Rapid Exome Sequencing Service for acutely unwell children with a likely monogenic disorder

Urgent referrals

The on-call Consultant Clinical Geneticist can be reached via UHS x6170 (Monday-Friday 9am-4pm)

Wessex contacts for general service enquiries:

Clinical Geneticist: Dr David Hunt, UHS x6170

Genomics Nurse: Phil Costello, UHS x6170

Genomic Medicine Service

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

Rapid Exome Sequencing Service for acutely unwell children with a likely monogenic disorder

The rapid exome sequencing service is provided by the network of Genomic Laboratory Hubs (GLHs) as part of the Genomic Medicine Service (GMS).

Although the R14 clinical indication (acutely unwell children with a likely monogenic disorder) is initially being tested by rapid whole exome sequencing, it will be transferred to a whole genome sequencing (WGS) platform when a clinically relevant turnaround time (as defined by NHS England) is achievable.

Description of current service provision

- The Royal Devon & Exeter NHS Foundation Trust, Exeter (South West GLH) is the sole provider of the ISO 15189:2012 accredited national rapid exome sequencing service, which was officially launched on **1st October 2019**
- The test comprises **whole exome sequencing** (sequencing of >20,000 protein coding genes) and variant interpretation (using ACMG variant interpretation guidelines), with a **maximum reporting time of 28 days** from sample receipt
- **Rapid exome sequencing does not replace other tests such as array CGH (e.g. for multiple congenital abnormalities), MS-MLPA (e.g. for Prader-Willi syndrome) and STR analysis (e.g. for**

myotonic dystrophy). Therefore, it is important to ensure that all appropriate first-line tests have been requested beforehand or in parallel through the local genetics laboratory (Wessex Regional Genetics Laboratory).

- **Testing will be performed at the discretion of the Exeter laboratory** and all cases will need to be discussed before any samples are sent
- Whilst most eligible patients are likely to be inpatients on NICU or PICU, **the service is intended for any acutely unwell child with a likely monogenic disorder in whom a molecular genetic diagnosis would alter management** - this being their own clinical management or in some cases family management (e.g. to enable diagnostic genetic testing of an ongoing pregnancy)
- If imminent demise is predicted then rapid exome sequencing will not usually be performed
- If there is insufficient DNA available from the proband for exome sequencing, it is possible to test for an autosomal recessive aetiology using parental samples (Stals *et al.,* 2018)
- **Testing can be requested for eligible patients by Consultants in Clinical Genetics, as well as other mainstream specialties such as Paediatrics and Neonatology following discussion with a local Consultant Clinical Geneticist**
- **Singletons, duos and family trios will be accepted – but family trios are preferred** when parental samples are available as this enables 'gene agnostic' analysis of the data and facilitates interpretation
- Appropriate panels of genes, selected from PanelApp, are applied to the data based on the patient's phenotype
- The patient's phenotype must be provided using Human Phenotype Ontology (HPO) terms on the test request form
- This service is nationally commissioned and NHS England is funding **700 proband tests in the first year of service**
- This is a national allocation to ensure **equity of access** and it is likely to be subject to review by NHS England

Local Process Map & Testing Pathway

Document to be inserted

Consent

Consent needs to be obtained before samples are sent for testing. The Exeter lab does not require a copy of a consent form to process the samples but states that 'the consent for genetic testing discussion should be documented as per current clinical practice'.

In practice, the conversation can be documented in the patient notes or, alternatively, the **Record of Discussion Form** can be used.

The following points should be raised:

- It is possible that no diagnosis will be made. This does not exclude an underlying genetic disorder. Whole exome sequencing is relatively new and our understanding of genomics is improving very quickly. As such, the interpretation that is made reflects current knowledge at the time the test was performed. Given that our knowledge of disease genes, pathogenicity of sequence variants and patient phenotypes will continue to improve with time, it is possible that future reanalysis of the sequence data may lead to a diagnosis. However, reanalysis is not performed routinely without request
- A result may be obtained that is difficult to interpret. Sometimes additional tests/assessments may be recommended to try to aid interpretation
- Rarely, genetic findings are identified that are important but completely unrelated to the clinical indication for the test. These are often referred to as 'incidental findings' and could have implications for the proband as well as other family members. Such findings are not actively sought and would only be reported if they are deemed 'medically actionable' (in other words, if by knowing about this finding early an individual could be offered some intervention or surveillance to potentially delay or prevent the onset of disease or improve the prognosis, then the result would be returned)
- Exome sequencing of a family trio detects biological relationships and can reveal non-maternity or non-paternity
- Since parental samples may be sequenced as well as the proband's, it is possible that reportable findings could have implications not only for the child but also for a parent and perhaps even wider family members as well

Further relevant information can be found in the report of the Joint Committee on Genomics in Medicine: Consent and confidentiality in genomic medicine

Other important considerations

If the proband was conceived using donor egg or sperm, please ensure that the Exeter laboratory are made aware. Parental samples can only be accepted if they are believed to be from biological parents.

It is important to enquire whether the proband or parents have received an allogeneic bone marrow/stem cell transplant; if so, a blood sample cannot be used for genetic testing.

Test Referral Form

Document to be hosted on Staffnet

Glossary

Array CGH – array Comparative Genomic Hybridisation. This is a form of detailed chromosome test, which looks for any missing or extra segments of chromosomal material. It does not detect balanced structural rearrangements of chromosomes and it does not entail any sequence analysis of the patient's DNA. It is typically used as a first-line test to investigate children with significant developmental delay/intellectual disability or multiple congenital malformations.

Autosomal recessive – refers to a mode of disease inheritance in which both the maternal and paternal copies of a given gene (from any of the chromosomes that are not sex chromosomes, i.e. chromosomes 1-22) have to be defective in order for disease to manifest.

Exome – refers to all of the exonic sequence found throughout the genome. Exons make up 1-2% of the whole genome. Exons include all of the protein-coding sequence of genes.

Monogenic – means that a single gene is involved. Monogenic disorders result from dysfunction of a given gene and follow Mendelian inheritance patterns.

MS-MLPA – Methylation-Specific Multiplex Ligation-dependent Probe Amplification. This test looks for methylation and dosage abnormalities and is used in the diagnosis of various conditions, especially imprinting disorders such as Prader-Willi syndrome, Angelman syndrome, Beckwith-Wiedemann syndrome and Russell-Silver syndrome.

NICU – Neonatal Intensive Care Unit

Phenotype – a description of an individual's observable traits or characteristics. The phenotype is determined by both genetic and environmental factors.

PICU – Paediatric Intesive Care Unit

Proband – the first affected individual in a family to undergo genetic investigation to establish the cause of disease

STR analysis – Short Tandem Repeat analysis. This is used to determine the overall number of short repeats in genetic sequence, such as the number of trinucleotide repeats in the myotonic dystrophy gene *DMPK*.

Variant – refers to any genetic finding that differs from the reference genome. There can be variants in sequence (e.g. single nucleotide variants) or dosage (e.g. copy number variants). Most genetic variation is tolerated and is part of normal human variation. Variants can be classified as being benign, likely benign, of uncertain significance, likely pathogenic or pathogenic.