

Genetic Tests That Give a Diagnosis

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While non-invasive cell-free DNA analysis can now diagnose some single gene disorders (see section on NIPD), most genetic conditions can only be diagnosed in pregnancy by using invasive procedures, usually chorionic villus sampling (CVS) or amniocentesis (amnio) to obtain a sample for genetic testing. Both these procedures can very occasionally cause a miscarriage. There is a 1 in 200 (or 0.5%) chance of this happening.

What follows is information on the different testing techniques that are used after these two procedures.

1. Rapid results after invasive procedures: QF-PCR and FISH

QF-PCR and FISH are two tests that can give a result quickly after CVS or amniocentesis.

QF-PCR (Quantitative Fluorescent Polymerase Chain Reaction) uses the sample from the CVS or amnio and looks for genetic markers related to chromosomes 21, 18 and 13 to give a result within 72 hours for Down's syndrome, Edwards' syndrome and Patau's syndrome. It can also be used to detect conditions associated with the sex chromosomes (X and Y chromosomes), such as Turner's syndrome (a condition where a baby girl has one X chromosome instead of the typical 2).

Another rapid technique is FISH (Fluorescence In Situ Hybridization). This uses a fluorescent dye to visualize and map genetic material, usually material associated with chromosomes 21, 18 and 13.

Potential Advantages: these rapid tests are the quickest way to get a diagnostic result for Down's syndrome, Edwards' syndrome and Patau's syndrome (most women will get their result within three days)

Potential Disadvantages: they only give a result on a limited number of conditions. In approximately 1% of cases the tests can fail to give a result, often because the sample contains blood from the mother.

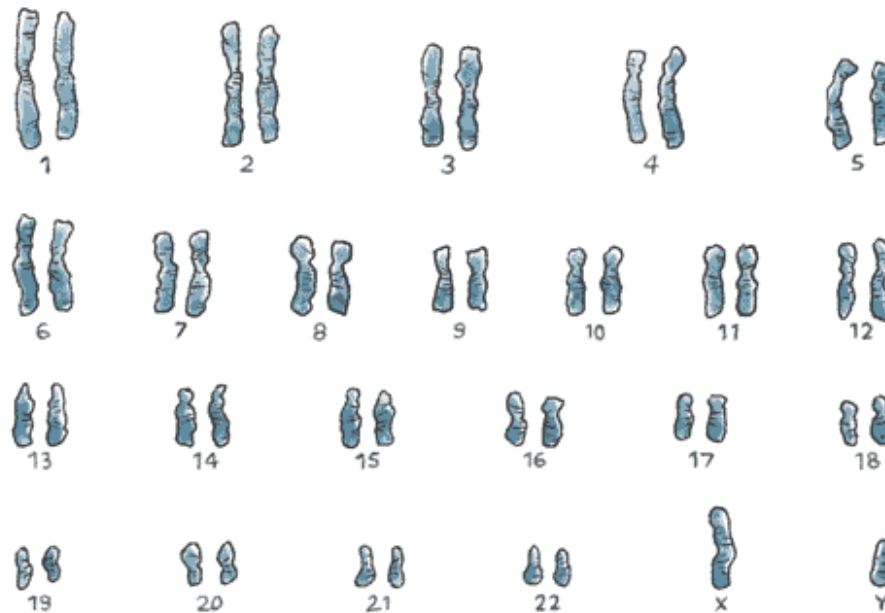
Because CVS samples come from the placenta, very occasionally the QF-PCR or FISH test will show a positive result for T21, T18 and T13 when the extra chromosome material is only in the placenta, not in the baby. If nothing on ultrasound scan suggests a baby has one of these conditions, it is usually necessary to do a further test on the sample such as karyotype or microarray or sometimes an amniocentesis will be required to be sure the baby has the condition.

The FISH test does not reveal other, less common chromosomal conditions unless the laboratory has set the test up to look for those specifically. Like QF-PCR, a result can be returned within 72 hours.

2. Karyotype

In use for over 50 years, this has been the traditional way to analyse chromosomes from a CVS or amnio sample. It takes longer to report a result because before analysis, cells are grown in the laboratory in order to separate out and identify all the chromosomes. Once the chromosomes have been identified, they are arranged in numbered order and a special dye is used to highlight regions or 'bands' of each chromosome. Then each chromosome is examined under a microscope to check for any changes that may be significant, e.g. changes in the structure of chromosomes, extra or missing chromosomes or parts of chromosomes or changes in position of chromosomes.

This is an example of a typical male karyotype (a female karyotype would have two x chromosomes):



Potential Advantages: karyotyping is a very well-established technique to diagnose major chromosome changes and gives more information than rapid testing. It can help determine whether a chromosome change is a ‘one off’ in a particular pregnancy or could be due to a parent carrying a chromosomal change they have passed on to the baby.

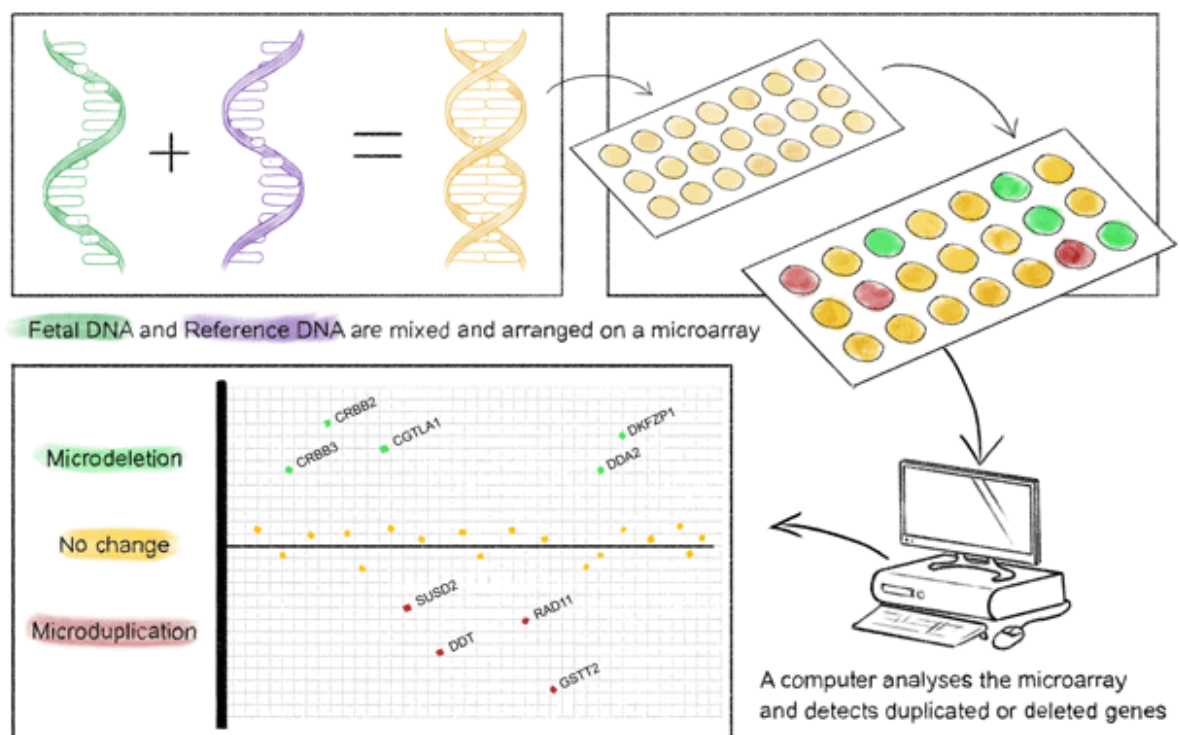
Potential Disadvantages: The genetic changes karyotyping can identify are limited to what can be seen under the microscope. Smaller ‘sub-microscopic’ changes that could be significant to a baby’s development could be missed.

3. Chromosomal Microarray Analysis (CMA)

Chromosomal microarray analysis (CMA) has started to replace karyotyping when scan findings suggest a genetic condition. This has happened because research has found that using CMA can increase the likelihood of providing a genetic diagnosis.

CMA can examine a baby's chromosomes in great detail. The laboratory technique compares a baby's DNA to a reference or typical DNA to check for changes. CMA can detect extra chromosomes (as in Down's syndrome) or missing or additional parts of chromosomes, but can go further to find very small changes in the DNA known as copy number variants (CNVs), where a number of genes are missing (microdeletion) or when there are extra genes (microduplication).

How CMA works:



Potential Advantages: CMA can examine chromosomes much more closely than a conventional karyotype so it might find significant genetic changes that would otherwise be missed.

Potential Disadvantages: CMA may reveal that the father of the baby is not who was assumed to be the father. CMA can detect genetic changes where it is difficult or impossible to predict whether they will affect a baby's development after birth.

While this more sensitive testing can sometimes find a small genetic change to explain why a baby is not developing as expected, it can also find changes that are of uncertain or unknown significance. What is known as a 'variant of

unknown significance' or VUS may or may not have an effect on the baby; there is not enough evidence of the effect of the change in other babies to have certainty. When there is uncertainty about the effect of the genetic change, the parents may be offered a blood test to check whether either the mother or father has the same variant. If a parent does have the same variant and is healthy, it can help predict the outcome for the baby.

4. Genetic sequencing – prenatal whole genome and exome sequencing (WGS and ES)

Sequencing (sometimes called 'next generation sequencing' or NGS) refers to new laboratory and computer technologies that can analyse multiple genes or even a whole genome within a time frame that will allow results to be reported within a pregnancy. It means scientists can look in much greater detail at genes than ever before.

Although it is relatively new, research suggests that sequencing can sometimes provide a genetic diagnosis when other tests have failed to do so. Sequencing the whole fetal genome means an extraordinary amount of information is generated, some of which will be very difficult and time-consuming to interpret. Researchers have found that sequencing the part of the fetal genome called **the exome** may be more practical and beneficial. The exome makes up no more than 2% of the whole genome but contains the majority (around 85%) of the genes that we know cause genetic disorders. This type of testing is known as exome sequencing or ES for short. You will sometimes hear it called R21 as this is the laboratory name for the test.

Sometimes the laboratory uses a 'gene panel' in the sequencing. This means they will only look for specific genetic changes that are known to affect the baby's development. Current prenatal gene panels include nearly 1000 genetic changes that we know cause developmental issues. This can avoid having to report results that may be very uncertain or difficult to interpret.

Exome sequencing is a new technology and is only just being introduced into the NHS. Most professional bodies recommend that it should only be offered when all other tests have failed to explain unusual scan findings. It does not

replace CMA because exome sequencing does not reliably detect genetic copy number variants.

At the time of writing it takes about three weeks to report a result. It will usually be necessary to take blood from both parents to check if any genetic change found in the baby, is also found in a parent. This is known as trio testing.

Potential Advantages: whole genome or exome sequencing could give useful diagnostic information when other genetic tests have not been able to. A genetic diagnosis may help parents understand the implications for a baby's development.

Potential Disadvantages: needs to be done after other genetic tests as cannot test for structural changes in chromosomes and some genetic conditions. As sequencing is used after other tests, it is possible that a diagnosis will come late in pregnancy.

This short animation may help with your decision-making.

Like CMA, exome and genome sequencing has the potential to provide information that may be uncertain, or genetic information that might show a condition that will not affect a child until they are adult. It might also find genetic information that might have implications for other family members or health implications for the mother.

5.Non-invasive prenatal diagnosis (NIPD)

Work is ongoing to provide diagnostic non-invasive (cell-free DNA) testing for some single gene disorders (A single gene disorder is a genetic condition caused by a change in one particular gene). This is commonly known as NIPD and uses the same technique as NIPT (a blood test from the mother) but unlike NIPT gives a definite answer as to whether a baby has a single gene disorder. Examples of single gene disorders are sickle cell disease and cystic fibrosis.

There are some inherited genetic conditions that can currently be diagnosed by NIPD by laboratories in the UK. If you know you carry a single gene disorder, you should speak to a genetic counsellor to see whether NIPD might be available.

NIPD can also be used to find out the sex of the baby, from 10 weeks of pregnancy. This can be helpful if expectant parents know they carry a 'sex-linked condition' (usually a condition that only affects boys such as Duchenne's muscular dystrophy).

Some private sector providers are offering NIPD for single gene disorders. It may be helpful to seek independent expert advice from a genetic counsellor or geneticist to see if it is available for your condition.

ARC - Call our helpline

Want to talk? We're here as often as you need us. Our helpline is answered by trained staff.

020 7713 7486

Monday to Friday: 10.00am – 5.30pm

Or text: **07908 683004**

Tuesday and Thursday: 8 – 10pm – email
info@arc-uk.org to arrange an evening call.

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