Conventional cytogenetic testing (karyotyping) has been the test of choice for detecting chromosomal imbalance during pregnancy, or following pregnancy loss. Analysis of all 23 pairs of chromosomes has detected aneuploidy (missing or extra chromosomes, such as Trisomy 21 at left) and large deletions or duplications of DNA.

Single Nucleotide Polymorphism microarray (SNP array) is a high-resolution test that can detect losses and gains of chromosomal material. SNP array has higher resolution and substantially better diagnostic yield than conventional karyotyping.

Advantages of SNP array over karyotyping

- Higher resolution – detects small but clinically significant abnormalities that would be missed by karyotyping
- Better diagnostic yield
- Does not require viable cells (beneficial in pregnancy loss investigations)
- Can distinguish fetal from maternal tissue (ensures the result reflects the genetic status of the fetus not mother)

How does microarray testing work?

We use the Illumina HumanCyto SNP-12 platform to provide SNP microarray testing for prenatal diagnosis, and for testing products of conception (POC)/pregnancy loss.

DNA is extracted from a patient’s fetal sample (CVS or amniocentesis), or tissue from POC. The DNA is applied to a glass slide that is covered with millions of tiny DNA probes, each of which corresponds to a specific DNA sequence from a specific region of each chromosome. The probes bind selectively to DNA fragments in the sample that have that sequence and come from that region. Fluorescent tags on the probes, a laser camera, and sophisticated software allow us to determine whether there is an excess or deficiency (duplication or deletion) of chromosomal material at each point.

What can microarrays detect?

- The analytical limit of detection of this assay is 100,000–500,000 base pairs of DNA.

  We review the clinical significance of all duplications and deletions identified. Some variations are benign, while others are known to be pathogenic. We may recommend studies of the parents to help clarify the clinical significance of a change of uncertain significance, or to exclude maternal cell contamination.

- SNP microarrays can also detect chromosomal regions where there is less variation in DNA sequence than would be expected.

  A lack of sequence variation on one chromosome (or part of a chromosome) may be due to uniparental disomy (UPD) i.e. that region of the fetal chromosomes is duplicated from one parent and lacking a contribution from the other parent. UPD can be associated with malformations or developmental delay, or with mosaic trisomy of the involved chromosome. A lack of sequence variation across multiple chromosomes may indicate consanguinity and be associated with an increased risk of an autosomal recessive disorder.
Limitations of microarray testing

Microarray testing cannot detect balanced chromosome rearrangements such as translocations or inversions. Balanced rearrangements do not change the overall amount of chromosomal material, and hence do not typically result in a clinical abnormality.

Low level mosaicism for deletions and duplications may not be detected by a microarray. If a mosaic abnormality e.g. monosomy X, is suspected, karyotype is the preferred test.

Microarrays can detect triploidy and some instances of tetraploidy, but tetraploidy due to reduplication of a diploid chromosomal complement (85% of cases) cannot be detected.

Mutations in single genes e.g. causing cystic fibrosis or fragile X syndrome, cannot be detected by microarray or karyotype.

If the mother has had an abnormal non-invasive prenatal test such as Harmony, the appropriate test on amniotic fluid or CVS is rapid prenatal FISH followed by karyotype. This will detect chromosome rearrangements that might be missed by microarray.

Complexities of microarray testing

The clinical interpretation of the deletions and duplications identified by microarray fall into three categories.

- ‘Known’ or ‘likely’ to be clinically significant. We advise the requesting clinician of such abnormal findings.
- Benign i.e. they frequently occur in the general population and do not cause disease. We do not include details of such changes in our reports.
- Clinical significance remains unknown. We advise the requesting clinician of such changes, but this report should not be the basis of major decisions about the management of the pregnancy. We will request samples from both parents as the presence of the change in an unaffected parent increases the likelihood that it is benign.

The interpretation of a chromosomal change is further complicated by some changes causing a highly variable clinical presentation, typically for neurodevelopmental abnormalities. It may not be possible to predict what the outcome will be for a particular fetus with such a chromosomal change. As the clinical presentation is variable, such a change may be inherited from an apparently unaffected parent.

Finally, test results may identify a deletion or duplication that is known to cause disease that might occur in later life i.e. unrelated to the reason for testing the fetus. Such a change may be inherited from a parent who, as yet, remains unaffected.

We recommend that patients in whom a change of unknown clinical significane, or of highly variable clinical presentation, or which could cause disease later in life be referred to a clinical genetics service for further assessment and counselling.


Requesting microarray testing

- Request ‘prenatal microarray testing’ or ‘pregnancy loss/POC microarray testing’ on a routine request form.
- Provide full clinical information including gestation, ultrasound findings etc to assist with interpretation of the laboratory findings.
- When requesting testing of parents to clarify the interpretation of findings in the fetus, please note the original laboratory number of the fetal microarray. When testing the father, please include details of the mother for cross-referencing.

Sample types, requirements and results

<table>
<thead>
<tr>
<th>Sample types</th>
<th>Requirements</th>
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<tbody>
<tr>
<td>Amniotic fluid</td>
<td>20–30 mL in 10 mL tubes</td>
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<tr>
<td>Chorionic villus samples</td>
<td>At least 15 mg (preferably greater than 20 mg) of chorionic villus sample is required, and must be provided in sterile transport medium (available from the laboratory)</td>
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<tr>
<td>Products of conception</td>
<td>Samples should be provided in a sterile culture or transport medium,</td>
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<tr>
<td>Parental blood samples</td>
<td>5 mL in EDTA + 5 mL in lithium heparin; minimum 1 mL in each</td>
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<tr>
<td>Microarray Results</td>
<td>Results are available in 2 weeks for prenatal specimens and 4 weeks for products of conception</td>
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The cost of microarray testing

The current MBS rebate for cytogenetic testing covers microarray testing (Item 73287). Additional samples from parents and siblings may be required in some cases to clarify preliminary microarray results; an MBS rebate will also apply for these samples (Item 73289).

If rapid prenatal FISH testing is also requested, this will incur a fee of $98 and is not rebated by Medicare.

For women with an abnormal Harmony® test done by Sonic Genetics, we provide rapid prenatal FISH and karyotype (not microarray); both tests will be done with no gap payment.

SNP array testing is overseen by genetic pathologist Dr James Harraway. Please contact Dr Harraway with any questions.

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