests or evaluation or assessment) S30 cfDNA S29 (free N2 (DNA or nucleic acid)) S28 S25 OR S26 OR S27 S27 (PlGF or hPGH) S26 (placenta* growth N1 (factor* or hormone*)) S25 S23 OR S24 S24 pregnancy protein* S23 (MH "Pregnancy Proteins+") S22 S20 OR S21 S21 (quad or quadruple) S20 S12 AND S15 AND S18 AND S19 S19 inhibin* S18 S16 OR S17

		S17 (UE3 or estriol) S16 (MH "Estriol") S15 S13 OR S14 S14 (afp or alpha fetoprotein*) S13 (MH "Alpha Fetoproteins") S12 S10 OR S11 S11 ((chorionic N2 gonadotrop*) or hcg) S10 MH "Gonadotropins, Chorionic") S9 S5 OR S6 OR S8 S8 S1 AND S7 S7 TI (screen* or diagnos* or test or tests or testing or detect*) S6 (MH "Prenatal Diagnosis+") S5 S1 AND S4 S4 S2 OR S3 S3 (MH "Genetic Screening") S2 (MH "Health Screening+") S1 (pregnan* or fetal or prenatal or perinatal or antenatal or antepartum or maternal or ?trimester) **(1361 results)**
Grey Literature		
Clinical Practice Guidelines		
AMA Clinical Practice Guidelines *www.topalbertadoctors.org/informed_practice/clinical_practice_guidelines.html*	14 January 2014	Browsed lists of guidelines **(0 results)**
CMA Infobase *http://mdm.ca/cpgsnew/cpgs/index.asp*	14 January 2014	Browsed lists of guidelines **(5 results)**
National Guideline Clearinghouse *www.ngc.gov*	14 January 2014	Prenatal or antenatal or trimester or fetal or maternal or pregnancy AND Diagnosis or Screening **(13 results)**
NICE Guidance *http://guidance.nice.org.uk/*	14 January 2014	Browsed lists of guidelines **(0 results)**
HTA Agencies		
CADTH	14 January 2014	PLGF or placental growth factor or placental growth hormone or non invasive prenatal or non invasive maternal or cell-free DNA or prenatal screening or maternal screening **(0 results)**
OHTAC	14 January 2014	Browsed list **(0 results)**
INESSS	15 January 2014	PLGF or placental growth factor or placental growth hormone or non invasive prenatal or non invasive maternal or cell-free DNA or prenatal screening or maternal screening **(0 results)**

UK HTA	15 January 2014	PLGF or placental growth factor or placental growth hormone or non invasive prenatal or non invasive maternal or cell-free DNA or prenatal screening or maternal screening **(2 results)**
MSAC- Australia	15 January 2014	Browsed list **(0 results)**
AHRQ	15 January 2014	Browsed list **(0 results)**
Search Engines		
TRIP *www.tripdatabase.com*	15 January 2014	PLGF or placental growth factor or placental growth hormone or non invasive prenatal or non invasive maternal or cell-free DNA or prenatal screening or maternal screening **(16 results)**
Google	15 January 2014	non invasive prenatal OR non invasive maternal OR cell-free DNA OR PLGF trisomy OR downs "placental growth factor" filetype:pdf **(12 results)**
Proquest Dissertations and Theses	15 January 2014	ti(non invasive prenatal OR non invasive maternal OR cell-free DNA OR PLGF OR placental growth factor) AND (trisomy OR downs) **(5 results)**

††, *, #, and ? are truncation characters that retrieve all possible suffix variations of the root word, for example, surg*, retrieves surgery, surgical, surgeon, etc.

Appendix T.D: Literature Search Results



Appendix T.E: Excluded Studies

A total of 87 reports were excluded. The primary reasons for exclusion were as follows:

1. The report was not primary research or of the appropriate design as described in the inclusion criteria (n = 15).
2. The report was not on the algorithm of interest (FT-Quad +/- NT + NIPT) (n = 66).
3. The report was not published in the English language (n = 2).

Also, at the time the review was completed, four reports had not been retrieved and evaluated and were considered "pending."

1. The report was not primary research or of the appropriate design as described in the inclusion criteria (n = 15).

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SECTION TWO: Economic Analysis

Charles Yan, PhD; Anderson Chuck, PhD, MPH

Objectives and Policy Questions

Research Questions

The primary research question being answered in this section is how alternative FASTS options compare to those specified in the Alberta Health policy directive of 12 December 2012 in terms of cost-effectiveness and budget impact in Alberta.

FASTS Options

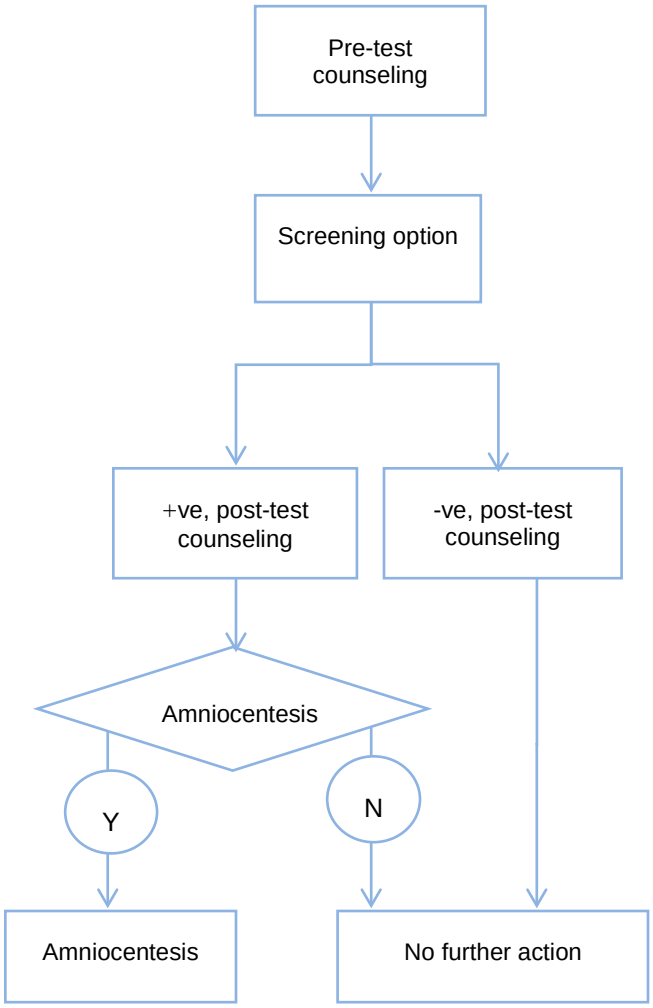
The alternative options being proposed are dependent on the availability of NT testing. Hence the comparative analysis examines the cost-effectiveness among options that are suitable when NT services are available, and then separately among those options when NT services are unavailable. FASTS options being assessed are shown in Table E.1, with a simplified flow diagram shown in Figure E.1. A detailed flow diagram of each option is shown in Appendix E.A.

TABLE E.1: SCREENING OPTIONS

Screening Option	Markers/Tests
When NT services are available	
Serum Integrated Prenatal Screening (SIPS) (AH directive)	PAPP-A in first trimester, AFP, uE3, hCG, and inhibin A in second trimester
Combined (AH directive)	NT, hCG, and PAPP-A
First trimester quadruple serum screening with NT and NIPT (1TQuad_NT+NIPT)	Free β-hCG, PAPP-A, PlGF, AFP, NT. Positives receive NIPT
NIPT alone	NIPT
SIPS+NIPT	PAPP-A in first trimester, AFP, uE3, hCG, and inhibin A in second trimester. Positives receive NIPT
Combined+NIPT	NT, hCG, and PAPP-A. Positives receive NIPT
When NT services are unavailable	
SIPS	PAPP-A in first trimester, AFP, uE3, hCG, and inhibin A in second trimester
1TQuad with a detection rate of 0.85 and NIPT ($1TQuad_{0.85}$ +NIPT)	Free β-hCG, PAPP-A, PlGF, AFP. Positives receive NIPT
1TQuad with a detection rate of 0.90 and NIPT ($1TQuad_{0.90}$ +NIPT)	Free β-hCG, PAPP-A, PlGF, AFP. Positives receive NIPT
1TQuad with a detection rate of 0.95 and NIPT ($1TQuad_{0.95}$ +NIPT)	Free β-hCG, PAPP-A, PlGF, AFP. Positives receive NIPT
NIPT alone	NIPT
SIPS+NIPT	PAPP-A in first trimester, AFP, uE3, hCG, and inhibin A in second trimester. Positives receive NIPT

Note: Although second trimester quadruple screening is still conducted in Alberta, it is not included in this analysis because the 2012 IHE report on FASTS showed it to be less cost-effective than SIPS.[11]

FIGURE E.1: SIMPLIFIED FLOW DIAGRAM OF SCREENING OPTIONS



Methods

The research questions were addressed through developing an Alberta-based cost-effectiveness and budget impact model.

Economic evaluation

Cost-effectiveness analysis (CEA) is an analytic approach for comparing the health benefits and resource expenditures associated with competing health technologies. A decision analytic simulation model was developed to evaluate the cost-effectiveness of the alternative FASTS.

The CEA adopted a payer perspective and considered direct medical service costs to the Alberta health system, including costs of physician, outpatient, and laboratory services. The time horizon for the analysis considered costs from initial screen to final diagnosis, and elucidated the screening option that provided the highest accuracy at the lowest cost to the health system. All analyses were conducted using Microsoft Excel 2003 and TreeAge Pro Suite (TREEAGE software Inc; Williamstown, MA).

Targeted prenatal abnormalities

The targeted prenatal abnormalities included trisomy 21, 18, 13, anencephaly, encephaloceles, and spina bifida. However, there were insufficient data available to inform the diagnostic precision of each screening option for all of the targeted prenatal abnormalities, with complete data only being only available for trisomy 21. Consequently, the economic analysis could only focus on trisomy 21.

Model inputs

The performance characteristics of the alternative screening options in terms of sensitivity and specificity were primary derived from the published literature and from the AHS FASTS advisory group report (see Table E.2). Epidemiological data including prevalence of the target prenatal abnormalities were derived from Alberta sources (see Table E.3). Data on the number of affected pregnancies came from Alberta Congenital Anomalies Surveillance System (ACASS). We analyzed data over 5 years and observed that the rate of affected pregnancies was relatively flat over time. As such, the yearly prevalence was estimated based on the average number of affected pregnancies over the 5-year period. Prevalence estimates were calculated by dividing the number of affected pregnancies by the number of live births in Alberta.

Cost data, including physician, outpatient, and laboratory services, were primarily derived from Alberta sources (see Table E.4). Laboratory costs were provided as a cost per test for each of the markers/tests required in the various screening options inclusive of labour, equipment, and supplies (that is, consumables). This data was provided by Calgary Laboratory Services, AHS Edmonton Zone, UAH laboratory services, and experts from advisory committee members appointed by AH to guide the evidence review.

Physician service costs included: the cost of generic consultation provided by a general practitioner (GP), obstetrician (OB), or midwife; the cost of invasive diagnosis; and the cost of pregnancy loss resulting from invasive diagnostic testing. Outpatient services included costs of NT and invasive diagnostic testing. Data for physician services were extracted from the Alberta physician claim database using billing codes listed in the Alberta schedule of medical benefits, while data for outpatient services were extracted from the Ambulatory Care Classification System (ACCS), based on the Canadian Classification of Health Interventions (CCI) Code for outpatient services. Note that cost data for NT and amniocentesis were not available in any administrative database, and were derived based on available local data within AHS. Costs were converted to 2013 Canadian dollars using the health component of the Canadian Consumer Price Index.

TABLE E.2: PERFORMANCE CHARACTERISTICS OF FASTS OPTIONS FOR SCREENING FOR TRISOMY 21

Option	Sensitivity	FPR/Specificity	Distribution‡	Source
1T QUAD_NT	0.942†	FPR 0.050†	Uniform	*
1T_Quad$_{0.85}$	0.850†	FPR 0.110†	Uniform	**
1T_ Quad$_{0.90}$	0.900†	FPR 0.170†	Uniform	**
1T_ Quad$_{0.95}$	0.950†	FPR 0.280†	Uniform	**
NIPT	0.995 [95% CI: 0.98, 1]	0.998	Beta	**
SIPS	0.88 [95% CI: 0.77, 0.95]	0.97 [95% CI: 0.96, 0.97]	Beta	4
Combined test	0.91 [95% CI: 0.84, 0.95]	0.94 [95% CI: 0.94, 0.94]	Beta	5

NIPT failure rate			
Failure rate for high-risk pregnancy	0.046§	Uniform	6
Failure rate for average-pregnancy	0.054 (0.008 ~ 0.099)¶	Uniform	7
Failure rate of a retest	0.25§	Uniform	***

† The performances were based on results of mathematical modeling analysis; no confidence interval or standard deviation are available. To assess impact of uncertainty in these values, we assumed a ±20% difference.

* Personal communication, Dr. Jo-Ann Johnson.

** Derived from the AHS FASTS advisory group report and the T-section of this report.

*** Personal communication, Dr. Sylvie Langlois.

‡ Refers to the mathematical distribution that is fitted to the specific input parameter for the purposes of conducting probabilistic sensitivity analysis.

§ No confidence interval or standard derivation available. To assess impact of uncertainty in these values, we assumed a ±20% difference.

¶ The study presented a range, based upon which an average rate was calculated.

FPR – False positive rate; NIPT – non-invasive prenatal testing; SIPS – Serum Integrated Prenatal Screening

TABLE E.3: PREGNANT WOMEN, LIVE BIRTHS, PREVALENCE AND CRITICAL ASSUMPTIONS†

Maternal age	Pregnant women in 2010	Live births in 2010	Prevalence of Down's Syndrome (DS)*
0-39	67,181	48,660	0.001652
Key assumption‡			
Description		**Value**	**Data Source**
Proportion consenting to invasive diagnosis following positive result		48.50%	5
Fetal loss after amniocentesis		0.90%	9

† Data on pregnant women, cases of prenatal abnormality, and Alberta live births were from AHW databases. Data on Alberta live births and pregnancy were available online. Available from: *www.health.alberta.ca/documents/Reproductive-Health-2011.pdf*

* Prevalence was derived by dividing cases of abnormality by live births.

‡ Assumptions were made based on evidence from literature and ERA reports.

TABLE E.4: COST INPUTS[†]

Cost item	Mean	Low limit	High limit	Source
Laboratory services				
Inhibin	$ 27.63	$ 20.62	$ 34.64	Calgary Laboratory Services; AHS Edmonton Zone, UAH laboratory services
hCG	$ 5.27	$ 2.44	$ 8.09	
AFP	$ 9.11	$ 4.49	$ 13.73	
UE3	$ 11.95	$ 6.13	$ 17.77	
PAPP-A	$ 39.31	$ 31.45	$ 47.17	
free ß–hCG	$ 37.28	$ 34.96	$ 39.60	
P1GF	$ 17.38	$ 13.90	$ 20.86	Personal communication with Dr. Jo-Ann Johnson
NIPT	$795.00	$595.00	$954.00	
Physician services				
NT measurement	$101.29	$ 81.03	$121.54	The Alberta Physician Claims database
Genetic counseling	$174.41	$156.82	$191.14	
Physician visit	$ 94.50	$ 75.60	$113.40	
Amniocentesis	$118.83	$ 97.46	$210.54	
Outpatient services[‡]				
NT measurement	$ 66.31	$ 53.05	$ 79.57	*
Induction of labour	$117.80	$ 25.85	$428.00	ACCS
Amniocentesis	$462.68	$370.15	$555.22	**

[†] All costs were in 2013 prices, and assigned Gamma distributions in sensitivity analysis based on the range of variation.

‡ based on AH administrative databases; majority of procedures were performed on an outpatient basis. These costs were therefore used to represent hospital costs for the procedures.

* Personal communication with Christine Brake, Manager, Ultrasound Department, the Royal Alexandra Hospital. The range is based on an assumption of ±20% variation from the mean value.

** Personal communication with Judy Chernos, Director, Cytogenetics Laboratory, Alberta Children's Hospital. The range is based on an assumption of a ±20% variation from the mean value. ACCS provided information related to outpatient procedures, including patient-specific drug and supply costs, functional centre direct costs such as salaries (excluding physician services), medical and surgical supplies, and functional centre indirect costs such as administration and support services.

Model outputs

The outputs generated from the model are as follows:

- cases detected (true positives)
- total non-cases detected (true negatives)
- total correctly diagnosed pregnancies (true positive and true negative)
- total falsely diagnosed cases (false positives)
- total falsely diagnosed non-cases (false negatives)
- total number of screening-related miscarriages resulting from invasive diagnostic testing
- costs of each screening option

Criteria for cost-effectiveness

The criteria for concluding that an alternative is cost-effective are as follows:

1. Alternatives that are both more costly and less effective than other alternatives are dominated and are considered NOT cost-effective. These are eliminated from further consideration.
2. Alternatives that are both less costly and more effective than other alternatives are dominant and are considered cost-effective. These are included for further consideration.
3. Alternatives that are both more costly and more effective (or less costly and less effective) are not dominant and their cost-effectiveness is uncertain:
    a. Within these alternatives, a situation of extended dominance can exist. That is, among these alternatives, some are more cost-efficient than others. Alternatives that are dominated by extension are not considered cost-effective and are excluded from further consideration.
    b. For the remaining alternatives that are not dominated by extension, cost-effectiveness is dependent upon whether the additional effectiveness is worth the additional costs, which is determined by examining the opportunity cost of adopting the technology.

Sensitivity analysis

It is important to provide information regarding the degree of variability (that is, uncertainty) in potential costs and effectiveness to enable decision-makers to evaluate the credible range of potential costs and outcomes. Therefore, a probabilistic sensitivity analysis was conducted using 5000 Monte Carlo simulations using the ranges listed in Tables E.2 and E.4 to generate the distribution of potential costs and effectiveness associated with each alternative screening option. A one-way sensitivity analysis was also conducted:

- to determine the break-even point in the total average cost per woman screened as the cost per test of NIPT decreases
- to determine the impact to the cost-effectiveness results as the cost per test of NIPT decreases

Impact of differential timing

Given that all costs and outcomes occur within one year, costs and outcomes are not discounted.

Budget impact analysis (BIA)

The BIA was conducted to assess the financial impact of screening options on the Alberta health system. We compare the incremental cost of adopting the options outlined in the Alberta Health Policy Directive with existing FASTS screening services in Alberta. We then also compare the incremental cost of adopting the option that is deemed to be the most cost-effective based on the results from this CEA. Data on existing FASTS screening services were taken from the 2012 IHE FASTS report.[11] It is assumed that volumes have not significantly changed over time, given that the capacity within the major provincial labs to conduct FASTS screening were already at maximum.

Other cost and clinical inputs applied in the BIA model were identical to the data used in the CEA. The BIA considered a 1-year time horizon given that pregnancies resolve within one year. All costs were presented in 2013 data.

Results

Costs and Effectiveness

Table E.5 shows the resulting costs and outcomes associated with each FASTS option. When examining only costs, 1TQuad+NIPT was associated with the lowest costs followed by SIPS, 1TQuad+10%NT+NIPT, 1TQuad+20%NT+NIPT Combined, and NIPT alone.

When NT services are available, the relative performance of each option, when examining outcomes, is as follows (Table E.5 does not show difference between options due to rounding):

- Cases Detected (TP) (from best to worst): NIPT alone, Combined, 1TQuad_NT+NIPT, Combined, Combined+NIPT, SIPS, and SIPS+NIPT. Same ordering when examining the number of FN.
- Non-Cases Detected (TN) (from best to worst): SIPS+NIPT, Combined+NIPT, 1TQuad_NT+NIPT, NIPT alone, SIPS, and Combined. Same ordering when examining the number of FP or Fetal Loss.
- Total Correctly Diagnosed (TP+TN) (from best to worst): Combined+NIPT, SIPS+NIPT, 1TQuad_NT+NIPT, NIPT alone, SIPS, and Combined.

When NT services are not available, the relative performance of each option when examining outcomes is as follows (Table E.5 does not show difference between options due to rounding):

- Cases Detected (TP) (from best to worst): NIPT alone, $1TQuad_{0.95}$+NIPT, $1TQuad_{0.90}$+NIPT, SIPS, SIPS+NIPT, and $1TQuad_{0.85}$+NIPT. Same ordering when examining the number of FN.
- Non-Cases Detected (TN) (from best to worst): SIPS+NIPT, $1TQuad_{0.85}$+NIPT, $1TQuad_{0.90}$+NIPT, $1TQuad_{0.95}$+NIPT, NIPT alone, and SIPS. Same ordering when examining the number of FP, Fetal Loss, or Total Correct.
- Total Correctly Diagnosed (TP+TN) (from best to worst): Combined+NIPT, SIPS+NIPT, 1TQuad_NT+NIPT, NIPT alone, SIPS, and Combined.

TABLE E.5: COSTS AND HEALTH OUTCOMES

Screening Option	Average total cost per pregnancy screened	Outcomes per 69,286 pregnancies screened*					
		Cases detected (TP)	Non-cases detected (TN)	Total correctly diagnosed (TP+TN)	FP	FN	Fetal loss
When NT services are available							
SIPS (AH directive)	$ 372.27	121	66,796	66,916	2342	17	11
SIPS+NIPT	$ 391.07	120	69,143	69,263	5	18	1
1TQUAD_NT+NIPT	$ 522.11	129	69,101	69,230	47	9	1
Combined (AH directive)	$ 530.47	125	65,015	65,140	4115	13	19
Combined+NIPT	$ 562.51	124	69,139	69,264	8	13	1
NIPT alone	$1068.81	137	68,083	68,220	1060	1	5
When NT services are not available							
SIPS (AH directive)	$ 372.27	121	66,796	66,916	2342	17	11
SIPS NIPT	$ 391.07	120	69,143	69,263	5	18	1
$1TQUAD_{0.85}$+NIPT	$ 402.14	117	69,045	69,161	102	21	1
$1TQUAD_{0.90}$+NIPT	$ 450.08	123	68,989	69,112	158	15	1
$1TQUAD_{0.95}$+NIPT	$ 537.93	130	68,886	69,016	261	8	2
NIPT alone	$1068.81	137	68,083	68,220	1060	1	5

* Represents the number of pregnancies in Alberta. Outcomes are rounded to the nearest whole number.

TP – true positive; TN – true negative; FP – false positive; FN – false negative; FL – fetal loss

Cost-effectiveness (examines incremental costs and outcomes)

When NT services are available

Figure E.2 shows the relative cost-effectiveness between the FASTS options when focusing on the number of DS cases detected. The straight line in the figure represents the efficiency curve where alternatives above or to the left of the curve are not cost-effective because they are more costly and less effective than (that is, have a lower value than) other options. The dominated options include SIPS+NIPT, Combined, and Combined+NIPT.

Of the remaining options, SIPS is associated with the lowest cost for the effectiveness produced followed by 1TQUAD_NT+NIPT, and NIPT alone. The associated cost per additional case detected (that is, the incremental cost-effectiveness ratio or ICER) between these options are as follows:

- Moving from SIPS to 1TQuad_NT+NIPT has an ICER of $1.26 million.
- Moving from 1TQuad_NT+NIPT to NIPT alone has an ICER of $4.76 million.

If the analysis were to focus on the options that provide information in the first trimester, then options employing SIPS would be excluded. The potential cost-effective options would be 1TQuad_NT+NIPT and NIPT alone, with an associated ICER of $4.76 million, as reported above.

Figure E.3 shows the relative cost-effectiveness between the FASTS options when focusing on the number of pregnancies correctly diagnosed. The dominated options include Combined, 1TQuad_NT+NIPT, Combined+NIPT, and NIPT alone. Of the remaining options, SIPS is associated with the lowest cost for the effectiveness produced, followed by SIPS+NIPT. The associated ICER between these options is $555. If the analysis were to focus on the options that provide information in the first trimester and exclude options employing SIPS, the potential cost-effective options would be 1TQuad_NT+NIPT and Combined+NIPT, with an associated ICER of $83,000.

When NT services are not available

Figure E.4 shows the relative cost-effectiveness between the FASTS options in the absence of NT services when focusing on the number of DS cases detected. The dominated options include SIPS+NIPT, $1TQuad_{0.85}$+NIPT, and $1TQuad_{0.90}$+NIPT.

Of the remaining options, SIPS is associated with the lowest cost for the effectiveness produced, followed by $1TQuad_{0.95}$+NIPT and NIPT alone. The associated ICERs between these options are as follows:

- Moving from SIPS to $1TQuad_{0.95}$+NIPT has an ICER of $1.22 million.
- Moving from $1TQuad_{0.95}$+NIPT to NIPT alone has an ICER of $5.37 million.

If the analysis were to focus on the options that provide information in the first trimester and exclude options employing SIPS, the potential cost-effective options would be $1TQuad_{0.85}$+NIPT, $1TQuad_{0.90}$+NIPT, $1TQuad_{0.95}$+NIPT, and NIPT alone. The associated ICERs between these options are as follows:

- Moving from $1TQuad_{0.85}$+NIPT to $1TQuad_{0.90}$+NIPT has an ICER of $480,000.
- Moving from $1TQuad_{0.90}$+NIPT to $1TQuad_{0.95}$+NIPT has an ICER of $890,000.
- Moving from $1TQuad_{0.95}$+NIPT to NIPT alone has an ICER of $5.37 million.

Figure E.5 shows the relative cost-effectiveness between the FASTS options in the absence of NT services when focusing on the number of pregnancies correctly diagnosed. The dominated options include $1TQuad_{0.95}$+NIPT, $1TQuad_{0.90}$+NIPT, $1TQuad_{0.85}$+NIPT, and NIPT alone. Of the remaining options, SIPS is associated with the lowest cost for the effectiveness produced followed by SIPS+NIPT. The associated ICER between these options is $555.

If the analysis were to focus on the options that provide information in the first trimester and excluded options employing SIPS, the only cost-effective options would be $1TQuad_{0.85}$+NIPT.

FIGURE E.2: COST-EFFECTIVENESS OF FASTS OPTIONS WHEN FOCUSING ON CASES DETECTED

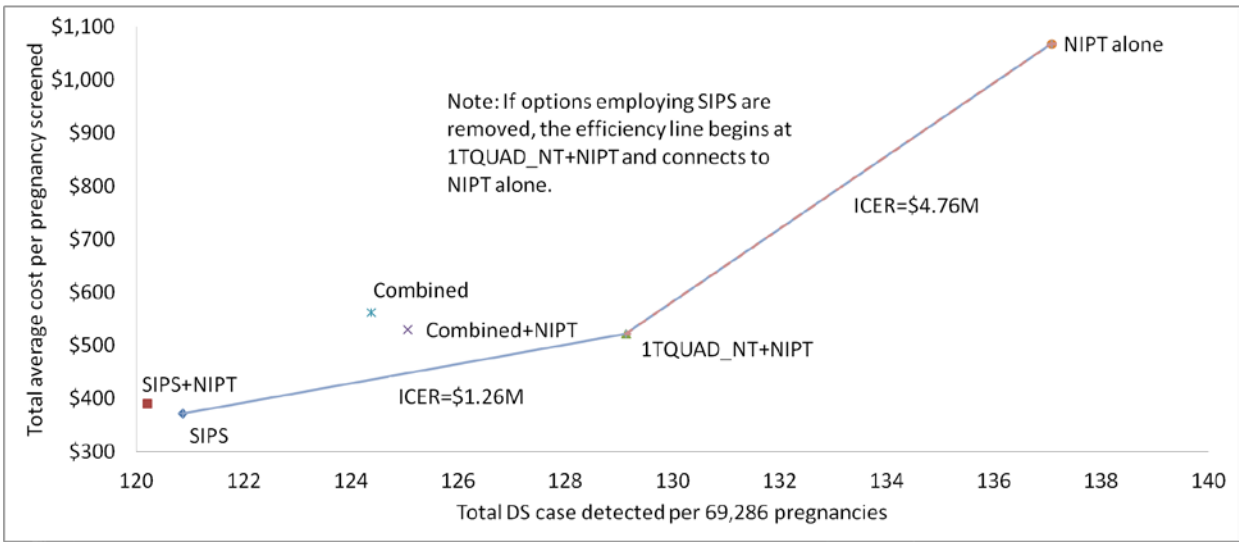


FIGURE E.3: COST-EFFECTIVENESS OF FASTS OPTIONS WHEN FOCUSING ON TOTAL PREGNANCIES CORRECTLY DIAGNOSED

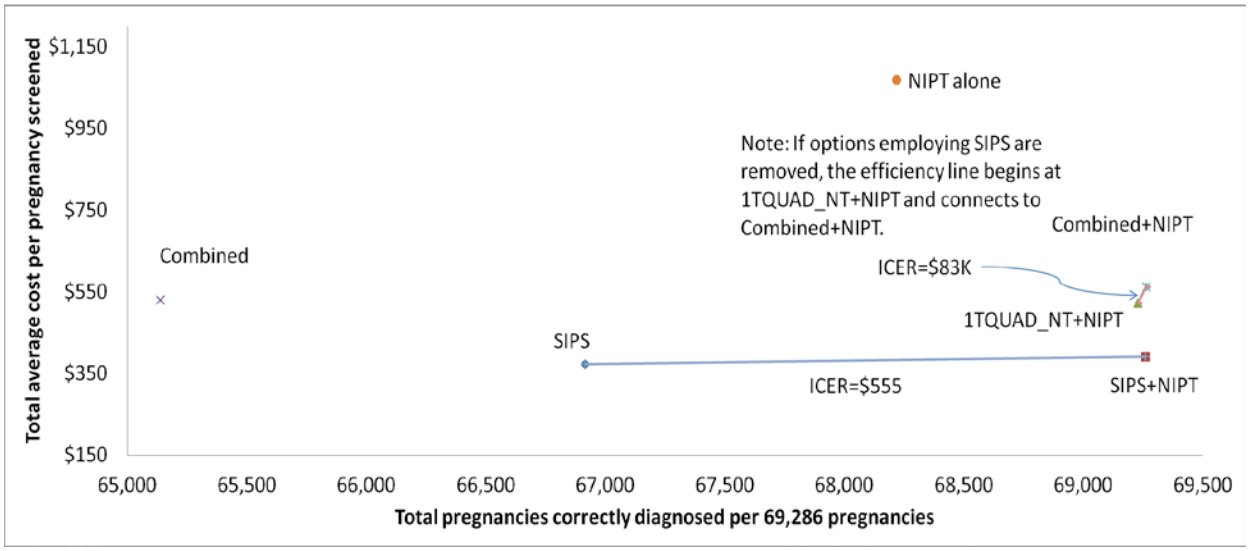


FIGURE E.4: COST-EFFECTIVENESS OF FASTS OPTIONS IN THE ABSENCE OF NT WHEN FOCUSING ON CASES DETECTED

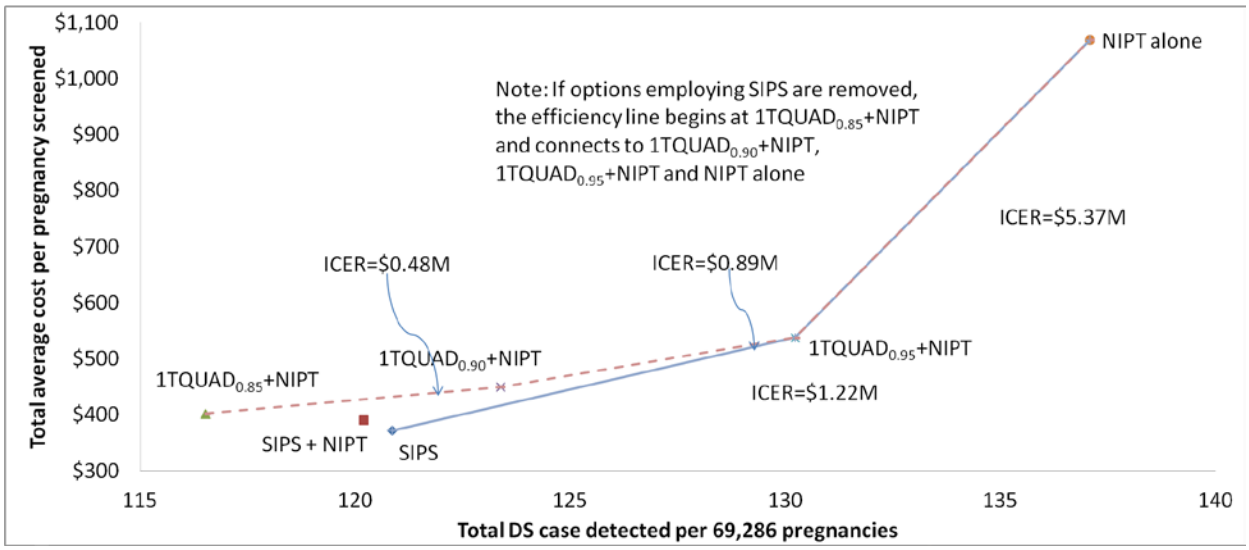
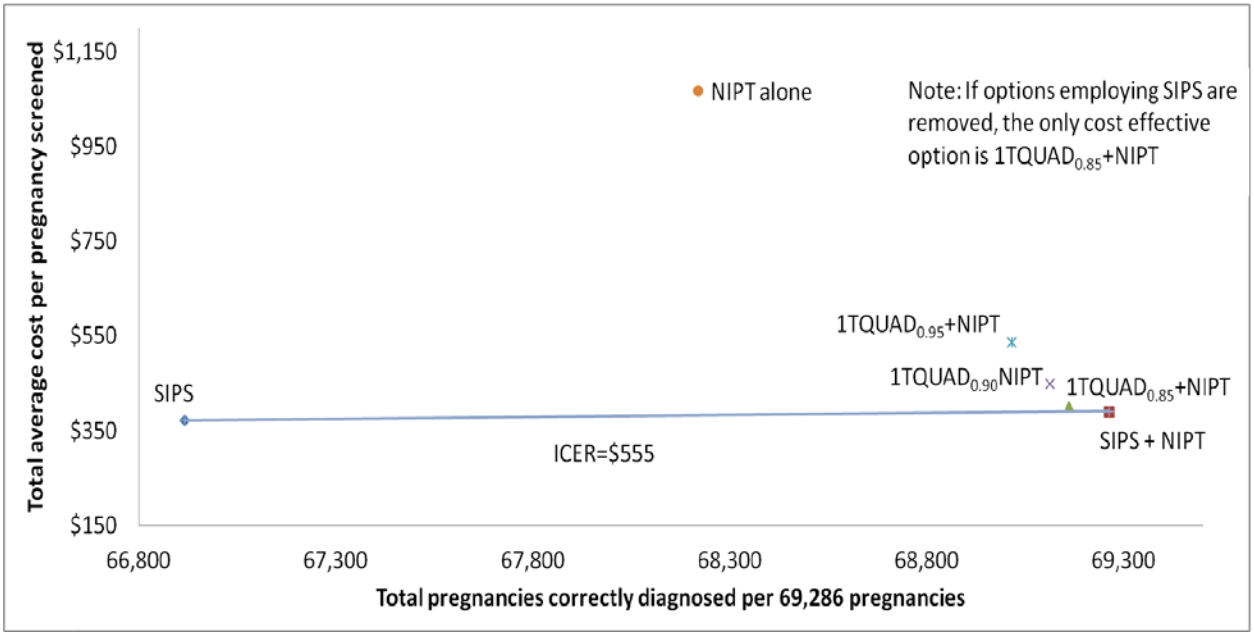


FIGURE E.5: COST-EFFECTIVENESS OF FASTS OPTIONS IN THE ABSENCE OF NT WHEN FOCUSING ON PREGNANCIES CORRECTLY DIAGNOSED



Sensitivity analysis

Figures E.6 and E.7 show the cost of NIPT for NIPT alone to be cost equivalent to the other options when NT services are and are not available, respectively (see Appendix E.B to view the impact to the cost-effectiveness results). Figure E.8 shows the cost-effectiveness frontier with effectiveness defined as the number of DS cases detected (for when NT services are available). The frontier shows the probability of being cost-effective over a range of cost-effectiveness thresholds. If decision-makers are not willing to buy more effectiveness (that is, if the willingness to buy another

case = 0), little uncertainty exists that SIPS is the most cost-effective option. However, once the willingness to pay is > 0, the uncertainty in the most cost-effective option increases. Between $2 million and $6 million, 1TQuad_NT+NIPT has the highest probability of being cost-effective, but the probability is around 50%. Beyond $6 million, the probability that NIPT alone is the most cost-effective monotonically increases.

When effectiveness is defined as the total number of correctly diagnosed pregnancies (see Figure E.9), if decision-makers are not willing to buy more effectiveness, there is little uncertainty that SIPS is the most cost-effective option. However, once the willingness to pay is >0, the uncertainty increases up to $600. Above $600, little uncertainty exists that SIPS+NIPT is the most cost-effective option.

Figure E.10 shows the cost-effectiveness frontier (for when NT services are not available) with effectiveness defined as the number of DS cases detected. If decision-makers are not willing to buy more effectiveness, little uncertainty exists that SIPS is the most cost-effective option. However, once the willingness to pay is >0, the uncertainty increases of never reaching greater than 50%. When effectiveness is defined as the total number of correctly diagnosed pregnancies (see Figure E.11), if decision-makers are not willing to buy more effectiveness, little uncertainty exists that SIPS is the most cost-effective option. However, once the willingness to pay is >0, the uncertainty increases. Above $2000, little uncertainty exists that SIPS+NIPT is the most cost-effective option.

FIGURE E.6: THE COST OF NIPT TESTING FOR NIPT ALONE TO BE COST EQUIVALENT TO OTHER FASTS OPTIONS WHEN NT SERVICES ARE AVAILABLE

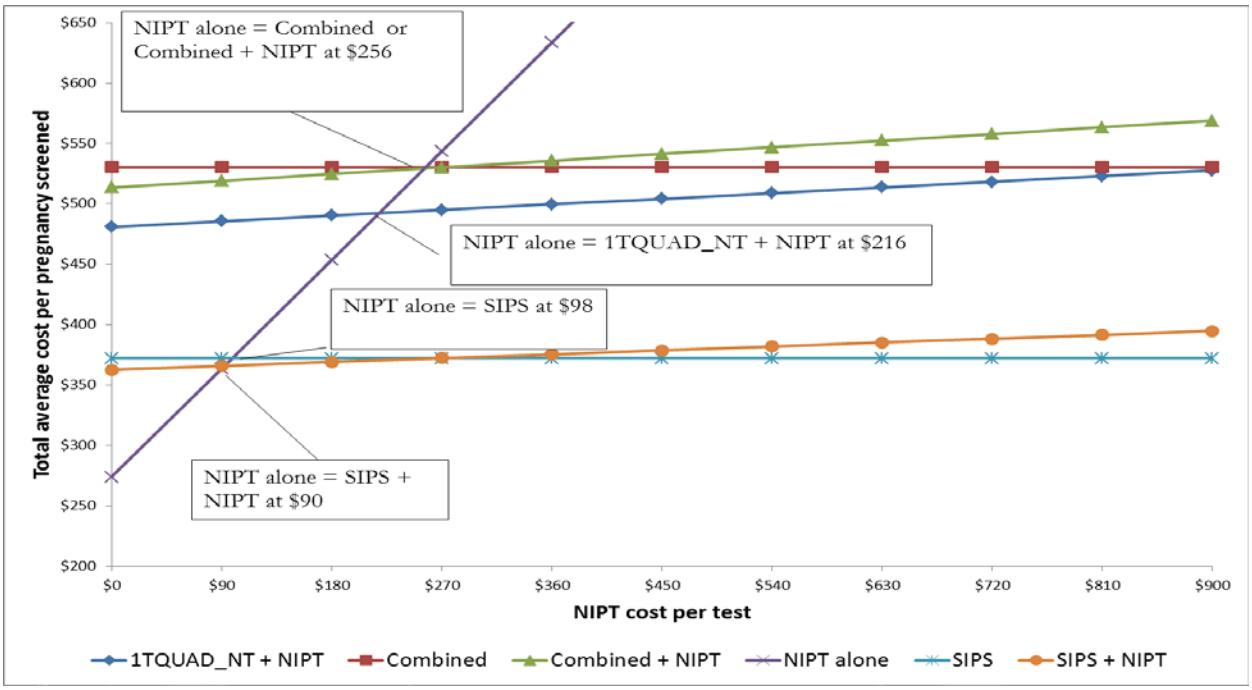


FIGURE E.7: THE COST OF NIPT TESTING FOR NIPT ALONE TO BE COST EQUIVALENT TO OTHER FASTS OPTIONS WHEN NT SERVICES ARE NOT AVAILABLE

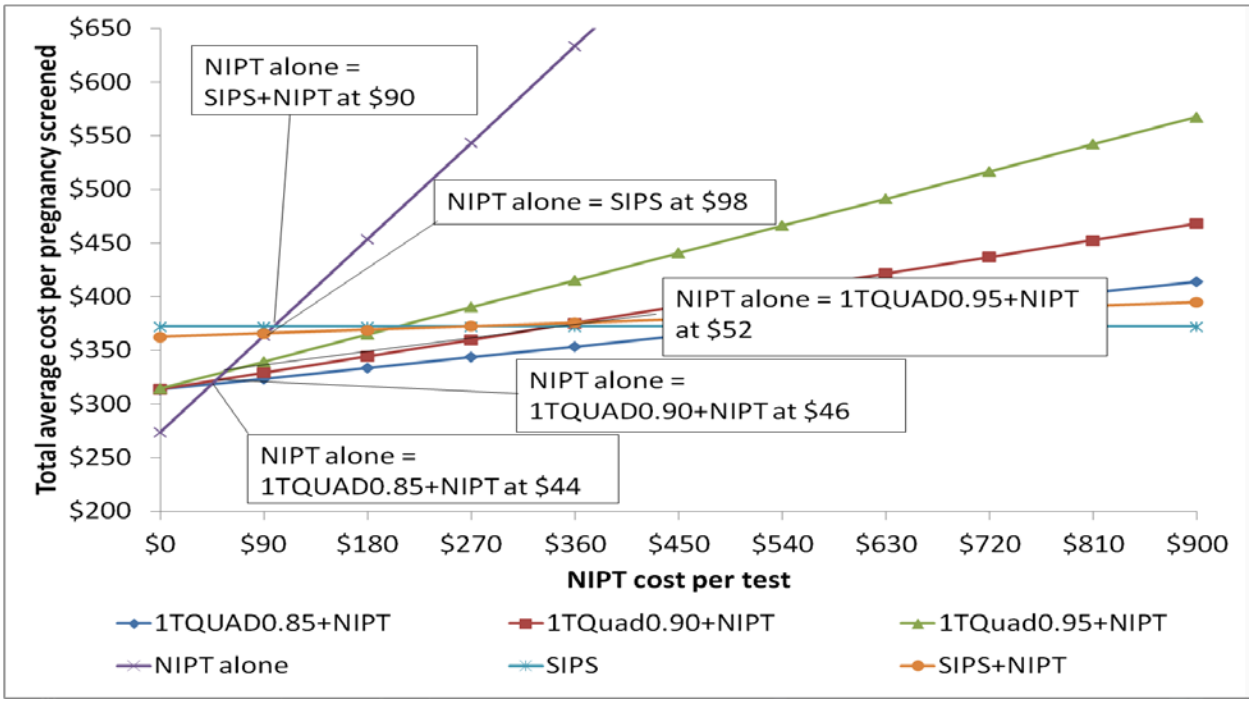


FIGURE E.8: COST-EFFECTIVENESS FRONTIER WITH EFFECTIVENESS DEFINED AS DS CASES DETECTED (FOR WHEN NT SERVICES ARE AVAILABLE)

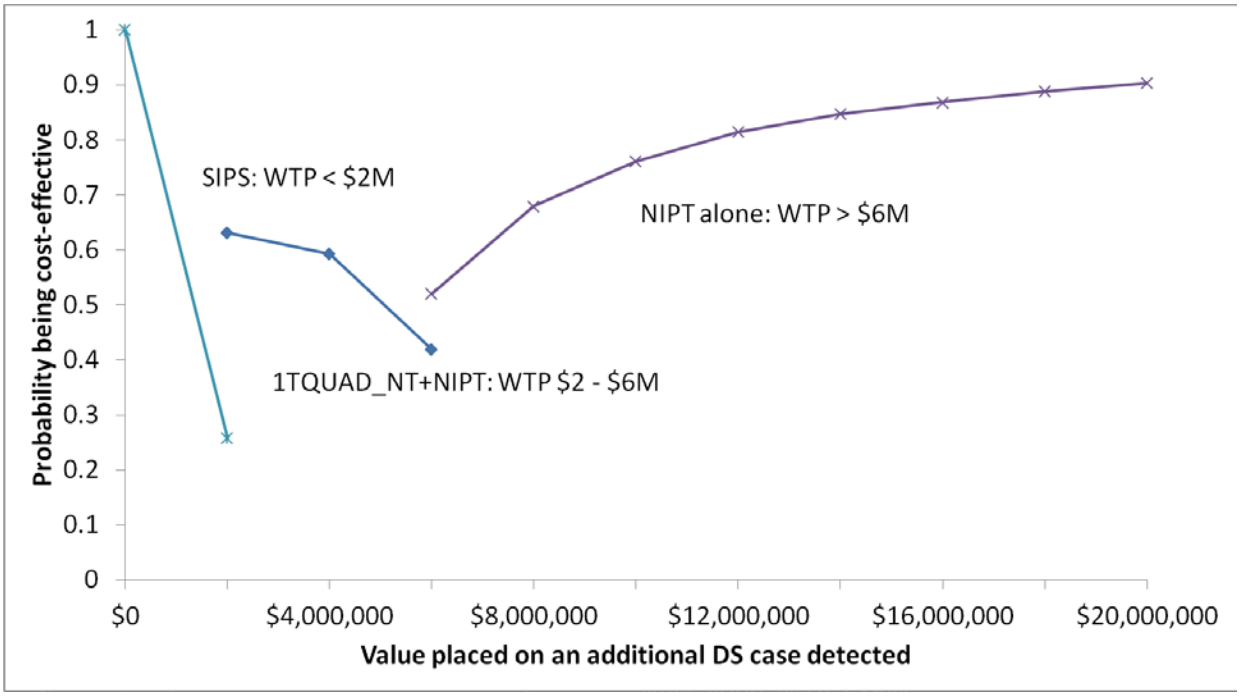


FIGURE E.9: COST-EFFECTIVENESS FRONTIER WITH EFFECTIVENESS DEFINED AS THE NUMBER OF PREGNANCIES CORRECTLY DIAGNOSED (FOR WHEN NT SERVICES ARE AVAILABLE)

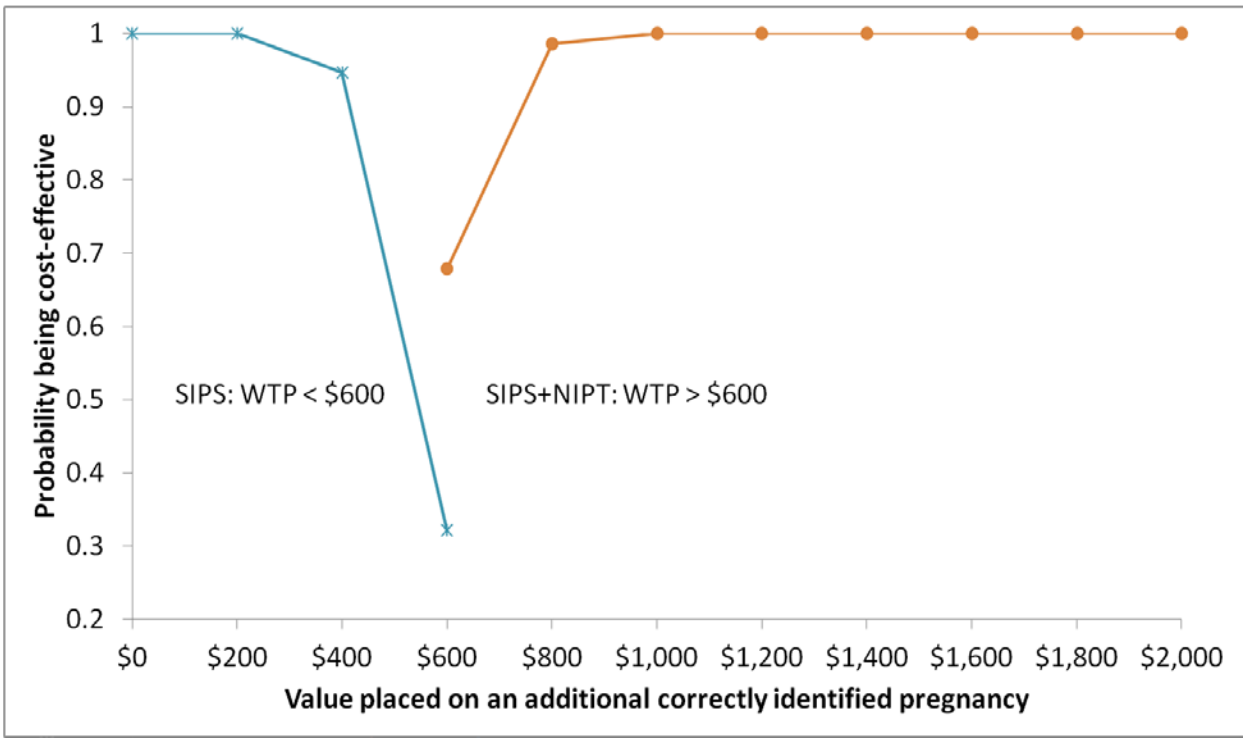


FIGURE E.10: COST-EFFECTIVENESS FRONTIER WITH EFFECTIVENESS DEFINED AS DS CASES DETECTED (FOR WHEN NT SERVICES ARE NOT AVAILABLE)

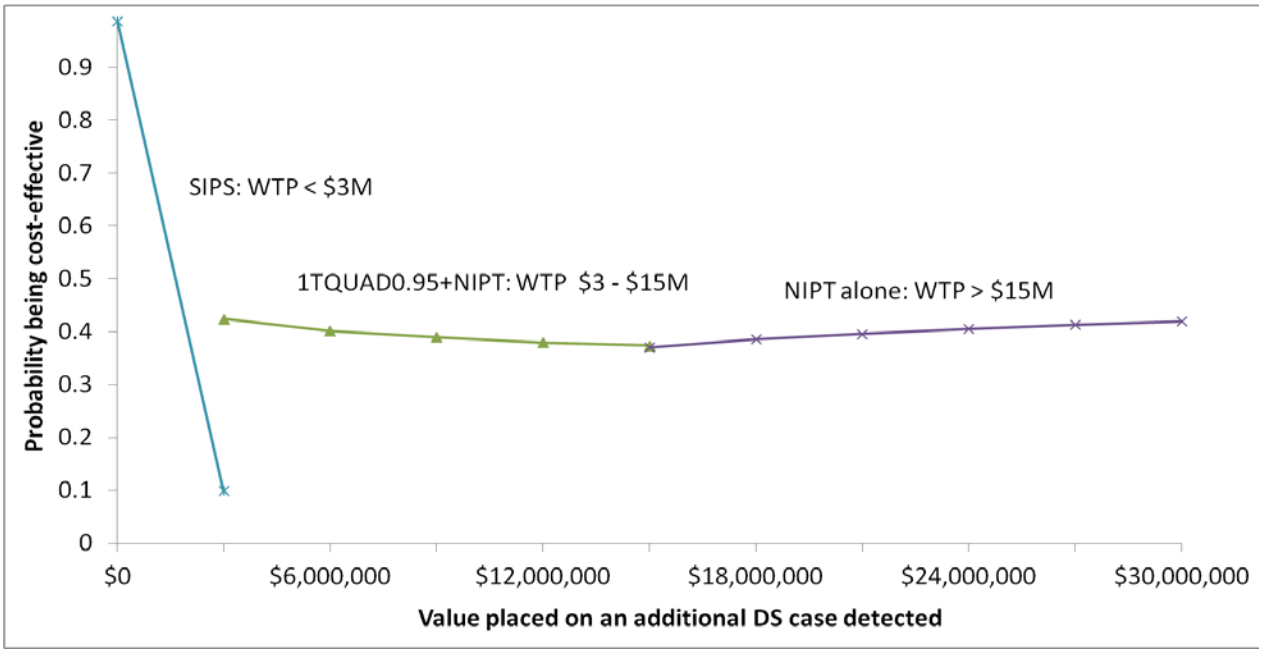
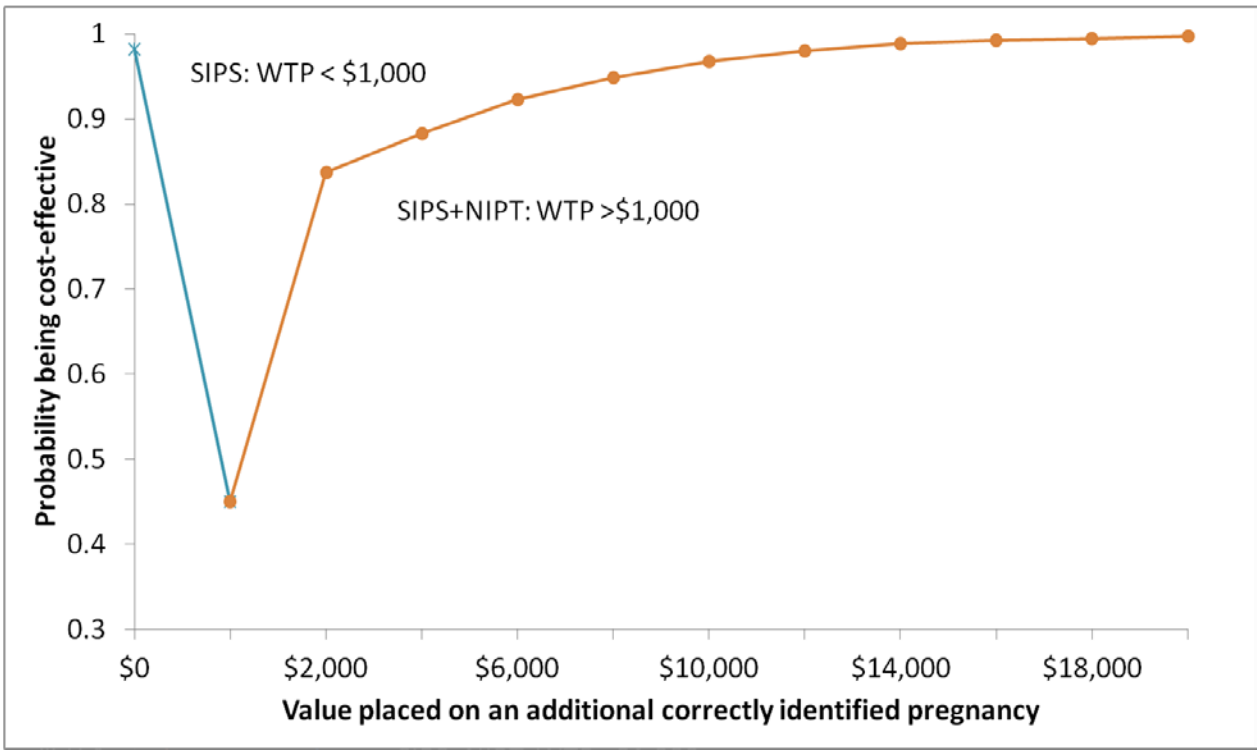


FIGURE E.11: COST-EFFECTIVENESS FRONTIER WITH EFFECTIVENESS DEFINED AS THE NUMBER OF PREGNANCIES CORRECTLY DIAGNOSED (FOR WHEN NT SERVICES ARE NOT AVAILABLE)



Budget impact analysis

TABLE E.6: RESULTS OF BUDGET IMPACT ANALYSIS

Strategy		Unit cost	2010 Screening Volumes (~35% pregnancies)		Expanding to 50% of pregnancies		Expanding to 70% of pregnancies		Expanding to 100% of pregnancies	
			n	Cost ($M)	Extra n*	Incr. cost ($M)	Extra n*	Incr. cost ($M)	Extra n*	Incr. cost ($M)
Status quo in practice but increase volumes	Combined	$530.47	12,543	$ 6.65	5117	$2.71	12,181	$ 6.46	22,777	$12.08
	Quad	$344.97	12,062	$ 4.16	4921	$1.70	11,714	$ 4.04	21,904	$ 7.56
	Total			$10.81		$4.41		$10.50		$19.64
SIPS for most (70%), combined for some (30%)	SIPS	$372.27	17,224	$ 6.41	7027	$2.62	16,727	$ 6.23	31,277	$11.64
	Combined	$530.47	7,382	$ 3.92	3011	$1.60	7169	$ 3.80	13,404	$ 7.11
	Total			$10.33		$4.21		$10.03		$18.75

SIPS+NIPT for most (70%), combined+NIPT for some (30%)	SIPS+NIPT	$391	17,224	$ 6.74	7027	$2.75	16,727	$ 6.54	31,277	$12.23
	Combined+NIPT	$563	7,382	$ 4.15	3011	$1.69	7169	$ 4.03	13,404	$ 7.54
	Total			$10.89		$4.44		$10.57		$19.77
NT Available to 18% of population**	$1TQUAD_{0.85}$+NIPT	$402.14	20,176	$ 8.11	8231	$3.31	19,594	$ 7.88	36,638	$14.73
	1TQUAD_NT+NIPT	$522.11	4,429	$ 2.31	1807	$0.94	4301	$ 2.25	8043	$ 4.20
	Total			$10.43		$4.25		$10.13		$18.93
NT Available to 30% of population	$1TQUAD_{0.85}$+NIPT	$402.14	17,224	$ 6.93	7027	$2.83	16,727	$ 6.73	31,277	$12.58
	1TQUAD_NT+NIPT	$522.11	7,382	$ 3.85	3011	$1.57	7169	$ 3.74	13,404	$ 7.00
	Total			$10.78		$4.40		$10.47		$19.58
NT Available to 50% of population	$1TQUAD_{0.85}$+NIPT	$402.14	12,303	$ 4.95	5019	$2.02	11,948	$ 4.80	22,341	$ 8.98
	1TQUAD_NT+NIPT	$522.11	12,303	$ 6.42	5019	$2.62	11,948	$ 6.24	22,341	$11.66
	Total			$11.37		$4.64		$11.04		$20.65
NT Available to 60% of population	$1TQUAD_{0.85}$+NIPT	$402.14	9,842	$ 3.96	4015	$1.61	9558	$ 3.84	17,872	$ 7.19
	1TQUAD_NT+NIPT	$522.11	14,763	$ 7.71	6023	$3.14	14,337	$ 7.49	26,809	$14.00
	Total			$11.67		$4.76		$11.33		$21.18

* These are estimates for the incremental increase.

** According to data from laboratory services, approximately 18% of pregnancies are screened with Combined testing indicating that NT services are available to at least 18% of the screening population.

Discussion

The objective of the economic analysis was to determine the value for money and budget impact of alternative FASTS options employing 1TQuad and/or NIPT compared to SIPS or Combined, which were the screening options specified in the Alberta Health policy directive of December 12, 2012. The FASTS options available were dependent on the availability of NT services.

When NT services are not available

In areas where NT services are not available, the FASTS options could include SIPS, SIPS+NIPT, $1TQuad_{0.85}$+NIPT, $1TQuad_{0.90}$+NIPT, $1TQuad_{0.95}$+NIPT or NIPT alone. When effectiveness is defined as the number of cases detected or the number of total pregnancies correctly diagnosed, SIPS and SIPS+NIPT are again the most cost-effective options for the same reasons described above.

However, when focusing on the options that provide information in the first trimester, the most cost-effective option is $1TQuad_{0.85}$+NIPT regardless of how effectiveness is defined. Note that when effectiveness is defined as the number of cases detected, NIPT alone could detect more cases at a higher cost but it is inhibited by its high ICER, leaving $1TQuad_{0.85}$+NIPT as the best option. Furthermore, when effectiveness is defined as the total number of pregnancies correctly diagnosed, $1TQuad_{0.85}$+NIPT dominates all other options (that is, it is the least costly and the most effective).

When NT services are available

In areas where NT services are available, the FASTS options could include SIPS, SIPS+NIPT, 1TQuad_NT+NIPT, Combined, Combined+NIPT, or NIPT alone. When effectiveness is defined as the number of cases detected, the results showed that SIPS+NIPT, Combined, and Combined+NIPT were eliminated from further consideration because better efficiency could be

achieved by other options (that is, other options provide better value for money). Of the remaining options, the incremental cost to detect one additional case was $1.2 million between SIPS and 1TQuad_NT+NIPT, and $4.76 million between 1TQuad_NT+NIPT and NIPT alone.

These ICERs not only indicate that additional resources would be required to adopt these options (that is, they are not cost saving or neutral) but, because of their magnitude, the opportunity cost (that is, the value/benefit foregone by not doing instead the next best available use of those resources) would also have to be significantly high to justify their adoption compared to SIPS. Consequently, SIPS is likely the most cost-effective option.

When effectiveness is defined as the total number or pregnancies correctly diagnosed, the cost-effective options include SIPS or SIPS+NIPT. Compared to SIPS, SIPS+NIPT is associated with an ICER of $555, suggesting that the addition of NIPT to SIPS adds value by minimizing the number of FPs that are significant enough that the incremental cost per additional correctly diagnosed pregnancy is $555 (close to being cost neutral per additional benefit). It is therefore likely that the addition of NIPT to SIPS is cost-effective.

However, the disadvantage with SIPS or SIPS+NIPT is that they do not provide information until the second trimester of pregnancy. If the analysis were to focus on only those options that provide information in the first trimester, the most cost-effective option among those listed above is 1TQuad_NT+NIPT, regardless of how effectiveness is defined.[*]

It must also be pointed out that examining options employing NT separately from those that do not systematically ignores the possibility that options that do not employ NT may be cost-effective in areas where NT services are available. Specifically, when examining options that provide information in the first trimester, it does not compare 1TQuad+NIPT at 85%, 90%, or 95% with that of 1TQuad_NT+NIPT. When making this comparison, $1TQuad_{0.85}$+NIPT is the most cost-effective option. The ICER associated with 1TQuad_NT+NIPT is prohibitively high (see Appendix E.C). This suggests that even when the options are limited to those that provide information in the first trimester of pregnancy, adopting options employing NT may not be the best value for money as compared to adopting $1TQuad_{0.85}$+NIPT. From a programmatic point of view, adopting options that do not rely on NT may be advantageous because it would better ensure that services are consistent across the province while ameliorating the capacity issues associated with NT, although it ignores the fact that NT provides other clinical information that may be useful in the management of pregnancy.

Feasibility of NIPT alone

NIPT alone was included as an option because of its potential to become used as a primary screen if its cost per test were to decline over time. If NIPT were cost neutral as compared to the other options, the interpretation of the cost-effectiveness results would focus solely on outcomes. When effectiveness is defined as the number of cases detected, NIPT would be the most cost-effective option because it detects the highest number of cases. NIPT alone would need to be cost neutral as

[*] NIPT alone (when effectiveness is defined as the number of cases detected) and Combined+NIPT (when effectiveness is defined as the total number of pregnancies correctly diagnosed) is potentially cost-effective compared to 1TQuad_NT+NIPT; but it would require that the opportunity cost of their adoption be significantly high.

compared to SIPS or, depending on the importance of receiving information in the first opposed to the second trimester of pregnancy, would need to be cost neutral as compared to 1TQuad_NT+NIPT or 1TQuad$_{0.85}$+NIPT when NT services are not available.

Based on our data and the economic framework used to conduct this analysis, the point at which NIPT is cost neutral in terms of the total average cost per screen is at approximately $98 per test when compared to SIPS,† $216 when compared to 1TQuad_NT+NIPT, and $44 when compared to 1TQuad$_{0.85}$+NIPT. When effectiveness is defined as the total number of pregnancies correctly diagnosed, NIPT alone is never the most cost-effective option even if it were cost neutral to the other options, because it is not associated with correctly identifying the greatest number of pregnancies.

Budget Impact

At existing screening volumes (n = 24,605), implementing the AH directive of a mix of SIPS and Combined would result in a budget impact of saving approximately $500,000. Adding NIPT to SIPS and Combined would add costs of approximately $70,000. Adopting a mix of 1TQuad$_{0.85}$+NIPT and 1TQuad_NT+NIPT, based on NT being available to 18% or 30% of pregnancies, would save approximately $39,000 and $3,000 respectively.

It is important to note that these are underestimates, given that increasing coverage would require capital investments that are not included in the calculations due to unavailability of data. According to the 2012 IHE report on FASTS,[11] in southern Alberta, existing laboratory capacity can conduct up to 70,000 screens per year for first trimester screens, while facilities in northern Alberta are already operating at capacity. Other cost components that are not included in the BIA are program based resources. This includes the cost of administrative and nursing staff to support the management of care for women receiving screening services. These are important cost considerations for screening services, given the time required for activities such as obtaining patient consent, explaining and providing educational materials, and patient coordination through the health system.

Caveats

No model can perfectly capture what is or will be observed in reality, and the findings should be evaluated in light of the following caveats.

1. The test characteristics were derived from modeling studies, and it is uncertain to what extent the test characteristics would potentially change if applied in a real population (see the T-section for further details).
2. The results are founded on the screening and testing options outlined in this report. Although in actual conditions variation will be present in how these tests are used depending on clinical presentation and patient history, the screening/testing options outlined in this

† Manufacturers have suggested that the price of NIPT could be reduced to $595 (personal communication, Dr. Jo-Ann Johnson, December 14, 2013). At a price of $500 per test, the costs of ICER are extremely high and do not alter the interpretation of the findings. See Appendix E.B for details.

report should, to the greatest extent permissible, be adhered to in order to achieve the economic outcomes described.

3. The CEA focused on T21, which ignores any value associated with detecting other abnormalities. However, the relevance of these other conditions is uncertain from the perspective of clinical and health outcomes.
4. Costs associated with additional infrastructure requirements, capital purchases, impact of software selection, and nursing and other staff, including training and education, were not included in the CEA or the BIA, due to lack of data and uncertainty regarding how FASTS screening services are to be provided across the province.
5. The economic analysis adopted a time frame from pregnancy until final diagnosis. Therefore, the analysis does not evaluate the screening options in terms of their impact on abortions, and excludes costs associated with abortions, delivery, and long-term health outcomes of infants having congenital abnormalities.
6. Individuals undergoing screening may not receive any benefit and may be exposed to iatrogenic health risks (for example, unnecessary invasive follow-up procedures resulting from false positive test results). Any emotional harm associated with false positive test results was not considered in the analysis.
7. When effectiveness is defined as the number of correctly identified pregnancies, it assumes that the value/weight of a case detected is equal to that of a non-case detected. Determining the explicit value society places on detecting a case of T21 versus detecting a non-case and resolving the debate about the societal burden associated with T21 is beyond the scope of the economic analysis.

Conclusion

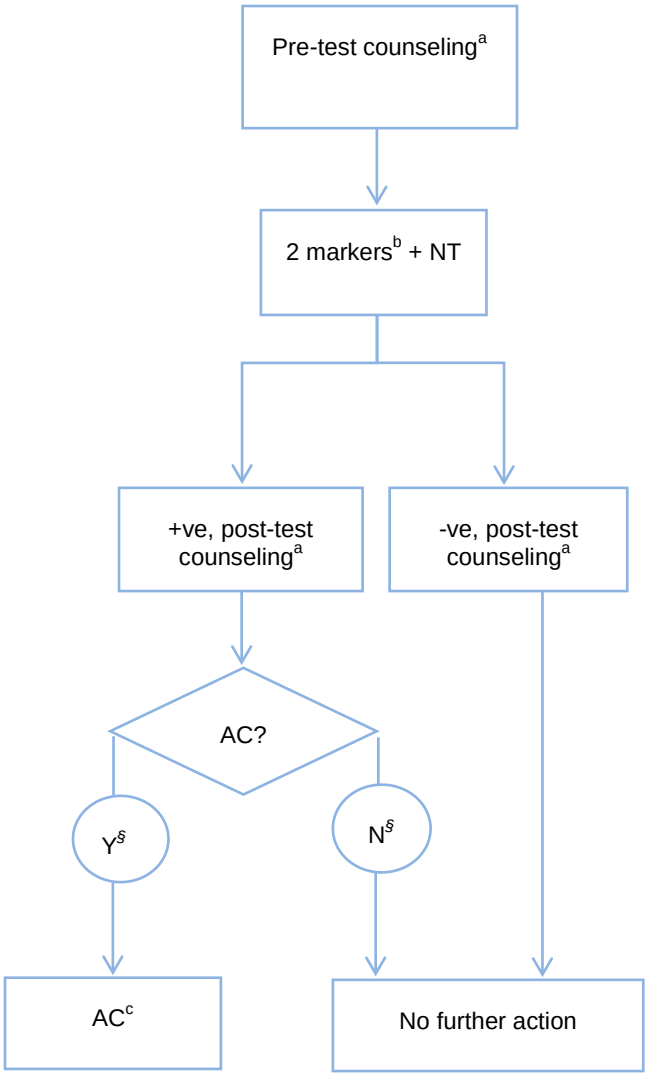
The argument that FASTS screening options should focus on the number of cases detected, and that high ICER associated with detecting additional cases may be justified when compared with the lifetime burden associated with T21, is not supported by the literature because of the potential for misleading conclusions.[1,2,3] Identifying the FASTS option that provides the best balance between costs and improvements in the precision of information for women undergoing screening requires not only careful consideration of the test characteristics and precision of the specific options, but considers these characteristics within the context of baseline risk (that is, incidence) and the resulting impact on the health system in terms of what additional value is achieved for the additional resources invested. The disproportionate increase in the ICER with each successive option reflects the fact that the resources needed to detect the next case increase for every case detected. Therefore, the most cost-effective option is the one that is the most efficient at identifying cases that are suitable for confirmatory testing and non-cases that do not require further testing, particularly at lower rates of incidence. Arguments of efficiency therefore favour a definition of effectiveness that better captures the total value of a screening option, and the focus should therefore be on overall accuracy.

If the testing characteristics used to populate the economic model are valid and reflect what would be observed in an actual screening population (refer to caveat #1 above), when effectiveness is defined as the number of correctly diagnosed pregnancies, SIPS+NIPT is the option that provides the best value for money. If the analysis focuses on the options that provide information in the first

trimester, 1TQuad$_{0.85}$+NIPT is the most cost-effective FASTS option in areas with or without NT services. If NT provides additional benefit to the clinical management of pregnant women beyond that of detecting T21 that justify its use, then the most cost-effective option in areas where NT services are available would be 1TQuad_NT+NIPT. Establishing a systematic, province-wide screening program with increased coverage of pregnancies will have net budget increases to physician, outpatient, and laboratory services.

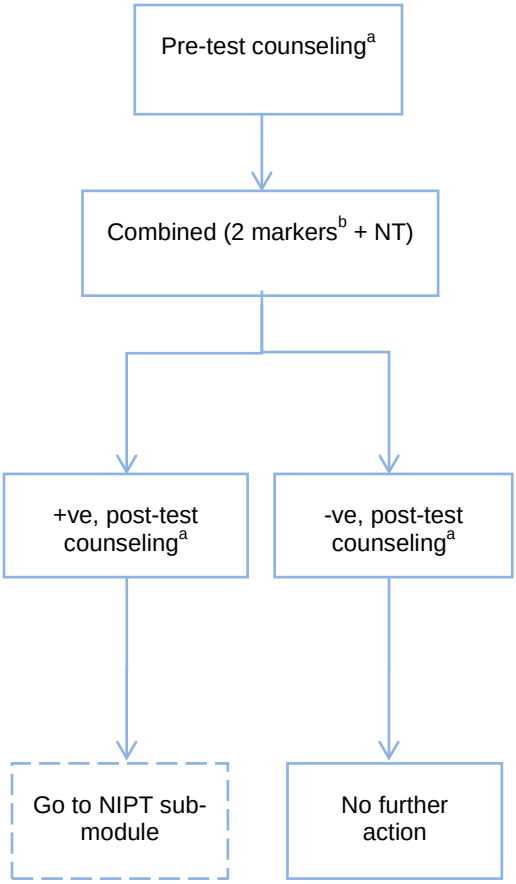
Appendix E.A: Screening Options

1. Combined test (2 markers + NT)



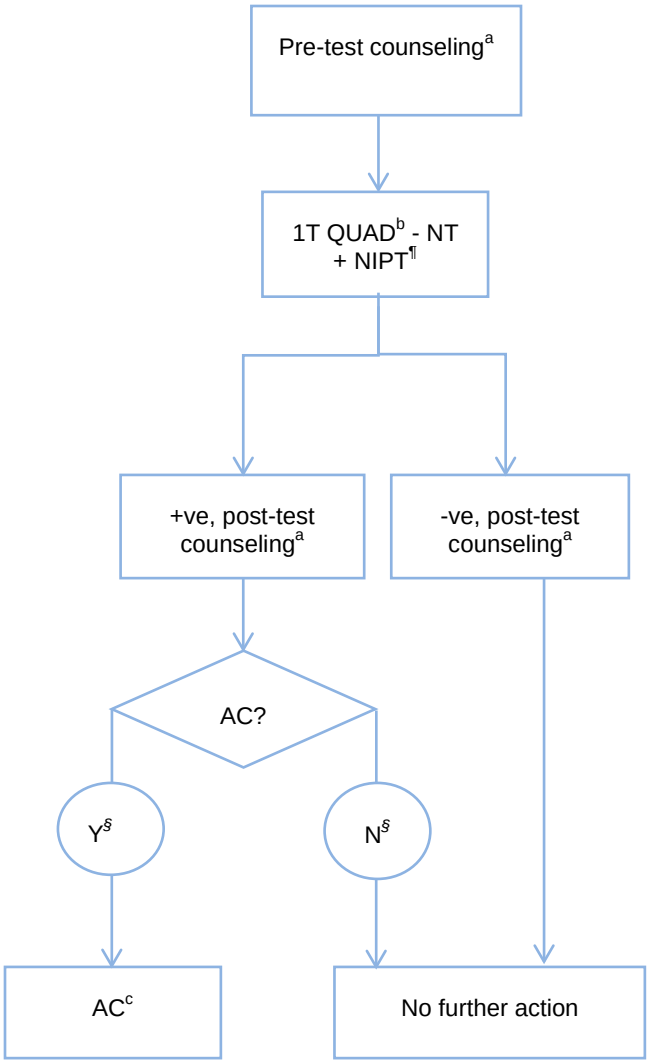
Note:
§: Denotes patient choice
a: Provided by a general practitioner (GP), obstetrician (OB), or midwife
b: Lab services, equipment, labour, software, and supplies
c: GP, inpatient, or outpatient

2. Combined test (2 markers + NT) + NIPT



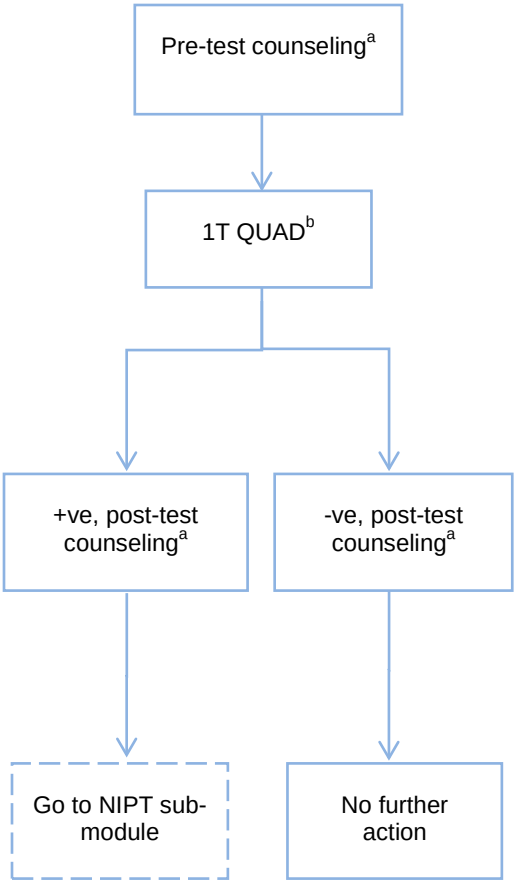
Note:
§: Denotes patient choice
a: Provided by a general practitioner (GP), obstetrician (OB), or midwife
b: Lab services, equipment, labour, software, and supplies
c: GP, inpatient, or outpatient

3. 1TQUAD - NT + NIPT



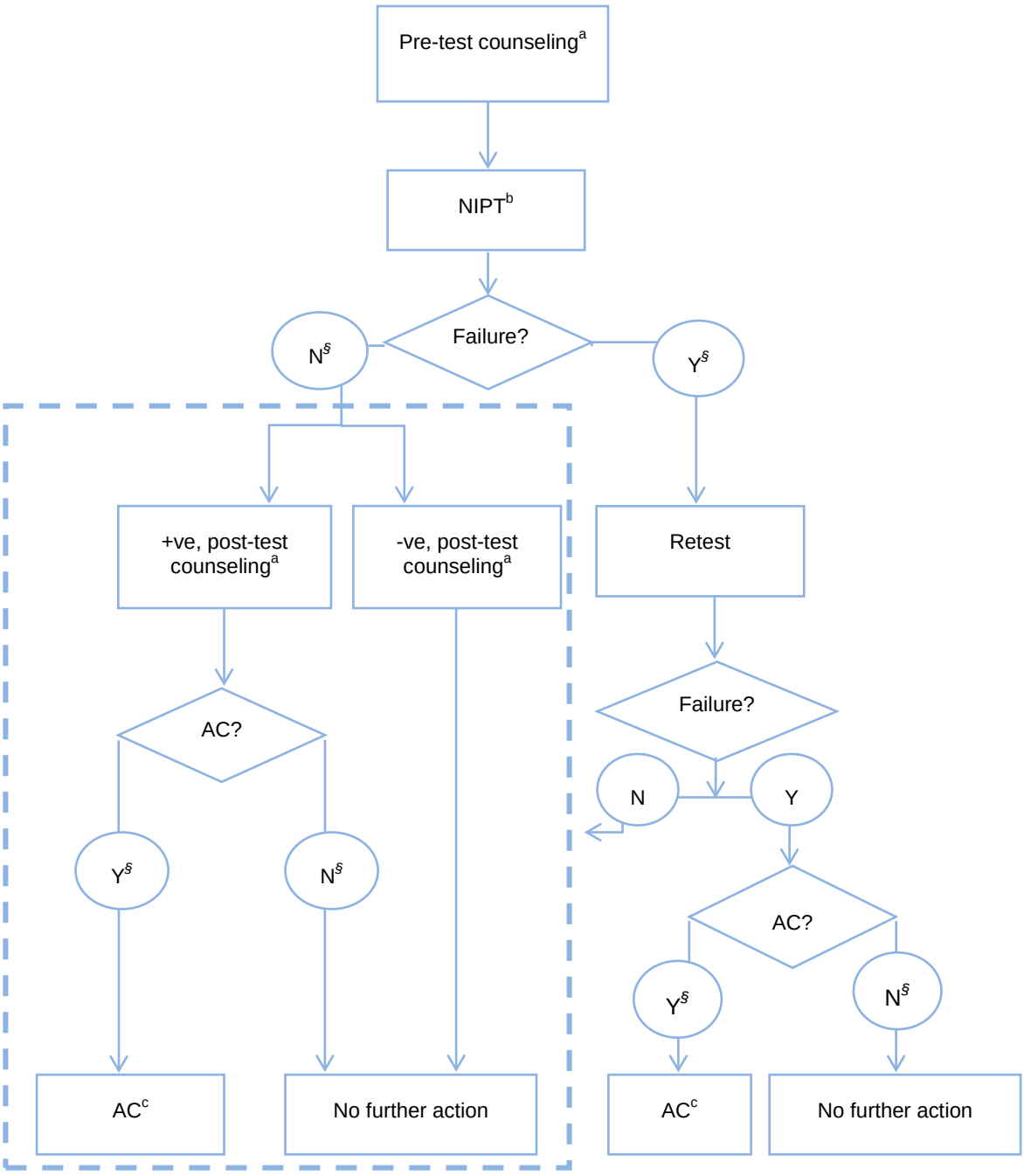
Note:
§: Denotes patient choice
a: Provided by a general practitioner (GP), obstetrician (OB), or midwife
b: Lab services, equipment, labour, software, and supplies
c: GP, inpatient, or outpatient

4. 1TQUAD + NIPT



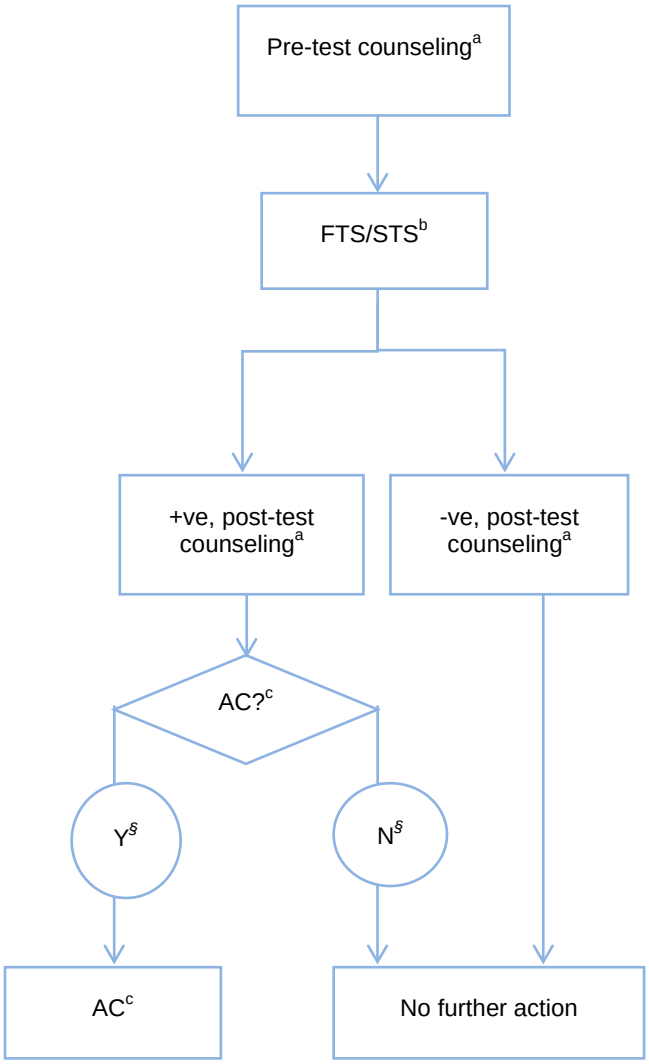
Note:
a: Provided by a general practitioner (GP), obstetrician (OB), or midwife
b: Lab services, equipment, labour, software, and supplies

5. NIPT alone



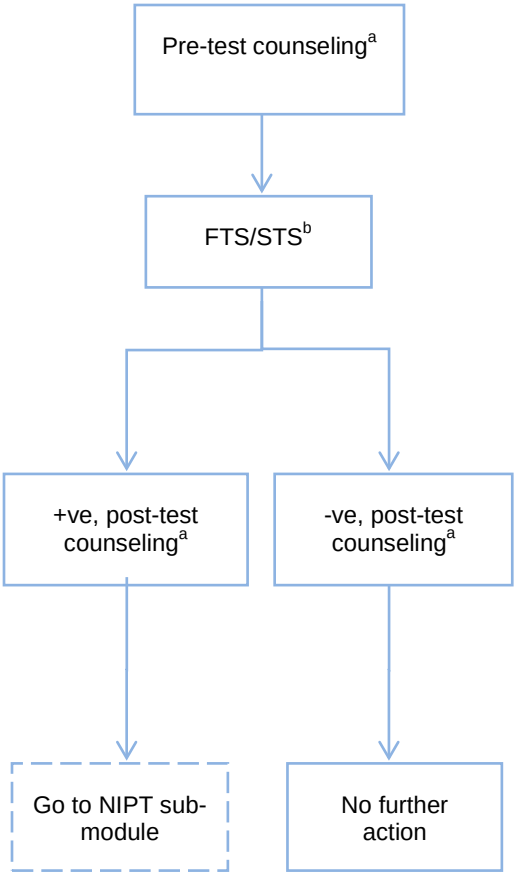
Note:
§: Denotes patient choice
a: Provided by a general practitioner (GP), obstetrician (OB), or midwife
b: Lab services, equipment, labour, software, and supplies
c: GP, inpatient, or outpatient

6. SIPS



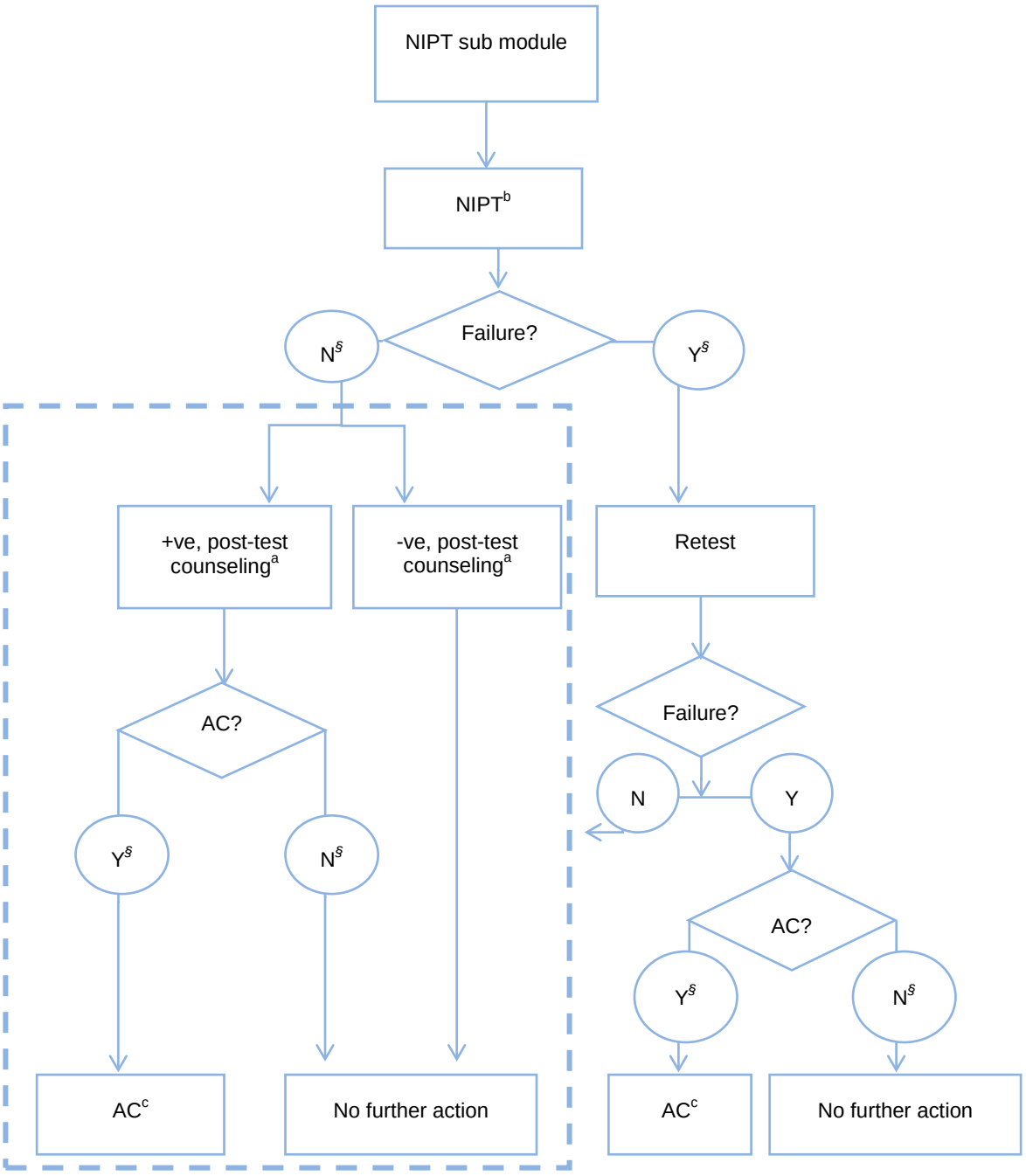
Note:
§: Denotes patient choice
a: Provided by a general practitioner (GP), obstetrician (OB), or midwife
b: Lab services, equipment, labour, software, and supplies
c: GP, inpatient, or outpatient
FTS: first trimester screening
STS: second trimester screening

7. SIPS + NIPT



Note:
a: Provided by a general practitioner (GP), obstetrician (OB), or midwife
b: Lab services, equipment, labour, software, and supplies

8. NIPT sub-module



Note:
§: Denotes patient choice
a: Provided by a general practitioner (GP), obstetrician (OB), or midwife
b: Lab services, equipment, labour, software, and supplies
c: GP, inpatient, or outpatient

Appendix E.B: Results of One-way Sensitivity Analysis by Changing NIPT Cost

TABLE E.B.1: SENSITIVITY ANALYSIS OVER A RANGE OF NIPT COSTS FROM $0 TO $900 WHEN EFFECTIVENESS IS DEFINED AS THE NUMBER OF DS CASES DETECTED AND NT IS AVAILABLE

NIPT cost	Strategy	Cost	TP	ICER	Dominance
$ 0	NIPT alone	$274	137	$0	
$ 0	SIPS+NIPT	$363	120	-$364,801	(Dominated)
$ 0	SIPS	$372	121	-$420,314	(Dominated)
$ 0	1TQUAD - NT + NIPT	$481	129	-$1,804,652	(Dominated)
$ 0	Combined (2 markers + NT) + NIPT	$514	124	-$1,308,211	(Dominated)
$ 0	Combined (2 markers + NT)	$530	125	-$1,478,381	(Dominated)
$ 90	NIPT alone	$364	137	$0	
$ 90	SIPS+NIPT	$366	120	-$8,588	(Dominated)
$ 90	SIPS	$372	121	-$36,097	(Dominated)
$ 90	1TQUAD - NT + NIPT	$486	129	-$1,061,106	(Dominated)
$ 90	Combined (2 markers + NT) + NIPT	$519	124	-$847,461	(Dominated)
$ 90	Combined (2 markers + NT)	$530	125	-$959,966	(Dominated)
$180	SIPS+NIPT	$369	120	$0	
$180	SIPS	$372	121	$335,331	
$180	NIPT alone	$454	137	$348,119	
$180	1TQUAD - NT + NIPT	$490	129	-$317,561	(Dominated)
$180	Combined (2 markers + NT) + NIPT	$525	124	-$386,710	(Dominated)
$180	Combined (2 markers + NT)	$530	125	-$441,552	(Dominated)
$270	SIPS	$372	121	$0	
$270	SIPS+NIPT	$372	120	-$6660	(Dominated)
$270	1TQUAD - NT + NIPT	$495	129	$1,026,648	
$270	Combined (2 markers + NT) + NIPT	$530	124	-$515,192	(Dominated)
$270	Combined (2 markers + NT)	$530	125	-$604,227	(Dominated)
$270	NIPT alone	$544	137	$425,984	
$360	SIPS	$372	121	$0	
$360	SIPS+NIPT	$376	120	-$348,652	(Dominated)
$360	1TQUAD - NT + NIPT	$500	129	$1,065,657	
$360	Combined (2 markers + NT)	$530	125	-$525,013	(Dominated)
$360	Combined (2 markers + NT) + NIPT	$536	124	-$527,902	(Dominated)
$360	NIPT alone	$634	137	$1,169,529	
$450	SIPS	$372	121	$0	
$450	SIPS+NIPT	$379	120	-$690,643	(Dominated)
$450	1TQUAD - NT + NIPT	$504	129	$1,104,667	
$450	Combined (2 markers + NT)	$530	125	-$445,798	(Dominated)
$450	Combined (2 markers + NT) + NIPT	$541	124	-$540,612	(Dominated)

$450	NIPT alone	$724	137	$1,913,075	
$540	SIPS	$372	121	$0	
$540	SIPS+NIPT	$382	120	-$1,032,635	(Dominated)
$540	1TQUAD - NT + NIPT	$509	129	$1,143,676	
$540	Combined (2 markers + NT)	$530	125	-$366,583	(Dominated)
$540	Combined (2 markers + NT) + NIPT	$547	124	-$553,322	(Dominated)
$540	NIPT alone	$814	137	$2,656,620	
$630	SIPS	$372	121	$0	
$630	SIPS+NIPT	$385	120	-$1,374,626	(Dominated)
$630	1TQUAD - NT + NIPT	$514	129	$1,182,685	
$630	Combined (2 markers + NT)	$530	125	-$287,369	(Dominated)
$630	Combined (2 markers + NT) + NIPT	$552	124	-$566,032	(Dominated)
$630	NIPT alone	$904	137	$3,400,165	
$720	SIPS	$372	121	$0	
$720	SIPS+NIPT	$388	120	-$1,716,618	(Dominated)
$720	1TQUAD - NT + NIPT	$518	129	$1,221,694	
$720	Combined (2 markers + NT)	$530	125	-$208,154	(Dominated)
$720	Combined (2 markers + NT) + NIPT	$558	124	-$578,742	(Dominated)
$720	NIPT alone	$994	137	$4,143,710	
$810	SIPS	$372	121	$0	
$810	SIPS+NIPT	$392	120	-$2,058,609	(Dominated)
$810	1TQUAD - NT + NIPT	$523	129	$1,260,703	
$810	Combined (2 markers + NT)	$530	125	-$128,940	(Dominated)
$810	Combined (2 markers + NT) + NIPT	$563	124	-$591,452	(Dominated)
$810	NIPT alone	$1084	137	$4,887,255	
$900	SIPS	$372	121	$0	
$900	SIPS+NIPT	$395	120	-$2,400,601	(Dominated)
$900	1TQUAD - NT + NIPT	$528	129	$1,299,713	
$900	Combined (2 markers + NT)	$530	125	-$49,725	(Dominated)
$900	Combined (2 markers + NT) + NIPT	$569	124	-$604,162	(Dominated)
$900	NIPT alone	$1174	137	$5,630,801	

TABLE E.B.2: SENSITIVITY ANALYSIS OVER A RANGE OF NIPT COSTS FROM $0 TO $900 WHEN EFFECTIVENESS IS DEFINED AS THE NUMBER OF TOTAL PREGNANCIES CORRECTLY IDENTIFIED AND NT IS AVAILABLE

NIPT cost	Strategy	Cost	TPTN	ICER	Dominance
$ 0	NIPT alone	$274	68,220	$0	
$ 0	SIPS+NIPT	$363	69,263	$5,906	
$ 0	SIPS	$372	66,916	-$283	(Dominated)
$ 0	1TQUAD - NT + NIPT	$481	69,230	-$248,191	(Dominated)
$ 0	Combined (2 markers + NT) + NIPT	$514	69,264	$19,485,644	
$ 0	Combined (2 markers + NT)	$530	65,140	-$283	(Dominated)
$ 90	NIPT alone	$364	68,220	$0	
$ 90	SIPS+NIPT	$366	69,263	$139	
$ 90	SIPS	$372	66,916	-$188	(Dominated)
$ 90	1TQUAD - NT + NIPT	$486	69,230	-$251,229	(Dominated)
$ 90	Combined (2 markers + NT) + NIPT	$519	69,264	$19,784,964	
$ 90	Combined (2 markers + NT)	$530	65,140	-$190	(Dominated)
$180	SIPS+NIPT	$369	69,263	$0	
$180	SIPS	$372	66,916	-$93	(Dominated)
$180	NIPT alone	$454	68,220	-$5628	(Dominated)
$180	1TQUAD - NT + NIPT	$490	69,230	-$254,267	(Dominated)
$180	Combined (2 markers + NT) + NIPT	$525	69,264	$20,084,284	
$180	Combined (2 markers + NT)	$530	65,140	-$97	(Dominated)
$270	SIPS	$372	66,916	$0	
$270	SIPS+NIPT	$372	69,263	$2	
$270	1TQUAD - NT + NIPT	$495	69,230	-$257,306	(Dominated)
$270	Combined (2 markers + NT) + NIPT	$530	69,264	$20,383,605	
$270	Combined (2 markers + NT)	$530	65,140	-$4	(Dominated)
$270	NIPT alone	$544	68,220	-$902	(Dominated)
$360	SIPS	$372	66,916	$0	
$360	SIPS+NIPT	$376	69,263	$97	
$360	1TQUAD - NT + NIPT	$500	69,230	-$260,344	(Dominated)
$360	Combined (2 markers + NT)	$530	65,140	-$2,603	(Dominated)
$360	Combined (2 markers + NT) + NIPT	$536	69,264	$20,682,925	
$360	NIPT alone	$634	68,220	-$6,512	(Dominated)
$450	SIPS	$372	66,916	$0	
$450	SIPS+NIPT	$379	69,263	$192	
$450	1TQUAD - NT + NIPT	$504	69,230	-$263,382	(Dominated)
$450	Combined (2 markers + NT)	$530	65,140	-$2,549	(Dominated)
$450	Combined (2 markers + NT) + NIPT	$541	69,264	$20,982,245	
$450	NIPT alone	$724	68,220	-$12,122	(Dominated)
$540	SIPS	$372	66,916	$0	

$540	SIPS+NIPT	$382	69,263	$286	
$630	SIPS	$372	66,916	$0	
$540	1TQUAD - NT + NIPT	$509	69,230	-$266,420	(Dominated)
$540	Combined (2 markers + NT)	$530	65,140	-$2,495	(Dominated)
$540	Combined (2 markers + NT) + NIPT	$547	69,264	$21,281,566	
$540	NIPT alone	$814	68,220	-$17,732	(Dominated)
$630	SIPS+NIPT	$385	69,263	$381	
$630	1TQUAD - NT + NIPT	$514	69,230	-$269,458	(Dominated)
$630	Combined (2 markers + NT)	$530	65,140	-$2441	(Dominated)
$630	Combined (2 markers + NT) + NIPT	$552	69,264	$21,580,886	
$630	NIPT alone	$904	68,220	-$23,342	(Dominated)
$720	SIPS	$372	66,916	$0	
$720	SIPS+NIPT	$388	69,263	$476	
$720	1TQUAD - NT + NIPT	$518	69,230	-$272,496	(Dominated)
$720	Combined (2 markers + NT)	$530	65,140	-$2387	(Dominated)
$720	Combined (2 markers + NT) + NIPT	$558	69,264	$21,880,206	
$720	NIPT alone	$994	68,220	-$28,952	(Dominated)
$810	SIPS	$372	66,916	$0	
$810	SIPS+NIPT	$392	69,263	$571	
$810	1TQUAD - NT + NIPT	$523	69,230	-$275,534	(Dominated)
$810	Combined (2 markers + NT)	$530	65,140	-$2333	(Dominated)
$810	Combined (2 markers + NT) + NIPT	$563	69,264	$22,179,527	
$810	NIPT alone	$1084	68,220	-$34,562	(Dominated)
$900	SIPS	$372	66,916	$0	
$900	SIPS+NIPT	$395	69,263	$666	
$900	1TQUAD - NT + NIPT	$528	69,230	-$278,572	(Dominated)
$900	Combined (2 markers + NT)	$530	65,140	-$2,279	(Dominated)
$900	Combined (2 markers + NT) + NIPT	$569	69,264	$22,478,847	
$900	NIPT alone	$1174	68,220	-$40,172	(Dominated)

TABLE E.B.3: SENSITIVITY ANALYSIS OVER A RANGE OF NIPT COSTS FROM $0 TO $900 WHEN EFFECTIVENESS IS DEFINED AS THE NUMBER OF DS CASES DETECTED AND NT IS NOT AVAILABLE

NIPT cost	Strategy	Cost	TP	ICER	Dominance
$ 0	NIPT alone	$274	137	$0	
$ 0	1TQUAD + NIPT (DR0.85)	$314	117	-$133,775	(Dominated)
$ 0	1TQUAD + NIPT (DR0.9)	$314	123	-$201,954	(Dominated)
$ 0	1TQUAD + NIPT (DR0.95)	$314	130	-$408,839	(Dominated)
$ 0	SIPS+NIPT	$363	120	-$364,801	(Dominated)
$ 0	SIPS	$372	121	-$420,314	(Dominated)
$ 90	1TQUAD + NIPT (DR0.85)	$324	117	$0	
$ 90	1TQUAD + NIPT (DR0.9)	$329	123	$57,165	
$ 90	1TQUAD + NIPT (DR0.95)	$340	130	$104,938	
$ 90	NIPT alone	$364	137	$244,848	
$ 90	SIPS+NIPT	$366	120	-$8,588	(Dominated)
$ 90	SIPS	$372	121	-$36,097	(Dominated)
$180	1TQUAD + NIPT (DR0.85)	$334	117	$0	
$180	1TQUAD + NIPT (DR0.9)	$345	123	$111,733	
$180	1TQUAD + NIPT (DR0.95)	$365	130	$204,904	
$180	SIPS+NIPT	$369	120	-$29,106	(Dominated)
$180	SIPS	$372	121	-$54,412	(Dominated)
$180	NIPT alone	$454	137	$898,534	
$270	1TQUAD + NIPT (DR0.85)	$344	117	$0	
$270	1TQUAD + NIPT (DR0.9)	$360	123	$166,301	
$270	SIPS	$372	121	-$335,451	(Dominated)
$270	SIPS+NIPT	$372	120	-$267,957	(Dominated)
$270	1TQUAD + NIPT (DR0.95)	$390	130	$304,870	
$270	NIPT alone	$544	137	$1,552,220	
$360	1TQUAD + NIPT (DR0.85)	$354	117	$0	
$360	SIPS	$372	121	$297,648	
$360	1TQUAD + NIPT (DR0.9)	$375	123	$88,819	
$360	SIPS+NIPT	$376	120	-$984	(Dominated)
$360	1TQUAD + NIPT (DR0.95)	$416	130	$404,836	
$360	NIPT alone	$634	137	$2,205,907	
$450	1TQUAD + NIPT (DR0.85)	$364	117	$0	
$450	SIPS	$372	121	$137,259	
$450	SIPS+NIPT	$379	120	-$690,643	(Dominated)
$450	1TQUAD + NIPT (DR0.9)	$391	123	$513,089	
$450	1TQUAD + NIPT (DR0.95)	$441	130	$504,802	
$450	NIPT alone	$724	137	$2,859,593	
$540	SIPS	$372	121	$0	
$540	1TQUAD + NIPT (DR0.85)	$374	117	-$23,130	(Dominated)

$540	SIPS+NIPT	$382	120	-$1,032,635	(Dominated)
$540	1TQUAD + NIPT (DR0.9)	$406	123	$937,359	
$540	1TQUAD + NIPT (DR0.95)	$466	130	$604,768	
$540	NIPT alone	$814	137	$3,513,279	
$630	SIPS	$372	121	$0	
$630	1TQUAD + NIPT (DR0.85)	$384	117	-$183,519	(Dominated)
$630	SIPS+NIPT	$385	120	-$1,374,626	(Dominated)
$630	1TQUAD + NIPT (DR0.9)	$422	123	$1,361,629	
$630	1TQUAD + NIPT (DR0.95)	$492	130	$704,734	
$630	NIPT alone	$904	137	$4,166,966	
$720	SIPS	$372	121	$0	
$720	SIPS+NIPT	$388	120	-$1,716,618	(Dominated)
$720	1TQUAD + NIPT (DR0.85)	$394	117	-$343,909	(Dominated)
$720	1TQUAD + NIPT (DR0.9)	$437	123	$1,785,899	
$720	1TQUAD + NIPT (DR0.95)	$517	130	$804,700	
$720	NIPT alone	$994	137	$4,820,652	
$810	SIPS	$372	121	$0	
$810	SIPS+NIPT	$392	120	-$2,058,609	(Dominated)
$810	1TQUAD + NIPT (DR0.85)	$404	117	-$504,298	(Dominated)
$810	1TQUAD + NIPT (DR0.9)	$453	123	$2,210,169	
$810	1TQUAD + NIPT (DR0.95)	$542	130	$904,666	
$810	NIPT alone	$1084	137	$5,474,338	
$900	SIPS	$372	121	$0	
$900	SIPS+NIPT	$395	120	-$2,400,601	(Dominated)
$900	1TQUAD + NIPT (DR0.85)	$414	117	-$664,687	(Dominated)
$900	1TQUAD + NIPT (DR0.9)	$468	123	$2,634,439	
$900	1TQUAD + NIPT (DR0.95)	$567	130	$1,004,632	
$900	NIPT alone	$1174	137	$6,128,025	

TABLE E.B.4: SENSITIVITY ANALYSIS OVER A RANGE OF NIPT COSTS FROM $0 TO $900 WHEN EFFECTIVENESS IS DEFINED AS THE NUMBER OF TOTAL PREGNANCIES CORRECTLY IDENTIFIED AND NT IS NOT AVAILABLE

NIPT cost	Strategy	Cost	TPTN	ICER	Dominance
$ 0	NIPT alone	$274	68,220	$0	
$ 0	1TQUAD + NIPT (DR0.85)	$314	69,161	$2924	
$ 0	1TQUAD + NIPT (DR0.9)	$314	69,112	-$361	(Dominated)
$ 0	1TQUAD + NIPT (DR0.95)	$314	69,016	-$357	(Dominated)
$ 0	SIPS+NIPT	$363	69,263	$33,495	
$ 0	SIPS	$372	66,916	-$283	(Dominated)
$ 90	1TQUAD + NIPT (DR0.85)	$324	69,161	$0	
$ 90	1TQUAD + NIPT (DR0.9)	$329	69,112	-$7,957	(Dominated)
$ 90	1TQUAD + NIPT (DR0.95)	$340	69,016	-$7,650	(Dominated)
$ 90	NIPT alone	$364	68,220	-$2,965	(Dominated)
$ 90	SIPS+NIPT	$366	69,263	$28,850	
$ 90	SIPS	$372	66,916	-$188	(Dominated)
$180	1TQUAD + NIPT (DR0.85)	$334	69,161	$0	
$180	1TQUAD + NIPT (DR0.9)	$345	69,112	-$15,552	(Dominated)
$180	1TQUAD + NIPT (DR0.95)	$365	69,016	-$14,943	(Dominated)
$180	SIPS+NIPT	$369	69,263	$24,204	
$180	SIPS	$372	66,916	-$93	(Dominated)
$180	NIPT alone	$454	68,220	-$5,628	(Dominated)
$270	1TQUAD + NIPT (DR0.85)	$344	69,161	$0	
$270	1TQUAD + NIPT (DR0.9)	$360	69,112	-$23,147	(Dominated)
$270	SIPS	$372	66,916	-$884	(Dominated)
$270	SIPS+NIPT	$372	69,263	$19,559	
$270	1TQUAD + NIPT (DR0.95)	$390	69,016	-$5,021	(Dominated)
$270	NIPT alone	$544	68,220	-$11,395	(Dominated)
$360	1TQUAD + NIPT (DR0.85)	$354	69,161	$0	
$360	SIPS	$372	66,916	-$575	(Dominated)
$360	1TQUAD + NIPT (DR0.9)	$375	69,112	-$30,742	(Dominated)
$360	SIPS+NIPT	$376	69,263	$14,913	
$360	1TQUAD + NIPT (DR0.95)	$416	69,016	-$11,223	(Dominated)
$360	NIPT alone	$634	68,220	-$17,162	(Dominated)
$450	1TQUAD + NIPT (DR0.85)	$364	69,161	$0	
$450	SIPS	$372	66,916	-$265	(Dominated)
$450	SIPS+NIPT	$379	69,263	$10,268	
$450	1TQUAD + NIPT (DR0.9)	$391	69,112	-$5587	(Dominated)
$450	1TQUAD + NIPT (DR0.95)	$441	69,016	-$17,426	(Dominated)
$540	SIPS	$372	66,916	$0	
$450	NIPT alone	$724	68,220	-$22,929	(Dominated)

$540	1TQUAD + NIPT (DR0.85)	$374	69,161	$45	
$540	SIPS+NIPT	$382	69,263	$5622	
$540	1TQUAD + NIPT (DR0.9)	$406	69,112	-$11,195	(Dominated)
$540	1TQUAD + NIPT (DR0.95)	$466	69,016	-$23,628	(Dominated)
$540	NIPT alone	$814	68,220	-$28,696	(Dominated)
$630	SIPS	$372	66,916	$0	
$630	1TQUAD + NIPT (DR0.85)	$384	69,161	$354	
$630	SIPS+NIPT	$385	69,263	$977	
$630	1TQUAD + NIPT (DR0.9)	$422	69,112	-$16,802	(Dominated)
$630	1TQUAD + NIPT (DR0.95)	$492	69,016	-$29,831	(Dominated)
$630	NIPT alone	$904	68,220	-$34,463	(Dominated)
$720	SIPS	$372	66,916	$0	
$720	SIPS+NIPT	$388	69,263	$476	
$720	1TQUAD + NIPT (DR0.85)	$394	69,161	-$3668	(Dominated)
$720	1TQUAD + NIPT (DR0.9)	$437	69,112	-$22,410	(Dominated)
$720	1TQUAD + NIPT (DR0.95)	$517	69,016	-$36,033	(Dominated)
$720	NIPT alone	$994	68,220	-$40,230	(Dominated)
$810	SIPS	$372	66,916	$0	
$810	SIPS+NIPT	$392	69,263	$571	
$810	1TQUAD + NIPT (DR0.85)	$404	69,161	-$8,314	(Dominated)
$810	1TQUAD + NIPT (DR0.9)	$453	69,112	-$28,018	(Dominated)
$810	1TQUAD + NIPT (DR0.95)	$542	69,016	-$42,235	(Dominated)
$810	NIPT alone	$1,084	68,220	-$45,997	(Dominated)
$900	SIPS	$372	66,916	$0	
$900	SIPS+NIPT	$395	69,263	$666	
$900	1TQUAD + NIPT (DR0.85)	$414	69,161	-$12,959	(Dominated)
$900	1TQUAD + NIPT (DR0.9)	$468	69,112	-$33,625	(Dominated)
$900	1TQUAD + NIPT (DR0.95)	$567	69,016	-$48,438	(Dominated)
$900	NIPT alone	$1,174	68,220	-$51,764	(Dominated)

Appendix E.C: Cost-Effectiveness of all FASTS Options

FIGURE E.C.1: COST-EFFECTIVENESS OF FASTS OPTIONS WHEN FOCUSING ON CASES DETECTED

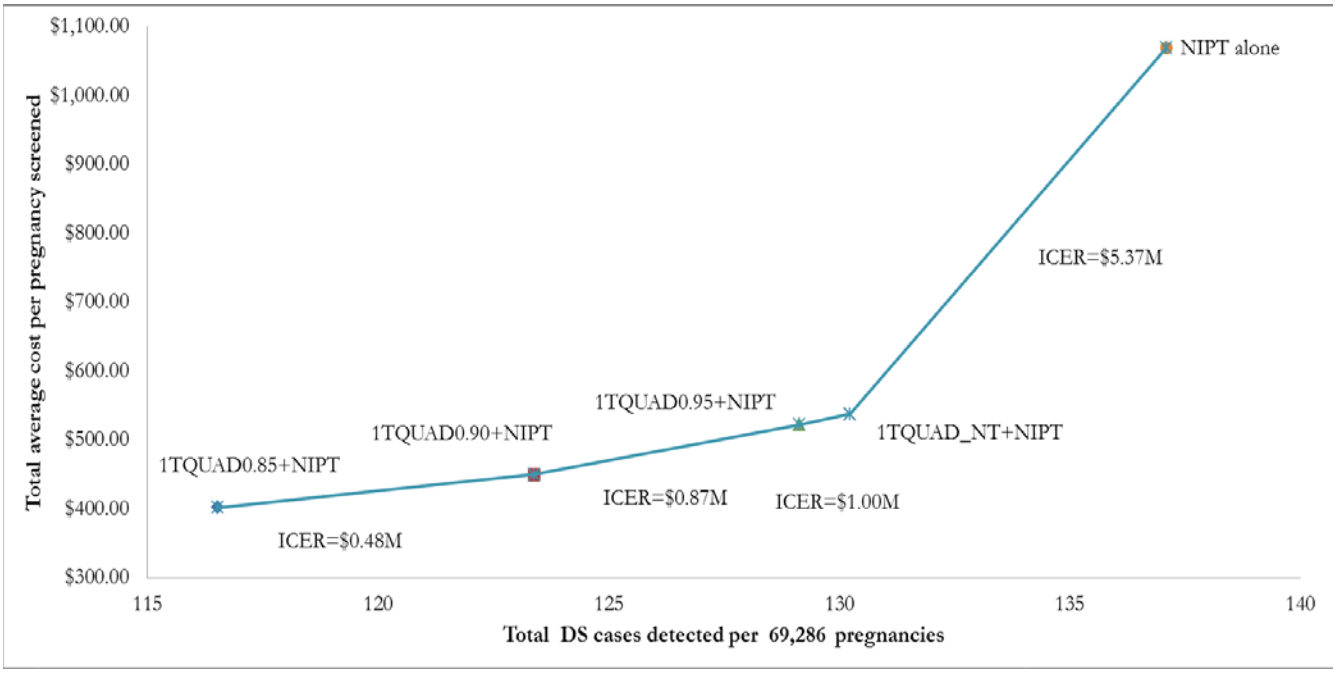
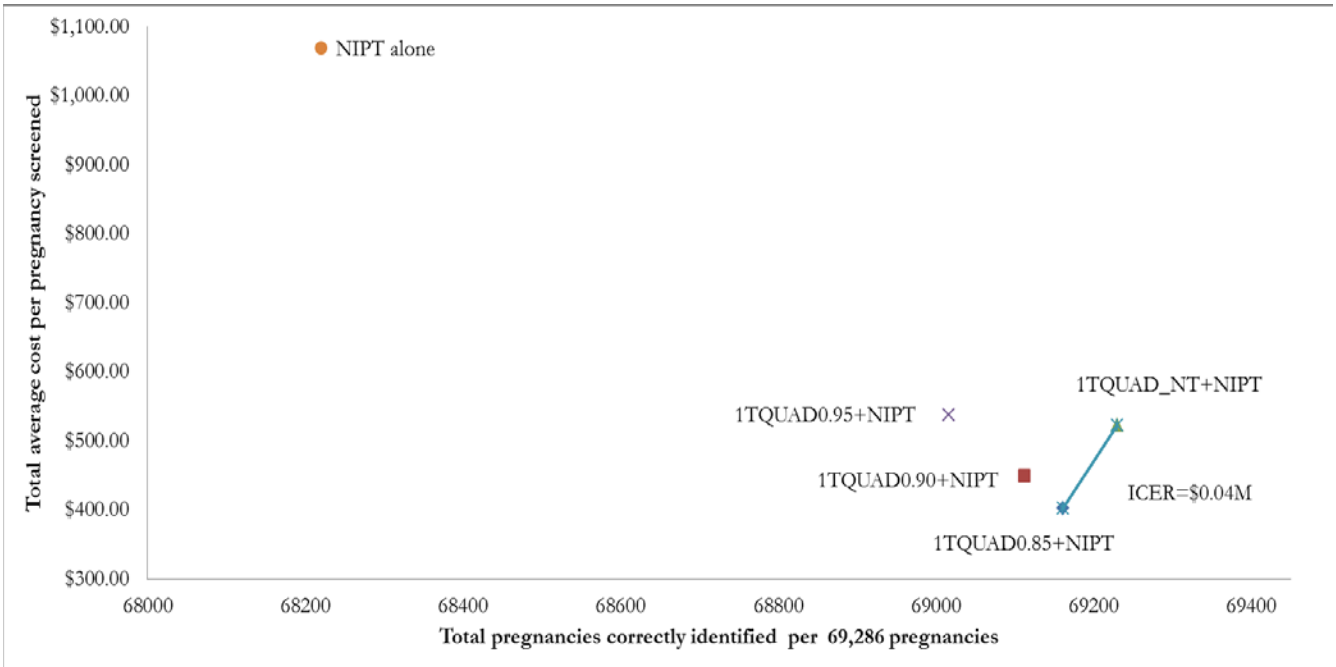


FIGURE E.C.2: COST-EFFECTIVENESS OF FASTS OPTIONS WHEN FOCUSING ON TOTAL PREGNANCIES CORRECTLY DIAGNOSED



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Author Contribution Statements

Mr. Ken Bond conducted the study conception, design, literature selection, quality assessment, and data extraction, analysis and interpretation of the technology effects and effectiveness section.

Ms. Christa Harstall provided critical comment on the design, literature selection, quality assessment, and data extraction, analysis and interpretation of the technology effects and effectiveness section.

Dr. Charles Yan contributed to the study conception, design, data analysis and interpretation of the economic analysis section

Dr. Anderson Chuck contributed to the study conception, design, data analysis and interpretation of the economic analysis section and was the project lead of the TE review.

Ms. Dagmara Chojecki contributed by developing and executing the literature search for the TE review.

This report examines the safety, screening accuracy, therapeutic efficacy, patient outcomes and cost effectiveness of first trimester Quad (1T-Quad) +/- NT and NIPT screening for fetal trisomies.

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