Rapid Exome Sequencing Service for fetal anomalies testing

Frequently Asked Questions

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1 Introduction

The Genomic Medicine Service (GMS) provides the national genomic testing for rare disease and cancer within the NHS in England by delivery of the National Genomic Test Directory.

This document outlines frequently asked questions in relation to the rapid exome sequencing service for testing for fetal anomalies with a likely monogenic disorder, clinical indication R21 within the National Genomic Test Directory.

2 Frequently asked questions

2.1 What is the rapid prenatal exome sequencing test?

An exome sequencing test sequences the protein-coding regions (exons), which represent <2% of the human genome. For the rapid prenatal exome sequencing test, the whole exomes of the trio (fetus, mother and father) will be sequenced and then analysed using a nationally agreed *"Fetal anomalies"* panel of >970 genes known to be associated with structural abnormalities that may present prenatally. This panel can be found at https://panelapp.genomicsengland.co.uk/panels/478/

2.2 Where can I find detailed information about the rapid prenatal exome sequencing service?

The guidance document *"Rapid Exome Sequencing Service for fetal anomalies testing"* has been published on NHS Futures and provides detailed information about the service, including service provision, eligibility criteria, and testing pathways. You can access this document and all documentation in relation to the service here: https://future.nhs.uk/NHSgenomics/view?objectId=22388144

2.3 What forms do I need to request a test for rapid prenatal exome sequencing, and where can I find these?

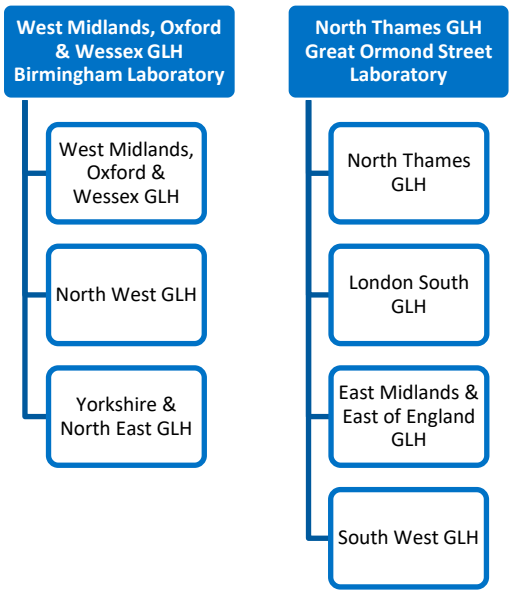
For each referral, the Home Genomic Laboratory Hub (GLH) will need to complete a test request form for the trio and record of discussion form for each parent being testing. All documentation required to request a test for R21 can be found here: https://future.nhs.uk/NHSgenomics/view?objectId=22388144.

2.4 What supporting information is available to parents being referred for a rapid prenatal exome sequencing test?

A supporting information leaflet for parents has been developed to support discussions with parents regarding testing. The information leaflet covers an overview of exome sequencing, the type of results you may get from exome sequencing, and what happens if you have the test. This leaflet is designed to accompany the discussions healthcare professionals will have with the parents and the record of discussion form and is not designed to be provided as a standalone document.

2.5 Which GLHs will be delivering the testing?

Two laboratories within the West Midlands, Oxford and Wessex GLH and the North Thames GLH will provide testing on behalf on the GMS due to their expertise and experience of the PAGE and BOOST studies. The testing for each GLH region has been allocated as follows;



2.6 What is the eligibility criteria for testing?

The testing criteria for rapid prenatal exome sequencing is:
Fetus with multiple, multisystem, major structural and selected isolated abnormalities *detected on fetal imaging where multidisciplinary review to include clinical genetics, tertiary fetal medicine specialists, clinical scientists and relevant paediatric specialists considers a* ***monogenic malformation disorder is likely*** *and molecular* ***diagnosis may influence pregnancy or early neonatal management*** *in the index pregnancy.*

Testing via R21 is not indicated in non-urgent settings, for example, where termination of pregnancy has been decided, or intrauterine death is imminent etc.

2.7 Who from the Home GLH will request the test?

The case must be discussed with a Clinical Geneticist, who will take responsibility for discussing the case with the Testing GLH and making the test request to the Testing GLH. The FMU team can complete the details on the test request form.

2.8 Do all cases need to be discussed with the Testing GLH?

Due to the urgent nature of this testing, there **must** be a discussion between the referring GLH and the Testing GLH to ensure to ensure eligibility of the referral.

2.9 What happens if it is not possible to have a trio available for testing?

If it is not possible to obtain all familial samples for trio analysis (mother, father and fetus), duo testing is accepted in exceptional circumstances (e.g. where one parent is not available or in instances of ovum or sperm donation). These referrals should be discussed with the Testing GLH and parents need to be advised of the potential decreased diagnostic yield in this circumstance.

2.10 What are the sample requirements for testing?

A minimum of 100ng of DNA must be available for testing. If this is not available, then the Home GLH must communicate with the Testing GLH to determine if the DNA sample available is suitable for exome sequencing. DNA extraction should be from amniocytes, chorionic villi, cultured cells or, exceptionally, fetal blood, and also from parental bloods. Protocols for DNA extraction can be obtained from your local GLH if required.

2.11 What other tests should be done by the Home GLH, in addition to the rapid prenatal exome sequencing test?

The Home GLH should perform QF-PCR for trisomy 13, 18 and 21 on the fetal sample and if the QF-PCR is negative, send the DNA samples (fetal and both parents) direct to the Testing GLH for rapid prenatal exome sequencing. The Home GLH should also perform microarray testing in parallel to the rapid prenatal exome sequencing test where appropriate and inform the Testing GLH of the results in a timely fashion.

2.12 What results will be reported for the rapid prenatal exome sequencing test?

Pathogenic and likely pathogenic variant(s) related to the phenotype or indication for rapid prenatal exome sequencing will be reported, as well as heterozygous pathogenic and likely pathogenic variants in recessive genes that are thought to be compatible with the scan findings. Class 3 variants (of uncertain significance) will **not** be reported, however limited exceptions may be made based on MDT discussions.

2.13 How long will it take to receive the report?

The Testing GLH will issue a preliminary report for probands with possible clinically relevant findings or issue a final report for probands with no detected clinically relevant findings within 14 days of the complete test request being received by the Testing GLH.

The Testing GLH will issue a final report for probands with confirmed clinically relevant findings within 21 days of the complete test request being received by the Testing GLH.

2.14 What alternative testing is available if rapid prenatal exome sequencing is not suitable or returns no pathogenic findings?

- R27 Congenital malformation and dysmorphism syndromes – can be used in non-urgent settings postnatally
- R387 Reanalysis of existing data – as whole exome sequencing was performed this can be reanalysed using a gene agnostic approach postnatally if additional findings suggest this might be helpful
- R14 Acutely unwell children with a likely monogenic disorder – can be used for urgent postnatal testing, e.g. where invasive prenatal testing is declined, or is done but the baby delivers before R21 testing is started and is acutely unwell.
- Or other targeted testing where the phenotype indicates, as per the National Genomic Test Directory (https://www.england.nhs.uk/publication/national-genomic-test-directories/)

3 Contact

If you have any questions or would like any additional information please contact ENGLAND.genomics@nhs.net, your local Home GLH, or your allocated Testing GLH (see 2.5, contact details below).

North Thames Genomic Laboratory Hub
gos-tr.londonnorthglhrapidsequencing@nhs.net, 0207 762 6886

West Midlands, Oxford & Wessex Genomic Laboratory Hub
bwc.rglprenatalexome@nhs.net, 0121 335 8027