Noninvasive prenatal testing for trisomy 21: Challenges for implementation in Australia

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The term ‘Non invasive prenatal testing’ is used to describe the rapidly emerging molecular technologies related to cell free DNA assessment that are being applied to prenatal screening for Down syndrome and other chromosomal abnormalities. This technology is now available to Australian women through a number of off-shore laboratories. We review the basis of this method of testing, the literature describing the effectiveness of NIPT in screening for trisomy 21 and the potential methods by which this tool could be incorporated into current screening strategies.

Key words: chromosomal abnormality, noninvasive prenatal test, prenatal screening, trisomy 21.

Introduction

In the last 18 months, a number of independent studies have reported that a fetus affected by Down syndrome can be effectively identified though ‘non-invasive’ molecular assessment of blood from high-risk women.\textsuperscript{1–10} This noninvasive prenatal test (NIPT) involves the analysis of cell-free DNA fragments in maternal plasma.\textsuperscript{11} The accuracy of NIPT for trisomy 21 has been demonstrated to be superior to all current methods of prenatal screening, both in high-risk and unselected populations.\textsuperscript{12,13} The test has been available in the United States and China for over 12 months and is now available in Australia. The rapid uptake of this test and its potential to revolutionise prenatal care make this an important topic for obstetricians to understand. In this review, we give a brief description of the laboratory processes involved in NIPT and discuss the advantages and limitations of this test. We also examine several potential models for incorporating this test into Australian prenatal care, where combined first-trimester screening currently dominates.

Cell-Free DNA in Maternal Plasma and Advances in Sequencing Technology

During pregnancy, a proportion of cell-free DNA in maternal plasma can be proven to be fetal in origin.\textsuperscript{11} This is believed to be a product of placental remodelling. As trophoblast cells undergo apoptosis, cell-free nucleic acids are released into the maternal circulation.\textsuperscript{14} These fragments are rapidly cleared after delivery and thus only reflect the genome of the current pregnancy.\textsuperscript{15,16} In circumstances where the fetus has unique paternally inherited DNA sequences (for example, a Y chromosome in a male fetus or the RHD gene where the mother is RhD negative) cell-free fetal DNA can be identified in maternal blood using conventional molecular genetic techniques such as PCR. This form of prenatal diagnosis is already used in clinical practice to determine fetal sex in pregnancies at risk of X-linked disease and in defining risk of isoimmunisation in sensitised RhD negative women.\textsuperscript{17,18} The technical challenge of assessing chromosome dosage in the fetus using maternal plasma is made harder by the absence of unique fetal DNA sequences. Recent advances in sequencing technology and bioinformatics were major breakthroughs for the assessment of fetal aneuploidy. In contrast to the noninvasive diagnosis of paternally inherited genes, NIPT for fetal aneuploidy involves the combined analysis of both maternal and fetal cell-free DNA. ‘Next generation’ or massively parallel sequencing (MPS) technology is used to sequence a portion of each DNA fragment in a maternal plasma sample. The sequence of each fragment is then mapped to a reference genome to identify its chromosome of
origin. The number of DNA fragments arising from each chromosome can then be counted, allowing the identification of fetal trisomy 21 by the relative overrepresentation of chromosome 21 in maternal plasma. The cell-free fetal DNA load is relatively small compared with the total (maternal and fetal) load: the median ‘fetal fraction’ is typically around 10%. Therefore, millions of sequence counts per sample have to be made to provide the statistical precision for a reliable diagnosis of trisomy 21.

**Clinical Validity Studies in High-Risk Women**

There are at least ten studies reporting the efficacy of noninvasive prenatal testing (NIPT) for trisomy 21 using next generation sequencing in high-risk populations (Table 1).1–10 Inclusion criteria included women undergoing invasive testing for advanced maternal age, high-risk screening result, family or personal history of a previous affected pregnancy, or another genetic condition meriting invasive testing. These studies, produced by academic groups in association with five commercial partners, vary in their sequencing and bioinformatic methodologies. From the sequencing perspective, massively parallel sequencing of random fragments of cell-free DNA in maternal plasma requires the analysis of a large number of DNA sequences, but provides the potential for genome-wide assessment of whole fetal chromosomes as well as subchromosomal abnormalities.3,6,20 In contrast, a targeted method that selectively analyses fragments from chromosomes 21, 18 and 13 is more cost-effective and has faster throughput, but has the potential disadvantage of providing less genomic information.5,7,8

Drawing these data together, the sensitivity of noninvasive prenatal testing for detecting trisomy 21 is 99.5% and the specificity is 99.8%. The positive likelihood ratio generated from a positive screening result is 497.5, whilst the negative likelihood ratio for a negative result is 0.005. This is therefore the most efficient screening tool available in screening for Down syndrome. Whilst the detection rate for trisomy 18 has also been shown to be 99%, detection rates for trisomy 13 are lower (79–92%).6,21 There are several reasons for this. First,

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Studies reporting the effectiveness of noninvasive prenatal testing for trisomy 21 in high-risk populations</th>
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<tbody>
<tr>
<td>Author and commercial partner</td>
<td>Gestational age</td>
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<tr>
<td>Ehrich et al.2</td>
<td>16 (8–36) weeks</td>
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<td>Sequenom</td>
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<tr>
<td>Chiu et al.1</td>
<td>13 weeks</td>
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<td>Sequenom</td>
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<tr>
<td>Palomaki et al.3</td>
<td>15 (9–21) weeks</td>
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<td>Sequenom</td>
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<tr>
<td>Sehnert et al.4</td>
<td>15 (10–28) weeks</td>
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<td>Verinata</td>
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<tr>
<td>Bianchi et al.6</td>
<td>16 (8–31) weeks</td>
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<td>Verinata</td>
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<tr>
<td>Sparks et al.8</td>
<td>18 (10–36) weeks</td>
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<tr>
<td>Ariosa</td>
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<tr>
<td>Norton et al.7</td>
<td>16 (10–38) weeks</td>
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<td>Ariosa</td>
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<tr>
<td>Ashoor et al.5</td>
<td>13 (11–13) weeks</td>
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<tr>
<td>Ariosa</td>
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<tr>
<td>Lau et al.9</td>
<td>14 (≥12) weeks</td>
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<tr>
<td>Beijing Genomics Institute</td>
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<tr>
<td>Zimmermann et al.10</td>
<td>17 (9–36) weeks</td>
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<td>Natera</td>
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<td>Total</td>
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*Results for both 8-plex and 2-plex sequencing shown. Only the 2-plex analysis was included in the overall calculation of sensitivity and specificity.
†Risk threshold of <1 in 100 used for positive result.
‡Only the results for the blinded validation set (n = 167) shown.
§Four patients with unclassifiable data were successfully resampled.
¶A ‘redraw’ rate of 7.7% and a ‘no call’ rate of 0.5% have been described more recently, although these data have not been published in a peer-reviewed journal.

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chromosome 13 has a lower guanine and cytosine content than chromosome 21, leading to a sequencing bias that requires statistical correction.\textsuperscript{22,23} Second, whilst the fetal fraction of cell-free DNA is increased in maternal serum of women carrying pregnancies affected by trisomy 21, this is not the case in trisomy 13, so test resolution is lower.\textsuperscript{24} Third, trisomy 13 is much less common than trisomy 21, reducing the precision of risk estimates. However, the four groups that currently operate commercial laboratories in the United States have now validated their tests for trisomies 18 and 13 in high-risk women.\textsuperscript{4–6, 10, 21, 23} Most also offer an option for reporting on sex chromosome abnormalities and gender. Sequenom is currently the only provider that offers their assay for use in multiple pregnancies.\textsuperscript{25}

NIPT in Mixed-Risk Screening Populations

Only two studies to date have examined the performance of NIPT in unselected or mixed-risk screening populations. A large cohort study of a first-trimester screening population found that NIPT performance for trisomy 21 was equivalent to that previously reported in high-risk populations.\textsuperscript{12} A multicentre study in China similarly found high sensitivity and specificity rates in a mixed-risk population in a routine clinical setting.\textsuperscript{13} These data are reassuring, given that the technical factor that most influences test performance, fetal fraction, appears unrelated to maternal age or pre-existing risk factors.

Test Failure and Fetal Fraction

Provision of an NIPT result is dependent on the DNA sample being of sufficient quality and on the fetal fraction being sufficient to allow precise segregation of normal and abnormal results during the bioinformatic analysis. Samples with low fetal fractions (<4%) may not produce an interpretable test result. Maternal venous blood samples can now be collected in specialised tubes with stabilisers that prevent maternal cellular breakdown, thereby maximising the fetal fraction of cell-free DNA.\textsuperscript{26} As a consequence, the proportion of cases that are unassessable due to low fetal fraction has been reduced from approximately 5 to <2%.\textsuperscript{7} The sample is robust enough to be transported at ambient temperature, reducing the cost of transferring samples to centralised laboratory facilities. This is particularly relevant for the Australian setting where samples are currently transported to overseas laboratories for analysis. Assay failure may also occur in up to 2% of samples, leading to overall test failure rates of 1–4%.

Two of the major biological factors affecting fetal fraction are gestational age and maternal weight. All current NIPT providers have a lower limit of 10 weeks gestational age for testing because the median fetal fraction is not reliably high enough until this gestation. By 11–13 weeks, the median fetal fraction is 10% and test failure rates are low.\textsuperscript{24} Maternal weight has an inverse relationship with fetal fraction; more than half of women weighing over 160 kg have a fetal fraction below that required for an adequate test performance.\textsuperscript{19} This may either be due to a dilutional effect within the maternal circulation or due to increased adipocyte turnover and concentrations of maternal cell-free DNA.\textsuperscript{24} However, there appears to be no association of fetal fraction with maternal age, fetal sex or other pre-existing risk factors for aneuploidy.

Multiple pregnancy also appears to result in a lower per fetus fetal fraction than singleton pregnancies, which exacerbates the technical challenges of performing NIPT in multiple pregnancies.\textsuperscript{27} Whilst there are a small number of studies examining NIPT in twins and triplet pregnancies, further data are required to determine the robustness of NIPT in multiples.\textsuperscript{25,28} As more data on the biological influences on fetal fraction emerges, compensatory techniques, including deeper sequencing, may be employed selectively to reduce test failures in these challenging samples.

NIPT as an ‘Advanced’ Screening Test for High-Risk Women

For most tests currently marketed, the bioinformatic process that defines positive and negative results on the basis of ‘Z’ scores inherently dictates that there will be false-positive and false-negative results. This test should therefore not be regarded as being diagnostic, but as being a highly effective screening test. Due to the low prevalence of Down syndrome in a population, the positive predictive value of the screening tool in a low-risk population will be, at best, 50% and abnormal results require confirmation by amniocentesis or chorionic villus sampling. False-positive results have been reported in association with maternal tumours.\textsuperscript{29} Cases of mosaicism have been detected, but, as the fetal component of cell-free DNA appears to originate from the trophoblast, it is important to recognise that fetal mosaics may be missed and confined placental mosaics may be reported as false positives.\textsuperscript{30,31}

Non-invasive prenatal test is currently positioned as an ‘advanced screening test’ for women at increased risk of aneuploidy (Fig. 1).\textsuperscript{32,33} Its excellent specificity allows women at increased risk of an affected fetus to more confidently decline invasive testing if the NIPT result is normal. However, it must be remembered that the invasive diagnostic test that usually follows a conventional high-risk screening result detects a whole range of chromosomal abnormalities in addition to trisomy 21, 13 and 18. Approximately 30% of abnormal results found after first-trimester screening involve other abnormalities than these common trisomies.\textsuperscript{34} This 30% rate is consistent with the cohort data from two of the large prospective studies of high-risk women undergoing NIPT. In these studies, trisomy 21 only comprised 40% of all the chromosome abnormalities detected by karyotype.\textsuperscript{6,7} When trisomies 21, 18, 13 and sex chromosome abnormalities were combined,
this made up 70% of chromosome abnormalities. NIPT providers now offer a routine combined assessment for these common trisomies and the sex chromosomes, which would be expected to have an additive effect on the screen positive rate.

The potential of NIPT to miss atypical chromosome abnormalities can be compared with that of rapid aneuploidy detection by quantitative fluorescence (qf)-PCR or fluorescence in situ hybridisation (FISH), which are commonly used after invasive testing. Extrapolating from data comparing the diagnostic yield of qfPCR to a full karyotype, up to one-third of chromosome abnormalities could be missed by NIPT. Whilst most of these abnormalities would be benign, 10% of these undetected abnormalities carry a substantial risk of phenotypic abnormality. High-risk women who are using NIPT to decide whether or not to proceed with invasive testing need to be aware that whilst a normal NIPT result may allow them to avoid the 1% risk of miscarriage associated with invasive testing, there is a 2.5% risk of an undetected atypical chromosomal anomaly. This needs to be balanced against the advantages of NIPT in removing pre- and post-test-related anxiety and the potential psychological impact of miscarrying a chromosomally normal fetus.

Furthermore, the recent introduction of prenatal chromosome microarrays has increased the resolution of chromosome analysis after invasive testing far beyond the traditional G-banded karyotype. Invasive testing with chromosome microarray analysis is now the preferred tool for karyotyping high-risk fetuses, such as those with structural anomalies visible on ultrasound. Approximately 6–8% of structurally abnormal fetuses have a submicroscopic deletion or duplication detected on chromosome microarray that would be missed through standard cytogenetic evaluation. In some Australian practices, prenatal chromosome microarrays have already replaced conventional karyotype for all pregnancies undergoing invasive testing. It is important to recognise that NIPT is unable to detect these submicroscopic abnormalities, although this may change in the future with improvements in sequencing depth.

Therefore, invasive testing is still recommended in the presence of a fetal structural anomaly.

NIPT and Prenatal Screening in Australia

Non-invasive prenatal testing is rapidly being adopted in the United States of America, where the traditional model of prenatal screening is significantly different to that offered in Australia. Most American women are screened through second trimester biochemistry – generally recognised as a test of modest efficacy (70% detection rate for trisomy 21 with 95% specificity). NIPT, like second trimester biochemical screening, involves collection of a maternal venous blood sample and therefore offers an easy alternative with significant improvements in test performance. In contrast, the majority of Australian women have combined first-trimester screening, which involves individualised risk assessment accounting for maternal age, the appearance of the fetus (through ultrasound imaging of nuchal translucency ± nasal bone) and biochemical measures of placental function (free β human chorionic gonadotrophin (βhCG) and pregnancy-associated plasma protein A (PaPP-A)). The baseline for test performance is higher than that seen in the United States; combined first-trimester screening identifies 90% of pregnancies affected by trisomy 21 at a 3% screen positive rate.

Direct replacement of first-trimester screening by NIPT may mean the loss of several benefits conferred by ultrasound assessment. As discussed above, combined first-trimester screening can detect a wide range of chromosome abnormalities beyond those assessed by NIPT.
ultrasound and biochemical screening components also have utility beyond the prediction of aneuploidy. Accurate dating, early diagnosis of multiple pregnancy and identification of chorionicity are important functions of first-trimester ultrasound.\textsuperscript{45} An increased nuchal translucency can also be a marker for other structural anomalies such as cardiac abnormalities.\textsuperscript{46} Approximately 44% of structural anomalies in euploid fetuses can also be identified at the time of the 12-week scan.\textsuperscript{47} Abnormal biochemistry, such as a low PaPP-A, is associated with adverse obstetric outcomes, including pre-eclampsia, intrauterine growth restriction and intrauterine fetal death.\textsuperscript{47–49}

Other jurisdictions that have high penetrance of first-trimester screening have concluded that NIPT would be best incorporated alongside existing screening programs, thus providing women with more effective screening but keeping the additional information obtained at the 11–13 week ultrasound.\textsuperscript{50} Whilst this may be the best option from a clinical and ethical perspective, it does not take any account of the economics of routine NIPT assessment; this test currently retails at $800–$1400 in Australia.

Limiting cost-benefit analysis to the detection of pregnancies affected by Down syndrome, direct replacement of combined first-trimester screening with NIPT would allow a 9% improvement in detection and a reduction in the screen positive rate from 5.0 to 0.2%. Five thousand women would need to be screened to detect one extra Down syndrome fetus, but 240 of them would avoid invasive testing. Assuming costs of $250 for combined first-trimester screening, $500 for invasive testing and $1000 for NIPT, such a policy replacing current testing strategies with NIPT will cost $3.6 million for each extra Down syndrome fetus detected and will prevent the loss of one normal pregnancy through miscarriage related to invasive testing. There is currently no published cost-benefit analysis demonstrating the advantage of this form of screening; although it is important to recognise that these models rarely account for the psychological impact of false-negative screening results or of iatrogenic injury.

**Models for Incorporation of NIPT into Clinical Practice**

There are currently no Australian guidelines defining the place of NIPT in prenatal screening and diagnosis. Guidelines produced by the American College of Obstetrics and Gynecology and by the International Society for Prenatal Diagnosis advise that the use of NIPT should be considered in ‘high risk’ pregnancies only.\textsuperscript{52,53} This advice, based on published data available to these groups at the time of making these recommendations, only takes advantage of the negative predictive value of NIPT to reducing invasive testing in high-risk women (Fig. 1). This model would reduce the invasive testing rate by >90% but would not alter the overall sensitivity of screening. It has the advantage that only 5% of women, with a high-risk combined first-trimester screen result, need have NIPT. It has the disadvantage that ‘atypical’ chromosomal abnormalities that would be detected by invasive testing will be missed by NIPT.

At the other end of the spectrum is the model proposed by Nicolaides et al.\textsuperscript{12} where NIPT would be offered to all women in conjunction with first-trimester ultrasound (Fig. 2). NIPT testing at 10 weeks and first-trimester ultrasound at 12 weeks would take full advantage of the superior detection rate of NIPT without losing the benefits of first-trimester ultrasound. The timing would also allow the small proportion of women who have NIPT test failure to access combined first-trimester screening (by offering both ultrasound and biochemical serum markers at 12 weeks). This model would reduce the invasive testing rate by >90% and increase the overall sensitivity of screening to 99%. It has the advantage that fetuses with structural anomalies are still assessed for atypical chromosomal abnormalities. It has the disadvantage that it is expensive.

A third model retains combined first-trimester screening as the primary screening tool and uses NIPT as a second tier screen for those at an intermediate risk to help define whether invasive testing is needed (Fig. 3). This takes advantage of the data demonstrating equivalent efficacy in an unselected first-trimester screening population\textsuperscript{12} and of the current strengths of combined first-trimester screening. Several providers in Australia are already providing NIPT using this model, with some minor variations in the threshold for high-risk pregnancies (1:10–1:50).

This contingent approach defines three rather than two risk groups after combined first-trimester screening. The first is a small (<0.5%) group of women who have a very high (>1:10) risk result or sonographically detected structural abnormalities.\textsuperscript{44–47} These women may be at higher risk of atypical chromosomal anomalies in the fetus and would benefit from being directed towards diagnostic testing (karyotype ± chromosome microarray). This group typically includes 70% of all fetuses affected by trisomy 21. At the other extreme, women with a risk <1:1000 are very unlikely to have a fetus affected by trisomy 21. In current practice, this risk cohort includes approximately 85% of pregnancies but only 1–2% of trisomy 21 fetuses.\textsuperscript{44} Further screening of this cohort by NIPT would not be cost-effective. In between these extremes lie a group of women with an intermediate level of risk (1:10–1:1000) who could be offered NIPT.

Counselling for women in this intermediate risk group will differ for those that have a risk between 1:10 and 1:300 (who would traditionally have been advised to have an invasive test) and those with a risk of 1:300–1:1000 (who would traditionally have been advised that they were of low risk). 4.5% of women who have a risk of 1:10–1:300 will avoid amniocentesis, but should be aware of the small risk of undetected atypical chromosomal abnormalities with NIPT. 8.5% of screened women, with a risk between 1:300 and 1:1000 would traditionally have been counselled that
their pregnancy was low risk; discussion of the difference of this assessment to amniocentesis would be less relevant. Whilst careful counselling would be necessary to avoid creating anxiety and undermining confidence in the cFTS results, this approach would give women greater freedom to determine their own risk thresholds for invasive testing or secondary screening with NIPT. 4.6% of women with risk estimates <1:300 still elect to have some form of invasive testing, so this approach actually has the potential to further reduce invasive testing rates whilst improving detection of trisomy 21.51

Contingent screening would result in a larger proportion (15%) of women being offered NIPT than those traditionally described as high risk and would provide an 8% increase in detection rates for trisomy 21. No clinical trials describing either the effectiveness or the acceptability of this approach have been published. This model also fails to incorporate data on the detection of chromosomes 18, 13 or monosomy X, which are now included in most commercial NIPT assays.

**Ethical Implications of NIPT**

One of the major ethical barriers to implementation of NIPT is the inequity of access to this test due to the financial cost. As women pay the entire cost themselves, NIPT will not be a feasible option for many women. There is a risk of creating dissatisfaction in cFTS by informing women that a superior test exists that is only available to wealthy women. Given that our current public system is of a high standard, we may be doing ourselves and our patients a disservice if we inadvertently undermine confidence in cFTS.

Other ethical implications of NIPT are not unique to this technology, but are exacerbations of general issues in

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**Figure 2** Using Non Invasive Prenatal Testing (NIPT) in addition to first trimester ultrasound (US) for all women. A decision to proceed to invasive testing depends on a positive NIPT result and/or finding of an abnormality on scan.

**Figure 3** An alternative ‘contingent’ model for Non Invasive Prenatal Testing (NIPT) as an adjunct/second tier screening tool after combined first trimester screening (cFTS).
prenatal diagnosis. Foremost amongst these concerns is that noninvasive testing will become a routine, without adequate pretest counselling and informed consent. 52 NIPT is particularly prone to this danger because it is a blood test that can be ordered along with many other early pregnancy tests, and it does not pose any miscarriage risk. Professional bodies are unanimous in concluding that NIPT should not be part of a routine prenatal laboratory assessment, but should be an informed choice made after pretest counselling and adequate opportunity for reflection. 32,33,53

An additional ethical consideration in NIPT is the potential for unintended diagnosis of a maternal condition. An important distinction of NIPT from current methods of prenatal testing is that it analyses maternal as well as fetal DNA. Women must be informed that there is a small, unquantified risk of incidental findings relevant to their own health as a result of NIPT. A reported example of this situation was the unexpected diagnosis of maternal 47,XXX in a woman with an euploid fetus. 54

Priorities for Australian Research

Now that the science of NIPT has been well validated, our profession must address the challenges of successful implementation of this technology. None of the clinical validation studies have assessed the effects of NIPT on clinical management or patient outcomes. Anecdotal evidence from the USA of substantial reductions in amniocenteses as a result of NIPT suggests that it is already having a major impact on clinical care.

We urgently need Australian data on the attitudes and preferences of patients and caregivers. The models outlined in this article make broad assumptions about women’s choices and clinical management decisions that may not be valid. Importantly, the effect of financial cost on decision-making is unknown. It is also unknown whether the additional diagnoses of Down syndrome via NIPT would result in a reduction in live births of affected infants. A recent survey from the Netherlands suggests that the availability of NIPT may lead to more women accepting Down syndrome screening without the intention to terminate an affected fetus. 55 This has obvious implications for economic cost-benefit analyses and highlights the need for more research.

Any prospect of NIPT achieving public funding support will require a cost-benefit analysis based on our own population data. At a minimum, current providers of NIPT in Australia should prospectively collect data on NIPT uptake and patient outcomes for audit and monitoring purposes. This information may also help inform future policy making.

Conclusions

There are currently no Australian guidelines defining the place of NIPT in prenatal screening and diagnosis, although drafting of an RANZCOG statement is underway. It appears to be too early to be prescriptive about the place of NIPT in Australia given that the costs are directly born by the patient and our established first-trimester screening program works well. As a first step, practitioners need to be informed about the benefits and limitations of the technology and be prepared to discuss these in a balanced manner with women. In particular, we should exercise caution regarding the performance of NIPT outside of trial conditions and recognise the reduced positive predictive value of NIPT when used on average or low-risk women.

Ideally, NIPT should be incorporated into a well-designed screening program based on informed decision-making and equity of access. The current ad hoc use of NIPT based upon patient request and ability to pay is suboptimal from a public health perspective. To determine whether there is a case for public funding of NIPT, we need to assess its cost-effectiveness within specific clinical pathways. Until then, inequity of access and inappropriate use may remain major barriers to maximising the benefits of NIPT in our country.

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