Non-Invasive Prenatal Testing (NIPT) represents a revolution in the information that a woman can access regarding the genetic health of her developing fetus. We can examine a blood sample from the mother and detect the fetal DNA that circulates within her blood, providing an accurate screening test for common chromosomal abnormalities in the fetus.
Non-invasive prenatal testing (NIPT) is a screening test for common chromosomal abnormalities of the fetus during pregnancy.

There are several methods in use for NIPT. Sonic Genetics regularly reviews the performance, scope and cost of these methods.

NIPT is primarily designed to screen for the common trisomies of chromosomes 13, 18 and 21 in singleton and twin pregnancies; the presence of a Y chromosome can also be detected.

In addition, abnormalities in the number of X and Y chromosomes can be screened in singleton pregnancies, but this is not reliable in twin pregnancies.

NIPT is an advanced screening test; it is not a diagnostic test. All abnormal or unexpected results should be reviewed carefully, with diagnostic (invasive) testing of the fetus performed before changing the management of the pregnancy.

NIPT does not screen for all abnormalities of chromosome number (aneuploidy) or microdeletions. It does not screen for other genetic disorders or birth defects.

The cost of NIPT is falling and is currently approximately $600; please refer to our website for the current price (sonicgenetics.com.au). This cost is not covered by Medicare or health insurance. NIPT is more expensive than conventional screening, but is much more accurate.

Key Points

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Considerations before using NIPT

NIPT is a new and powerful investigation that carries major clinical implications for mother and fetus. Before proceeding with the test, it is vital that

- clinicians understand the purpose, performance and limitations of the test
- patients are informed about these aspects of the investigation, and
- appropriate consent is provided before the test is initiated.

Sonic Genetics requires that patients provide written consent for this test to assure the clinician and patient that these issues are understood. This leaflet provides a brief overview of these matters. Please contact us on 1800 010 447 or check our website, sonicgenetics.com.au, if you require further information.

As with any prenatal test, NIPT may provide information that contributes to major medical decisions, such as termination of pregnancy. Clinicians and patients must understand the strengths and limitations of the test, and patients must provide informed consent.
What is NIPT?

NIPT is an advanced screening test for common chromosomal abnormalities. NIPT is more accurate than other screening tests, such as the combined first trimester screen (fetal ultrasound plus maternal serum screening). However, NIPT is not 100% accurate and should not be regarded as a diagnostic test. All abnormal results should be confirmed by invasive testing before making significant clinical decisions, e.g. termination of pregnancy. An unexpected normal result, e.g. in a fetus with malformations, may also warrant invasive testing.

How does NIPT work?

NIPT involves sequencing millions of short fragments of DNA in maternal plasma. Some of these fragments will have come from the placenta, and most will be from the mother. By comparing each fragment’s DNA sequence with a reference sequence of the normal human genome, we can count the number of fragments derived from each chromosome. In a mother with a chromosomally normal fetus, the proportion of fragments from each chromosome will be within a narrow normal range. But if the fetus has an abnormal number of chromosomes, the fetal contribution for that chromosome will be abnormal and will distort the overall proportion.

A number of different methods have been developed for NIPT, and others are under development. Sonic Genetics regularly reviews the various implementations of NIPT and assesses their performance, scope and cost.

Maternal blood contains DNA fragments from both the mother and the fetus. NIPT involves measuring the proportions of these DNA fragments that come from each chromosome. Changes in these proportions can indicate that the fetus has a chromosome abnormality.
What does NIPT screen for?

NIPT screens for Down syndrome (trisomy 21), Edwards syndrome (trisomy 18) and Patau syndrome (trisomy 13). These are the most common autosomal trisomies. They cause moderate to profound intellectual disability and are associated with major congenital malformations.

Sex chromosome abnormalities, such as Turner syndrome (45,X) and Klinefelter syndrome (47,XXY), can also be detected, but with reduced accuracy. Sex chromosome abnormalities are often clinically milder than other chromosomal abnormalities. Testing for sex chromosome abnormalities will also reveal the fetal gender.

It is important to note that chromosomal abnormalities vary widely in the severity of the problems they cause. Some methods can detect trisomies of other chromosomes; these trisomies may be regarded as being less significant in the long term, as they almost always cause a spontaneous miscarriage. NIPT is also being extended to detect rare, small deletions in specific areas of certain chromosomes; these more recent developments also have reduced accuracy.

The scope of NIPT is changing rapidly as the accuracy and range of abnormalities being assessed improves. Sonic Genetics regularly reviews the NIPT methods available to ensure that we provide women with the best test. Please contact us on 1800 010 447 or refer to our website, sonicgenetics.com.au, for the latest specification of the test we offer. The cost of NIPT is also changing, and the website will have the most up-to-date information on our NIPT test options and prices.

What is NOT included in the NIPT test?

NIPT does not detect every genetic abnormality in the fetus, or every developmental problem that might occur during pregnancy.

NIPT will not detect the following conditions:

1. Less common or ‘atypical’ chromosomal abnormalities. These make up 20% of all chromosomal abnormalities, and occur more commonly in pregnancies with fetal malformations or with high risk scores on combined first trimester screening. These abnormalities can often be detected by invasive genetic testing, i.e. CVS or amniocentesis.
2. A specific mutation that might be known to run in the family, e.g. cystic fibrosis or Huntington disease. Please contact us on 1800 010 447 if you are concerned about this possibility.
3. Non-chromosomal disorders, such as neural tube defects, placental abnormalities and intra-uterine growth retardation.

This list of exclusions is not complete.

NIPT is a screening test for common aneuploidies, i.e. abnormalities in chromosomal number. It is not a screening test for every genetic abnormality.

How accurate is NIPT?

NIPT is highly accurate, detecting more than 99% of fetuses with Trisomy 21, and more than 95% of fetuses with Trisomy 18, Trisomy 13 or abnormalities of sex chromosomes. These are much better detection rates than we observe with conventional first trimester screening for these trisomies (90% for trisomy 21, 50% for trisomy 13 and 50% for trisomy 18). NIPT is also much better at identifying fetuses with normal chromosomes than conventional first trimester screening; more than 99.9% of normal fetuses are categorised correctly by NIPT, versus 95% by conventional first trimester screening.

NIPT is a very good screening test, but it is not a diagnostic test. There will occasionally be a difference between the result of the test and the actual chromosomal status of the fetus. This may be due to the statistical design of the test, or to biological factors, such as the fetus and placenta having different numbers of chromosomes.

Can NIPT be used for twin pregnancies?

There is less experience with twin pregnancies than with singleton pregnancies. Nonetheless, the accuracy of the test for detecting trisomies 21, 18 and 13 appears to be very good, provided the laboratory is advised that it is a twin pregnancy. It is essential that the laboratory be advised if the woman has two or more fetuses. This includes the presence of a non-viable fetus together with its viable twin, as the non-viable fetus may be releasing DNA into the maternal circulation.

Abnormalities of sex chromosome number cannot be reliably detected in a twin pregnancy, but it is possible to determine if at least one twin has a Y chromosome.

This test has not been validated for triplet pregnancies.

NIPT is accurate in singleton and twin pregnancies, but may not be accurate with triplets (or more). It is essential that the laboratory be advised of multiple pregnancies.
How should the NIPT result be interpreted?

The accuracy of NIPT varies with the prior risk that the woman has an affected fetus. Three general scenarios are considered below.

### Woman who is at low risk (1 in 1,000, or 0.1%) of her fetus having a chromosomal abnormality

This may apply to a young woman with normal fetal ultrasound, or a woman with a low risk result from conventional first trimester screen.

<table>
<thead>
<tr>
<th>If the NIPT result is normal:</th>
<th>If the NIPT result is ABNORMAL:</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is highly likely that the result is correct, and that the fetus does not have any of the chromosome abnormalities tested.</td>
<td>It is likely but not definite that the result is correct, and that the fetus has a chromosome abnormality. The probability of the result being correct varies from 30-90% for different chromosomal abnormalities.</td>
</tr>
<tr>
<td>In such a low risk setting, a normal result from NIPT is correct in more than 999 cases out of 1000. The power of NIPT to correctly identify a normal fetus is the main clinical benefit of this test.</td>
<td>An abnormal NIPT result is more likely to be correct than an abnormal conventional first trimester screen. Nonetheless, an abnormal NIPT result must be confirmed by invasive testing by CVS or amniocentesis before making major medical decisions.</td>
</tr>
</tbody>
</table>

### Woman who is at increased risk (1 in 100, or 1%) of her fetus having a chromosomal abnormality

This may apply to an older woman, or a woman with an increased risk result from conventional first trimester screen.

<table>
<thead>
<tr>
<th>If the NIPT result is normal:</th>
<th>If the NIPT result is ABNORMAL:</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is likely that the result is correct, and that the fetus does not have any of the chromosome abnormalities tested.</td>
<td>It is highly likely but not definite that the result is correct, and that the fetus has a chromosome abnormality. The probability of the result being correct varies from 80-95% for different chromosomal abnormalities.</td>
</tr>
<tr>
<td>In this setting, a normal result from NIPT is correct in more than 99.5 cases out of 100. The power of NIPT to correctly identify a normal fetus is the main clinical benefit of this test.</td>
<td>In this setting, an abnormal NIPT result must be confirmed by invasive testing by CVS or amniocentesis before making major medical decisions.</td>
</tr>
</tbody>
</table>

### Woman who is at high risk (1 in 10, or 10%) of her fetus having a chromosomal abnormality

This may apply to a woman whose fetus has malformations on ultrasound, or who has a very high risk from conventional first trimester screening.

NIPT is not recommended in this setting. A normal result is increasingly likely to be incorrect. It is also possible that the fetus has a chromosomal abnormality other than the ones tested by NIPT. Invasive testing by CVS or amniocentesis should be considered.

NIPT is a very good test, but it is not perfect. Abnormal results should be confirmed by invasive testing before acting on that result. Invasive tests may also be appropriate in the case of an unexpectedly normal result.
Should a woman have conventional first trimester screening and ultrasound as well as NIPT?

NIPT is more accurate than conventional first trimester screening but conventional screening still has a place in prenatal care. These tests measure different things, i.e. genetic code versus physical shape and biochemical function.

- If a woman has both conventional first trimester screening and NIPT, the conventional screening can provide complementary information regarding chromosome abnormalities and placental health that is not addressed by NIPT. The result from each test can also inform the interpretation of the other.
- An alternative strategy is for a woman to have conventional first trimester screening initially, and then have NIPT only if this shows her to be at increased risk. This strategy is cheaper overall (fewer women have NIPT), but the lower detection rate by conventional screening compared with NIPT means that some fetuses with Trisomy 21, 13 or 18 will be missed. It would be a matter for the doctor and patient to decide whether the risk of trisomy determined by conventional screening is sufficiently low that NIPT is not required.

Conventional first trimester screening and ultrasound still have important roles in prenatal care, and should be offered whether or not a woman has NIPT.

Arranging a test

**When**
The test can only be performed after 10 weeks’ gestation, and then at any time up to term. This test has not been validated at earlier gestations, as the concentration of fetal DNA in maternal plasma is too low prior to 10 weeks.

**How**
A 10 mL blood sample is collected into a specific tube. The specific tube must be used to ensure that the DNA in the maternal plasma is not degraded.

**Where**
Testing is only available at specific collection centres, and is sometimes only performed on specific days (please call 1800 010 447 for details)

NIPT request form

We require a specific request form that must be signed by both requesting doctor and patient.

When requesting this test, the following information must be included:

- All patient details including
  - gestation
  - age of the mother
  - height and weight of the mother
  - indications for testing
- ultrasound findings
- the result from conventional first trimester screening
- Singleton or twin pregnancy
- All referring doctor information completed, including a fax number

Both the patient and the doctor are required to sign the request form to confirm that the patient has been adequately counselled.

How long does the test take?

We aim to provide you with the test result within 5–8 business days. In our hands, 90% of results are provided within 8 days.

On rare occasions, the NIPT test fails. This may be due to there being too little fetal DNA in the mother’s blood sample, or to problems in the shipping or analysis of the sample. The amount of fetal DNA in maternal blood increases during the pregnancy, and it is usually possible to provide a result with a repeat blood sample. The need for such a repeat sample is usually not known until the final stages of the analysis.

What does the test cost?

At the time of writing, NIPT is not rebated by Medicare nor covered by private health insurance. Please visit www.sonicgenetics.com.au to find out the current price, or call us on 1800 010 447.

Payment is required in advance.

In the rare circumstance that a repeat sample is required, the repeat test is performed at no additional cost.