Technology in the prenatal setting is advancing at an exceptional rate, and these advancements will likely result in major changes to current pregnancy screening and testing paradigms. In Australia, prenatal testing is increasingly becoming a routine part of antenatal care and pregnant women are offered an assortment of screening and diagnostic tests, which give them information about their fetus, and can identify potential anomalies before it is born. In Victoria (Australia), each year approximately 4% of babies will be born with a birth defect or fetal abnormality1 many of which are diagnosed in uterus.

Greater than 97% of women in Victoria have at least one or more ultrasounds during pregnancy2 and greater than 80% of pregnant women take up screening for Down syndrome, with the majority having First Trimester Combined Screening (FTCS). FTCS combines maternal serum analytes — pregnancy associated plasma protein-A (PAAP-A) and beta human chorionic gonadotrophin (free β-hCG) — with results from the nuchal translucency ultrasound to give a risk figure for Down syndrome and Trisomy 18. Approximately 5% of women will receive a false positive result from FTCS3, meaning they screen positive for Down syndrome or Trisomy 18 and do not have an affected pregnancy.

Women who are considered to be “increased risk” either because of a screening result or ultrasound finding are offered invasive diagnostic testing whereby a fetal sample is obtained via chorionic villus sampling (CVS) or amniocentesis and sent for conventional or molecular karyotyping (microarray). These tests carry a miscarriage risk of up to 1% above the background rate of miscarriage4.

There has been increasing demand for a safe and reliable alternative to invasive diagnostic testing and very recently, noninvasive prenatal testing (NIPT) has become commercially available to women in America (2012), Australia and many other countries, including Brazil (2013). NIPT is an advanced screening test, which relies on the fact that small fragments of cell-free fetal DNA and RNA circulate in maternal serum5. In the first and second trimesters of pregnancy, approximately 6–10% of total cell free DNA (cfDNA) circulating in maternal serum is thought to be fetal in origin; this fetal fraction rises to 10–20% in the third trimester6,7. Using massively parallel sequencing technology, scientists can sequence cfDNA fragments in maternal plasma and detect specific chromosome aneuploidies such as trisomies 21, 13 and 188-17, much earlier in pregnancy than has previously been possible,
and without having to perform an “invasive” procedure. There are currently five different companies marketing NIPT to obstetricians and pregnant women in Victoria. A summary of the key features of each test can be found in Table 1.

There are many advantages to NIPT, the most significant of which, is that it provides highly accurate information about Down syndrome without a miscarriage risk. Thus it is likely to reduce the number of invasive tests being performed. However, there are also a number of ethical considerations, which need to be taken into account when implementing NIPT in clinical practice.

### Ethical aspects of offering noninvasive prenatal testing

1. **Is the Noninvasive Prenatal Testing affordable?**

   The cost of noninvasive testing is currently prohibitive for many Australians. The most economical test retails at $850 AUD (~ $890 USD) with the other four tests retailing from $1,250–1,450 AUD ($1,300 to $1,500 USD). Currently there are no subsidies provided by Australia's government funded universal healthcare system (Medicare) or by any of the private health insurance providers so these costs are wholly paid by the patient. While it is likely NIPT will become more cost effective in the future, the current pricing raises equity concerns as women who cannot afford the test are at a disadvantage.

2. **It is important that women and their referring doctors understand the limitations of the Noninvasive Prenatal Testing**

   NIPT is an advanced screening test and while the sensitivity is high (i.e. >99% for Down syndrome), it does not provide a definitive result. The false positive rate is approximately 1% and thus, patients who received a positive result for aneuploidy are advised to have prenatal diagnosis to confirm this result. The origin of the cell free fragments of fetal DNA is thought to be from placental trophoblast cells\(^5,18\), therefore there is a risk of confined placental mosaicism\(^18\). Equally, where no aneuploidy is detected, there is a residual risk that the pregnancy may be affected.

   The resolution of NIPT is not as high as current diagnostic testing however, this will likely improve in the future. Current NIPT providers are offering detection of Trisomy 21, 18, 13 and in some cases sex chromosome aneuploidy. In contrast, conventional karyotyping provides structural and numerical information on all 23 pairs of chromosomes, which means many abnormalities currently detected by karyotyping will not (at present) be detected with NIPT. Furthermore, molecular karyotyping (microarray) has become the first tier test in Victoria for prenatal patients with abnormal ultrasound findings\(^19\). Array based technology provides a significantly higher resolution (100 fold increase) when compared with conventional karyotyping\(^20,21\). It is able to detect copy number variants (gains or losses in DNA) across the genome and provides increased detection of “pathogenic” and “likely pathogenic” abnormalities\(^19\). There has been suggestion that array based technology should be the first tier test for all patients having prenatal diagnostic testing\(^22\). It can provide useful clinical information, which will not be detected with current NIPT technology. Thus, it is important patients are making informed decisions about NIPT and about the detail of information they want to receive about their pregnancy, balanced with the miscarriage risks of invasive diagnostic testing. Where ultrasound examination has identified structural abnormalities or multiple soft markers, array-based technology should be recommended in preference to NIPT as it will provide the most comprehensive clinical information.

### Table 1. Summary of noninvasive prenatal tests available in Melbourne (April, 2013)

<table>
<thead>
<tr>
<th>Lab</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>False positive rate</th>
<th>Test failure rate</th>
<th>Chromosomes tested</th>
<th>Cost</th>
<th>Timing</th>
<th>Available for multiple pregnancies</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>99.1% for T21 &gt;99.9% for T18 91.7% for T13</td>
<td>99.9% for T21 99.6% for T18 99.7% for T13</td>
<td>0.2%</td>
<td>0.8%</td>
<td>21, 13, 18, X, Y</td>
<td>$1,450 AUD</td>
<td>From 10 weeks 0 days</td>
<td>Yes</td>
</tr>
<tr>
<td>B</td>
<td>99.9% for T21 97.4% for T18 87.5% for T13</td>
<td>99.8% for T21 99.6% for T18 99.9% for T13</td>
<td>0.2%</td>
<td>&gt;1%</td>
<td>21, 13, 18, X, Y</td>
<td>$1,250 AUD</td>
<td>From 10 weeks 0 days</td>
<td>No</td>
</tr>
<tr>
<td>C</td>
<td>&gt;99% for T21 &gt;99% for T18 &gt;99% for T13</td>
<td>100% for T21 100% for T18 100% for T13</td>
<td>0%</td>
<td>‘low’</td>
<td>21, 13, 18, X, Y</td>
<td>$1,250 AUD</td>
<td>From 9 weeks 0 days</td>
<td>No</td>
</tr>
<tr>
<td>D</td>
<td>&gt;99% for T21 &gt;99% for T18 &gt;99% for T13</td>
<td>100% for T21 100% for T18 100% for T13</td>
<td>0%</td>
<td>&lt;3%</td>
<td>21, 13, 18</td>
<td>$1,250 AUD</td>
<td>From 12 weeks 0 days</td>
<td>No</td>
</tr>
<tr>
<td>E</td>
<td>98% for T18 80% for T13</td>
<td>–</td>
<td>0.1%</td>
<td>&lt;3%</td>
<td>21, 13, 18 and Y</td>
<td>$850 AUD</td>
<td>From 10 weeks 0 days</td>
<td>No</td>
</tr>
</tbody>
</table>
3. The importance of informed decision-making

Studies have shown that many women take up Down syndrome screening in pregnancy because they view it as a “routine” test and as such often have inadequate knowledge and understanding of prenatal screening and diagnostic tests. This implies that a large number of women are not making informed decisions about having prenatal testing.

Given that NIPT has a much higher sensitivity when compared with any of the current screening programs, it is even more imperative that women understand the conditions that are being tested for and are given balanced and up to date information. Pre-test counselling is therefore crucial in ensuring women not only understand the limitations of the test, but that they have thought about whether or not they want this information about their fetus, and what they would do in the event of an adverse result. As NIPT involves a safe and simple blood test rather than a miscarriage risk, there is a danger that participation will be passive as it has been with current pregnancy screening programs.

Facilitating informed decision-making is one of the central tenants of genetic counselling practice. Genetic counsellors provide women with non-directive information and support to promote autonomous decision-making, and are well placed to provide pre-test counselling to all women considering NIPT.

4. Access to termination of pregnancy

When a fetal abnormality is detected during pregnancy women and their partners are faced with the difficult choice deciding whether or not to continue the pregnancy based on their understanding and perceptions of the abnormality and its potential impact on their lives. Victorian records concur with overseas data, indicating that the majority of women will choose to have an abortion following a prenatal diagnosis of Down syndrome.

In Australia, abortion law falls under state and territory jurisdiction and in most states it remains in the criminal statutes. However, abortion has been decriminalised in the Australian Capital Territory, Western Australia and Victoria. In Victoria, abortion is permitted until 24 weeks of pregnancy or later if 2 doctors believe it is medically appropriate.

In Brazil, abortion is “only permitted so save a woman’s life, or in cases of rape” and recently in cases of anencephaly. Thus, women cannot legally access an abortion on the grounds of fetal abnormality. When faced with the diagnosis of a fetal abnormality, there is a risk that women in Brazil and (other countries where abortion is illegal) may choose clandestine and unsafe means of procuring an abortion thereby putting their own health at risk.

It is important women undertaking NIPT in countries where abortion is not permitted understand that they will not have safe and legal access to this procedure, and are making informed choices about whether or not they want this information about their fetuses prior to birth.

For many women and their partners, having access to NIPT will allow them to prepare for the birth of a child with Down syndrome. In the past, women who would continue their pregnancy regardless of the diagnosis of a fetal abnormality, may have decided not to take up prenatal diagnosis due to the miscarriage risks. NIPT is able to provide these families with highly accurate information about Down syndrome, Trisomy 13 and 18 without a miscarriage risk. As such, the number of women continuing the pregnancy knowing that their baby is affected by one of these conditions is likely to increase, which will pose additional resource demands for fetal medicine units and perinatal palliative care programs. It is ethically imperative that when offering prenatal screening and testing, women and their partners are provided with appropriate medical and social resources to ensure that they are well supported regardless of whether or not they choose to continue their pregnancy.

References


