

# New screen on the block: non-invasive prenatal testing for fetal chromosomal abnormalities

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## ABSTRACT

Non-invasive prenatal testing (NIPT) is a new screen for fetal chromosomal abnormalities. It is a screening test based on technology that involves the analysis of fetoplacental DNA that is present in maternal blood. This DNA is then analysed for abnormalities of specific chromosomes (eg 13, 18, 21, X, Y). NIPT has a much higher screening capability for chromosomal abnormalities than current combined first trimester screening, with ~99% sensitivity for trisomy 21 (Down syndrome) and at least a 10-fold higher positive predictive value. The low false-positive rate (1–3%) is one of the most advertised advantages of NIPT. In practice, this could lead to a significant reduction in the number of false-positive tests and the need for invasive diagnostic procedures. NIPT is now suitable for singleton and twin pregnancies and can be performed from ~10 weeks in a pregnancy. NIPT is not currently publicly funded in most countries. However, the increasing availability of NIPT commercially will likely lead to an increase in demand for this as a screening option. Given the high numbers of women who visit a general practitioner (GP) in their first trimester, GPs are well-placed to also offer NIPT as a screening option. A GP's role in facilitating access to this service will likely be crucial in ensuring equity in access to this technology, and it is important to ensure that they are well supported to do so.

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## Introduction

Prenatal testing for chromosomal abnormalities has been part of antenatal care in New Zealand for the last 40 years. Screening initially used maternal age as an indication for invasive procedures such as amniocentesis and, more recently, it combines the results from blood tests (B-HCG and Pregnancy Associated Plasma Protein A) and a Nuchal translucency ultrasound in the first trimester or maternal serum screening in the second trimester. In the last 4–5 years, a new technology has emerged for the screening of fetal chromosomal abnormalities – non-invasive prenatal testing (NIPT). The aim of this viewpoint article is to provide a summary of current understanding of NIPT, to discuss how NIPT may fit within general practice, and the role of general practitioners (GPs) in providing this new technology.

## What is non-invasive prenatal testing (NIPT)?

Non-invasive prenatal testing (NIPT) is a screening test based on technology that analyses the fetoplacental DNA present in maternal blood (Table 1).<sup>1–3</sup> This technology is based on the discovery in 1997 that cell-free DNA, including that from the fetus and placenta, can be isolated and analysed from the blood of pregnant women.<sup>1,2,4</sup> NIPT was first released in Hong Kong in August 2011 and soon after was introduced commercially in the US in October 2011. Clinical translation of NIPT technologies has advanced rapidly. Commercially available NIPT identifies the most frequently observed chromosome aneuploidies, including Down syndrome (trisomy 21), Edward syndrome (trisomy 18), Patau syndrome (trisomy 13), and common sex chromosome aneuploidies

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such as Turner syndrome (X) and Klinefelter syndrome (XXY).<sup>1-3</sup> NIPT is not a diagnostic test, but its high sensitivity (true positive rate) and specificity (true negative rate) make it an attractive alternative to the serum screens and ultrasound currently in use.

For determining both fetal sex and rhesus D status, NIPT is considered diagnostic.<sup>5</sup> The National Institute for Clinical Excellence (NICE) has recommended it as a 'cost-effective option to guide antenatal prophylaxis with anti-D immunoglobulin, provided that the overall cost of testing is £24 (approx. NZ\$40) or less.'<sup>6</sup> NIPT may prove beneficial in New Zealand, especially in light of the National Maternity Monitoring Group's work around improving the management of rhesus disease.<sup>7</sup> NIPT can also be used (where familial incidence indicates) to screen for single-gene disorders such as cystic fibrosis, Huntington's disease and thanatophoric dysplasia.<sup>5</sup> Furthermore, proof of concept has been demonstrated for sub-chromosomal abnormalities such as copy number variants or microdeletions, which may lead to a variety of conditions involving physical abnormality and cognitive delay.<sup>1</sup> As of 2014, tests are commercially available for abnormalities on chromosomes 1p, 5p, 15q, 22q, 11q, 8q and 4p.40,41. The specificity and sensitivity of these tests, however, has not yet been validated. Proof of concept genome-wide screening has also been demonstrated, but again, not clinically validated.<sup>1,8</sup>

## Clinical performance of NIPT

The clinical performance of NIPT is reported as 99% sensitive for trisomy 21, with positive predictive values ranging from 45% to 99%,<sup>4,9-12</sup> which even at the lower range is 10-fold better than current antenatal screening.<sup>13</sup> The low false-positive rate (1-3%) is one of the most advertised advantages of NIPT. In practice, this could potentially lead to a significant reduction in false-positive tests, and the need for invasive diagnostic procedures. In terms of other trisomic conditions, sensitivities (based on meta-analyses) for NIPT are reported to be between 91%<sup>10</sup> to 93%<sup>12</sup> for trisomy 18 and 90%<sup>10</sup> to 95%<sup>12</sup> for trisomy 13 (with positive predictive values at 84% and 87% respectively).<sup>9</sup>

## Clinical and technical considerations

Non-invasive prenatal testing (NIPT) is not a diagnostic test, with confirmation required by invasive diagnostic procedures such as amniocentesis.<sup>2,4</sup> NIPT cannot detect neural tube defects, but combining NIPT with a first trimester scan may overcome this potential disadvantage.<sup>14</sup> False-positive results have been reported, although at much lower rates than current screening, and are thought to occur due to discrepancy between the chromosomal make-up of the cells in the placenta and the cells in the baby, the fetal death of a co-twin or maternal malignancy.<sup>2,4</sup> Because fetoplacental DNA is present early in pregnancy, NIPT can be performed from as early as 10 weeks in pregnancy or even earlier. The freely circulating fragments of DNA remain in the maternal circulation for only hours or, at most, a day or two after each pregnancy, making it suitable for pregnancy-specific testing.<sup>2,4</sup>

In terms of technical considerations, all tests have a limit of detection. For NIPT, this is linked directly to the amount of fetoplacental DNA compared to all DNA, which includes maternal DNA.<sup>2,4</sup> In turn, the amount of fetoplacental DNA, the 'fetal fraction', is linked to gestational age (which increases over time) and influenced by maternal BMI (where fetoplacental DNA is 'diluted' due to larger circulatory volume).<sup>2,4</sup> The technical aspect of NIPT platforms and the way the risk result is generated (either comparing

Table 1. Salient points regarding screening with non-invasive prenatal testing (NIPT)

NIPT overview	NIPT limitations
NIPT is based on technology that analyses fetoplacental DNA circulating in the maternal blood stream	NIPT is not a diagnostic test
It is an advanced screen for chromosomal abnormalities	It does not screen for structural defects
NIPT can be used from 10 weeks in pregnancy	Currently not publicly available, and costs~ NZ\$600
Samples are processed in New Zealand and sent overseas for analysis	Not suitable for triplet and higher multiples
Turn-around time for results is usually within 1 week	Depending on the analytical approach, NIPT may not be suitable for donor pregnancies

to a hypothetical or maternal genotype) also influences what type of pregnancy is amenable to NIPT screening.<sup>4</sup> For example, NIPT screens based on SNP (single nucleotide polymorphism) technology, such as Panorama® (Natera Inc., USA) are not suitable for donor pregnancies. The issue of reporting fetal fraction is considered to be an important aspect of quality assurance to providers,<sup>15</sup> and in counselling and reporting the results back to pregnant women.

As with all tests, NIPT does fail to produce a result, reportedly ~5% of the time.<sup>4</sup> This is thought to be due to inadequate blood volume being drawn and hemolysis during transportation or storage.<sup>16</sup> A failed result may be due to a failure in extracting DNA, amplification or sequencing, and may require another blood sample being taken, which could contribute to a negative experience for the expectant mother and delay in obtaining the result.<sup>16</sup>

### Access to NIPT in New Zealand

Currently, NIPT is available to all women in New Zealand on a user-pays service (a for-profit-model) and it is not regulated. Anecdotal evidence suggests that NIPT is being accessed on an ad-hoc basis, with some District Health Boards (DHBs) offering an appointment at obstetric clinics for the blood draw, and others not. Women must also pay for a private obstetric consultation in addition to the NIPT screen. The cost of an NIPT screen is ~ \$500–\$600, rising to over \$2000 with expanded screens, which for a large number of New Zealand women and whānau, would be prohibitive.

The National Screening Unit (NSU) and Ministry of Health are currently exploring the implementation of NIPT in New Zealand, and it is likely to be funded in some form. It may, for example, be offered only to women who have a risk result from serum and ultrasound screening, which is similar to the UK<sup>17</sup> and Canada, but emerging evidence indicates that women want NIPT as a first-line option,<sup>18,19</sup> as do maternity care providers.<sup>20</sup>

The American College of Medical Genetics and Genomics 2016 statement describes 'New evidence strongly suggests that NIPS can replace

conventional screening for Patau, Edwards, and Down syndromes across the maternal age spectrum, for a continuum of gestational age beginning at 9–10 weeks, and for patients who are not significantly obese.'<sup>21</sup> In the Netherlands, NIPT has been offered since 2014 as an alternative option to invasive testing for pregnant women at increased risk of having a child with trisomy 21, 18 or 13 based on the first trimester combined test (cut-off 1:200) or because of a previous child with these trisomies.<sup>22</sup> In 2016, the National Screening Committee in the UK announced that starting in 2018 (to allow time for training), NIPT will be publicly funded initially as a contingent screen dependent on selected risk cut-off scores. The introduction of NIPT in the UK has come about from a concerted and considerable amount of work and research over 10 years, covering areas such as detailed health economic evaluation, optimal ways to deliver education to women and healthcare professionals, and evaluation of sensitivity and specificity of NIPT for aneuploidy when performed in a NHS regional genetics laboratory.<sup>23</sup> Although the UK could well-serve as a model for New Zealand, the increasing availability (influenced by increasing market pressure) of NIPT in New Zealand implies an urgent need for practice support around this technology.<sup>24</sup>

### Requesting NIPT in New Zealand

There is no capability, as yet, for NIPT samples to be analysed in New Zealand, as all samples and resultant health information are analysed and stored overseas. Currently, at the time of publishing there are four options for NIPT analytical services available to New Zealand women: (1) Victorian Clinical Genetics Services (percept™, Australia); (2) BGI Diagnostics (Nifty™, China); (3) Southern Community Laboratories (SCL) (Harmony™, USA); and (4) sequenca (Sequenom tests: VisibiliT™, MaterniT®21, MaterniT21® PLUS and MaterniT™ GENOME). A referral by a GP, obstetric provider or midwife is required for SCL where an additional appointment needs to be made for the blood draw, and the test costs \$675 (at the time of article submission). All of the testing companies require women to be at least 10 weeks gestation, as this usually means that there is sufficient fetal fraction for the test to be carried out. A typical turnaround time is ~7 days.

Requesting clinicians usually provide pre- and post-test counselling.

### What is the role of GPs and what do they need?

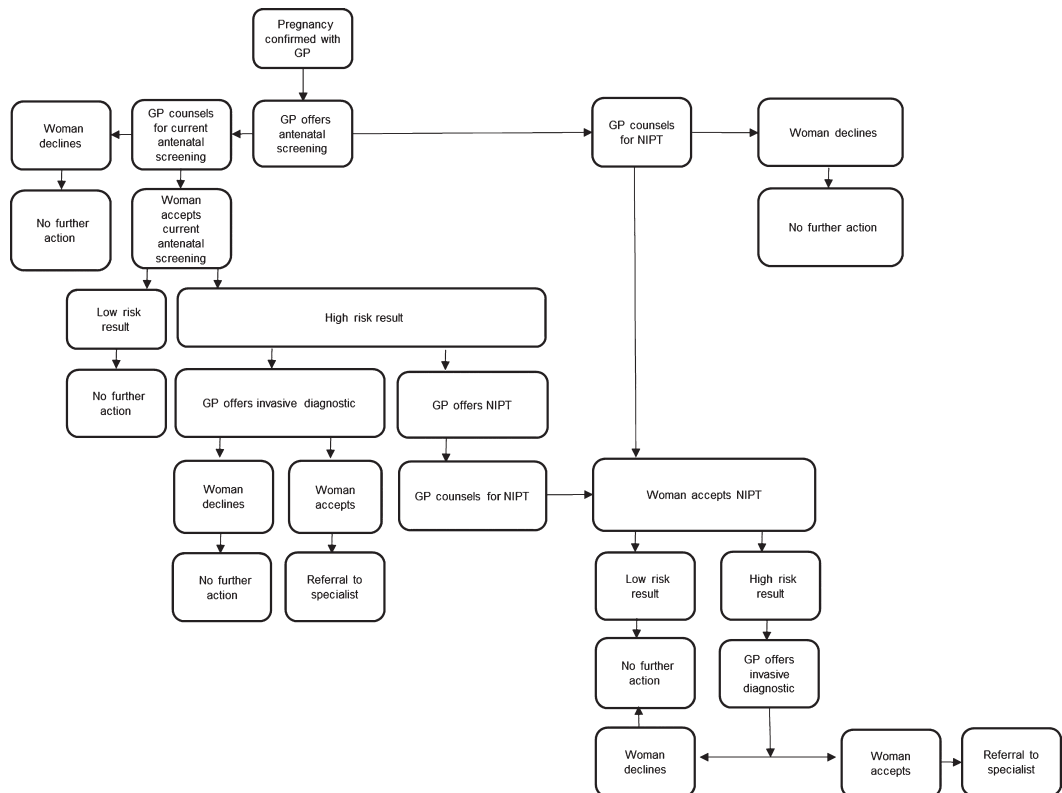
Although GPs are not usually lead maternity carers (LMCs) following changes to the maternity care system in 1996, they are still often the first point of contact and entry point to antenatal care with ~60% women seeing their GP in their first trimester of pregnancy.<sup>7</sup> GPs may be asked to provide NIPT services by women and they are well-placed (as are midwives) to do so. It is plausible that GPs could provide NIPT before a woman books with her LMC, and make the referral to specialist care as appropriate (Fig. 1). This could be a component of a more integrated model of maternity care, with GPs supporting first trimester screening and navigation to a LMC, and fulfilling the recommendation of expedient access to antenatal screening.<sup>25</sup>

Currently, there are no clinical guidelines for the provision of NIPT and no framework for a publicly funded service. A possible next step could be to develop a NIPT care pathway for general practices; for example, as outlined in Fig. 1. Determining what primary healthcare providers need in order to offer NIPT is paramount; for example, education around NIPT, ongoing support, information for women and their whānau. It is also important to establish whether GPs want to provide this service and how involved they want to be in the screening care pathway. In terms of fee structure for the practice, consideration of practice processes would also be needed for failed screens and communication of results.

### Facilitating informed choice

Given that participation in antenatal screening is optional, informed choice about participation is crucial,<sup>26-33</sup> and relationships that GPs have with women may benefit the counselling process.

Figure 1. Proposed pathway for the provision of current antenatal screening with non-invasive prenatal testing (NIPT). In the event of a low-risk result, women would be offered an 18- to 20-week morphology scan



Informed choice is particularly important when an enhanced technology is being introduced alongside an existing service. A dichotomous service, as is currently in place (where a woman can choose current antenatal screening with some co-payment required for ultrasound, compared with NIPT where women pay all the costs), raises an important issue around equitable access. It may mean that providers will have to be flexible and mindful in their counselling and facilitation of informed choice so as not to promote one screen over another (because of the considerable differences in cost, balanced against the screening performance of NIPT). At the same time, women need to be aware that these options exist.

## Summary

With such a high-performing screen, the clinical advantage of NIPT over current screening is clear. There is a high degree of urgency in ensuring equity in access to this technology, and given that GPs and other primary healthcare providers are well-placed to be at the forefront of offering NIPT, it is important to ensure that they are well supported to do so.

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#### COMPETING INTERESTS

The authors declare no competing interests.