Pregnancy Related Rapid Sequencing (R14) Service

BACKGROUND

The Prenatal Assessment of Genomes and Exomes (PAGE) study in the UK published findings in 2019 following the whole exome sequencing of 596 trios and 14 duos with fetal structural anomalies. This study reported a diagnostic yield of 8.5% (Lord et al., 2019 PMID: 30712880). In addition, research has shown that WGS can increase the diagnostic yield of congenital malformation and/or dysmorphisms in comparison to traditional array and gene panel testing (Sweeney *et al* 2021, PMID: 33888711; 100,000 Genomes Project Pilot Investigators 2021, PMID: 34758253).

Where a couple has had a previously affected child or pregnancy and there is an ongoing unaffected pregnancy, a diagnosis for the affected proband can give vital information to the family to inform further genetic testing and decisions. Therefore, this service is an urgent 14 calendar day test for the previously affected proband, not for the ongoing unaffected pregnancy. Note that for affected children that are alive and have a developing phenotype, the appropriate test for their clinical indication (e.g. Intellectual disability, epilepsy gene panel etc) should be requested urgently.

The equivalent NHSE Test Directory code for this test is R14. Please note that WINGS is the appropriate R14 test for urgent testing in acutely unwell children. For affected, ongoing pregnancies, Fetal Anomalies Gene Panel (FAGP; R21) testing may be appropriate.

Please contact the laboratory as soon as possible to expect receipt URGENT samples

RECOMMENDED CLINICAL REFERRAL CRITERIA

Urgent WGS/WES testing is **ONLY** available through referral from Clinical Genetics.

Essential Criteria

- Fetal malformation with a likely genetic cause where fetal loss, termination of pregnancy, or miscarriage has already occurred and there is an ongoing *unaffected* pregnancy.
- OR affected child that has not had previous testing and there is an ongoing *unaffected* pregnancy.
- DNA sample is available from **both** parents and they are willing to consent to testing

Diagnostic screening by sequence analysis:
Next Generation Sequencing (NGS) of the **whole genome** using Illumina PCR-Free assay and sequenced on Illumina NovaSeq 6000 platform. Sequences are aligned to human genome assembly GRCh38 (hg38). This aims to cover 97% of coding region exons ±20 base pairs to a minimum vertical depth of 20X, whilst 89% of the entire genome will be covered at a minimum of 20X. Please note WGS will only be used for blood samples

Next Generation Sequencing (NGS) enrichment of the **whole exome** using Nonacus Cell3™ Target ExomeCG kit and sequenced on Illumina NovaSeq 6000 platform. Sequences are aligned to human genome assembly GRCh38 (hg38). This aims to cover 95% of coding region exons ±5 base pairs to a minimum vertical depth of 20X. Please note WES will be used for tissue and prenatal fluid samples.

Where **trio** samples are available variants in green genes from the 'Paediatrics Disorders' (R27) PanelApp gene panel will be analysed followed by a gene agnostic approach to identify potential causative variants.

Copy number variants will be detected using array technology.

Please refer to PD-GEN-WGSTestInfo and PD-GEN-WESTestInfo for more information.

Family follow-up: Testing for known familial variants in any of the genes in the panel using Sanger sequencing

REPORTING TIMES

Analysis	TAT (calendar days)
Urgent Whole Genome /Exome Sequencing	14
Family follow-up	42

Prices are available on request

Sample Requirements	Contact Details
▪ **PROBAND** – >1ml blood, EDTA (preferred) & LiHep or tissue or prenatal fluid samples ▪ **MATERNAL** blood sample – 3-4ml, EDTA & LiHep ▪ **PATERNAL** blood sample – 3-4ml, EDTA & LiHep Please label samples with three identifiers and date of collection **All samples must be accompanied by a fully completed Pregnancy Related Rapid Sequencing (R14) sequencing request form**	All Wales Genomics Laboratory, Institute of Medical Genetics, University Hospital of Wales, Heath Park, Cardiff CF14 4XW Tel: 029 2074 2641 Fax: 029 2074 4043 lab.genetics.cav@wales.nhs.uk medicalgenomicswales.co.uk

Links
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