

Referring Whole Genome Sequencing (WGS) for a Rare Disease

Clinician's How-To Guide

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A. WGS Checklist



1: Check WGS eligibility

On the <u>National Genomic Test Directory (PDF)</u> check "WGS" is indicated under "Methods" in Associated Tests.

2: Complete the Test Order Form

One **Test Order form** per family

3: Consent and complete the Record of Discussion form(s)

After consenting the patient, complete a <u>Record of Discussion</u> for each individual in the family being tested (+ a <u>Consultee form</u> if patient is an adult lacking capacity)

4: Organise WGS samples

Provide the patient and family members being tested with completed <u>Sample Forms</u> to take with them to their local hospital/phlebotomy

5: Send the Record of Discussion forms and Test Order Form to the laboratory

Send to gos-tr.wgsnorththamesglh@nhs.net and save a copy to your records

B. WGS Pathways

There are **two** suggested pathways for WGS referrals. One is by requesting and consenting for WGS yourself, and another is by requesting via a Genomic Practitioner/Associate.

Genomic Practitioner/Associate: gos-tr.ntgenomicsassociate@nhs.net

role established to help meet the demands of genetic testing, with a specialised knowledge of WGS.

- Point of contact between consultants and the laboratory
- WGS request help consenting, forms, sample collection, sample chasing
- Track WGS activation and dispatch

Non-WGS genetic testing, clinical details, decisions on clinical urgency and feeding back clinical information/WGS results to patients are **NOT** part of the role.



	Genomic Medicine Servic
Eligibility for Mai	nstream Genetic Testing
Key: Consultant (page4) Determine whether WGS (only the page4) WGS (patient a	fulfils NGTD criteria er this is a singleton patient to be tested) or trio nd both parents to be tested) binations (i.e patient + siblings), ry
Patient	t Appointment
to make sure the genetic referra	consent discussion ne patient is happy with the
? Requesting via	Genomic Practitioner YES
Patient Appointment [cont.] Go through entire consent discussion Complete Record of Discussion (page 7) - can be virtually completed or with the patient face- to-face) (+ Consultee form if adult lacking capacity) Provide Patient Information Leaflets and video link Provide Sample Form(s) (page 11) to all family members being tested Save forms to Electronic Patient Record	O Send Test Order Form to Genomic Practitioner (gostr.ntgenomicsassociate@nhs.net) Genomic Practitioner Appointment O Go through consent discussion Complete Record of Discussion (+ Consultee form if adult lacking capacity) Provide Patient Information Leaflets and video link Provide Sample Form(s) to all family members being tested (if not done by consultant) O Send forms to department pathway coordinator to save to Electronic Patient Record
Following the Appointment	Following the Appointment
Send Record of Discussion form(s) and Test Order form to gos- tr.wgsnorththamesglh@nhs.net	O Send Record of Discussion form(s) and Test Order form to gos- tr.wgsnorththamesglh@nhs.net
Confirm with laboratory that all	Confirm with laboratory that all

has been activated

has been activated

C. Eligibility for WGS



Patient eligibility for WGS clinical indications can be found on the <u>NHS England » National genomic test</u> <u>directory</u>. If you need to determine which genes/panels are included in a clinical indication, please visit <u>PanelApp.</u>

R59 Early onset or syndromic epilepsy

The Clinical Code/Indication

Testing Criteria

Unexplained epilepsy with clinical suspicion of a monogenic cause including:

- Onset under 2 years, OR
- Clinical features suggestive of specific genetic epilepsy, for example Dravet syndrome, OR
- Additional clinical features: intellectual disability, autism spectrum disorder, structural abnormality (e.g. dysmorphism, congenital malformation), unexplained cognitive/memory decline

Testing may occasionally be appropriate where age of onset is between 2 and 3 years and following clinical agreement by a specialist MDT.

Overlapping indications

- R110 Segmental overgrowth disorders Deep sequencing test should be used where megalencephaly
 is present to allow detection of somatic mosaic variants
- R14 Acutely unwell children with likely monogenic disorder should be used in acutely unwell children with epilepsy

NOTE: If a metabolic disorder is suspected, testing should be carried out either using R89 or R98 or under an alternative metabolic-related clinical indication

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

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

Neurology

Associated Tests

Check whether you are eligible for requesting this test

It is not a requirement to perform microarray testing in addition to WGS but microarray testing can be performed where appropriate

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R59.2	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray
R59.3	Epilepsy - early onset or syndromic WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Genetic epilepsy syndromes (402)	WGS

Make sure WGS is an associated test

If trio is indicated, include parents if available

D. Forms required:



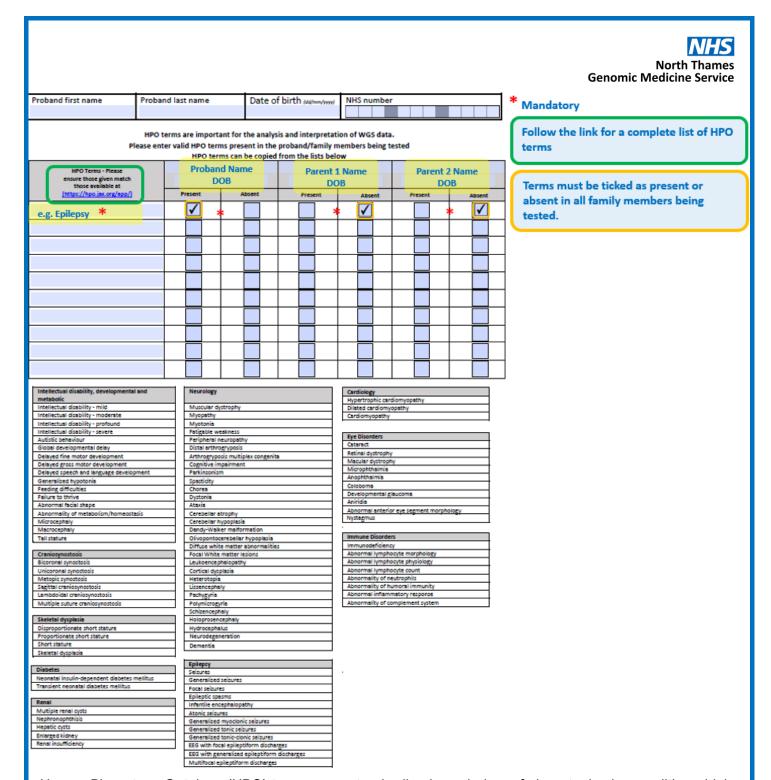
Two forms must be sent **electronically** to the NT GLH (<u>gos-tr.wgsnorththamesglh@nhs.net</u>): The Test Order Form (see page 5) and the Record of Discussion (

Blood samples (1xEDTA tube per patient) must be sent with the NT GLH <u>Sample Form</u> (see page <u>11</u>).

1. The Test Order Form: completed by the consultant

Genomic Medic	ine Service	_		RARE AND INHER	ITED DISEASES			7	* Mandatory		
Whole Genome PLEASE DO NOT			est					1	Check on the National Genomic Test Directory whether you are eligible for		
Requesting orga GLH laboratory:		Your hoNorth T	spital hames GL	LH					requesting this test		
Proband's first n	ame		L	ife status ≭	Ethnicit	y *					
*				☐ Alive ☐ Decea	sed			·	If only one parent available, select		
Proband's last name			amily test 🜟 Singleton 🔲		r (provide n	umber):		"other" and type "DUO" in the adjacent box			
Date of birth (44)	mm/yyyy) Hospital	number		Relevant clinical inf Please include any previou		with date(s) and	any other pe	ortinent			
Gender *	emale Oth	Please state in clinic box if karyotypic an IET sex differ from giver	cal information	dinical information							
Postcode *					u are orderin	_			Reasons for urgent testing must be		
NHS number *	:				ry of clinical	picture			provided		
				 Family h 							
Reason NHS Nur			. i		r previous te	_	been				
Patient not eligi Other (please pr	ble for NHS number (e rovide reason):	e.g. foreign national)	underta	ken (when/v	where)			The main R code detailed in the		
Test request									National Genomic Test Directory. Only		
Clinically urgen				Test Directory Clinical Indication & code (reason for testing)				ting)	WGS-eligible R codes are available in		
There is currently no u to prioritise some case				*				-	the drop-down menu Additional panels (including non-WGS		
considered urgent.		,	_								
				Proband's age of onset * years months					panels) can be requested here		
Additional panel(R89) D	Disease penetrance Specific rare or inherited diseases that				es that			
use panels with panel t http://panelapp.genom		se Virtual' -		Complete are suspected or have been confirmed							
				□ Incomplete					If penetrance is unknown, select		
Family members	to be tested (n	ot required for p	roband only	referrals)					'Incomplete"		
First name	Last name	Date of birth (or p	Number		itus	Ethnicity		lationship proband	If fil i- illl		
					•		•		If one or more family member is included		
					_				in the test (duo/trio WGS), add details		
Samples being se	ent to GLH DNA	extraction lab	(only require	ed if also using this fo	orm for sample c	ollection)					
First name	Last name	Date of birth	Sample ID	Collection date / time	Sample type	Sample volume	Comm	nents	Not required to complete when using a		
					•				Sample Form (page 11)		
					•	1					
					•						
Responsible clinician / consultant 🜟			Main contact (if different from responsible clinician/consultant)				ultant)				
Name:			Name:								
Department address:			Department address:								
Phone:				Diameter Control of the Control of t							
				Phone:							
Email:				Email:							
I have at	ttached a copy of	the Record of D	Discussion fo	orm for all individual	5						

Patient conversation taken place; Record of Discussion form to follow



Human Phenotype Ontology (HPO) terms are a standardised vocabulary of phenotypic abnormalities which are important for the analysis and interpretation of WGS data.

Please complete accurately for each family member being tested (present/absent boxes ticked).

A complete list can be found at <u>Human Phenotype Ontology (jax.org)</u>.

Follow this <u>link</u> for more information on how to use HPO terms in a clinical context.

HPO terms are very important for increasing the chances of finding a potential diagnosis via the panel agnostic exomiser variant prioritisation analysis that is carried out if the panel-tiering analysis is negative. If choosing HPO terms is done properly, this would also reduce the need for further analysis.

2. The <u>Record of Discussion</u> - completed by the consultant or Genomic Practitioner



Page 3 (pictured) of the document to be completed after a full consent conversation – a summary of the conversation is listed on Page 1 and 2 (not pictured). This can be completed remotely (i.e. consent appointment over the phone/virtual). Information on what to include in the consent conversation is detailed page 8-10.

For adults lacking capacity, please also complete the **Consultee form**.

	NHS	Genamic Mediane Service. Record of Discussi	on Form version 4.03,			* Mandatory
First name * Last name *		NHS number (or postcode	if notknown)	Genomics	NHS 01-NGIS-ROD (V4.03)	Manuatory
Confirma	tion of Your	Genomic Test a	nd Resea	arch Cho	ices	
	ve had the opportunity choice is indicated be	to discuss information aboutow.	t genomic testin	g, I agree to the	genomic test,	
		the National Genomic Resear		*	YES NO]
B. I agree th Research	A STATE OF THE PROPERTY OF THE PROPERTY OF	nder sample may contribute to	the National Ge	enomic	YES NO	
Patient name *		Signature	Date			
		7		1 = = 1	y y y y	Mandatory signature for children,
If you are signing please sign below		someone else (children, adul	ts without capac	city or deceased	patients) then	adults lacking capacity or deceased patients
Parent Guardiar please amendas app	n Consultee name ropriate	Signature	Date			- if patient is an adult lacking capacity, a separate Consultee form must be
		<u> </u>		1 - 1	Y Y Y Y	completed in addition to the Record of Discussion
Healthcare p	rofessional use	only				
To be completed i	by the healthcare profe	essional recording the patient	's choices.			A reason why the National Genomic
Patient category *		y (choices advised by consultee)			tient's best interests) beased individual)	Research library has not been discussed must be given (i.e. if A is ticked as NO)
Testtype *	Rare and Inherited D	iseases - WGS	Cancer (paired tumo	ur normal) - WGS		
If answer to research choice A is NO	The state of the s		nappropriate to have Other	discussion		
Remote consent		y clinician, no patient signature	80			The Record of Discussion form can be
Responsible clinician	*		50			completed remotely if the patient
Hospital number						appointment is virtual/over the phone
i		f., .			1	
Healthcare profe	essional name *	Signature	Date			
SE .			0 8			

E. Consent Requirements:



1. WGS Consenting via the Genomic Practitioner

It is important to note that the consultant **ultimately has responsibility for patient consent**. Therefore, it is essential that you make sure the patient is happy to proceed with the genetic testing before referring them. The Genomic Practitioner would then speak to the patients and all family members to be tested and fill the Record of Discussion form.

a. Consultant Preliminary Discussion with the Patient:

- What WGS is reading through all the DNA and analysing specific areas (virtual panels) NOT gene agnostic
- 2. <u>Managing expectations Turnaround time</u> from the point that all blood samples/consent forms have arrived at the laboratory
 - a. 12 months (routine tests) (as of August 2024)
 - b. 12 weeks (urgent tests) (as of August 2024)
- 3. <u>Understanding that the patient will be contacted by a Genomic Practitioner</u>

The Genomic Practitioner will discuss the National Genomic Research Library with the patient.

If possible, please provide Patient Information Leaflets and the WGS video link

2. WGS Consenting yourself

a. Full Consent Conversation required:

	Individuals aged 16+ years with capacity	Children (less than 16 years)	Adults without capacity	Individuals who are deceased
Clinical test	RoD reviewed with each individual	RoD reviewed with parent/guardian	RoD reviewed with person acting in best interests of the patient	RoD reviewed with appropriate relative

- 1. What WGS is reading through all the DNA and analysing specific areas (virtual panels)
- 2. Small blood sample required for each family member
- 3. <u>Turnaround time</u> from the point that all blood samples have arrived at the laboratory
 - a. 12 months (routine tests) (as of August 2024)
 - b. 12 weeks (urgent tests) (as of August 2024)

4. Family Implications

- a. Implications on other family members or future pregnancies
- Opportunities for relatives to have access to screening, predictive genetic testing and/or information about reproductive choices based on these results or family history
- c. Importance of sharing results with family members if a pathogenic variant is found (it is helpful to start early conversations about this rather than only after the results are available)

5. Uncertainty



- Results may find a variant of uncertain/unknown significance (VUS) = a genetic change that may affect the way the gene is working, but there is not enough evidence available to confirm this as a disease-causing or likely diseasecausing variant.
- b. May require a referral for further genetic testing via Clinical Genetics Service
- c. Variants of uncertain significance should not be used to make clinical decisions for the individua or family members
- d. This result may change over time as this can be re-analysed in future

6. <u>Unexpected Information/ Incidental Findings</u>

- Pathogenic variants may be identified that are unrelated to the reason for the genetics referral, and may indicate an underlying predisposition to a different phenotype (e.g. risk of further cancer or diagnosis with other possible health problems)
- b. These are not routinely looked for and they are rare to come across as the laboratory focuses analysis on virtual panels relevant to the genetic referral
- The results will NOT inform all health conditions currently, there are no additional looked-for findings, however these may still be found by chance
- Misattributed parentage is another example of incidental findings

7. DNA storage

- a. The blood sample will be sent to the laboratory and DNA will be extracted
- b. This DNA will continue to be stored (approximately 30 years) unless the patient requests this to be destroyed
- c. This DNA can be accessed by other laboratories within the NHS Genomic Medicine Service
- d. The DNA will not be used for further genetic testing without consent however, this may be used as a control sample for testing other family members
- e. DNA is not always of sufficient quality and another sample may be required to complete testing

8. Data storage

- Data includes patient's health and genomic information, which can be securely access on an ongoing basis by NHS healthcare professionals
- b. Data is stored behind various NHS firewalls
- c. National (identifiable) and international (non-identifiable) comparison of data for greater understanding of significance of any results may be required
- d. Germline variants may be shared for relatives to access testing (limited identifiers to process the test) but medical information will not be shared with relatives
- e. Genomic data may be re-analysed in future as new evidence can occasionally change results
- The report will be available on the patient's clinical record

b. The <u>National Genomic Research Library</u> (Genomics England)



	Individuals aged 16+ years with capacity	Children (less than 16 years)	Adults without capacity	Individuals who are deceased				
NGRL	The research choice is captured within the RoD. There is an additional 'Participation in the NGRL' form to note the individual's choice if this was not made at the time when the clinical test was discussed.							
	No additional forms	OPTIONAL assent form signed by child	MANDATORY form signed by consultee	No additional forms				

For adults lacking capacity, a <u>Consultee form</u> is also required (will be completed by the Genomic Practitioner if using this pathway).

- 1. What it is a comprehensive database that enables approved researchers to access *de-identified* genomic data, health data and samples
- 2. Research participation is an opt in process (they can choose to take part)
- 3. Who can access national and international scientists, researchers, and healthcare companies
- 4. Data accessed
 - a. The Data is de-identified (pseudonymised) each patient record is given a unique identification number instead of name, DOB and contact details
 - b. The data available included data about the sample, the raw data of the sample analysis, the patient clinical data (information about their condition that was submitted when ordering WGS) and secondary clinical data from NHS and GP records
- 5. Patients may be <u>re-contacted</u> for years to come by GE or clinical team
 - a. Certain approved staff within Genomics England will be able to see both identified and deidentified patient data to inform patients about any diagnosis found or to access a clinical trial
 - b. They will NOT be contacted for marketing purposes
- 6. They can withdraw from research and data sharing at any time
 - a. Partial withdrawal: the patient is happy for their data to continue to be stored but they do not wish to be contacted by Genomics England
 - b. Full withdrawal: all data will no longer be included in any future data releases for further research access

F. Sample Form



A completed NT GLH <u>Sample Form</u> with patient details <u>must</u> be attached to the labelled blood tube (1x EDTA) for WGS. A printed copy of the typed (not handwritten) <u>Test Order Form</u> can also be sent with labelled blood tubes.

From November 2025, the laboratory has implemented a "WGS Incomplete Referrals" Pathway – e-mails will be sent to consultants when a WGS sample is a received as a reminder to send Record of Discussions and Test Order Forms. If these forms are not received by the laboratory, WGS will not be activated. Sample forms with "DNA for storage" will also be accepted.

If the patient is unable to provide a blood sample, a saliva kit can also be accepted. In this case, please provide the patient with a completed <u>Sample Form</u>, a saliva kit (e.g. OG-600 or OG-500 kits) and a pre-paid envelope with the GLH address:

North Thames GLH, Rare & Inherited Disease Genomic Laboratory Specimen Reception, Level 5 Barclay House, 37 Queen Square, London WC1N 3BH

UKAS Nemical	d Street hildren	th Thames Genomic Inherited Disease Go Level 5 Barclay Queen Square, Lond	nomic Labo House	oratory	Londo	ity College h Hospitals oundation Trust	* Mandatory	
Please note that forms re	eceived with missing	g information (patient	/ referrer/ te	st eligibility/ u	tility) will no	t be tested.		
I. Patient Details (Use FOUR pa			1			II MANDATORY*)		
SURNAME":	FIRST NAME":		_			de full name)*:		
*	, , ,	ĸ	11	, consultant (ricase provi	de full flame) .		
DATE OF BIRTH":	Sex at Birth:	k	*					
NHS Number* (Mandatory*): *	Hospital No/You	r Ref:	NHS.net	email (for que	ries)*:	•		
manager (manager) j.	Trospitarito, roa		Departm	ent*: *			1	
Ethnicity:	GOSH Family ID (If known):	Hospital	(No initials, p	ease provid	e full name/address)*		
Patient Address & Postcode:			*					
GP Name & Address:			Referring	Clinician: I hav	e discussed	genomic testing with	ut week at away et a to the	1
Gr Name & Address:			this patier page 2). C	nt and have ret consent is not r	ained a recor equired for D	d of discussion (see NA storage.	If WGS' or the WGS Clinical Code is indicated (and 'Diagnostic ticked),	
Consanguineous: Yes No							the laboratory will send you a	
Please select ONE option for repo	rt and provide deta	ils:					reminder to send Record of	
Email (NHS.net email):								
Outreach Portal Submitter ID:							Discussion(s) and the Test Order Form.	
Post:							Form.	
III. Specimen Details If high ri	sk please specify:	Sample Type	Date / Time Collected Collected By			Collected By		
High Risk Specimen? Yes No							For WGS samples, it is also possible to send sample forms as "DNA for	
° Clinical Indication Code:	R "w	GS", or WGS Clini	ical R code Urgent Routine			rgent Routine	storage" by leaving Clinical Indication Code blank and ticking:	
THIS FORM IS FOR POSTNATAL NO For NHS England referrals, please ref https://www.enaland.nhs.uk/publicat	er to the National Ger	nomic Test Directory for				TED OVERLEAF)	'DNA storage (no testing) - Requesting clinicians will receive a	
DNA storage (no testing)		EDTA	Contact lab to activate testing on stored DNA			g on stored DNA	notification that DNA has been	
DNA based testing: Diagnostic Carrier	Dradictiva	EDTA	(Provide R code, eligibility details and clinical utility)			tails and clinical utility)	stored but the laboratory will not	
							send any reminders for missing	
Nijmegen	iii Anaemia/ Bioom/	Littilum Hepar	"	(Fromue K cour	, engionity be	tens and chilical dunity)	forms	
Rapid testing (infants): trisom	y 13/18 trisom	y 21 EDTA / Lithium	n Heparin	SRY (chror	nosomal sex)		
IV. Reason for referral (Please gi	ve details of previous	genetic investigations i	in the family,	if any.)				
							If only requesting a sample for WGS, this section is optional (as this	
(For familial/cascade/follow up testing	, provide index patien	t name and DOB, NHS n	o. or index po	atient report.)			information will be included in the Test	
V. Clinical Utility — Please indi	cate category of C	Clinical Utility AND	provide de	tails.			Order Form).	
Patient management (determining	therapeutic decision	s and/or clinical investig	ations and/or	r surveillance p	rogramme)		· · · · · · · · · · · · · · · · · · ·	
Patient, parents, or adult relative	reproductive decision	making					If requesting other non-WGS genetic	
Unaffected relatives are seeking p	redictive testing						testing (e.g. microarray, WES), please	
Details:							include clinical information	
VI. Eligibility — Please provide	details to confirm	patient meets NH	SE eligibilit	ty criteria fo	the test(s)	requested.		

The form is double sided (page-2 not pictured) – please make sure to print <u>both</u> <u>sides</u> as information on the back is needed for phlebotomy and the processing of samples at the laboratory.



G. More resources:

1. Genomics Resources

What is Genomics?

Genomics 101: Genomics in Healthcare

The Genomics Era: The Future of Genetics in Medicine

RCGP Genomics Toolkit

New Conditions Factsheet (Genomics Education Programme)

2. WGS Resources

Guide-to-requesting-WGS-RD-Nov-20.pdf (hee.nhs.uk)

Requesting whole genome sequencing: information for clinicians - Genomics Education Programme (hee.nhs.uk)

Test order forms - North Thames GMS : North Thames GMS (norththamesgenomics.nhs.uk)

Whole Genome Sequencing - North Thames GMS: North Thames GMS (norththamesgenomics.nhs.uk)

Rare Diseases Test Order Forms and Clinician Packs (scroll to Rare Disease- whole genome sequencing (WGS)

Whole Genome Sequencing Animation - North Thames GMS

Genomic Question Time drop-in session (Teams link)

- First Thursday of the month 12:30-13:00
- Passcode: aDYRNt
- Or contact us on: nt-gmsa@gosh.nhs.uk

Whole Genome Sequencing - Genetic Test Ordering

How useful did you find this how-to guide? Please let us know how we can improve.