MAR
2022

Sonic Genetics

Information for Doctors

Screening options for non-invasive prenatal testing (NIPT)

A fetal chromosome disorder can occur in any pregnancy. Chromosome disorders can be due to the gain or loss of an entire chromosome (aneuploidy, that is, trisomy or monosomy, respectively) or the gain or loss of part of a chromosome (duplication or deletion, respectively).

The clinical significance of a chromosome abnormality varies according to three factors:

- **The number and type of genes involved.** Chromosomes 21, 18 and 13 have the smallest numbers of genes, and fetuses with trisomy for any of these chromosomes can survive to term. Trisomies of other chromosomes involve more genes and usually result in early fetal loss. Depending on the number and type of genes involved, small deletions and duplications can occur in healthy individuals or cause congenital malformations and intellectual disability. Larger duplications and deletions have a stronger association with these adverse outcomes as more genes are involved.
- **Whether the abnormality involves a sex chromosome.** An abnormality involving the number of X or Y chromosomes is typically less severe than an abnormality involving the autosomes (the numbered chromosomes).
- **Whether the abnormality is mosaic.** A chromosome abnormality may be limited to a subset of cells in the fetus or placenta; this is described as a 'mosaicism'. The clinical significance of the abnormality will depend both on the chromosome abnormality itself and on which tissues have that abnormality.

NIPT can potentially screen for a range of chromosome abnormalities. For some of these abnormalities, the clinical significance is clear; for others, the abnormality may be of uncertain clinical significance. A patient's doctor determines what scope of NIPT will be requested for the patient. The doctor must ensure that this reflects the patient's wish for information; the patient's acceptance of the potential uncertainty regarding the clinical significance of some abnormalities; and the availability of a suitable care pathway in the event that the test result is consistent with a high probability of an abnormality.

NIPT is a screening test and cannot provide a diagnostic result for a chromosome abnormality. As a screening test, there will sometimes be false-positive and false-negative results. The sensitivity and specificity of each test is outlined below.

Please note that the accuracy of NIPT is critically dependent on knowing the gestation of the pregnancy and the number of fetuses. The presence of a major malformation may be sufficient to warrant invasive genetic testing (chorionic villus sampling or amniocentesis), thus removing the need for NIPT. NIPT is not a test of fetal viability because retained products of conception can continue to be a source of feto-placental DNA in the maternal circulation for weeks or months.

For these reasons, we recommend that a dating ultrasound scan is performed prior to a sample being collected for NIPT. NIPT cannot provide a validated result at a gestation of less than 10 weeks, in the presence of a demised twin, or with three or more fetuses. Maternal aneuploidy, transplant or malignancy would also invalidate the NIPT result and therefore NIPT cannot be performed through our service in these settings.

Information for Doctors

NIPT for trisomies of chromosomes 21, 18 or 13

These trisomies account for 70-80% of chromosome abnormalities identified in babies. A baby with one of these common trisomies will typically have congenital malformations and intellectual disability. The chance of these trisomies rises with maternal age.

The primary purpose of NIPT is to screen for these three trisomies. This is the default scope of NIPT provided by Sonic Genetics and it is included in every NIPT result. Other NIPT options (below) will not be reported unless specifically requested by the doctor prior to sample collection.

	Trisomy 21, 18 or 13
Sensitivity (% affected pregnancies correctly identified as affected)	>99%
1-specificity (% unaffected pregnancies incorrectly identified as affected)	0.1%

Please note: These figures refer to the sensitivity and specificity of NIPT for detecting each trisomy independently

If a woman has a 'high probability' result for a common trisomy, the positive predictive value (PPV) will vary with the prior chance of the fetus being affected, and is typically greater than 50%. False-positive cases can occur due to biological or technical factors, including placental mosaicism for the trisomy. For this reason, irreversible decisions regarding the management of a pregnancy should not be implemented until the screening result is confirmed. We recommend prompt specialist assessment, potentially including ultrasound and karyotype of a chorionic villus sample (CVS) or amniocentesis sample.

Sonic Genetics offers a free genetic counselling session for women in this situation.^ Rapid cytogenetic analysis of a CVS or amniocentesis sample is available through Sonic Genetics at no cost to the patient. For further information, please refer to the relevant fact sheets and resources on our website.

Option: NIPT for fetal sex [no charge]

NIPT can test for the presence of the Y chromosome. If detected in a singleton pregnancy, the result is interpreted as indicating a male fetus; if a Y chromosome is detected in a twin pregnancy, the result is interpreted as there being at least one male fetus.

NIPT for fetal sex is available for no additional charge in singleton and twin pregnancies. This option must be requested by the doctor prior to collection of the maternal blood sample. We do not accept such requests from patients. Other NIPT assays will not be reported unless specifically requested.

The accuracy of NIPT for fetal sex is greater than 99%. However, please note that NIPT is a screening test and the result should not be the basis for decisions regarding the management of the pregnancy, for example, if there is a risk of an X-linked disorder. Incorrect results can occur due to placental or maternal mosaicism.

Option: NIPT for sex chromosome aneuploidy [no charge]

The gain or loss of a sex chromosome does not necessarily cause congenital malformations or result in intellectual disability. Many people with XXX or XYY have no physical or functional evidence of the aneuploidy. On the other hand, people with 45,X (Turner syndrome) or XXY (Klinefelter syndrome) have impaired fertility and may have congenital malformations or learning difficulties. Other, less common, sex chromosome abnormalities are more serious. It can be difficult to predict the potential outcome for a particular child. The chance of the fetus having XXX or XXY increases with maternal age; the chance of the fetus having 45,X or XYY is not related to maternal age.

	Sex chromosome aneuploidy
Analytical sensitivity (% affected pregnancies correctly identified)	95.9%
1-analytical specificity (% unaffected pregnancies incorrectly identified)	0.15%

Please note: These figures refer to the sensitivity and specificity of the test for detecting the chromosome abnormality, not the sensitivity and specificity for predicting the clinical outcome.

Screening for sex chromosome aneuploidy is available in singleton pregnancies for no additional charge; it is not available in twin pregnancies. This option must be requested by the clinician prior to collection of the maternal blood sample. Other NIPT options will not be reported unless specifically requested. Please note that identification of sex chromosome aneuploidy will reveal the sex of the fetus, even if this option had not been selected.

If a woman has a 'high probability' result for a sex chromosome aneuploidy, the PPV will vary with the prior chance of the fetus being affected. False-positive cases can occur due to placental or maternal mosaicism for that aneuploidy. For this reason, irreversible decisions regarding the management of the pregnancy should not be implemented until the screening diagnosis is confirmed. We recommend prompt specialist assessment, potentially including ultrasound and karyotype of a CVS or amniocentesis sample.

Sonic Genetics offers a free genetic counselling session for women in this situation.^ Rapid cytogenetic analysis of a CVS or amniocentesis sample is available through Sonic Genetics at no cost to the patient. For further information, please refer to the relevant fact sheets and resources on our website.

Option: Genome-wide NIPT [additional charge]

Sonic Genetics also offers the option of a genome-wide NIPT that provides assessment for other chromosome abnormalities for an additional fee. Genome-wide NIPT is available in singleton and twin pregnancies.

Genome-wide NIPT can detect two categories of abnormality involving any of the autosomes. Please note that the test performance, clinical interpretation and management of genome-wide NIPT are different to NIPT for the common trisomies and sex chromosomes described above; the requesting clinician should confirm that the patient recognises and accepts these differences.

- Large duplications and deletions

Genome-wide NIPT can screen for duplications and deletions that are large, that is, greater than 7 million DNA bases (7 Mb) in size; this is equivalent to a chromosome segment that is approximately 1/6th the size of chromosome 21. This assessment does not include the X and Y chromosomes. This is a screening test for large *de novo* abnormalities and is not a suitable test for familial chromosome translocations or for small deletions, such as 22q11; please contact the laboratory for advice about the genetic investigations for such instances.

Large chromosome duplications and deletions are uncommon and are typically associated with congenital malformations and intellectual disability. Smaller abnormalities are more common and can be associated with intellectual disability and congenital malformations, or can be found in unaffected people; NIPT does not screen for smaller chromosome abnormalities.

	Duplication/deletion
Sensitivity (% affected pregnancies correctly identified)	74.1%
1-specificity (% unaffected pregnancies incorrectly identified)	0.2%

If a woman has a 'high probability' result for a large duplication or deletion, the PPV is typically 30-50%. False-positive cases can occur due to placental mosaicism for that abnormality. For this reason, irreversible decisions regarding the management of the pregnancy should not be implemented until the screening diagnosis is confirmed. We recommend prompt specialist assessment, including ultrasound and consideration of microarray analysis (not karyotype) of a CVS or amniocentesis sample. Each parent should have chromosome microarray analysis to assist in interpretation of the fetal result.

Sonic Genetics offers a free genetic counselling session for women in this situation.^ Microarray studies of a CVS or amniocentesis sample and of the parents are available through Sonic Genetics at no cost to the patient. For further information, please refer to the relevant fact sheets and resources on our website.

- Rare aneuploidies

Genome-wide NIPT can also detect mosaic aneuploidy involving the autosomes. In singleton pregnancies, this assessment also includes the X and Y chromosomes, that is, assessment for sex chromosome aneuploidy.

Trisomy for any chromosome other 21, 18, 13, X and Y, and monosomy for any chromosome other than X and Y, is typically a mosaic abnormality involving the placenta. In some cases, there may also be chromosome mosaicism involving the fetus. The ability of NIPT to detect such mosaicism will depend on the size of the chromosome involved and the proportions of the placenta and fetus involved; NIPT cannot detect all mosaic chromosome abnormalities.

	Rare aneuploidy
Analytical sensitivity (% affected pregnancies correctly identified)	96.4%
1-analytical specificity (% unaffected pregnancies incorrectly identified)	0.2%

Please note: These figures refer to the sensitivity and specificity of the test for detecting the chromosome abnormality, not the sensitivity and specificity for predicting the clinical outcome.

The identification of a rare mosaic aneuploidy carries very different clinical implications compared with the abnormalities described earlier. If the aneuploidy is restricted to part of the placenta, this may compromise placental function without directly compromising fetal development. Overall, approximately half of pregnancies with a rare mosaic aneuploidy will proceed to an uneventful birth. For the remainder, there may be a variety of adverse pregnancy outcomes (fetal death in utero, miscarriage, intrauterine growth retardation, fetal malformation) due to placental dysfunction, the fetus also being mosaic for the abnormality, or uniparental disomy of imprinted chromosomes. These risks vary with different aneuploidies.

If a woman has a 'high probability' result for a rare aneuploidy, there is an increased risk of an adverse pregnancy outcome. The risk varies with different aneuploidies and is not well defined. Before considering any irreversible decisions regarding the management of the pregnancy, there should be careful assessment of the status of the pregnancy. We recommend prompt specialist assessment, including review of placental function, fetal growth and morphology, and potentially genetic studies for aneuploidy and uniparental disomy on a CVS or amniocentesis sample. Specific guidance is included in the NIPT report.

Sonic Genetics offers a free genetic counselling session for women in this situation.^ Cytogenetic studies of a CVS or amniocentesis sample is available through Sonic Genetics at no cost to the patient. For further information, please refer to the relevant fact sheets and resources on our website.

Arranging NIPT

Please use the dedicated NIPT request form. We cannot accept other request forms as we require consent by both patient and doctor as outlined on the form. This form can be downloaded from the Sonic Genetics website and also is available electronically via a number of practice management systems (currently on Best Practice, Medical Director and Genie).

The patient must finalise payment and booking for the test online (as detailed on the request form) or by calling Sonic Genetics on 1800 010 447. Medicare and health insurance do not cover the cost of NIPT. The NIPT test costs $425; the options of fetal sex and sex chromosome aneuploidy are available at no additional charge; the genome-wide NIPT option costs an additional $70.*

Results are provided within 3–8 business days of the laboratory receiving the sample, and are available electronically via Sonic Dx or downloaded to your practice management system; fax and hard copy reports are also available.

On rare occasions, we are unable to provide a report regarding the common trisomies (and of any options requested). We may recommend a repeat sample collection and analysis (at no additional cost). This outcome usually reflects the complex biology of pregnancy rather than a technical failure of the assay. Nonetheless, we will provide a full refund of the test cost on request should there be no result for the three common trisomies.

There are also rare instances in which we can report on the common trisomies but not the free options of fetal sex or sex chromosome aneuploidy; in this situation we do not offer a refund of the test cost.

^ Details regarding referral for counselling is provided on relevant reports. Terms and conditions apply. See sonicgenetics.com.au/dr/nipt/gc
* Correct at time of printing. Please refer to our website for current pricing.

SHG-MKT-0274-00.1