v1.0, release date: 21/05/2021

NHS
Central & South
Genomic Laboratory Hub

Clinicians Guide to the Genomic Medicine Service

Requesting Genomic tests using the National Genomics Test Directory and PanelApp for Rare Disease

Authors: Gavin Ryan, Kate Glover, Simon Thomas, Katherine Lachlan, Dom McMullan, Ed Blair

Contents

Please note this version of this document (v1.0) is only relevant to the current clinical testing phase of Whole Genome Sequencing, and only for Rare Disease. Further versions of this document will be made available as it is updated in line with new guidance for Whole Genome Sequencing. Please see glossary in appendix 1 for further information on specific terms used in this document.

Background

From 1st February 2021 the seven Genomics Laboratory Hubs (GLH) in England will be delivering testing for the Genomic Medicine Service (GMS). The GMS will standardise genomic testing across England. This will help to ensure equity and quality of genomic testing nationally. The testing strategy will also improve efficiency and productivity of the GLHs. 'Core' tests will be performed by each of the 7 GLHs, while others will be "Specialist Tests" performed at a limited number of GLHs. This distinction should not impact on clinical care or existing sample pathways as in most cases the local Genomic laboratory will still be responsible for receiving samples, extracting DNA and forwarding DNA to the laboratory which provides the relevant "Specialist Test".

The tests available as part of the GMS for Rare Disease are listed in the National Genomic Test Directory for rare and inherited disease. Eligibility criteria for genomic testing are described in an accompanying PDF document. These can be found at the following URL:

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

The current version of the test directory is for 2020/21. The test directory is expected to be updated annually, and clinicians and laboratories will have the opportunity to provide feedback and request further clinical indications to be added to the test directory (see FAQs section for further information on this). The 2021/22 version is expected to be released in the Summer.

Any referral, whether on a standard genetic test referral form or a WGS test order form, should provide a clear and concise clinical indication for testing. This will include details such as what testing has been completed previously, whether the patient currently has features of the disorder to be tested for, and if so their specific clinical features, or if testing is presymptomatic. It will be extremely important to note whether there are other affected family members and if they have been tested and if the outcome of that testing is known. If possible, the report for a previously tested family member should be included or referenced.

National Genomic Test Directory

As discussed above the GMS aims to provide equitable and affordable access to a modern genomic laboratory service. To achieve these outcomes changes to past clinical and laboratory testing strategies have been agreed nationally. The new testing strategies will in general not use sequential single gene analyses and will where possible employ more efficient gene panel tests and when indicated Whole Genome Sequencing (WGS). This will require clinicians to become familiar with sections of the test directory relevant to their clinical practice.

The National Genomic Test Directory identifies the most appropriate test for each clinical indication and the testing methodology by which it will be delivered. There are 530 different clinical indications listed which link to eligibility criteria found in the PDF document. These tests should only be requested by relevant specialist clinicians; however clinicians who have previously requested tests will still be able to do so regardless of the stipulations within the eligibility criteria document. Each clinical indication will also have at least one test ID, and each test ID will relate to a different test component and test method. It is important to remember that each clinical indication may have multiple test methods because of differing technologies used to identify different types of genetic variation. Some clinical indications will only have one test method. These may be panel testing looking at a number of genes in a patient, or another method such as microarray. For example, shown below is the clinical indication and testing methods available for R21 'Fetal anomalies with a likely genetic cause'. Test ID .1 relates to common aneuploidy testing, .2 to WES or Large Panel testing, and .3 relates to Microarray testing. In most cases the order of testing for different test ID's will be dependent on current standard of care practices within the laboratories of the GLH. Where it might be unclear which test ID may be required as part of testing for a specific clinical indication, the laboratory may contact the clinician to discuss this.

Clinical indication ID	Clinical Indication	Eligibility Criteria Page Number	Test ID	Target/Genes	Test Method
R21	Fetal anomalies with a likely genetic cause	101	R21.1	Genomewide	Common aneuploidy testing
			R21.2	Fetal anomalies (478)	WES or Large Panel
			R21.3	Genomewide	Microarray

Figure 1. Test ID and related Test Method for a Clinical Indication.

In order to identify a relevant test, clinicians can use a number of routes. This can be done using either the test directory Spreadsheet or the PDF eligibility document. The test directory automatically has a

filter box available under each column heading. Filtering under the clinical group can provide a list of clinical indications available under a specialism (figure 2).

Clinical indication ID	Clinical Indication	Test ID	Test Method	Clinical Group
R26	Likely common aneuploidy	R26.1	Common aneuploidy testing	Developmental disorders
R27	Congenital malformation and dysmorphism syndromes - microarray and sequencing	R27.1	WES or Large Panel	Developmental disorders
		R27.2	Microarray	Developmental disorders
		R27.3	WGS	Developmental disorders
R28	Congenital malformation and dysmorphism syndromes – microarray only	R28.1	Microarray	Developmental disorders
R29	Intellectual disability – microarray, fragile X and sequencing	R29.1	WES or Large Panel	Developmental disorders
		R29.2	Microarray	Developmental disorders
		R29.3	STR testing	Developmental disorders
		R29.4	WGS	Developmental disorders
R377	Intellectual disability – microarray only	R377.1	Microarray	Developmental disorders
R47	Angelman syndrome	R47.1	Methylation testing	Developmental disorders
		R47.2	MLPA or equivalent	Developmental disorders
R48	Prader-Willi syndrome	R48.1	Methylation testing	Developmental disorders
		R48.2	MLPA or equivalent	Developmental disorders
R53	Fragile X	R53.1	STR testing	Developmental disorders
R69	Hypotonic infant	R69.1	Methylation testing	Developmental disorders
		R69.2	WES or Large Panel	Developmental disorders
		R69.3	Microarray	Developmental disorders
		R69.4	STR testing	Developmental disorders
		R69.5	WGS	Developmental disorders
R312	Parental sequencing for lethal autosomal recessive disorders	R312.1	WES	Developmental disorders

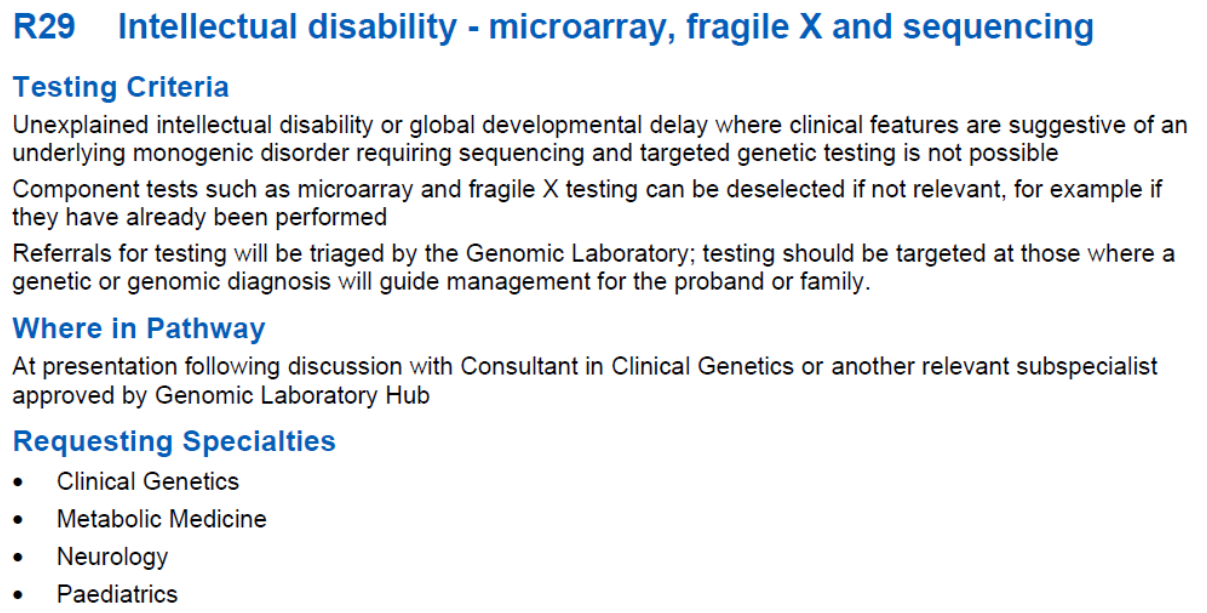
Figure 2. Test Directory indications filtered by Developmental disorders Clinical Group.

Alternatively, if the clinical indication is known then the user can either search for that indication by filtering under the Clinical Indication column to identify the ID i.e. the R number, or use Ctrl+F on the keyboard to open up a search box and search the test directory Spreadsheet. Once the R number is known then it is recommended to filter under the Test ID column using that R number as this will allow the user to see all of the different tests available under that specific clinical indication.

This information can also be seen in the Rare and inherited disease eligibility criteria document. Some users may find it easier to navigate this PDF document where all of the information within the test directory is contained, plus information on specialisms which are eligible to request testing under the specific indication. Clinicians who have previously requested tests will still be able to do so regardless of the stipulations within the eligibility criteria document.

The contents page of the PDF document splits the document into sections based on clinical specialist group, for example a section on Cardiology clinical indications available, and a section on Neurology clinical indications. It will provide the testing criteria required, any overlapping indications which might

be relevant, where in the pathway testing should be requested, and the specialities that are eligible to request the testing (figure 3). The associated tests, as present in the test directory spreadsheet, are also present under each clinical indication described.



R29 Intellectual disability - microarray, fragile X and sequencing

Testing Criteria

Unexplained intellectual disability or global developmental delay where clinical features are suggestive of an underlying monogenic disorder requiring sequencing and targeted genetic testing is not possible

Component tests such as microarray and fragile X testing can be deselected if not relevant, for example if they have already been performed

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

Where in Pathway

At presentation following discussion with Consultant in Clinical Genetics or another relevant subspecialist approved by Genomic Laboratory Hub

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology
- Paediatrics

Figure 3. R29 Intellectual disability clinical indication on Testing Criteria for Rare and Inherited Disease.

How to know what genes are tested in a panel as part of a clinical indication

PanelApp is an accredited publicly-available knowledgebase used to create virtual gene panels. These have been reviewed and curated by a dedicated team of clinical and scientific disease specific experts. Any clinician can register to become reviewers and suggest addition of genes to panels. This tool has been used to create standardised panels to be used across the GMS by all NHS laboratories, and the PanelApp knowledgebase is located at:

https://panelapp.genomicsengland.co.uk/

A colour coding system is used to determine which genes are to be analysed as part of GMS testing protocols (figure 4). Only genes/entities coloured green are analysed as part of the sequencing analysis for a defined gene panel. Genes/entities included on panels may be genes, copy number variants or short tandem repeats.

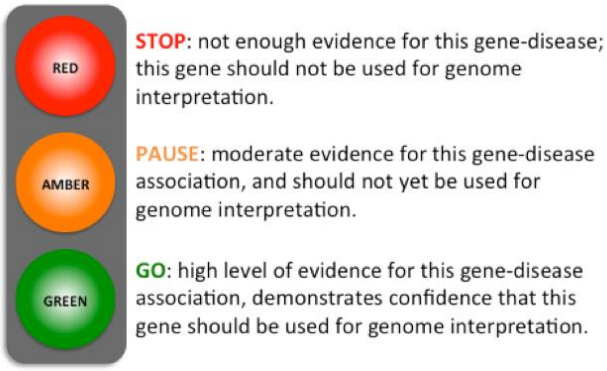


Figure 4. Traffic-light system used to rate genes on PanelApp gene panels.

PanelApp have also now made available a version of PanelApp which contains only the Genomic Medicine Service panels that are available (i.e. no panels listed that were only available for 100,000 Genomes Project or Research testing). This should be the first location for clinicians to check when looking for panels that can be tested for as part of the Genomic Medicine Service. The panel pages for this version of PanelApp only contain the green genes that will be tested for. This PanelApp version can be found at:

https://nhsgms-panelapp.genomicsengland.co.uk/

How to identify relevant test where a specific gene is suspected

If a patient's clinical features suggests a specific single gene, then the clinician can search for this gene on the 'Genes and Entities' section which can be selected at the top of the GMS PanelApp main page. The gene can then be entered into the search box to bring up all of the panels that this gene is present in (figure 5). More than one panel may be appropriate depending on the patient phenotype.

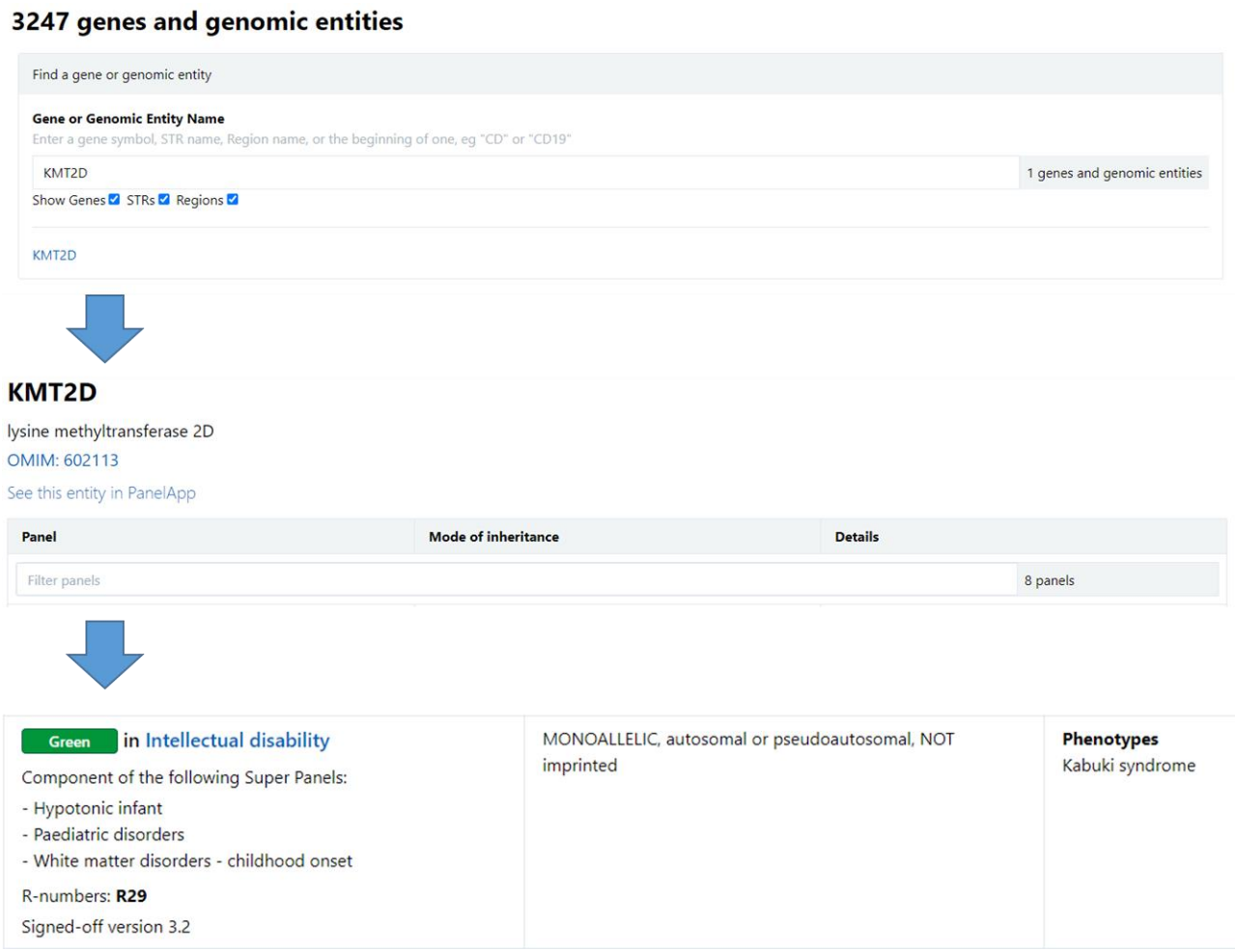


Figure 5. Searching for genes within PanelApp.

How to identify relevant test where a panel of genes are required

If a patient has features which are indicated for panel testing but the specific panel required is not known; if a clinical indication (R code) is entered on the form then the laboratory will be able to determine the testing required. There should also be part of the clinical indication name noted on the referral form as handwritten R codes could be misinterpreted. However, it is still important for the referring clinician to know what testing they are requesting. A user can search for a panel by selecting 'Panels' at the top of the GMS PanelApp main page. They can then search for a panel either using suitable keywords i.e. 'Intellectual' for Intellectual Disability panel (note: will only search for words present in panel name or Relevant disorders listed), or by using the R code from the test directory. For example, searching using R29 will bring up the Intellectual Disability panel (figure 6).

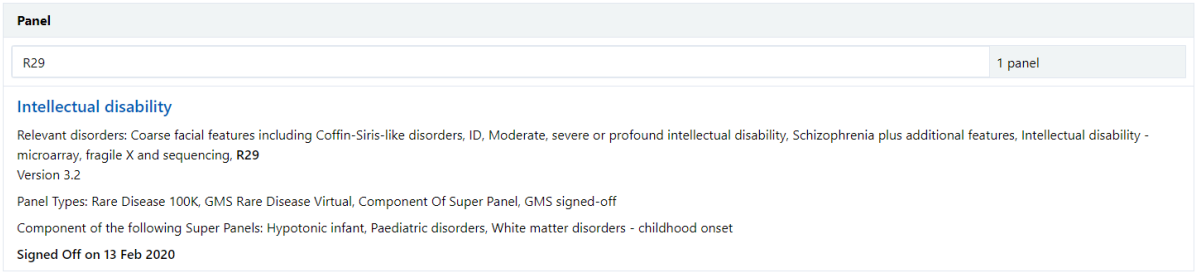


Figure 6. Relevant disorders for panels including R code found on PanelApp.

Each panel that is available for GMS testing will have a GMS signed off version that can be downloaded from that panel's page on the main PanelApp website.

GMS versions of panels are planned to be reviewed annually and updated following these reviews.

How to identify the most relevant test in the test directory

If the referring clinician needs to determine which clinical indication would be most appropriate for testing then they can do so using either the National Genomic Test Directory Spreadsheet, or the PDF eligibility document. To determine which indication is most appropriate the user can either filter the 'Clinical Group' column on the spreadsheet, or go to the specific specialist group on the PDF eligibility document, to see all of the clinical indications which come under that specialism. For example, if a patient has a neurological condition then the user can search the different clinical indications available under this specialism (figure 7). In most cases what has been written on a referral form previously will be sufficient to initiate the testing required; however in some cases the laboratory may contact the clinician to determine the most appropriate test. It is important that the clinician makes it clear which clinical indication is required for their patient's testing.

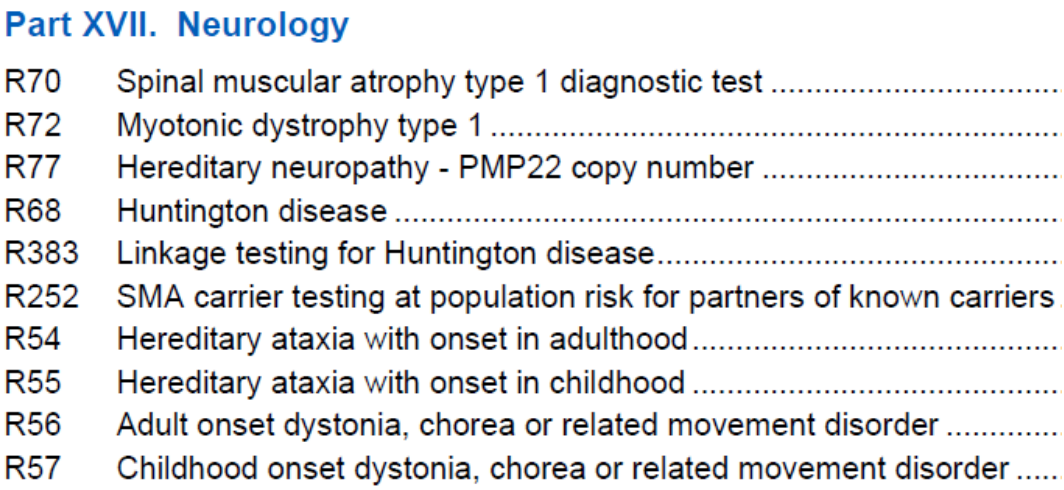


Figure 7. Examples of clinical indications for Neurology specialism available on PDF eligibility document.

Whole Genome Sequencing – indications and test ordering

WGS is currently available for 21 clinical indications (figure 8). However, NHSE have established criteria to gradually transfer increasing numbers of test indications to WGS. This will allow the GLHs to provide a rapid standard pipeline for genomic testing. The GLH laboratory will circulate updated WGS indication lists as this is updated by NHSE.

ID	Clinical indication	C&S GLH Interpreting lab	Indicative Patients for C&S Geography (NHSE Activity estimates 19/20)	Total Green gene number in PanelApp
R27.3	Congenital malformation and dysmorphism syndromes - microarray and sequencing	Referring lab	154	2007
R29.4	Intellectual disability – microarray, fragile X and sequencing	Referring lab	2313	1139
R69.5	Hypotonic infant	Referring lab	96	1559
R143.4	Neonatal diabetes	SWGLH	10	29
R98.2	Likely inborn error of metabolism - targeted testing not possible	Birmingham	578	698
R104.3	Skeletal dysplasia	Oxford	116	386
R100.3	Rare syndromic craniosynostosis or isolated multisuture synostosis	Oxford	19	55
R54.3	Hereditary ataxia with onset in adulthood	Oxford	193	186
R55.4	Hereditary ataxia with onset in childhood	Oxford	193	246
R59.3	Early onset or syndromic epilepsy	Oxford	540	425
R61.4	Childhood onset hereditary spastic paraplegia	Birmingham	58	70
R83.3	Arthrogryposis	Birmingham	19	132
R381.2	Other rare neuromuscular disorders	Birmingham	58	186
R84.4	Cerebellar anomalies	Oxford	21	246
R85.2	Holoprosencephaly - NOT chromosomal	Birmingham	21	11
R86.3	Hydrocephalus	Birmingham	39	69
R87.3	Cerebral malformation	Oxford	39	78
R88.3	Severe microcephaly	Birmingham	35	95
R109.3	Childhood onset leukodystrophy	Birmingham	58	1473
R193.4	Cystic renal disease	SW GLH	35	79
R89.3	Ultra-rare and atypical monogenic disorders	Referring lab	1156	N/A

Figure 8. Clinical indications eligible for WGS testing in phase 1 with activity estimates and typical PanelApp gene content

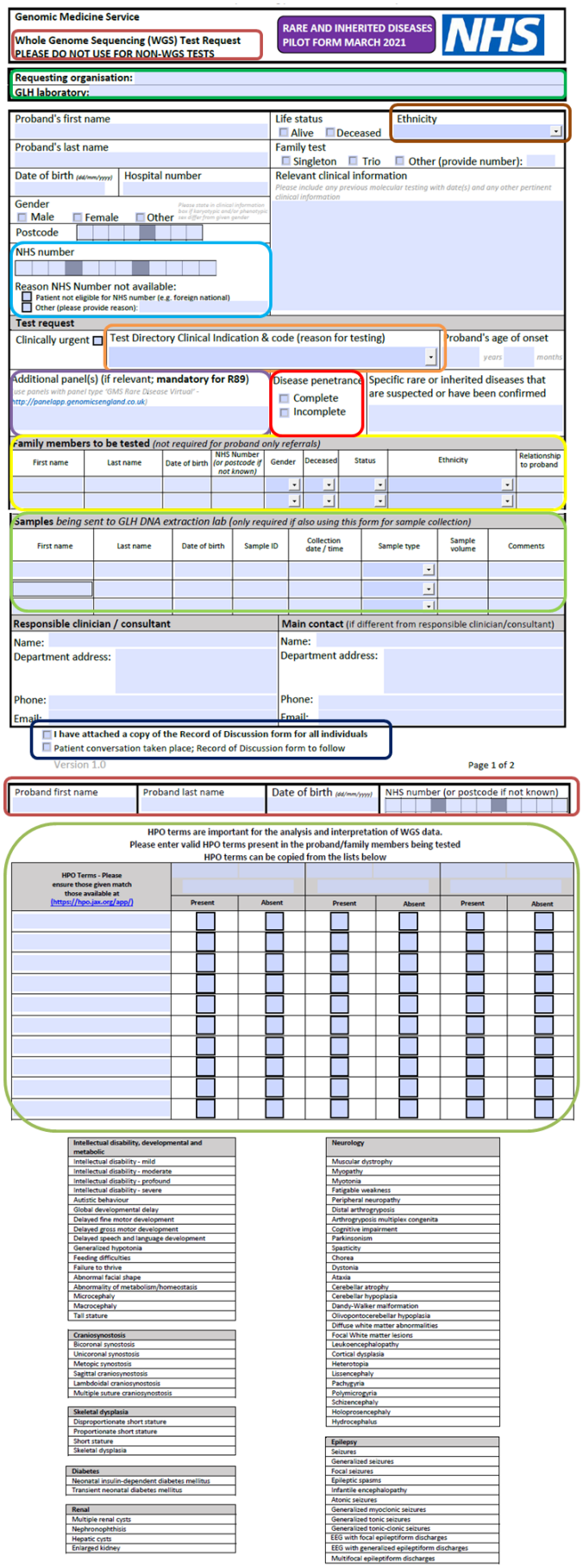
To order WGS the patient must have a completed test order form, a "record of discussion" for WGS and one of the approved clinical indications must be requested. These clinical indications will relate to one or more analytical panels. Additional panels can also be requested (see 'Completing a WGS test order form' section below) but must have panel type **GMS Rare Disease Virtual** on PanelApp. Please see appendix 3 for a list of the available panels that can be selected as additional panels. On the additional panels section of the WGS test form the clinician can just add the panel name for the panels that are required.

For many of these clinical indications a microarray test will also automatically be performed, if it has not previously for the patient, as part of standard of care testing. The microarray report may be received prior to or following the WGS report. In future, as copy number variation calling is further validated on WGS data then concurrent microarray testing may cease.

Completing a WGS test order – Rare Disease (RD) referrals

A WGS test order form and record of discussion form must be completed for WGS testing. Currently forms are being e-mailed, once completed by clinicians, to either the local genomics laboratory or to the GLH e-mail address at bwc.centralsouthGLH@nhs.net. Samples can then be sent with standard genetics laboratory referral forms to the local genomics laboratory to enable easier processing through phlebotomy if this is the pathway required for obtaining a patient blood sample.

- Specific WGS testing request forms:
  - **Test Order Management (TOM/TOF) form** (WGS test request form – a single form is required for rare disease proband and rare disease family members).
  - **Record Of Discussion (ROD) form** (all sides of the form must be completed and returned).
  - Forms are shown below in figures 9 and 10 with guidance on all of the different sections which require completion.
  - A self-defined ethnicity is required to be completed on the test order form to enable uploading of referral.
- Each family should have 1 completed Test Order form, and each family member should have 1 completed ROD.
- All forms should be completed in full and all pages are required for each form.
- These forms are for WGS testing only; if non-WGS testing, that isn't present on the additional panels in appendix 3, is required in addition to WGS please complete a separate standard genetics laboratory referral form.
- WGS for a rare disease referral ideally requires samples from 3 individuals - affected proband and biological parents.
- The majority of Phase 1 indications will be Paediatric referrals and will have large gene panels applied resulting in the "Tiering" of a large number of variants. Inheritance data is vital to efficient variant interpretation. Figure 1 gives an indication of the number genes typically examined for these indications.
- We recommend acquisition of trios for **all** Paediatric referrals
- Singletons (proband only) and duos (proband and one parent) can be accepted following prior agreement with the laboratory. The use of a trio for WGS testing provides a more efficient and higher quality analysis and a trio should always be referred where possible.
- For an RD trio would require:
  - 1 X RD TOM form
  - 3 X ROD forms
- Consenting for participation in the National Genomic Research Library via the Record Of Discussion form will ideally take place upfront, however it is possible to obtain consent for this following submission of patients for WGS (should select No on form if not consented for at this time). If a patient does not wish to participate in research then this **does not exclude** them from clinical WGS.
- Consenting for testing can be performed via telephone/video call and the clinician may sign the form by proxy.
- Stored DNA samples can be used for WGS testing, however fresh blood samples are preferred where possible, and stored DNA samples will be required to have been extracted by a UKAS-accredited laboratory and pass quality assurance checks.



For WGS testing only – if non-WGS testing is required in addition to WGS please use separate standard referral form

Requesting organisation: your hospital GLH laboratory to receive sample: Central & South

Ethnicity required to be entered for patient

Important to include an NHS number as required for the WGS pipeline

This should be the main clinical indcation (R code) – only record ONE in this box and must be WGS eligible clinical indication (see figure 9)

List any additional panels required (see appendix 3 for all additional panels available)

Disease penetrance options alter variant filtering so important to select most appropriate and applicable option

Important to detail the clinical status of family members as this can affect the filtering of variants based on expected inheritance

Specific QC guidelines to be adhered to if requesting stored DNA to be used. If possible a fresh blood sample is preferred

Indicate if RODs and TOM to be received together or if ROD to follow

Ensure patient details are correct and complete across both sides of the form

Add HPO terms that apply to patient and tick whether these are present in proband and parents who were referred.

Figure 9. Proband TOM form guidance

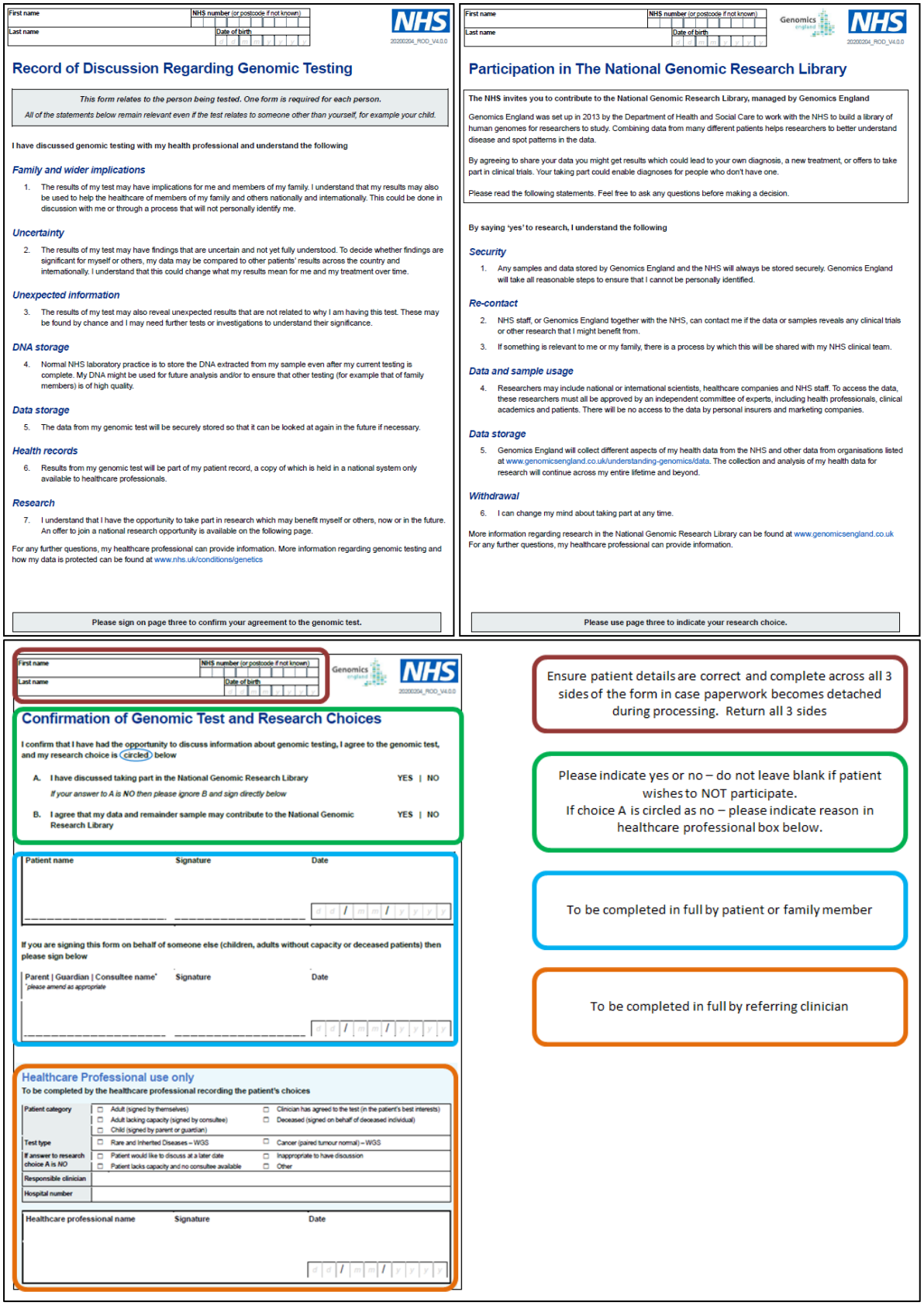


Figure 10. ROD form guidance

Genomic Medicine Service FAQs

What Is a GLH?

Genomic testing in the NHS is being provided through a national testing network, consolidating and enhancing the existing laboratory provision. This will create a world class genomic testing resource for the NHS and underpin the NHS Genomic Medicine Service and deliver on our commitments as part of the NHS Long Term Plan.

The national genomic testing service is delivered through a network of seven Genomic Laboratory Hubs (GLHs), each responsible for coordinating services for a particular part of the country.

The seven GLHs are:

- Central and South Genomic Laboratory Hub led by Birmingham Women's and Children NHS Foundation Trust
- East Genomic Laboratory Hub led by Cambridge University Hospitals NHS Foundation Trust
- North West Genomic Laboratory Hub led by Manchester University NHS Foundation Trust
- North Thames Genomic Laboratory Hub led by Great Ormond Street Hospital for Children NHS Foundation Trust
- South East Genomic Laboratory Hub led by Guy's and St Thomas' NHS Foundation Trust
- South West Genomic Laboratory Hub led by North Bristol NHS Trust
- North East and Yorkshire Genomic Laboratory Hub led by The Newcastle upon Tyne Hospitals NHS Foundation Trust

Why do we need the GLH network?

The NHS is developing a new national genomic medicine service, which will require collaboration with clinical organisations locally, regionally, and nationally. Close working between clinicians in many specialities and genomic laboratory staff will be critically important to the success of this venture.

Genomic data underpins

- Personalised medicine e.g. avoiding toxic treatments, targeted interventions
- Precise diagnoses in cancer and rare disease
- Disease prevention and screening
- Precise prognosis and treatment e.g. tumour agnostic therapies
- Research opportunities for patients e.g. access to clinical trials for cancer
- Industry collaboration
- Improved public health
- Equity of access even for very rare disorders

The NHS England Board set out its strategic approach to build a National Genomic Medicine Service. This comprises a number of key elements:

1. A national genomic laboratory service through a network of Genomic Laboratory Hubs
2. A new National Genomic Test Directory to underpin the genomic laboratory network

3. A national Whole Genome Sequencing service and supporting informatics infrastructure developed in partnership with Genomics England

4. A clinical genomic medicine service supported by an evolved Genomic Medicine Service Alliance (GMSA)

5. A national co-ordinating and oversight function within NHS England (Genomics Unit)

Building on the work of the 100,000 Genomes Project, NHSE has developed a national genomic laboratory service based around 7 Genomic Laboratory Hubs (GLH). The GLHs will allow the NHS in England to deliver high throughput, safe, equitable and affordable genomic testing to the whole population. This will reduce the inequities introduced by historical unequal local funding settlements for genomics as funding of investigations within the "National Test Directory" will be centrally funded. It will allow specific GLH laboratories to build greater expertise in specialist test areas. It will reduce unnecessary duplication and waste and encourage an environment of innovation.

What is a GMSA?

In February 2020 NHSE/I issued guidance on the creation of seven Genomic Medicine Service Alliances (GMSAs) across England.

GMSAs are a key part of the NHS GMS. The GMSAs will work with clinical teams and the GLHs to further embed genomic medicine into healthcare across a range of settings. The embedding work will require partnership between established genomic clinical services, other clinical teams in primary, secondary and tertiary care, nursing and midwifery, pharmacy, the Cancer Alliances, the AHSN, academia and Health Education England.

Will these changes affect my clinical practice?

In short, yes, we will all see an impact on our day to day clinical practice. Clinicians who could not access genomic tests because of local "funding issues" will no longer face that barrier. Patients with rare disease, who may have gone undiagnosed or faced a long diagnostic odyssey, will now have access to state of the art genomic tests. Increasingly these data will be used to direct personalised medicine, further targeted investigation and personalised pharmacological intervention. The GMS will also help forge strong links to a National Genomic Research strategy that will permit all patients access to clinical trials or research programs.

How is this affordable?

We are fortunate to work within a national health system that can, when we work together, deliver economies of scale that would not be accessible to any of us on an individual basis. To make the delivery of genomic testing affordable, the 7 GLHs, working with NHSE have leveraged these economies of scale by rationalising and streamlining how we deliver genomic testing in our health

service. This will mean however, that the clinician's traditional approach to genomic testing will also need to be modified. The "gene by gene" approach to investigation of patients with rare disease is no longer acceptable to patients or affordable for the NHS. As clinicians, we will have to find new ways of working to allow us to deliver the full benefit of the GMS to the greatest number of our patients. This will necessitate changes to how we have worked for many years.

Testing FAQs

I want to order a test but cannot find a matching clinical indication. What do I do?

If you know the gene you want tested then please see the 'How to know what genes are tested in a panel as part of a clinical indication' section above which discusses finding a panel(s) and R code/Clinical Indication appropriate for that gene. If you do not know the gene you want tested then please contact your local genomics laboratory who will be able to assist you in finding a relevant test. There are some referrals which do not currently have a relevant Clinical Indication present on the test directory. The GLH medical team will advise as to the most appropriate immediate course of action. The laboratories will be collating these omissions to feedback to NHS England (NHSE).

How do I know if I can refer a patient or whether I need to refer the patient to clinical genetics or another speciality?

The PDF eligibility document that accompanies the test directory spreadsheet details who can order specific tests. If you wish to order a specific test but you feel the test directory discourages this, then please discuss this with a senior member of the GLH medical team. There will be flexibility in appropriate clinical settings and clinicians will be guided through the testing process. It is unlikely that your local Clinical genetics service will accept referrals in the form of "Please see this patient to arrange genetic testing". If a clinical genetics opinion, advice or assistance is required you should contact your clinical genetics team as you would now. Genomic testing does not replace clinical opinion.

Which diagnosis or panel does the R89 Ultra-rare and atypical monogenic disorders clinical indication relate to for WGS?

The R89 indication does not relate to a specific diagnosis, panel or super-panel. As such, it is not expected that this indication will be required to be used in many scenarios, however it can be used when a bespoke set of panels is required. This requires R89 to be entered into the Test Directory Clinical Indication & code box on the WGS test order form, and the additional panels box to be completed with the relevant panels with a GMS Rare Disease Virtual panel type. It is expected that the R89 indication will be utilised where a number of different panels are required for a patient but these aren't available as part of any current WGS or non-WGS pathway, however the family would benefit from trio testing.

How do I request sequential testing of individual genes for my patients?

As part of the rationalisation required to make the GMS and the GLHs affordable within the NHS, many tests previously delivered as standalone, single gene tests, by a large number of the Regional Genetic Laboratories will now be provided in more modern ways. They may be combined into a panel test and delivered by a laboratory within the GLH network. Depending upon the test indication, it may be more appropriate for patients to be offered WGS at a much earlier stage of their diagnostic pathway. Clinicians will need to work with the GLH and tools such as the National Test Directory and PanelApp to determine the most clinically appropriate and efficient way of delivering high quality care.

I am sure of my patient's genetic diagnosis and I only want to test my patient for a certain gene. How do I request this?

To achieve the longer term ambitions of the GMS and benefit the greatest number of patients, single gene testing is not available for most genes that are tested by sequencing in the GMS. Clinicians should request a panel that will provide the data required. However, you should also note the gene on the referral form in order to allow the laboratory to guide testing.

If I request a test for a single gene that is now part of a panel will the laboratory select that panel and process the request?

If it is clear that the test can only be done by one panel, then yes the laboratory will process that request. If multiple alternative panels are available with that gene the laboratory may contact you to determine which is the most appropriate panel for testing based on the patient's clinical features.

The routine tests I use are not covered by a WGS indication, what should I do?

In this circumstance it is likely that you can continue to request tests as you have done before. If in the future these tests are covered by a WGS indication the laboratory team will endeavour to let you know that WGS is now the preferred test pipeline for your patients.

Are most tests now delivered by WGS?

Most clinical indications are **not** delivered by WGS. The majority of clinical indications from the test directory will be delivered by other methods depending upon the clinical indication. However, when WGS is indicated, it is likely to be the most efficient way of delivering the data you require for optimal patient care. It will be imperative that all members of the GMS including referring clinicians and laboratory staff understand the need to embrace opportunities for economies of scale where available.

The xxxx clinical indication has a .1 test ID with test method of 'WES or Large Panel' and another test ID of WGS. Which is available for testing?

This clinical indication is eligible for WGS testing but the WES or Large Panel test method is part of interim testing for this clinical indication while WGS testing is being ramped up. Clinicians recruiting to WGS during the "Live Clinical Testing" phase of WGS (mostly Clinical Geneticists) should recruit trios for WGS for these indications where possible.

How do I refer a patient for a WGS test and non-WGS tests? Do I need separate referral forms and bloods for each referral?

WGS test order forms can either be sent by e-mail to bwc.centralsouthGLH@nhs.net, or sent with the samples. It is expected that most samples will be sent with a standard genetics laboratory referral form also. Any non-WGS testing can be documented on the standard genetics laboratory referral form. Non-WGS tests required, that are not listed under additional panels in appendix 3, should **not** be put onto the WGS test order form.

What will happen if I request a test not knowing that the clinical indication is eligible for WGS testing?

You will be contacted and advised by the genomics laboratory that your patient is eligible for WGS. We will encourage a referral for WGS.

What do I do if WGS is indicated but not currently available?

This situation should be discussed with one of the GLH senior scientists and/or a senior member of the GLH medical team (See Appendix 4). If there is a clear omission in the test directory, this can be corrected through the test directory review process. If alternative testing strategies are available these can be implemented.

My patient has an eligible clinical indication for WGS testing but only the proband and one parent are available for testing. Can I still request WGS testing?

We recommend that a proband is recruited with both biological mother and father for WGS testing; however it is recognised in some instances this is not possible and only a duo or singleton is available. In these instances it is acceptable to send a duo or singleton sample and request, however this should only be when a parent(s) sample will not be available, due to adoption for example, and not that it is inconvenient to obtain a parental sample. This can be documented on the test order form or discussed previously with the GLH via the bwc.centralsouthglh@nhs.net e-mail account.

Can a trio be a proband, one parent and affected sibling?

As part of NHSE guidance a trio is only considered a trio when it is a proband, mother and father. For WGS testing, where there is only one parental sample available but two affected siblings this should be submitted as a duo of one parent and one affected child (proband). The sibling will then be tested for by an appropriate orthogonal test if a variant is identified. It is possible that two affected siblings can be recruited together; however this is only in exceptional circumstances where it is almost certain that the siblings have the same disorder, and will require prior discussion with NHSE.

I have a family with two siblings with different phenotypes. How should they be recruited for WGS testing?

As part of NHSE guidance these should be submitted as separate probands. If parental samples are available then these should be submitted under two different test requests and so parents will be sequenced twice. One blood sample from each parent will usually be sufficient for this though and they will not need to be re-bled. Parents will be sequenced twice due to informatics requirements as part of the sequencing and pipeline.

What is the turnaround time for WGS?

There is currently a 6-week turnaround time from when DNA samples are sent to Illumina for sequencing for laboratories to receive the data back for analysis, and then a 6-week turnaround time for laboratories to issue a report once data has been received back. As processes become smoother it is expected that the majority of cases will be reported quicker than this 12 week turnaround. However, it is important to note that this turnaround time will not start until all samples, test order form and record of discussion forms for the family have been received and it is considered that all information required for WGS testing to proceed has been received. The clinician will be notified when samples have been sent for WGS.

Does WGS provide urgent turnaround times?

In the medium to longer term it is certainly the ambition of the GMS to provide an "urgent WGS" service. If an urgent analysis of a gene no longer provided as a standalone test the GLH will be able to provide other test strategies. These will need to be discussed with the clinical scientists and the GLH medical leads. A number of approaches including panel testing or rapid turnaround Whole Exome Sequencing may be discussed. However, this testing will only be available for very urgent cases.

There are genes that should be tested for my patient but they are not green on any panels?

You can register as a reviewer on PanelApp and add genes, or evidence for a gene-phenotype fit, for consideration in next version of a panel. You can also contact the laboratory to discuss options for testing in-house or in an external laboratory. There may be an additional charge for any non-GMS commissioned testing that is requested.

How do I look at downloaded data for a panel from PanelApp?

The panel data can be downloaded from the panel page as a text file that can be opened in the Notepad program. This can be used to check if a gene is green on that version of the panel. To look at this data within Excel the user can open a new Excel Spreadsheet, click Ctrl-A within the Notepad program to select all the data, click Ctrl-C to copy this data and then in the Excel Spreadsheet click Ctrl-V to paste this data into Excel.

Can WGS testing be requested for patients who had a negative 100,000 Genomes Project result?

It is possible to request WGS for patients where a diagnosis was not obtained from the 100K project, however in most circumstances this may not be likely to yield a diagnosis for the patient, as the panels used for testing may be similar to those used for the patient in the 100K project. There may be benefit in testing patients by WGS if for example; they were recruited to 100K as a singleton/duo but now could be recruited to WGS as a trio, or they did not have CNV calling performed on their 100K data by GELs pipeline. To also note, reanalysis of 100K data for patients can currently be performed (only on Rare Disease 100K panel types on PanelApp) but longer-term plans by GEL may mean that these patients may need to be re-sequenced for any further analysis to take place.

I would like to request URGENT single gene sequencing for Rett syndrome. How do I do this?

Currently, for some single genes, such as *MECP2* for Rett syndrome, urgent testing can be performed under the R398 indication with proband-only testing. You should contact the laboratory to discuss if testing is available for the gene you are interested in by single-gene sequencing. Patients who require urgent testing may also be eligible for R14 Rapid Exome sequencing, and this should be discussed with Clinical Genetics if patient is thought to be eligible for this testing. For cases that are negative by single-gene testing it is likely that WGS or other panel testing will be recommended.

Appendix 1 - Glossary

Clinical Indication – the test to be requested for patient as relevant to their phenotype/clinical features.

Genomics England (GEL) – Company set up and owned by Department of Health and Social Care. Aim to set up the 100,000 Genomes Project and the infrastructure required for Whole Genome Sequencing within the NHS. Responsible for the pipeline that Whole Genome Sequencing data will go through before data is sent back to laboratories for analysis.

Genomic Laboratory Hub (GLH) – seven hubs responsible for co-ordinating services and delivering genomic testing for their areas as part of the Genomic Medicine Service.

Genomic Medicine Service (GMS) – The service that provides genomic testing throughout England.

Genomic Medicine Service Alliance (GMSA) – organisations that are responsible for embedding genomics and the Genomic Medicine Service within healthcare.

National Genomics Research Library – a database that stores all of the data for patients who have consented to have their genomics data, obtained from WGS testing, stored for research use. This data will only be accessible by research groups approved by Genomics England.

National Genomics Test Directory – Document which sets out the testing available as part of the Genomic Medicine Service, the method of testing that will be provided and the eligibility criteria.

Orthogonal testing – testing used for confirmation of sequencing where required. This may be Sanger sequencing, Microarray or other test methods as appropriate.

R code – a unique code relating to a single clinical indication. R codes may have IDs of .1 or .2 etc, which relate to different test methods for the clinical indication.

Virtual gene panel – a panel applied to a patient's sequencing data. Patients having WES or WGS will have all genes sequenced but only those on the virtual panels relevant to the clinical indication and test request will be analysed.

Appendix 2 – Panel types on PanelApp

GMS signed-off – panel that has a signed-off version for the GMS and is able to be used for GMS testing.

GMS Rare Disease Virtual – panel that can be used as an additional panel for WGS.

Super Panel – panel that is made up of two or more component panels.

Component Of Super Panel – panel that contributes to a Super Panel.

Rare Disease 100K – panel that was available for the 100,000 genomes project. May not be available for GMS testing if GMS signed-off is also not listed as a panel type.

Research – panel only available for research testing but not for clinical testing.

Appendix 3 – Panels that can be selected as additional panels for WGS testing

Specialism	Panels available
Cardiology	Thoracic aortic aneurysm and dissection
	Hypertrophic cardiomyopathy – teen and adult
	Dilated cardiomyopathy – adult and teen
	Arrhythmogenic cardiomyopathy
	Cardiomyopathies – including childhood onset
	Primary lympoedema
	Sudden cardiac death
	Cardiac arrhythmias
	Laterality disorders and isomerism
Developmental disorders	Paediatric disorders (super panel)
	Intellectual disability
	Hypotonic infant (super panel)
	Rare multisystem ciliopathy (super panel)
Dermatology	Segmental overgrowth disorders
	Ectodermal dysplasia
	Epidermolysis bullosa and congenital skin fragility
	Ichthyosis and erythrokeratoderma
	Palmoplantar keratodermas
	Autosomal recessive primary hypertrophic osteoarthropathy
	Xeroderma pigmentosum, Trichothiodystrophy or Cockayne syndrome
	Pigmentary skin disorders
	Cutaneous photosensitivity with a likely genetic cause
	Epidermodysplasia verruciformis
	Vascular skin disorders
	Rare genetic inflammatory skin disorders
Endocrinology	Monogenic diabetes
	Diabetes – neonatal onset
	Congenital hyperinsulinism
	Congenital hypothyroidism
	Disorders of sex development
	Growth failure in early childhood
	Hypogonadotropic hypogonadism idiopathic
	Severe early-onset obesity
	Congenital adrenal hypoplasia
	Familial hyperparathyroidism
	Hypocalciuric hypercalcaemia
	Familial hypoparathyroidism
	Hypophosphataemia or rickets
	Lipodystrophy – childhood onset
	Pituitary hormone deficiency
	Primary pigmented nodular adrenocortical disease
	Familial tumoral calcinosis

	Hyperthyroidism
Eyes	Corneal dystrophies
	Cataracts
	Retinal disorders
	Structural eye disease
	Aniridia
	Albinism or congenital nystagmus
	Optic neuropathy
	Stickler syndrome
	Congenital fibrosis of the extraocular muscles
Fetal Medicine	Fetal anomalies
Gastrohepatology	Non-acute porphyrias
	Cholestasis
	Polycystic liver disease
	Pancreatitis
	Intestinal failure
Haematology	Confirmed Fanconi anaemia or Bloom syndrome
	Bleeding and platelet disorders
	Cytopenia – NOT Fanconi anaemia
	Rare anaemia
	Iron metabolism disorders
	Thrombophilia
Hearing	Hearing loss
Immunology	Primary immunodeficiency
Lipids	Familial hypercholesterolaemia – targeted panel
	Lipoprotein lipase deficiency
Metabolic	Neuronal ceroid lipofuscinosis
	Inborn errors of metabolism
Mitochondrial	Mitochondrial disorders
Musculoskeletal	Craniosynostosis
	Ehlers-Danlos syndromes
	Osteogenesis imperfecta
	Skeletal dysplasia
	Amelogenesis imperfect
	Clefting
	Limb disorders
Neurology	White matter disorders – childhood onset
	White matter disorders – adult onset
	Cerebral vascular malformations
	Neuromuscular disorders
	Hereditary ataxia – adult onset
	Hereditary ataxia and cerebellar anomalies – childhood onset
	Adult onset movement disorder
	Childhood onset dystonia or chorea or related movement disorder
	Neurodegenerative disorders – adult onset
	Genetic epilepsy syndromes

	Hereditary spastic paraplegia – adult onset
	Hereditary spastic paraplegia – childhood onset
	Paroxysmal central nervous system disorders
	Skeletal muscle channelopathy
	Hereditary neuropathy NOT PMP22 copy number
	Arthrogryposis
	Holoprosencephaly
	Hydrocephalus
	Cerebral malformations
	Severe microcephaly
Renal	Cystic renal disease
	Haematuria
	Proteinuric renal disease
	Membranoproliferative glomerulonephritis
	Renal tubulopathies
	Atypical haemolytic uraemic syndrome
	Amyloidosis
	Nephrocalcinosis or nephrolithiasis
	Unexplained paediatric onset end-stage renal disease
Respiratory	Surfactant deficiency
	Hereditary haemorrhagic telangiectasia
	Pulmonary arterial hypertension
	Respiratory ciliopathies including non-CF bronchiectasis
	Pneumothorax - familial

Appendix 4 – Contact details

Genomic Laboratory Hub : bwc.centralsouthGLH@nhs.net

West Midlands Regional Genetics Laboratory: bwc.genetics.lab@nhs.net

Oxford Regional Genetics Laboratory: orh-tr.dutyscientist.oxfordgen@nhs.net

Wessex Regional Genetics Laboratory: shc-tr.WRGLdutyscientist@nhs.net

Rare Disease clinical lead for Oxford: Ed.Blair@ouh.nhs.uk

Rare Disease clinical lead for Birmingham: swati.naik@nhs.net

Rare Disease clinical lead for Wessex/Southampton: Katherine.Lachlan@uhs.nhs.uk