King's College Hospital
NHS Foundation Trust

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Patient information leaflet: First-trimester cfDNA testing 07/12/2021 (Version 5)

Cell-free DNA test for women with combined chance of 1:100 or higher

You are being invited to take part in a research study. Before you decide whether to take part it is important for you to understand why the research is being done and what it will involve. Please take your time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. If you have any questions or require any further information please contact the study co-ordinators at King's College Hospital.

What is trisomy 21, 18 or 13?
In humans, there are 23 types of chromosomes and most people have a pair of each one of these chromosomes (therefore a total of 46 chromosomes). In trisomy, there are three rather than two of a particular chromosome (total of 47 chromosomes). The most common trisomy is that of chromosome 21. Some other trisomies include those of chromosome 18 and chromosome 13.

- Trisomy 21 (Down's syndrome) is associated with intellectual disabilities and some physical defects, most commonly heart abnormalities. The life expectancy is about 60 years.
- Trisomies 18 (Edward's syndrome) and trisomy 13 (Patau's syndrome) are associated with severe mental handicap and several physical defects. Most affected individuals die before or soon after birth and they rarely survive beyond the first year of life.

What is 22q11.2 Deletion Syndrome?

- 22q11.2 deletion syndrome is caused by a missing piece of chromosome 22. It occurs in close to 1 in 2,000 pregnancies. The majority of children with 22q11.2 deletion have heart defects, learning challenges, and susceptibility to infection. Some children with the condition also have intellectual disability, feeding problems, speech delays, kidney problems, and/or seizures. Children with 22q11.2 deletion have an increased chance of autism, and may develop psychiatric conditions later in life.

- Early prenatal testing for 22q11.2 deletion provides families and doctors with important information in order to properly care for the pregnancy and the newborn. Babies with 22q11.2 deletion may have special healthcare needs. Some babies with 22q11.2 deletion need surgery in the newborn period.

Invasive test
The only way to know for sure whether or not the baby has a chromosomal condition is by having an invasive test such as chorionic villus sampling (at 11-15 weeks) or amniocentesis (at 16 weeks or later). However, these tests involve the introduction of a needle into the uterus to take a sample of the placenta (CVS) or amniotic fluid (amnio) and they carry a risk of miscarriage of about 1%.

What is the cell free DNA test?

- This is not an invasive test and does not carry any risk to the baby.
- The test analyses DNA in maternal blood and gives a strong indication of whether the baby is at very high or very low chance of having trisomies 21, 18 or 13 or 22q11.2 deletion. The test has been shown to detect more than 99% of babies with trisomy 21, 98% of babies with trisomy 18, 90% of babies with trisomy 13 and 75% of babies with 22q11.2 deletion. The test does not detect mosaicism or partial trisomies.
- The cfDNA test does not provide information on other rare chromosomal abnormalities. If the scan at 11-13 weeks shows a high nuchal translucency (more than 4.5 mm) or major defects, such as exomphalos (an abdominal wall defect in which the intestines remain outside of the abdomen in a sac), holoprosencephaly (the brain fails to develop into two hemispheres), heart abnormalities or megacystis (an abnormally large or distended bladder), the risk for some rare chromosomal defects may be high. In such cases you may choose to have CVS or amnio.

What is the purpose of the study?
The combined test that you had has shown that your risk of having a baby with Down's syndrome (trisomy 21) or Edward's or Patau's syndrome (trisomy 18/13) is 1:100 or higher. You now have three options:

- No further test.
- The cfDNA test. This test is offered in some private clinics and it has been introduced at King's College Hospital free of charge as part of a research study.
- Invasive test (CVS or amnio).

The purpose of the study is to confirm the previously shown high accuracy of the cfDNA test, examine the uptake by women and determine the best way of introducing this test in all NHS hospitals.

The study will also evaluate the performance of the cfDNA test in screening for 22q11.2 deletion in women with a high chance of having a baby with Down's syndrome or Edward's or Patau's syndrome from the combined test and in women with fetuses with cardiac defects diagnosed during pregnancy.

Why have I been chosen?
At King's College Hospital we offer the cfDNA test to all women whose chance for trisomy 21 or trisomy 18 or 13 from the combined test is 1:100 or higher as an alternative to invasive testing or we have found that there is fetal cardiac defect..

Do I have to take part?
It is up to you whether or not to take part in the study. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the care you receive.

What will happen to me if I take part?
If you are willing to take part in the study, firstly, we will ask for your permission to store your residual serum/plasma, following biochemical testing (β-hCG and PAPP-A) as part of routine screening for trisomies 21, 18 and 13, for future research, and secondly, we will send your blood sample, which will be anonymised, to a company called Ariosa Diagnostics, in Belgium, who will carry out the Harmony test. This company will not have any of your personal details. However, you will be given an unique number so that we can link your results from Ariosa Diagnostics, with your details within our system. There will be no further clinical testing on this blood and your blood sample will be discarded once we have confirmed the results with you. Ariosa Diagnostics Inc. will not use your blood sample for any other purpose.

What do I have to do?
All you need to do is to let us know if you would like to take part in the study. There are no other restrictions as to what you can or cannot do.

When do I expect to get the results of the cell free DNA test?
The results will be available within 10 days. As soon as we receive them, we will contact you by telephone / email or by letter.

What would the results of the cell free DNA test show?

- If the cfDNA test shows that there is a **very-high chance** that the baby has trisomy 21 or 18 or 13 or 22q11.2 deletion it does not mean that the baby definitely has one of these defects. In about 1 in 1,000 pregnancies with a normal baby, the test shows a very-high risk for trisomies. It is therefore essential that you have a CVS so that you can be certain if the baby has one of these conditions or not.
- If the cfDNA test shows that there is a **very-low chance** (less than 1:10,000) that the baby has trisomy 21 or 18 or 13 or 22q11.2 deletion it is unlikely that the baby has one of these conditions.

What are the possible disadvantages and risks of taking part?

- You might experience discomfort, slight bruising and fainting during blood draw.
- The cfDNA test will only tell you if your baby has a very-high or very-low chance of being affected by trisomies 21, 18 and 13. The alternative of having an invasive test will give you information on all chromosomal abnormalities.

What are the possible benefits of taking part?
You can avoid the risk of miscarriage from an invasive test. It will also test for 22q11.2 deletion.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions [Argyro Syngelaki on 07518103639 or argyro.syngelaki@nhs.net]. If you are unhappy and wish to complain formally, you can contact the Patient Advice and Liaison Service (PALS) at 02032993601 or email kch-tr.PALS@nhs.net.

In the event that something does go wrong and you are harmed during the research and this is due to someone‘s negligence then you may have grounds for a legal action for compensation against King’s College Hospital but you may have to pay your legal costs.

Will my records be kept confidential?

All information collected about you during this study will be kept strictly confidential. Any information that leaves the hospital will have your name and address removed so that you cannot be recognised from it.

What if relevant new information becomes available?

Sometimes we get new information about the investigation being studied. If this happens, your research doctor will tell you and discuss whether you should continue in the study. If you decide not to carry on, your research doctor will make arrangements for your care to continue. If you decide to continue in the study (s)he may ask you to sign an agreement outlining the discussion.

What will happen to the results of the study?

Once the study is complete, the results will be published in a medical journal. You will not be identified in any report or publication. If you like, you will be able to find out the results of the studyby contacting the study co-ordinator.

Who is organising and funding the research?

The study will be supported by a grant from The Fetal Medicine Foundation (UK Charity No: 1037116). The Chief Investigator for the study, Prof Kypros Nicolaides, is also the director of the Fetal Medicine Foundation. The cost of collection and analysis of the samples will be covered by ROCHE. The Sponsors for the study are King’s College Hospital NHS Foundation Trust and King's College London.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by South East Coast Surrey Research Ethics Committee.