Non-Invasive Prenatal Diagnosis

North East Thames Regional Genetics Laboratory at Great Ormond Street Hospital for Children NHS Foundation Trust
About Great Ormond Street Children’s Hospital

Great Ormond Street Children’s Hospital (GOSH) in London is a centre of excellence with over 50 different paediatric specialities and 300 world-class consultants under one roof. GOSH is one of the world’s top five children’s hospitals.

GOSH hosts the North East Thames Regional Genetics Laboratory (NETRGL) and the RAPID project. NETRGL is an ISO15189 accredited NHS laboratory providing a diagnostic testing service to a population of five million patients resident in the North East Thames Region of London.

An extensive range of cytogenetic and molecular genetic diagnostic testing services are offered including comprehensive chromosome analysis for postnatal and prenatal referrals, and diagnostic, carrier and predictive testing for a wide range of single gene disorders.

The RAPID (Reliable Accurate Prenatal non-Invasive Diagnosis) project is based in NETRGL and is a programme grant for applied research funded by National Institute for Health Research (RP-PG-0707-10107).

The aim of the RAPID programme is to improve the quality of NHS prenatal diagnostic services by evaluating early non-invasive prenatal diagnosis (NIPD) based on cell-free fetal (cff) DNA in maternal plasma. As a result of this programme non-invasive prenatal diagnosis (NIPD) now has UKGTN approvals for a number of conditions and tests which are offered as part of our clinical service through NETRGL.

Development is ongoing for a number of conditions such as haemoglobinopathies and SMA, but here we describe the range of tests currently available.
Non-invasive prenatal diagnosis (NIPD)

(NIPD) represents a safe alternative to the invasive prenatal test because it only requires a blood sample from the mother. We believe that GOSH was the first centre worldwide to offer a clinical service from an accredited laboratory.

How does it work?

In order to determine whether the baby has a genetic condition we need to test the baby’s DNA. When a woman is pregnant, there is a small amount of her baby’s DNA circulating in her bloodstream. This is called cell free fetal DNA (cffDNA), so by testing a maternal blood sample we can analyse the baby’s DNA. This provides a safe alternative to traditional invasive tests.

Testing may be offered for the following reasons:

- There is a clinical indication, for example an abnormality seen on an ultrasound scan
- There is an increased risk of a genetic condition in the baby, usually because the couple already have an affected child and so there is a risk to any future pregnancy

Conditions we can test for:

- Fetal sex determination (this is only available where the pregnancy is at risk of a sex-linked disorder)
- Cystic Fibrosis – we offer two types of service for CF. We can offer paternal mutation exclusion when parents carry different CF mutations, but if the baby has inherited the paternal mutation an invasive test may be required to see if the maternal mutation has also been inherited. However, if there is DNA available to test from another child in the family, affected or unaffected, we may be able to offer definitive NIPD. We can also offer NIPD to parents who carry the same mutation.
- FGFR3-related skeletal conditions, for example achondroplasia and thanatophoric dysplasia
- FGFR2-related Craniosynostosis including Apert syndrome
NIPD for other conditions

This is a bespoke diagnostic service we offer for couples at risk of having a baby with a serious genetic condition because of a family history of a condition not covered by the tests described above. We only offer the service for conditions where invasive prenatal diagnosis would usually be considered appropriate.

Test development

We prefer to work up bespoke NIPD tests before pregnancy. Please contact the laboratory to discuss at the earliest opportunity as NIPD may not be possible for certain mutation types and test development can take up to eight weeks. In order to develop the test we need blood from both parents.

We will issue a report indicating whether we have successfully developed a bespoke NIPD test for use in any future pregnancy.

Once successfully developed, we would be able to offer NIPD to look for presence of the causative mutation in cfDNA. A report should be ready within 5 working days of receiving the blood sample.

Examples of bespoke tests we have developed:

In the last 2 years we have developed individualised NIPD for around 30 families and delivered bespoke NIPD in more than 20 pregnancies. Examples of conditions we have tested include:

- Osteogenesis Imperfecta (COL1A1 & COL1A2)
- Tuberous sclerosis (TSC2)
- Diastrophic Dysplasia (SLC26A2)
- Neurofibromatosis (NF1)
- Spastic paraplegia (SPAST)
- Rhabdoid Tumour Predisposition Syndrome (SMARCB1)
- Renal tubular dysgenesis (ACE)
- Coffin-Siris syndrome 1 (ARID1B)
- Cornelia de Lange syndrome 1 (NIPBL)
NIPD – other considerations

Test limitations:
To avoid reporting a negative result because there was not enough fetal DNA present in the mother’s blood we look for DNA markers in the maternal blood that are not present in the mother’s DNA. Occasionally the fetus and mother have the same markers and we are therefore unable to confirm the presence of cffDNA—this will be indicated on the report.

This test may not be applicable in multiple pregnancies unless there are associated ultrasound abnormalities, where it may be a very useful test, avoiding risk of miscarriage for the unaffected twin.

Turnaround time:
Once the sample is received at NETRGL in London, test results will be available in the following times:

NIPD testing: five working days

Bespoke NIPD test development: eight weeks

Sample requirements:

NIPD:
Maternal blood (at least 10ml) at 9+ weeks gestation AND a further 10ml sample taken one week later

If the patient is 12+ weeks and there are ultrasound finding compatible with the diagnosis, then a single 20ml sample is acceptable

Bespoke NIPD test development:
Maternal and paternal blood (4ml) or DNA sample (50ul)
Proband DNA (essential for de novo cases)
Copy of mutation report

Blood samples MUST be taken into EDTA or Streck tubes. EDTA samples should reach the laboratory within 24 hours of blood sampling, Streck tubes must arrive within five days.
It is essential that referrals come through Clinical Genetics or an antenatal clinic so that information on ultrasound scans, family history and genetic risk may be provided. This service is only available from nine weeks gestation onwards.
Contact Information

- For patient enquiries and counselling please contact:
  Tel: +44 (0) 20 7762 6871
  samantha.edwards5@nhs.net

- For healthcare professionals:
  Tel: +44 (0) 20 7829 7850
  fiona.mckay@gosh.nhs.uk
  Genetics.Labs@gosh.nhs.uk