Canadian Agency for Drugs and Technologies in Health

RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

TITLE: Non-invasive Prenatal Testing: A Review of the Cost Effectiveness and Guidelines

DATE: 10 February 2014

CONTEXT AND POLICY ISSUES

Frequency of occurrence of fetal chromosomal abnormalities is approximately 1 in 160 live births.[1] The majority of these abnormalities are aneuploidy.[1] Aneuploidy is a type of chromosomal abnormality where the number of chromosomes present is abnormal. Trisomy involves one extra chromosome (i.e. three copies of one chromosome). Such abnormalities include Down syndrome (DS) - an extra chromosome 21 (trisomy 21, T21), Edwards syndrome - an extra chromosome 18 (trisomy 18, T18), and Patau syndrome – an extra chromosome 13 (trisomy 13, T13).[2,3]

Prenatal fetal testing and assessment can be undertaken using invasive and non-invasive methods. There are several prenatal screening strategies for determining risk of fetal chromosomal abnormalities. Conventional screening strategies are based on biochemical assays of maternal blood and ultrasound measurements.[4] These screening tests are non-invasive and the false positive rate is about 5% and failure to detect abnormalities is up to 20% in case of T21.[5] Invasive methods include amniocentesis and chorionic villus sampling (CVS). Amniocentesis involves obtaining a small amount of amniotic fluid, which contains fetal tissues, from the amniotic sac surrounding a developing fetus and examining the fetal DNA for genetic abnormalities. CVS involves sampling of the chorionic villus (placental tissue) and testing it for chromosomal abnormalities. These invasive methods have a small but definite risk of fetal and maternal complications such as fetal injury and miscarriage.[6] These invasive methods have greater sensitivity and low false positive rates and are considered the gold standard in prenatal diagnosis.[6]

Recent advances in genomic sequencing and bioinformatics have led to development of noninvasive detection methods with detection rates approaching those obtained with amniocentesis and CVS.[6] Recently, a novel prenatal testing method has become available. This method, known as non-invasive prenatal testing (NIPT), is a molecular approach for assessing fetal aneuploidy using cell-free fetal deoxyribonucleic acid (cffDNA) from the plasma of pregnant

women.[2,6] NIPT has a false positive rate of about 0.2% and detection rate of about 98% for Down syndrome.[7] NIPT has been used for assessing abnormalities such as trisomy 21, trisomy 18, and trisomy 13.[2,3] Approximately 10% to 15% of the cell free deoxyribonucleic acid (DNA) in maternal blood comprises of cffDNA.[8] The half-life of cffDNA is short and clears from maternal circulation soon after delivery.[2,8] Hence, there is no risk of fetal DNA persisting from one pregnancy to the next and confounding test results.[2,9] The cost of NIPT ranges from US$800 to US$2000 in the USA and from US$500 to US$1500 elsewhere.[2] A Canadian economic study[10] reported a cost range of C$600 to C$800 for NIPT. Among other factors, cost implications for introducing this new technology in clinical practice will need to be considered. At present there is some uncertainty around the incorporation of NIPT into current strategies for prenatal screening and diagnosis.

The purpose of this report is to provide information on the cost-effectiveness of non-invasive pre-natal testing and to describe evidence-based guidelines for its use.

RESEARCH QUESTIONS

1. What is the cost effectiveness of non-invasive prenatal testing?

2. What are the evidence-based guidelines regarding the use of non-invasive prenatal testing?

KEY FINDINGS

When current prenatal testing programs were compared with alternate programs incorporating NIPT, program costs were increased in three studies and decreased in one study. Considering these discrepancies, results need to be interpreted with caution. At the present time, universal screening with NIPT appears to increase costs substantially and is unlikely to be feasible. However, use of NIPT in contingent screening, where only a certain proportion of pregnant women determined by the degree of risk receive NIPT, may be feasible.

One guideline recommended the use of NIPT as an option for women at high risk in lieu of amniocentesis, and in case of a positive NIPT result, that no decision should be made without confirmatory invasive diagnostic testing.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 1), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between Jan 1, 2009 and Jan 14, 2014.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications, selected potentially relevant articles for retrieval of full-text publications for further investigation and evaluated the full-text publications for final selection, according to the criteria listed in Table 1.

Table 1: Selection Criteria

Population	Pregnant women
Intervention	Screening strategies including non-invasive prenatal testing (NIPT)
Comparator	Screening strategies without NIPT (e.g. aminiocentesis)
Outcomes	Guidelines and recommendations Cost effectiveness
Study Designs	Health technology assessment (HTA), systematic review (SR) and meta-analysis (MA), cost-effectiveness study and evidence based guideline

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria in Table 1, if they were published prior to 2009.

Critical Appraisal of Individual Studies

Critical appraisal of a study was conducted based on an assessment tool appropriate for the particular study design. The checklist of Drummond et al.[11] was used for economic studies and the AGREE checklist[12] for guidelines.

For the critical appraisal, a numeric score was not calculated. Instead, the strength and limitations of the study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 260 citations. Upon screening titles and abstracts, 232 articles were excluded and 28 potentially relevant articles were selected for full-text review. One potentially relevant article was identified from the grey literature. Of these 29 articles, 24 did not satisfy the inclusion criteria and were excluded and five reports were selected. These five reports comprised four economic studies and one evidence-based guideline. No relevant health technology assessment was identified. Details of the study selection process are outlined in Appendix 1.

Summary of Study Characteristics

Characteristics of the included cost-effectiveness studies and guideline are summarized below and details are provided in Appendix 2 and 3. Descriptions of the various strategies such as

combined test, integrated test, quadruple test and contingent screening are presented in Appendix 2.

Cost-effectiveness studies

Four[5,10,13,14] relevant economic studies were identified. Three[5,10,13] were cost effectiveness studies and one[14] was a cost consequence study. One study[10] was published in 2014 from Canada, two studies[5,14] were published in 2013 from the USA, and one study[13] was published in 2013 from Australia. All the studies compared various strategies using conventional methods with those incorporating cffDNA testing. One study[13] compared two strategies, two studies[5,14] compared three strategies and one study[10] compared eight strategies. All studies were from a payer perspective. The time period examined was five years in one study[5], two years in one study,[13] one year in one study[10] and not reported in one study.[14] All the studies conducted their analyses with respect to the detection of Down syndrome pregnancies

Guidelines

One evidence-based guideline[15] with recommendations on the use of NIPT was identified. It was published in 2013 by the Society of Obstetricians and Gynecologists of Canada (SOGC). It provided guidance on non-invasive prenatal detection of Down syndrome, Trisomy 18 and Trisomy 13

Summary of Critical Appraisal

Strengths and limitations of the studies and guideline are summarized below and details are provided in Appendix 4.

Cost-effectiveness studies

Four[5,10,13,14] cost-effectiveness studies were identified. The objectives, study perspective and the strategies compared were stated in all four studies. The time horizon was provided in three studies, and was appropriate for the outcomes measured.[5,10,13] Sensitivity analyses were conducted in three studies.[5,13,14] Clinical data were obtained from meta-analyses in one study,[14] from databases and published reports in two studies,[10,13] and from published reports in one study.[5] All studies were based on several assumptions. It is difficult to know definitively how closely the assumptions reflect real world scenarios as some parameters (e.g. uptake of NIPT) can be quite variable. In all four studies only Down syndrome was considered in the analyses and other abnormalities such as trisomy 13 and 18 which could be detected by NIPT were not considered. Other abnormalities which cannot be detected by NIPT but would be diagnosed through traditional karyotyping were also not considered.

Guidelines

One evidence-based guideline[15] with recommendations on the use of NIPT was identified. The committee members comprised of individuals with expertise in relevant areas such as obstetrics and gynecology and medical genetics and disclosure statements were received from them. The scope was stated and details of the literature search were provided. Evidence on which the guideline was based was derived from studies identified through a systematic literature search. Patient input, economic implications or organizational barriers to implementation were not discussed.

Summary of Findings

The overall findings from the economic studies and guideline are summarized below and details are available in Appendices 5 and 6.

What is the cost effectiveness of non-invasive prenatal testing (NIPT)?

Four[5,10,13,14] relevant cost-effectiveness studies were identified.

One Canadian study[10] investigated the performance and cost of incorporating NIPT in a publicly funded prenatal testing program. It examined eight strategies, two strategies were current programs that did not include NIPT and six strategies were programs that included NIPT. The number of invasive procedures required was decreased with programs incorporating NIPT compared to current programs not including NIPT. The total program costs varied between C$17,353,789 and C$17,580,080 with the current programs; varied between C$ 17,353,081 and C$21,372,742 with the contingent programs which included NIPT and was C$85,146,250 for the program having primary NIPT as a replacement for the current program. The Down syndrome cases detected prenatally were 154 with the current programs, ranged between 253 and 337 with the contingent programs which included NIPT and 297 for the program having primary NIPT as replacement for the current program. The costs per prenatally diagnosed pregnancy with Down syndrome varied between C$112,919 and C$114,391 with the current programs; between C$63,383 and C$71,474 with the contingent programs which included NIPT and C$286,428 for the program having primary NIPT as replacement for the current program.

One US study[14] investigated the costs of avoiding a birth with Down syndrome if NIPT was to replace conventional screening (combined or quadruple) in case of universal screening or contingent screening. For universal screening using NIPT, the marginal cost per Down syndrome birth avoided replacing the combined test with NIPT was US$ 8,050,000 if NIPT cost US$2000 and US$1,420,000 if NIPT cost US$500. For universal screening using NIPT, the marginal cost per Down syndrome birth avoided replacing the quadruple test with NIPT was US$ 4,010,000 if NIPT cost US$2000 and US$797,000 if NIPT cost US$500. The marginal cost was estimated as the difference in total cost between strategies divided by the difference in detection rates. The above numbers were calculated assuming the cost of invasive testing (CVS/ amniocentesis) to be US$1000. For contingent screening (assuming 10% needing NIPT), the marginal cost per Down syndrome birth avoided replacing the combined test with NIPT was US$1,580,000 if NIPT cost US$2000 and US$189,000 if NIPT cost US$500. For contingent screening (assuming 20% needing NIPT), the marginal cost per Down syndrome birth avoided replacing the combined test with NIPT was US$2,290,000 if NIPT cost US$2000 and US$436,000 if NIPT cost US$500. A more restrictive approach for use of NIPT is the case of NIPT replacing invasive prenatal diagnosis in women who have positive conventional screening tests and would have been offered CVS or amniocentesis. In such cases, the average cost per Down syndrome birth avoided was US$201,000 if NIPT cost US$2000 and US$155,000 if NIPT cost US$500 when the positive test results were obtained using the combined test. Also, the average cost per Down syndrome birth avoided was US$194,000 if NIPT cost US$2000 and US$139,000 if NIPT cost US$500 when the positive test results were obtained using the quadruple test

One US study[5] examined the cost-effectiveness of conventional screening using either first trimester combined (FTS) or integrated (INT) screening versus NIPT with NIPT being used only

for high-risk pregnancies. A theoretical cohort of 4,000,000 pregnant women was considered. There were fewer invasive procedures required, greater number of Down syndrome cases detected and fewer euploid fetal losses when NIPT was used in comparison to FTS or INT. The screening costs were US$3,785,688,398; US$3,919,378,508; and US$3,402,844,207 for FTS, INT and NIPT screening strategies respectively. The costs per Down syndrome pregnancy detected were US$1,125,314; US$1,042,417; and US$705,528 for FTS, INT and NIPT screening strategies respectively. The screening costs per pregnant woman were US$946.42; US$979.84; and US$850.71 for FTS, INT and NIPT respectively.

One Australian study[13] compared the cost-effectiveness of the current practice of first trimester testing (FTS) with an alternate model of NIPT for high risk patients following FTS (FTS/NIPT). There were fewer invasive diagnostic tests and procedure related miscarriages with the alternate model with FTS/NIPT compared with the current practice with FTS. The total costs for testing were AUD$3,565,542 and AUD$3,911,278 with FTS and FTS/NIPT respectively. The costs per Down syndrome case confirmed were AUD$51,372 and AUD$56,360 respectively.

What are the evidence-based guidelines regarding the use of non-invasive pre-natal testing (NIPT)?

The SOGC guideline[15] stated that use of NIPT using cffDNA should be an option available for women at high risk in lieu of amniocentesis and that in case of a positive NIPT result, no decision should be made without confirmatory invasive diagnostic testing.

Details on the grading of recommendations are provided in Appendix 3 and detailed recommendations statements are provided in Appendix 6.

Limitations

The economic studies are based on several assumptions. Assumptions made may not accurately reflect uptake, provider and patient attitudes and preferences, hence this could impact costs included in the analyses

There is variation in assumptions, cost, and protocols included in the economic studies hence comparison between studies is difficult. This may also contribute to inconsistencies in results obtained from the various studies, hence results need to be interpreted with caution.

All the studies investigated cost-effectiveness or cost-consequence considering only detection of Down syndrome and other chromosomal abnormalities were not considered.

One evidence-based guideline[15] was identified. The report was termed as a “Committee Opinion”, however a systematic approach appears to have been taken to identify the evidence.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

When current prenatal testing programs were compared with alternate programs incorporating NIPT, program costs were increased in three studies and decreased in one study. In the light of these discrepancies, results need to be interpreted with caution. Considering that less invasive procedures were required when NIPT was included in the prenatal program, NIPT has the

potential of improving the pregnant women's experience of prenatal testing. More cases of Down syndrome were detected when NIPT was incorporated in the programs compared to the current programs. At the present time, universal screening with NIPT appears to increase costs substantially and is unlikely to be feasible. However, use of NIPT in contingent screening, where only a certain proportion of pregnant women determined by the degree of risk receive NIPT, may be feasible.

One guideline[15] stated that use of NIPT using cffDNA should be an option available for women at high risk in lieu of amniocentesis and that in case of a positive NIPT result, no decision should be made without confirmatory invasive diagnostic testing. This finding is in agreement with two reports,[16,17] not included here as the methodology used in developing the recommendations was unclear, which provided similar guidance as the SOGC guidelines. One report[16] was from the International Society for Prenatal Diagnosis (ISPD) and another report[17] was from American College of Obstetricians and Gynecologists (ACOG) Committee on Genetics and the Society for Maternal-Fetal Medicine (SMFM) Publications Committee.

Several factors may need to be considered if NIPT is incorporated into the current screening and diagnosis practice. Social and ethical issues may need to be considered. While the increased fetal information available with NIPT may provide greater reassurance, it may also cause increased anxiety or generate unjust outcomes surrounding fetal selection and elective abortion.

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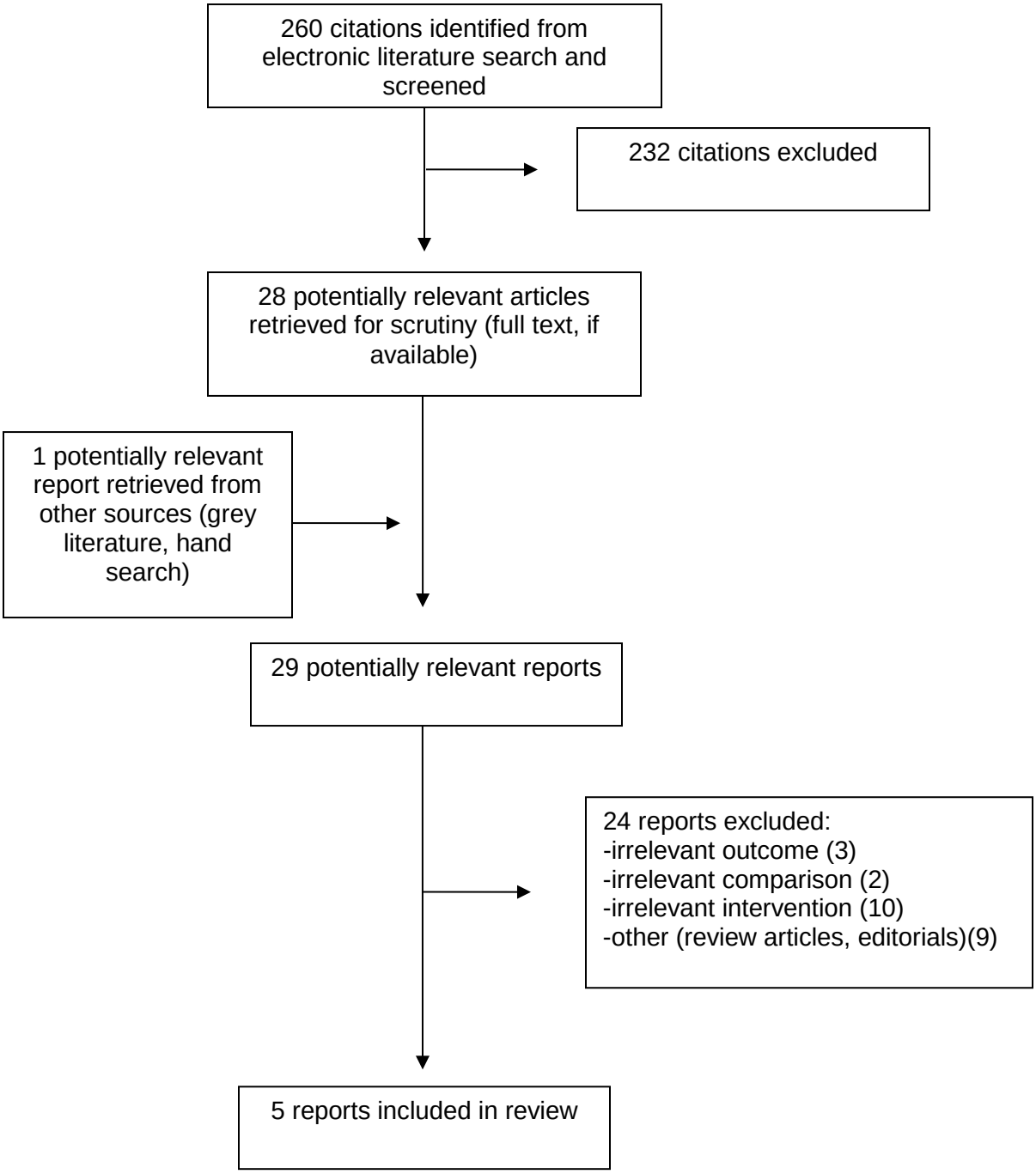
ABBREVIATIONS

ACOG	American College of Obstetricians and Gynecologists
cfDNA	cell free DNA
cffDNA	cell free fetal DNA
CVS	chorionic villus sampling
DNA	deoxyribonucleic acid
DS	Down syndrome
FTS	first trimester screening
INT	integrated screening
ISPD	International Society for Prenatal Diagnosis,
NIPT	non-invasive prenatal testing
NA	not applicable
NR	not reported
NT	nuchal translucency
SMFM	Society for Maternal-Fetal Medicine
SOGC	Society of Obstetricians and Gynecologists of Canada
T21	Trisomy 21 (Down syndrome)

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Studies

First Author, Publication Year, Country	Study Design	Patient Characteristics	Comparison	Outcomes
Economic studies				
Okun,[10] 2014, Canada	Cost-effectiveness analysis Public health sector perspective Time period: 1 years	Pregnant women (Number of pregnancies = 144,570)	Eight strategies compared: "(1) the current program (no cffDNA), (2) the current program with First Trimester Screening (FTS) as the NT-based primary screen (no cffDNA), (3) a program substituting current screening with primary cffDNA, (4) contingent cffDNA with current FTS performance, (5) contingent cffDNA at a fixed price to result in overall cost neutrality,(6) contingent cffDNA with an improved detection rate (DR) of FTS, (7) contingent cffDNA with higher uptake of FTS, and (8) contingent cffDNA with optimized FTS (higher uptake and improved DR)" P. no page number	Cost and clinical outcomes
Cuckle,[14] 2013, USA	Cost-consequence analysis Public health sector perspective Time period: NR	Pregnant women participating in prenatal testing	Three strategies compared: "(1) universal cfDNA screening replacing all current screening modalities, (2) 'contingent' cfDNA for 10% to 20% of women with the highest risks based on conventional screening, and (3) cfDNA replacing invasive prenatal diagnosis for women who have positive conventional screening tests and	Cost and clinical outcomes

First Author, Publication Year, Country	Study Design	Patient Characteristics	Comparison	Outcomes
			would currently be offered chorionic villus sampling (CVS) or amniocentesis." P.636-37	
O'Leary, [13] 2013, Australia	Cost-effectiveness analysis Public health sector perspective Time period: 2 years	Women at high risk of having a Down syndrome pregnancy A cohort of 32,478 women in the first trimester of their pregnancy	Two strategies compared. Model1: Current first trimester screening (FTS) Model 2: Prenatal testing pathway including NIPT i.e. FTS with NIPT (FTS/NIPT)	Cost and clinical outcomes
Song,[5] 2013, USA	Cost-effectiveness analysis Payer perspective Costs considered for first 5 years of life with Down syndrome	Women of age 35 years or greater or with a family history that indicates higher risk or had a positive conventional screening test result. A theoretical cohort of 4,000,000 pregnant women representative of the annual number of births in USA	Three strategies were compared. NIPT compared with first trimester combined screening (FTS) or integrated screening (INT) NIPT was used as first line for women of age ≥ 35 years or at increased risk and second line for women with positive conventional screening test. FTS included measurement of serum markers and first trimester ultrasound including determination of nuchal translucency. INT included FTS as well as Quad screening of serum markers	Cost and clinical outcomes

First Author, Publication Year, Country	Study Design	Patient Characteristics	Comparison	Outcomes
AF = alpha-fetoprotein, cffDNA = cell free fetal DNA, CVS = chorionic villous sampling, DNA = deoxyribonucleic acid, DR = detection rate, FTS = first trimester test, hCG = human chorionic gonadotrophin, INT =integrated test, NIPT = non-invasive prenatal testing, NT = nuchal translucency, PAPP-A = pregnancy associated plasma protein, uE3 = unconjugated estriol				
Notes : **Definitions of various procedures**[4] **Combined test:** "First-trimester test based on combining NT measurement (NT, ultrasound measurement of width of area of translucency at back of fetal neck early in pregnancy) with free β-hCG, PAPP-A, and maternal age." P.175.e4 **Quadruple test (Quad):** "Second-trimester test based on measurement of AFP, uE3, free β -hCG (or total hCG), and inhibin-A together with maternal age." P.175.e4 **Integrated test (INT):** "Integration of measurements performed at different times of pregnancy into single test result. Unless otherwise qualified, "integrated test" refers to integration of NT and PAPP-A in first trimester with quadruple test markers in second. First-trimester screening marker results are not analyzed until second-trimester markers are evaluated, at which point they are both assessed together." P. 175.e4 **Contingent screening:** "Screening in which first-trimester test (NT, free β -hCG, and PAPP-A) is used to triage population of women screened into 3 groups: 1 group (high-risk screen-positive) that is immediately offered diagnostic test (CVS), second group (screen-negative) that receives no further screening, and third intermediate group (or lower-risk screen-positive) that has second-trimester markers measured (quadruple test markers) and first-trimester measurements reused to form integrated test." P. 175.e4				

APPENDIX 3: Grading of Recommendations and Levels of Evidence

Guideline Society or Institute, Year	Recommendation grade	Level of Evidence
SOGC,[15] Canada, 2013	"A. There is good evidence to recommend the clinical preventive action B. There is fair evidence to recommend the clinical preventive action C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making D. There is fair evidence to recommend against the clinical preventive action E. There is good evidence to recommend against the clinical preventive action F. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making" p. 178	"I: Evidence obtained from at least one properly randomized controlled trial II-1: Evidence from well-designed controlled trials without randomization II-2: Evidence from well–designed cohort (prospective or retrospective) or case–control studies, preferably from more than one centre or research group II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees" p. 178
SOGC = Society of Obstetricians and Gynecologists of Canada		

APPENDIX 4: Summary of Study Strengths and Limitations

First Author, Publication Year, Country	Strengths	Limitations
Economic studies		
Okun,[10] 2014, Canada	• Objectives were stated. • The strategies compared were stated • Time horizon and perspective were stated • Clinical data were obtained from databases and published reports • Cost data were obtained from databases	• Sensitivity analyses were not conducted but several models were compared • Several assumptions were made which may not always be applicable • Only Down syndrome is considered in this analyses and other abnormalities such as trisomy 13 and 18 which could be detected by NIPT were not considered • Other abnormalities which cannot be detected by NIPT but would be diagnosed through traditional karyotyping were not considered
Cuckle,[14] 2013, USA	• Objectives were stated. • The strategies compared were stated • Perspective was stated • Clinical data was obtained from meta-analyses • Sensitivity analyses were conducted	• The sources of cost data were not clear • Several assumptions were made which may not always be applicable • Time period was not stated. • Only Down syndrome is considered in this analyses and other abnormalities such as trisomy 13 and 18 which could be detected by NIPT were not considered • Other abnormalities which cannot be detected by NIPT but would be diagnosed through traditional karyotyping were not considered
O'Leary,[13] 2013, Australia	• Objectives were stated. • The strategies compared were stated • Time horizon and perspective were stated • Clinical data were obtained from databases and published reports • Cost data were obtained from databases • Sensitivity analyses were conducted	• Several assumptions were made which may not always be applicable • Only Down syndrome is considered in this analyses and other abnormalities such as trisomy 13 and 18 which could be detected by NIPT were not considered • Other abnormalities which cannot be detected by NIPT but would be diagnosed through traditional karyotyping were not considered

First Author, Publication Year, Country	Strengths	Limitations
Song,[5] 2013, USA	• Objectives were stated. • The strategies compared were stated • Time horizon and perspective were stated • Clinical data were obtained from published reports • Cost data were obtained from databases and published reports • Sensitivity analyses were conducted	• Several assumptions were made which may not be applicable in all cases • Only Down syndrome is considered in this analyses and other abnormalities such as trisomy 13 and 18 which could be detected by NIPT were not considered • Other abnormalities which cannot be detected by NIPT but would be diagnosed through traditional karyotyping were not considered
Guideline		
SOGC,[15] 2013, Canada	• The scope was clearly stated. • The guideline development group comprised of individuals from relevant areas such as obstetrics and gynecology and medical genetics. • Literature search methods were described. • Recommendations were clear • Disclosure statements from all committee members had been received	• Unclear if patient input was sought • Cost implications or organizational barriers were not discussed.

APPENDIX 5: Main Study Findings and Authors' Conclusions

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td>Systematic reviews</td><td></td></tr>
<tr><td>Okun,[10] 2014, Canada</td><td>
Main Findings:
<table>
<tr><td colspan="6">Performance and cost outcomes with various scenarios of prenatal screening for Down syndrome.</td></tr>
<tr><th>Scenario</th><th>DS cases detected prenatally</th><th>Total program cost (C$)</th><th>Cost per woman screened (C$)</th><th>Cost per prenatally diagnosed pregnancy with DS (C$)</th><th>Cost per additional prenatally diagnosed pregnancy with DS (C$)</th></tr>
<tr><td>1</td><td>154</td><td>17,353,789</td><td>179</td><td>112,919</td><td>NA</td></tr>
<tr><td>2</td><td>154</td><td>17,580,080</td><td>182</td><td>114,391</td><td>NA</td></tr>
<tr><td>3</td><td>297</td><td>85,146,250</td><td>879</td><td>286,428</td><td>472,139</td></tr>
<tr><td>4</td><td>253</td><td>17,619,839</td><td>182</td><td>69,583</td><td>2,673</td></tr>
<tr><td>5</td><td>253</td><td>17,353,081</td><td>179</td><td>68,530</td><td>0</td></tr>
<tr><td>6</td><td>282</td><td>20,184,795</td><td>208</td><td>71,474</td><td>21,933</td></tr>
<tr><td>7</td><td>302</td><td>20,836,046</td><td>180</td><td>68,913</td><td>23,423</td></tr>
<tr><td>8</td><td>337</td><td>21,372,742</td><td>185</td><td>63,383</td><td>21,900</td></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
Conditions/ assumptions: Total pregnancies = 144570; uptake of prenatal screening 67% (for 1 to 6) and 80% for (7& 8); NIPT cost C$795 (for 3,4, 6,7), C$744 (for 5) and C$600 (for 8).
<table>
<tr><th>Scenario</th><th>Description</th></tr>
<tr><td>1</td><td>Current program (no cffDNA)</td></tr>
<tr><td>2</td><td>Current program modeled with FTS as primary NT-based screen (no cffDNA)</td></tr>
<tr><td>3</td><td>Primary cffDNA as replacement for the current program</td></tr>
<tr><td>4</td><td>Contingent cffDNA with current FTS performance</td></tr>
<tr><td>5</td><td>Contingent cffDNA with overall cost neutrality</td></tr>
<tr><td>6</td><td>Contingent cffDNA with an improved DR of FTS</td></tr>
<tr><td>7</td><td>Contingent cffDNA with higher uptake of FTS</td></tr>
<tr><td>8</td><td>Contingent cffDNA with optimized FTS performance with improved DR and higher uptake of FTS</td></tr>
</table>
Authors' Conclusion:
"Contingent models of cffDNA testing can improve overall screening performance while maintaining the provision of an 11 to 13 week scan. Costs are modestly increased, but cost per prenatally detected case of DS is decreased." P. not numbered
</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td>Cuckle,[14] 2013, USA</td><td>

Main Findings:

Universal cell free DNA (cfDNA) screening: marginal cost* per DS birth avoided by replacing the combined test or the quadruple test

Unit cost (US$)		Marginal cost per DS birth avoided (US$)	
cfDNA testing	CVS/amniocentesis	Replacing combined	Replacing quadruple
2000	1000	8,050,000	4,010,000
1500	1000	5,840,000	2,940,000
1000	1000	3,630,000	1,870,000
500	1000	1,420,000	797,000

*Marginal cost was estimated by the difference in total cost between protocols divided by the difference in detection rates
Unit cost of combined test and quadruple test were respectively US$150 and US$100 respectively

Contingent cell free DNA (cfDNA) screening: marginal cost* per DS birth avoided by replacing the combined test

Proportion needing cfDNA testing	Unit cost of cell free DNA testing (US$)	Marginal cost per DS birth avoided (US$)
10%	2000	1,580,000
	1500	1,110,000
	1000	652,000
	500	189,000
20%	2000	2,290,000
	1500	1,670,000
	1000	1,050,000
	500	436,000

*Marginal cost was estimated by the difference in total cost between protocols divided by the difference in detection rates
Unit cost of invasive prenatal diagnosis was US$1000

Cell-free DNA replacing invasive prenatal diagnosis: average cost per DS birth avoided and fetal loss prevented after a positive combined or quadruple test

Unit cost (US$) for cfDNA test	Average cost (US$)			
	DS birth avoided		Fetal loss prevented	
	Combined test - positive	Quadruple test - positive	Combined test - positive	Quadruple test - positive
2000	200,000	194,000	227,000	216,000
1500	185,000	176,000	121,000	112,000
1000	170,000	157,000	14,000	8,000
500	155,000	139,000	none*	none*

*none: total cost lower when cfDNA used
For unit cost of combined test and quadruple test of US$150 and US$100 respectively and fetal loss rate of 0.5%

Authors' Conclusion:

"Universal cfDNA screening for Down syndrome will only become affordable by public health purchasers if costs fall substantially. Until this happens, the contingent use of cfDNA is recommended." P. 636

</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td>O'Leary,[13] 2013, Australia</td><td>
Main Findings:
There were fewer invasive diagnostic tests and procedure related miscarriages for FTS/NIPT model compared with current practice. Using NIPT as an intermediary step before offering invasive diagnostic testing would increase the cost of prenatal testing by A$345,700 (9.7%) and by A$553,500 (15.5%) assuming NIPT uptake of 75.3% and 100% respectively, over a period of two years.
<table>
<tr><td colspan="4">Comparison of current practice including FTS and an alternate model including as well NIPT (FTS/NIPT) for screening and diagnosis</td></tr>
<tr><td>Outcome</td><td>Current practice* - FTS</td><td colspan="2">Alternate model* - FTS/NIPT</td></tr>
<tr><td>Diagnostic test uptake</td><td>0.753</td><td>0.753</td><td>1.00</td></tr>
<tr><td>High risk confirmed T21</td><td>69</td><td>69(68)</td><td>75-76 (74)</td></tr>
<tr><td>Cost of screening (A$)</td><td>3,030,197</td><td>3,030,197</td><td>3,030,197</td></tr>
<tr><td>Cost of invasive diagnostic testing† (A$)</td><td>535,344</td><td>256,481 (264,015)</td><td>258,749 (269, 010)</td></tr>
<tr><td>Cost of NIPT</td><td>NA</td><td>625,050</td><td>830,079</td></tr>
<tr><td>Total cost of testing (A$)</td><td>3,565,542</td><td>3,911,278 (3,919,262)</td><td>4,119,025 (4,129,486)</td></tr>
<tr><td>Cost per T21 confirmed case (A$)</td><td>51,372</td><td>56,360</td><td>54,186 (55,373)</td></tr>
<tr><td>Incremental cos-effectiveness ratio (ICER)</td><td></td><td>NA</td><td>83,724 (109,108)</td></tr>
<tr><td colspan="4">*Base case results are presented and sensitivity analyses results are presented within parenthesis. For base case the sensitivity and specificity of NIPT was assumed to be 100% and for sensitivity analyses, a worst case scenario was considered with sensitivity and specificity of NIPT assumed to be 98% and 97% respectively.
†Includes all Down syndrome cases confirmed by diagnostic testing irrespective of the screening results.</td></tr>
</table>
Authors' Conclusion:
" Based on the uptake of screening and diagnostic testing in a retrospective cohort of first-trimester screening in Western Australia, the implementation of NIPT would reduce the number of invasive diagnostic tests and the number of procedure-related fetal losses and increase the cost by 9.7% over two years. Policy planning and guidelines are urgently required to manage the funding and demand for NIPT services in Australia." P. 425
</td></tr>
<tr><td>Song,[5] 2013, USA</td><td>
Main Findings:
<table>
<tr><td colspan="2">Comparison of cost and clinical outputs for three prenatal screening strategies in the base case scenario using a theoretical cohort of 4,000,000 pregnant women.</td></tr>
<tr><td>Outcome</td><td>Screening strategy</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings and Authors' Conclusion</th></tr>
<tr><td></td><td>
<table>
<tr><th></th><th>FTS</th><th>INT</th><th>NIPT</th></tr>
<tr><td>Invasive procedures performed</td><td>108,364</td><td>108,760</td><td>5330</td></tr>
<tr><td>T21 detected</td><td>3364</td><td>3760</td><td>4823</td></tr>
<tr><td>Euploid fetal losses</td><td>525</td><td>525</td><td>3</td></tr>
<tr><td>Cost per T21 detected (US$)</td><td>1,125,314</td><td>1,042,417</td><td>705,528</td></tr>
<tr><td>Screening strategy cost (US$)</td><td>3,785,688,398</td><td>3,919,378,508</td><td>3,402,844,207</td></tr>
<tr><td>Screening cost per pregnant woman (US$)</td><td>946.42</td><td>979.84</td><td>850.71</td></tr>
<tr><td colspan="4">Note: Baseline cost of NIPT was assumed to be US$795</td></tr>
</table>

NIPT appeared to be the dominant strategy as it was associated with higher T21 detection and lower euploid fetal losses at a lower cost compared to FTS or INT. Sensitivity analyses showed that NIPT was the dominant screening strategy over INT in all scenarios considered and was dominant over FTS in most scenarios. Down syndrome cost was assumed to be US$677,000 for base case and ranged between US$400,000 and US$800,000 for sensitivity analyses. If Down syndrome cost was assumed to be below US$212,000 then NIPT became more costly than FTS but was still less costly than INT.

Authors' Conclusion:
"NIPT leads to improved T21 detection and reduction in euploid fetal loss at lower total healthcare expenditures." P. 1180</td></tr>
<tr><td colspan="2">DS = Down syndrome, FTS = first trimester screening, INT = integrated screening, NA = not applicable, NIPT = non-invasive prenatal testing, NT = nuchal translucency</td></tr>
</table>

APPENDIX 6: Guidelines and Recommendations

Guideline Society, Author, Country, Year	Recommendations
SOGC,[15] Canada, 2013	"Non-invasive prenatal testing using massive parallel sequencing of cell-free fetal DNA to test for trisomies 21, 18, and 13 should be an option available to women at increased risk in lieu of amniocentesis. Pretest counselling of these women should include a discussion of the limitations of non-invasive prenatal testing. (II-2A) No irrevocable obstetrical decision should be made in pregnancies with a positive non-invasive prenatal testing result without confirmatory invasive diagnostic testing. (II-2A) Although testing of cell free fetal DNA in maternal plasma appears very promising as a screening test for Down syndrome and other trisomies, studies in average-risk pregnancies and a significant reduction in the cost of the technology are needed before this can replace the current maternal screening approach using biochemical serum markers with or without fetal nuchal translucency ultrasound. (III-A)" p. 177
SOGC = Society of Obstetricians and Gynecologists of Canada	