NON INVASIVE FOETAL DNA TESTING
(Also referred to as NON INVASIVE PRENATAL TESTING OR NIPT)

Introduction

Non-invasive foetal DNA tests analyse cell-free DNA circulating in the pregnant mother's blood. It is a new option in prenatal testing for Down syndrome (trisomy 21) and other common chromosomal conditions (trisomies 18 and 13), X and Y chromosome conditions, as well as other chromosome abnormalities including microdeletions. It is not meant to replace other screening tests, but rather is a highly accurate supplement.

Types of Fetal DNA Tests

Several laboratories based in America now can accurately test for foetal DNA abnormalities. These can be catogorized as either basic tests for the major trisomies, or a more comprehensive test to include other conditions. The tests currently offered at the Medical Chambers are one of two basic tests (**Harmony test** from Ariosa, or **VisibiliT test** from Sequenom) or a comprehensive test, **MaterniT21 PLUS** extended test from Sequenom. Currently MaterniT21 Plus is the most comprehensive test available anywhere and the Medical Chambers is first clinic to offer it in the U.K. The table on the following page summarizes the differences between the tests and the conditions tested for. However, the scope of these tests is rapidly changing so please also review our website for updates.

How Does it Work and what are the risks?

A blood sample is taken from the mother between week10 and 20 of pregnancy. The test analyses DNA from the foetus and placenta which circulates in the mother's blood and clears within hours of giving birth. The test is non-invasive: it carries no risk to mother or baby. This is the major advantage over “invasive” tests such as chorionic villus sampling (CVS)and amniocentesis, both of which carry a small risk of miscarriage.

Accuracy

Non-invasive foetal DNA testing has been proven to be very accurate with a >99.5% detection rate. As a result, it has replaced genetic amniocentesis for most patients who previously would have chosen that option, and now also gives the same high level of reassurance to lower risk patients without a risk to the pregnancy. The accuracy and type of other chromosome abnormalities tested varies with the laboratory. As a side benefit, X and Y analysis also can determine foetal sex with >99% accuracy.

Limitations

No single medical test is perfect. It is important to note that if the test results are positive, it does not necessarily mean that the foetus is definitely affected, although it is highly likely. For this reason, in the event of a positive result, follow-up testing by an invasive procedure is recommended.

A negative test does not exclude foetal Down syndrome but markedly reduces that risk with only a tiny chance of a false negative reading. For the most accurate results, the patient would still have a first trimester combined screen, or at least a nuchal scan near 12 weeks. As an example, the chance of foetal Down syndorme for a 35 year old woman who has both negative foetal DNA testing and a normal combined screen will be reduced from approximately 1 in 250, to 1 in a million. Not all types of chromosome abnormalities are detected, although the list of chromosome abnormalities which are tested continues to grow.

If the ultrasound scan shows usually large nuchal translucency or other major physical defect, the risk for some rare chromosomal defects increases. In such cases, the mother may choose to have a CVS or an amniocentesis.

Non-invasive prenatal testing does not provide information on other physical defects such as spina bifida, or information on foetal growth. It is therefore advisable that the mother has all the usual ultrasound scans during her pregnancy.

Repeat samples

There needs to be enough foetal DNA in the maternal blood to reliably analyse. If there is insufficient foetal DNA in the sample another blood sample from the mother may be required. This will be processed in the laboratory at no extra charge. Harmony has approximately 3% failure rate, and MaterniT21 PLUS has less than 1% failure rate.

Conditions Tested

• Trisomy 21 (also called Down syndrome) is the most common trisomy at the time of birth. It is associated with moderate to severe intellectual disabilities and may also lead to digestive disease, congenital heart defects and other malformations.
• Trisomy 18 (Edwards syndrome) and Trisomy 13 (Patau syndrome) are associated with a high rate of miscarriage. These babies are born with severe brain abnormalities and often have congenital heart defects as well as other birth defects. Most affected individuals die before or soon after birth, and very few survive beyond the first year of life. Ultrasound is also very accurate for suspecting trisomies 18 and 13.
• Sex chromosome conditions. All of the tests can accurately determine fetal sex (male or female). Sex chromosome abnormalities occur when there is a missing, extra, or incomplete copy of one of the sex chromosomes. There is controversy whether sex chromosome abnormalities should be tested since the outcome is usually favourable, so you will need to decide whether you want sex chromosomes tested.
• Other chromosomes abnormalities and microdeletions tested for vary with the laboratory and are summarized on the comparison chart. Sequenom tests for a number of microdeletions.

Time of Test Result

Currently all tests are processed in America, and the results take about 5-7 business days to return. The mother's information will be transferred outside of the European Union. Please be aware that the laws applicable to her personal data in the USA are different from those operating in the UK.

Role of Ultrasound

ALL patients should also have a nuchal scan near 12 weeks because a)) the most accurate results are obtained when the results are correlated with a first trimester combined screen, or at least a nuchal scan., b) some structural abnormalities – such as abnormalities of the brain, face, abdominal wall, face, extremities and occasionally the heart- can sometimes be detected as early as 12 weeks, c) increased nuchal translucency is a non-specific finding that can indicate the presence of abnormalities other than foetal aneuploidy.

Nuchal translucency scans can be performed between 11 weeks and 13 weeks 6 days but other foetal anatomy is best after 12 weeks. Patients may wanto to have their 12 week nuchal scan and non-invasive foetal DNA test performed on the same day. However, because non-invasive

foetal DNA testing can be performed as early as 10 weeks, other patients may choose to have the blood test performed then (after a limited ultrasound to confirm viability) and then return for a nuchal scan or combined screen at 12-13 weeks. We highly recommend all ultrasounds be performed at TMCK because of the very high quality of ultrasounds performed here. However, if patients are comfortable with having their ultrasound performed elsewhere, we also allow that option.

COMPARISON OF NON INVASIVE FETAL DNA TESTS: MaterniT21 PLUS vs. Harmony

MaterniT21 PLUS	Harmony	VisibiliT	Condition	Chromosome Condition	Prevalence in general population	Affects
x	x	x	Down syndrome	Trisomy 21 (extra 21st chromosome)	1 in 700	Heart defects, mental delay, other
x	x	x	Edward syndrome	Trisomy 18 (extra 18th chromosome)	1 in 3000	Variable but typically heart defects, marked mental delay, other. Neonatal death
x	x	x	Patau syndrome	Trisomy 13 (extra 13th chromosome)	1 in 8000	Multiple severe abnormalities including heart defects, cleft lip/ palate, kidney abnormalities, other. Fetal or neonatal death.
x	x		Turner syndrome	X0 (missing X chromosome)	1 in 2500 female births (1 in 5000 birth overall)	Short stature, may have heart defects, kidney, skeletal abnormalities, webbed neck, infertility, other. May die before birth Normal intelligence
x	x		Sex chromosome abnormalities	XXX, XYY, XXYY, XXY (Klinefelter syndrome	1 in 500 Kleinefelter affects 1 in 1000 males	Usually mild to few affects Kleinfelters with infertility, may have learning disabilities
x			DiGeorge syndrome	22q11-	1 in 4,000	Heart defects, cleft palate, immune deficiency, learning disabilities, delay, other
x			Cri-du-chat syndrome	5p-	1 in 50,000	Severe developmental delay, microcephaly, hypotonia, heart defects
x			Angelman syndrome Prader-Willi Syndrome	15q-	1 in 20,000	Developmental delay, other
x			1p36 deletion syndrome	1p-	1 in 10,000	Developmental delay, brain abnormalities, heart defects, other
x			Trisomy 16	Trisomy 16 (extra 16th chromosome)	1 in 100 pregnancies 1 in 50,000 births	Multiple abnormalities leading to abortion or early fetal death
x			Trisomy 16 mosaic	Partial trisomy 16	?	Intrauterine growth delay, may be heart defects, developmental delay, may lead to fetal death
x			Trisomy 22	Trisomy 22 (extra 22nd chromosome)	1 in 200 pregnancies 1 in 40,000 births	Multiple abnormalities leading to abortion or early fetal death
x			Trisomy 22 mosaic	Partial trisomy 22	?	Growth delay, developmental delay, abnormalities of head, face, heart defects.
<1%	3%	3%	Failure Rate			