Antenatal screening for aneuploidy—surveying the current situation and planning for non-invasive prenatal diagnosis in New Zealand

Ashley Eastwood, Dianne Webster, Juliet Taylor, Richard Mackay, Alison McEwen, Jan Sullivan, Rachel Pope-Couston, Peter Stone

ABSTRACT

AIMS: To gauge clinical opinion about the current system and possible changes as well as providing a forum for education about Non-Invasive Prenatal Testing (NIPT).

METHODS: A series of workshops for doctors and midwives, supported by the National Screening Unit of the Ministry of Health and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists, were held in the main centres of New Zealand. Following a brief education session, a structured evaluation of current screening and future possibilities was undertaken by questionnaire.

RESULTS: One hundred and eight maternity carers participated in 5 workshops. Over 40% identified barriers to current screening. More than 60% would support NIPT in the first trimester. The majority of carers provided their own counselling support for women.

CONCLUSIONS: The survey has shown general enthusiasm for the introduction of publically funded NIPT into prenatal screening in New Zealand. Barriers to utilisation of the current system have been identified and enhancements to screening performance with guidelines around conditions to be screened for would be supported.

Prenatal screening for aneuploidy and other conditions is undergoing a revolution. The commercialisation of non-invasive prenatal screening (NIPT), based on the isolation of feto-placental cell-free DNA in the maternal circulation, has been a major breakthrough because of massively improved performance compared with all other previous testing. This leads to far fewer false positive results and hence, fewer invasive tests. In addition, the false negative rate is also very low.1

A decade ago, it was observed that the prenatal screening offered at that time in New Zealand was not optimal or best practice,2 and after a considerable investigation and consultation, the current system was introduced by the National Screening Unit (NSU) of the Ministry of Health. The enhanced process commenced in February 2010. The system was named Quality Improvements in the Screening for Down Syndrome and other conditions. As part of quality improvement, it was intended to produce a monitoring report and this is now available.3 Now, a decade on, times have changed again and the new technology (NIPT) offers significant improvement over the current screening system based on maternal serum analytes and a first trimester ultrasound scan measure of nuchal translucency.

In addition to technological advances, it has become apparent from the National...
Screening Unit’s monitoring report of the quality improvement process that the performance of the system has been less than expected in terms of the persons screened as well as the detection and false positive rates. A detailed analysis of this is ongoing, but it may be that the main factor determining the detection rates has been the quality of the first trimester ultrasound scanning as serum performance meets international standards.

The part charge that the first trimester scan now attracts from all providers, except the public hospitals, has also been suggested as a barrier to access to first trimester screening for some women.

The introduction of a new screening process within the Antenatal and Newborn Screening system in the NSU would require justification, redesign of the screening pathway and funding. In the case of NIPT, interests—both commercial and clinical—have seen it become available in the private sector, with the woman paying the total cost of testing. This situation challenges the NSU to formulate a position on the introduction of NIPT within a publically-funded equitable antenatal screening process.

In order to gauge clinical opinion about the current system and possible changes, as well as providing a forum for education about NIPT, the NSU and the Royal Australian and New Zealand College of Obstetrics and Gynaecology (RANZCOG NZC) jointly sponsored five national workshops to which doctors and midwives were invited to both learn and provide feedback in the interactive sessions.

The aim of this report is to describe the consultation process and present the results.

**Method**

In March 2015, the National Screening Unit (NSU), together with RANZCOG NZC conducted a series of workshops in the main centres of New Zealand: Auckland (National Women’s Health, Auckland City Hospital and Middlemore Hospital), Wellington, Christchurch and Dunedin.

The workshop was publicised by the RANZCOG NZC and through the clinical directors of all maternity units. Midwives were also invited.

The workshops were designed to provide background information and some upskilling for the clinicians, as well as being an opportunity for the NSU to gauge opinion about the current antenatal screening situation and a future with NIPT.

In the first part of the workshops, four short presentations were given. These included a review of the current screening process and its performance, a brief synopsis of NIPT, and possible scenarios for introducing publically-funded NIPT into prenatal screening in New Zealand.

Representatives from the Genetic Health Service New Zealand provided an overview of the service and a discussion of chromosomal and genetic conditions of relevance to screening. Finally, an explanation the roles of the NSU and how it might proceed with consideration of NIPT was presented by the Clinical Director of the NSU.

<table>
<thead>
<tr>
<th>Table 1: Workshop Questionnaire.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you order non-invasive prenatal testing (NIPT) now?</td>
</tr>
<tr>
<td>2. Who is your provider of NIPT?</td>
</tr>
<tr>
<td>3. Who do you offer NIPT to?</td>
</tr>
<tr>
<td>4. Are women asking for NIPT?</td>
</tr>
<tr>
<td>5. Are there any barriers to NT scanning in your area?</td>
</tr>
<tr>
<td>6. What are the conditions that are important to be detected by first trimester screening?</td>
</tr>
<tr>
<td>7. Is information on low PAPP-A clinically useful?</td>
</tr>
<tr>
<td>8. Who provides support to women following increased risk results?</td>
</tr>
<tr>
<td>9. What do you think of replacing the first trimester scan and serums with NIPT?</td>
</tr>
<tr>
<td>10. What do you think of keeping the first trimester ultrasound scan (without NT) and replacing first trimester screening with NIPT?</td>
</tr>
</tbody>
</table>
Particular attention was paid to the processes for optimising the current screening pathways and explanations of NIPT. A discussion of the value of first or second trimester serum analytes was considered beyond the scope of the workshops, which were intended primarily to focus on anomaly screening rather than early assessments of placental function or fetal growth.

Following the presentations, a 10 question structured questionnaire was presented to the participants, who were encouraged to ask questions and seek clarification before formulating their responses. The questions are shown in Table 1. Following the workshops, one of the presenters and a member of the Antenatal and Newborn Screening Division of the NSU collated all the responses.

The results of this questionnaire were collated using Microsoft Excel. The answers to each question were tallied. A note was made of the fact that not every participant answered each question. Fractions were calculated using total number who answered each question. Respondents were also encouraged to write free text, and these responses have helped inform the discussion and explanation of results of this survey.

Results

Of the more than 120 attendees, 108 completed the 10 question evaluations, although some respondents did not answer all questions. Table 2 shows the professional status of participants in each centre and overall. In the North Island, one midwife worked in rural as well as urban practice. In the South Island, public specialists did some rural or provincial clinics as well as urban practice. Too few practitioners were engaged in solely rural practice to make meaningful comment about the effect of location on screening offer.

Responses to questions

Question 1: Do you order non-invasive prenatal testing (NIPT) now?

Already 19.4% of participants are ordering NIPT for their patients.

Question 2: Who is your provider of NIPT?

The majority, 65% do not know who were NIPT providers at the time. Note however, that the number included Registrars and Midwives who were not able to request testing at the time of asking.

Question 3: Who do you offer NIPT to?

Of the participants that are offering NIPT, 39.3% are offering them to women at high risk and 45.5% only offer NIPT at maternal request.

Question 4: Are women asking for NIPT?

In the group of specialists who replied that they do request NIPT, they stated that in 30% of the testing, women had asked for NIPT. Only 2 participants in Dunedin had had women ask for NIPT, compared to 12 who were asked in Christchurch. (At the time of the survey, specialists in Dunedin stated that they were not offering NIPT as it was not a public option).

Question 5: Are there any barriers to NT scanning in your area?

Money and access were stated to be the two biggest barriers to NIPT: 40.3% of participants thought that cost was one of the barriers to NIPT; 34.4% thought both cost and access were. At Middlemore Hospital, where most of the participants were midwives, many stated that money was a barrier to NT scanning, and 75%
thought that money and access would be a barrier to NIPT. At that time, midwives were unable to request NIPT from the one laboratory working as an agent for an international NIPT company, but at the time of writing, this has changed. Regional discrepancies were apparent; no maternity provider in Dunedin was offering NIPT to their patients due to their understanding that it was not available publically.

**Question 6: What are the conditions that are important to be detected by first trimester screening?**

The participants were asked what conditions were the most important to be detected by first trimester screening, from Trisomy 21 only to Trisomies T21, T18, T13, or also sex chromosomes XY and other significant aneuploidy. 69.9% of overall participants answered that they would like all of the above conditions screened for. Two participants only wanted Trisomy 21 screened for.

Further regional discrepancies were evident with this question: 76% of Auckland City Hospital and 74.3% of Middlemore participants wanted all conditions screened for, compared to 36.4% of Dunedin participants.

**Question 7: Is information on low PAPP-A clinically useful?**

**Serum Analytes**

Currently, requestors are specifically informed of highly abnormal levels of the biochemical markers (over 5 or under 0.2 multiples of the median value). Over 86% of participants answered that information on low PAPP-A was clinically useful. This was in the context of participants not having been provided with any discussion on the utility of these measures, noting that while low levels of PAPP-A have been associated with adverse pregnancy outcomes, there is little intervention available and no known clinical utility. The question related to the proposal of replacing the current first trimester serum screen with NIPT.

**Question 8: Who provides support to women following increased risk results?**

More than 50% of participants would provide the support themselves. 20% would refer to a genetic counsellor and 8.6% would offer a social worker.

**Question 9: What do you think of replacing the first trimester scan and serums with NIPT?**

**Question 10: What do you think of keeping the first trimester ultrasound scan (without NT) and replacing first trimester screening with NIPT?**

Figure 2 shows 31.6% of participants wanted to replace the scans and serum with NIPT. 41.6% disagreed and 23.8% did not know. However, when asked if the scan could be retained but without the NT and without a part charge, 60.1% of participants would like to keep the first trimester scan.
ultrasound scan (without nuchal translucency) and replace first trimester screening with NIPT. 18.4% did not wish to do this and 20.4% did not know.

Conclusions

NIPT is now well established in New Zealand in the private sector, with a number of providers offering screening for a range of conditions at differing costs to the requestor. Except in exceptional circumstances, such as ambiguous results after conventional screening and where there are clinical reasons to avoid invasive testing, it is not available to women in the public sector. This creates inequality, especially as it is without doubt that NIPT has superior performance in the screening for common aneuploidies compared with the current screening tests.

In addition to inequality, NIPT, which is currently performed only by laboratories overseas, produces results from providers that are not readily accessible as would be the case should the testing be done in this country. Issues of quality control, range of conditions screened for, and test performance have been variably reported and would need to meet strict requirements of a national screening process or programme. Our survey data show that in only 20% of cases do clinicians currently refer to genetic services for advice. Any increase in referral due to difficulties explaining complex results after expanded NIPT would place and increased workload requirement on the current genetic services.

The results of the survey presented in this report clearly show concerns with the current screening system, and the majority of respondents not only would support the introduction of NIPT, but further, would forego the use of the nuchal translucency (NT) scan. When asked should there be a structured checklist for the first trimester scan, there was support for this. The exact nature of a structured checklist was not specified, but in the discussions during the workshops, issues of pregnancy dating, chorionicity in multiple pregnancy and major abnormality, such as cystic hygroma, abdominal wall or limb defects were mentioned. It is unclear if there would be quality issues associated with such an approach.

When our participants were asked who they offer NIPT to, 40% of them are offering it to women at high risk, for example advanced maternal age. It is interesting to note that it has been well shown previously that maternal age is a very poor screen, with a detection rate for Trisomy 21 of only 30%. In addition, NIPT has been shown to be equally effective in terms of its performance in so called high- and low-risk women. Thus, it is reasonable to offer the testing to all women and not on the basis of maternal age alone. The enthusiasm for the introduction of NIPT in to publically-funded screening in New Zealand is matched by a not dissimilar survey of service user views in the UK, which suggested a high uptake of the testing.

Respondents were interested in the future shape of a screening pathway which included NIPT. Best possible performance, screening for what were deemed to be important conditions, rather than only Trisomy 21 or Trisomies 21, 18 and 13, and equity of access were all important factors in supporting change. These factors are remarkably consistent with the guiding principles used when the current system was established in 2010. In achieving a future shape, some compromise of trade-offs were recognised, and it was clear that the concerns about ultrasound were prominent.
amongst these. It was recognised that cost analyses are difficult to perform, and the cost of false negative screening is rarely included in modelling estimates.

Information about the current screening outcomes has shown that not all sonographers performing the NT scan met accepted standards as applied in the UK. Some sonographers perform insufficient NT scans to be able have their measures statistically analysed, and some sonographers scan with a bias which does affect the performance of NT in the screening algorithm. As it seemed more likely that under measuring the NT occurred, this would impact on the true positive or detection rate and also explain the false positive rate in the Monitoring report. It appeared to be the view of the participants in the recent survey, either expressed or reflected in the responses, that the strategies of trying to re-educate the sonographers, and/or increase numbers scanned by individual sonographers, may not likely effect real change in the short-term. The enthusiasm for the introduction of NIPT also suggested that there may be less support for trying to improve ultrasound performance when, even the best reported detection rates for common aneuploidies with first trimester combined screening, at 88–90% for Trisomy 21, are much less than with NIPT at >97–98%, with a false positive rate of 0.1%, compared with around 2.5% for the current screening.

First trimester ultrasound has other very important functions, including dating, detection of multiple pregnancy and its chorionicity, and the exclusion of severe fetal structural abnormality. The survey participants considered that the NSU could develop a checklist of structural abnormalities that could be realistically sought, but not include NT, due to the quality issues discussed. The participants also considered that public funding for a first trimester scan and the morphology scan performed between 18 and 22 weeks gestation should remain.

The strength of the NSU-RANZCOG NZC series of interactive sessions was that the opportunity to be updated and express views was welcomed by the participants, and by holding the meetings in 5 centres, enabled local participation. In Middlemore, Christchurch and Dunedin, a large number of the clinicians who would be offering screening, or who see women with complex pregnancies, did attend. In Auckland, a number of the private specialists who currently offer and arrange NIPT attended and offered their experiences. In addition, hospital registrar trainees who were aware of NIPT, but could not offer it, also expressed comments about that situation. Attendees in Wellington included a midwife for a very remote area, as well as midwives and doctors for a tertiary and a secondary obstetric centre. While the overall of attendees does not represent a majority of maternity care providers in the country, it did provide a snap-shot of views which were remarkably consistent. The value of the exercise was particularly in facilitating the NSU in hearing views of clinicians. Value to RANZCOG NZC included the opportunity to update trainees and specialists, and also to work collaboratively with the midwives who were invited to the sessions.

The limitations of such an approach to gaining a snap-shot include the sample size, that is, the number of attendees and the information that was presented by the speakers on which the respondents could base their answers. Prior to the meetings, the presenters had worked with the NSU to ensure that a clear consistent series of talks was given, especially important for the Genetic Health Service New Zealand, which had a different presenter in some centres. In interactive sessions, information imparted may vary according to the nature of questions asked, and this has the potential to influence responses given. However, the person who was responsible for running the questionnaire evaluation was not one of the presenters, and she endeavoured to maintain a focus on the theme of each question in the evaluation process.

Ultimately, the aim was to help inform both participants and NSU. It was apparent that there was a desire to introduce NIPT, that it needed to be introduced in a way that had structure so that it could fit into prenatal screening, and that, given its potential, it be used for more than simply screening for the common aneuploidies, namely Trisomies 21, 18 and 13. Having said that, caution was expressed about attempting to test for ‘everything’, and also caution about testing or revealing fetal gender for non-medical reasons was raised as an important issue.
It would appear from the results that the NSU can have confidence that the introduction of NIPT would have clinical support, and that in introducing this, changes to first trimester screening can be made, rather than simply adding this on as an extra test. Given that NIPT is already available in New Zealand as an unregulated and unfunded test, it would seem that there is some urgency in developing guidelines around its use and embracing it in nationally-funded prenatal screening. Cost need not necessarily delay NIPT, as modelling has shown options which are similar to current expenditure for enhanced performance.\(^7,8\) A cost modelling project is in progress in New Zealand, but has yet to report. This survey may in a small way assist in the introduction of NIPT for all women who wish to use it in New Zealand.

**Competing interests:**
The authors assisted in the design and participated in the presentation of the seminars from which the data for this report was obtained.

**Acknowledgements:**
The authors wish to acknowledge Dr Jane O’Hallahan for her presentations and the staff of Antenatal and Newborn Screening in the National Screening Unit in particular Ms Kathy Bendikson and Ms Sian Burgess and Ms Jane Cumming RANZCOG for assistance with the workshops. Genetic Health Service NZ also helped facilitate the workshops.

**Author information:**
Ashley Eastwood, Obstetrics and Gynaecology, Middlemore Hospital, Auckland; Dianne Webster, LabPlus, Auckland District Health Board; Juliet Taylor, Genetic Health New Zealand - Northern Hub, Auckland District Health Board; Richard Mackay, Canterbury Health Laboratories, Canterbury District Health Board; Alison McEwen, Genetic Health Service NZ-Central Hub, Capital and Coast District Health Board; Jan Sullivan, Genetic Health Service NZ - South Island Hub, Christchurch Hospital; Rachel Pope-Couston, Genetic Health Service NZ-Northern Hub, Auckland District Health Board; Peter Stone, Obstetrics and Gynaecology, The University of Auckland, Auckland.

**Corresponding author:**
Peter Stone, Obstetrics and Gynaecology, The University of Auckland, Auckland.
p.stone@auckland.ac.nz

**URL:**

**REFERENCES:**


3. Antenatal Screening for Down Syndrome and Other Conditions:

4. Personal Communication (Dr Dianne Webster)


