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Results: NIPT, at a base case price of $795, was more clinically effective and less costly (dominant) over both FTS and INT. NIPT detected 4,823 T21 cases based on 5,330 invasive procedures. FTS detected 3,364 T21 cases based on 108,364 procedures and INT detected 3,760 cases based on 108,760 procedures. NIPT detected 65% and 85% more T21 cases compared to INT and FTS, respectively while reducing invasive procedures by >95% and reducing euploid fetal losses by >99%. Total costs were $3,786M with FTS, $3,919M with INT and $3,403M with NIPT.

Conclusions: NIPT leads to improved T21 detection and reduction in euploid fetal loss at lower total healthcare expenditures.
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Based on a U.S. Population

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Introduction

Prenatal testing for fetal Down syndrome, which is most commonly caused by trisomy 21 (T21), is routinely performed for the majority of the 4 million women who give birth each year in the United States[1][2]. Testing for Down syndrome prenatally may involve non-invasive screening tests and/or invasive diagnostic tests such as amniocentesis or CVS. Conventional screening typically involves screening with blood serum markers in conjunction with ultrasound followed by diagnostic invasive procedures for screen positive results. Screening tests are non-invasive and safe but have false positive rates of approximately 5% and fail to detect up to 20% of T21 cases[3]. Screening tests can require multiple visits and specialized ultrasound assessments which are not universally available[4]. While numerous conventional screening methods are available, first trimester combined screening or both first plus second trimester markers integrated are preferred given their higher detection rates relative to other screening methods[5–7]. First trimester combined screening has the additional benefit of providing risk assessment earlier in pregnancy[8]. First trimester combined screening and integrated screening have T21 detection rates of 82-87% and 88-95%, respectively, at false positive rates of 5%[5, 9, 3]. Invasive procedures such as chorionic villus sampling (CVS) and amniocentesis are highly accurate but carry a risk of procedure related miscarriage[10].

A novel prenatal testing method that evaluates cell-free DNA (cfDNA) in maternal blood has recently become available. Non-invasive prenatal testing (NIPT) with cfDNA has been shown to be highly accurate, with T21 detection rates >99% at false positive rates <0.1%, across numerous studies[4, 11–16]. Professional societies have recently endorsed the use of NIPT for high risk pregnancies including its use for primary screening in women 35 years and older[17, 18]. Cost-effectiveness analyses have previously reported on conventional screening strategies for T21 detection[19, 20, 9]. One study has looked at the cost-effectiveness of NIPT but this was limited to NIPT being used solely as a contingent or
secondary screen[21]. As NIPT is a newer and more expensive test than the traditional screening tests, economic evaluation is an important part of evaluating NIPT for wider clinical adoption.

The objective of this study was to evaluate the cost-effectiveness of conventional screening with either first trimester combined or integrated screening versus NIPT with NIPT being used only for high-risk pregnancies.

**Methods**

Using DATA Pro (TreeAge Software Inc., Williamston, MA), we created a decision-analytic model to compare different prenatal screening strategies for fetal T21 detection in a general screening population. The screening strategies compared consisted of: (1) first trimester combined screening (FTS) which included measurement of serum markers pregnancy associate plasma Protein A (PAPP-A) and β-hCG as well as 1st trimester ultrasound including nuchal translucency (NT) measurement, (2) integrated screening (INT) which included FTS as well as Quad screening of serum markers (AFP, estriol, hCG, Inhibin A), and (3) non-invasive prenatal testing (NIPT) with cfDNA analysis in which NIPT was performed first line in women 35 years and older or in those with a medical or family history to place them at increased risk, or performed as a second line test in those who had a positive conventional screening test. The general structure of the Markov model is shown in Figure 1.

We searched MEDLINE from 1997 to 2012 for English-language literature using the terms DS, trisomy 21, prenatal screening, non-invasive prenatal diagnosis, non-invasive prenatal testing, and cell-free DNA analysis. In addition, we reviewed abstracts from national meetings, data from Medicare, and relevant data from Ariosa Diagnostics (San Jose, CA), Sequenom (San Diego, CA), and Verinata (Redwood City, CA), which represent companies marketing a non-invasive prenatal test.
For the analysis, we used a cohort of 4,000,000 pregnant women which represents the current estimated annual number of births in the U.S. The analysis is based on the entire cohort of women undergoing prenatal testing in the first trimester for each of the screening strategies with screening uptake rates as per Table 1. For each screening strategy, the first branch assigns probabilities for those that opt for screening versus those that decline screening. For those that proceed with screening, tests can result in true positives, false positives, true negatives, and false negatives. Invasive testing following a screening test is possible for each of the screening outcomes although the rates of invasive testing are higher for those that test positive versus those that test negative (Table 1). Fetal loss from invasive testing complications are captured as well as fetal loss from spontaneous and elective termination of pregnancies. In the model, fetal T21 is considered diagnosed only if confirmed by invasive testing. The estimated prevalence of T21 at time of screening (1st trimester) was 1 in 530 for the entire population and then adjusted accordingly when segregating into high and low risk women.

All costs are represented in 2012 USD. Cost items, which are listed in Table 1, included those associated with screening tests, invasive testing, office visits and counseling, termination procedures, and birth of children with T21. When possible, the Medicare 2012 Fee Schedule was used to estimate cost inputs. A range of cost values based on published literature were used for sensitivity analysis. The cost for screening and invasive testing was based on the total cost which included any expected payments by insurance as well as patient co-pays. Cost for performing a screening test was inclusive of the blood tests and imaging. For FTS and INT screening, a physician office visit cost was also included since NT requires a certified ultrasonographer and referral from a general practitioner or Ob/Gyn to a specialist may be necessary. NIPT testing following a positive conventional screen also incurred a physician office visit cost. The baseline cost for NIPT was $795 based on the lowest published list price (Harmony
Prenatal Test, Ariosa Diagnostics) and varied widely in sensitivity analysis. The baseline cost for Down syndrome was estimated based on direct medical costs as well as indirect costs. In sensitivity analysis, the cost of Down syndrome was also evaluated based solely on direct medical costs for the first 5 years of life as this may be of interest from a payer perspective[22]. Costs were adjusted with the medical component of the CPI and future costs discounted at 3%.

The primary outcomes of the analyses were total costs of each screening strategy, number of fetal T21s diagnosed and number of non-T21 fetal losses due to invasive procedures for each screening strategy. One-way sensitivity analyses were performed on all cost and effectiveness variables over the ranges specified in Tables 1 and 2. Two-way sensitivity analysis was performed on NIPT costs, FTS and INT costs, Down syndrome costs, termination rates, as well as detection and false positive rates of different screening modalities.

**Results**

Based on modeling, prenatal screening with NIPT led to higher T21 detection and fewer euploid fetal losses at a lower cost over both first trimester combined (FTS) and integrated (INT) screening, thereby making NIPT the dominant screening strategy (Table 2). Based on the cohort of 4 million pregnant women in the base case, NIPT detected 4,823 fetal T21 cases while FTS and INT detected 3,364 and 3,760 T21 cases, respectively. FTS led to 108,364 invasive procedures and INT led to 108,760 invasive procedures whereas NIPT led to 5,330 procedures. The number of euploid fetal losses due to unnecessary invasive procedures with FTS and INT was 525 for both strategies and was 3 with NIPT. In regards to clinical outcomes, NIPT detected 28-43% more T21 cases as compared to FTS and INT, and NIPT reduced invasive procedures by >95% and reduced by >99% the number of euploid fetal losses due to unnecessary invasive testing.
The cost per T21 case detected is shown in Table 2. As compared to FTS and INT, NIPT had a cost per T21 case detected that was 37% and 32% lower, respectively. The total screening strategy costs were $382,844,191 less with NIPT as compared to FTS and $516,534,401 less with NIPT as compared to INT. The savings with NIPT are driven both from reductions in invasive testing as well as Down syndrome costs (Figure 2). The additional benefit of fewer euploid fetal losses with NIPT was not assigned any economic value in the model. The screening cost per pregnant woman was $850.71 with NIPT, $946.42 with FTS, and $979.84 with INT.

Sensitivity analysis was performed on key variables using the ranges shown in Table 1. In one-way sensitivity analysis, NIPT remained the dominant strategy over INT in all analyses, and NIPT was dominant over FTS in the majority of analyses. At a Down syndrome cost of less than $212,000, NIPT was no longer cost saving compared to FTS. At the lowest Down syndrome cost of $150,000, the incremental cost of NIPT over FTS was $50,378,720 for the entire cohort or $12.59 per pregnant woman. Two-way sensitivity analysis on NIPT cost and Down syndrome birth cost demonstrated that NIPT remained cost saving compared to FTS at a NIPT cost of $697 or less at all Down syndrome birth costs. The lower Down syndrome birth cost in sensitivity analysis was chosen to specify only the direct medical costs in the first 5 years of life. A two-way sensitivity analysis on NIPT cost and accuracy of FTS and INT demonstrated that NIPT remained cost saving regardless of the false positive rate or T21 detection rate with FTS and INT.

**Discussion**

NIPT was the dominant screening strategy over both FTS and INT in our baseline assumptions as it led to more T21 cases identified, fewer invasive procedures and in turn fewer related euploid losses, and lower...
costs. Given the higher accuracy of NIPT, these findings are not entirely unexpected. False positive rates of less than 0.1% with NIPT allows for better triage of women to determine with greater specificity who should undergo invasive testing. The false positive rate of 5% with conventional screening methods such as FTS or INT not only leads to an unnecessary financial cost, but also to euploid fetal losses and maternal anxiety. With so much focus in health reform on achieving the Triple Aim of better health care quality, better access to care, and lower costs[23], it appears that NIPT may be one of those health care advances that will meet the Triple Aim.

In sensitivity analysis, NIPT remained the dominant screening strategy over INT in all scenarios and was dominant over FTS in most scenarios. Costs associated with NIPT and Down syndrome had the greatest influence on whether FTS or NIPT was the least costly screening strategy. At Down syndrome costs below $212,000, NIPT became more costly than FTS, but remained less costly than INT. Even at the lowest Down syndrome cost of $150,000, the incremental cost of using NIPT was only $12.59 per pregnant women. Since NIPT increases T21 detection by 1,459 cases and reduces euploid fetal loss by 522 cases as compared to FTS, the additional cost seems quite reasonable.

A previous cost-effectiveness analysis on NIPT only evaluated NIPT in the context of a secondary screen[21]. Our model evaluated NIPT in high risk women defined as those women who were not only screen positive from conventional screening, but also women who were 35 years and older. As per recent professional society guidelines such as those from the American Congress of Obstetrics and Gynecology and the Society for Maternal-Fetal Medicine[17, 18], NIPT is recommended in women 35 years and older, those with a prior medical or family history for increased trisomy risk, and in those women who are classified as high risk for trisomy based on other prenatal screening (including
ultrasound). This is the first study to demonstrate the cost-effectiveness of NIPT based on these recommendations from professional societies.

As with any cost-effectiveness analysis, there are limitations. The analysis is based on a theoretical cohort of women as well as assumptions on screening performance, uptake, and cost. Geography as well as provider and patient attitudes could lend towards different baseline assumptions. However, in our sensitivity analysis, the general observation of NIPT’s benefits over conventional screening methods held up. The analysis was also performed based on a U.S. population. Screening practices and costs can be quite different in other countries and so the findings here may not be generalizable outside the U.S. Our analysis also focused on NIPT being utilized in a high-risk population only. As future clinical data unfolds in support of the utility of NIPT in both low and high risk women, future cost-effectiveness analyses looking at NIPT in this context can be done.

NIPT represents a technological advance in prenatal screening that has high accuracy for fetal T21 detection. Based on our cost-effectiveness model looking at the U.S. population, NIPT when used for high-risk women can detect more T21 cases and at the same time reduce unnecessary invasive procedures and in turn fewer related euploid fetal losses. These clinical benefits are realized in the setting of also achieving cost savings. Future work should examine patient preferences towards such testing and the incorporation of such testing in broader populations.

Declaration of interest

KS and TM are paid employees of Ariosa Diagnostics

ABC is a clinical advisor for Ariosa Diagnostics
References


of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians
12(1):9–18


Table 1. Probability and cost variables

<table>
<thead>
<tr>
<th>Probability Variables</th>
<th>Baseline Estimate</th>
<th>Range</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td>T21 1st trimester prevalence, all women</td>
<td>1 in 530</td>
<td>(1 in 400 to 1 in 600)</td>
<td>[24, 19]</td>
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<tr>
<td>Proportion of T21 surviving to live birth</td>
<td>75%</td>
<td>(70-80%)</td>
<td>[19, 20]</td>
</tr>
<tr>
<td>FTS detection rate for T21</td>
<td>85%</td>
<td>(80-90%)</td>
<td>[3, 19]</td>
</tr>
<tr>
<td>FTS false positive rate for T21</td>
<td>5%</td>
<td>(2-10%)</td>
<td>[3, 19]</td>
</tr>
<tr>
<td>INT detection rate for T21</td>
<td>95%</td>
<td>(90-95%)</td>
<td>[3, 19]</td>
</tr>
<tr>
<td>INT false positive rate for T21</td>
<td>5%</td>
<td>(2-10%)</td>
<td>[3, 19]</td>
</tr>
<tr>
<td>NIPT detection rate for T21</td>
<td>99%</td>
<td>(98-99.9%)</td>
<td>[3, 19]</td>
</tr>
<tr>
<td>NIPT false positive rate for T21</td>
<td>0.10%</td>
<td>(0.01-0.2%)</td>
<td>[3, 19]</td>
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<tr>
<td>Proportion of women 35 years and older (AMA)</td>
<td>14%</td>
<td>(13-15%)</td>
<td>[25]</td>
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<tr>
<td>Proportion referred to another provider for FTS or INT</td>
<td>70%</td>
<td>(50-90%)</td>
<td>data on file</td>
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<tr>
<td>Proportion electing to undergo screening with FTS or INT</td>
<td>70%</td>
<td>(50-90%)</td>
<td>[3, 19]</td>
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<tr>
<td>Proportion AMA electing to undergo screening with NIPT</td>
<td>70%</td>
<td>(70-90%)</td>
<td>-</td>
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<tr>
<td>Proportion screen positive with FTS or INT that undergo screening with NIPT</td>
<td>100%</td>
<td>(95-100%)</td>
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<tr>
<td>Proportion that undergo invasive testing following positive FTS or INT</td>
<td>75%</td>
<td>(60-95%)</td>
<td>[3, 19]</td>
</tr>
<tr>
<td>Proportion that undergo invasive testing following positive NIPT</td>
<td>99%</td>
<td>(95-99%)</td>
<td>-</td>
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<tr>
<td>Fetal loss risk from invasive testing</td>
<td>1 in 200</td>
<td>(1 in 100 to 1 in 1,000)</td>
<td>[19, 26, 10]</td>
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<tr>
<td>Proportion electing to terminate with positive screening test</td>
<td>75%</td>
<td>(60-99%)</td>
<td>[19, 27]</td>
</tr>
</tbody>
</table>

**Cost Variables (USD)**

<p>| Cost of office visit with counseling | $120 | ($40-200) | see text |
| Cost of 1st trimester serum screen | $42.66 | ($30-100) | see text |
| Cost of 2nd trimester serum screen | $144.07 | ($75-300) | see text |
| Cost of NIPT | $795 | ($695-995) | data on file |
| Cost of 1st trimester ultrasound | $131.73 | ($75-300) | see text |
| Cost of NT | $127.98 | ($75-200) | see text |</p>
<table>
<thead>
<tr>
<th>Cost of invasive testing</th>
<th>$1,300</th>
<th>($500-2,000)</th>
<th>see text, [19, 20]</th>
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<tbody>
<tr>
<td>Cost of elective termination</td>
<td>$600</td>
<td>($350-1,200)</td>
<td>[19, 20]</td>
</tr>
<tr>
<td>Cost of Down syndrome</td>
<td>$677,000</td>
<td>($400,000-800,000)</td>
<td>[19, 20]</td>
</tr>
</tbody>
</table>
Fig 1. Simplified Markov model diagram showing FTS, INT, and NIPT screening flow
Fig 2. Cost breakdown for each screening strategy