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Rapid exome sequencing service guidance

Fetal anomalies testing

Version 1, July 2021

Contents

Introduction	2
Background.....	2
Service Provision	2
Eligibility criteria	3
Testing pathways	5
Role of the testing GLH.....	8
Roles and responsibilities	11
R21 – rapid sequencing considerations	12
Supporting Information.....	13
Appendix 1: R21 Rapid Prenatal Exome Sequencing test request form, record of discussion form and information sheet for parents.....	15
Appendix 2: ISPD statement.....	20

Introduction

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

This guidance document defines expectations of the rapid exome sequencing service for testing for fetal anomalies with a likely monogenic disorder, clinical indication R21 within the National Genomic Test Directory.

Background

Rapid testing for fetal anomalies by exome sequencing is a NHS service which will build on the experience of the PAGE and BOOST research studies to offer results in a clinically actionable timeframe.

Currently no laboratory is ISO 15189:2012 accredited to provide this service therefore the two laboratories within the Central and South Genomic Laboratory Hub (GLH), involved in the PAGE study, and the North Thames GLH, involved in the PAGE and BOOST studies, will provide testing of individuals eligible under R21 on behalf of the GMS. These laboratories are in the process of accrediting this test to ISO 15189:2012 through an extension of scope, accreditation expected by March 2021.

Service provision

In summary:

- Rapid exome sequencing will be performed for a nationally agreed panel of genes known to cause disorders which may present prenatally.
- Referral for testing will follow discussion with clinical genetics and the mother's local management team.
- Testing should be likely to inform clinical management of the ongoing index pregnancy.
- Routine rapid aneuploidy testing will be performed first. Those with no genomic diagnosis will then undergo exome sequencing and microarray in parallel, where indicated.

- Trio testing (both parents and the fetus) is the preferred option to aid rapid interpretation.
- All relevant familial samples, fetal growth charts, imaging details and pedigree should be supplied at the same time with a test request form and record of discussion form to the Testing GLH together with any other relevant clinical details.

Eligibility criteria

Table 1: Testing criteria for this clinical indication are as listed in the National Genomic Test Directory¹

Clinical indication	Testing criteria	Stage in pathway for testing	Test requesting specialties
R21	Fetus with multiple multisystem major structural and selected other abnormalities detected on fetal imaging where multidisciplinary review to include clinical genetics, tertiary fetal medicine specialists, clinical scientists and – where appropriate – relevant paediatric specialists considers a monogenic malformation disorder is likely and molecular diagnosis may influence pregnancy or early neonatal management in the index pregnancy.	Following review by a fetal medicine expert and after discussion with a consultant clinical geneticist.	Clinical genetics (FMU team can complete the test request form but the case must be discussed with a clinical geneticist who takes responsibility for making the request and discussing with relevant GLHs)

Clinical examples

- Fetuses with multiple anomalies, suspected skeletal dysplasias (IUGR should be excluded), large echogenic kidneys with a normal bladder, major CNS abnormalities (excluding neural tube defects), multiple contractures (excluding isolated bilateral talipes).
- Nuchal translucency of greater than 6.5mm plus another anomaly (that can include a minor finding) with a normal array CGH.

¹ <https://www.england.nhs.uk/publication/national-genomic-test-directories/>

- Isolated non-immune fetal hydrops (detected at or after the routine 18-20-week scan in the second or third trimesters), defined as fluid/oedema in at least two compartments (eg skin, pleural, pericardial or ascites) with a normal array CGH.
- Persistent nuchal translucency (>3.5mm) can only be considered in the presence of other structural abnormalities in two or more systems.
- Minor 'markers of aneuploidy' – choroid plexus cysts, echogenic foci, mild renal pelvis dilation, small nasal bone, long bones on 3rd centile etc are excluded.
- Mild ventriculomegaly should only be considered as an abnormality if the posterior horn is persistently >11mm. Under these circumstances it is not considered a major CNS abnormality in isolation.

Referral for testing may be at any point in pregnancy where it will influence clinical management.

Exclusion criteria:

- Confirmed aneuploidy or pathogenic copy number variant consistent with fetal anomalies detected by microarray
- Fetuses with confirmed thanatophoric dysplasia, achondroplasia or Apert syndrome on other relevant rapid tests (R23, R24, R25, R306 or R309) are excluded.
- Cases where familial causative variant(s) are known - targeted testing should be performed
- For cases where sonographic findings indicate a specific monogenic disorder, targeted testing should be applied where appropriate
- Where termination of pregnancy has already been decided or when fetal demise has occurred or is imminent then rapid exome sequencing will not be performed. Appropriate testing should be implemented postnatally using the R27 clinical indication (congenital malformation and dysmorphism syndromes – microarray and sequencing).

Testing pathways

Summary

Two GLH laboratories will perform exome sequencing on behalf of the GMS. Based on current service provision and previous research and translational experience, Central and South GLH and North Thames GLH have been assigned this service.

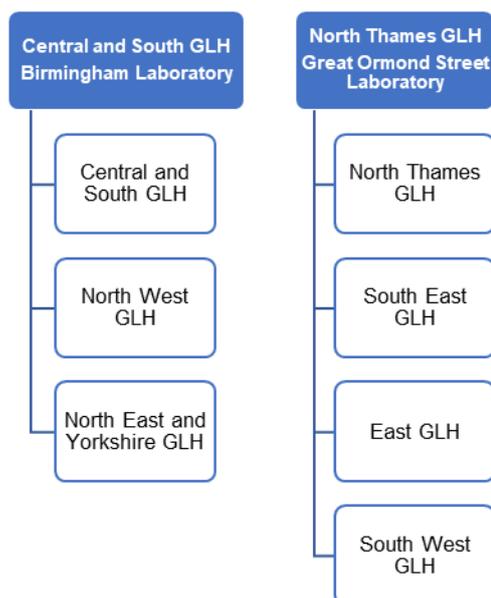
The capacity of each laboratory and expected volume of referrals defines the referral pathways from each GLH to the testing laboratories. However due to the urgent nature of this testing, there must be a discussion between the referring GLH and the testing GLH to ensure eligibility of the referral.

All referrals must be reviewed by a local clinical geneticist who will liaise with the fetal medicine team to complete the rapid prenatal exome sequencing request form, including patient details, HPO terms and contact details (email addresses and telephone numbers) for the clinical geneticist and fetal medicine requesting clinician, and complete the record of discussion form (see Appendix 1).

The local clinical geneticist should discuss the referral with the teams at the Testing GLH to confirm eligibility. If approved following discussion the request form and record of discussion form will be completed and the Home GLH will notify the Testing GLH when to expect the samples. Test request and samples should be sent to the Home GLH who will extract the DNA, perform rapid aneuploidy exclusion and start microarray analysis if appropriate. A copy of the record of discussion form should be made available for the patient.

The Home GLH will email the completed test request form for the trio and record of discussion for each parent to the Testing GLH. The Home GLH will then check the forms and if satisfactorily completed and the testing criteria is met then submit the samples to the Testing GLH – see flow diagram below: (Figure 1)

Figure 1: Default referral pathways



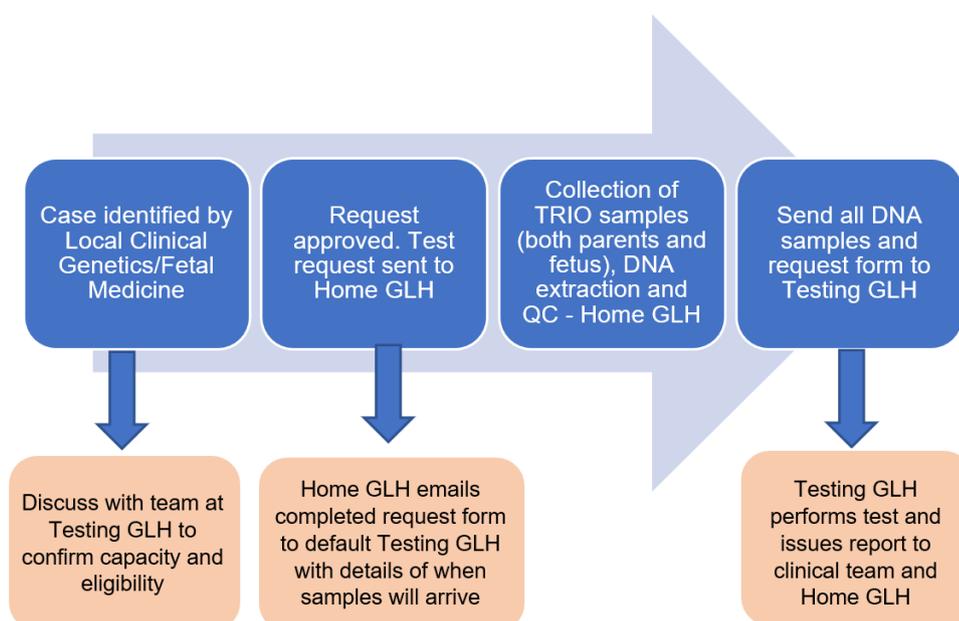
Role of the Home GLH

The role of the Home GLH (where the proband has been referred) is as follows:

- Ensure record of discussion form has been provided.
- Collection of all familial samples for trio analysis (mother, father, fetus). Duo testing is accepted in exceptional circumstances (eg where one parent is not available or in instances of ovum or sperm donation), and these referrals should be discussed with the Testing GLH and parents need to be advised of the potential decreased diagnostic yield in this circumstance.
- DNA extraction from amniocytes, chorionic villi or, exceptionally, fetal blood and from parental bloods.
- QC concentration (double-stranded DNA concentration using a Qubit method). 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.
- Discussion with Testing GLH to confirm current testing eligibility.
- Review of the completed test request form and record of discussion form and submission to testing GLH prior to sending samples.

- Notifications of expected samples and confirmation of dispatch to Testing GLH.
- Dispatch of samples to Testing GLH by courier service or first-class post as soon as all familial samples are ready for dispatch.
- Perform QF-PCR for trisomy 13, 18 and 21 on fetal sample and if negative send DNA direct to Testing GLH for exome sequencing.
- If maternal cell contamination (MCC) is detected in the fetal sample (eg via the QF-PCR), inform the Testing GLH as soon as possible as fetal samples showing MCC will not be accepted for exome sequencing. It is recommended that DNA from cultured cells is provided to the Testing GLH.
- Perform microarray testing in parallel where appropriate and inform Testing GLH of results.
- Inform Testing GLH if urgent testing is no longer required. (Fetal demise, termination of pregnancy or abnormal array result has been obtained)
- Participation in service evaluation data collection as required.
- Testing of future pregnancies should be undertaken as appropriate by the Home GLH.

Figure 2: Summary of the role of the Home GLH



Role of the testing GLH

The role of the Testing GLH (either the default Testing GLH indicated in Figure 1, or the second Testing GLH) is as follows:

- Approval of the test.
- Provision of an ISO 15189:2012 accredited service for rapid exome sequencing for referrals outlined in this document.
- Discuss referral with the referring GLH.
- Pre-log the request for testing upon receipt of the completed request form.
- Discussion with Home GLH to confirm current testing capacity, if required.
- Confirmation to the Home GLH of sample receipt and activation of testing as soon as the samples are received.
- Interpretation of the exome sequencing data and validation testing if appropriate, ie for presence of de novo pathogenic and likely pathogenic CNVs and small indels. The presence of SNVs are not required to be validated. This should be following discussion with referring geneticist
- If Home GLH indicates that urgent testing is no longer required, continue with analysis with a routine turnaround time.
- Issue of fully clinically interpreted reports in collaboration with the referring consultant clinical geneticist and referring fetal medicine unit if required.
- Participation in service evaluation data collection as required.

Analysis

Analysis for R21 will use a nationally agreed panel of genes known to cause disorders which can present prenatally. This will be reviewed and updated as appropriate in line with NHS England and NHS Improvement processes. Referring clinicians should specify particular genes/panels that should be applied at the time of referral if appropriate. The Testing GLH will confirm these are available on the fetal panel but may extend analysis if genes are not on the panel but are approved for analysis for a clinical indication (ie green genes) in the National Genomic Test Directory.

The GMS fetal disorders gene panel will be applied (specifically for genes which cause phenotypes which may present in the prenatal period and can be detected on fetal imaging). A panel-based approach to analysis will be taken in line with recommendations of the International Society for Prenatal Diagnosis on the use of

genome-wide sequencing for fetal diagnosis (ISPD, SMFM and PQF 2018), see Appendix 2.

The GMS Fetal disorders panel was developed from the Developmental Disorders Gene2Phenotype database (DDG2P) and additional genes reported in four recent, large scale studies of fetal exome/genome sequencing (Lord et al., 2019, Chandler et al., 2018, Normand et al., 2018 and Petrovski et al., 2019). Genes were individually reviewed according to the standard PanelApp guidelines and in line with NHS England and NHS Improvement processes. Genes were included that cause phenotypes that may present in the prenatal period and be detected on fetal imaging as determined by expert review supplemented by systematic literature search for the gene name together with any of 'fetal', 'prenatal' or 'antenatal'.

The gene list can be accessed at: panelapp.genomicsengland.co.uk/panels/478/. The gene panel content will be reviewed in line with NHS England and NHS Improvement processes.

Single nucleotide variants (SNVs), small indels (< 50 base pairs in size) and copy number variants (CNVs) must be analysed.

No secondary findings, unrelated to the indication for testing will be looked for, for example cancer susceptibility, hypercholesterolaemia etc. Very occasional incidental findings may be revealed as part of the diagnosis, for example BRCA1/BRCA2 pathogenic variants in the parents in a fetus found to have Fanconi anaemia.

There will be potential to share pipelines across GLHs to enable provision and standardise analysis and sample 'data-swap' between provider laboratories to provide external quality assurance.

Reporting pathways

The Testing GLH will communicate a preliminary result to the referring clinician and Clinical Geneticist by email. If no likely disease-causing variant is identified, a formal report will be issued shortly thereafter to the requesting clinician and clinical geneticist with a copy to the Home GLH.

If a variant (or variant pair) is identified that is considered likely causative, the Testing GLH will communicate details of the variant(s) with a request for feedback from the clinical team as to whether this is considered a plausible diagnosis and

whether it explains the entire phenotype. Following variant confirmation by an orthogonal method (where appropriate), a formal report will be issued.

In the situation where the identified variant(s) or variant pair(s) identified requires discussion with the referring clinician and clinical geneticist, the email from the Testing GLH will include details of the variant(s), current evidence for variant classification, relevant publications and links to websites such as OMIM. This email initiates a multi-disciplinary discussion that can also involve external experts. Where required, a teleconference or WebEx will be arranged in order for the clinical team and Testing GLH (and any external experts) to discuss the case, decide upon any further testing or investigations, and agree the variant classification for the report.

The Testing GLH will comply with the ACGS practice guidelines for variant interpretation and reporting:

- Pathogenic / likely pathogenic variant(s) that are considered to be causal are included in the formal report.
- A heterozygous pathogenic / likely pathogenic variant in a recessive gene that is thought to be compatible with the scan findings will be reported.
- On occasion, variant(s) of uncertain clinical significance are identified that are thought to have possible clinical relevance such that reclassification to likely pathogenic may be possible. If, after further review and MDT discussion, these variants remain of uncertain significance they will be included in the formal report as a record of the further discussions.
- All other variants considered to be benign, of uncertain clinical significance or without highly predictable clinical effect are not included in the report.

Incidental findings

Testing will focus on identifying disease-causing variants of direct relevance to the clinical referral and additional findings will not be actively sought. The testing strategy aims to reduce the likelihood of identifying pathogenic variants that predispose to other rare diseases but the possibility of incidental findings cannot be excluded. Such findings may be discussed with the referring clinician on a case-by-case basis. Trio exome sequencing will reveal possible non-paternity (or non-maternity) and this result would be discussed with the referring clinician.

Turnaround times

Table 2: Turnaround times

Stage	Start of stage	End of stage	Targeted TAT (calendar days) ²
Testing GLH activity 1	All samples and required data received from Home GLH	Issue of preliminary report for probands with possible clinically relevant finding or issue of final report for probands with no detected clinically relevant finding	14
Testing GLH activity 2	All samples and required data received from Home GLH	Issue of final report for probands with confirmed clinically relevant finding	21

Roles and responsibilities

Rapid sequencing services rely heavily on appropriate patient selection to ensure testing is focused on those with the greatest likelihood of benefit. Clinical geneticists will be involved in patient selection and variant interpretation and reporting, working closely with specialists in the fetal medicine context, and clinical scientists.

GLHs will be responsible for arranging workloads such that adequate capacity is available to prioritise urgent cases for interpretation and reporting.

The service will be audited with regard to referral and diagnostic rates and reviewed at monthly meetings attended by the testing laboratories, NHS England and NHS Improvement and the lead for prenatal exome sequencing from the other five GLHs. Audit data will be presented and reviewed. At six months diagnostic rates, eligibility and referral pathways will be reviewed and changes made if necessary, depending on review outcome and funding.

² From receipt of all family samples and relevant clinical details at Testing GLH

R21 – rapid sequencing considerations

Consent

Consent will follow the national patient choice model and can be performed by healthcare professionals who have undergone the relevant training. See appendix 1 for the record of discussion form for use in recording of patient choice.

The following points should be discussed by the clinical team with the parents prior to exome sequencing:

- It is possible that there may be no diagnosis after testing.
- A result may be obtained that is difficult to interpret and will still leave some uncertainty.
- Trio exome sequencing (mother, father and fetus) will reveal possible non-paternity (or non-maternity) and this result would be discussed with the referring clinician.
- The interpretation of the sequencing results is based on what problems are seen in the fetus using various imaging modalities, but this is limited compared to examination after birth. It is possible in cases with no prenatal diagnosis that findings after birth may initiate reanalysis of the sequencing data and identify the cause. Reanalysis of the exome sequencing data will only be undertaken if additional results, examinations suggest this could be useful. This should be the subject of a new referral to the Testing GLH under R387 (reanalysis of existing data).
- As analysis targeted to conditions that may present with imaging abnormalities prenatally is being performed then conditions that do not have abnormalities detectable with fetal imaging eg autism and many metabolic conditions will not be identified.
- As analysis targeted to conditions that may present prenatally is being performed then secondary findings such as cancer susceptibility genes in the fetus or parents will not usually be identified. However, as parental samples are being sequenced as well as the fetus then findings may be identified that could affect the parents' own health or have implications for

future pregnancies. If this is the case then these will be discussed with the parents.

- This is a new area and the understanding of DNA sequences is improving all the time. Result disclosure and post-test counselling will be based on knowledge that is current at the time of result interpretation. Potential changes over time are likely to occur in our knowledge of disease genes, pathogenicity of sequence variants and fetal phenotypes. This includes the possibility that a known condition may be identified after birth and that the findings identified prenatally have not been previously reported, ie as part of delivering this service we may identify the prenatal presentation of known genes with a previously unrecognised fetal phenotype. This means that reanalysis of the sequencing data at a later time may reveal the causative mutation.

Review

The testing criteria and requesting specialties for R21 referrals will be kept under review in line with NHS England and NHS Improvement processes. These services will be evaluated regularly during implementation and rolled out more broadly where evidence indicates that this can be achieved effectively. In addition, the content of the GMS Fetal disorders gene panel will be continuously reviewed to ensure an appropriate test and analysis are performed for these referrals.

Supporting Information

Chandler N, et al. Rapid prenatal diagnosis using targeted exome sequencing: a cohort study to assess feasibility and potential impact on prenatal counseling and pregnancy management. *Genet Med.* 2018 Nov;20(11):1430-1437

Drury S et al. Exome sequencing for prenatal diagnosis of fetuses with sonographic abnormalities. *Prenat Diagn.* 2015;35:1010-7.

Lord J, et al. Prenatal exome sequencing analysis in fetal structural anomalies detected by ultrasonography (PAGE): a cohort study. *Lancet.* 2019 Feb 23;393(10173):747-757.

Normand EA et al. Clinical exome sequencing for fetuses with ultrasound abnormalities and a suspected Mendelian disorder. *Genome Med.* 2018 Sep 28;10(1):74

Petrovski S et al. Whole-exome sequencing in the evaluation of fetal structural anomalies: a prospective cohort study. *Lancet.* 2019 Feb 23;393(10173):758-767

International Society for Prenatal Diagnosis; Society for Maternal and Fetal Medicine; Perinatal Quality Foundation. Joint Position Statement from the International Society for Prenatal Diagnosis (ISPD), the Society for Maternal Fetal Medicine (SMFM), and the Perinatal Quality Foundation (PQF) on the use of genome-wide sequencing for fetal diagnosis. *Prenat Diagn.* 2018 Jan;38(1):6-9

Appendix 1: R21 Rapid Prenatal Exome Sequencing test request form, record of discussion form and information sheet for parents

Test request form (pages 1 and 2):

Please contact the Testing Laboratory by telephone or e-mail BEFORE sending any samples
 North Thames GLH Tel: 0207 762 6886 Email: gos-tr.londonnorthglhrapidsequencing@nhs.net
 West Midlands, Oxford and Wessex GLH Tel: 0121 335 8027 Email: bwc.rglprenatalexome@nhs.net



Genomic Medicine Service
National Genomic Test Directory Clinical Indication R21 Rapid Prenatal Exome Sequencing Test Request

SECTION 1 - To be completed by referring fetal medicine unit

Before completing this form please confirm that testing has been discussed with and agreed by clinical genetics. Email addresses must be provided for the responsible FMU clinician and clinical geneticist.

CONSENT: Informed consent must have been obtained for all family members and the "Record of Discussion regarding exome sequencing" form must be filled in and attached to this referral form.

Date of form completion: _____

Maternal and pregnancy details

Surname: _____	Date of birth: dd/mm/yyyy _____	Ethnicity: _____
Forename: _____	Gestation: _____ weeks _____ days	Fetal Gender (by scan): <input type="checkbox"/> Male <input type="checkbox"/> Female <input type="checkbox"/> Undetermined
Hospital number: _____	Paternal sample available?: <input type="checkbox"/> Yes <input type="checkbox"/> No	Consanguinity: <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown
NHS number (or postcode if not known) _____	Additional information: <small>i.e. please specify if IVF pregnancy/gamete donor etc.</small> _____	

Paternal details:

Surname	Forename	Date of birth dd/mm/yyyy	NHS number	Ethnicity
_____	_____	_____	_____	_____

Clinical details:

Please list main clinical features in fetus and attach scan report(s):
 Growth charts must also be included if applicable.

Relevant family history or obstetric history: Yes No If yes, please give details

Relevant clinical features in parents: Yes No If yes, please give details

Referrer details:

Responsible FMU clinician:	Email address for report: (nhs.net)
Forename: _____	_____
Surname: _____	Telephone number: _____
Hospital: _____	_____
Clinical geneticist:	Email address for report: (nhs.net)
Forename: _____	_____
Surname: _____	Telephone number: _____
Hospital: _____	_____
Clinical genetics departmental shared email address : (nhs.net) _____	

Continued on next page

SECTION 2 - To be completed by referring laboratory

Please confirm with which Laboratory this test has been discussed: <input type="checkbox"/> North Thames GLH <input type="checkbox"/> West Midlands, Oxford and Wessex GLH		
Fetal DNA extracted from:	<input type="checkbox"/> Amniocytes <input type="checkbox"/> Cultured cells - amniocytes <input type="checkbox"/> CVS <input type="checkbox"/> Cultured cells - CVS <input type="checkbox"/> Fetal blood <input type="checkbox"/> Cultured cells - fetal blood	Date of invasive test: <small>dd/mm/yyyy</small> <input type="text"/>
Other genetic testing done or in progress: Please attach reports	qfPCR: <input type="checkbox"/> Yes Result: <input type="text"/> <input type="checkbox"/> In progress	
	Microarray: <input type="checkbox"/> Yes Result: <input type="text"/> <input type="checkbox"/> No <input type="checkbox"/> In progress	
	Other (specify genes/panels): Result: <input type="text"/>	
Required samples: Fetal DNA, Maternal DNA, Paternal DNA (paternal sample can be omitted if not obtainable) Please email the completed form to the Testing Laboratory BEFORE sending any samples.		
Please send at least 100ng of DNA per individual to the appropriate laboratory: North Thames GLH, Specimen Reception Level 5 Barclay House, 37 Queen Square, London WC1N 3BH West Midlands, Oxford and Wessex GLH, DNA Laboratory, Birmingham Women's Hospital, Edgbaston, Birmingham B15 2TG		
Laboratory contact:	Email address for report: <small>(nhs.net)</small>	
Forename: <input type="text"/>	<input type="text"/>	
Surname: <input type="text"/>	Telephone number: <input type="text"/>	
Lab: <input type="text"/>	<input type="text"/>	

CHECKLIST - Before sending please ensure the following are included with this request form

- Fetal DNA sample
- Maternal DNA sample
- Paternal DNA sample (unless no way to obtain this)
- Copy of scan report(s), including growth charts if applicable
- Copy of genetic report(s): qfPCR plus any other tests done
- Copy of "Record of Discussion regarding exome sequencing" form

Record of discussion form (pages 1 and 2)

Patient first name:	
Patient last name:	
Date of birth (dd/mm/yyyy):	
NHS number: (or Postcode, if not known)	



Record of discussion regarding prenatal exome sequencing

This form relates to the person being tested.

All of the statements below remain relevant even if the test relates to someone other than yourself, for example your baby. One form is required for each parent being tested.

I have discussed exome sequencing with my health professional and understand that:

1. This test includes genes with current evidence for a causal link with structural problems in a baby that can be detected by imaging. It does not include genes linked to conditions that only present after birth, for example developmental delay or autism.
2. Prenatal imaging does not allow us to examine the baby in as much detail as we can after birth. In some cases, more information after delivery will prompt further tests that may enable a genetic diagnosis.

Family and wider implications

3. The results of my test may have implications for me and members of my family, including revealing information about a child's biological parents. I understand that my results may also be used to help the healthcare of members of my family and others nationally and internationally. This could be done in discussion with me or through a process that will not personally identify me.

Uncertainty

4. The results of my test may have findings that are uncertain and not yet fully understood. To decide whether findings are significant for myself or others, my data may be compared to other patients' results across the country and internationally. I understand that as new knowledge becomes available this could change what my results mean for me and my treatment over time.

Unexpected information

5. The results of my test may also reveal unexpected results that are not related to why I am having this test. These may be found by chance and I may need further tests or investigations to understand their significance.

DNA storage

6. Normal NHS laboratory practice is to store the DNA extracted from my sample even after my current testing is complete. My DNA might be used for future analysis and/or to ensure that other testing (for example that of family members) is of high quality.

Data storage

7. The data from my test will be securely stored so that it can be looked at again in the future if necessary.

Health records

8. Results from my test will be part of my patient record, only available to healthcare professionals.

Service evaluation and audit

9. As this is a new test in the NHS it is important to monitor how the test is performing. To do this healthcare professionals may need to collect relevant information about me from my medical record after my test result, or to look at information about my test. Any data collected will be stored in a way that does not personally identify me.

Research

10. I understand that I may have the opportunity to take part in research which may benefit myself or others, now or in the future. If relevant opportunities arise, I consent to being contacted to discuss these.

For any further questions, my healthcare professional can provide information. More information regarding genetic testing and how my data is protected can be found at <https://www.nhs.uk/conditions/genetics/>.

Please sign on page 2 to confirm your agreement to testing.

Patient first name:	
Patient last name:	
Date of birth (dd/mm/yyyy):	
NHS number: (or Postcode, if not known)	



Confirmation of your genetic test and research choices:

I confirm that I have had the opportunity to discuss information about prenatal exome sequencing and potential research opportunities.

- A. I confirm that I have had the opportunity to discuss information about prenatal exome sequencing and agree to testing (circle your answer) YES | NO
- B. I agree to being contacted to discuss relevant research opportunities in future YES | NO

Patient name:	Signature:	Date: (dd/mm/yyyy)
...../...../.....
If applicable:		
Parent / Guardian / Consultee name: (amend as appropriate)	Signature:	Date: (dd/mm/yyyy)
...../...../.....

Healthcare professional use only:

To be completed by the healthcare professional recording the patient's choices

Healthcare professional name:	Signature:	Date: (dd/mm/yyyy)
...../...../.....

Hospital number:		
Patient category:	Adult (signed by themselves)	
	Adult lacking capacity (signed by consultee)	
Responsible clinician:		

Information leaflet for parents (pages 1 and 2)



Information on Prenatal Exome Sequencing for Parents

As part of your care, your doctor may offer you various tests to try and identify a genetic cause for the unexpected findings detected in your pregnancy. Your doctor will discuss this with you in more detail at your appointment. One of these tests is called Prenatal Exome Sequencing.

What is exome sequencing?

To answer this, it's helpful to first understand that the genome is the body's 'instruction manual', containing nearly all the information needed to create, run and repair the human body. The genome is made up of a chemical code called DNA, consisting of a series of nucleotides or 'letters' that can be 'read' using a technique called sequencing. There are over 3 billion letters in the entire genome but only a small percentage of these (~2%) directly translate into proteins, which are the main building blocks and tools within the body. This ~2% is called the exome and it is the portion of the DNA where we most frequently find the changes that cause genetic conditions.

Exome sequencing reads through all of the DNA letters within the exome, allowing us to look at a person's genes in great detail. This is one of the tests you may be offered to see if we can find a change in your unborn baby's DNA that might be the cause of the unexpected findings that have been noticed on ultrasound scanning. We will need to compare your unborn baby's exome with yours (both parents if possible) to help us tell the difference between harmless changes which can run in families and those changes which may be causing a genetic condition.

In this test we analyse the sequencing results using a targeted approach. This means we only examine the genes that we currently think may affect how the baby develops in the womb. In addition, as prenatal imaging does not allow us to examine the baby in as much detail as we can after birth, sometimes information after delivery may prompt further tests that may enable a diagnosis.

What results might you get from exome sequencing?

- **No relevant result** - This means that we have not identified a cause for the unexpected findings in your pregnancy. In the future, as knowledge and technology improves, we may be able to find the cause and we will discuss when you should seek further advice, for example if you are planning another pregnancy.
- **Relevant result** – This means we have identified a DNA change which clearly explains the unexpected findings in your pregnancy. This may give you more information about the condition affecting your unborn baby and play a part in your decisions about how to proceed with your pregnancy. It may also inform you about the risk of the same condition happening again in any future pregnancies. Sometimes this information may guide your medical team as to how best to manage your pregnancy, delivery and treatment in the newborn period.
- **Uncertain result** – This means that we have found a DNA change which *could* explain the findings in your pregnancy, but more tests or research may be needed to determine if this is relevant or not. In some cases, we cannot be sure whether a change is the cause of your unborn baby's condition or just part of normal variation. This might become clearer with time and as our knowledge of the genome improves.
- **Incidental finding** – Very rarely, the test may reveal an unexpected change in your unborn baby's DNA which may not be related to the features seen on ultrasound scanning but could have other health implications for the baby, for you, your family or future pregnancies.



As with all health data, the data from your genomic test will be stored securely within the NHS so that we can reanalyse it in light of new knowledge and understanding.

What will happen if I am offered exome sequencing?

Your doctor will explain the test in more detail, why you are being offered it and how you will get your results. You will be asked to sign a consent form if you agree to the test, understand what results you might get and when. You will be able to ask any questions you have. If you agree to have the test, you will be asked to have a procedure called amniocentesis or chorionic villus sampling (CVS) to obtain a sample of the baby's DNA. If you have already had one of these procedures, you will simply be asked to agree to some of this sample being used for exome sequencing. Both parents will also be asked to provide a blood sample. Results are usually available after 2-3 weeks and your doctor will discuss these with you.

Evaluating the new service

As this is a new test in the NHS it is important to for us to monitor how the test is performing. To do this it may be necessary for healthcare professionals to collect relevant information from your medical record after your test result, or to look at information about your test. This will be done in a way that does not personally identify you. This may help us improve the service we are offering.

Contributing to research

In many cases, once we understand the underlying genetic cause of a condition we can work with researchers in our universities and industry to develop new treatments in future. We will also ask your permission for us to contact you should any relevant research studies become available, so these can be discussed with you in more detail.

Your doctor will discuss all this with you and answer any questions you may have and then ask you to sign a form to say whether you consent to exome sequencing or not, and if you agree to being contacted about any new research. If you decide not to have exome sequencing or not to be re-contacted, you will still receive the best possible care from your healthcare team. The same applies no matter what the result of your exome sequencing may be, should you choose to have the test.

If you want to discuss this further Antenatal Results and Choices (ARC) is a national charity providing impartial information and support around prenatal screening and diagnosis.
Helpline: 020 7713 7356 Email: info@arc-uk.org web: www.arc-uk.org

Appendix 2: ISPD statement

International Society for Prenatal Diagnosis; Society for Maternal and Fetal Medicine; Perinatal Quality Foundation. Joint Position Statement from the International Society for Prenatal Diagnosis (ISPD), the Society for Maternal Fetal Medicine (SMFM), and the Perinatal Quality Foundation (PQF) on the use of genome-wide sequencing for fetal diagnosis. Prenat Diagn. 2018 Jan;38(1):6-9

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