Sonic Genetics
Quality is in our DNA

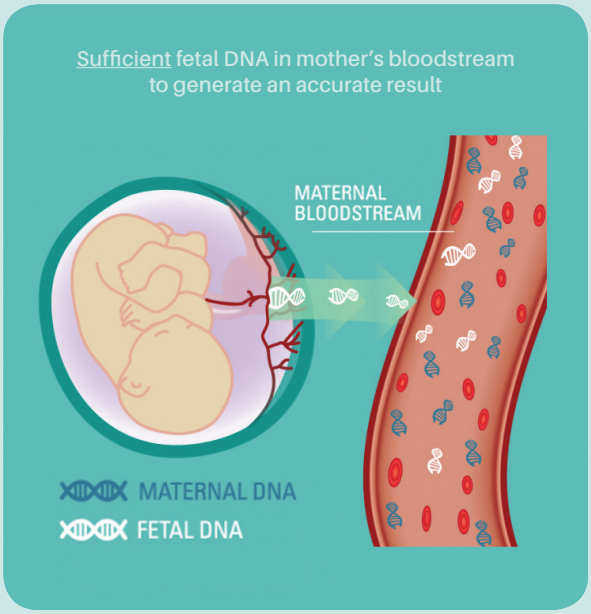
harmony®
PRENATAL TEST
performed in Australia

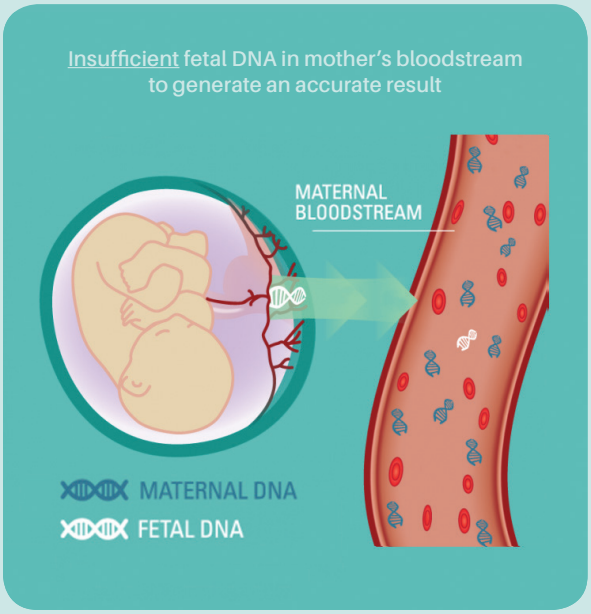
Why do some Harmony Prenatal Tests not provide a result?

What is the basis of non-invasive prenatal testing?

- During pregnancy, maternal plasma contains fragments of DNA from the mother and from the placenta ('fetal DNA').
- The proportion of DNA fragments from particular chromosomes is usually very stable throughout pregnancy and in different women.
- If there is an excess of fetal fragments from one chromosome, the proportion of fragments from that chromosome will be changed.
- If there is sufficient fetal DNA in the sample, the Harmony test can either confirm that the proportion of fragments is as expected (**low risk result**) or detect a change in proportion (indicating that the fetal DNA is **high risk for an abnormality**).
- In rare instances, the Harmony test cannot tell whether the fetal DNA is low risk or not i.e. a result cannot be reported.

Our commitment to quality means that we will only provide a result when there is very clear evidence for, or against, the presence of a specific abnormality. The reason why we cannot report a specific test usually reflects the complex biology of genetics and pregnancy, and is not due to a failing in the laboratory. This leaflet explains some of these biological reasons.





The Harmony test for trisomy 21, 18, and 13 cannot be reported after one blood collection.

This occurs in 3% of pregnant women tested by Sonic Genetics.

The usual reason for this is that there is too little fetal DNA (compared with maternal DNA) in the mother's plasma i.e. 'low fetal fraction'. Low fetal fraction can be due to a relative excess of maternal DNA, and this can vary over time. Low fetal fraction is more likely in women with increased body weight. It may also be more likely in the presence of infection and inflammation, or after exercise.

This outcome can also occur if the mother or fetus has some subtle benign variations in chromosome structure ("copy number variants") that make estimating the proportion of fragments from a chromosome unreliable at the fetal fraction in the sample. In some instances, the DNA in the sample has degraded during collection and shipping to the laboratory, and the quality is insufficient for a reliable result. These factors interfere with quality control ('QC') of the test.

It is worth repeating the Harmony test (at no charge) because two-thirds of women will get a result on re-testing.

The Harmony test for trisomy 21, 18, and 13 cannot be reported after a second blood collection.

This occurs in 1% of pregnant women tested by Sonic Genetics i.e. in one third of those whose test could not be reported after the first collection.

This outcome can be due to persistent low fetal fraction or quality control issues discussed above.

It is not worth repeating the Harmony test. A decision about invasive genetic testing should be based on assessment of all risk factors identified, and may require specialist consultation.

It is not worth using another form of non-invasive prenatal test. Other tests do not estimate the fetal fraction accurately and may provide false reassurance.

The Harmony test reports a result for trisomy 21, 18, and 13, but not for fetal gender.

This outcome, together with results which cannot report on sex chromosome abnormalities, occurs in 0.5% of pregnant women tested by Sonic Genetics.

The Y chromosome (indicating a male fetus) is much smaller than the chromosomes assessed for trisomies, and determining the presence or absence of the Y chromosome can be compromised by factors which do not limit reporting of the chance of trisomy. These factors include the fetal fraction being at the lower end of the acceptable range for trisomy testing, benign variation in the structure of the Y chromosome, and the quality of the DNA in the sample.

The Harmony test does not report a result unless there is very clear evidence for the presence, or absence, of the fetal Y chromosome.

It is not worth repeating the Harmony test. It is unlikely that the repeat test will provide a result for fetal gender. A decision about using fetal ultrasound or invasive genetic testing to document fetal gender should be based on assessment of need and any risk factors identified.

The Harmony test reports a result for trisomy 21, 18, and 13, but not for sex chromosome abnormalities.

This outcome, together with results which cannot report on fetal gender, occurs in 0.5% of pregnant women tested by Sonic Genetics.

Assessment for fetal sex chromosome abnormality involves assessment of the number of fetal Y chromosomes and the number of fetal X chromosomes. Both assessments raise specific challenges.

As noted in the section regarding fetal gender (above), the fetal Y chromosome is small and there are a number of technical and biological challenges in determining the number of Y chromosomes.

Determining the number of fetal X chromosomes is also challenging for a number of reasons:

- Most of the DNA in plasma comes from the mother (two X chromosomes), and the test must count the number of X chromosomes (one, two or three) in the smaller component of DNA from the fetus.
- Benign variation in the structure of the X chromosome ("copy number variants") is relatively common. This variation could be in the maternal or fetal DNA, and complicates the reliable assessment of fetal X chromosome number.
- The mother or placenta may have some cells with an abnormal number of X chromosomes. This is relatively common, and need not be associated with any abnormality of cell function. Nonetheless, this variation complicates reliable assessment of fetal X chromosome number.

The Harmony test does not report a result unless there is very clear evidence for the presence, or absence, of a sex chromosome abnormality.

It is not worth repeating the Harmony test. It is unlikely that the repeat test will provide a result for sex chromosome abnormality. A decision about using fetal ultrasound or invasive genetic testing to assess the fetal sex chromosomes should be based on assessment of need and any risk factors identified.

For further information on the Harmony testing process, test results, and other Frequently Asked Questions please visit www. sonicgenetics.com.au/nipt, or call 1800 010 447 to speak with one of our clinical geneticists or genetic pathologists.

Non-invasive prenatal testing services based on cell-free DNA analyses are not diagnostic; results should be confirmed by diagnostic testing. For further information, including scientific and peer-reviewed publications, please refer to our website, www.sonicgenetics.com.au/nipt or call us on 1800 010 447.

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The published evidence that is the basis for this leaflet is detailed in other leaflets about Harmony™ available on the Sonic Genetics website.

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