Genetics of Obesity Testing for Children and Young People

David Lim, Padraig Dixon, Nikki Davis, Helen Stewart

Background

Genetic testing for obesity is now accessible from NHS Genomics England which is free to clinicians at point of request.

The benefits of a genetic diagnosis include:

- Accurate diagnosis
- Access to targeted treatment
- Screening for associated features
- Improves mental health and quality of life for CYP and families
- Reduces stigma by demonstrating an organic cause for obesity
- Potential access to research programmes and treatments including novel medications which are emerging rapidly in this field
- Cascade testing of relatives will also help guide surgical and medical treatment options in adult and transition services, e.g. bariatric surgery
- Enables genetic counselling
- Avoids unnecessary safeguarding

Aims

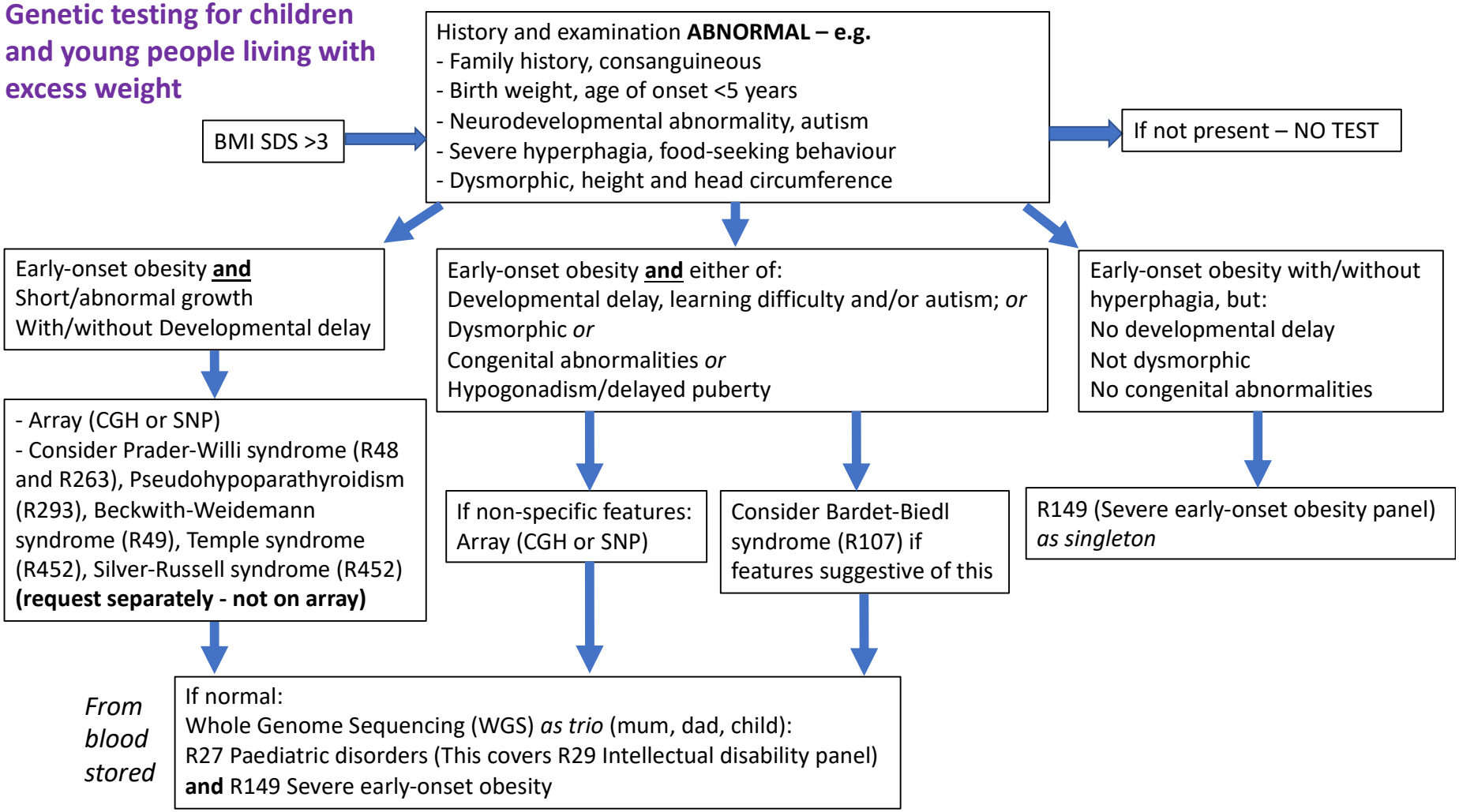
A multi-disciplinary working group (comprising General Paediatrics, Paediatric Endocrinology, and Clinical and Laboratory Genetics) has designed a genetic testing pathway aimed to estimate and achieve the maximum balance of cost effectiveness and benefit to CYP and families.

We would be grateful if your centre could support this by adopting this pathway for clinical use, and collect data alongside this for our analysis.

N/B cost-effectiveness will be dependent on testing those that are eligible, providing detailed phenotypic information and maintaining a good diagnostic yield.

There will be ongoing work with the GLH (genomics laboratory hub) and NHSE test evaluation board to ensure that the test criteria and who can request test are fit for purpose.

Genetic testing for children and young people living with excess weight



N/B refer to National Genomic Test Directory for more details on each of the 'R' codes (unique clinical indication codes) and associated testing criteria

Examples of genetic causes of obesity and associated features

Syndrome	Examples of associated features	Genetic investigation to request
Albright Hereditary Osteodystrophy (Pseudohypoparathyroidism Type 1A)	Short metacarpals, rounded facies, +/- hypocalcaemia	R293
Alstrom syndrome	Retinal one-rod dystrophy, sensorineural hearing loss, dilated cardiomyopathy, hypergonadotrophic hypogonadism	R106
Bardet–Biedl syndrome	Retinal cone-rod dystrophy, postaxial polydactyly, intellectual disability, hypogonadotropic hypogonadism, genitourinary malformations, renal malformations	R107
Beckwith-Weidemann syndrome	Overgrowth, hemihypertrophy, macroglossia, neonatal hypoglycaemia, umbilical hernia/other abdominal wall defect	R49
Börjeson–Forssman–Lehmann syndrome	Intellectual disability, seizures, hypogonadism, developmental delay, large ears	R149
Carpenter syndrome	Turricephaly (tower-shaped skull), polydactyly, syndactyly, short stature, undescended testes, intellectual disability	R27
Cohen syndrome	Failure to thrive in infancy, hypotonia, joint hypermobility, microcephaly, prominent incisors	R149
Grebe syndrome	Marked distal limb reduction, polydactyly, normal facies	R104
Prader-Willi Syndrome	Hypotonia, developmental delay, short stature, failure to thrive in infancy followed by hyperphagia and obesity, hypothalamic dysregulation (e.g. hypogonadotropic hypogonadism), sleep disordered breathing	R48
Silver-Russell syndrome	Growth retardation, relative macrocephaly, body asymmetry, motor and/or speech delay, premature adrenarche	R452
Temple syndrome	Growth retardation, hypotonia, joint laxity, motor delay, early onset puberty	R452
ROHHAD syndrome	Rapid onset obesity, hypothalamic dysfunction, hypoventilation, autonomic dysfunction	-
Turner syndrome	Short female, broad chest, wide spacing of nipples, congenital lymphoedema	Array
WAGR syndrome	Wilms tumour, aniridia, genitourinary anomaly, mental retardation	Array
16p11.2 deletion	Developmental delay, seizures, autism, severe obesity in early childhood, severe insulin resistance	Array

Steps

1. Determine if the child is suitable for genetic testing based on the pathway, through history and examination.
2. Please complete 'Dyken's Hyperphagia Questionnaire' as a screening tool for hyperphagia.
3. If suitable for genetic testing, please complete 'Genetics of Obesity Clinical Assessment Form'.
4. Based on the child's phenotype/clinical features, determine which genetic tests are suitable based on the pathway at the appropriate stages.
    a. R149 (severe early-onset obesity panel)
    b. Microarray
    c. Specific imprinting disorders – Prader-Willi syndrome, Pseudohypoparathyroidism, Temple syndrome, Beckwith-Wiedemann syndrome, Silver-Russell syndrome
    d. R27 (congenital malformation and dysmorphism syndromes) - Whole genome sequencing ; plus R149
5. Complete relevant test request forms and obtain blood samples. Please see below.
6. Please submit forms for our analysis:
    a. Hyperphagia Questionnaire
    b. Genetics of Obesity Clinical Assessment Form

Dyken's Hyperphagia Questionnaire

(1) How upset does your child generally become when denied a desired food?
___ Not particularly upset at all
___ A little upset
___ Somewhat upset
___ Very upset
___ Extremely upset
(2) How often does your child try to bargain or manipulate to get more food at meals?
___ A few times a year
___ A few times a month
___ A few times a week
___ Several times a week
___ Several times a day
(3) Once your child has food on their mind, how easy is it for you or others to re-direct your child away from food to other things?
___ Extremely easy, takes minimal effort to do so
___ Very easy, takes just a little effort to do so
___ Somewhat hard, takes some effort to do so
___ Very hard, takes a lot of work to do so
___ Extremely hard, takes sustained and hard work to do so
(4) How often does your child forage through the trash for food?
___ Never
___ A few times a year
___ 1–2 times a month
___ 1–3 times a week
___ 4 to 7 times a week
(5) How often does your child get up at night to food seek?
___ Never
___ A few nights a year
___ 1–2 nights a month
___ 1–3 nights a week
___ 4 to 7 nights a week
(6) How persistent is your child in asking or looking for food after being told "no" or "no more"?
___ Lets go of food ideas quickly and easily
___ Lets go of food ideas pretty quickly and easily
___ Somewhat persistent with food ideas
___ Very persistent with food ideas
___ Extremely persistent with food ideas
(7) Outside of normal meal times, how much time does your child spend talking about food or engaged in food-related behaviors?
___ Less than 15 minutes a day
___ 15 to 30 minutes a day
___ 30 minutes to an hour
___ 1 to 3 hours a day
___ more than 3 hours a day

(8) How often does your child try to steal food (that you are aware of?)
___ A few times a year
___ A few times a month
___ A few times a week
___ Several times a week
___ Several times a day
(9) When others try to stop your child from talking about food or engaging in food-related behaviors, it generally leads to:
___ No distress or upset
___ Mild distress or upset
___ Moderate distress or upset
___ Severe distress or upset
___ Extreme distress, behaviors can't usually be stopped
(10) How clever or fast is your child in obtaining food?
___ Not particularly clever or fast
___ A little clever or fast
___ Somewhat clever or fast
___ Very clever or fast
___ Extremely clever of fast
(11) To what extent to food-related thoughts, talk, or behavior interfere with your child's normal daily routines, self-care, school, or work?
___ No interference
___ Mild interference; occasional food-related interference in completing school, work, or hygiene tasks
___ Moderate interference; frequent food-related interference in completing school, work, or hygiene tasks
___ Severe interference; almost daily food-related interference in completing school, work, or hygiene tasks
___ Extreme interference, often unable to participate in hygiene tasks or to get to school or work due to food-related difficulties
Additional items:
(12) How old was your child when they first showed an increased interest in food?
(13) How variable is your child's preoccupation or interest in food?
___ Hardly ever varies
___ Usually stays about the same
___ Goes up and down occasionally
___ Goes up and down quite a lot
___ Goes up and down all the time

About Dyken's Hyperphagia Questionnaire

Hyperphagia is a key symptom in patients with monogenic obesity, but the assessment is challenging.

The Dyken's Hyperphagia Questionnaire was originally designed and validated for patients with Prader-Willi syndrome to assess their specific food-related preoccupations and problems (Dykens et al., 2007).

The questionnaire is filled out by the parents and includes 13 items. Each item has a 5-point Likert scale, where "0" means "not a problem" and "5" means "severe/frequent problem".

- Scores of the questions 1 to 11 are summarised in a total hyperphagia score (possible range: 11–55).
- In addition, three subscores are calculated: **hyperphagic behaviour** (question 2, 4, 5, 8, and 10, possible range: 5–25), **hyperphagic drive** (question 1, 3, 6, 9, possible range: 4–20) and **hyperphagic severity** (question 7 and 11, possible range: 2–10).
- Questions 12 "How old was your child when they first showed an increased interest in food?" and 13 "How variable is your child's preoccupation or interest in food?" do not load on any factor but reveal more information about the onset and the diurnal variability of hyperphagia

Further research to Dykens' Hyperphagia Questionnaire showed that it may be a good tool to assess food-related behaviour and drive to eat caused by hyperphagia in young patients with monogenic and syndromic obesity with or without intellectual disabilities (Zorn et al, 2022).

However, it is important to note that Dykens' Hyperphagia Questionnaire does not measure the individual hunger sensations and food intake, which are also important parts of hyperphagia. Therefore, one method alone is currently not sufficient to assess and represent the complexity, quality and severity of hyperphagia.

Genetics of Obesity Clinical Assessment Form

Patient's name: _____ Sex: Male / Female

DOB: _____ NHS number: _____

Ethnic group: Asian or Asian British / Black, Black British, Caribbean or African
Mixed/ multiple ethnic groups / White

Medical History

Birth weight: _____kg Gestational age at birth: _____weeks

Congenital abnormalities: Yes / No

If yes, details: _____

_____

Short stature (below mid-parental centile): Yes / No Age of obesity onset: _____

History of hyperphagia - complete Dyken's Questionnaire

Developmental delay or learning difficulties: Yes / No

If yes, details: _____

Hearing impairment: Yes / No *If yes, details:* _____

Vision impairment: Yes / No *If yes, details:* _____

Neurodevelopmental abnormality : Yes / No

- Autistic spectrum disorder : formal diagnosis / clinician suspect / parent suspect
- ADHD: formal diagnosis / clinician suspect / parent suspect
- Other: _____

Delayed puberty: Yes / No

If yes, details: _____

Any comorbidities of obesity: _____

_____

Any other issues: _____

_____

Family History

- Are the parents related to each other (consanguineous)? Yes / No
- Family history of early-onset obesity? Yes / No
- Family history of diabetes? Yes / No
- Family history of bariatric surgery? Yes / No

Examination

Height: _____ Height SDS or centile: _____

Weight: _____ Weight SDS or centile: _____ % excess weight: _____

BMI: _____ BMI SDS or centile: _____

Head circumference: _____ Head circumference SDS or centile: _____

Tanner stage: _____ Acanthosis nigricans: Yes / No

Hair colour: Black / Brown / Blonde / Red

Dysmorphic features: Yes / No

If yes, details: _____

Pattern of fat distribution: Generalised / Central obesity / Other: _____

Any other positive findings: _____

Investigations

R149 panel: Yes / No Date sent:_____ Date of result: _____

Result: _____

Array CGH/SNP: Yes / No Date sent:_____ Date of result: _____

Result: _____

R107 panel : Yes / No Date sent:_____ Date of result: _____

Result: _____

Imprinting disorder: Yes / No Date sent:_____ Date of result: _____

Result (include which condition tested): _____

WGS R27: Yes / No Date sent:_____ Date of result: _____

Result: _____

Any change to management: _____

Implications for family: _____

Non-Whole Genome Sequencing Referral Forms

GMSA	Non-WGS Test Order Form link	Non-WGS Genetics Consent Form Link	Laboratory Contact Details
Central and South: Rare disease – Central and South Genomics Service			
Wessex	https://www.salisbury.nhs.uk/media/xwdiaffh/rarediseasereferralformv-2-4_auth.pdf		shc-tr.WRGLdutyscientist@nhs.net
Oxford	Oxford Genetics Laboratories request form	Record of discussions regarding testing and/or storage of genetic material	dutyscientist.oxfordgenetics@ouh.nhs.uk
Birmingham	rarediseaseandreproductivegenomicstestrequestmay2022pdf.pdf		bwc.genetics.lab@nhs.net
East: Rare disease tests - non WGS | East Genomics			
Cambridge	Rare disease tests - non WGS | East Genomics	Rare_Disease_RoD_NON_WGS_v5.pdf	geneticslaboratories@nhs.net
Nottingham	Rare disease tests - non WGS | East Genomics	Rare_Disease_RoD_NON_WGS_v5.pdf	NUHNT.MolecularGenetics@nhs.net
Leicester	Rare disease tests - non WGS | East Genomics	Rare_Disease_RoD_NON_WGS_v5.pdf	uho-tr.uhlcytogenetics@nhs.net
North Thames: Test order forms - North Thames GMS : North Thames GMS			
GOSH/UCLH	Genetic-Test-Request-Form.pdf	NTGLH_Record-of-Discussion_v1.pdf	gos-tr.norththamesgenomics@nhs.net
North West: North West Genomic Laboratory Hub - Manchester University NHS Foundation Trust			
Manchester/ Liverpool	DOC4900-Genomic-Testing-Request-Form-Rare-Disease.docx		mft.genomics@nhs.net
North East: Referral Forms - North East and Yorkshire Genomic Medicine Service North East and Yorkshire Genomic Medicine Service			
Newcastle	411.027-Rare-Disease-Referral-Form-v3.1.pdf		NUTH.DNA@nhs.net
Sheffield	411.027-Rare-Disease-Referral-Form-v3.1.pdf		sheffield.diagnosticgenetics@nhs.net
Leeds	411.027-Rare-Disease-Referral-Form-v3.1.pdf		leedsth-tr.DNA@nhs.net
South East: NHS South East GLH and NHS South East GMSA			
GSTT/KCH	SE-GLH-Non-WGS-Genetic-Test-Request-Form-August-2023-v1.5.pdf	Non-WGS-RoD-v1.1.pdf	gst-tr.southeastglh@nhs.net
South West: SWGLH Sample and Test Information | North Bristol NHS Trust			
Bristol	https://www.nbt.nhs.uk/sites/default/files/document/GMS%20Test%20Order%20Form%20v2.1.pdf		SWGLHenquiries@nbt.nhs.uk

Whole Genome Sequencing

- Whole Genome Sequencing (WGS) is the most comprehensive form of genomic testing currently in clinical use
- Can be requested by Paediatrics team by completing Test Order Form
- Consented by Genomic Practitioner (or trained clinical/nurse practitioner)
- WGS: sequencing of the whole genome will take place, although diagnostic analysis will focus on panels of known genes associated with the clinical presentation
- Analysis by PANEL: panels selected depending on PHENOTYPE which is entered as HPO (Human Phenotype Ontology) terms
- **Request as trio (child, father, mother) -** however, it is acceptable to refer a duo (proband and one biological parent) or singleton where one or more parents are not available.
- **WGS requires:**
    - **Test Order Form (TOF) x1**
    - **Record of Discussion (RoD) x3 (for each person tested)**
    - **A blood sample for each family member** - based on our genetic testing pathway, the child should already have had recent DNA stored in the genetic lab - the lab will check for their stored sample if you write this on the TOF
- All forms are available on your local Genomic Laboratory Hub (GLH) website – direct links below:
    - Central and South GLH
    - East GLH
    - North East and Yorkshire GLH
    - North Thames GLH
    - North West GLH
    - South East GLH
    - South West GLH

Useful Youtube video on how to complete WGS forms produced by Central & South Genomic Medical Service: https://www.youtube.com/watch?v=8OLFTjBxHrM

WGS Record of Discussion (RoD) form

- This is mandatory for WGS
- This can be done by a trained clinical/nurse practitioner or the Genomic Practitioner from your trust's Genetics department
- You will need to complete a RoD form for every family member to be tested – for a trio WGS test, three RoD forms will need to be completed
- This is a nationally standardised form which can be downloaded from here: https://www.england.nhs.uk/wp-content/uploads/2021/09/nhs-genomic-medicine-service-record-of-discussion-form.pdf
- This guide highlights key points to cover during conversations with patients/families about WGS and the opportunity to participate in the National Genomic Research Library (NGRL), based on statements on the RoD form: https://www.genomicseducation.hee.nhs.uk/wp-content/uploads/2019/11/Guide-to-requesting-WGS-RD-Nov-20.pdf

- Patient information leaflets are available here:
    - https://www.england.nhs.uk/wp-content/uploads/2021/07/genome-sequencing-rare-disease-patient-information.pdf
    - https://www.england.nhs.uk/wp-content/uploads/2021/07/genome-sequencing-rare-disease-patient-information-easy-read.pdf
    - https://www.eastgenomics.nhs.uk/for-patients-and-carers/considering-whole-genome-sequencing/translated-patient-information/ (for translated languages)
- Further information on the National Genomic Research Library can be found here:
    - https://www.genomicseducation.hee.nhs.uk/supporting-the-nhs-genomic-medicineservice/national-genomic-research-library-information-for-clinicians/ (for clinicians)
    - https://www.genomicsengland.co.uk/patients-participants/taking-part/resources (for patients)

Example of documentation of conversation with family

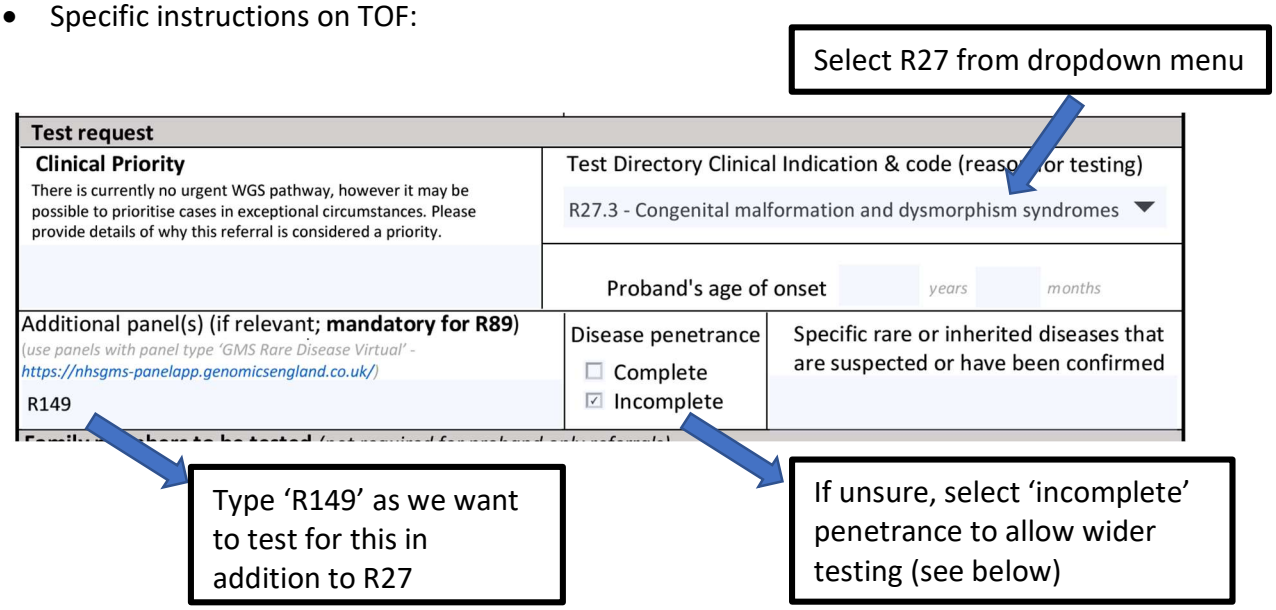
" explained our new whole genome sequencing service following on from 100,000 genomes project. This allows us to compare samples from mum, dad and child. We read every letter of every gene and the letters in between then analyse the relevant ones. We aim to find a primary diagnosis. We do not look for additional features. We may find things incidentally. When we do the testing we may get a result that is definitely abnormal and therefore diagnostic, difficult to interpret or normal as far as we can tell. When we make a diagnosis we may diagnose something that is rare or more common. Sometimes we may diagnose something very serious and in other cases we may find reassuring information that simply explains the child's features. We may determine how a condition arose and this may have implications for family members and their family planning. You will be offered access to research as appropriate.

You were keen to proceed with this. Please find enclosed forms for both parents to have blood taken. Please ask your GP practice nurse to take the blood and forward it to our laboratory. We have DNA stored from ……*(edit accordingly)* I will forward your notes to our genomic practitioner who will go through the consent forms with you and the results will then take about 9 months."

WGS Test Order Form

- Special TOF for WGS, as opposed to general genomic tests: https://www.england.nhs.uk/wp-content/uploads/2024/07/gms-test-order-form-rare-disease-v1.5.pdf
- Complete the form digitally (in PDF form) – save form onto your computer first before starting
- Email to lab
- Further information can be found here: https://www.genomicseducation.hee.nhs.uk/genotes/knowledge-hub/how-to-complete-a-test-order-form-for-wgs/
- If incorrect or insufficient clinical information is provided, or if incorrect information is included about the family history, potentially relevant genomic findings may not be identified during analysis of WGS

- Specific instructions on TOF:



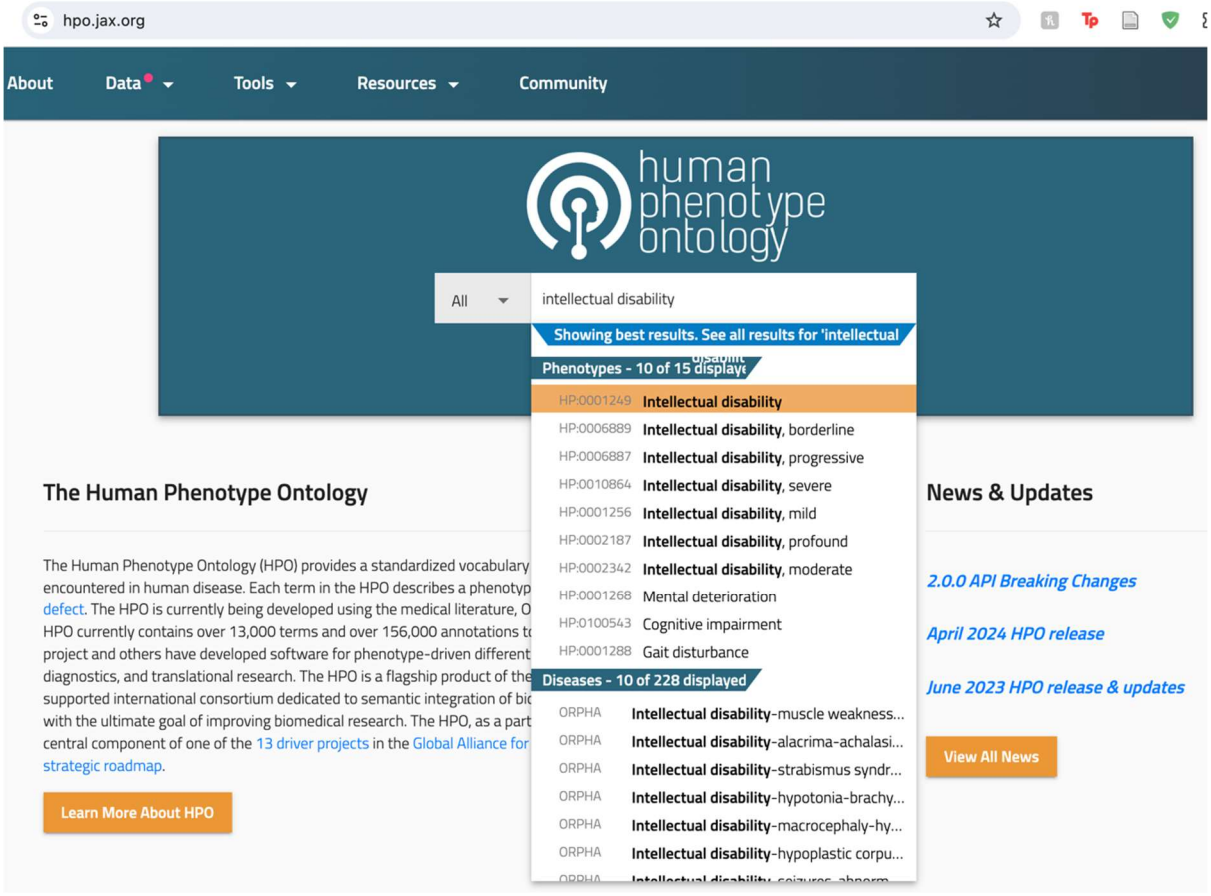
A note on penetrance selection

- The penetrance selected on the TOF has a direct impact on the variants in the patient that pass the filtering performed by the bioinformatics pipeline.
- Select **'complete penetrance'** if: a) both parents are definitely unaffected, or b) if a parent AND the proband have the SAME phenotype / gene-related condition.
- Where '**complete penetrance'** is selected, and family members referred for testing are entered as unaffected, variants present in both the patient and in family members will be filtered out and not analysed (for variants in genes with autosomal dominant or some X-linked mode-of-inheritance). If a family member is referred for testing and entered as affected then only variants which are present in affected members of the family will pass the filtering and be analysed.
- Select **'incomplete penetrance'** if: a) one parent may be mildly affected, or b) there is a family history indicating that incomplete penetrance is suspected.
- Where '**incomplete penetrance'** is selected then variants in unaffected family members referred, and inherited by the patient, will not be filtered out.

HPO terms are important for the analysis and interpretation of WGS data.
Please enter valid HPO terms present in the proband/family members being tested
HPO terms can be copied from the lists below

HPO Terms - Please ensure those given match those available at (https://hpo.jax.org/app/)	Juliet	Science	James	Science	Mary	Science
	06/06/2013		01/02/1980		01/01/1980	
	Present	Absent	Present	Absent	Present	Absent
Intellectual disability - moderate	✓			✓		✓
Global developmental delay	✓			✓		✓
Short stature				✓		✓
Broad thumb HP:0011304				✓		✓

Enter HPO terms – must match those available on HPO website (see below)



Example of completed Test Order Form (TOF) for WGS

NHS Genomic Medicine Service, WGS Test Request Rare Disease, July 2024, v1.5 to be used for WGS go-live. This document is subject to version control and is regularly updated. Please confirm you are using the current version by contacting your local Genomic Laboratory Hub.

Genomic Medicine Service

Whole Genome Sequencing (WGS) Test Request
PLEASE DO NOT USE FOR NON-WGS TESTS

RARE AND INHERITED DISEASES

NHS

Requesting organisation: Oxford University Hospitals

GLH laboratory: Central and South

Proband's first name Tessa	**Life status** ☑ Alive ☐ Deceased **Ethnicity** White British
Proband's last name Tester	**Family test** ☐ Singleton ☑ Trio ☐ Other (provide number):
Date of birth *(dd/mm/yyyy)* 01/01/2020 **Hospital number** 12345	**Relevant clinical information** *Please include any previous molecular testing with date(s) and any other pertinent clinical information* BMI 40 Urine and blood profile normal Abdominal ultrasound normal Non-consanginous parents array negative
Gender ☐ Male ☑ Female ☐ Other *Please state in clinical information box if karyotypic and/or phenotypic sex differ from given gender*	
Postcode O X 3 7 L E	
NHS number 1 1 1 2 2 2 3 3 3 3 **Reason NHS Number not available:** ☐ Patient not eligible for NHS number (e.g. foreign national) ☐ Other (please provide reason):	

Test request

Clinical Priority
There is currently no urgent WGS pathway, however it may be possible to prioritise cases in exceptional circumstances. Please provide details of why this referral is considered a priority.

Test Directory Clinical Indication & code (reason for testing)
R27.3 - Congenital malformation and dysmorphism syndromes

Proband's age of onset 4 *years* 0 *months*

Additional panel(s) (if relevant; mandatory for R89)
(use panels with panel type 'GMS Rare Disease Virtual' - https://nhsgms-panelapp.genomicsengland.co.uk/)
R149

Disease penetrance
☐ Complete
☑ Incomplete

Specific rare or inherited diseases that are suspected or have been confirmed

Family members to be tested *(not required for proband only referrals)*

First name	Last name	Date of birth	NHS Number *(or postcode if not known)*	Gender	Deceased	Status	Ethnicity	Relationship to proband
Jane	Tester	01/01/1987	444 555 6666	Female	No	Unaffected	White British	Mother
John	Tester	01/01/1985	777 888 9999	Female	No	Affected	White British	Father

Samples *being sent to GLH DNA extraction lab (only required if also using this form for sample collection)*

First name	Last name	Date of birth	Sample ID	Collection date / time	Sample type	Sample volume	Comments
Tessa	Tester	01/01/2020					
Jane	Tester	01/01/1987					
John	Tester	01/01/1985					

Responsible clinician / consultant	**Main contact** (if different from responsible clinician/consultant)
Name: Dr John Smith	Name:
Department address: Department Hospital Address	Department address:
Phone: 01865 111 869	Phone:
Email: john.smith@nhs.net	Email:

☑ **I have attached a copy of the Record of Discussion form for all individuals**
☐ Patient conversation taken place; Record of Discussion form to follow

Proband first name	Proband last name	Date of birth *(dd/mm/yyyy)*	NHS number
Tessa	Tester	01/01/2020	111 222 3333

HPO terms are important for the analysis and interpretation of WGS data.
Please enter valid HPO terms present in the proband/family members being tested.
HPO terms can be copied from the lists below, however please note these are not comprehensive lists of available terms.

HPO Terms - Please ensure those given match those available at (https://hpo.jax.org/app/)	Tessa Tester 01/01/2020		Jane Tester 01/01/1987		John Tester 01/01/1985	
	Present	Absent	Present	Absent	Present	Absent
Intellectual disability - moderate	✓			✓		✓
Autistic behaviour	✓			✓		✓
Obesity	✓			✓	✓	
Childhood-onset truncal obesity	✓			✓		✓
Abnormal facial shape	✓			✓		✓
Polyphagia	✓			✓	✓	

Intellectual disability, developmental and metabolic
Intellectual disability - mild
Intellectual disability - moderate
Intellectual disability - profound
Intellectual disability - severe
Autistic behaviour
Global developmental delay
Delayed fine motor development
Delayed gross motor development
Delayed speech and language development
Generalized hypotonia
Feeding difficulties
Failure to thrive
Abnormal facial shape
Abnormality of metabolism/homeostasis
Microcephaly
Macrocephaly
Tall stature

Craniosynostosis
Bicoronal synostosis
Unicoronal synostosis
Metopic synostosis
Sagittal craniosynostosis
Lambdoidal craniosynostosis
Multiple suture craniosynostosis

Skeletal dysplasia
Disproportionate short stature
Proportionate short stature
Short stature
Skeletal dysplasia

Diabetes
Neonatal insulin-dependent diabetes mellitus
Transient neonatal diabetes mellitus

Renal
Multiple renal cysts
Nephronophthisis
Hepatic cysts
Enlarged kidney
Renal insufficiency

Neurology
Muscular dystrophy
Myopathy
Myotonia
Fatigable weakness
Peripheral neuropathy
Distal arthrogryposis
Arthrogryposis multiplex congenita
Cognitive impairment
Parkinsonism
Spasticity
Chorea
Dystonia
Ataxia
Cerebellar atrophy
Cerebellar hypoplasia
Dandy-Walker malformation
Olivopontocerebellar hypoplasia
Diffuse white matter abnormalities
Focal White matter lesions
Leukoencephalopathy
Cortical dysplasia
Heterotopia
Lissencephaly
Pachygyria
Polymicrogyria
Schizencephaly
Holoprosencephaly
Hydrocephalus
Neurodegeneration
Dementia

Epilepsy
Seizures
Generalized seizures
Focal seizures
Epileptic spasms
Infantile encephalopathy
Atonic seizures
Generalized myoclonic seizures
Generalized tonic seizures
Generalized tonic-clonic seizures
EEG with focal epileptiform discharges
EEG with generalized epileptiform discharges
Multifocal epileptiform discharges

Cardiology
Hypertrophic cardiomyopathy
Dilated cardiomyopathy
Cardiomyopathy

Eye Disorders
Cataract
Retinal dystrophy
Macular dystrophy
Microphthalmia
Anophthalmia
Coloboma
Developmental glaucoma
Aniridia
Abnormal anterior eye segment morphology
Nystagmus

Immune Disorders
Immunodeficiency
Abnormal lymphocyte morphology
Abnormal lymphocyte physiology
Abnormal lymphocyte count
Abnormality of neutrophils
Abnormality of humoral immunity
Abnormal inflammatory response
Abnormality of complement system