BMJ Open  Expansion of non-invasive prenatal screening to the screening of 10 types of chromosomal anomalies: a cost-effectiveness analysis

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ABSTRACT

Objectives To determine the cost-effectiveness of the addition of chromosomal anomalies detectable by non-invasive prenatal screening (NIPS), in a prenatal screening programme targeting common aneuploidies.

Design, setting and participants A simulation study was conducted to study the addition of chromosomal anomalies detectable by NIPS (sex chromosome aneuploidies, 22q11.2 deletion syndrome, large deletion/duplication >7 Mb and rare autosomal trisomies) to five basic strategies currently aiming the common trisomies: three strategies currently offered by the public healthcare systems in Canada, whose first-tier test is performed with biochemical markers, and two programmes whose first-tier test consists of NIPS-based methods.

Outcome measures The total number of cases of chromosomal anomalies detected and the costs related to the consumptions of medical services.

Results The most effective and the most cost-effective option in almost all prenatal screening strategies is the option that includes all targetted additional conditions. In the strategies where NIPS is used as first-tier testing, the cost per additional case detected by adding all possible additional anomalies to a programme that currently targets only common trisomies is $25,710 (95% CI $25,489 to $25,934) for massively parallel shotgun sequencing and $57,711 (95% CI $57,141 to $58,292) for targeted massively parallel sequencing, respectively. The acceptability curves show that at a willingness-to-pay of $500,000 per one additional case detected, the expansion of NIPS-based methods for the detection of all possible additional conditions has a 90% probability of being cost-effective.

Conclusion From an economic perspective, in strategies that use NIPS as a first-tier screening test, expanding the programmes to detect any considered chromosomal anomalies other than the three common trisomies would be cost-effective. However, the potential expansion of prenatal screening programmes also requires consideration of societal issues, including ethical ones.

INTRODUCTION

More than 400,000 Canadian pregnant women receive a routine prenatal screening each year. Prenatal screening for chromosomal anomalies in Canada, as in many other countries, tends to be limited to the detection of common aneuploidies, T21, T13 and T18. Currently, the most common procedure involves a three-stage process, with biochemical testing and ultrasound as a first-tier screening test, non-invasive prenatal screening (NIPS) as a second-tier test for positive cases and invasive confirmatory testing for NIPS-positive cases. The first tier of the Canadian prenatal screening programmes can be summarised into three strategies including the serum integrated prenatal screening test (SIPS) without nuchal translucency (NT) ultrasound, the first-trimester screening (FTS), with NT ultrasound and first-trimester serum markers, and the integrated prenatal screening (IPS), including NT ultrasound and first plus second-trimester serum markers. However, these tests could lead to a high number of false-positive cases, which increases the

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Our protocol follows the recommendations for best practices of the Guidelines for Health Economic Evaluation of the Canadian Agency For Drugs And Technologies In Health.

⇒ This study was supervised by an experts’ team who validated the models, data on parameters, costs and screening strategies that reflect the current various prenatal screening programmes in Canada.

⇒ We confirmed the robustness of our result by performing sensitivity analyses with a wide range of parameters to account for the uncertain parameters.

⇒ One of the limitations of this study is the scarcity of some data. Some parameters had to be estimated by experts.

⇒ The cost of the screening for non-currently screened anomalies had to be estimated by experts.


Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-069485).

Received 22 October 2022
Accepted 18 August 2023

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number of unnecessary invasive tests. The diagnostic procedure is costly and could lead to miscarriages, which affects mostly euploid fetuses. Therefore, there is an interest in finding an alternative to these conventional approaches.

Non-invasive prenatal screening analyses the fetal DNA that circulates in maternal blood. There are different NIPS methods, massively parallel shotgun sequencing (MPSS) analyses all fetal DNA randomly, and targeted massively parallel sequencing (TMPS) analyses the target fetal DNA. Compared with the conventional screening approaches, NIPS is found to be a more accurate and cost-effective method to screen for the three most common aneuploidies, when used as a second-tier test in high-risk pregnancies.

The decreasing cost of NIPS, which is expected to decrease further over the next few years, provides the opportunity to include other chromosomal anomalies in a screening programme efficiently and allows the consideration of NIPS as a first-tier test.

This project aimed at measuring the expected cost-effectiveness of expanding a Canadian prenatal screening programme for the detection of fetal sex chromosome aneuploidies (SCAs), rare autosomal aneuploidies (RATs) and/or microdeletions in addition to the common chromosomal anomalies.

METHODOLOGY
This article complies with the recommendation of the Consolidated Health Economic Evaluation Reporting Standards 2022.

Overview of the simulation
The general simulation approach consists in drawing and parameterising individual trees for each condition that could eventually become part of a prenatal NIPS-based screening programme.

In Canada, prenatal screening programmes to detect fetal chromosomal anomalies vary from one province to another. However, all programmes target at least two conditions: T21 and T18. Therefore, the baseline option (reference option) consists of a T21 and T18 screening programme. These conditions are the common denominators of all NIPS-based prenatal screening programmes. The other options include adding condition-specific trees to this baseline tree. All possible combinations of trees were generated.

Study population
The virtual population consisted of 100,000 singleton pregnant women, who have similar characteristics to Quebec’s pregnant women aged 14–49 years in terms of age distribution and risk for a fetal chromosomal anomaly. These women had a prenatal screening test in their first trimester of pregnancy. Women with multiple pregnancies were excluded as they were not eligible for NIPS due to its supposed limitations when the study was undertaken.

Patient and public involvement
None.

Study location
Models built for the study reflect the Prenatal Screening Programmes that exist across the Canadian provinces. Nevertheless, data related to the costs were based on data from the Province of Quebec, because it is one of the largest provinces and because it has good documentation of costs in its publicly funded healthcare system.

Comparators (screening options)
In Canada, prenatal screening programmes to detect fetal chromosomal anomalies vary from one province to another. These programmes were categorised into five strategies: (1) SIPS, (2) IPS, (3) FTS, (4) MPSS-based NIPS and (5) TMPS-based NIPS (online supplemental file 3, table S3).1) The first-tier test in the first three groups consisted of biochemical markers, while in the last two strategies, it consisted of NIPS. In each strategy, the reference option consisted of a screening programme for the detection of T21 and T18. The other options consisted of a programme for the detection of T21 and T18, combined with any possible combination with the following conditions: T13, 45,X, 47,XXX, 47,XXY, 47,XYY, 22q11.2 deletion syndrome, large deletion/duplication >7 Mb and RATs, except for TMPS, as the approach is unsuitable for the screening of RATs, and large deletions and duplication >7 Mb. In total, 800 options were studied, 256 options in the SIPS and IPS strategies each, 128 options in the FTS and MPSS each, and 32 options in the TMPS strategy.

Perspective
In Canada, prenatal care is provided free of charge. This study was, therefore, conducted based on the public healthcare system payer’s perspective.

Time horizon and discount rate
The model allows to follow pregnant women from screening for chromosomal anomalies up to the pregnancy outcome. As the duration of the follow-up is under 1 year, no discounting was necessary.

Study outcome
The main outcome consisted of the number of cases detected and the total costs related to the consumption of medical services related to the screening status. The mean of the total costs, the number of cases detected in total and by screening options, as well as their 95% CI, were computed. Thereafter, the incremental costs, incremental effects and incremental cost-effectiveness ratios (ICERs) were calculated.

Model
A semi-Markov agent-based model was built, representing a pregnant woman’s journey from the prenatal visit when
the screening test is performed up to the end of her pregnancy.

Online supplemental file 1, figure S1.1 represents the first three initial strategies that are characterised by a screening approach based on biochemical tests as the first-tier test, with or without an NT ultrasound exam. The decision tree starts with the probability that a pregnant woman accepts or declines to take the biochemical-screening test. The tree considers then that if the test is positive, there are four options. Women can: (1) receive an NIPS-based second-tier screening test, (2) receive a confirmation test, (3) decide to terminate the pregnancy or (4) decline further testing. If the woman decides to receive an NIPS-based second-tier screening test and if the test is positive, she can: (1) terminate the pregnancy, (2) receive a confirmation test or (3) refuse the confirmation test. Moreover, in the case of a twice-inconclusive result, the models consider that the woman can decline or accept further testing (a confirmation test or a second NIPS test). If the second NIPS is positive, the woman is offered a confirmation test that she can refuse. The confirmation test consists of a quantitative fluorescent PCR (QF-PCR) if NIPS is positive for T21, T18, T13, SCAs and RATs, followed by a karyotype if the QF-PCR result is positive. If NIPS is positive for micro-deletion/duplication syndromes, a chromosome microarray analysis (CMA) is offered. Online supplemental file 1, figure S1.2 represents the last two initial strategies that consist of using the two NIPS-based approaches as a first-tier screening test: the MPSS-based and TMPSS-based methods. The decision trees in these strategies consider the probabilities that a pregnant woman accepts or declines to take the screening. If the first-tier NIPS test is positive, women can: (1) terminate the pregnancy, (2) receive a confirmation test or (3) refuse the confirmation test. Moreover, the models consider that, in case of a twice-inconclusive result, the woman can decline further testing or accept an ultrasound. The woman is offered a diagnostic test (CMA) if the ultrasound detects fetal anomalies. If the ultrasound yields a negative result, she is offered a quadruple markers serum screening test (QUAD) as the test can be done up to 21 weeks. If the QUAD is positive, a confirmation test (QF-PCR) is proposed, which the woman can refuse. The confirmation test consists of a QF-PCR if NIPS is positive for T21, T18, T13, SCAs and RATs. A karyotype is used to confirm the positive results from QF-PCR. Besides, CMA is offered if NIPS is positive for microdeletion/duplication syndromes.

Parameterisation

Data related to events and outcomes were retrieved from the literature. Their relevance was assessed by two experts, a geneticist (SL) and an obstetrician (FA) who are coauthors of the paper. When no relevant data were available, experts’ opinion was provided for the following parameters: (1) the decision of pregnant women in case of an NIPS test inconclusive result; (2) the acceptance rate of NIPS for SCAs, subchromosomal abnormalities and RATs and (3) the decision of pregnant women in case of a first-tier NIPS test positive result. Parameters included the prevalence of chromosomal/subchromosomal anomalies, the probabilities of an event, the tests’ performance, and the direct costs for the public healthcare system. The values used for the baseline simulations were the average values from the Canadian data. If Canadian data were not available the average values from the most similar countries were used, otherwise, the experts’ opinions were used. Values used for the sensitivity analyses were the CIs of the parameter built by retrieving the lowest and highest values found in the literature or using an assumption of ±10% if such data could not be found (see supplementary documents 1 and 2 for more details).

Prevalence of chromosomal anomalies

The prevalence of chromosomal/subchromosomal anomalies with their ranges was retrieved from the literature. Average values were used for the baseline simulations. Lower and upper values were used for sensitivity analyses (online supplemental file 1, table S1.1).3 13–21

Event probabilities

Probabilities of events detailed in online supplemental file 1, table S1.1–S1.9 were retrieved from the literature. To define basic values, a prioritisation of the literature was performed. Data on the Canadian population were prioritised, followed by data from the western countries. When no information was available, assumptions were made by consensus between two experts. Probabilities include the acceptance of the screening tests, the tests’ performance, and the decision by women regarding further interventions when they receive a positive or inconclusive result.

Measurement and valuation of costs

The costs used in this study were estimated in Canadian dollars for the fiscal 2019–2020 year. The total costs consisted of the costs related to medical services consumed during the journey of the pregnant women, from the prenatal visit when the screening test is performed until the end of the pregnancy. Cost items were extracted from Canadian clinical guidelines.2 22 23 They include the cost of services associated with the screening procedure (medical consultation, genetic counselling, laboratory tests, confirmation tests, imaging, etc) and the cost of medical services related to the following events: procedure-related loss of the fetus (risk of miscarriage for chorionic villus sampling and amniocentesis); termination of pregnancy in case of fetal aneuploidy; follow-up of the pregnancy until delivery and delivery costs. The Quebec public provincial average prices were used to calculate all unit prices. Unit prices for activity centres were calculated using 2019–2020 data. Facilities used were valued through the Quebec Ministry of Health financial reports that collect data through activity centres. All clinically activity centres unit prices were overheaded using the direct approach to take into consideration the support activity centres.24 For
the centres of activity for laboratory and imaging tests, we used the medical biology laboratories activity centre and medical imaging activity centre,26 27 to identify the weight of each test concerned. The average price paid to physicians by the Quebec public health insurance plan (see online supplemental file 2) for more detail on the cost items).26 27

Hypotheses
The models are based on the following hypotheses:

- **Parameterisation**
  A woman can get pregnant only once during the recruitment period.

- **Simulation process**
  - Because the NIPS-MPSS method is considered poorly applicable for the screening of 22q11.2 deletion syndrome (high-resolution requirement leads to double price of the test), we assumed that this condition will be looked for through the NIPS-TMPS approach.
  - When women choose to decline/be tested for one condition at the beginning of the screening process, the choice applies to the other conditions.
  - When a fetus has more than one condition detected:
    - If there is a spontaneous loss (whether due to procedure related or condition related) for one condition, the loss implies an interruption in the screening process for other conditions.
    - If a woman decides to have an abortion due to a condition detected, the abortion will interrupt the screening process of the other conditions.
    - If the simulation leads to a situation where one condition screened for ends with a spontaneous loss after an invasive test, and the other one with a spontaneous loss or an induced abortion, the loss following the invasive test applies to both.
    - If the simulation leads to a situation where one condition screened for ends with a spontaneous loss and the other condition ends with induced abortion, the spontaneous loss applies to both.
    - If the simulation leads to a situation where testing for two conditions is inconclusive or positive, the cost of each of the conditions will be the cost of the condition with the highest cost.
    - If the simulation leads to a situation where a common test for two conditions has a positive result for one condition but is inconclusive for the other condition, the inconclusive result applies to both.
    - If the simulation leads to a situation where one condition screened for ends with induced abortion after the NIPS positive result and the other condition ends with induced abortion after the confirmation test positive result, the induced abortion after the NIPS positive result applies to both.

Simulations
The models were run on the SCHNAPS platform using the CEDAR and GRAHAM supercomputers of the Digital Research Alliance of Canada (ex-Compute Canada).28 The simulations for baseline results were repeated 1000 times with different virtual populations. The data were extracted by Spyder Software (V.5.1.5).29

Validation
The decision trees and the parameters that were used to run the simulations were validated by consensus by the two experts. Bayesian methods by Markov Chain Monte Carlo simulations were used to validate and calibrate the model. The models were considered valid if the predefined simulation result values differ by less than 5% from expected. The total number of cases detected (T21 and T18) and the total cost of each pregnancy based on their pregnancy journey (eg. a pregnant woman decided to end her pregnancy after receiving confirmation of having a child with Down syndrome) were used as predefined variables. Moreover, we performed five simulations, one per each starting tree (the initial condition screened) with the cost items considered in another study performed in Canada, to ensure that our results are comparable with the literature and that differences essentially come from the diminution of the NIPS test costs over time.9

Statistical analyses
For the statistical analysis, we performed both the intrastrategy and interstrategy comparisons. The intrastrategy and interstrategy comparisons refer to the prenatal screening groups listed in online supplemental file 3, table S3.1.

Intrastrategy comparison
For each option, the mean of the total costs, the number of total cases detected, as well as their 95% CI, were computed. Thereafter, the incremental costs, incremental effects and ICERs were calculated to compare the options in each strategy (five initial trees).

Interstrategy comparison
Interstrategy comparisons were done for the overall most cost-effective options for each strategy. Interstrategy comparisons were also performed taking into account different candidate conditions for an expansion of the programme, to provide information that can be interpreted along with broader societal and ethical issues:
- Common aneuploidies (T21, T18 and T13).
- All conditions.
- Common aneuploidies plus 45,X syndrome.
- Common aneuploidies plus 22q11.2 deletion syndrome.
- Common aneuploidies plus RATs.
- Common aneuploidies plus SCAs.
- Common aneuploidies plus 22q11.2 deletion syndrome and large deletion/duplication>7Mb.
- Common aneuploidies plus SCAs and RATs.
Sensitivity analyses
Probabilistic sensitivity analyses (PSAs) were performed by Monte Carlo simulations considering the distribution functions of each of the parameters simultaneously. We assumed that event probabilities (eg, uptake rates, test performance) follow a beta distribution and that the cost of the medical service (items) follows a gamma distribution.

The simulations were performed with 5000 iterations. Cost-effectiveness acceptability curves (CEACs) were produced to examine the effect of willingness-to-pay (WTP) per additional case detected on the cost-effectiveness of the various options taking into consideration the uncertainty of the parameters. WTP is the cost that a government would eventually be willing to pay for one additional case detected. We calculated the probability of each option being cost-effective at different amounts (from 0 to $500 000). To confirm the robustness of the intrastrategy comparison, PSAs were performed with the remaining options in MPSS and TMPS strategies. Moreover, for interstrategy comparison, PSA was performed to examine the robustness of each screening strategy.

RESULTS
Online supplemental file 3, table S3.1 presents the prenatal screening strategies. Simulations were performed on five models. Each model (strategy) allows for a comparison of relevant options given the first-tier screening test used. Three models refer to screening approaches that begin with biochemical and/or ultrasound tests (SIPS, IPS and FTS) and two refer to the use of NIPS as a first-tier test (MPSS and TMPS). In each model, options consist of all possible combinations of chromosomal conditions whose screening can be added to the screening process starting with the first-tier test. Moreover, when biochemical markers were used as first-tier tests and NIPS as a second-tier test, options included additional NIPS-detectable conditions. Based on the experts’ opinion regarding the conditions that would reasonably be acceptable for the Canadian Public Healthcare System.

Intrastrategy comparison
Reference in intrastrategy comparisons consisted of the least costly combination. Because of the number of combinations, we present in this article only the least costly combinations and the ones considered by the experts as important to present.

Serum integrated prenatal screening
Table 1 presents the results of the comparison between options belonging to the strategy with SIPS as a first-tier test. It shows that there are no significant differences between options in terms of costs, and

### Table 1
Baseline results of the intrastrategy comparison, SIPS as the first-screening test

<table>
<thead>
<tr>
<th>No</th>
<th>Combination</th>
<th>Total cost (CAD) (95% CI)</th>
<th>Total case detected (95% CI)</th>
<th>ΔCost (CAD) (95% CI)</th>
<th>ΔEffect (95% CI)</th>
<th>Sequential ICER (CAD) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Initial combination plus T13, SCAs and 22q11.2 deletion</td>
<td>$406,339 (201) ($406,338 612 to $406,341 026)</td>
<td>239 (237 to 241)</td>
<td>$5540 (6222 to 6617)</td>
<td>3 (3 to 3)</td>
<td>$1847 (741 to 2206)</td>
</tr>
<tr>
<td>2</td>
<td>All 10 conditions</td>
<td>$406,344 (741) ($406,340 834 to $406,347 642)</td>
<td>242 (240 to 244)</td>
<td>$3583 (3261 to 4511)</td>
<td>2 (2 to 2)</td>
<td>Dominated by combination 2</td>
</tr>
<tr>
<td>3</td>
<td>Initial combination plus T13, SCAs and RATs</td>
<td>$406,350 (726) ($406,349 095 to $406,352 153)</td>
<td>237 (236 to 241)</td>
<td>$450 (426 to 474)</td>
<td>1 (1 to 1)</td>
<td>Dominated by combination 2</td>
</tr>
<tr>
<td>4</td>
<td>Initial combination plus T13 and SCAs</td>
<td>$406,350 (220) ($406,346 193 to $406,353 647)</td>
<td>237 (236 to 241)</td>
<td>$5479 (5359 to 6005)</td>
<td>3 (2 to 2)</td>
<td>Dominated by combination 2</td>
</tr>
<tr>
<td>5</td>
<td>Initial combination plus T13 and SCAs</td>
<td>$406,350 (726) ($406,349 095 to $406,352 153)</td>
<td>237 (236 to 241)</td>
<td>$3583 (3261 to 4511)</td>
<td>2 (2 to 2)</td>
<td>Dominated by combination 2</td>
</tr>
<tr>
<td>6</td>
<td>Initial combination plus T13 and 22q11.2 deletion</td>
<td>$406,354 (147) ($406,350 176 to $406,358 118)</td>
<td>237 (236 to 241)</td>
<td>$5406 (5342 to 10 476)</td>
<td>4 (4 to 4)</td>
<td>Dominated by combination 2</td>
</tr>
<tr>
<td>7</td>
<td>Initial combination plus T13 and 45,X</td>
<td>$406,354 (631) ($406,350 604 to $406,358 657)</td>
<td>237 (236 to 241)</td>
<td>$9890 (9769 to 11 015)</td>
<td>4 (4 to 4)</td>
<td>Dominated by combination 2</td>
</tr>
<tr>
<td>8</td>
<td>Initial combination plus T13 and SCAs</td>
<td>$406,356 (132) ($406,355 406 to $406,356 217)</td>
<td>237 (236 to 241)</td>
<td>$16571 (16572 to 17 575)</td>
<td>7 (7 to 7)</td>
<td>Dominated by combination 2</td>
</tr>
<tr>
<td>9</td>
<td>Initial combination plus T13 and 45,X</td>
<td>$406,356 (227) ($406,355 988 to $406,356 856)</td>
<td>237 (236 to 241)</td>
<td>$18 186 (18 164 to 19 214)</td>
<td>7 (7 to 7)</td>
<td>Dominated by combination 2</td>
</tr>
<tr>
<td>10</td>
<td>Initial combination (T21, T18)</td>
<td>$406,366 (328) ($406,362 280 to $406,370 368)</td>
<td>231 (229 to 232)</td>
<td>$22 587 (21 453 to 22 726)</td>
<td>12 (11 to 12)</td>
<td>Dominated by combination 2</td>
</tr>
</tbody>
</table>

Bold values indicate the additional cost per one additional case detected compared to the previous option.

CAD, Canadian dollar; ICER, incremental cost-effectiveness ratio; Initial combination, combination consists of T21 and T18; MMs, microdeletion microduplications; RATs, rare autosomal trisomies; SCAs, sex chromosome aneuploidies; SIPS, serum integrated prenatal screening.
effectiveness. The least costly option in this strategy is the option consisting of T21 and T18 plus T13, SCAs and 22q11.2 deletion. The most effective and the most cost-effective options are the option that includes all 10 conditions together. However, the 95% CIs of the total costs and number of cases detected within the options in SIPS strategy overlap.

Integrated prenatal screening
In the IPS strategy, similar findings as in SIPS were observed. There are no significant differences between options in terms of costs and effectiveness. The least costly option consists of the programme targeting all 10 conditions. The most effective and most cost-effective option in this strategy was that which includes the search for T13, SCAs and 22q11.2 deletion (online supplemental file 3, table S3.2). However, the 95% CIs of the total costs and number of cases detected within the options in IPS strategy overlap.

First-trimester screening
There are no significantly differences between the total costs and number of cases detected within option in this strategies. The total costs and number of cases detected overlap. The least costly, most effective and the most cost-effective option targets all 10 conditions (online supplemental file 3, table S3.3).

Massively parallel shotgun sequencing
Results of the strategy with MPSS as a first-tier test show significant differences between options in terms of total costs and the total number of cases detected. The addition of any condition considered in this study would be cost-effective. The more conditions included in the screening programme, the higher the total cost and the number of cases detected. The least costly option is the initial option targeting the three common trisomies (T21, T18 and T13). The costliest option is the option that includes the 10 conditions. Nevertheless, this option is the most effective and most cost-effective (table 2).

Targeted massively parallel sequencing
Similar findings can be observed in the TMPS strategy. There are significant differences between options in terms of total costs and the total number of cases detected. Adding conditions to the screening list brings results that are similar to the MPSS strategy in terms of benefit. However, the number of cases detected is lower (online supplemental file 3, table S3.4).

Interstrategy comparison
Interstrategy comparisons were performed on the following programmes: programmes that target (1)

### Table 2 Baseline results of the interstrategy comparison, MPSS as the first-screening test

<table>
<thead>
<tr>
<th>No</th>
<th>Combination</th>
<th>Total cost (CAD)</th>
<th>Total case detected (95% CI)</th>
<th>ΔCost (95% CI)</th>
<th>ΔEffect (95% CI)</th>
<th>Sequential ICER (CAD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Least costly (initial combination, T21, T18, T13)</td>
<td>$C437\text{567\text{941}}$ ($C437\text{560\text{523}}$ to $C437\text{575\text{360}}$)</td>
<td>517 (515 to 520)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Initial combination plus RATs</td>
<td>$C437\text{579\text{050}}$ ($C437\text{571\text{828}}$ to $C437\text{586\text{272}}$)</td>
<td>521 (519 to 524)</td>
<td>$C1\text{11\text{108}}$ ($C1\text{10\text{912}}$ to $C1\text{11\text{305}}$)</td>
<td>4 (4 to 4)</td>
<td>$C2\text{735}$ ($C2\text{664}$ to $C2\text{829}$)</td>
</tr>
<tr>
<td>3</td>
<td>Initial combination plus 45.X</td>
<td>$C437\text{881\text{485}}$ ($C437\text{884\text{159}}$ to $C437\text{898\text{812}}$)</td>
<td>561 (558 to 564)</td>
<td>$C3\text{12\text{436}}$ ($C3\text{12\text{331}}$ to $C3\text{13\text{254}}$)</td>
<td>39 (39 to 40)</td>
<td>$C7\text{932}$ ($C7\text{284}$ to $C7\text{990}$)</td>
</tr>
<tr>
<td>4</td>
<td>Initial combination plus SCAs and RATs</td>
<td>$C437\text{969\text{707}}$ ($C437\text{962\text{287}}$ to $C437\text{977\text{127}}$)</td>
<td>597 (594 to 600)</td>
<td>$C7\text{822\text{22}}$ ($C7\text{812\text{99}}$ to $C7\text{813\text{15}}$)</td>
<td>36 (35 to 37)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Initial combination plus SCAs</td>
<td>$C437\text{970\text{758}}$ ($C437\text{963\text{508}}$ to $C437\text{978\text{009}}$)</td>
<td>591 (588 to 594)</td>
<td>$C7\text{927\text{3}}$ ($C7\text{916\text{9}}$ to $C7\text{934\text{9}}$)</td>
<td>30 (30 to 31)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Initial combination plus 22q11.2 deletion</td>
<td>$C439\text{321\text{757}}$ ($C439\text{314\text{021}}$ to $C439\text{329\text{492}}$)</td>
<td>545 (542 to 548)</td>
<td>$C1\text{430\text{271}}$ ($C1\text{429\text{863}}$ to $C1\text{430\text{680}}$)</td>
<td>16 (−16 to −16)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Initial combination plus SCAs and 22q11.2 deletion</td>
<td>$C439\text{704\text{178}}$ ($C439\text{696\text{347}}$ to $C439\text{712\text{010}}$)</td>
<td>617 (614 to 621)</td>
<td>$C1\text{812\text{693}}$ ($C1\text{812\text{188}}$ to $C1\text{813\text{197}}$)</td>
<td>56 (55 to 57)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Initial combination plus MMUs</td>
<td>$C442\text{566\text{363}}$ ($C442\text{557\text{424}}$ to $C442\text{575\text{302}}$)</td>
<td>678 (675 to 682)</td>
<td>$C4\text{674\text{877}}$ ($C4\text{673\text{265}}$ to $C4\text{674\text{690}}$)</td>
<td>118 (117 to 118)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>All 10 conditions</td>
<td>$C442\text{924\text{947}}$ ($C442\text{915\text{901}}$ to $C442\text{933\text{993}}$)</td>
<td>757 (652 to 761)</td>
<td>$C5\text{033\text{462}}$ ($C5\text{031\text{742}}$ to $C5\text{035\text{811}}$)</td>
<td>196 (194 to 198)</td>
<td>$C2\text{571\text{0}}$ ($C2\text{549\text{890}}$ to $C2\text{593\text{434}}$)</td>
</tr>
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</table>

Bold values indicate the additional cost per one additional case detected compared to the previous option.

CAD, Canadian dollar; ICER, Incremental Cost Effectiveness Ratio; Initial combination, combination consists of T21, T18 and T13; MMUs, microdeletion microduplications; MPSS, massively parallel shotgun sequencing; RATs, rare autosomal trisomies; SCAs, sex chromosome aneuploidies.
common aneuploidies (T21, T18 and T13; (2) all 10 conditions; (3) common aneuploidies plus 45,X; (4) common aneuploidies plus 22q11.2 deletion syndrome; (5) common aneuploidies plus RATs; (6) common aneuploidies plus SCAs; (7) common aneuploidies plus 22q11.2 deletion syndrome and large del/dup >7Mb and (8) common aneuploidies plus SCAs and RATs. Simulations showed that differences in terms of costs and effectiveness are expected depending on which test is used as a first-tier test. The strategies of NIPS as first-tier tests (MPSS and TMPS) tend to be costlier but also more effective than the strategies starting with biochemical tests, whatever the conditions included in the screening programme (online supplemental file 3, tables S3.5–S3.12).

Sensitivity analyses

Intrastrategy comparison

Our baseline results show that a programme aiming at detecting all possible candidate conditions is the most cost-effective option in SIPS, FTS, MPSS and TMPS approaches, but not in the IPS approach. Moreover, the acceptability curves show that in the NIPS strategies where NIPS is used as a first-tier screening test, the option targeting all possible conditions has a 90% probability of being cost-effective at a WTP of $C50 000 per additional case detected (figures 1 and 2).

Interstrategy comparisons

The baseline results showed that the FTS as the first-tier screening test is the least costly strategy. Therefore, FTS was used as the reference approach for all interstrategy comparisons. Simulations with baseline values show that NIPS-MPSS-based methods as first-tier screening test for the screening of all 10 conditions are expected to be cost-effective at a WTP $C78 599 (95% CI $C78 279 to $C100 236) per additional case detected (online supplemental file 3, table S3.5). However, when the uncertainty of key parameters is taken into consideration, the probability of MPSS-based NIPS approaches being cost-effective is reduced. The probability is about 50% at a WTP of $C250 000 per additional case detected (figure 3).

DISCUSSION

Principal findings

Acceptability curves show that in strategies that use NIPS as a first-tier test, expanding programme targeting the common trisomies to include the 10 conditions makes this option have a 90% probability of being cost-effective at a WTP of $C50 000 per additional case detected. One noted that the addition of any condition considered in this study would also be cost-effective. However, they are dominated or subject to extended dominance through the option consisting of all 10 conditions. Simulations also suggest that first-tier NIPS strategies would be more effective than biochemical strategies but also more costly.

Interpretation of the findings

When biochemical markers are used as first-tier screening tests, there are no significant differences between options in terms of costs and effectiveness. Moreover, their 95% CI overlap. The main explanation for this observation is that the screening approach would detect only a
small percentage of new conditions, compared with the current screening procedure which targets only (T21 and T18). This is because a positive biochemical test is required to proceed to the NIPS-based second-tier test that can detect the candidate conditions. Moreover, costs between options are quite similar probably because the cost of screening represents less than 10% of the total cost. The increase in the screening cost due to the increase in conditions tested for has therefore little impact on the total cost. This increase is also compensated by the diminution of the average costs associated with fewer deliveries and more induced abortions expected from expanding a screening programme to new conditions.

When NIPS methods are used as first-tier screening tests, the least costly option is, as expected, the screening option that targets only the common trisomies. The more costly option targets all possible conditions considered in this study. This observation lies in the fact that the expansion of NIPS involves adding conditions for which the screening test is less performant. The CI for the sensitivity and specificities of screening tests for candidate options can be wide because of the paucity of performance data on NIPS. Many false positive cases, due to low PPVs, will require additional tests to assess the absence of anomalies.

Results of the intrastrategy comparisons show that the most effective and cost-effective options are options consisting of a screening programme for common trisomies. The main reason that leads to the difference between TMPS and MPSS is the difference in the total number of possible conditions that can be screened with both of them. MPSS can be used to screen for more conditions. However, the CI of the test performance for the screening of additional conditions is wide, leading to many false positive cases, hence, unnecessary costs for the confirmation tests. These results indicate the importance of the performance of the test.

Simulations across strategies show that the strategies consisting of options using biochemical tests as first-tier screening tests are less costly and lead to fewer cases detected, compared with screening strategies whose first-test is an NIPS test. Moreover, when the programme targets all possible conditions considered in this study, the probability that NIPS, compared with the least costly approach (FTS), becomes cost-effective is about 50% at a WTP of $250,000 per additional case detected. Nevertheless, with the expected reduction of the NIPS testing cost, the investment amount needed will certainly diminish considerably in the short term. Offering NIPS as a first-tier test seems likely to be unavoidable in the near future.

Nevertheless, because of ethical concerns, a programme screening for the 10 conditions might be socially undesirable, as a positive result might lead to an abortion for a condition that has little impact on the intellectual ability of a person affected. This is why simulations were also conducted in such a way that results might reflect the hesitancy to add some candidate conditions to a screening programme. Moreover, the regulation about abortion varies among countries, especially, like the time until when abortion is legal. Therefore, the timeliness of strategies should be taken into consideration according to the specificity of each country. Furthermore, the effect, the severity and the penetrance of each 10 conditions differ. Specific information regarding each disease would allow parents to make the most relevant decision, notably, on abortion.

Lastly, in this study, women with multiple pregnancies were excluded as they were not eligible for NIPS. Nevertheless, a recent review demonstrated a similar performance of NIPS in singleton and twin pregnancies. Thus, our results may possibly apply to multiple pregnancies, but this should be confirmed by a specific study.

Strengths of the study
The first strength of the study comes from the fact that our protocol follows the best practice for health economic evaluation guidelines from the Canadian Agency For Drugs And Technologies In Health. Moreover, this study was supervised by an expert team who validated the models, data on parameters, costs and screening strategies that reflect the current various prenatal screening programmes in Canada. Moreover, our simulations were cost-effective compared with the option consisting of a screening programme for common trisomies. Moreover, we also observed that TMPS strategy comes out as the more costly but also less effective compared with MPSS strategy.
performed taking into account various situations faced or that could be faced by decision-makers. The situations related to the present first-tier test available, and the sociological and ethical issues that might make some conditions poor candidates for a screening programme. In total, nearly 800 options were analysed.

Furthermore, we confirmed the robustness of our result by performing sensitivity analyses with a wide range of parameters to account for the uncertain parameters.

Limitations of the study
One of the limitations of this study is the scarcity of some data. There are some parameters (e.g., the decision of pregnant women if the inconclusive result of NIPS, the acceptance rate of NIPS as first-tier) that we could not retrieve from the literature on whether Canadian or other countries-based populations. Moreover, some parameters based on the scarcity of data (the performance of NIPS for detection of some SCAs, MM and RAs), hence, leading to large CIs.

Another limitation is the fact that the cost structure of the study is based on the information extractable from the Quebec healthcare administrative data banks. When an item is not offered by the public healthcare system as are the screening tests for candidate conditions evaluated in this study, it might be difficult to define how much they would cost and were provided to the population. For example, in the province of Quebec, screening for chromosomal anomalies of the fetus is limited to the search of T21, 13 and 18. The number of technical units needed to calculate costs that would be attached to the detection of another condition is more complex to detect, as the 22q11.2 deletion syndrome is unknown. In addition, the cost of NIPS might still be decreasing when additional conditions are added to the screening list. This could compensate for an increase in technical units’ numbers for the test, hence its cost compared with the present NIPS test cost. Nevertheless, the impact of a higher cost, if it increases, will be probably low, considering that it would represent a percentage of the cost of screening tests, that count for less than 10% of the total cost. Furthermore, in the sensitivity analyses on which are based the results and our conclusions, we took into account this concern by considering the CIs of the NIPS cost. The large CI likely includes the expected future cost of the expanded test.

Final limitation come from the fact that the burden of disease is not equal among the 10 chromosomal anomalies that we included in this study, for instance, children with Down syndrome has more severe intellectual disability compared with those with SCAs. Therefore, each decision-maker needs to take this point into consideration before making decisions.

CONCLUSION
From an economic perspective, in the NIPS as a first-tier test strategies, the expansion of NIPS to any chromosomal anomalies other than the three common trisomies is expected to be cost-effective. Ethical issues are now at the centre of the decision-making process when having to deal with the question of the expansion of an NIPS-based prenatal screening programme.

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Acknowledgements The authors would like to thank the Canadian Institutes for Health Research (CIHR), grant # #13527 for the financial support.

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Funding This work was supported by PEGASUS 2 project, which funded by Genome Canada, the Canadian Institutes for Health Research, Genome Quebec, Genome BC, Genome Alberta, the Quebec Ministère de l’enseignement supérieur, de la recherche, de la science et de la technologie, the Fonds de recherche Québec—Santé, the Fondation de l’Université Laval and the Centre de recherche du CHU de Québec. Grant #13527.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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