National Genomic Test Directory

Testing Criteria for Rare and Inherited Disease

Version 7.1 January 2025 (Official)

Summary

The National Genomic Test Directory identifies the most appropriate test for each clinical indication and the testing methodology by which it should be delivered. The National Genomic Test Directory is set out in a separate excel document available at the following location: https://www.england.nhs.uk/publication/national-genomic-test-directories/

This eligibility criteria document supplements the National Genomic Test Directory by setting out which patients should be considered for testing under that indication, and the requesting specialties is a list of the clinical specialties who would be expected to request the test.

To develop the National Genomic Test Directory and testing criteria, NHS England convened an expert panel for rare disease. The panel brought together clinicians, scientists, health economists, policy experts, public representatives and patient organisations. The panel developed a methodology to reflect the changing technology and consider the optimal testing for a clinical condition, rather than a specific gene, to ensure the NHS is receiving the best value from genomic tests across all clinical indications.

The NHS standard contract stipulates that only tests in the National Genomic Test Directory are commissioned and paid for by the NHS and that they must be delivered by a Genomic Laboratory Hub (or their sub-contractors), to the standards set in the service specification. Each NHS Trust has been mapped to a single Genomic Laboratory Hub for the provision of testing.

If you have any questions about the genomic testing available in your area, please contact your local Genomic Laboratory Hub. More information about the Genomic Laboratory Hubs can be found here: https://www.england.nhs.uk/genomics/genomic-laboratory-hubs/.

Document overview

Clinical Indications

The following elements are presented for each clinical indication:

- **Clinical Indication Name**: name of the clinical indication, preceded by unique clinical indication code.
- **Testing Criteria**: description of the patients who should receive the test.
- **Overlapping Indications**: pointers to other clinical indications with overlapping presentations or genomic targets.
- **Where in Pathway**: guidance as to where the genetic test should usually sit in the patient pathway, particularly with respect to other diagnostic investigations
- **Requesting Specialties**: specialties that will be routinely permitted to request the test

  Requesting specialties have been nationally agreed as appropriate specialties for referrals for testing. The list of requesting specialties is not designed to operate at a very specific level or to limit test requests to just those clinical specialities listed if established alternatives are in place, as pathways will differ across the country, e.g. a specialist with the job title 'paediatric craniofacial surgeon' would potentially be grouped within 'Surgery' or 'Paediatrics'.

  If GLHs receive test requests from clinicians whose role doesn't fall within a single requesting specialty, or whose clinical specialty is not listed for that clinical indication, the GLH can process that test if it is appropriate as per their agreed local pathways, and the eligibility criteria for the clinical indication is being met.
- **Specialist Service Group**: specialist service group that covers the clinical indication. The options are:
  - Core;
  - Cardiology;
  - Audiology;
  - Endocrinology;
  - Ophthalmology;
  - Gastrohepatology;
  - Haematology;
  - Immunology;
  - Inherited cancer;
  - Metabolic;
  - Mitochondrial;
  - Musculoskeletal;
  - Neurology;
  - Renal;
  - Respiratory;
  - Dermatology;
  - Prenatal;

Associated Tests

The associated tests contain information about the tests which routinely constitute the target for the clinical indication. It is expected that all tests listed under a particular clinical indication will be routinely performed, unless there is clear clinical or scientific rationale not to do so.

Information provided includes:

Optimal Family Structure: optimal family structure for testing if relevant relatives are available. The options are:

- Singleton;
- Trio;
- Singleton or Trio;
- Parents only; and
- Other

Scope: the type of variation to be detected. The options are:

- Small variant detection;
- Copy number variant detection to genomewide resolution;
- Copy number variant detection;
- Short tandem repeat analysis;
- Complex variant detection;
- Balanced rearrangement detection;
- Aneuploidy detection;
- Methylation analysis;
- Uniparental disomy detection;
- Identity testing;
- DNA repair defect detection; and
- Other

Target Type: the type of target at which the variants need to be detected. The options are:

- Genomewide;
- Panel of genes or loci;
- Single gene(s); and
- Single interval

Target Name: names of the gene(s)or panel at which the variant type should be detected

Test Method: test method to be used. The options are:

- WGS (Whole Genome Sequencing);
- WES (Whole Exome Sequencing);
- Large panel;
- Medium panel;
- Small panel;
- Single gene sequencing;
- Targeted variant testing;
- STR testing;
- MLPA or equivalent;
- Microarray;
- Common aneuploidy testing;
- Karyotype;
- FISH;
- DNA repair testing;
- Methylation testing;
- Uniparental Disomy (UPD) testing;
- X-inactivation testing;
- Identity testing;
- Microsatellite instability;
- NIPT (Non Invasive Prenatal Testing);
- NIPD (Non Invasive Prenatal Diagnosis);
- Other

Test Ordering

Clinicians wishing to request genomic tests can do so by;

- Requesting the clinical indication (name and unique code of the clinical indication), in instances where the clinical indication to be tested is known
- If the clinician is aware that some of the constituent tests which are offered as part of the clinical indication are not needed, they can specify to the laboratory which constituent tests are required and which aren't.
- As much relevant clinical details as possible should be provided to aid interpretation of results

Clinicians should follow local process to request genomic tests using the most appropriate Clinical Indication code. The Genomic Laboratory Hub will review the test request and relevant clinical information and select the most appropriate constituent test(s) to facilitate the test request. Testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

Glossary

- Where the term ‘maternal’ is used this refers to the genetic contribution, from parent to offspring, from an ovum and the term ‘paternal’ refers to the parental contribution from a sperm.
- In the context of **X linked early onset conditions**, where the eligibility criteria relate to a specific sex, this is referring to the sex assigned at birth and hence should be appropriately applied in trans gender individuals.
- Singleton – the patient
- Duo – testing of patient performed simultaneously alongside one of their biological parents
- Trio – testing of patient performed simultaneously alongside both biological parents
- SNVs – Small nucleotide variants
- CNVs – Copy number variants
- ACGS – Association of Clinical Genomic Science (variant classification guidelines)
- ACMG – American College of Medical Genetics (variant classification guidelines)

Find Text in Document

To search the National Genomic Test Directory - Testing Criteria for Rare and Inherited Disease:

1. Press CTRL+F (Windows) or CMD+F (Mac)
2. In text box, enter search term
3. The first match will be highlighted
4. Press Enter or click the arrow keys to navigate between results

Content

Part V. Ophthalmology

Part VI. Fetal (including NIPD)

Part VII. Gastrohepatology

Part VIII. Haematology

Part XII. Lipids

Part XIII. Metabolic

Part XIV. Mitochondrial

Part XV. Mosaic and structural chromosomal disorders

Part XVI. Musculoskeletal

Part XVII. Neurology

Part XVIII. Renal

Part XIX. Respiratory

Part XX. Dermatology

Part XXI. Ultra-rare and atypical monogenic disorders

Part XXII. Multi-purpose tests

Change Log

Part I. Acutely unwell children

R14 Acutely unwell children with a likely monogenic disorder

Testing Criteria

Acutely unwell children with a likely monogenic disorder

For more detailed guidance for R14 please see http://exeterlaboratory.com/genetics/genome-sequencing/

Where clinical features and/or non genetic investigations are pathognomonic of a single gene disorder, no test is available and molecular testing is required urgently to guide management, R14 may be requested.

Overlapping indications

- R26 Likely common aneuploidy test should be used first where the cause is considered likely to be a common aneuploidy
- R28 Congenital malformation and dysmorphism syndromes – microarray should be undertaken in parallel where clinically indicated. Where the cause is highly likely to be chromosomal, for example where the clinical features are characteristic of Williams syndrome, then microarray should be undertaken in advance of the R14 test.

Where in Pathway

Following discussion with Clinical Genetics, the child's local management team and the testing laboratory, or in line with locally agreed patient identification criteria

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Multi specialty

Associated Tests

.

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R14.1	Acutely unwell children with a likely monogenic disorder	Trio(Duo or Singleton accepted when necessary)	Small variants and CNVs	Trio gene agnostic or Panel of genes or loci in singletons or duos	Trio gene agnostic or appropriate panels in singletons or duos	WGS

Part II. Cardiology

R137 Congenital heart disease - microarray

Testing Criteria

Individual with tetralogy of Fallot, interrupted aortic arch or truncus arteriosus, or other forms of congenital heart disease with cleft palate and / or disorder of calcium homeostasis

Exclusion criteria

Non-syndromic Congenital Heart Disease (CHD) outside of the above eligibility criteria should not be tested under R137

Overlapping indications

- R26 Likely common aneuploidy test should be used for patients with coarctation of the aorta and features suggestive of Turner syndrome
- R27 Paediatric disorders – likely monogenic or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations. R27 should NOT be used for isolated CHD, even in the presence of a recurrence in the family.
- R140 Elastin-related phenotypes

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

- Cardiology
- Clinical Genetics
- Fetal Medicine
- Paediatrics
- Pathology

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R137.1	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray

R125 Thoracic aortic aneurysm or dissection

Testing Criteria

1. Thoracic aortic aneurysm* or dissection with onset before age 50, OR
2. Thoracic aortic aneurysm* or dissection with onset before age 60 with a first degree relative with thoracic aortic aneurysm or dissection, OR
3. Thoracic aortic aneurysm* or dissection before age 60 with no classical cardiovascular risk factors, OR
4. Thoracic aortic aneurysm* or dissection before age 60 with features suggestive of aortopathy, e.g. arterial tortuosity, OR
5. Clinical features suggestive of Loeys-Dietz syndrome, OR
6. Features of Marfan syndrome giving a systemic Ghent score of ≥7, following assessment by a clinical geneticist or specialist with expertise in aortopathy, OR
7. High clinical suspicion of a condition predisposing to aortic/arterial disease AND diagnostic testing for other conditions such as Ehlers Danlos syndrome (where indicated) has not identified a causative variant
8. Any deceased individual with a thoracic aortic aneurysm* or dissection detected at autopsy meeting one of the above criteria and who have relatives who will benefit from cascade testing using a genetic diagnosis will be suitable for post-mortem genetic testing.

*Thoracic aortic aneurysm defined as:

- In children: z score >2 for body surface area
- In adults: dilatation >38 mm

Testing should be carried out following assessment in a clinical service specialising in management of patients with aortopathy, including support from clinical genetics; testing may occasionally be appropriate outside these criteria following discussion in an aortic genetics MDT

Overlapping Indications

- R27 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

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

- Cardiology
- Clinical Genetics

Specialist Service Group

- Cardiology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R125.1	Thoracic aortic aneurysm or dissection	Singleton	Small variants, CNVs	Panel of genes or loci	Thoracic aortic aneurysm or dissection (700)	WES or Medium Panel

R127 Long QT syndrome

Testing Criteria

A firm clinical diagnosis of Long QT syndrome, as indicated by:

1. QTc ≥500ms in repeated 12-lead ECGs, OR
2. LQTS risk score ≥3.5 (Schwartz et al, 2011. PMID: 22083145), OR
3. QTc ≥480 ms in repeated 12-lead ECGs AND an unexplained syncopal episode
4. QTc ≥480 ms in repeated 12-lead ECGs AND a history of sudden unexplained death under the age of 60 in a first / second degree relative

A secondary cause for QT prolongation should be excluded prior to testing

Testing should be carried out in parallel with expert phenotypic assessment, for example in an Inherited Cardiac Clinic (ICC), including support from clinical genetics; testing may occasionally be appropriate outside these criteria following discussion in an ICC MDT

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

- Cardiology
- Clinical Genetics

Specialist Service Group

- Cardiology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R127.1	Long QT syndrome Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Long QT syndrome (76)	Small panel

R128 Brugada syndrome and cardiac sodium channel disease

Testing Criteria

A firm clinical diagnosis of Brugada syndrome and/or sodium channel disease, as indicated by:

1. Spontaneous type 1 (“coved-type”) ST-segment elevation (characterized by ST-segment elevation ≥2 mm (0.2 mV) in ≥1 right precordial leads (V1–V3) positioned in the 4th, 3rd, or 2nd intercostal space), OR
2. Type 1 ST-segment elevation unmasked using a sodium channel blocker, AND 1 of the following:
    a. Documented VF or polymorphic VT, OR
    b. Syncope of probable arrhythmic cause, OR
    c. A family history of sudden cardiac death at <45 years old with negative autopsy, OR
    d. A coved-type ECGs in family members, OR
    e. Nocturnal agonal respiration OR
    f. Premature atrial arrhythmias at age <30 years
3. Suspicion of sodium channel disease including atrial arrhythmias, sinus node dysfunction, conduction disease and/or QT prolongation, predominantly in children and young people.

NOTE: Clinical evaluation in young probands and cascade testing in families will incorporate assessment for other features of sodium channel disease such as sinus node disease, atrial arrhythmias, conduction disease, dilated cardiomyopathy and long QT syndrome (LQT3 subtype) that may coexist with or supplant type 1, 2 or 3 Brugada ECG patterns. Brugada ECG patterns may be present even in sodium channel genotype negative patients.

Testing should be carried out in parallel with expert phenotypic assessment, for example in an Inherited Cardiac Clinic (ICC), including support from clinical genetics; testing may occasionally be appropriate outside these criteria following discussion in an ICC MDT.

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

- Cardiology
- Clinical Genetics

Specialist Service Group

- Cardiology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R128.1	Brugada syndrome and cardiac sodium channel disease Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Brugada syndrome (13)	Small panel

R129 Catecholaminergic polymorphic VT

Testing Criteria

A firm clinical diagnosis of CPVT based on one of the following:

1. A structurally normal heart, normal ECG, and unexplained exercise or catecholamine-induced bidirectional VT or polymorphic ventricular premature beats or VT/VF in an individual under 40 years of age, OR
2. A patient with a structurally normal heart who manifests exercise-induced premature ventricular contractions (PVCs) or bidirectional/polymorphic VT/VF, with a positive family history of CPVT, where a symptomatic family member is unavailable for testing, OR
3. A structurally normal heart and coronary arteries, normal ECG, and unexplained exercise or catecholamine-induced bidirectional VT or polymorphic ventricular premature beats or VT/VF in an individual over 40 years of age

Testing should be carried out in parallel with expert phenotypic assessment, for example in an Inherited Cardiac Clinic (ICC), including support from clinical genetics; testing may occasionally be appropriate outside these criteria following discussion in an ICC MDT.

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

- Cardiology
- Clinical Genetics

Specialist Service Group

- Cardiology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R129.1	Catecholaminergic polymorphic VT Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Catecholaminergic polymorphic VT (214)	Small panel

R130 Short QT syndrome

Testing Criteria

A firm clinical diagnosis of Short QT syndrome, as indicated by:

1. A QTc ≤330 ms, OR
2. A QTc <360 ms, AND one or more of the following:
   a. Family history of SQTS,
   b. Family history of sudden death at age ≤40
   c. Survival of a VT/VF episode in the absence of heart disease

Testing should be carried out in parallel with expert phenotypic assessment, for example in an Inherited Cardiac Clinic (ICC), including support from clinical genetics; testing may occasionally be appropriate outside these criteria following discussion in an ICC MDT.

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

- Cardiology
- Clinical Genetics

Specialist Service Group

- Cardiology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R130.1	Short QT syndrome Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Short QT syndrome (224)	Small panel

R131 Hypertrophic cardiomyopathy

Testing Criteria

A firm clinical diagnosis of hypertrophic cardiomyopathy as indicated by:

1. An adult with wall thickness ≥15 mm in one or more LV myocardial segments, that is NOT explained solely by loading conditions (principally hypertension), with age of onset below 60
2. A child under the age of 18 with LV wall thickness more than two standard deviations greater than the predicted mean (z-score >2, where a z-score is defined as the number of standard deviations from the population mean)
3. Otherwise unexplained increased LV wall thickness ≥13 mm in one or more LV myocardial segments, in a patient with a first degree relative with unequivocal disease (LVH ≥15 mm), where a family member with unequivocal disease is unavailable for testing
4. A deceased individual with pathologically confirmed HCM for post-mortem DNA analysis

Genetic testing is recommended in patients meeting the above criteria who have relatives who will benefit from cascade testing using a genetic diagnosis.

Testing should be carried out in parallel with expert phenotypic assessment, for example in an Inherited Cardiac Clinic (ICC), including support from clinical genetics; testing may occasionally be appropriate outside these criteria following discussion in an ICC MDT.

Overlapping indications

R135 Paediatric or syndromic cardiomyopathy should be used where atypical features suggest a broader range of genes should be tested. All patients tested under R135, must meet the eligibility criteria for R135.

Where in Pathway

At presentation

Requesting Specialties

- Cardiology
- Clinical Genetics

Specialist Service Group

- Cardiology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R131.1	Hypertrophic cardiomyopathy WES or medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Hypertrophic cardiomyopathy - teen and adult (49)	WES or Medium Panel

R132 Dilated and arrhythmogenic cardiomyopathy

Testing Criteria

A firm clinical diagnosis of dilated cardiomyopathy (DCM) or arrhythmogenic cardiomyopathy (ACM) as indicated by:

1. Left ventricular end diastolic diameter (LVEDD) greater than 2 standard deviations, AND/OR
   a. Reduced ejection fraction (EF) to less than 45%, adjusted for age and sex, AND
   b. Age of onset below 65 years, OR
   c. DCM with conduction defects, with age of onset below 65 years

OR

2. Left and/or biventricular cardiomyopathy associated with variable degrees of myocardial dysfunction and/or myocardial fibrosis PLUS ventricular arrhythmias (including prior cardiac arrest) following exclusion of other aetiologies including inflammatory disorders

OR

3. A deceased individual with pathologically confirmed DCM or ACM and age of onset below 65 years suitable for post-mortem DNA analysis.

OR

4. Patient with DCM or ACM at any age if they have a first degree relative with confirmed diagnosis of DCM or ACM

Genetic testing is recommended for patients meeting the above criteria with:

1. Relatives who will benefit from cascade testing using genetic diagnosis, AND/OR
2. Features suggesting an increased risk of sudden death, including conduction defects, atrial arrhythmia or family history of sudden death

Patients with ventricular dilatation secondary to coronary artery disease or pressure/volume overload should NOT be tested

Patients with DCM due to other precipitants (such as myocarditis, alcohol, peripartum, chemotherapy) should only be tested following consultation with an expert

Testing should be carried out in parallel with expert phenotypic assessment, for example in an Inherited Cardiac Clinic (ICC), including support from clinical genetics; testing may occasionally be appropriate outside these criteria following discussion in an ICC MDT

Overlapping indications

- R135 Paediatric or syndromic cardiomyopathy should be used where atypical features suggest a broader range of genes should be tested

Where in Pathway

At presentation

Requesting Specialties

- Cardiology
- Clinical Genetics

Specialist Service Group

- Cardiology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R132.1	Dilated and arrhythmogenic cardiomyopathy	Singleton	Small variants, CNVs	Panel of genes or loci	Dilated cardiomyopathy - teen and adult (652)	WES or Medium Panel

R391 Barth syndrome

Testing Criteria

Clear clinical and biochemical diagnosis of Barth syndrome in a male patient:

1. Some or all of cardiomyopathy, neutropenia, skeletal myopathy, prepubertal growth delay, distinctive facial features, and history of unexplained recurrent miscarriage or stillbirths or sudden death in the family, AND
2. Positive cardiolipin result (MLCL/CL ratio) where available; (patients may also have raised 3MGA)

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 assessment by a consultant in cardiology, neonatology, neurology or paediatrics, or following clinical assessment as part of the Barth Syndrome highly specialised service

Requesting Specialties

- Cardiology
- Clinical Genetics
- Neonatology
- Neurology
- Paediatrics

Specialist Service Group

- Cardiology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R391.1	TAZ Single gene sequencing	Singleton	Small variants	Single gene(s)	TAZ (1308)	Single gene sequencing >=10 amplicons

R133 Arrhythmogenic right ventricular cardiomyopathy

Testing Criteria

A firm clinical diagnosis of arrhythmogenic right ventricular cardiomyopathy as indicated by:

1. An individual meeting a definite diagnosis according to the Modified Task Force Criteria (Marcus et al 2010; PMID: 20172912), with age of onset below age 50 OR
2. A deceased individual with pathologically confirmed ARVC and relatives who will benefit from cascade testing using genetic diagnosis. OR
3. Identification of a pathogenic or likely pathogenic variant in an ARVC associated gene would complete diagnostic task force criteria for ARVC.

Testing should be carried out in parallel with expert phenotypic assessment, for example in an Inherited Cardiac Clinic (ICC), including support from clinical genetics; testing may occasionally be appropriate outside these criteria following discussion in an ICC MDT

Overlapping indications

- R132 Dilated cardiomyopathy should be used if disease is left-sided or biventricular, or there is phenotypic overlap with dilated cardiomyopathy

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

- Cardiology
- Clinical Genetics

Specialist Service Group

- Cardiology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R133.1	Arrhythmogenic right ventricular cardiomyopathy Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Arrhythmogenic cardiomyopathy (134)	Small panel

R135 Paediatric or syndromic cardiomyopathy

Testing Criteria

1. Cardiomyopathy of onset <12 years with no non-genetic explanation, OR
2. Individuals of any age with cardiomyopathy as their primary clinical presentation, where there is also a second condition, dysmorphism or other feature(s) suggestive of a syndromic cause such as a Rasopathy.

Testing should be carried out in parallel with expert phenotypic assessment, for example in an Inherited Cardiac Clinic (ICC) or specialist paediatric cardiology service, including support from clinical genetics; testing may occasionally be appropriate outside these criteria following discussion in an ICC MDT.

Testing Criteria for Semi-Rapid Testing

- Acutely unwell children where monogenic paediatric cardiomyopathy is considered highly likely to be the primary cause of the phenotype in the patient.

- Cases should meet the standard eligibility criteria for R135, AND

- Where testing will provide an immediate change to treatment or clinical management for the patient eg. To inform a decision about cardiac transplant, therapeutic intervention or prenatal testing for an ongoing at risk pregnancy.

- The patient is either not eligible for the R14 pathway or Rapid R135 is considered to be the more appropriate test.

Note: Cases where cardiomyopathy is part of a more complex presentation or the clinical presentation is highly suggestive of a fully penetrant monogenic disorder should be considered for R14 instead of rapid R135.

Overlapping indications

- In individuals where cardiomyopathy is one of multiple features of a likely multisystem disorder R27 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be used to enable testing of broader targets and familial testing where available
- Specific cardiomyopathy categories R131, R132 or R133 should be used where features are typical of non-syndromic hypertrophic, dilated or arrhythmogenic cardiomyopathy in individuals over the age of 12

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

Where in Pathway for Semi-Rapid Testing

At presentation following clinically relevant, rapidly available investigations. All cases must be agreed in advance with the testing laboratory.

Requesting Specialties

- Cardiology
- Clinical Genetics

Requesting Specialties for Semi-Rapid Testing

- Clinical Genetics
- Cardiology
- Neonatology

Specialist Service Group

- Cardiology

Associated Tests (see next page)

R135.3 is only for semi urgent testing

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R135.2	Paediatric or syndromic cardiomyopathy	Trio or Singleton	Small variants, CNVs	Panel of genes or loci	Cardiomyopathies - including childhood onset (749)	WGS
R135.3	Paediatric or syndromic cardiomyopathy	Trio	Small variants, CNVs	Panel of genes or loci	Cardiomyopathies - including childhood onset (749)	WES

R136 Primary lymphoedema

Testing Criteria

Primary lymphoedema with or without syndromic manifestations, with no known explanation

If in doubt whether testing is indicated, refer for specialist investigation to a specialist clinic such as those based in Derby or at St Georges Hospital in London

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
- Other

Specialist Service Group

- Cardiology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R136.1	Primary lymphoedema WES or medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Primary lymphoedema (65)	WES or Medium Panel

R138 Sudden unexplained death or survivors of a cardiac event

Testing Criteria

1. Sudden death with normal Post Mortem below the age of 40, OR
2. Sudden death with normal Post Mortem below the age of 60, with a family history of unexplained sudden death under the age of 40 in a first / second degree relative (in whom no Post Mortem was carried out), OR
3. Sudden death with normal Post Mortem below the age of 60, with a family history of unexplained sudden death under the age of 60 in a first / second degree relative (where the relative also had a normal Post Mortem)

Where available, the Post Mortem should include assessment by an expert in cardiac autopsy.

Where a cause can be identified via Post Mortem or through clinical assessment of surviving relatives, the appropriate specific Clinical Indication for testing should be used.

Testing should be carried out in parallel with assessment of surviving relatives in an Inherited Cardiac Clinic (ICC), including support from clinical genetics; testing may occasionally be appropriate outside these criteria following discussion in an ICC MDT or an opinion from an expert in cardiac autopsy.

Survivors of proven cardiac arrest (idiopathic ventricular fibrillation) with:

1. no phenotype detectable on comprehensive evaluation including coronary assessment, cardiac imaging and ECG provocation testing (idiopathic ventricular fibrillation) AND
2. under the age of 45.

Testing should be carried out in parallel with expert phenotypic assessment, for example in an Inherited Cardiac Clinic (ICC), including support from clinical genetics; testing may occasionally be appropriate outside these criteria following discussion in an ICC MDT.

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. for cardiac arrest survivors or relatives

Where in Pathway

At presentation

Requesting Specialties

- Cardiology
- Clinical Genetics

Specialist Service Group

- Cardiology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R138.1	Sudden unexplained death or survivors of a cardiac event WES or medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Sudden cardiac death (841)	WES or Medium Panel

R328 Progressive cardiac conduction disease

Testing Criteria

Unexplained progressive conduction abnormalities with onset before age 50 years, with a structurally normal heart and in the absence of a skeletal myopathy

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

- Cardiology
- Clinical Genetics

Specialist Service Group

- Cardiology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R328.1	Progressive cardiac conduction disease WES or small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Progressive cardiac conduction disease (506)	WES or Small Panel

R384 Generalised arterial calcification in infancy

Testing Criteria

Generalised arterial calcification with onset in the neonatal period

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Neonatology

Specialist Service Group

- Cardiology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R384.1	Generalised arterial calcification in infancy	Singleton	Small variants	Small panel	ABCC6; ENPP1 (1337)	Small panel

R140 Elastin-related phenotypes

Testing Criteria

1. Congenital heart disease of a type associated with Elastin variants, with an autosomal dominant pattern of inheritance in at least 3 family members, OR
2. Supravalvular aortic stenosis characteristic of Elastin variants

Overlapping indications

- R28 Congenital malformation and dysmorphism syndromes – microarray only should be used for patients with clinical features strongly suggestive of Williams syndrome
- R27 Paediatric disorders test should be used for individuals with syndromic forms of cutis laxaR125 Thoracic aortic aneurysm or dissection test should be used for individuals with primarily aortic/large arterial involvement, with some features of cutis laxa

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

- Cardiology
- Clinical Genetics

Specialist Service Group

- Cardiology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R140.1	ELN Single gene sequencing	Singleton	Small variants	Single gene(s)	ELN (1322)	Single gene sequencing >=10 amplicons

R441 Unexplained death in infancy and sudden unexplained death in childhood

Testing Criteria

1. Sudden death in child less than 18 years that remains unexplained after the standard investigation protocols including post mortem AND

2. DNA available from proband and both biological parents for trio WGS analysis OR

3. DNA available from proband and one biological parent only

Where in Pathway

After standard SIDS/SUDC protocol including post mortem have been completed. Following specialist MDT discussion of patients that may be suitable for WGS (including eg. pathology, designated doctor for child deaths, clinical genetics as appropriate). Consent will need to be obtained from family.

Requesting Specialties

- Clinical Genetics
- Paediatrics

Specialist Service Group

- Multi specialty

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R441.1	Unexplained death in infancy and sudden unexplained death in childhood WGS	Trio or duo	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Unexplained death in infancy and sudden unexplained death in childhood (1220)	WGS

R454 Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy

Testing Criteria

Testing is available to patients with:

1. symptomatic obstructive hypertrophic cardiomyopathy who have a New York Heart Association class of 2 to 3 **AND**
2. are eligible for treatment with mavacamten in line with NICE TA 913 (where mavacamten is an add on to individually optimised standard care that includes beta blockers, non-dihydropyridine calcium-channel blockers or disopyramide, unless these are contraindicated).

Where in Pathway

At prescribing decision

Requests for this test will only be accepted from centres that are commissioned to prescribe Mavacamten.

Requesting Specialties

- Cardiology

Specialist Service Group

Cardiology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R454.1	Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy	Singleton	*2, *3 and *17 alleles	Single gene	CYP2C19	Targeted variant testing

Part III. Developmental disorders

R26 Likely common aneuploidy

Testing Criteria

Clinical features strongly suggestive of trisomy 13, 18 or 21, Turner syndrome or other sex chromosome aneuploidy in the postnatal setting

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

Overlapping indications

- R297 Possible structural chromosomal rearrangement – karyotype,
- R265 Chromosomal mosaicism – karyotype,
- R314 Ambiguous genitalia presenting neonatally; plus any other follow-on tests should be considered in cases with a negative result
- R401 Common aneuploidy testing - prenatal test should be used for prenatal testing

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Community Paediatrics
- Neonatology
- Paediatrics

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R26.1	Genomewide Common aneuploidy testing - postnatal	Singleton	Aneuploidy	Genomewide	Genomewide	Common aneuploidy testing

R27 Paediatric disorders

Testing Criteria

- Congenital malformations and/or dysmorphism highly suggestive of an underlying monogenic disorder where targeted genetic testing is not possible.
- Unexplained moderate/severe/profound global developmental delay or unexplained moderate/severe/profound intellectual disability, and where clinical features are highly suggestive of an underlying monogenic disorder requiring sequencing and targeted genetic testing is not possible.
- Craniofacial dysmorphism in combination with additional issues with health or development suggestive of a single genomic explanation, e.g. intellectual disability, congenital malformation, organ dysfunction.
- Syndromic overgrowth or overgrowth in combination with intellectual disability or developmental delay.
- Adults with congenital malformation and dysmorphism syndromes, however the clinical utility of testing should be made clear on the request form e.g. to inform a clinical management decision or reproductive choice.
- Fetus from a demised/non-continued pregnancy, with multiple major structural abnormalities detected on fetal ultrasound or post-mortem examination and where a monogenic malformation disorder is considered highly likely

Exclusion criteria

- Isolated Congenital Heart Disease and other isolated congenital malformations where the likelihood of a monogenic disorder is low are not eligible for testing under this indication.
- Isolated craniofacial dysmorphism is not an indication for testing; exceptions to this can only be made following multidisciplinary discussion with clinical genetics.

R28 microarray testing is not a requirement prior to R27 being initiated in patients with a possible monogenic cause of a syndromic paediatric disorder in whom there are no recognisable features of a specific chromosome disorder (eg 22q11 deletion syndrome).

Overlapping indications

- R14 Acutely unwell infants with a likely monogenic disorder test should be used instead where relevant where a rapid result is required
- R412 Fetal anomalies with a likely genetic cause – non urgent can be used in a fetus where insufficient DNA is available for R27
- R28 Congenital malformation and dysmorphism syndromes – microarray, should be considered prior to R27 in patients suspected of having a recognisable chromosomal disorder e.g. 22q11 deletion syndrome.

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
- Paediatric neurology
- Paediatrics
- Community Paediatrics

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R27.3	Paediatric disorders	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Paediatric disorders (486)	WGS

R28 Congenital malformation and dysmorphism syndromes – microarray only

Testing Criteria

Clinical features highly suggestive of a chromosomal cause, for example individuals with features characteristic of Williams syndrome.

Where possible, the chromosomal disorder suspected should be specified on the test request form.

R28 microarray testing is not a requirement prior to R27 being initiated in patients with a possible monogenic cause of a syndromic paediatric disorder in whom there are no recognisable features of a specific chromosome disorder (e.g. 22q11 deletion syndrome).

Overlapping indications

- R27 Paediatric disorders test should be used instead where the likelihood of a chromosomal cause is lower
- R26 Likely common aneuploidy test should be used where clinical features are strongly suggestive of trisomy 13, 18 or 21, Turner syndrome or other sex chromosome aneuploidy

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 a Clinical Geneticist to consider whether broader testing is more appropriate

Requesting Specialties

- Clinical Genetics
- Community Paediatrics
- Metabolic Medicine
- Neonatology
- Neurology
- Paediatrics

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R28.1	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray

R29 Intellectual disability

Testing Criteria

Unexplained moderate/severe/profound global developmental delay or unexplained moderate/severe/profound intellectual disability, and where clinical features are suggestive of an underlying monogenic disorder requiring sequencing and targeted genetic testing is not possible.

R377 microarray testing is not a requirement prior to R29 being initiated in patients with moderate/severe/profound intellectual disability in whom a monogenic cause of their clinical presentation is suspected.

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.

Overlapping indications

- R377 Intellectual disability – microarray only
- R27 Paediatric disorders – should be used for children and adults with features suggestive of a syndromic diagnosis.

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
- Community Paediatrics

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R29.4	Intellectual disability	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Intellectual disability (285)	WGS

R377 Intellectual disability - microarray only

Testing Criteria

Unexplained moderate/severe/profound global developmental delay or unexplained moderate/severe/profound intellectual disability.

R377 microarray testing is not a requirement prior to R29 or R27 being initiated in patients with moderate/severe/profound intellectual disability in whom a monogenic cause of their clinical presentation is suspected.

Overlapping indications

- R27 Paediatric disorders should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

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
- Community Paediatrics
- Neurology
- Paediatrics
- Psychiatry

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R377.1	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray

R47 Angelman syndrome

Testing Criteria

1. Molecular findings suggestive of Angelman syndrome from, for example microarray, exome or genome analysis such as likely isodisomy or deletion at 15q11-13; OR
2. Clinical features strongly suggestive of Angelman syndrome

Overlapping indications

- R27 Paediatric disorders or other relevant broader tests should be used in preference individuals where Angelman syndrome is plausible but not highly likely
- R263 Confirmation of uniparental disomy test should be used to confirm likely UPD detected on methylation and copy number testing

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

Following identification of likely assessment by a Consultant Clinical Geneticist or Paediatric Neurologist

Requesting Specialties

- Clinical Genetics
- Genomics laboratory
- Neurology
- Community paediatrics

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R47.1	AS/PWS critical region Methylation testing	Singleton	Methylation	Single interval	AS/PWS critical region	Methylation testing
R47.2	AS/PWS critical region MLPA or equivalent	Singleton	CNVs	Single interval	AS/PWS critical region	MLPA or equivalent

R48 Prader-Willi syndrome

Testing Criteria

1. Molecular findings suggestive of Prader-Willi syndrome from, for example microarray, exome or genome analysis such as likely isodisomy or deletion at 15q11-13; OR
2. Clinical features strongly suggestive of Prader-Willi syndrome

Overlapping indications

- R27 Paediatric disorders or other relevant broader tests should be used in preference individuals where Prader-Willi syndrome is plausible but not highly likely.
- R263 Confirmation of uniparental disomy test should be used to confirm likely UPD detected on methylation and copy number testing

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

Following assessment by a Consultant Clinical Geneticist

Requesting Specialties

- Clinical Genetics
- Genomics laboratory
- Neonatology
- Community paediatrics
- Neurology
- Paediatrics
- Endocrinology

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R48.1	AS/PWS critical region Methylation testing	Singleton	Methylation	Single interval	AS/PWS critical region	Methylation testing
R48.2	AS/PWS critical region MLPA or equivalent	Singleton	CNVs	Single interval	AS/PWS critical region	MLPA or equivalent

R69 Hypotonic infant

Testing Criteria

Neonates or infants with unexplained hypotonia where the clinical picture is suggestive of a central cause, i.e. particularly where the baby is not alert, but lethargic or sleepy

Overlapping indications

- R70 Spinal muscular atrophy type 1 diagnostic test and/or R48 Prader Willi syndrome and/or R72 Myotonic dystrophy and/or other tests for neuromuscular causes should be used where the baby is alert and responsive and the floppiness appears static over a period of days
- **R14 Acutely unwell children with a likely monogenic disorder, should be used for acutely unwell neonates with hypotonia. Please note that myotonic dystrophy, SMA and Prader Willi syndrome are not tested for within R14 and need to be requested separately**

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 after exclusion of sepsis or hypoglycaemia as causes

Requesting Specialties

- Clinical Genetics
- Community Paediatrics
- Neonatology
- Neurology
- Paediatrics

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R69.5	Hypotonic infant W	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Hypotonic infant (490)	WGS
R69.6	Hypotonic infant STR confirmatory testing	As appropriate	STRs	Single gene(s)	Hypotonic infant (490) STR	STR testing

R312 Parental sequencing for lethal autosomal recessive disorders

Testing Criteria

1. Lethal disorder with likely autosomal recessive inheritance in which there is limited or no DNA from the deceased individual, AND
2. Both parents are available for testing

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

As appropriate

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Other

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R312.1	Relevant panels in PanelApp or gene agnostic WES or large panel	Parents only	Small variants, CNVs	Panel of genes or loci	Relevant panel(s) in PanelApp	WES or large panel

Part IV. Endocrinology

R402 Premature ovarian insufficiency

Testing Criteria

1. Four consecutive months of unexplained amenorrhoea (primary or secondary), AND
2. Elevated serum FSH of >30IU/L on two separate occasions at least 6 weeks apart, AND
3. Age of onset is <30 years, AND
4. Non-genetic causes have been excluded including presence of thyroid and adrenal auto-antibodies

Overlapping indications

- R54 Hereditary ataxia with onset in adulthood test should be used in preference in individuals with adult onset ataxia given the broad range of possible causes

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

N/A

Requesting Specialties

- Clinical Genetics
- Endocrinology
- Gynaecology

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R402.1	Karyotype.	Singleton	Structural variants	Genomewide	Genomewide	Karyotype
R402.2	FMR1 STR testing	Singleton	STRs	Single interval	FMR1 STR	STR testing

R314 Ambiguous genitalia presenting neonatally

Testing Criteria

Neonatal presentation with ambiguous genitalia, where genetic sex requires rapid establishment for management purposes

Overlapping indications

- R180 Congenital adrenal hyperplasia diagnostic test may be required if aneuploidy test and biochemical investigations suggest this is the likely diagnosis
- R146 Differences in sex development test may be required if underlying diagnosis still unclear after aneuploidy test, CAH test (where relevant) and biochemical investigations

Where in Pathway

Urgently at presentation, in parallel with biochemical investigations for potential salt-losing crisis where CAH is the likely diagnosis

Requesting Specialties

- Clinical Genetics
- Endocrinology
- Neonatology

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R314.1	Sex chromosomes Common aneuploidy testing	Singleton	Aneuploidy	Genomewide	Sex chromosomes	Common aneuploidy testing
R314.2	Sex chromosomes Karyotype	Singleton	Karyotype or equivalent	Genomewide	Sex chromosomes	Karyotype

R106 Alstrom syndrome

Testing Criteria

Clinical features strongly indicative of a diagnosis of Alstrom syndrome including at least two of the following:

1. Hepatobiliary disease
2. Retinal degeneration
3. Childhood onset obesity
4. Renal disease

Overlapping indications

- R27 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals overlapping or atypical presentations where features are not characteristic of Alstrom syndrome specifically

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

- Cardiology
- Clinical Genetics
- Endocrinology
- Ophthalmology

Specialist Service Group

- Endocrinology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R106.1	ALMS1 Single gene sequencing	Singleton	Small variants	Single gene(s)	ALMS1 (1210)	Single gene sequencing >=10 amplicons

R141 Monogenic diabetes

Testing Criteria

1. **Patients with isolated diabetes** should be tested if they have:

a. **Diabetes diagnosed young** (≤35 years in White Europeans and ≤30 years in high prevalence ethnic groups).

AND

b. **Unlikely to have Type 1 diabetes** because:
They are not on insulin treatment.
OR
They are on insulin treatment with all autoantibodies tested negative (minimum testing of GADA and IA2A) and a random non-fasting C peptide value ≥200pmol/l

AND

c. **Have features suggestive of MODY:**
An HbA1c at diagnosis of diabetes <7.5% (58mmol/mol), if diagnosed under 18 years of age,
OR
BMI <30kg/m^2 adult (child BMI <95th centile) **and** a parent with diabetes (if White) or BMI <27kg/m^2 (child BMI <95th centile) **and** a parent with diabetes (if high prevalence type 2 diabetes ethnic group).
OR
Have a MODY probability score ≥20% if not insulin treated and ≥10% if insulin treated (see https://www.diabetesgenes.org/exeter-diabetes-app/ModyCalculator)

2. **Syndromic diabetes:** Patients with diabetes **AND** non-autoimmune extra-pancreatic features

- Diabetes diagnosed young

AND

- Unlikely to have type 1 diabetes (see 1b) or type 2 diabetes.

AND

- Non-autoimmune extra pancreatic features suggestive of syndromic monogenic diabetes
  e.g.
  - Cystic renal disease and/or congenital anomaly of kidney or urinary tract
  - Bilateral sensorineural deafness
  - Developmental delay
  - Developmental defects
  - Cardiomyopathy
  - Optic atrophy
  - Microcephaly

3. **Diabetes with severe insulin resistance**

- Patients have features of severe insulin resistance in the absence of obesity:
  - Acanthosis nigricans
    OR
  - A fasting insulin ≥150pmol/l if not insulin treated **OR** if insulin treated an insulin requirement >3U/kg/day

AND

- Diabetes that is unlikely to be type 1 diabetes (see 1.0 above) or type 2 diabetes (BMI<30kg/m^2 if white (<95th in children) or BMI <27kg/m^2 (<95th in children) if high prevalence type 2 diabetes group).

Overlapping indications

- R158 Lipodystrophy – childhood onset test should be used for congenital severe syndromic forms of lipodystrophy
- R142 Glucokinase-related fasting hyperglycaemia test should be used for asymptomatic fasting hyperglycaemia

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; HbA1C testing is required prior to genetic testing

Requesting Specialties

- Clinical Genetics
- Endocrinology
- Nephrology

Specialist Service Group

- Endocrinology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R141.1	Monogenic diabetes WES or medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Monogenic diabetes (472)	WES or Medium Panel

R142 Glucokinase-related fasting hyperglycaemia

Testing Criteria

Fasting glucose noted to be raised ≤35 years

AND

Asymptomatic stable fasting hyperglycaemia (5.5-8mmol/L) (minimum 2 independent laboratory fasting blood glucose test results)

OR

HbA1c 36-58mmol/mol (5.5-7.5%)

In pregnancy

a) Gestational diabetes with fasting glucose 5.5-8mmol/l.

AND

b) BMI <30kg/m^2 if white, or BMI <27kg/m^2, if high prevalence type 2 diabetes ethnic group.

Features that support a diagnosis in pregnancy: persistent fasting hyperglycaemia post pregnancy or previous babies with normal birthweight despite maternal hyperglycaemia.

HbA1c and fasting glucose results must be available prior to genetic testing.

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

HbA1C and fasting glucose results must be available prior to genetic testing

Requesting Specialties

- Clinical Genetics
- Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R142.1	GCK Single gene sequencing	Singleton	Small variants	Single gene(s)	GCK (1338)	Single gene sequencing >=10 amplicons

R143 Neonatal diabetes

Testing Criteria

All patients diagnosed with diabetes diagnosed less than 9 months of age

Marked hyperglycaemia is common in very preterm patients due to an immature pancreas. These individuals should be referred for genetic testing only if hyperglycaemia requiring insulin treatment is still present at 32 weeks equivalent gestational age.

Where possible, clinicians are asked to submit samples from the probands parents for the DNA to be stored (R346) to allow follow-up of variants

Order of testing

Start with treatment response screen for sulphonylurea-sensitive genes by using R143.1

Continue to panel test if negative

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
- Endocrinology
- Genomics laboratory
- Neonatology

Specialist Service Group

- Endocrinology

Associated Tests

Please note all the tests below will be undertaken for R143 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R143.1	ABCC8; KCNJ11	Singleton	Small variants	Small panel	ABCC8; KCNJ11 (1369)	Small panel
R143.3	6q24 Methylation testing	Singleton	Methylation	Single interval	6q24	Methylation testing
R143.4	Diabetes - neonatal onset WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants	Panel of genes or loci	Diabetes - neonatal onset (293)	WGS

R145 Congenital hypothyroidism

Testing Criteria

1. Congenital hypothyroidism, thyroid hypoplasia or agenesis with or without syndromic features, OR
2. Thyroid dyshormonogenesis, OR
3. Raised serum thyroid stimulating hormone (TSH) level:
    a. With enlarged thyroid gland, OR
    b. In the absence of thyroid autoantibodies

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
- Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R145.1	Congenital hypothyroidism WES or Medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Congenital hypothyroidism (31)	WES or Medium panel

R329 Familial dysalbuminaemic hyperthyroxinaemia

Testing Criteria

Raised serum T4 with inappropriately non-suppressed serum TSH

[Attempt to exclude assay interference as a cause of the abnormal TFT result prior to genetic test]

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
- Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R329.1	ALB Single gene sequencing	Singleton	Small variants	Single gene(s)	ALB (1333)	Single gene sequencing >=10 amplicons

R182 Hyperthyroidism

Testing Criteria

Hyperthyroidism where common causes have been excluded:

1. Clinical exclusion of common causes such as toxic solitary nodules or multinodular goitre, AND
2. Graves disease excluded by negative TSH receptor autoantibodies when the patient is biochemically hyperthyroid, AND
3. Patient presenting below the age of 18 OR patient has a first degree relative with unexplained hyperthyroidism

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
- Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R182.1	Hyperthyroidism Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Hyperthyroidism (236)	Small panel

R146 Differences in sex development

Testing Criteria

XX or XY chromosomal sex is confirmed AND one of:

1. Ambiguous genitalia
2. Evidence of gonadal dysgenesis
3. Clinical symptoms of adrenal hypoplasia
4. Under virilisation in an individual assigned male at birth
5. Virilisation in an individual assigned female at birth
6. Urine steroid profile suggestive of DSD
7. Pubertal failure
8. Precocious puberty
9. Primary amenorrhea
10. Very early onset hypertension with evidence of pubertal or electrolyte disturbance

NOTE: Panel testing may be appropriate in patients with abnormal sex chromosome karyotypes, if on expert review the karyotype result is not thought to explain the DSD phenotype

NOTE: The common Congenital Adrenal Hyperplasia (CAH) gene CYP21A2 is too complex to examine using a next generation sequencing test under this indication. If a diagnosis of CAH due to 21-hydroxylase deficiency is suspected please request additional testing (see overlapping indications)

Overlapping indications

- R314 Ambiguous genitalia presenting neonatally should be used to establish karyotypic sex in urgent neonatal situations
- R180 Congenital adrenal hyperplasia diagnostic test should be used before the panel test where CAH is the likely diagnosis; the common CAH gene CYP21A2 is too complex to examine using a next generation sequencing test under this indication
- R297: Possible structural chromosomal rearrangement – karyotype may be required to identify structural sex chromosome abnormalities which might not be detected via common aneuploidy testing

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

After urgent neonatal testing is complete where indicated, in the absence of a diagnosis; at presentation for non-neonatal situations

Requesting Specialties

- Clinical Genetics
- Endocrinology
- Gynaecology

Specialist Service Group

- Endocrinology

Associated Tests

Please note all the tests below will be undertaken for R146 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R146.1	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray
R146.2	Differences in sex development WES or medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Differences in sex development (9)	WES or Medium Panel

.

R452 Silver Russell Syndrome and Temple Syndrome

Testing Criteria

Clinical features strongly indicative of a diagnosis of Silver-Russell syndrome, as assessed by the presence of 3 or more of the features below*:

1. Small Gestational Age (birth weight and/or birth length): ≤−2 standard deviation score (SDS) for gestational age
2. Postnatal growth failure: Height at 24 ± 1 months ≤−2 SDS or height ≤−2 SDS below mid-parental target height
3. Relative macrocephaly at birth: Head circumference at birth ≥1.5 SDS above birth weight and/or length
4. Protruding forehead: Forehead projecting beyond the facial plane on a side view as a toddler (1–3 years)
5. Body asymmetry: Leg length discrepancy of ≥0.5 cm or arm asymmetry or leg length discrepancy <0.5 cm with at least two other asymmetrical body parts (one non-face)
6. Feeding difficulties and/or low BMI: BMI ≤−2 standard deviations at 24 months or current use of a feeding tube or cyproheptadine for appetite stimulation

   *See Wakeling et al 2017, PMID: 27585961

OR

Clinical features suggestive or Temple Syndrome

Overlaping indications

- R88 Severe microcephaly test should be used for patients with primary microcephaly – microcephalic dwarfism spectrum.
- R159 Pituitary hormone deficiency test should be used where more than one pituitary hormone is deficient as the cause of growth failure
- R104 Skeletal dysplasia should be considered if overlapping features are present and should be used where clinical features indicative of a likely monogenic skeletal dysplasia
- R52 Short stature – SHOX deficiency – where clinical features are strongly indicative of SHOX deficiency
- R453 Monogenic short stature – if the primary clinical presentation is short stature and not skeletal dysplasia or a more complex paediatric syndromic disorder
- R27 Paediatric Disorders if the presentation appears syndromic
- R26 Likely common aneuploidy for suspected Turner Syndrome

Where in Pathway

At presentation,.

Requesting Specialties

- Clinical Genetics
- Endocrinology
- Paediatrics

Specialist Service Group

- Endocrinology

Associated Tests

Please note: the methylation-sensitive MLPA assay commonly used for this clinical indication includes probes for the chromosome 7 and chromosome 11 loci associated with Silver-Russell syndrome as well as loci on chromosome 14 associated with Temple syndrome.

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R452.1	Silver Russell Syndrome and Temple Syndrome	Singleton	CNVs and methylation status	Single interval	11p15 imprinted growth regulatory region and UPD7 and UPD14 growth regulatory critical regions	Methylation testing

R453 Monogenic short stature

Testing Criteria

1. Height < -3 Standard Deviation Scores (SDS) below the mean at the age of at least 2 years,

- in the absence of microcephaly AND
- with a normal short stature screen (but no requirement for normal dynamic growth hormone test)

OR

2. Height -2 to -3 SDS below the mean at the age of at least 2 years,

- in the absence of microcephaly AND
- with a normal short stature screen (but no requirement for normal dynamic growth hormone test) AND
- height 3 centiles below mid parental centile AND
- following discussion at a specialist MDT that includes paediatric endocrinology and clinical genetics.

Testing may occasionally be appropriate outside of the above criteria following clinical agreement at a specialist MDT that includes paediatric endocrinology and clinical genetics.

The reason for testing outside of this criteria must be discussed and agreed with the testing laboratory prior to sending samples and discussing with the patient/family.

Overlapping indications

- R452 Silver Russell Syndrome and Temple Syndrome
- R88 Severe microcephaly – if the presentation includes severe microcephaly
- R27 Paediatric disorders – if the presentation appears syndromic
- R52 Short stature – SHOX deficiency
- R104 Skeletal dysplasia – if there is disproportion or a skeletal survey suggestive of primary bone pathology (outside of the SHOX remit)
- R26 Likely common aneuploidy for suspected Turner Syndrome

Where in Pathway

At presentation,.

Requesting Specialties

- Clinical Genetics
- Endocrinology
- Paediatrics

Specialist Service Group

- Endocrinology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R453.1	Monogenic short stature	Singleton	Small variants, CNVs	Panel of genes or loci	TBC	WES or Medium panel

R49 Beckwith-Wiedemann syndrome

Testing Criteria

Clinical features suggestive of Beckwith-Wiedemann syndrome defined as:

1. One or more cardinal feature, OR
2. Two or more suggestive features

Cardinal features

- Macroglossia*
- Exomphalos
- Lateralized overgrowth*
- Multifocal and/or bilateral Wilms tumour or nephroblastomatosis
- Hyperinsulinism (lasting >1 week and requiring escalated treatment)
- Pathology findings: adrenal cortex cytomegaly, placental mesenchymal dysplasia or pancreatic adenomatosis

Suggestive features:

- Birthweight >2 SDS above the mean
- Facial naevus simplex
- Polyhydramnios and/or placentomegaly
- Ear creases and/or pits
- Transient hypoglycaemia (lasting <1 week)
- Typical Beckwith–Wiedemann spectrum tumours (neuroblastoma, rhabdomyosarcoma, unilateral Wilms tumour, hepatoblastoma, adrenocortical carcinoma or phaeochromocytoma)
- Nephromegaly and/or hepatomegaly
- Umbilical hernia and/or diastasis recti

*See Brioude et al 2018, PMID: 29377879

Overlapping indications

- R27 Paediatric disorders test should be used for overgrowth syndromes where Beckwith-Wiedemann syndrome is unlikely
- R50 Isolated hemihypertrophy or macroglossia test should be used where those features are present in isolation
- R263 Confirmation of uniparental disomy test should be used to confirm likely UPD detected on methylation and copy number testing

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, in parallel with renal ultrasound scan to look for Wilms tumour or Wilms precursor lesions and referral for Clinical Genetics consultation.

Requesting Specialties

- Cancer
- Clinical Genetics
- Endocrinology
- Neonatology
- Paediatrics

Specialist Service Group

- Endocrinology

Associated Tests

Please note all the tests below will be undertaken for R49 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R49.1	11p15 imprinted growth regulatory region Methylation testing	Singleton	Methylation	Single interval	11p15 imprinted growth regulatory region	Methylation testing
R49.2	11p15 imprinted growth regulatory region MLPA or equivalent	Singleton	CNVs	Single interval	11p15 imprinted growth regulatory region	MLPA or equivalent
R49.3	CDKN1C Single gene sequencing	Singleton	Small variants	Single gene(s)	CDKN1C (1309)	Single gene sequencing >=10 amplicons

R50 Isolated hemihypertrophy or macroglossia

Testing Criteria

Isolated hemihypertrophy, OR

Isolated macroglossia

Overlapping indications

- R49 Beckwith-Wiedemann syndrome test should be used where additional features suggestive of Beckwith-Wiedemann syndrome are present
- R452 Silver Russell Syndrome and Temple Syndrome test should be used where additional features suggestive of Silver-Russell syndrome are present
- R26 Likely common aneuploidy test should be used where macroglossia occurs in the presence of features suggestive of Down syndrome
- R27 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with complex or syndromic presentations not suggestive of Beckwith-Wiedemann syndrome, Silver-Russell syndrome or Down syndrome.
- R263 Confirmation of uniparental disomy test should be used to confirm likely UPD detected on methylation and copy number testing

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, in parallel with renal ultrasound scan to look for Wilms tumour or Wilms precursor lesions and referral for Clinical Genetics consultation

Requesting Specialties

- Clinical Genetics
- Paediatrics

Specialist Service Group

- Endocrinology

Associated Tests

Please note all the tests below will be undertaken for R50 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R50.1	11p15 imprinted growth regulatory region Methylation testing	Singleton	Methylation	Single interval	11p15 imprinted growth regulatory region	Methylation testing
R50.2	11p15 imprinted growth regulatory region MLPA or equivalent	Singleton	CNVs	Single interval	11p15 imprinted growth regulatory region	MLPA or equivalent

R267 Temple syndrome – maternal uniparental disomy 14

Testing Criteria

1. Clinical features suggestive of Temple syndrome, OR
2. Molecular findings indicative of UPD 14 in which methylation analysis is required to differentiate maternal UPD 14 from paternal UPD 14

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

Specialist Service Group

- Endocrinology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R267.1	UPD14 critical region Methylation testing	Singleton	Methylation	Single interval	UPD14 critical region	Methylation testing

R268 Kagami-Ogata syndrome – paternal uniparental disomy 14

Testing Criteria

1. Clinical features suggestive of Kagami-Ogata syndrome (paternal UPD14), OR
2. Molecular findings indicative of UPD 14 in which methylation analysis is required to differentiate paternal UPD 14 from maternal UPD 14

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

Specialist Service Group

- Endocrinology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R268.1	UPD14 critical region Methylation testing	Singleton	Methylation	Single interval	UPD14 critical region	Methylation testing

R149 Severe early-onset obesity

Testing Criteria

BMI more than 3 standard deviations above the mean, with onset before the age of 5 years, in the absence of significant syndromic features, and with no explanation

Overlapping indications

- R27 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

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
- Endocrinology
- Paediatrics

Specialist Service Group

- Endocrinology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R149.1	Severe early-onset obesity WES or Medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Severe early-onset obesity (130)	WES or Medium panel

R150 Congenital adrenal hypoplasia

Testing Criteria

Adrenal insufficiency as defined below, with no evidence of autoimmune Addisons disease, no biochemical evidence of congenital adrenal hyperplasia, and no other identifiable cause:

1. Combined primary glucocorticoid and mineralocorticoid insufficiency, OR
2. Isolated primary glucocorticoid insufficiency, OR
3. Isolated primary mineralocorticoid insufficiency

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
- Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R150.1	Congenital adrenal hypoplasia Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Congenital adrenal hypoplasia (145)	Small panel

R180 Congenital adrenal hyperplasia diagnostic test

Testing Criteria

Biochemically diagnosed Congenital Adrenal Hyperplasia (CAH) and at least one of the following:

1. Ambiguous genitalia or virilisation in an infant assigned female at birth, OR
2. Precocious puberty, OR
3. Accelerated pre-pubertal growth childhood with advanced bone age and evidence of adrenal steroid abnormality, OR
4. Salt-losing crisis in the neonatal period, OR
5. Infant electrolyte disturbance

Overlapping indications

- R314 Ambiguous genitalia presenting neonatally test may be required before or in parallel to establish the diagnosis, particularly in the neonatal setting
- R146 Differences in sex development test may be required after urgent neonatal testing if the diagnosis still isn't clear.

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
- Endocrinology
- Neonatology
- Paediatrics

Specialist Service Group

- Endocrinology

Associated Tests

Please note all the tests below will be undertaken for R180 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R180.1	CYP21A2 Single gene sequencing	Singleton	Small variants	Single gene(s)	CYP21A2 (1317)	Single gene sequencing >=10 amplicons
R180.2	CYP21A2 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	CYP21A2 (1317)	MLPA or equivalent

R388 Linkage testing for congenital adrenal hyperplasia

Testing Criteria

Families with a confirmed diagnosis of 21-hydroxylase congenital adrenal hyperplasia with no detectable variant in CYP21A2 who require linkage testing to guide management or advice

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

As appropriate

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Endocrinology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R388.1	CYP21A2 Linkage testing	Multiple affected individuals	Other	Single gene(s)	CYP21A2	Linkage Analysis

R181 Congenital adrenal hyperplasia carrier testing

Testing Criteria

Testing in partners of known carriers of CAH where management of a current or future pregnancy depends on the result

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 the time of reproductive planning

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Endocrinology

Associated Tests

Please note all the tests below will be undertaken for R181 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R181.1	CYP21A2 Targeted variant testing	Singleton	Small variants	Single gene(s)	CYP21A2	Targeted variant testing
R181.2	CYP21A2 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	CYP21A2	MLPA or equivalent

R183 Glucocorticoid-remediable aldosteronism (GRA)

Testing Criteria

Primary hyperaldosteronism with one of:

1. Presentation under the age of 30, OR
2. Family history of primary hyperaldosteronism or stroke below the age of 40

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
- Endocrinology
- Nephrology

Specialist Service Group

- Endocrinology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R183.1	CYP11B1/CYP11B2 gene fusion Targeted variant testing	Singleton	Complex variant detection	Single interval	CYP11B1/CYP11B2 gene fusion	Targeted variant testing

R344 Primary hyperaldosteronism - KCNJ5

Testing Criteria

Primary hyperaldosteronism presenting under the age of 10 years

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
- Endocrinology
- Nephrology

Specialist Service Group

- Endocrinology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R344.1	KCNJ5 Single gene sequencing	Singleton	Small variants	Single gene(s)	KCNJ5 (1380)	Single gene sequencing <10 amplicons

R160 Primary pigmented nodular adrenocortical disease

Testing Criteria

Primary pigmented nodular adrenocortical disease, OR

Clinical diagnosis of ACTH-independent Cushing syndrome of unknown aetiology.

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
- Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R160.1	Primary pigmented nodular adrenocortical disease Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Primary pigmented nodular adrenocortical disease (566)	Small panel

R293 Albright hereditary osteodystrophy, pseudohypoparathyroidism pseudopseudohypoparathyroidism, acrodysostosis and osteoma cutis

Testing Criteria

Individuals with a clear clinical diagnosis of Albright hereditary osteodystrophy, pseudohypoparathyroidism or pseudopseudohypoparathyroidism, acrodysostosis and osteoma cutis based on clinical, radiological and/or biochemical assessment

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
- Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

Please note all the tests below will be undertaken for R293 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R293.1	Albright hereditary osteodystrophy, pseudohypoparathyroidism pseudopseudohypoparathyroidism, acrodysostosis and osteoma cutis Small panel	Singleton	Small variants, CNV	Panel of genes or loci	Albright hereditary osteodystrophy, pseudohypoparathyroidism pseudopseudohypoparathyroidism, acrodysostosis and osteoma cutis (1209)	Small panel
R293.2	GNAS DMRs Methylation testing	Singleton	Methylation	Single interval	GNAS DMRs	Methylation testing
R293.3	STX16 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	STX16	MLPA or equivalent

R151 Familial hyperparathyroidism or Hypocalciuric hypercalcaemia

Testing Criteria

Familial Primary Hyperparathyroidism

i) <50y,

OR

ii) any age with

a) a confirmed or relevant family history, OR

b) multiglandular disease or hyperplasia in the presence of relevant family history, OR

c) parathyroid carcinoma or atypical or cystic adenoma, OR

d) ossifying fibroma(s) of the maxilla and /or mandible.

Hypocalciuric hypercalcaemia

Hypercalcaemia with hypocalciuria (calcium clearance: creatinine clearance ratio <0.02), usually with normal PTH

Overlapping indications

- R319 Calcium-sensing receptor phenotypes single gene test should be considered in neonatal hyperparathyroidism
- R217 and R218 Multiple endocrine neoplasia indications should be used where there are features of multiple endocrine neoplasia including hypercalcaemia
- R226 parathyroid carcinoma should be used for individuals with confirmed parathyroid carcinoma

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
- Endocrinology
- Surgery (head/neck/endocrine)
- Oncology

Specialist Service Group

- Endocrinology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R151.1	Familial hyperparathyroidism or Hypocalciuric hypercalcaemia Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Familial hyperparathyroidism or Hypocalciuric hypercalcaemia (480)	Small panel

R153 Familial hypoparathyroidism

Testing Criteria

Non-syndromic hypoparathyroidism with low calcium levels and low or inappropriately normal serum PTH, with no detectable cause

Testing of patients who are normocalcaemic may occasionally be appropriate after consultation with an expert in calcium homeostasis

Overlapping indications

- R293 Albright hereditary osteodystrophy, pseudohypoparathyroidism and pseudopseudohypoparathyroidism test should be used where there is high clinical suspicion of one of these diagnoses

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
- Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R153.1	Familial hypoparathyroidism Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Familial hypoparathyroidism (312)	Small panel

R154 Hypophosphataemia or rickets

Testing Criteria

Hypophosphataemia with no identifiable cause, with evidence of decreased renal phosphate reabsorption, which has or could lead to presentation with rickets

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
- Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R154.1	Hypophosphataemia or rickets Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Hypophosphataemia or rickets (482)	Small panel

R319 Calcium-sensing receptor phenotypes

Testing Criteria

1. Neonatal hyperparathyroidism, OR
2. Likely clinical diagnosis of autosomal dominant hypocalcaemia with hypercalciuria

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
- Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R319.1	CASR Single gene sequencing	Singleton	Small variants	Single gene(s)	CASR (1312)	Single gene sequencing >=10 amplicons

R157 IPEX - Immunodysregulation Polyendocrinopathy and Enteropathy, X-Linked

Testing Criteria

Males with type 1 diabetes mellitus in early infancy or childhood, AND ANY TWO of the features below, OR

Males with absent regulatory T cells, AND ONE of the features below:

- Hypothyroidism
- Severe enteropathy
- Eczema
- Autoimmune cytopenias
- One of the above 4 features plus a family history compatible with X-linked inheritance

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
- Endocrinology
- Gastroenterology
- Immunology

Specialist Service Group

- Endocrinology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R157.1	FOXP3 Single gene sequencing	Singleton	Small variants	Single gene(s)	FOXP3 (1350)	Single gene sequencing >=10 amplicons

R156 Carney complex

Testing Criteria

Two or more of the features from the list below (with histological confirmation where relevant), OR

One feature from the list below (with histological confirmation where relevant) and an affected first degree relative:

- Spotty skin pigmentation with typical distribution (lips, conjunctiva, vaginal and penile mucosa)
- Myxoma (cutaneous and mucosal)
- Cardiac myxomas
- Breast myxomatosis or fat-suppressed MRI suggestive of this finding
- PPNAD or paradoxical positive response of urinary glucocorticosteroid excretion to dexamethasone administration during Liddles test
- Acromegaly due to GH-producing adenoma
- Large cell calcifying Sertoli cell tumour (LDDST) or characteristic calcification on testicular ultrasound
- Thyroid carcinoma or multiple, hypoechoic nodules on thyroid ultrasound in a young patient
- Psammomatous melanotic schwannomas (PMS)
- Blue nevus, epithelioid blue nevus
- Breast ductal adenoma
- Osteochondromyxoma

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
- Dermatology
- Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R156.1	PRKAR1A Single gene sequencing	Singleton	Small variants	Single gene(s)	PRKAR1A (1313)	Single gene sequencing >=10 amplicons

R148 Hypogonadotropic hypogonadism

Testing Criteria

Hypogonadotropic hypogonadism (absent or incomplete puberty with low LH/FSH in the context of low testosterone/oestradiol), with or without anosmia, with no detectable cause

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
- Endocrinology
- Gynaecology

Specialist Service Group

- Endocrinology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R148.1	Hypogonadotropic hypogonadism Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Hypogonadotropic hypogonadism idiopathic (650)	Small panel

R159 Pituitary hormone deficiency

Testing Criteria

Biochemical evidence of deficiency of at least two pituitary hormones of neonatal or childhood onset.

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
- Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R159.1	Pituitary hormone deficiency WES or Medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Pituitary hormone deficiency (483)	WES or Medium panel

R217 Endocrine neoplasia

Testing Criteria

Testing of individual (proband) affected with endocrine abnormalities where the individual +/- family history meets one of the following criteria:

1. Multiple endocrine neoplasia type 1 (MEN1). The proband has:
   a. Parathyroid multiglandular disease (hyperplasia/ adenomas) (<35 years), OR
   b. Any pituitary adenoma or insulinoma (< 20years), OR
   c. Pituitary macroadenoma (<30 years), OR
   d. ≥2 MEN1-related endocrine abnormalities (any age), OR
   e. ≥1 MEN1-related endocrine abnormality and ≥1 MEN1-related non-endocrine tumours (any age), OR
   f. ≥1 MEN1-related endocrine abnormality and a first degree relative has ≥1 MEN1-related endocrine abnormality

   MEN1-related endocrine abnormalities include:
   - Parathyroid hyperplasia/multiglandular adenomas
   - Pituitary tumors
   - Endocrine tumors of the gastro-entero-pancreatic (GEP) tract
   - Carcinoid tumors
   - Adrenocortical tumors

   MEN1-related non-endocrine tumours include:
   - facial angiofibromas
   - collagenomas
   - meningioma

2. Familial isolated pituitary adenoma (FIPA)

- Isolated pituitary adenoma developing under the age of 35, with at least one first degree relative with an isolated pituitary adenoma

3. X-linked acrogigantism

- Onset of excess of growth hormone diagnosed by age 20 years in male patients, with increased growth velocity and/or tall stature (height >2 standard deviations above the mean, or >3 standard deviations over mid-parental height)
- If testing on blood is negative and clinical suspicion of this diagnosis is strong, please contact the testing laboratory to discuss sending a fresh frozen tissue or skin biopsy sample to identify a mosaic form of the condition

NOTE: All cancers should be histologically confirmed

Where a patient doesn't meet the stated criteria but there is strong clinical suspicion of a monogenic predisposition to endocrine neoplasia, testing can go ahead after discussion in a specialist MDT meeting

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
- Endocrinology
- Surgery (head/neck/endocrine)
- Oncology

Specialist Service Group

- Endocrinology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R217.1	Endocrine neoplasia Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Endocrine neoplasms (648)	Small panel

R223 Inherited phaeochromocytoma and paraganglioma excluding NF1

Testing Criteria

Testing of individual (proband) affected with cancer where the individual +/- family history meets one of the following criteria. The proband has:

1. Phaeochromocytoma <60 years, OR
2. Any paraganglioma OR metastatic phaeochromocytoma at any age, OR
3. Phaeochromocytoma / paraganglioma with loss of staining for SDH proteins on IHC, OR
4. Bilateral phaeochromocytoma (any age), OR
5. Phaeochromocytoma and renal cell carcinoma (any age), OR
6. Phaeochromocytoma / paraganglioma (any age) AND ≥1 relative (first / second / third degree relative) with phaeochromocytoma / paraganglioma / renal cell cancer (any age) / gastrointestinal stromal tumour

NOTE: The proband's cancer and majority of reported cancers in the family should have been confirmed

NOTE: Testing under this clinical indication does not include NF1

Overlapping indications

- R363 Inherited predisposition to GIST should be used where GIST is a prominent cancer type in the family
- M13 Phaeochromocytoma should be used for somatic testing

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
- Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R223.1	Inherited phaeochromocytoma and paraganglioma excluding NF1 Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Inherited phaeochromocytoma and paraganglioma excluding NF1 (649)	Small panel

R144 Congenital hyperinsulinism

Testing Criteria

Hypoglycaemia accompanied by one of the following, with no identifiable cause:

1. During an episode of hypoglycaemia there is a requirement for the glucose infusion to be at a rate of >8mg/kg/min, OR
2. Detectable serum insulin or c-peptide when the blood glucose is <3mmol/l, OR
3. Suppressed or undetectable serum fatty acids and ketone bodies

Where possible, clinicians are asked to submit samples from the probands parents for the DNA to be stored (R346) to allow follow-up of variants

Order of testing

- Start with ABCC8 and KCNJ11 single gene tests to determine surgical management
- Continue to panel test if negative

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
- Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

Please note all the tests below will be undertaken for R144 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R144.1	ABCC8; KCNJ11	Singleton	Small variants,	Small panel	ABCC8; KCNJ11	Small panel
R144.2	Congenital hyperinsulinism Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Congenital hyperinsulinism (308)	Small panel

R158 Lipodystrophy - childhood onset

Testing Criteria

Individuals with a clinical diagnosis of childhood onset lipodystrophy, with features likely to include lipoatrophy affecting the trunk, limbs and face, acromegaloid features, progeroid features, hepatomegaly, elevated serum triglycerides and severe insulin resistance with early development of diabetes,

AND

Acquired causes have been excluded

OR

Individuals with the following features of severe insulin resistance:

• Acanthosis nigricans

OR

• A fasting insulin >150pmol/l if not insulin treated OR if insulin treated an insulin requirement >3U/kg/day

AND

Are not obese (BMI <30kg/m2 if white (<95th centile for weight in children) or BMI <27kg/m2 (<95th centile for weight in children) if high prevalence type 2 diabetes group).

Overlapping indications

- R141 Monogenic diabetes test should be used for adult onset lipodystrophy with insulin resistance or diabetes
- R27 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

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
- Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R158.1	Lipodystrophy childhood onset	Singleton	Small variants, CNVs	Panel of genes or loci	Lipodystrophy - childhood onset (546)	Small panel

R218 Multiple endocrine neoplasia type 2

Testing Criteria

Testing of individual (proband) affected with endocrine abnormalities where the individual +/- family history meets one of the following criteria. The proband has:

1. MTC (any age), OR
2. ≥2 MEN2-related endocrine abnormalities (any age), OR
3. ≥1 MEN2-related endocrine abnormality and a first degree relative with ≥1 MEN2-related endocrine abnormality

MEN2-related endocrine abnormalities include: Medullary Thyroid Carcinoma (MTC), Phaechromocytoma/paraganglioma, Parathyroid adenoma/hyperplasia, Hirschprungs disease

NOTE: The proband's cancer and majority of reported cancers in the family should have been confirmed

Overlapping indications

- R217 Endocrine neoplasia test should be used where a broader presentation is under investigation

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
- Endocrinology
- Surgery (head/neck/endocrine)
- Oncology

Specialist Service Group

- Endocrinology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R218.1	RET Single gene sequencing	Singleton	Small variants	Single gene(s)	RET (1366)	Single gene sequencing >=10 amplicons

R226 Inherited parathyroid cancer

Testing Criteria

Testing of individual (proband) affected with parathyroid carcinoma

NOTE: The probands tumour and majority of reported tumours in the family should have been confirmed

Overlapping indications

- R151 Familial hyperparathyroidism test should be used where benign forms of hyperparathyroidism are under investigation

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
- Endocrinology
- Surgery (head/neck/endocrine)
- Oncology

Specialist Service Group

- Endocrinology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R226.1	CDC73 Single gene sequencing	Singleton	Small variants	Single gene(s)	CDC73 (1348)	Single gene sequencing >=10 amplicons

R162 Familial tumoral calcinosis

Testing Criteria

Individuals with a diagnosis of familial tumoral calcinosis, with or without hyperphosphataemia

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
- Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R162.1	Familial tumoral calcinosis Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Familial tumoral calcinosis (552)	Small panel

R417 Multi Locus Imprinting Disorder (MLID)

Testing Criteria

R417.1

A positive molecular diagnosis of an imprinting disorder resulting from, an imprinting disturbance (eg. Beckwith Wiedemann syndrome due to hypomethylation of KCNQ1OT1TSS-DMR (IC2) or Silver-Russell syndrome due to hypomethylation of H19-IGF2 IG-DMR (IC1), but not an imprinting disorder caused by a copy number variant or uniparental disomy

MILD testing may occasionally be appropriate in patients in whom an imprinting disorder is suspected, after expert clinical examination and discussion with Clinical Genetics, but where standard of care testing has not confirmed a molecular diagnosis.

R417.2

A positive molecular diagnosis of MLID: i.e. imprinting disturbance involving two or more imprinted loci. Sequencing must be performed on the proband and maternal sample for genes in panel R417.2.

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.

Overlapping indications

- R143 Neonatal diabetes (ZFP57)

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Endocrinology
- Paediatrics
- Genomics Laboratory

Specialist Service Group

- Endocrinology

Associated Tests

Please note all the tests below will be undertaken for R417 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R417.1	Multi Locus Imprinting Disorder MLPA	Singleton	Methylation	Panel of genes or loci	genes on chromosomes: 6, 7, 11, 14, 15, 19, 20. (PLAGL1, GRB10, MEST, H19, KCNQ1, GTL2, SNRPN, PEG3, GNAS)	MS-MLPA
R417.2	Multi Locus Imprinting Disorder Small panel	Singleton	Small variants	Panel of genes or loci	Multi locus imprinting disorders (1109)	Small panel

R440 Hereditary isolated diabetes insipidus

Testing Criteria

1. Biochemical features consistent with a diagnosis of diabetes insipidus (relevant biochemistry results and results of DDAVP testing, where appropriate, should be provided on the test request form to aid interpretation of the genetic results) AND
2. Exclusion of acquired causes of diabetes insipidus including primary polydipsia, trauma, malignancy, infection, autoimmune disease, drugs (eg. antibiotics, antifungals and antiviral agents)

Overlapping indications

- R198 Renal tubulopathies

Where in Pathway

At presentation

Requesting Specialties

- Nephrology
- Clinical Genetics

  Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R440.1	Hereditary isolated diabetes Insipidus small panel	Singleton	Small variants, CNVs	Panel of genes or loci	AVP, AVPR2, AQP2	Small panel

Part V. Ophthalmology

R107 Bardet Biedl syndrome

Testing Criteria

Clinical features strongly indicative of a diagnosis of Bardet-Biedl syndrome including four or more primary features or three primary features and two or more secondary features:

1. Primary features:
    a. Retinal dystrophy
    b. Renal abnormalities
    c. Obesity
    d. Polydactyly
    e. Learning difficulties
    f. Hypogonadism in an individual assigned male at birth
2. Secondary features:
    a. Speech disorder/delay
    b. Strabismus/cataracts/astigmatism
    c. Brachydactyly/syndactyly
    d. Developmental delay
    e. Polyuria/polydipsia
    f. Ataxia/poor coordination/imbalance

Overlapping indications

- R27 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with overlapping or atypical presentations where features are not characteristic of Bardet-Biedl syndrome specifically

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
- Nephrology
- Ophthalmology

Specialist Service Group

- Ophthalmology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R107.1	Bardet Biedl syndrome WES or large panel	Singleton	Small variants, CNVs	Panel of genes or loci	Bardet Biedl syndrome (543)	WES or Large Panel

R31 Bilateral congenital or childhood onset cataracts

Testing Criteria

Unexplained bilateral congenital or childhood onset cataracts

Overlapping indications

- R36 Structural eye disease test should be used in individuals with cataract in the context of microphthalmia or other structural eye disease
- R27 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

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, after urine reducing substances

Where additional features are strongly suggestive of congenital infection, a TORCH screen should be performed before testing

Requesting Specialties

- Clinical Genetics
- Ophthalmology

Specialist Service Group

- Ophthalmology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R31.3	Bilateral congenital or childhood onset cataracts WGS (phase 2)	Trio or singleton	Exon level CNVs, Small variants	Panel of genes or loci	Bilateral congenital or childhood onset Cataracts (230)	WGS

R32 Retinal disorders

Testing Criteria

Unexplained retinal disease that is likely to be monogenic

Overlapping indications

- R27 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations
- R33 X-linked retinitis pigmentosa test should be used where features are consistent with X-linked retinitis pigmentosa

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 assessment by a Consultant Ophthalmologist expert in inherited eye disease

Requesting Specialties

- Clinical Genetics
- Ophthalmology

Specialist Service Group

- Ophthalmology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R32.2	Retinal disorders WGS (phase 2)	Trio or singleton	Exon level CNVs, Small variants	Panel of genes or loci	Retinal disorders (307)	WGS

R33 Possible X-linked retinitis pigmentosa

Testing Criteria

Unexplained retinal disease with features consistent with X-linked retinitis pigmentosa in whom variants at RPGR exon ORF15 have not been excluded

Order of testing

- RPGR exon ORF15 to be analysed first and if uninformative, consider R32 WGS

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 assessment by a Consultant Ophthalmologist expert in inherited eye disease

Requesting Specialties

- Clinical Genetics
- Ophthalmology

Specialist Service Group

- Ophthalmology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R33.1	RPGR exon ORF15 Targeted variant testing	Singleton	Small variants	Single interval	RPGR exon ORF15	Targeted variant testing

R36 Structural eye disease

Testing Criteria

1. Microphthalmia or anophthalmia or uveoretinal coloboma where there is evidence to support a likely monogenic cause, for example bilateral disease, consanguinity or additional ocular and non-ocular features, OR
2. Unilateral or bilateral congenital / developmental glaucoma, OR
3. Bilateral developmental glaucoma or anterior segment malformation, except where there is evidence of a non-genetic cause, OR
4. Aniridia with family history

Overlapping indications

- R27 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations
- R38 Sporadic aniridia test should be used instead for sporadic classical aniridia

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 assessment by a Consultant Ophthalmologist. Cases with multiple malformations or syndromic features should have been discussed with a Consultant Clinical Geneticist.

Requesting Specialties

- Clinical Genetics
- Ophthalmology

Specialist Service Group

- Ophthalmology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R36.2	Structural eye disease WGS (phase 2)	Trio or singleton	Exon level CNVs, Small variants	Panel of genes or loci	Structural eye disease (509)	WGS

R38 Sporadic aniridia

Testing Criteria

Sporadic classical bilateral aniridia including those with features suggestive of WAGR syndrome.

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

- Oncology
- Clinical Genetics
- Ophthalmology
- Paediatrics

Specialist Service Group

- Ophthalmology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R38.2	Sporadic aniridia Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Sporadic aniridia (510)	Small panel

R39 Albinism or congenital nystagmus

Testing Criteria

1. Albinism or generalised cutaneous hypopigmentation with or without ocular involvement, OR
2. Unexplained congenital nystagmus without a causative lesion on MRI brain

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 assessment by a Consultant Ophthalmologist (for ophthalmic presentations)

Requesting Specialties

- Clinical Genetics
- Dermatology
- Ophthalmology

Specialist Service Group

- Ophthalmology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R39.1	Albinism or congenital nystagmus WES or Medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Albinism or congenital nystagmus (511)	WES or Medium panel

R41 Optic neuropathy

Testing Criteria

Unexplained optic neuropathy

Overlapping indications

- R42 Leber hereditary optic neuropathy test should be used where clinical features are consistent with Leber hereditary optic neuropathy

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 expert by a Consultant Ophthalmologist

Requesting Specialties

- Clinical Genetics
- Ophthalmology

Specialist Service Group

- Ophthalmology

Associated Tests

Please note all the tests below will be undertaken for R41 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R41.1	Optic neuropathy WES or Medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Optic neuropathy (186)	WES or Medium panel
R41.3	Optic neuropathy	Singleton	Targeted variant testing	Three common LHON variants	Three common LHON variants	Targeted variant testing

R43 Blepharophimosis ptosis and epicanthus inversus

Testing Criteria

Clinical features indicative of a likely clinical diagnosis of blepharohimosis, ptosis and epicanthus inversus syndrome (BPES) including the presence of all of the following: blepharophimosis, ptosis, epicanthus inversus AND telecanthus

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
- Ophthalmology

Specialist Service Group

- Ophthalmology

Associated Tests

Please note all the tests below will be undertaken for R43 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R43.1	FOXL2 Single gene sequencing	Singleton	Small variants	Single gene(s)	FOXL2 (1310)	Single gene sequencing <10 amplicons
R43.2	FOXL2 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	FOXL2 (1310)	MLPA or equivalent
R43.3	FOXL2 STR testing	Singleton	STRs	Single gene(s)	FOXL2 STR (1310)	STR testing

R46 Congenital fibrosis of the extraocular muscles

Testing Criteria

Individuals with a suspected clinical diagnosis of congenital fibrosis of the extraocular muscles

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
- Neurology
- Ophthalmology

Specialist Service Group

- Ophthalmology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R46.1	Congenital fibrosis of the extraocular muscles Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Congenital fibrosis of the extraocular muscles (512)	Small panel

R262 Corneal dystrophy

Testing Criteria

Corneal dystrophy of likely monogenic aetiology

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 assessment by a Consultant Ophthalmologist expert in inherited eye disease

Requesting Specialties

- Clinical Genetics
- Ophthalmology

Specialist Service Group

- Ophthalmology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R262.1	Corneal dystrophy WES or Medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Corneal dystrophies (658)	WES or Medium panel

R45 Stickler syndrome

Testing Criteria

Clinical features indicative of likely Stickler syndrome

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 and/or as part of clinical assessment for the Stickler Highly Specialised Service

Requesting Specialties

- Clinical Genetics
- Ophthalmology

Specialist Service Group

- Ophthalmology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R45.1	Stickler syndrome Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Stickler syndrome (3)	Small panel

R420 Pseudoxanthoma elasticum

Testing Criteria

Individuals who have characteristic features of Pseudoxanthoma elasticum:

- Papules or plaques on the skin of the neck and/or flexural creases (antecubital fossae, axillae, groin, or popliteal fossae) and/or calcified dystrophic elastic fibres on biopsied skin using a von Kossa or similar stain) AND/OR
- Retinal finding (angioid streaks, *peau d'orange*, or choroidal vascularization).

Overlapping indications

- R384 Generalised arterial calcification in infancy

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Ophthalmology

Specialist Service Group

- Ophthalmology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R420.1	Pseudoxanthoma elasticum	Singleton	Small variants, CNVs	Panel of genes or loci	ABCC6, ENPP1 (1381)	Small panel

Part VI. Fetal (including NIPD)

R401 Common aneuploidy testing - prenatal

Testing Criteria

Prenatal findings requiring common aneuploidy testing including:

1. abnormal first trimester combined screening, OR
2. characteristic findings of a common aneuploidy on ultrasound scan

Overlapping indications

- R22 Fetus with a likely chromosomal abnormality, OR
- R21 Fetus with a likely genetic cause

tests should be used where additional copy number of sequence analysis is required

Where in Pathway

N/A

Requesting Specialties

- Clinical Genetics
- Fetal Medicine
- Obstetrics

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R401.1	Genomewide Common aneuploidy testing – prenatal	Singleton	Aneuploidy	Genomewide	Genomewide	Common aneuploidy testing

R445 Common aneuploidy testing - NIPT

Testing Criteria

Any previous pregnancy with reported full trisomy of chromosomes 13, 18 or 21, meeting the following criteria:

Inclusion:

- From 10 weeks (gestational age confirmed by dating scan) and up to 21 weeks and 6 days (21+6) of pregnancy.
- Two attempts at NIPT per pregnancy can be offered.

Exclusion:

- Maternal cancer (unless in remission)
- Blood transfusion in the last 4 months (whole blood or plasma)
- Bone marrow or organ transplant recipient
- Vanished twin pregnancy (an empty second pregnancy sac or a second pregnancy sac containing non-viable fetus)
- Maternal T21
- Maternal balanced translocation or mosaicism of T21, T18 or T13
- Immunotherapy in the current pregnancy, excluding IVIg treatment
- Stem cell therapy
- Previous pregnancy was not a full trisomy (reciprocal translocation or partial trisomy)
- The current pregnancy was conceived using a donor egg (unless the egg for this pregnancy is from the same egg donor used in a previous pregnancy diagnosed with Down's, Edward's or Patau's syndrome)

Overlapping indications

- R401 Common aneuploidy testing – prenatal should be used where amniocentesis or Chorionic villus sampling (CVS) taken.

Where in Pathway

Samples to be taken by trained midwife or Clinical Genetics Unit and sent directly to the testing laboratory using the same sample referral routes as per the Fetal Anomaly Screening Programme.

Requesting Specialties

- Clinical Genetics
- Specialist Midwifery

Specialist Service Group

- Prenatal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R445.1	Common aneuploidy testing NIPT	Singleton	Aneuploidy	Chromosome 13, 18 and 21	Chromosomes 13, 18 and 21	NIPT

R318 Recurrent miscarriage with products of conception available for testing

Testing Criteria

Recurrent miscarriage with products of conception available for testing – defined as three or more miscarriages.

Overlapping indications

- R297 Possible structural chromosomal rearrangement - karyotype test may be used for parents of recurrent miscarriage in exceptional circumstances
- R22 Fetus with a likely chromosomal abnormality, should be used in:
  - cases of isolated miscarriage with additional features suggestive of chromosome abnormality
  - cases of third trimester intrauterine death or still birth in the absences of other likely causes
- R27 Paediatric disorders or R412 Fetal anomalies with a likely genetic cause - non urgent, should be used in cases of fetal anomaly with likely genetic cause

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
- Fetal Medicine
- Gynaecology
- Obstetrics

Specialist Service Group

- Core

Associated Tests

Please note all the tests below will be undertaken for R318 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R318.1	Genomewide Common aneuploidy testing - miscarriage	Singleton	Aneuploidy	Genomewide	Genomewide	Common aneuploidy testing
R318.2	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray

R22 Fetus with a likely chromosomal abnormality

Testing Criteria

This indication is relevant to:

- ongoing pregnancies OR
- where there has been fetal loss, termination of pregnancy or miscarriage, accompanied by additional features suggestive of chromosome abnormality OR
- third trimester intrauterine death or still birth in the absence of other likely causes

Overlapping indications

- R401 Common aneuploidy testing – prenatal or R26 Likely common aneuploidy should be used where only common aneuploidy testing is indicated
- R21 Fetal anomalies with a likely genetic cause test should be used where it is considered more appropriate and following discussion with a Clinical Geneticist
- R318 Recurrent miscarriage with products of conception available for testing can be used where there has been recurrent miscarriage in the absence of additional features suggestive of chromosomal abnormality
- R27 Paediatric disorders or R412 Fetal anomalies with a likely genetic cause - non urgent, should be used for non-urgent testing (e.g. where there is miscarriage, imminent fetal loss, or termination of pregnancy) in cases of fetal anomaly with likely genetic cause

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
- Fetal Medicine
- Pathology

Specialist Service Group

- Core

Associated Tests

Please note all the tests below will be undertaken for R22 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R22.1	Genomewide Common aneuploidy testing – prenatal	Singleton	Aneuploidy	Genomewide	Genomewide	Common aneuploidy testing
R22.2	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray

R21 Fetal anomalies with a likely genetic cause

Testing Criteria

For more detailed guidance for R21 outlined in the fetal whole exome service guidance documentation please contact your local Genomic Laboratory Hub.

Fetus with multiple major structural abnormalities detected on fetal ultrasound where multidisciplinary review to include clinical genetics, tertiary fetal medicine specialists, clinical scientists and, where appropriate, relevant paediatric specialists considers a monogenic malformation disorder is likely

This indication is relevant in ongoing pregnancies where a genetic diagnosis may influence management of the ongoing pregnancy and NOT where there is imminent fetal loss or termination of pregnancy, or miscarriage has already occurred

NOTE: This indication is for use when rapid/urgent testing is required. Please use R412 for non-urgent testing

Clinical examples

• Fetuses with multiple anomalies, suspected skeletal dysplasias (IUGR should be excluded), large echogenic kidneys with a normal bladder, major CNS abnormalities (excluding neural tube defects), multiple contractures (excluding isolated bilateral talipes).
• Nuchal translucency measured between 11 and 14 weeks gestation of greater than 6.5mm plus another anomaly (that can include a minor finding) with a normal array CGH
• Isolated non-immune fetal hydrops (detected at or after the routine 18-20-week scan in the second or third trimesters), defined as fluid/oedema in at least two compartments (e.g. skin, pleural, pericardial or ascites) with a normal array CGH
• Persistent nuchal translucency (>3.5mm) can only be considered in the presence of other structural abnormalities in two or more systems.
• Minor 'markers of aneuploidy' – choroid plexus cysts, echogenic foci, mild renal pelvis dilation, small nasal bone, long bones on 3rd centile etc are excluded.
• Mild ventriculomegaly should only be considered as an abnormality if the posterior horn is persistently >11mm on two or more scans. Under these circumstances it is not considered a major CNS abnormality in isolation
• Abnormality of the corpus callosum, either partial or complete agenesis – either in isolation or with other anomalies
• Pregnancies of consanguineous couples that do not strictly fulfil the above criteria, but where a monogenic disorder is considered likely
• Recurrences of particular fetal anomalies in pregnancies of the same couple that do not strictly fulfil the above criteria, but where a monogenic disorder is considered likely due to the recurrence. Neural tube defects excluded

The two criteria below can be considered as eligibility criteria alone or in association with other major abnormalities. Requests will not be actioned without having doppler evidence.

- Small for gestational age can be considered as eligible for R21 under the following circumstances; all measurements <3rd percentile with a confirmed early ultrasound estimated date of delivery (EDD) scan, including abdominal circumference (AC) and head circumference (HC), and no evidence of placental insufficiency including normal fetal and maternal dopplers, no history of previous FGR, PAPP-A (if measured) not low, no maternal history of SLE etc and no past obstetric history of FGR or still birth.
- Isolated short long bones can be considered as an abnormality and eligible for R21 under the following circumstances; all long bones <3rd percentile with a confirmed early ultrasound EDD, and HC and AC within normal limits, and no evidence of placental insufficiency including normal fetal and maternal dopplers, no history of previous IUGR, PAPP-A (if measured) not low, no maternal history of SLE etc and no past obstetric history of FGR or still birth

Exclusion criteria

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

postnatally using the R27 clinical indication (Paediatric disorders).
• Fetal growth restriction with measurements ≤3rd percentile and evidence of placental insufficiency including abnormal fetal and/or maternal dopplers, low PAPP-A (if measured), past history of FGR or still birth, maternal illness such as SLE cannot be considered as an indication for R21 unless there are other major abnormalities present that indicate a likely genetic aetiology.

Overlapping indications

- R22 Fetus with a likely chromosomal abnormality test should be used instead where findings indicate that a chromosomal cause should be looked for but the additional yield of genomewide sequencing is considered insufficient
- R27 Paediatric disorders should be used for non-urgent testing e.g. where there is imminent fetal loss or termination of pregnancy, or miscarriage has already occurred
- Where findings indicate that there is a likely diagnosis R24 Achondroplasia, R25 Thanatophoric dysplasia or of R23 Apert syndrome, those tests should be used instead
- R14 Acutely unwell children with a likely monogenic disorder should be used for urgent testing in the postnatal setting

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

Following review in a tertiary fetal medicine unit and after discussion with a Consultant Clinical Geneticist

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

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Prenatal

Associated Tests

Please note all the tests below will be undertaken for R21 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R21.1	Genomewide Common aneuploidy testing – prenatal	Singleton	Aneuploidy	Genomewide	Genomewide	Common aneuploidy testing
R21.2	Fetal anomalies WES or large panel	Trio	Small variants, CNVs	Panel of genes or loci	Fetal anomalies (478)	WES or Large Panel
R21.3	Genomewide Microarray	Singleton	Genomewide	Genomewide	Genomewide	Microarray

R412 Fetal anomalies with a likely genetic cause – non urgent

Testing Criteria

Fetus from a demised/non-continued pregnancy, with multiple major structural abnormalities detected on fetal ultrasound or post-mortem examination (by autopsy, imaging, metabolic and/or histological tests) and where multidisciplinary review (clinical genetics, tertiary fetal medicine specialists, clinical scientists and, where appropriate, relevant paediatric specialists) consider a monogenic malformation disorder is likely.

Only for cases where it is not possible to test via R27 (e.g. when there is insufficient DNA for WGS).

Testing should be primarily targeted to those families for which this test may influence future pregnancies.

For more detailed guidance for R412, outlined in the non-urgent fetal exome service guidance documentation, please contact your local Genomic Laboratory Hub.

Overlapping indications

- R27 Paediatric disorders should be used for non-urgent testing e.g. where there is imminent fetal loss or termination of pregnancy, or miscarriage has already occurred
- R14 Acutely unwell children with a likely monogenic disorder, if there is an ongoing unaffected pregnancy and testing is urgent, R14 would be appropriate.
- R21 Fetal anomalies with a likely genetic cause, should be used for ongoing pregnancies where a molecular diagnosis would change clinical management.

Where in Pathway

Following normal aneuploidy and microarray result and exclusion of maternal cell contamination of the DNA sample.

Requesting Specialties

- Clinical Genetics and/or other appropriate specialist referring clinician

Specialist Service Group

- Prenatal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R412.1	Fetal anomalies WES or Large Panel	Trio	Small variants, CNVs	Panel of genes or loci	Fetal anomalies (478)	WES or Large Panel

R251 Non-invasive prenatal sexing

Testing Criteria

Pregnancy requiring non-invasive prenatal sex determination to inform management in pregnancies at risk of severe sex-linked disorders, those affecting one sex in particular or where genitalia are ambiguous

Testing may not be possible in multiple pregnancies. In such cases contact the laboratory for discussion

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

Testing performed after 7 weeks in pregnancy as confirmed by dating scan

Requesting Specialties

- Clinical Genetics
- Fetal Medicine

Specialist Service Group

- Prenatal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R251.1	Sex determination NIPD	Singleton	Other	Single interval	Other	NIPD

R249 NIPD using paternal exclusion testing for very rare conditions where familial variant is known

Testing Criteria

Testing can be offered when paternal exclusion testing can be offered in families at risk of a recessive disorder when parents carry different varints or where the father has an autosomal dominant variant or is known mosaic for a variant. NIPD should only be offered for conditions where invasive testing would otherwise be offered and following discussion with the testing laboratory.

Note: pre-pregnancy work up (R389) is required to enable confirmation that NIPD is possible and to allow timely delivery in pregnancy

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.

Testing should be discussed in advance with the testing laboratory to ensure that necessary samples and validation work has been performed

Testing may not be possible in multiple pregnancies. In such cases contact the laboratory for discussion

Where in Pathway

Testing performed after 8 weeks in pregnancy as confirmed by dating scan

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Prenatal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R249.1	Specific target NIPD	Singleton	Other	Single interval	As per tested relative	NIPD

R250 NIPD for congenital adrenal hyperplasia - CYP21A2 haplotype testing

Testing Criteria

1. Pregnancy at risk of 21 hydroxylase deficiency requiring NIPD by haplotype testing following discussion with testing laboratory, AND
2. Parents have had a previous child affected with CAH and have both been confirmed as carriers, AND
3. DNA is available from the parents and the affected child, AND
4. Current pregnancy has been confirmed as XX

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.

Requests should be discussed in advance with the testing laboratory to ensure that necessary samples and validation work has been performed

Testing is not currently possible for consanguineous couples

Testing may not be possible in multiple pregnancies. In such cases contact the laboratory for discussion

Where in Pathway

Testing performed after 8 weeks in pregnancy as confirmed by dating scan. Note pre-pregnancy work up (R389) is required to enable confirmation that NIPD is possible and to allow timely delivery in pregnancy

Requesting Specialties

- Clinical Genetics
- Fetal Medicine

Specialist Service Group

- Prenatal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R250.1	CYP21A2 NIPD	Singleton	Haplotype testing	Single gene(s)	CYP21A2	NIPD

R304 NIPD for cystic fibrosis - haplotype testing

Testing Criteria

1. Pregnancy at risk of cystic fibrosis for which NIPD by haplotype testing is required following discussion with testing laboratory, where parents are not consanguineous AND
2. Each partner carries a confirmed variant and DNA is available from both parents, AND
3. DNA is available from either an affected child/pregnancy OR a confirmed unaffected non-carrier child/pregnancy

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.

Testing is not currently possible for consanguineous couples

Testing may not be possible in multiple pregnancies. In such cases contact the laboratory for discussion

Where in Pathway

Testing performed after 8 weeks in pregnancy as confirmed by dating scan

Requesting Specialties

- Clinical Genetics
- Fetal Medicine

Specialist Service Group

- Prenatal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R304.1	CFTR NIPD - Haplotype Testing	Singleton	Haplotype testing	Single interval	CFTR	NIPD

R305 NIPD for cystic fibrosis - variant testing

Testing Criteria

1. Pregnancy at risk of cystic fibrosis due to known CFTR variant(s) for which NIPD by variant testing is required following discussion with testing laboratory, AND
2. Both parents confirmed to be carriers of a different variant, AND
3. Father is a carrier of one of the following CFTR variants p.(Phe508del), c.489+1G>T, p.(Gly542*), p.(Gly551Asp), p.(Trp1282*) p.(Arg553*), p.(Ile507del), p.(Arg560Thr), p.(Ser549Asn), p.(Ser549Arg)

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

Testing performed after 9 weeks in pregnancy as confirmed by dating scan

Requesting Specialties

- Clinical Genetics
- Fetal Medicine
- Obstetrics

Specialist Service Group

- Prenatal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R305.1	CFTR NIPD	Singleton	Other, Small variants	Single gene(s)	CFTR	NIPD

R306 NIPD for Apert syndrome - variant testing

Testing Criteria

Pregnancy in which NIPD for Apert syndrome is required

Either:

1. Abnormal ultrasound findings suggestive of Apert syndrome with acrocephaly, proptosis AND symmetrical syndactyly, OR
2. At risk pregnancy due to paternal Apert syndrome OR a previous pregnancy with confirmed Apert syndrome

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

Testing performed after 8 weeks in pregnancy as confirmed by dating scan

Requesting Specialties

- Clinical Genetics
- Fetal Medicine

Specialist Service Group

- Prenatal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R306.1	FGFR2 NIPD – Apert	Singleton	Small variants	Single gene(s)	FGFR2	NIPD

R307 NIPD for Crouzon syndrome with acanthosis nigricans - variant testing

Testing Criteria

Pregnancy in which NIPD for Crouzon syndrome with acanthosis nigricans is required due to paternal Crouzon syndrome with acanthosis nigricans and the variant is confirmed OR a previous pregnancy with confirmed Crouzon syndrome with acanthosis nigricans with variant confirmed

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

Testing performed after 8 weeks in pregnancy as confirmed by dating scan

Requesting Specialties

- Clinical Genetics
- Fetal Medicine

Specialist Service Group

- Prenatal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R307.1	FGFR3 NIPD – Crouzon	Singleton	Small variants	Single gene(s)	FGFR3	NIPD

R308 NIPD for FGFR2-related craniosynostosis syndromes - variant testing

Testing Criteria

Pregnancy in which NIPD for FGFR2-related craniosynostosis is required due to paternal FGFR2-related craniosynostosis with causative variant confirmed OR a previous pregnancy with confirmed FGFR2-related craniosynostosis with variant confirmed

Where in Pathway

Testing performed after 8 weeks in pregnancy as confirmed by dating scan

Requesting Specialties

- Clinical Genetics
- Fetal Medicine

Specialist Service Group

- Prenatal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R308.1	FGFR2 NIPD - non-Apert FGFR2-related craniosynostosis	Singleton	Small variants	Single gene(s)	FGFR2	NIPD

R309 NIPD for FGFR3-related skeletal dysplasias - variant testing

Testing Criteria

Pregnancy in which NIPD for FGFR3-related skeletal dysplasia is required

1. Abnormal ultrasound findings compatible with sonographic diagnosis of achondroplasia or other rare FGFR3-related skeletal dysplasia including Muenke syndrome, hypochondroplasia or hypochondroplasia with acanthosis nigricans:
   a. Femoral length within the normal range at the routine 18-20-week scan, AND
   b. Femur length and all long bones below the 3rd percentile after 25 weeks gestation, AND
   c. Head circumference on or above 95th percentile or above the normal range for gestation at diagnosis and/or frontal bossing present, AND
   d. Fetal and maternal dopplers should be normal
   e. Other features may include polyhydramnios or short fingers

   OR
2. Abnormal ultrasound findings compatible with sonographic diagnosis of thanatophoric dysplasia or severe achondroplasia with developmental delay:
   a. All long bones below the 3rd percentile from early pregnancy, AND
   b. Small chest with short ribs, AND
   c. At least one of: bowed femora, frontal bossing, cloverleaf skull, short fingers

   OR
3. At risk pregnancy due to paternal FGFR3-related skeletal disorder OR a previous pregnancy with confirmed FGFR3-related skeletal disorder

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.

Testing may not be possible in multiple pregnancies. In such cases contact the laboratory for discussion.

Where in Pathway

Testing performed after 8 weeks in pregnancy as confirmed by dating scan

Requesting Specialties

- Clinical Genetics
- Fetal Medicine

Specialist Service Group

- Prenatal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R309.1	FGFR3 NIPD - non-Crouzon FGFR3-related skeletal dysplasias	Singleton	Small variants	Single gene(s)	FGFR3	NIPD

R310 NIPD for Duchenne and Becker muscular dystrophy - haplotype testing

Testing Criteria

Pregnancy at risk of Duchenne or Becker muscular dystrophy due to known variant for which NIPD by variant testing is required following discussion with testing laboratory

Samples should be available from additional family members to permit testing. Please discuss with the testing laboratory.

Testing is not currently possible for consanguineous couples

Testing may not be possible in multiple pregnancies. In such cases contact the laboratory for discussion

Where in Pathway

Testing performed after 8 weeks in pregnancy as confirmed by dating scan, and following a NIPD fetal sexing result that together indicate a single XY fetus

Requesting Specialties

- Clinical Genetics
- Fetal Medicine

Specialist Service Group

- Prenatal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R310.1	Dystrophin NIPD	Singleton	Haplotype testing	Single gene(s)	Dystrophin	NIPD

R311 NIPD for spinal muscular atrophy - variant testing

Testing Criteria

1. Pregnancy at risk of spinal muscular atrophy due to known SMN1 variant(s) for which NIPD by variant testing is required following discussion with testing laboratory, AND
2. Both parents confirmed to be carriers

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.

Requests should be discussed in advance with the testing laboratory to ensure that necessary samples and validation work has been performed

Testing may not be possible in multiple pregnancies. In such cases contact the laboratory for discussion

Where in Pathway

Testing performed after 8 weeks in pregnancy as confirmed by dating scan

Requesting Specialties

- Clinical Genetics
- Fetal Medicine

Specialist Service Group

- Prenatal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R311.1	SMN1 NIPD	Singleton	Exon level CNVs	Single gene(s)	SMN1	NIPD

R423 NIPD for Retinoblastoma haplotype testing

Testing Criteria

1. Singleton pregnancy at risk of retinoblastoma following discussion with testing laboratory, where either parent or their previous child has a confirmed diagnosis of heritable retinoblastoma by genetic testing (ie maternal, paternal or de novo inheritance) AND
2. For paternal or de novo inheritance - DNA is available from both parents (and affected child where appropriate) OR

   For maternal inheritance testing, DNA must be available from both parents and a previous child (affected or unaffected confirmed genetically) and the parents must be non-consanguineous

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.

Requests should be discussed in advance with the testing laboratory to ensure that necessary samples and validation work has been performed.

Testing is not possible in multiple pregnancies.

Where in Pathway

Testing performed after 8 weeks in pregnancy as confirmed by dating scan. N.B. If testing is to be performed using a bespoke NIPD assay, pre-pregnancy work up (R389) is required to enable confirmation that NIPD is possible and to allow timely delivery in pregnancy.

Requesting Specialties

- Clinical Genetics
- Fetal Medicine

Specialist Service Group

- Prenatal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R423.1	NIPD for Retinoblastoma	Singleton	Haplotype testing	Single gene(s)	RB1	NIPD

R389 NIPD - pre-pregnancy test work-up

Testing Criteria

Testing on parental and other family samples to prepare for NIPD in a planned future pregnancy.

Note: this should only be requested in families who qualify for NIPD under the relevant indication and may require further multi-disciplinary or laboratory discussion before approval

Where in Pathway

Prior to the pregnancy in which NIPD is planned

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- NIPD

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R389.1	Specific target NIPD pre-pregnancy work-up	Parents only	Other	Single gene(s)	As per familial diagnosis	NIPD

R433 NIPD for Monogenic diabetes, subtype glucokinase

Testing Criteria

Pregnancies at 50% risk of maternally inherited monogenic diabetes, subtype glucokinase.

Patients will have undergone genetic testing for monogenic diabetes (indications R141 or R142) and have confirmed genetic diagnosis of GCK monogenic diabetes.

Overlapping indications

- R142 Glucokinase-related fasting hyperglycaemia
- R141 Monogenic diabetes

Where in Pathway

Testing would be performed in pregnancy as confirmed by the first trimester dating scan (after 12 weeks).

Requesting Specialties

- Clinical Genetics
- Endocrinology
- Obstetrics
- Specialist Diabetes Clinics

Specialist Service Group

- Prenatal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R433.1	GCK NIPD	Singleton	Other	Single interval	GCK	NIPD

Part VII. Gastrohepatology

R168 Non-acute porphyrias

Testing Criteria

Clinical diagnosis of any of the non-acute types of porphyria, including:

- Porphyria cutanea tarda
- Congenital erythropoietic porphyria
- Erythropoietic protoporphyria
- Coproporphyria

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 or after clinical assessment by a highly specialised service

Requesting Specialties

- Dermatology
- Haematology
- Hepatology
- Neurology

Specialist Service Group

- Gastrohepatology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R168.1	Non-acute porphyrias Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Non-acute porphyrias (513)	Small panel

R169 Acute intermittent porphyria

Testing Criteria

Clinical features of acute intermittent porphyria (AIP), AND

ALA, PBG, or total porphyrin testing suggests diagnosis of AIP

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 or after clinical assessment by a highly specialised service

Requesting Specialties

- Clinical Genetics
- Dermatology
- Gastroenterology
- Hepatology
- Neurology
- Paediatrics

Specialist Service Group

- Gastrohepatology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R169.1	HMBS Single gene sequencing	Singleton	Small variants	Single gene(s)	HMBS (1207)	Single gene sequencing >=10 amplicons

R170 Variegate porphyria

Testing Criteria

Clinical features of variegate porphyria, AND

ALA, PBG, or total porphyrin testing suggests diagnosis of VP

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
- Dermatology
- Gastroenterology
- Hepatology
- Neurology

Specialist Service Group

- Gastrohepatology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R170.1	PPOX Single gene sequencing	Singleton	Small variants	Single gene(s)	PPOX (1401)	Single gene sequencing >=10 amplicons

R171 Cholestasis

Testing Criteria

Neonatal conjugated hyperbilirubinaemia where multifactorial and infective causes have been excluded, OR

Unexplained cholestasis developing below the age of 18 (It may occasionally be appropriate to test individuals presenting over the 18 under this indication following expert review) OR

Persistence of unexplained cholestasis beyond 3 months or recurrence of otherwise unexplained cholestasis, including those with a suspected precipitating drug OR

Cholestasis of pregnancy onset in the second trimester or serum bile acids >42umol/mL in the third trimester

Testing may occasionally be appropriate outside these criteria following discussion at the national gastrohepatology genomics MDT.

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
- Hepatology
- Metabolic Medicine
- Neonatology
- Paediatrics (on agreement with paediatric hepatologist)

Specialist Service Group

- Gastrohepatology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R171.1	Cholestasis WES or Medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Cholestasis (544)	WES or Medium Panel

R172 Wilson disease

Testing Criteria

High suspicion of Wilson disease, as evidenced by some or all of low caeruloplasmin, high liver copper, high urinary copper, high free copper, Kayser–Fleischer rings

Overlapping indications

- R98 Likely inborn error of metabolism, R27 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with atypical features in whom a broader differential diagnosis is under consideration

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
- Hepatology
- Metabolic Medicine
- Neurology
- Psychiatry
- Paediatrics

Specialist Service Group

- Gastrohepatology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R172.1	ATP7B Single gene sequencing	Singleton	Small variants	Single gene(s)	ATP7B (1405)	Single gene sequencing >=10 amplicons

R173 Polycystic liver disease

Testing Criteria

Patients with multiple hepatic cysts with no explanation

Overlapping indications

- R193 Cystic renal disease test should be used where patients have both renal and hepatic cysts
- R27 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

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
- Hepatology

Specialist Service Group

- Gastrohepatology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R173.1	Polycystic liver disease WES or small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Polycystic liver disease interim (653)	WES or Small Panel

R175 Pancreatitis

Testing Criteria

1. Clinical diagnosis of recurrent acute pancreatitis (at least 2 attacks), OR
2. Chronic pancreatitis, OR
3. First episode of acute pancreatitis occurring below the age of 18, OR
4. First episode of acute pancreatitis with a first degree relative who has had pancreatitis

In patients where there are no identifiable acquired causes (e.g. gallstones or history of excessive alcohol intake)

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
- Gastroenterology
- Hepatology

Specialist Service Group

- Gastrohepatology

Associated Tests

Please note all the tests below will be undertaken for R175 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R175.1	Pancreatitis Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Pancreatitis (386)	Small panel
R175.2	PRSS1	Singleton	Small variants	Single interval	PRSS1	Single gene testing (<10 amplicons)

R176 Gilbert syndrome

Testing Criteria

Unconjugated hyperbilirubinaemia in the absence of haemolysis, where a molecular diagnosis will contribute to management

Where in Pathway

Test should be requested when a molecular diagnosis will contribute to management

Requesting Specialties

- Clinical Genetics
- Hepatology
- General Practice

Specialist Service Group

- Gastrohepatology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R176.1	UGT1A1 Targeted variant testing	Singleton	Small variants	Single gene(s)	UGT1A1	Targeted variant testing

R177 Hirschsprung disease

Testing Criteria

Diagnosis of Hirschsprung disease

Overlapping indications

- R27 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

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
- Gastroenterology
- Neonatology
- Paediatrics (including Paediatric surgeons)

Specialist Service Group

- Gastrohepatology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R177.1	RET Single gene sequencing	Singleton	Small variants	Single gene(s)	RET (1346)	Single gene sequencing >=10 amplicons

R331 Intestinal failure or congenital diarrhoea

Testing Criteria

- Intestinal failure occurring under the age of 18, with dependence on parenteral nutrition over a period of months, with no identifiable underlying cause. **OR**
- Infants presenting with severe and persistent diarrhoea that arises in the neonatal period (first 28 days of life). Severity is defined as requirement for critical care input or parenteral nutrition at any point and persistence for at least 14 days. The disease must be unrelated to surgical short bowel **OR**
- Congenital Short Bowel Syndrome (approx. 50cm in length compared to ~250cm).

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.

Overlapping indications

- R15 Primary immunodeficiency test should be used where the presentation is indicative of infantile inflammatory bowel disease

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Gastroenterology
- Neonatology
- Paediatrics

Specialist Service Group

- Gastrohepatology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R331.1	Intestinal failure WES or small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Intestinal failure (514)	WES or Small Panel

R438 Paediatric pseudo-obstruction syndrome

Testing Criteria

The diagnosis of PPOS is confirmed on the presence of at least 2 of the following criteria:
1) Manometric evidence of small intestinal neuromuscular involvement
2) radiological evidence of recurrent and/or persistently dilated loops of small intestine with air fluid levels
3) presence of the genetic, metabolic or other conditions associated with PPOS
4) inability to maintain adequate nutrition and/or growth on oral feeding alone

Overlapping indications

Patients with intestinal failure should be tested using R331 Intestinal failure or congenital diarrhoea

Where in Pathway

At presentation or following assessment by the highly specialised service.

Requesting Specialties

- Clinical Genetics
- Gastroenterology
- Neonatology
- Paediatrics

Specialist Service Group

- Gastrohepatology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R438.1	Paediatric pseudo-obstruction syndrome WES or medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Paediatric pseudo-obstruction syndrome (1217)	WES or Medium Panel

Part VIII. Haematology

R361 Haemoglobinopathy trait or carrier testing

Testing Criteria

Individuals who are likely to have or carry a clinically significant haemoglobinopathy trait other than sickle cell disease based on initial protein testing or red cell indices

Overlapping indications

- R362 Carrier testing for sickle cell disease should be used for individuals likely to carry the common HbS variant

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

Following haemoglobin electrophoresis

Requesting Specialties

- Clinical Genetics
- Haematology
- Obstetrics

Specialist Service Group

- Haematology

Associated Tests

Please note all the tests below will be undertaken for R361 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R361.1	HBA1; HBA2; HBG1; HBG2; HBB	Singleton	Small variants	Small panel	HBA1; HBA2; HBG1; HBG2; HBB (1342)	Small panel
R361.2	HBA1; HBA2; HBG1; HBG2; HBB MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	HBA1; HBA2; HBG1; HBG2; HBB (1342)	MLPA or equivalent

R362 Carrier testing for sickle cell disease

Testing Criteria

Individuals who are likely to carry sickle cell disease based on initial protein testing

Overlapping indications

- R361 Carrier testing for haemoglobinopathies should be used in individuals likely to be carriers of other haemoglobinopathies

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

Following haemoglobin electrophoresis

Requesting Specialties

- Clinical Genetics
- Haematology
- Obstetrics

Specialist Service Group

- Haematology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R362.1	HbS variant Targeted variant testing	Singleton	Small variants	Single interval	HbS variant	Targeted variant testing

R90 Bleeding and platelet disorders

Testing Criteria

Individuals with a bleeding or platelet disorder of likely monogenic aetiology where there are multiple possible causative genes

Overlapping indications

Testing using one of the following targeted indications should be used where appropriate:

- R112 Factor II deficiency
- R115 Factor V deficiency
- R116 Factor VII deficiency
- R117 Factor VIII deficiency
- R118 Factor IX deficiency
- R119 Factor X deficiency
- R120 Factor XI deficiency
- R121 von Willebrand disease
- R122 Factor XIII deficiency
- R123 Combined vitamin K-dependent clotting factor deficiency
- R124 Combined factor V and VIII deficiency

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 consultation with Consultant Haematologist and following relevant functional haemostasis testing

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R90.1	Bleeding and platelet disorders WES or medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Bleeding and platelet disorders (545)	WES or Medium Panel

R93 Thalassaemia and other haemoglobinopathies

Testing Criteria

Clinical features indicative of likely thalassaemia or other clinically significant haemoglobinopathy

Overlapping indications

- R92 Rare anaemia test should be used in individuals with atypical features in whom other diagnoses are likely
- R361 Carrier testing for haemoglobinopathy test should be used in individuals who are likely to be carriers of a haemoglobinopathy or haemoglobinopathy trait

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
- Fetal Medicine
- Haematology
- Obstetrics
- Paediatrics

Specialist Service Group

- Haematology

Associated Tests

Please note all the tests below will be undertaken for R93 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R93.1	HBA1; HBA2; HBG1; HBG2; HBB MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	HBA1; HBA2; HBG1; HBG2; HBB (1397)	MLPA or equivalent
R93.2	HBA1; HBA2; HBG1; HBG2; HBB	Singleton	Small variants	Small panel	HBA1; HBA2; HBG1; HBG2; HBB (1397)	Small panel

R94 HbSS sickle cell anaemia

Testing Criteria

Likely HbSS sickle cell anaemia on haemoglobin electrophoresis

Overlapping indications

- R93 Thalassaemia and other haemoglobinopathies should be used where there is a suspicion of other forms of sickle cell disease (e.g. Hb SC, sickle beta thalassaemia) or S/HPFH.
- R92 Rare anaemia test should be used in individuals with atypical features in whom other diagnoses are likely
- R362 Carrier testing for sickle cell anaemia test should be used in individuals who are suspected to be carriers

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
- Fetal Medicine
- Haematology
- Obstetrics
- Paediatrics

Specialist Service Group

- Haematology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R94.1	HbS variant Targeted variant testing	Singleton	Small variants	Single interval	HbS variant	Targeted variant testing

R372 Newborn screening for sickle cell disease in a transfused baby

Testing Criteria

Newborn screening for sickle cell disease in a baby who has already been transfused

Where in Pathway

As per protocol

Requesting Specialties

- Appropriate specialist referring clinician

Specialist Service Group

- Screening

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R372.1	HbS variant Targeted variant testing	Singleton	Small variants	Single interval	HbS variant	Targeted variant testing

R95 Iron overload - hereditary haemochromatosis testing

Testing Criteria

Unexplained iron overload (with raised transferrin saturation and/or serum ferritin) suggestive of hereditary haemochromatosis

Overlapping indications

- R96 Iron metabolism disorders - not common HFE variants should be used instead where hereditary haemochromatosis is not the likely diagnosis, or HFE common variants have already been tested for

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

- Cardiology
- Clinical Genetics
- Haematology
- Hepatology
- General practice

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R95.1	HFE common variants Targeted variant testing	Singleton	Small variants	Single interval	HFE common variants	Targeted variant testing

R96 Iron metabolism disorders - NOT common HFE variants

Testing Criteria

Iron overload (with raised transferrin saturation and/or serum ferritin) or features of other disorders of iron metabolism in which common HFE variants have been excluded or are unlikely

Overlapping indications

- R95 Iron overload - hereditary haemochromatosis testing should be used where hereditary haemochromatosis due to common HFE variants is likely

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

- Cardiology
- Clinical Genetics
- Haematology
- Hepatology

Specialist Service Group

- Haematology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R96.1	Iron metabolism disorders Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Iron metabolism disorders (515)	Small panel

R97 Thrombophilia with a likely monogenic cause

Testing Criteria

- Clinical features indicative of a likely monogenic venous thrombophilia as assessed by a consultant haematologist
- Testing should typically be targeted at those with venous thromboembolic disease at less than 40 years of age, is spontaneous or associated with weak environmental risk factors and which is present in at least one first degree relative
- Testing should only be used where it will impact on clinical management

Where in Pathway

At presentation following consultation with Consultant Haematologist

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R97.1	Thrombophilia WES or small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Thrombophilia (516)	WES or Small Panel

R112 Factor II deficiency

Testing Criteria

Clinical features characteristic of factor II deficiency

Overlapping indications

- R90 Bleeding and platelet disorders test should be used where features are not typical

NOTE: This test is NOT for factor II related thrombophilia. See Thrombophilia with a likely monogenic cause

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 functional haemostasis testing

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R112.1	F2 Single gene sequencing	Singleton	Small variants	Single gene(s)	F2 (1325)	Single gene sequencing >=10 amplicons

R115 Factor V deficiency

Testing Criteria

Clinical features characteristic of factor V deficiency

Overlapping indications

- R90 Bleeding and platelet disorders test should be used where features are not typical

NOTE: This test is NOT for factor V Leiden. See Thrombophilia with a likely monogenic cause

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 functional haemostasis testing

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

Please note all the tests below will be undertaken for R115 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R115.1	F5 Single gene sequencing	Singleton	Small variants	Single gene(s)	F5 (1327)	Single gene sequencing >=10 amplicons
R115.2	F5 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	F5 (1327)	MLPA or equivalent

R116 Factor VII deficiency

Testing Criteria

Clinical features characteristic of factor VII deficiency

Overlapping indications

- R90 Bleeding and platelet disorders test should be used where features are not typical

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 functional haemostasis testing

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

Please note all the tests below will be undertaken for R116 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R116.1	F7 Single gene sequencing	Singleton	Small variants	Single gene(s)	F7 (1328)	Single gene sequencing >=10 amplicons
R116.2	F7 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	F7 (1328)	MLPA or equivalent

R117 Factor VIII deficiency

Testing Criteria

Clinical features characteristic of factor VIII deficiency

Overlapping indications

- R90 Bleeding and platelet disorders test should be used where features are not typical

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 functional haemostasis testing

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

Please note all the tests below will be undertaken for R117 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R117.1	F8 Targeted variant testing	Singleton	Small variants	Single gene(s)	F8 (1329)	Targeted variant testing
R117.2	F8 Single gene sequencing	Singleton	Small variants	Single gene(s)	F8 (1329)	Single gene sequencing >=10 amplicons
R117.3	F8 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	F8 (1329)	MLPA or equivalent

R118 Factor IX deficiency

Testing Criteria

Clinical features characteristic of factor IX deficiency

Overlapping indications

- R90 Bleeding and platelet disorders test should be used where features are not typical

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 functional haemostasis testing

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

Please note all the tests below will be undertaken for R118 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R118.1	F9 Single gene sequencing	Singleton	Small variants	Single gene(s)	F9 (1326)	Single gene sequencing >=10 amplicons
R118.2	F9 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	F9 (1326)	MLPA or equivalent

R119 Factor X deficiency

Testing Criteria

Clinical features characteristic of factor X deficiency

Overlapping indications

- R90 Bleeding and platelet disorders test should be used where features are not typical

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 functional haemostasis testing

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

Please note all the tests below will be undertaken for R119 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R119.1	F10 Single gene sequencing	Singleton	Small variants	Single gene(s)	F10 (1330)	Single gene sequencing <10 amplicons
R119.2	F10 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	F10 (1330)	MLPA or equivalent

R120 Factor XI deficiency

Testing Criteria

Clinical features characteristic of factor XI deficiency

Overlapping indications

- R90 Bleeding and platelet disorders test should be used where features are not typical

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 functional haemostasis testing

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

Please note all the tests below will be undertaken for R120 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R120.1	F11 Single gene sequencing	Singleton	Small variants	Single gene(s)	F11 (1331)	Single gene sequencing >=10 amplicons
R120.2	F11 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	F11 (1331)	MLPA or equivalent

R121 von Willebrand disease

Testing Criteria

Clinical features characteristic of von Willebrand disease

Overlapping indications

- R90 Bleeding and platelet disorders test should be used where features are not typical

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 functional haemostasis testing

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

Please note all the tests below will be undertaken for R121 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R121.1	VWF Single gene sequencing	Singleton	Small variants	Single gene(s)	VWF (1404)	Single gene sequencing >=10 amplicons
R121.2	VWF MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	VWF (1404)	MLPA or equivalent

R122 Factor XIII deficiency

Testing Criteria

Clinical features characteristic of factor XIII deficiency

Overlapping indications

- R90 Bleeding and platelet disorders test should be used where features are not typical

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 functional haemostasis testing

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R122.1	F13A1; F13B	Singleton	Small variants	Small panel	F13A1; F13B (1332)	Small panel

R123 Combined vitamin K-dependent clotting factor deficiency

Testing Criteria

Clinical features characteristic of combined vitamin K-dependent clotting factor deficiency

Overlapping indications

- R90 Bleeding and platelet disorders test should be used where features are not typical

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 functional haemostasis testing

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R123.1	VKORC1; GGCX	Singleton	Small variants	Small panel	VKORC1; GGCX (1316)	Small panel

R124 Combined factor V and VIII deficiency

Testing Criteria

Clinical features characteristic of combined factor V and VIII deficiency

Overlapping indications

- R90 Bleeding and platelet disorders test should be used where features are not typical

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 functional haemostasis testing

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R124.1	Combined factor V and VIII deficiency Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Combined factor V and VIII deficiency (517)	Small panel

R92 Rare anaemia

Testing Criteria

Rare anaemias of likely monogenic aetiology

Overlapping indications:

R93 Thalassaemia test should be used where the diagnosis is likely to be thalassaemia

R94 HbSS sickle cell disease test should be used where the diagnosis is likely to be HbSS sickle cell disease

- R27 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

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 exclusion of likely acquired causes

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

Please note all the tests below will be undertaken for R92 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R92.1	HBA1; HBA2; HBG1; HBG2; HBB; RPL11; RPL35A; RPS17; RPS19; RPS26; RPL5; PKLR MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	HBA1; HBA2; HBG1; HBG2; HBB; RPL11; RPL35A; RPS17; RPS19; RPS26; RPL5; PKLR	MLPA or equivalent
R92.2	HBA1; HBA2; HBG1; HBG2; HBB	Singleton	Small variants	Small panel	HBA1; HBA2; HBG1; HBG2; HBB	Small panel
R92.3	Rare anaemia WES or medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Rare anaemia (518)	WES or Medium Panel

R91 Cytopenia - NOT Fanconi anaemia

Testing Criteria

Persistent or recurrent cytopenia or pancytopenia of unknown cause where Fanconi anaemia is unlikely

This includes unexplained isolated aplastic anaemia, thrombocytopenia or neutropenia

Overlapping indications

- R258 Cytopenia – Fanconi breakage testing indicated should be used where exclusion of Fanconi anaemia using chromosome breakage testing is clinically indicated
- R313 Neutropaenia consistent with ELANE variants test should be used in cases of neutropaenia where ELANE variants are plausible and have not been excluded
- R27 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

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 exclusion of acquired causes including relevant auto-antibodies

Requesting Specialties

- Clinical Genetics
- Haematology
- Immunology

Specialist Service Group

- Haematology

Associated Tests

Please note all the tests below will be undertaken for R91 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R91.1	Cytopenia - NOT Fanconi anaemia WES or medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Cytopenia - NOT Fanconi anaemia (519)	WES or Medium Panel
R91.2	RPL11; RPL35A; RPS17; RPS19; RPS26; RPL5; DKC1; TERT; TERC MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	RPL11; RPL35A; RPS17; RPS19; RPS26; RPL5; DKC1; TERT; TERC	MLPA or equivalent

R258 Cytopenia - Fanconi breakage testing indicated

Testing Criteria

Persistent or recurrent bicytopenia or pancytopenia where exclusion of Fanconi anaemia by chromosome breakage testing is clinically indicated

Overlapping indications

- R91 Cytopenia - NOT Fanconi anaemia test should be used where exclusion of Fanconi anaemia by chromosome breakage testing is not clinically indicated

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
- Haematology
- Immunology

Specialist Service Group

- Haematology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R258.1	Fanconi breakage DNA repair defect testing	Singleton	DNA repair	Genomewide	Fanconi breakage	DNA repair defect testing
R258.2	Confirmed Fanconi anaemia or Bloom syndrome WES or Small panel medium	Singleton	Small variants, CNVs	Panel of genes or loci	Confirmed Fanconi anaemia or Bloom syndrome (508)	WES or Small Panel
R258.3	Confirmed Fanconi anaemia or Bloom syndrome	Singleton	Exon level CNVs	Panel of genes or loci	Confirmed Fanconi anaemia or Bloom syndrome (508)	MLPA or equivalent

R259 Nijmegen breakage syndrome

Testing Criteria

1. Molecular findings suggestive of Nijmegen breakage syndrome from genome, exome or other genomic analysis, OR
2. Clinical features characteristic of Nijmegen breakage syndrome

Overlapping indications

- R27 Paediatric disorders, R89 Ultra-rare and atypical monogenic disorders or other broad tests should be used except where clinical features are characteristic of Nijmegen breakage syndrome
- Prenatal diagnosis or cascade testing by chromosome breakage testing will be requested via R240 Diagnostic testing for known familial variant(s)

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

N/A

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Haematology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R259.1	Nijmegen breakage DNA repair defect testing	Singleton	DNA repair	Genomewide	Nijmegen breakage	DNA repair defect testing
R259.2	NBN Single gene sequencing	Singleton	Small variants	Single gene(s)	NBN (1376)	Single gene sequencing >=10 amplicons

R229 Confirmed Fanconi anaemia or Bloom syndrome - variant testing

Testing Criteria

Confirmed diagnosis of Fanconi anaemia or Bloom syndrome from chromosome breakage analysis requiring variant testing

Overlapping indications

- R91 Cytopenia - NOT Fanconi anaemia test should be used where exclusion of Fanconi anaemia using chromosome breakage testing is clinically indicated
- R260 Fanconi anaemia or Bloom syndrome - chromosome breakage testing test should be used instead where clinical features strongly suggestive of Fanconi anaemia or Bloom syndrome
- In other cases where testing is based on clinical features, R27Paediatric disorders , R89 Ultra-rare and atypical monogenic disorders or other broad genomic tests should typically be used except where clinical features are strongly suggestive of Fanconi anaemia or Bloom syndrome

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

Following chromosome breakage analysis

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R229.1	Confirmed Fanconi anaemia or Bloom syndrome Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Confirmed Fanconi anaemia or Bloom syndrome (508)	Small panel

R260 Fanconi anaemia or Bloom syndrome - chromosome breakage testing

Testing Criteria

1. Molecular findings suggestive of Fanconi anaemia or Bloom syndrome from genome, exome or other genomic analysis, OR
2. Clinical features strongly suggestive of Fanconi anaemia or Bloom syndrome

Overlapping indications

R258 Cytopenia – Fanconi breakage testing indicated should be used instead where testing is based on haematological clinical features

- In other cases where testing is based on clinical features, R27 Paediatric disorders, R89 Ultra-rare and atypical monogenic disorders or other broad genomic tests should typically be used except where clinical features are strongly suggestive of Fanconi anaemia or Bloom syndrome
- Prenatal diagnosis or cascade testing by chromosome breakage testing will be requested via R240 Diagnostic testing for known familial variant(s)

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

N/A

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R260.1	Fanconi breakage DNA repair defect testing	Singleton	DNA repair	Genomewide	Fanconi breakage	DNA repair defect testing

R313 Neutropaenia consistent with ELANE variants

Testing Criteria

1. Isolated neutropaenia where ELANE variants are plausible and have not been excluded, AND
2. Family history should NOT indicate autosomal recessive disease, AND
3. Clinical presentation is non-syndromic

Overlapping indications

- R91 Cytopenia – NOT Fanconi anaemia or R258 Cytopenia – Fanconi breakage testing indicated tests should be used where features are atypical of ELANE variants
- R27 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

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

After exclusion of acquired causes including autoimmune neutropaenia caused by anti-neutrophil antibodies

Requesting Specialties

- Clinical Genetics
- Haematology
- Immunology

Specialist Service Group

- Haematology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R313.1	ELANE Single gene sequencing	Singleton	Small variants	Single gene(s)	ELANE (1372)	Single gene sequencing <10 amplicons

R338 Monitoring for G(M)CSF escape variants

Testing Criteria

Individuals on G(M)CSF requiring detection of escape variants

Where in Pathway

As per relevant clinical protocol

Requesting Specialties

- Haematology
- Immunology

Specialist Service Group

- Haematology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R338.1	CSF3R Single gene sequencing	Singleton	Small variants	Single gene(s)	CSF3R (1358)	Single gene sequencing >=10 amplicons

R347 Inherited predisposition to acute myeloid leukaemia (AML)

Testing Criteria

Affected individual (proband) where the individual +/- family history meets one of the following criteria. The proband has:

1. AML/MDS AND a pre-existing disorder of platelet function, OR
2. AML/MDS AND ≥1 relative (first / second / third degree relative) with AML/ MDS/ unexplained cytopenia / aplastic anaemia

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.

Overlapping indications

- M80 Acute myeloid leukaemia should be used for somatic testing

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R347.1	Inherited predisposition to acute myeloid leukaemia AML Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Inherited predisposition to acute myeloid leukaemia (AML) (525)	Small panel

R366 Inherited susceptibility to acute lymphoblastoid leukaemia (ALL)

Testing Criteria

Testing of affected individual (proband) where the individual +/- family history meets one of the following criteria

The proband has:

Acute Lymphoblastic Leukaemia (ALL), AND

1. One first / second / third degree relative with ALL, OR
2. Two first / second / third degree relatives with myeloid/lymphoid/platelet disorder

NOTE: All diagnoses must be medically documented

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.

Overlapping indications

- M91 Acute lymphoblastic leukaemia should be used for somatic testing

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R366.1	PAX5; ETV6	Singleton	Small variants	Small panel	PAX5; ETV6 (1349)	Small panel

R405 Hereditary Erythrocytosis

Testing Criteria

1. Clinical features of a likely erythrocytosis of monogenic aetiology

2. Exclusion of secondary causes of erythrocytosis and acquired bone marrow disorders such as myeloproliferative neoplasm

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.

Overlapping Indications

- M85 Myeloproliferative neoplasm should be used for somatic testing for exclusion of acquired myeloproliferative neoplasm

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R405.1	Hereditary Erythrocytosis Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Hereditary Erythrocytosis (157)	Small panel

R406 Thrombocythaemia

Testing Criteria

1. Clinical features of a likely thrombocythaemia of monogenic aetiology

2. Exclusion of secondary causes of thrombocythaemia and acquired bone marrow disorders such as myeloproliferative neoplasm

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.

Overlapping Indications

- M85 Myeloproliferative neoplasm should be used for somatic testing for exclusion of acquired myeloproliferative neoplasm

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R406.1	Thrombocythaemia Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Thrombocythaemia (945)	Small panel

Part IX. Audiology

R65 Aminoglycoside exposure posing risk to hearing

Testing Criteria

Significant exposure to aminoglycosides posing risk of ototoxicity

This indication would be relevant to:

1. individuals with a predisposition to gram negative infections for example due to known respiratory disease (e.g. bronchiectasis, cystic fibrosis) or due to structural or voiding genitourinary tract disorders, OR
2. individuals with hearing loss who have been exposed to aminoglycosides

Overlapping indications

- R67 Monogenic hearing loss should be used in individuals with unexplained hearing loss

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

As appropriate

Requesting Specialties

- Appropriate specialist referring clinician

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R65.1	Aminoglycoside exposure posing risk to hearing	Singleton	Small variants	Single interval	MT-RNR1 m.1555A>G m.1095T>C m.1494C>T	Targeted variant testing

R67 Monogenic hearing loss

Testing Criteria

Likely or possible monogenic hearing loss

Hearing loss should be confirmed and bilateral

Cases of unilateral hearing loss are accepted IF there are:

(1) additional features suggesting a syndromic hearing loss diagnosis such as Waardenburg / BOR / CHARGE **OR**

(2) a family history of bilateral/unilateral hearing loss consistent with a monogenic cause (for example supported by audiograms).

Overlapping indications

- R27 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

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 diagnosis, including at confirmation of unexplained hearing loss in the newborn period

Requesting Specialties

- Audiology/Audiovestibular Medicine
- Clinical Genetics
- Ear, Nose and Throat
- Paediatrics

Specialist Service Group

- Audiology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R67.1	Hearing loss WES or large panel	Singleton	Small variants, CNVs	Panel of genes or loci	Hearing loss (126)	WES or Large Panel

Part X. Immunology

R155 Autoimmune Polyendocrine Syndrome

Testing Criteria

Individuals with a clinical diagnosis of autoimmune polyendocrine syndrome

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
- Endocrinology
- Immunology

Specialist Service Group

- Immunology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R155.1	AIRE Single gene sequencing	Singleton	Small variants	Single gene(s)	AIRE (1215)	Single gene sequencing >=10 amplicons

R15 Primary immunodeficiency or monogenic Inflammatory Bowel Disease

Testing Criteria

Suspected primary immunodeficiency diagnosed by a consultant immunologist

Indications include patients with any of the eight International Union of Immunological Societies (IUIS) categories of primary immunodeficiency:

1. Combined immunodeficiency, with or without associated features and abnormal T cell numbers or function. This may include abnormal naïve T cells, TRECs, repertoire, proliferations (e.g. PHA), reversed Cd4/8 ratio or increased gamma delta T cells)
2. Predominantly antibody deficiencies with low or absent vaccine responses
3. Diseases of immune dysregulation including haemophagocytic lymphohistiocytosis (HLH)
4. Congenital defects of phagocyte number, function or both. This should be evidenced by low phagocytic204 numbers and/or abnormal DHR/NBT/phagocytosis/L selectin shedding, Cd11a,b,c or CD18, or abnormal migration or adhesion
5. Defects in intrinsic and innate immunity
6. Autoinflammatory disorders
7. Complement deficiencies with abnormal complement function
8. Testing under these criteria would also include young children with inflammatory bowel disease, defined as: bloody diarrhoea, severe failure to thrive and severe intestinal inflammation with histology consistent with chronic inflammatory intestinal pathology, of onset under 6 years of age

OR

Suspected monogenic IBD diagnosed by a consultant paediatric gastroenterologist, gastroenterologist or immunologist:

1. Infantile onset IBD less than 2 years onset; very early onset IBD (<6years of onset) with severe course (requiring biologics or surgery) or relevant comorbidities and extraintestinal manifestations
2. Testing may occasionally be appropriate outside these criteria following discussion in a specialist MDT, (for example paediatric or young adult IBD with documented severity criteria e.g. relevant family history, comorbidities and extraintestinal manifestations such as infection susceptibility).

Testing Criteria for Semi-Rapid Testing

- Acutely unwell children or adults where primary immunodeficiency or monogenic severe inflammatory bowel disease is considered highly likely to be the primary cause of the phenotype in the patient.

- Cases should meet the standard eligibility criteria for R15, AND

- Where testing will provide an immediate change to treatment or clinical management for the patient.

Notes:

- Cases where the primary clinical indication is NOT primary immunodeficiency or monogenic severe inflammatory bowel disease or where immunodeficiency is part of a more complex presentation should be considered for R14 instead of rapid R15.

- Where a specific immunodeficiency is suspected based on immunological studies (eg X-linked SCID due to IL2RG pathogenic variants) the relevant clinical indication (eg R235 SCID with features of gamma chain deficiency) should be requested instead of rapid R15.

- Please provide relevant immunology data that may aid interpretation of results.

- Clinically urgent cases where the patient is not acutely unwell or where there would be no change to management should be submitted for R15 Primary Immunodeficiency by whole genome sequencing but requested urgently.

- Testing is performed on the proband but please send parental samples if available in order to expedite any further testing that may be required.

Overlapping indications

- R16 Severe combined immunodeficiency with adenosine deaminase deficiency test should be used in individuals with ADA deficiency
- R234 Severe combined immunodeficiency with PNP deficiency test should be used in individuals with PNP deficiency
- R235 Severe combined immunodeficiency with gamma chain deficiency test should be used in individuals with low or absent gamma chain or low or absent STAT5 pTyr to IL-2,7, and 15
- R17 Lymphoproliferative syndrome with low or absent SAP expression test should be used in individuals with absent SAP expression
- R232 Lymphoproliferative syndrome with low or absent perforin expression test should be used in individuals with absent perforin expression
- R18 Lymphoproliferative syndrome with low or absent XIAP expression test should be used in individuals with absent XIAP expression
- R19 Autoimmune lymphoproliferative syndrome with defective apoptosis test should be used in individuals with defective Fas-mediated apoptosis, elevated alpha double negative T cells, elevated sFAS or elevated vitamin B12
- R233 Agammaglobulinaemia with low or absent BTK expression test should be used in individuals with absent BTK expression
- R20 Wiskott-Aldrich syndrome test should be used in individuals with a likely diagnosis of WAS
- R204 Amyloidosis with no identifiable cause test should be used in cases with confirmed amyloidosis
- R239 Incontinentia pigmenti testing should be used where there is a high clinical sucpicion of this diagnosis. This is because the R15 test is not optimised to detect variants in the IKBKG gene and some diagnoses may be missed.

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

N/A

Where in Pathway for Semi-Rapid Testing

At presentation following clinically relevant, rapidly available investigations. All cases must be agreed in advance. Please contact gosh.geneticslab@nhs.net to discuss prior to submitting samples.

Requesting Specialties

- Clinical Genetics
- Haematology
- Immunology

  Gastroenterology

Requesting Specialties for Semi-Rapid Testing

- Clinical Genetics
- Immunology
- Neonatology

Specialist Service Group

- Immunology

Associated Tests

R15.5 is only for semi urgent testing

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R15.4	Primary immunodeficiency or monogenic inflammatory bowel disease WGS (phase 2)	Trio or singleton	Exon level CNVs, Small variants	Panel of genes or loci	Primary immunodeficiency or monogenic inflammatory bowel disease (398)	WGS
R15.5	Primary immunodeficiency or monogenic inflammatory bowel disease WES	Singleton	Exon level CNVs, Small variants	Panel of genes or loci	Primary immunodeficiency or monogenic inflammatory bowel disease (398)	WES

R413 Autoinflammatory Disorders

Testing Criteria

1. Evidence of recurrent or continuous inflammation (localised or systemic) of otherwise undetermined cause, which fluctuate apparently randomly, either periodically or irregularly **AND**
2. Infectious and autoimmune testing will have been non-diagnostic.

Attacks typically start during childhood but symptoms can also begin during adolescence or even in later adulthood. Main symptom is fever. Other symptoms include serositis (peritonitis, pleuritis and pericarditis), recurrent stroke-like episodes, myalgia, arthralgia and rash, CNS, gastrointestinal and respiratory symptoms.

Overlapping indications

- R15 Primary immunodeficiency or monogenic Inflammatory Bowel Disease

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Immunology
- Rheumatology
- Dermatology
- Gastroenterology
- Paediatrics

Specialist Service Group

- Immunology

Associated Tests

Please note all the tests below will be undertaken for R413 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R413.1	Autoinflammatory Disorders medium panel	Singleton	Small variant detection, CNVs	Panel of genes or loci	Autoinflammatory Disorders (1075)	Medium Panel or WES

R16 Severe combined immunodeficiency with adenosine deaminase deficiency

Testing Criteria

T-cell negative/low B-cell negative/low NK-cell negative/low SCID with ADA deficiency

Overlapping indications

- R15 Primary immunodeficiency panel test should be used where clinical and laboratory features are not typical and a broader range of genes are potentially causative

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

Following assessment by a highly specialised service for severe combined immunodeficiency service

Requesting Specialties

- Clinical Genetics
- Immunology

Specialist Service Group

- Immunology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R16.1	ADA Single gene sequencing	Singleton	Small variants	Single gene(s)	ADA (1388)	Single gene sequencing >=10 amplicons

R235 SCID with features of gamma chain deficiency

Testing Criteria

Males with T-cell negative B-cell positive SCID with low or normal NK-cells with low or absent gamma chain OR low or absent STAT5 pTyr to IL2, IL7, and IL15

Overlapping indications

- R15 Primary immunodeficiency panel test should be used where clinical and laboratory features are not typical and a broader range of genes are potentially causative

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 gamma chain and STAT5 tyrosine phosphorylation analysis or following assessment by a highly specialised service for severe combined immunodeficiency service

Requesting Specialties

- Clinical Genetics
- Immunology

Specialist Service Group

- Immunology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R235.1	IL2RG Single gene sequencing	Singleton	Small variants	Single gene(s)	IL2RG (1386)	Single gene sequencing <10 amplicons

R234 Severe combined immunodeficiency with PNP deficiency

Testing Criteria

T-cell negative/low B-cell negative/low NK-cell negative/low severe combined immunodeficiency with PNP deficiency

Overlapping indications

- R15 Primary immunodeficiency panel test should be used where clinical and laboratory features are not typical and a broader range of genes are potentially causative

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 PNP analysis or following assessment by a highly specialised service for severe combined immunodeficiency service

Requesting Specialties

- Clinical Genetics
- Immunology

Specialist Service Group

- Immunology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R234.1	PNP Single gene sequencing	Singleton	Small variants	Single gene(s)	PNP (1389)	Single gene sequencing <10 amplicons

R17 Lymphoproliferative syndrome with absent SAP expression

Testing Criteria

Haemophagocytic lymphohistiocytosis (HLH) or other lymphoproliferative disorders affecting males consistent with SAP-related disease and low or absent SAP expression

Typical features may include EBV infection, gammaglobulinaemia or bone marrow aplasia

Overlapping indications

- R15 Primary immunodeficiency panel test should be used where clinical and laboratory features are not typical and a broader range of genes are potentially causative

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 SAP expression analysis

Requesting Specialties

- Clinical Genetics
- Haematology
- Immunology

Specialist Service Group

- Immunology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R17.1	SH2D1A Single gene sequencing	Singleton	Small variants, CNVs	Single gene(s)	SH2D1A (1353)	Single gene sequencing <10 amplicons

R18 Haemophagocytic syndrome with absent XIAP expression

Testing Criteria

Haemophagocytic lymphohistiocytosis (HLH) affecting males consistent with XIAP-related disease and low or absent XIAP expression

Typical features include inflammatory bowel disease or colitis

Overlapping indications

- R15 Primary immunodeficiency panel test should be used where clinical and laboratory features are not typical and a broader range of genes are potentially causative

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 XIAP expression analysis

Requesting Specialties

- Clinical Genetics
- Haematology
- Immunology

Specialist Service Group

- Immunology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R18.1	XIAP Single gene sequencing	Singleton	Small variants	Single gene(s), CNVs	XIAP (1344)	Single gene sequencing >=10 amplicons

R232 Haemophagocytic syndrome with absent perforin expression

Testing Criteria

Haemophagocytic syndrome with low or absent perforin expression

Overlapping indications

- R15 Primary immunodeficiency panel test should be used where clinical and laboratory features are not typical and a broader range of genes are potentially causative

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 perforin expression analysis

Requesting Specialties

- Clinical Genetics
- Haematology
- Immunology

Specialist Service Group

- Immunology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R232.1	PRF1 Single gene sequencing	Singleton	Small variants	Single gene(s)	PRF1 (1343)	Single gene sequencing <10 amplicons

R19 Autoimmune lymphoproliferative syndrome with defective apoptosis

Testing Criteria

Lymphoproliferative syndrome or other lymphoproliferative disorders consistent with FAS-related disease with:

- abnormal Fas-mediated apoptosis, OR
- elevated alpha beta double negative T cells, OR
- elevated sFAS, OR
- elevated Vitamin B12

Overlapping indications

- R15 Primary immunodeficiency panel test should be used where clinical and laboratory features are not typical and a broader range of genes are potentially causative

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 analysis of Fas-mediated apoptosis

Requesting Specialties

- Clinical Genetics
- Haematology
- Immunology

Specialist Service Group

- Immunology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R19.1	FAS Single gene sequencing	Singleton	Small variants	Single gene(s)	FAS (1214)	Single gene sequencing >=10 amplicons

R233 Agammaglobulinaemia with absent BTK expression

Testing Criteria

Clinical features in males suggestive of X-linked agammaglobulinaemia with low or absent BTK expression OR males with absent B cells

Overlapping indications

- R15 Primary immunodeficiency panel test should be used where clinical and laboratory features are not typical and a broader range of genes are potentially causative

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 BTK expression analysis

Requesting Specialties

- Clinical Genetics
- Immunology

Specialist Service Group

- Immunology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R233.1	BTK Single gene sequencing	Singleton	Small variants	Single gene(s)	BTK (1208)	Single gene sequencing >=10 amplicons

R20 Wiskott-Aldrich syndrome

Testing Criteria

Clinical presentation suggestive of Wiskott-Aldrich syndrome (WAS) and limited or absent expression of WASP

The diagnosis should be considered in any male with small platelets

Overlapping indications

- R15 Primary immunodeficiency panel test should be used where clinical features are not typical and a broader range of genes are potentially causative

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 WASP expression analysis or following assessment by a highly specialised service for severe combined immunodeficiency service

Requesting Specialties

- Clinical Genetics
- Haematology
- Immunology

Specialist Service Group

- Immunology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R20.1	WAS Single gene sequencing	Singleton	Small variants	Single gene(s)	WAS (1406)	Single gene sequencing >=10 amplicons

R341 Hereditary angioedema types I and II

Testing Criteria

1. Recurrent non-urticarial angioedema, usually of gradual onset involving the peripheries, gut or larynx, usually of gradual onset and lasting 1-5 days and presenting without a family history, AND
2. Abnormal serum C1INH concentration or function

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

Following C1INH testing

Requesting Specialties

- Clinical Genetics
- Dermatology
- Immunology

Specialist Service Group

- Immunology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R341.1	SERPING1 Single gene sequencing	Singleton	Small variants, CNVs	Single gene(s)	SERPING1 (1345)	Single gene sequencing >=10 amplicons

R368 Hereditary angioedema type III

Testing Criteria

Recurrent non-urticarial angioedema, usually of gradual onset involving the peripheries, gut or larynx, usually of gradual onset and lasting 1-5 days and presenting without a family history, AND

Normal serum C1INH concentration or function

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

Following complement testing

Requesting Specialties

- Clinical Genetics
- Dermatology
- Immunology

Specialist Service Group

- Immunology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R368.1	F12 hotspot Targeted variant testing	Singleton	Small variants	Single interval	F12 hotspot	Targeted variant testing

R436 Hereditary alpha tryptasaemia

Testing Criteria

Persistently raised mast cell tryptase of 8.0ng/ml or above

Where in Pathway

Clinical suspicion in patients with persistent increased baseline serum tryptase, usually in the context of negative investigation for mastocytosis and other myeloproliferative neoplasms (MPN)

Requesting Specialties

- Immunology
- Haematology
- Paediatrics
- Allergy specialists
- Dermatology

Specialist Service Group

- Immunology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R436.1	Hereditary alpha tryptasaemia	Singleton	Small variants	Single interval	TPSAB1	Targeted variant testing

Part XI. Inherited cancer

R207 Inherited ovarian cancer (without breast cancer)

Testing Criteria

1. High grade non mucinous epithelial ovarian cancer (EOC) OR serous tubal intraepithelial carcinoma (STIC)at any age

OR

2. Epithelial ovarian cancer (EOC) OR serous tubal intraepithelial carcinoma (STIC) AND

a. ≥1 first degree relative with EOC OR serous tubal intraepithelial carcinoma (STIC) , OR

b. ≥1 second degree relative with EOC OR serous tubal intraepithelial carcinoma (STIC) (intervening relative without ovaries or deceased) OR

c. ≥2 second / third degree relatives with EOC OR serous tubal intraepithelial carcinoma (STIC)

Deceased affected individual (proband) can be tested if:

a. A previously stored constitutional DNA/blood sample is available AND
   i. Criteria 1 OR 2 are reached, OR family Manchester score of 20 AND
   ii. No living affected individual is available for genetic testing

OR

b. If no stored constitutional DNA/blood sample is available, but appropriate tissue is available (tumour or normal) AND
   i. Criteria 2 are reached OR family Manchester score of 20 AND
   ii. No living affected individual is available for genetic testing

NOTE: The proband's cancer and majority of reported cancers in the family should have been confirmed

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

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.

Overlapping indications

- M2 Ovarian carcinoma should be used for somatic testing

Where in Pathway

At presentation

Requesting Specialties

- Oncology
- Clinical Genetics
- Gynaecology

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R207.1	Inherited ovarian cancer without breast cancer Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Inherited ovarian cancer (without breast cancer) (143)	Small panel

R208 Inherited breast cancer and ovarian cancer

Testing Criteria

1. **Living affected individual (proband)** with breast* or high grade ovarian cancer where the individual +/- family history meets one of the criteria. The proband has:
   a. Breast cancer (age <40 years), OR
   b. Bilateral breast cancer (age < 60 years), OR
   c. Triple negative breast cancer (age < 60 years), OR
   d. Assigned male at birth and affected with breast cancer (any age), OR
   e. Breast cancer (age <45 years) and a first degree relative with breast cancer (age <45 years), OR
   f. Combined pathology-adjusted Manchester score ≥15 or single gene pathology adjusted score of ≥10 or BOADICEA/CanRisk score ≥10% OR
   g. Ashkenazi Jewish ancestry and breast cancer at any age
   h. ≥ 1 grandparent from Westray (Orkney) or Whalsay (Shetland) and breast cancer at any age
2. **Living affected individual with pancreatic cancer** AND family history of breast*/high grade ovarian/prostate cancer with a pathology adjusted Manchester score of ≥ 15/CanRisk score of 10%.
3. **Living affected individual with prostate cancer** AND a family history of breast/ovarian/pancreatic cancer with a pathology adjusted Manchester score of ≥ 15/CanRisk score of 10%.
4. **Deceased affected individual** with breast* or high grade ovarian cancer with:
   a. A stored DNA, blood or tissue sample is available for DNA extraction, AND
   b. Pathology-adjusted Manchester score ≥17 or CanRisk score ≥15%, AND
   c. No living affected individual is available for genetic testing
5. **Living unaffected** individual with:
   a. first degree relative affected by breast* or serous ovarian cancer, AND
   b. Combined pathology-adjusted Manchester score ≥20 or BOADICEA/CanRisk score of ≥20% for affected relative or BOADICEA/CanRisk score of ≥10% for unaffected relative AND
   c. No living affected individual is available for genetic testing, AND
   d. No deceased affected individual with tumour material available for testing

   Note for living unaffected individuals:

   Where more than one family member may be eligible for unaffected testing, the residual probability of a causative pathogenic variant in the family should be considered, taking into account prior normal unaffected tests.

NOTES

- ***Breast cancer definition includes high grade DCIS, LCIS is not included.**
- **The proband's cancer and majority of reported cancers in the family should have been confirmed**
- **The pathology adjusted Manchester score involved incorporation of pathology data for the tested proband alone, i.e. pathology need not be sought for other family members.**
- **Ovarian cancer: Fallopian Tube and Primary Peritoneal cancers can be included**
- **BRCA1/BRCA2 testing should not typically have previously been performed. Exceptions may include, for example, patients who have been tested through the Jewish Community's NHS BRCA-Testing Programme for BRCA1/BRCA2 and not received a molecular diagnosis**
- **Testing of unaffected and deceased individuals can only be offered by Clinical Genetics**

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

Overlapping indications

- M2 Ovarian carcinoma should be used for somatic testing
- M3 Breast cancer should be used for somatic testing
- R444 NICE approved PARP inhibitor treatment

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

- Oncology
- Clinical Genetics
- Surgery

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R208.1	Inherited breast and ovarian cancer	Singleton	Small variants, CNVs	Small panel of genes	Inherited breast and ovarian cancer (635)	Small panel

R210 Inherited MMR deficiency (Lynch syndrome)

Testing Criteria

All new diagnoses of colorectal and endometrial cancer should have tumour MSI / IHC as outlined in the cancer test directory and the Lynch syndrome handbook for Alliances in order to identify dMMR tumours and additional testing that suggests Lynch Syndrome. This may include BRAF testing in MLH1 deficient colorectal cancers and somatic MLH1 hypermethylation testing in BRAF negative colorectal cancers and all MLH1 deficient uterine cancers. Somatic MLH1 hypermethylation testing is included on the Cancer Test Directory under M1.5.

1. **Clinical Criteria for germline testing in an affected individual**
   The proband has a dMMR tumour where results of additional testing suggest Lynch syndrome. This may include BRAF testing in MLH1 deficient colorectal cancers and somatic MLH1 hypermethylation testing in BRAF negative colorectal cancers and all MLH1 deficient uterine cancers
   a. The affected proband comes from a modified Amsterdam criteria positive family irrespective of the dMMR status of the tumour
   b. Personal or family history suggestive of Constitutional Mismatch Repair Deficiency (CMMRD) with Wimmer score =>3
   c. Deceased affected individual meets criteria and a previously stored constitutional blood/DNA sample is available.

2. **Clinical criteria for MSI /IHC testing on a stored tumour sample prior to germline testing**
   a. Personal/family history of colorectal cancers reaching Modified Amsterdam Criteria (≥ 3 cases of Lynch related cancer over ≥2 generations with ≥1 case diagnosed <50 years) OR
   b. Any lynch-related cancer* <50 years (excluding isolated pancreas, prostate or gastric cancers)
   c. Two Lynch-related cancers (any age, one is colorectal or endometrial), OR
   d. Lynch-related cancer and ≥ 1 first degree relative has Lynch-related cancer (both occurred ≤60 years, one is colorectal or endometrial), OR
   e. Lynch-related cancer and ≥ 2 relatives (first / second / third degree relatives) have Lynch-related cancer (all occurring ≤75years, one is colorectal or endometrial), OR
   f. Lynch-related cancer and ≥ 3 relatives (first / second / third degree relatives) have Lynch-related cancer (occurring any age, one is colorectal or endometrial)

*Lynch-related cancers comprise: Colorectal cancer, Endometrial cancer, Epithelial ovarian cancer, Urothelial cancers, Transitional cell cancer of renal pelvis, cholangiocarcinoma, Small bowel and upper gastrointestinal cancers, Glioblastoma, endocervical cancer, multiple sebaceous tumours, prostate, gastric and pancreas

3. **Clinical Criteria for somatic (tumour) Lynch syndrome panel testing**
   a. Proband has colorectal or endometrial cancer with a dMMR tumour with normal BRAF and somatic MLH1 hypermethylation analysis AND germline testing did not reveal a pathogenic variant OR personal/family pattern of disease whereby demonstration of acquired MMR variants (and therefore exclusion of constitutional MMR abnormality) enables downscaling of surveillance
   b. Deceased affected individual with colorectal or endometrial cancer ≤60 years AND tumour featuring high/intermediate MSI or loss of staining of MMR protein(s) on IHC, AND one first degree relative with Lynch-related cancer ≤60 AND no living affected individual is available for genetic testing.

4. **Clinical Criteria for germline testing in an unaffected individual**
   a. First degree relative affected with Lynch-related cancer, AND
   b. Family history of colorectal cancer/Lynch-related cancers reaches Amsterdam Criteria (≥3 cases over ≥2 generations with ≥1 case affected <50 years) AND
   c. Tumour sample analysis from affected family member has been attempted and is not possible, failed, indeterminate or indicates MMR deficiency (via IHC or MSI), AND
   d. Somatic sequencing is not possible, or failed, AND
   e. No living affected individual is available for genetic testing

5. **Criteria for germline MLH1 promoter methylation**
   a. Families where MLH1 promotor methylation has been identified in tumour tissue in >1 affected individual with colorectal cancer ≤ 60

NOTE: The proband's cancer and majority of reported cancers in the family should have been confirmed

Testing of unaffected individuals can only be carried out by Clinical Genetics Services

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

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.

Overlapping indications

- M1.9 Multi-target NGS panel - small variant (MLH1, MSH2, MSH6, PMS2, POLE, POLD1) (M1 Colorectal carcinoma) should be used for somatic testing

Where in Pathway

At presentation following tumour studies (IHC/MSI)

Requesting Specialties

- Clinical Genetics
- Oncology
- Surgery*
- Gastroenterology
- Histopathology

* Surgery to cover colorectal and gynecological surgeons

Specialist Service Group

- Core

Associated Tests

Please note all the tests below will be undertaken for R210 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R210.2	Inherited MMR deficiency Lynch syndrome Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Inherited MMR deficiency (Lynch syndrome) (503)	Small panel
R210.4	Germline MLH1 promotor methylation	Singleton	Methylation	Single gene(s)	MLH1	Methylation testing
R210.6	Inherited MMR deficiency (Lynch syndrome)	Singleton	Exon level CNVs	PMS2	PMS2	MLPA or equivalent

R211 Inherited polyposis and early onset colorectal cancer - germline test

Testing Criteria

Living affected individual (proband) where the individual +/- family history meets **one** of the criteria. The proband has:

1. Any colorectal cancer OR endometrial cancer diagnosis under 40 years
2. Any small bowel cancer diagnosis under 40 years
3. Proband has endometrial or colorectal cancer (CRC) with ≥2 siblings with CRC/EC, where at least 1 diagnosed <50
3. ≥5 adenomatous polyps and colorectal cancer, OR
4. ≥5 adenomatous polyps (age <40 years), OR
5. ≥10 adenomatous polyps (age <60 years, OR
6. ≥20 adenomatous polyps (age ≥ 60 years), OR
7. ≥5 adenomatous polyps (age <60 years) and first degree relative with ≥5 adenomatous polyps or CRC (age <60 years), OR
8. A clinical diagnosis of serrated polyposis syndrome* IF:
   a. patient aged < 50 OR
   b. family history of ≥1 affected FDR with SPS OR
   c. evidence of dysplasia within any polyp

   *Clinical diagnosis of Serrated Polyposis Syndrome:
   a. Five or more serrated lesions/polyps proximal to the rectum all being at least 5 mm in size with two or more being at least 10mm in size,
   b. More than 20 serrated lesions/polyps of any size distributed through the large bowel with at least five being proximal to the rectum.

9. Hamartomatous polyposis syndromes:
   a. ≥ 5 hamartomatous polyps of the colorectum, OR
   b. ≥ 2 hamartomatous polyps throughout the GI tract, OR
   c. ≥ 1 hamartomatous polyp and a first / second degree relative has hamartomatous polyp.

Deceased affected individual (proband) where all the following are met;

(i) the individual +/- family history meets one of the above criteria, AND
(ii) a previously stored constitutional blood/DNA sample is available, AND
(iii) no living affected individual is available for genetic testing, AND
(iv) after discussion at specialist cancer genetics MDT

NOTE: The majority of polyps are histologically confirmed

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

Overlapping indications

- Inherited polyposis – somatic test should be used if no living affected individual is available for germline testing, no germline DNA sample has been stored from a deceased affected individual, and a molecular diagnosis is required to advise living relatives
- M1 Colorectal carcinoma should be used for somatic testing

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
- Gastroenterology
- Surgery*

*Surgery to cover colorectal surgeons

Specialist Service Group

- Core

Associated Tests

Please note all the tests below will be undertaken for R211 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R211.1	Inherited polyposis and early onset colorectal cancer - germline testing	Singleton	Small variants, CNVs	Panel of genes or loci	Inherited polyposis (504)	Small panel
R211.3	Inherited polyposis and early onset colorectal cancer - germline testing	Singleton	Exon level CNVs	PMS2	PMS2	MLPA or equivalent

R414 APC Associated Polyposis

Testing Criteria

Testing in children / young adults who may be too young to have developed bowel polyps. To be done prior to colonoscopy, on the basis of one or more of the following APC-associated findings:

1. Multifocal or bilateral CHRPE as assessed by experienced Ophthalmologist, OR
2. Aggressive fibromatosis/Desmoid tumour (CTNNB1 WT where testing performed) OR
3. Cribriform-morular variant of papillary thyroid cancer OR
4. Hepatoblastoma OR
5. Multiple osteomas of skull and mandible or multiple dental abnormalities (unerupted teeth, supernumerary teeth with dentigerous cysts or odontomas) in children/young adults
6. Affected individual of any age with gastric polyposis meeting GAPPs criteria* OR
7. Medulloblastoma with polyposis

Deceased affected individual (proband) where all the following are met;

(i) the individual +/- family history meets one of the above criteria, AND

(ii) a previously stored constitutional blood/DNA sample is available, AND

(iii) no living affected individual is available for genetic testing, AND

(iv) after discussion at specialist cancer genetics MDT

*Footnote: Diagnostic criteria of GAPPS (Worthley et al. Gut. 2012 May;61(5):774-9). GAPPs criteria apply to all individuals and not just children or young adults.

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

Overlapping indications

R211 for individuals with polyposis who should proceed to full polyposis panel

R359 Childhood solid tumor panel

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Surgery
- Oncology*

  *including paediatrics

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R414.1	APC Associated Polyposis	Singleton	small variant detection, CNVs	Single gene	APC (1212)	Single gene sequencing ≥ 10 amplicons

R212 Peutz Jeghers Syndrome

Testing Criteria

Living affected individual (proband) where the individual +/- family history meets one of the criteria.

1. ≥2 PJS-type hamartomatous polyps, OR
2. ≥1 PJS-type hamartomatous polyp and characteristic mucocutaneous pigmentation, OR
3. Characteristic mucocutaneous pigmentation age <10, OR
4. Sex cord tumours with annular tubules (SCAT) at any age
5. Adenoma malignum of the cervix at any age
6. ≥1 PJS-type hamartomatous polyp, AND ≥1 first / second degree relative with:
   a. ≥1 PJS-like feature, OR
   b. ≥2 PJS-related cancers (the two cancers can be in the same or different relatives), OR
7. Characteristic mucocutaneous pigmentation, AND ≥1 first / second degree relative with:
   a≥1 PJS-like feature, OR
   b. ≥2 PJS-related cancers (the two cancers can be in the same or different relatives)

Deceased affected individual (proband) where all the following are met;

(i) the individual +/- family history meets one of the above criteria, AND
(ii) a previously stored constitutional blood/DNA sample is available, AND
(iii) no living affected individual is available for genetic testing, AND
(iv) after discussion at specialist cancer genetics MDT

PJS-like features: characteristic mucocutaneous pigmentation, PJS-type hamartomatous polyps

PJS-related cancers: epithelial colorectal, gastric, pancreatic, breast, and ovarian cancers, sex cord tumors with annular tubules (SCTAT), adenoma malignum of the cervix, and Sertoli cell tumors (LCST) of the testes

NOTE: The majority of polyps should be histologically confirmed

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

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/at follow-up

Requesting Specialties

- Clinical Genetics
- Dermatology
- Gastroenterology
- Surgery

Specialist Service Group

- Inherited cancer

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R212.1	STK11 Single gene sequencing	Singleton	Small variants, CNVs	Single gene(s)	STK11 (1377)	Single gene sequencing >=10 amplicons

R213 PTEN Hamartoma Tumour Syndrome

Testing Criteria

Living affected individual (proband) where the individual +/- family history meets ONE of the criteria.

1. Macrocephaly AND Mucocutaneous lesions comprising one of the following:
   a. ≥ 6 facial papules, of which ≥ 3 are trichilemmoma,
   b. Cutaneous facial papules AND oral mucosal papillomatosis,
   c. Oral mucosal papillomatosis AND acral keratosis,
   d. ≥6 palmoplantar keratosis.
2. Macrocephaly AND ≥1 major criteria
3. Macrocephaly AND ≥ 3 minor criteria
4. Cerebellar dysplastic gangliocytoma (Adult Lhermitte-Duclos disease (LDD))
5. Cleveland Clinic PTEN risk calculator score corresponding to probability of pathogenic/likely pathogenic variant of 10%

PTEN-HTS-related mucocutaneous lesions comprise:

- Cutaneous facial papules, including trichilemmomas
- Oral mucosal papillomatosis
- Acral (dorsal) keratoses
- Palmoplantar keratoses

Major criteria:

- Breast cancer
- Epithelial thyroid cancer (non-medullary)
- Macrocephaly (occipital frontal circumference ≥97th percentile)
- Endometrial carcinoma

Minor criteria:

- Other thyroid lesions (e.g., adenoma, multinodular goitre)
- Intellectual disability (IQ ≤75)
- Hamartomatous intestinal polyps
- Fibrocystic disease of the breast
- Lipomas
- Fibromas
- Genitourinary tumours (especially renal cell carcinoma)
- Genitourinary malformation
- Uterine fibroids
- Oesophageal glycogenic acanthosis

Deceased affected individual (proband) where all the following are met;

(i) the individual +/- family history meets one of the above criteria, AND
(ii) a previously stored constitutional blood/DNA sample is available, AND
(iii) no living affected individual is available for genetic testing, AND
(iv) after discussion at specialist cancer genetics MDT

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

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/at follow-up

Requesting Specialties

- Clinical Genetics
- Dermatology
- Neurology

Specialist Service Group

- Inherited cancer

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R213.1	PTEN Single gene sequencing	Singleton	Small variants, CNVs	Single gene(s)	PTEN (1382)	Single gene sequencing >=10 amplicons

R214 Nevoid Basal Cell Carcinoma Syndrome or Gorlin syndrome

Testing Criteria

1. Living individual affected (proband) where the individual history meets:
   a. ≥ 1 major OR
   b. ≥ 2 minor criteria
2. Major criteria:

- Lamellar (sheet-like) calcification of the falx or clear evidence of calcification in an individual younger than age 20 years
- Jaw keratocyst: odontogenic keratocyst histologically
- Palmar/plantar pits (two or more)
- SHH medulloblastoma, confirmed on tumour testing
- Multiple basal cell carcinomas (BCCs) (>5 under 50)

3. Minor criteria:

- Childhood medulloblastoma where SHH pathway in tumour has not been investigated (also called primitive neuroectodermal tumor [PNET])
- Lympho-mesenteric or pleural cysts
- Macrocephaly (OFC >97th centile)
- Cleft lip/palate
- Vertebral/rib anomalies observed on chest x-ray and/or spinal x-ray; bifid/splayed/extra ribs; bifid vertebrae
- Preaxial or postaxial polydactyly
- Ovarian/cardiac fibromas
- Ocular anomalies (cataract, developmental defects, and pigmentary changes of the retinal epithelium)

Deceased affected individual (proband) where all the following are met;

(i) the individual +/- family history meets one of the above criteria, AND
(ii) a previously stored constitutional blood/DNA sample is available, AND
(iii) no living affected individual is available for genetic testing, AND
(iv) after discussion at specialist cancer genetics MDT

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

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/at follow-up

Requesting Specialties

- Clinical Genetics
- Dermatology

Specialist Service Group

- Inherited cancer

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R214.1	PTCH1; SUFU	Singleton	Small variants, CNVs	Small panel	PTCH1; SUFU (1373)	Small panel

R215 Hereditary diffuse gastric cancer

Testing Criteria

1. Living affected individual (proband) where the individual +/- family history **meets one of the criteria**. The proband has:
   a. Diffuse gastric cancer (<50 years).
   b. gastric in situ signet ring cells or pagetoid spread of signet ring cells under 50 years
   c. diffuse gastric cancer at any age with a personal history or FDR with cleft lip or cleft palate.
   d. double primary diffuse gastric cancer and lobular breast cancer (both <70 years).
   e. diffuse gastric cancer and ≥ 1 FDR/SDR with diffuse gastric cancer at any age.
   f. diffuse gastric cancer at any age and ≥1 FDR/SDR with lobular breast cancer <70 years.
   g. Lobular breast cancer and ≥FDR/SDR has diffuse gastric cancer (≥ 1 case occurred < 70 years).
   h. 2 cases of lobular breast cancer < 50 years e.g. bilateral or multiple ipsilateral tumours
   i. Bilateral lobular breast cancer < 70 years
   j. diffuse gastric cancer in any individual of Maori ethnicity

Deceased affected individual (proband) where all the following are met;

(i) the individual +/- family history meets one of the above criteria, AND

(ii) a previously stored constitutional blood/DNA sample is available, AND

(iii) no living affected individual is available for genetic testing, AND

(iv) after discussion at specialist cancer genetics MDT

NOTE: At least one cancer should be histologically confirmed

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

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/at follow-up

Requesting Specialties

- Clinical Genetics
- Gastroenterology
- Surgery*

*Surgery to cover upper gastro-intestinal surgeons

Specialist Service Group

- Inherited cancer

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R215.1	Hereditary diffuse gastric cancer	Singleton	Small variants, CNVs	Small panel	CDH1; CTNNA1 (1221)	Small panel

R216 Li Fraumeni Syndrome

Testing Criteria

Living affected individual (proband) where the individual +/- family history meets **ONE** of the criteria.

The proband has:

1. Rhabdomyosarcoma (≤ 5 years),
2. Rhabdomyosarcoma of embryonal anaplastic subtype (any age)
3. Adrenocortical cancer (any age),
4. Choroid plexus cancer (any age),
5. Breast cancer (≤ 30 years),
6. HER2 positive breast cancer (≤ 35 years),
7. Hypodiploid acute lymphoblastic leukaemia (<18 years)
8. SHH medulloblastoma (<18 years)
9. Jaw osteosarcoma (<18 years)
10. ≥2 LFS-related cancers (both occurring ≤ 46 years; two breast cancers not eligible),
11. ≥1 LFS-related cancer with ≥1 first / second degree relative with ≥1 LFS-related cancer (one case ≤ 46 years, the other case ≤ 56 years; two breast cancers not eligible),
12. Cancer with ≥2 first / second degree relatives with cancer; across the family there is:
    i. 1 individual with sarcoma ≤ 45 years, AND
    ii. 1 individual with any cancer ≤ 45 years, AND
    iii. 1 individual with either a sarcoma OR any cancer occurring ≤ 45 years

13. Proband with personal history of 2 or more POT1-associated cancers (cutaneous melanoma, chronic lymphocytic leukaemia, angiosarcoma, glioma but excluding two cases of cutaneous melanoma) OR Proband with POT1 associated cancer and ≥1 FDR/SDR affected with a POT1 associated cancer (excluding two cases of cutaneous melanoma)

Deceased affected individual (proband) where all the following are met;

(i) the individual +/- family history meets one of the above criteria, AND

(ii) a previously stored constitutional blood/DNA sample is available, AND

(iii) no living affected individual is available for genetic testing, AND

(iv) after discussion at specialist cancer genetics MDT

LFS-related cancers comprise: soft tissue sarcomas, osteosarcomas, adrenocortical carcinoma, central nervous system tumours and breast cancers including malignant phylloides tumours

NOTE: The proband's cancer and majority of reported cancers in the family should have been confirmed

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

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.

Overlapping indications

- The relevant cancer clinical indication (M coded) should be used for somatic testing (TP53)

Where in Pathway

At presentation/at follow-up

Requesting Specialties

- Clinical Genetics
- Oncology*

  *including paediatrics

Specialist Service Group

- Inherited cancer

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R216.1	Li Fraumeni Syndrome (1222) - small panel	Singleton	Small variants, CNVs	Small panel	TP53, POT1(1222)	Small panel

R219 Retinoblastoma

Testing Criteria

Testing of phenotypically affected individual where the proband has Retinoblastoma (unilateral, bilateral or multifocal) +/- family history. RB1 somatic test can be undertaken instead in tumour material where indicated.

Deceased affected individual (proband) where all the following are met;

(i) the individual +/- family history meets one of the above criteria, AND

(ii) a previously stored constitutional blood/DNA sample is available, AND

(iii) no living affected individual is available for genetic testing, AND

(iv) after discussion at specialist cancer genetics MDT

Testing in most patients will be arranged as part of management at one of the Highly Specialised Retinoblastoma Services

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

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present.

Overlapping indications

- M166 Retinoblastoma (paediatric) or the relevant cancer clinical indication (M coded) should be used for somatic testing

Where in Pathway

At presentation/at follow-up

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Inherited cancer

Associated Tests

Please note all the tests below will be undertaken for R219 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R219.1	RB1 Single gene sequencing	Singleton	Small variants	Single gene(s)	RB1 (1384)	Single gene sequencing >=10 amplicons
R219.2	RB1 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	RB1 (1384)	MLPA or equivalent

R220 Wilms tumour with features suggestive of predisposition

Testing Criteria

Wilms tumour, multiple nephrogenic rests or nephroblastomatosis with **ONE** or more of the following:

1. diagnosis <2 years, OR
2. Bilateral disease, OR
3. multifocal disease, OR
4.. Family history of Wilms tumour, OR
5. Unexplained proteinuria or renal failure, OR
6. Hypospadias, undescended testes or ambiguous genitalia, OR
7. Gonadoblastoma

Deceased affected individual (proband) where all the following are met;

(i) the individual +/- family history meets one of the above criteria, AND
(ii) a previously stored constitutional blood/DNA sample is available, AND
(iii) no living affected individual is available for genetic testing, AND
(iv) after discussion at specialist cancer genetics MDT

Overlapping indications

- Individuals with aniridia should be tested via the R38 Aniridia indication
- Individuals with hemihypertrophy, macroglossia or multiple features suggestive of Beckwith-Wiedemann should be tested via the R50 Isolated hemihypertrophy or macroglossia or R49 Beckwith-Wiedemann syndrome indication
- M18 Renal cell carcinoma or the associated pediatric cancer clinical indication (M173, M180, M165, M212) should be used for somatic testing

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

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/at follow-up

Requesting Specialties

- Clinical Genetics
- Oncology*
  including paediatrics

Specialist Service Group

- Inherited cancer

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R220.1	Wilms tumour with features suggestive of predisposition	Singleton	Small variants, CNVs	Small panel	Wilms tumour with features suggestive of predisposition (1108)	Small panel
R220.3	Wilms tumour with features suggestive of predisposition	Singleton	Methylation	Single interval	11p15 imprinted growth regulatory region	Methylation testing

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R220.4	Wilms tumour with features suggestive of predisposition	Singleton	CNVs	Single interval	11p15 imprinted growth regulatory region	MLPA or equivalent

R358 Familial rhabdoid tumours

Testing Criteria

Living affected individual (proband) where the proband has atypical teratoid/rhabdoid tumour (any age) OR Small cell carcinoma of the ovary, hypercalcaemic type (SCCOHT) (any age)

Deceased affected individual (proband) where all the following are met;

(i) the individual +/- family history meets one of the above criteria, AND
(ii) a previously stored constitutional blood/DNA sample is available, AND
(iii) no living affected individual is available for genetic testing, AND
(iv) after discussion at specialist cancer genetics MDT

NOTE: The proband's cancer should have been confirmed

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

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.

Likely to need to specify high coverage depth to detect mosaic SMARCB1 and SMARCA4 variants

Overlapping indications

- M120 Atypical teratoid/rhabdoid tumour (ATRT) should be used for somatic testing

Where in Pathway

At presentation/at follow-up

Requesting Specialties

- Clinical Genetics
- Oncology*

  * including paediatrics

Specialist Service Group

- Inherited cancer

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R358.1	Familial rhabdoid tumours Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Rhabdoid tumour predisposition (600)	Small panel

R359 Childhood solid tumours

Testing Criteria

Any presentation of an invasive solid tumour diagnosed at age ≤25, where no other Testing Criteria are met, OR other test did not identify pathogenic variant, AND the patient has NOT been investigated through:

1. Tumour WGS, OR
2. Another large germline cancer susceptibility panel, OR
3. Exome test through GMS or an alternative route

Deceased affected individual (proband) where all the following are met;

(i) the individual +/- family history meets one of the above criteria, AND

(ii) a previously stored constitutional blood/DNA sample is available, AND

(iii) no living affected individual is available for genetic testing, AND

(iv) after discussion at specialist cancer genetics MDT

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

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.

Overlapping indications

- The associated paediatric cancer clinical indication (M coded) should be used for somatic testing

Where in Pathway

At presentation/at follow-up

Requesting Specialties

- Oncology
- Clinical Genetics

Specialist Service Group

- Inherited cancer

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R359.1	Childhood solid tumours WES or Medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Tumour predisposition - childhood onset (243)	WES or Medium panel

R224 Inherited renal cancer

Testing Criteria

Testing of individual (proband) affected with renal cancer where the individual +/- family history meets one of the following criteria. The proband has

1. Renal cancer (≤ 46 years), OR
2. Type 2 papillary HLRCC associated RCC (WHO pathology definition) OR tubulo-papillary renal tumour at any age , OR
3. Bilateral/multifocal renal cancer (any age), OR
4. A renal cancer AND first degree relative with renal cancer, both cases diagnosed under 60 years of age
5. renal cancer AND second degree relative with renal cancer, both cases diagnosed under 50 years of age
6. Renal cancer and features of inherited cancer syndrome such as:
    - Cerebellar/spinal haemangioblastoma
    - Retinal angioma
    - Phaeochromocytoma/paraganglioma
    - Spontaneous pneumothorax
    - Fibrofolliculomas
    - Trichodiscomas
    - Cutaneous Leiomyomata
    - Uterine leiomyomas (under 40 years of age with pathology suggesting FH variant)
    - Mesothelioma
    - Uveal melanoma

Deceased affected individual (proband) where all the following are met;

(i) the individual +/- family history meets one of the above criteria, AND

(ii) a previously stored constitutional blood/DNA sample is available, AND

(iii) no living affected individual is available for genetic testing, AND

(iv) after discussion at specialist cancer genetics MDT

Referral to Clinical Genetics is required for karyotype in families with ≥3 FDR/SDR with renal cancer following MDT discussion

NOTE: The proband's cancer and majority of reported cancers in the family should have been confirmed

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

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.

Overlapping indications

- M18 Renal cell carcinoma or the associated pediatric cancer clinical indication (M173, M180, M165, M212) should be used for somatic testing

Where in Pathway

At presentation/at follow-up

Requesting Specialties

- Clinical Genetics
- Urology

  Nephrology

Specialist Service Group

Inherited cancer

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R224.1	Inherited renal cancer Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Inherited renal cancer (521)	Small panel

R225 Von Hippel Lindau syndrome

Testing Criteria

Testing of individual (proband) affected with VHL-related tumours where the individual/family history meets one of the following criteria:

a. Retinal angioma, spinal or endolymphatic sac tumour (<40 years), OR
b. Cerebellar OR spinal haemangioblastoma (<60 years), OR
c. ≥2 VHL-related tumours (any age), OR
d. ≥1 VHL-related tumour and a first degree relative with ≥1 VHL-related tumour (where one of the tumours is retinal angioma / hemangioblastoma)

Deceased affected individual (proband) where all the following are met;

(i) the individual +/- family history meets one of the above criteria, AND
(ii) a previously stored constitutional blood/DNA sample is available, AND
(iii) no living affected individual is available for genetic testing, AND
(iv) after discussion at specialist cancer genetics MDT

VHL-related tumours comprise: Retinal angioma, Spinal or cerebellar hemangioblastoma, adrenal or extra-adrenal pheochromocytoma, Renal cell carcinoma, multiple renal and/or pancreatic cysts, endolymphatic sac tumors, papillary cystadenomas of the epididymis or broad ligament, neuroendocrine tumour of the pancreas

NOTE: The proband's cancer and majority of reported cancers in the family should have been confirmed

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

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/at follow-up

Requesting Specialties

- Clinical Genetics
- Endocrinology
- Nephrology
- Neurology
- Ophthalmology
- Urology
- Neurosurgery

Specialist Service Group

- Inherited cancer

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R225.1	VHL Single gene sequencing	Singleton	Small variants, CNVs	Single gene(s)	VHL (1403)	Single gene sequencing >=10 amplicons

R254 Familial melanoma

Testing Criteria

Testing of phenotypically affected individual (proband) where the individual +/- family history meets **ONE** of the following criteria. The proband has:

a. ≥1 melanoma < 18 years
b. ≥2 melanomas and/or melanomas in situ age <30 years, OR
c. ≥3 melanoma and/or melanomas in situ at any age, OR
d. Melanoma and/or melanoma in situ AND ≥2 relatives (first / second / third degree relatives) with melanoma and/or melanoma in situ, OR
e. Melanoma and/or melanoma in situ AND ≥1 first degree relative with melanoma and/or melanoma in situ; one individual has multiple melanomas and/or melanomas in situ, OR
f. ≥1 Melanoma and/or melanoma in situ OR melanoma and/or melanoma in situ and atypical moles AND ≥1 first degree relative with pancreatic cancer aged <60, OR
g. Atypical moles AND ≥2 relatives (first / second degree relatives) with melanoma and/or melanoma in situ, OR

Deceased affected individual (proband) where all the following are met;

(i) the individual +/- family history meets one of the above criteria, AND
(ii) a previously stored constitutional blood/DNA sample is available, AND
(iii) no living affected individual is available for genetic testing, AND
(iv) after discussion at specialist cancer genetics MDT

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

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.

Overlapping indications

- M7 Melanoma (adult) and M187 Uveal melanoma should be used for somatic testing

Where in Pathway

At presentation/at follow-up

Requesting Specialties

- Clinical Genetics
- Dermatology

Specialist Service Group

- Inherited cancer

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R254.1	Familial melanoma Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Familial melanoma (522)	Small panel

R422 BAP1 associated tumour predisposition syndrome

Testing Criteria

Individual has ONE of the following:

1. Individual with a personal history of two or more core BAP1 associated tumours (mesothelioma, uveal melanoma, cutaneous melanoma, renal cell cancer or BAP1 inactivated melanocytic tumour- BIMT) (excluding two cases of melanoma)
2. Individual with a personal history of two or more inactivated melanocytic tumours (BIMT) (Also known as BAPoma, atypical Spitz naevus, Melanocytic BAP1-associated intradermal tumor (MBAIT) or nevoid melanoma-like melanocytic proliferation (NEMMP)
3. Individual with a personal history of a BAP1 associated tumour and a first degree relative with a BAP1 core associated tumour (mesothelioma, uveal melanoma, cutaneous melanoma, renal cell cancer or BAP1 inactivated melanocytic tumour- BIMt) (excluding two cases of melanoma or renal cancer)
4. Individual with mesothelioma (less than 60 years) in the absence of asbestos exposure
5. Individual with uveal melanoma (<40 years)

Deceased affected individual (proband) where all the following are met;

(i) the individual +/- family history meets one of the above criteria, AND

(ii) a previously stored constitutional blood/DNA sample is available, AND

(iii) no living affected individual is available for genetic testing, AND

(iv) after discussion at specialist cancer genetics MDT

BAP1 associated tumours= uveal melanoma, cutaneous melanoma, basal cell cancer, BAP1-inactivated melanocytic tumors (BIMT), malignant mesothelioma (lung or peritoneal), renal cell carcinoma, meningioma, cholangiocarcinoma or hepatocellular carcinoma.

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

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.

Overlapping indications

R254 Familial melanoma

R214 Nevoid Basal Cell Carcinoma Syndrome or Gorlin syndrome

R224 Inherited renal cancer

Where in Pathway

At presentation/at follow-up

Requesting Specialties

- Clinical Genetics
- Dermatology
- Oncology

Specialist Service Group

- Inherited cancer

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R422.1	BAP1 associated tumour predisposition syndrome	Singleton	Small variants, CNVs	Single gene	BAP1 (1216)	Single gene sequencing >=10 amplicons

R363 Inherited predisposition to GIST

Testing Criteria

Testing of affected individual (proband) where the individual +/- family history meets the following criteria:
The proband has GIST (gastrointestinal stromal tumour):

1. Diagnosed age before age 50, OR
2. With ≥1 relative (first / second / third degree relative) with GIST, phaeochromocytoma / paraganglioma

NOTE: The proband's cancer and majority of reported cancers in the family should have been confirmed

Deceased affected individual (proband) where all the following are met;

(i) the individual +/- family history meets one of the above criteria, AND
(ii) a previously stored constitutional blood/DNA sample is available, AND
(iii) no living affected individual is available for genetic testing, AND
(iv) after discussion at specialist cancer genetics MDT

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

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.

Overlapping indications

- M8 Gastrointestinal stromal tumour should be used for somatic testing
- R223 Inherited phaeochromocytoma and paraganglioma excluding NF1

Where in Pathway

At presentation/at follow-up

Requesting Specialties

- Clinical Genetics
- Endocrinology
- Gastroenterology

Specialist Service Group

- Inherited cancer

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R363.1	Inherited predisposition to GIST Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Inherited predisposition to GIST (523)	Small panel

R364 DICER1-related cancer predisposition

Testing Criteria

1. Testing of affected individual (proband) where the individual has one of the following diagnoses:

Pleuropulmonary blastoma or Lung cyst(s) in childhood, especially if multi-septated, multiple or bilateral; Thoracic, uterine, cervical or ovarian embryonal rhabdomyosarcoma; Cystic nephroma; Genitourinary sarcoma including undifferentiated sarcoma in childhood; Ovarian Sertoli Leydig tumour; Gynandroblastoma; Genitourinary/gynaecologic neuroendocrine tumors; Childhood-onset multinodular goitre or differentiated thyroid cancer (papillary or follicular); Ciliary body medulloepithelioma; Nasal chondromesenchymal hamartoma; Pineoblastoma; Pituitary blastoma, OR

2. Testing of affected individual where there is a combination of two of the following diagnoses, either both in one affected individual or in two affected first degree relatives;

Lung cyst(s) in adults; Wilms tumor; Multinodular goiter or differentiated thyroid cancer; Embryonal rhabdomyosarcoma other than thoracic or gynaecologic; Poorly differentiated neuroendocrine tumour; Undifferentiated sarcoma; Macrocephaly

Deceased affected individual (proband) where all the following are met;

(i) the individual +/- family history meets one of the above criteria, AND

(ii) a previously stored constitutional blood/DNA sample is available, AND

(iii) no living affected individual is available for genetic testing, AND

(iv) after discussion at specialist cancer genetics MDT

NOTE: The proband's cancer and majority of reported cancers in the family should have been confirmed

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

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.

Overlapping indications

- M245 Ovarian sex cord stromal tumours

Where in Pathway

At presentation/at follow-up

Requesting Specialties

- Clinical Genetics
- Paediatric oncology
- Paediatric endocrinology

Specialist Service Group

- Inherited cancer

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R364.1	DICER1 related cancer predisposition Single gene sequencing	Singleton	Small variants, CNVs	Single gene(s)	DICER1 (1320)	Single gene sequencing >=10 amplicons

R365 Fumarate hydratase-related tumour syndromes

Testing Criteria

Testing of affected individual (proband) with hereditary leiomyomatosis and renal cell cancer (HLRCC) or other FH deficiency disorder where the individual +/- family history meets one of the following criteria. The proband has:

a. Type 2 papillary, HLRCC associated RCC (WHO pathology definition) OR tubulo-papillary renal tumour at any age, OR

b. Two of: cutaneous leiomyomata, renal tumour (any histology) , OR uterine leiomyomata with classic histological features < 40 years OR

c. Cutaneous leiomyomata AND one first / second / third degree relative with renal tumour, OR

d. Cutaneous leiomyomata AND two first / second / third degree relatives with cutaneous leiomyomata OR uterine leiomyomata with classic histological features < 40 years, OR

e. Uterine leiomyomata with classic histological features (age <40) OR

f. Multiple cutaneous leiomyomata

Deceased affected individual (proband) where all the following are met;

(i) the individual +/- family history meets one of the above criteria, AND

(ii) a previously stored constitutional blood/DNA sample is available, AND

(iii) no living affected individual is available for genetic testing, AND

(iv) after discussion at specialist cancer genetics MDT

NOTE: Cutaneous leiomyomata should be histologically confirmed; uterine leiomyomata and renal tumours should be medically documented

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

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.

Overlapping indications

- M18 Renal cell carcinoma or the associated pediatric cancer clinical indication (M173, M180, M165, M212) should be used for somatic testing
- M246 Uterine smooth muscle tumours

Where in Pathway

At presentation/at follow-up

Requesting Specialties

- Clinical Genetics
- Dermatology
- Urology
- Nephrology

Specialist Service Group

- Inherited cancer

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R365.1	FH Single gene sequencing	Singleton	Small variants	Single gene(s)	FH (1335)	Single gene sequencing >=10 amplicons

R367 Inherited pancreatic cancer

Testing Criteria

Testing of affected individual (proband) where the individual +/- family history meets one of the following criteria. The proband has:

1. Pancreatic cancer age <60, OR
2. Pancreatic cancer age <70, AND
   a. Breast cancer age <60, melanoma age <60, OR ovarian cancer, OR
   b. One first / second degree relative with pancreatic cancer age <60, OR
   c. Two or more first / second degree relatives with any of breast cancer age <60, melanoma age <60, OR ovarian cancer OR two or more with pancreatic cancer (any age)

Deceased affected individual (proband) where all the following are met;

(i) the individual +/- family history meets one of the above criteria, AND

(ii) a previously stored constitutional blood/DNA sample is available, AND

(iii) no living affected individual is available for genetic testing, AND

(iv) after discussion at specialist cancer genetics MDT

NOTE: The proband's cancer and majority of reported cancers in the family should have been confirmed. Pancreatic cancer is adenocarcinoma and not neuroendocrine tumour.

If there is a family history of BRCA related cancers (breast, ovarian, prostate and pancreatic), please consider if R208 Inherited Breast Cancer panel testing is required.

If there is a family history of melanoma, please consider if R254 Familial Melanoma panel testing is required.

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

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.

Overlapping indications

- M219 Pancreatic cancer should be used for somatic testing

Where in Pathway

At presentation/at follow-up

Requesting Specialties

- Clinical Genetics
- Gastroenterology
- Oncology

Specialist Service Group

- Inherited cancer

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R367.1	Inherited pancreatic cancer Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Inherited pancreatic cancer (524)	Small panel

R404 Testing of unaffected individuals for inherited cancer predisposition syndromes

Testing Criteria

Germline testing of unaffected individuals for specific inherited cancer predisposition syndromes where the following criteria are met:

1. There are no living affected relatives available for testing, AND
2. Any applicable somatic testing on deceased relatives tumour samples has been performed first, AND
3. The individual to be tested is deemed to have ≥10% chance of having a monogenic variant (deceased first degree relative with ≥20% chance), AND
4. This is agreed by specialist cancer genetics MDT

For testing for hereditary breast and ovarian cancer and inherited MMR deficiency (Lynch syndrome), unaffected individuals must meet criteria as specified under relevant indications R208/R215

NOTE: All cancers must be confirmed

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Core and Inherited cancer; depending on the cancer of suspicion

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R404.1	Inherited cancer predisposition gene sequencing	Singleton	Small variants, CNVs	Single gene(s)	As dictated by clinical indication	Single gene sequencing >=10 amplicons
R404.3	Relevant inherited cancer panel Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Relevant inherited cancer panel	Small panel

R430 Inherited prostate cancer

Testing Criteria

- Proband diagnosed with prostate cancer at <50 years
- Ashkenazi Jewish ancestry and prostate cancer at any age
- ≥1 grandparent from Whalsay (Shetland) and prostate cancer at any age
- Proband diagnosed with metastatic prostate cancer <60 years
- Proband diagnosed with prostate cancer with a CanRisk score of >10% and where they do not meet criteria for R208, R207 or R210 - see overlapping Clinical Indications

Deceased affected individual (proband) where all the following are met;

(i) the individual +/- family history meets one of the above criteria, AND

(ii) a previously stored constitutional blood/DNA sample is available, AND

(iii) no living affected individual is available for genetic testing, AND

(iv) after discussion at specialist cancer genetics MDT

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present.

Overlapping indications

- R208 Inherited breast cancer and ovarian cancer - Proband affected with prostate cancer who has a personal/family history of other BRCA related cancers see R208 (BRCA related cancers = breast, ovarian, pancreatic, prostate).
- R207 Inherited ovarian cancer (without breast cancer)
- R210 Inherited MMR deficiency (Lynch syndrome) - For prostate cancer with personal/family history of other Lynch related cancers see R210 (See list of Lynch related cancers in R210).
- R444 NICE approved PARP inhibitor treatment
- M218 prostate cancer should be used for somatic testing

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
- Oncology
- Urology

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R430.1	Inherited prostate cancer	Singleton	Small variants, CNVs	Small panel of genes	Inherited prostate cancer (1223)	Small panel

R444 NICE approved PARP inhibitor treatment

Testing Criteria

Testing Criteria only applies to patients not meeting R208/R430 criteria AND with current cancer diagnosis for treatment decisions.

R444.1 Breast Cancer

1. For people with triple negative breast cancer who have received neo-adjuvant chemotherapy: residual invasive cancer in the breast, the resected lymph nodes (non-pathological complete response) or both at the time of surgery
2. For people with triple-negative breast cancer having adjuvant chemotherapy:
    - node-positive OR
    - node-negative cancer with a primary tumour ≥ 2 cm
3. For people with hormone receptor-positive, HER2-negative breast cancer who have received neoadjuvant chemotherapy:
    - residual invasive cancer in the breast, the resected lymph nodes (non-pathologic complete response) or both at the time of surgery, AND
    - a CPS + EG score of ≥3 based on pre-treatment clinical and posttreatment pathological stage, receptor status and histological grade
4. For people with hormone receptor-positive, HER2-negative breast cancer having adjuvant chemotherapy:
    - 4 or more pathologically confirmed positive lymph nodes.
5. For people who have HER2-negative locally advanced or metastatic breast cancer:
    - Patients should have been previously treated with an anthracycline and/or a taxane in the neo/adjuvant, locally advanced or metastatic setting unless patients were not suitable for these treatments.
    - Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine-based therapy, or be considered unsuitable for endocrine-based therapy.

R444.2 Prostate Cancer

Metastatic, castration-resistant prostate cancer where somatic tumour testing (M218.1) has failed.

Overlapping indications

- R208 Inherited breast cancer and ovarian cancer
- R430 Inherited prostate cancer
- M3 breast cancer should be used for somatic testing
- M218 prostate cancer should be used for somatic testing

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 earliest stage, either at primary surgery or after neo-adjuvant chemotherapy

Requesting Specialties

- Clinical Genetics
- Surgery
- Oncology

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R444.1	NICE approved PARP inhibitor treatment – breast cancer	Singleton	Small variants, CNVs	Small panel of genes	BRCA1; BRCA2;	Small panel
R444.2	NICE approved PARP inhibitor treatment – prostate cancer	Singleton	Small variants, CNVs	Small panel of genes	BRCA1, BRCA2	Small panel

Part XII. Lipids

R134 Familial hypercholesterolaemia

Testing Criteria

Dutch (or Welsh) lipid clinic score >5, OR

Simon Broome criteria indicate possible FH (following assessment in a specialist Lipid Clinic or Familial Hypercholesterolaemia service)

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

- Cardiology
- Chemical Pathology
- Clinical Genetics
- Metabolic Medicine
- Paediatrics

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R134.1	Familial hypercholesterolaemia Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Familial hypercholesterolaemia – targeted panel (772)	Small panel

R324 Familial Chylomicronaemia Syndrome (FCS)

Testing Criteria

1. Fasting triglycerides >20mmol/L, AND
2. Exclusion of secondary causes of hypertriglyceridaemia e.g. excess alcohol, uncontrolled diabetes

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

- Cardiology
- Chemical Pathology
- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R324.1	Familial Chylomicronaemia Syndrome (FCS) Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Lipoprotein lipase deficiency (527)	Small panel

Part XIII. Metabolic

R380 Niemann Pick disease type C

Testing Criteria

Clinical and laboratory features characteristic of Niemann-Pick disease type C

Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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 laboratory testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Please note all the tests below will be undertaken for R380 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R380.1	NPC1; NPC2	Singleton	Small variants	Small panel	NPC1; NPC2 (1347)	Small panel
R380.2	NPC1; NPC2 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	NPC1; NPC2 (1347)	MLPA or equivalent

R98 Likely inborn error of metabolism

Testing Criteria

Clinical feature of a likely inborn error of metabolism where targeted testing is not possible

Testing Criteria for Semi-Rapid Testing

- Children or adults with a suspected likely inborn error of metabolism, where a rapid diagnosis will direct immediate treatment or medical care of the patient, and:

- Biochemical testing and/or enzyme analysis specifically points to one particular gene and condition, or to a subset of genes and conditions for which specific testing can be provided using a “slice” or small subset of genes of the R98.2 gene panel.

- This testing pathway is not intended as an exclusion test for patients with a broad differential diagnosis, and without a specific diagnosis from biochemical testing/enzyme analyses. These referrals will not be accepted and will be directed to the WGS route.

- The patient is either not eligible for the R14 pathway or Rapid R98 is considered to be the more appropriate test.

Overlapping indications

- Targeted tests for specific metabolic disorders should be used where clinical features or biochemical/enzyme testing results are rapidly available and strongly suggestive of the relevant disorder(s)

Where in Pathway

At presentation following clinically relevant, rapidly available investigations

Where in Pathway for Semi-Rapid Testing

At presentation following clinically relevant, rapidly available investigations. All cases must be agreed in advance with the testing laboratory.

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Requesting Specialties for Semi-Rapid Testing

- Clinical Genetics
- Metabolic Medicine
- Neurology
- Neonatology

Specialist Service Group

- Metabolic

Associated Tests

R98.3 is only for semi urgent testing

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R98.2	Inborn errors of metabolism WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Inborn errors of metabolism (467)	WGS
R98.3	Inborn errors of metabolism WES	Trio	Exon level CNVs, Small variants	Panel of genes or loci	Inborn errors of metabolism (467)	WES

R270 Smith-Lemli-Opitz syndrome

Testing Criteria

Clinical and biochemical features characteristic of Smith-Lemli-Opitz syndrome

Overlapping indications

- R98 Likely inborn error of metabolism, R27 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with atypical features in whom a broader differential diagnosis is under consideration

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 biochemical testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Please note all the tests below will be undertaken for R270 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R270.1	DHCR7 Single gene sequencing	Singleton	Small variants	Single gene(s)	DHCR7 (1392)	Single gene sequencing >=10 amplicons
R270.2	DHCR7 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	DHCR7 (1392)	MLPA or equivalent

R231 Neuronal ceroid lipofuscinosis

Testing Criteria

Clinical and laboratory features characteristic of Neuronal ceroid lipofuscinosis including presence of vacuolate lymphocytes, presence of pathological inclusions on tissue biopsy or enzyme deficiency

Overlapping indications

- R271 Neuronal ceroid lipofuscinosis type 2 test should be considered where clinical features are specific to CLN2
- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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 histological analysis and/or enzyme testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R231.2	Neuronal ceroid lipofuscinosis Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Neuronal ceroid lipofuscinosis (526)	Small panel

R271 Neuronal ceroid lipofuscinosis type 2

Testing Criteria

Clinical and laboratory features characteristic of neuronal ceroid lipofuscinosis type 2

Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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 histological analysis and/or enzyme testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R271.1	TPP1 Single gene sequencing	Singleton	Small variants	Single gene(s)	TPP1 (1371)	Single gene sequencing >=10 amplicons

R334 Cystinosis

Testing Criteria

1. Paediatric presentation with nephropathic cystinosis, OR
2. Adult presentation with non-nephropathic cystinosis

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
- Gastroenterology
- Metabolic Medicine
- Nephrology
- Neurology
- Ophthalmology

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R334.1	CTNS Single gene sequencing	Singleton	Small variants, CNVs	Single gene(s)	CTNS (1319)	Single gene sequencing >=10 amplicons

R335 Fabry disease

Testing Criteria

- In males: clinical and laboratory features characteristic of Fabry disease following alpha-galactosidase A enzyme testing
- In females: clinical features characteristic of Fabry disease

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

Following alpha-galactosidase A enzyme testing

Requesting Specialties

- Cardiology
- Clinical Genetics
- Dermatology
- Metabolic Medicine
- Nephrology
- Ophthalmology

Specialist Service Group

- Metabolic

Associated Tests

Please note all the tests below will be undertaken for R335 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R335.1	GLA Single gene sequencing	Singleton	Small variants	Single gene(s)	GLA (1323)	Single gene sequencing <10 amplicons
R335.2	GLA MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	GLA (1323)	MLPA or equivalent

R325 Lysosomal acid lipase deficiency

Testing Criteria

Biochemically established lysosomal acid lipase deficiency

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

- Chemical Pathology
- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R325.1	LIPA Single gene sequencing	Singleton	Small variants	Single gene(s)	LIPA (1354)	Single gene sequencing >=10 amplicons

R323 Sitosterolaemia

Testing Criteria

Elevated plasma beta-sitosterol with development of xanthomata before the age of 30

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

- Cardiology
- Chemical Pathology
- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R323.1	ABCG5; ABCG8	Singleton	Small variants	Small panel	ABCG5; ABCG8 (1391)	Small panel

R286 Tay-Sachs disease

Testing Criteria

Clinical and laboratory features characteristic of Tay-Sachs disease

Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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 laboratory testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R286.1	HEXA Single gene sequencing	Singleton	Small variants	Single gene(s)	HEXA (1396)	Single gene sequencing >=10 amplicons

R272 Gaucher disease

Testing Criteria

Clinical features and glucocerebrosidase activity indicative of Gaucher disease types 1, 2, or 3, including the perinatal lethal and cardiovascular subtypes.

Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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 enzyme testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology
- Cardiology

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R272.1	GBA Single gene sequencing	Singleton	Small variants	Single gene(s)	GBA (1336)	Single gene sequencing >=10 amplicons

R273 Glycogen storage disease V

Testing Criteria

Clinical and laboratory features characteristic of Glycogen storage disease type V including:

1. Elevated baseline serum CK, AND
2. Characteristic lactate/lactate:ammonia profile after exercise

Overlapping indications

- Broader R274 Glycogen storage disease panel test should be used where a broader differential diagnosis of glycogen storage diseases is under consideration
- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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 laboratory testing

Requesting Specialties

- Cardiology
- Clinical Genetics
- Hepatology
- Metabolic Medicine
- Neurology
- Paediatrics

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R273.1	PYGM Single gene sequencing	Singleton	Small variants	Single gene(s)	PYGM (1340)	Single gene sequencing >=10 amplicons

R274 Glycogen storage disease

Testing Criteria

Clinical and laboratory features characteristic of Glycogen storage disease:

1. Persistent hypoglycaemia with other metabolic disorders excluded, AND one or more of the following
    a. Persistent hepatomegaly in childhood, OR
    b. Liver biopsy suggestive of glycogen storage disease, OR
    c. Neuromuscular presentation suggestive of glycogen storage disease, OR
    d. Affected first degree relative

OR

2. Glycogen accumulation in the relevant tissue, AND one or more of the following:
    a. Evidence of liver involvement: hepatomegaly OR hypoglycaemia with other metabolic disorders excluded, OR
    b. Evidence of muscle involvement: myalgia OR rhabdomyolysis OR muscle weakness, OR
    c. Evidence of cardiac involvement: cardiomegaly OR cardiomyopathy, OR
    d. Other general evidence - at least two of: myopathy, cardiomyopathy, respiratory weakness, vacuolar myopathy on muscle biopsy, pathological pattern on oligosaccharides

Overlapping indications

- R273 Glycogen storage disease V test should be considered where clinical features are specific to Glycogen storage disease V (McArdle disease)
- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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 laboratory testing

Requesting Specialties

- Cardiology
- Clinical Genetics
- Hepatology
- Metabolic Medicine
- Neurology
- Paediatrics

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R274.1	Glycogen storage disease WES or medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Glycogen storage disease (528)	WES or Medium Panel

R276 Lysosomal storage disorder

Testing Criteria

1. Clinical phenotype or radiological signs suggesting a lysosomal storage disorder, AND
2. Abnormal urine MPS or oligosaccharides screen or white cell enzymes analysis that are indicative of lysosomal storage disorder but do not allow more targeted testing

Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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 laboratory testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R276.1	Lysosomal storage disorder WES or medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Lysosomal storage disorder (529)	WES or Medium Panel

R288 GM1 Gangliosidosis and Mucopolysaccharidosis Type IVB

Testing Criteria

Clinical and laboratory features characteristic of GM1 Gangliosidosis or Mucopolysaccharidosis Type IVB

Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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 laboratory testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R288.1	GLB1 Single gene sequencing	Singleton	Small variants	Single gene(s)	GLB1 (1341)	Single gene sequencing >=10 amplicons

R277 Mucopolysaccharidosis type IH/S

Testing Criteria

Clinical and laboratory features characteristic of Mucopolysaccharidosis type IH/S (Hurler-Scheie syndrome)

Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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 laboratory testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R277.1	IDUA Single gene sequencing	Singleton	Small variants	Single gene(s)	IDUA (1360)	Single gene sequencing >=10 amplicons

R280 Krabbe disease – GALC deficiency

Testing Criteria

Clinical and laboratory features characteristic of Krabbe disease due to GALC deficiency

Overlapping indications

- R281 Krabbe disease - Saposin A deficiency should be used in individuals with clinical and laboratory features characteristic of atypical Krabbe disease due to Saposin A deficiency
- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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 laboratory testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Please note all the tests below will be undertaken for R280 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R280.1	GALC Single gene sequencing	Singleton	Small variants	Single gene(s)	GALC (1351)	Single gene sequencing >=10 amplicons
R280.2	GALC MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	GALC (1351)	MLPA or equivalent

R281 Krabbe disease - Saposin A deficiency

Testing Criteria

Clinical and laboratory features characteristic of atypical Krabbe disease due to Saposin A deficiency

Overlapping indications

- R280 Krabbe disease – GALC deficiency should be used in individuals with clinical and laboratory features characteristic of atypical Krabbe disease due to GALC deficiency
- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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 laboratory testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R281.1	PSAP Single gene sequencing	Singleton	Small variants	Single gene(s)	PSAP (1352)	Single gene sequencing >=10 amplicons

R278 Mucopolysaccharidosis type II

Testing Criteria

Clinical and laboratory features characteristic of Mucopolysaccharidosis type II

Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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 laboratory testing

Requesting Specialties

- Cleft clinics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Please note all the tests below will be undertaken for R278 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R278.1	IDS Single gene sequencing	Singleton	Small variants	Single gene(s)	IDS (1361)	Single gene sequencing >=10 amplicons
R278.2	IDS Targeted variant testing	Singleton	Small variants	Single gene(s)	IDS (1361)	Targeted variant testing

R287 Mucopolysaccharidosis type IVA

Testing Criteria

Clinical and laboratory features characteristic of Mucopolysaccharidosis type IVA

Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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 laboratory testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R287.1	GALNS Single gene sequencing	Singleton	Small variants	Single gene(s)	GALNS (1364)	Single gene sequencing >=10 amplicons

R289 Mucolipidosis II and III Alpha/Beta

Testing Criteria

Clinical and laboratory features characteristic of Mucolipidosis II or Mucolipidosis III Alpha/Beta

Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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 laboratory testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R289.1	GNPTAB Single gene sequencing	Singleton	Small variants	Single gene(s)	GNPTAB (1359)	Single gene sequencing >=10 amplicons

R290 Mucopolysaccharidosis type VI

Testing Criteria

Clinical and laboratory features characteristic of Mucopolysaccharidosis type VI

Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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 laboratory testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R290.1	ARSB Single gene sequencing	Singleton	Small variants	Single gene(s)	ARSB (1365)	Single gene sequencing >=10 amplicons

R291 Mucopolysaccharidosis type IIIA

Testing Criteria

Clinical and laboratory features characteristic of Mucopolysaccharidosis type IIIA

Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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 laboratory testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R291.1	SGSH Single gene sequencing	Singleton	Small variants	Single gene(s)	SGSH (1362)	Single gene sequencing >=10 amplicons

R292 Mucopolysaccharidosis type IIIB

Testing Criteria

Clinical and laboratory features characteristic of Mucopolysaccharidosis type IIIB

Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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 laboratory testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R292.1	NAGLU Single gene sequencing	Singleton	Small variants	Single gene(s)	NAGLU (1363)	Single gene sequencing >=10 amplicons

R282 Niemann-Pick disease type A or B

Testing Criteria

Clinical and laboratory features characteristic of Niemann-Pick disease type A or B

Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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 laboratory testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R282.1	SMPD1 Single gene sequencing	Singleton	Small variants	Single gene(s)	SMPD1 (1375)	Single gene sequencing >=10 amplicons

R285 Sandhoff disease

Testing Criteria

Clinical and laboratory features characteristic of Sandhoff disease

Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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 laboratory testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R285.1	HEXB Single gene sequencing	Singleton	Small variants	Single gene(s)	HEXB (1385)	Single gene sequencing >=10 amplicons

R283 Phenylketonuria

Testing Criteria

1. Likely phenylketonuria identified following diagnostic metabolic testing **OR**
2. Testing patients diagnosed with PKU to indicate sapropterin responsiveness

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

Following neonatal screening or diagnostic metabolic testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R283.1	PAH Single gene sequencing	Singleton	Small variants, CNVs	Single gene(s)	PAH (1378)	Single gene sequencing >=10 amplicons

R450 Diagnostic testing for Isovaleric acidaemia

Testing Criteria

Likely isovaleric acidaemia identified following diagnostic metabolic testing

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. In the case of isovaleric acidaemia, this means that testing is almost exclusively used at those in whom biochemical results indicate a likely pseudodeficiency allele is present.

Testing following newborn screening should follow the established sample and testing pathways set out in the newborn screening protocol and use code R279

Where in Pathway

Following diagnostic metabolic testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neonatology
- Obstetrics
- Paediatrics

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R450.1	Diagnostic testing for Isovaleric acidaemia	Singleton	Small variants	Single interval	IVD	Single gene sequencing >=10 amplicons

R279 Isovaleric acidaemia newborn screening follow up

Testing Criteria

Likely isovaleric acidaemia identified following neonatal screening

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. In the case of isovaleric acidaemia, this means that testing is almost exclusively used at those in whom biochemical results indicate a likely pseudodeficiency allele is present.

Testing following newborn screening should follow the established sample and testing pathways set out in the newborn screening protocol

Where in Pathway

Following neonatal screening

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neonatology
- Obstetrics
- Paediatrics

Specialist Service Group

- Screening

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R279.1	IVD common pseudodeficiency variant Targeted variant testing	Singleton	Small variants	Single interval	IVD common pseudodeficiency variant	Targeted variant testing

R451 Diagnostic testing for MCADD - Medium-chain acyl-CoA dehydrogenase deficiency – full ACADM sequencing

Testing Criteria

Likely MCADD identified following diagnostic metabolic testing and where testing of common variants or full screen of the ACADM gene is required

Overlapping indications:

Testing following newborn screening should follow the established sample and testing pathways set out in the newborn screening protocol and use codes R105 and R403

Where in Pathway

Following diagnostic metabolic testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neonatology
- Paediatrics

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R451.1	Diagnostic testing for MCADD full ACADM sequencing	Singleton	Small variants	Other	ACADM (1355)	Single gene sequencing <10 amplicons

R105 MCADD - Medium-chain acyl-CoA dehydrogenase deficiency – common variant newborn screening follow up

Testing Criteria

Likely MCADD identified following neonatal screening requiring testing of the common ACADM c.985G>A variant

Testing following newborn screening should follow the established sample and testing pathways set out in the newborn screening protocol

Where in Pathway

Following neonatal screening

Requesting Specialties

- Clinical Genetics
- Neonatology
- Obstetrics
- Paediatrics

Specialist Service Group

- Screening

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R105.1	ACADM common pathogenic variants Targeted variant testing	Singleton	Small variants	Single interval	ACADM common pathogenic variants	Targeted variant testing

R403 MCADD - Medium-chain acyl-CoA dehydrogenase deficiency – full ACADM sequencing newborn screening follow up

Testing Criteria

Likely MCADD identified following neonatal screening requiring testing of the full ACADM gene

Overlapping indications:

- R105 MCADD - Medium-chain acyl-CoA dehydrogenase deficiency – common variant test should be used in the first instance except where the testing laboratory specifically guides otherwise

Testing following newborn screening should follow the established sample and testing pathways set out in the newborn screening protocol

Where in Pathway

N/A

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neonatology
- Paediatrics

Specialist Service Group

- Screening

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R403.1	MCADD Single gene sequencing	Singleton	Small variants	Other	ACADM (1355)	Single gene sequencing <10 amplicons

R449 Diagnostic testing for Glutaric acidaemia I

Testing Criteria

Likely glutaric acidaemia type 1 identified following diagnostic metabolic testing

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.

Testing following newborn screening should follow the established sample and testing pathways set out in the newborn screening protocol and use code R275

Where in Pathway

Following diagnostic metabolic testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neonatology
- Obstetrics
- Paediatrics

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R449.1	GCDH Single gene sequencing	Singleton	Small variants	Single gene(s)	GCDH (1339)	Single gene sequencing >=10 amplicons

R275 Glutaric acidaemia I newborn screening follow up

Testing Criteria

Likely glutaric acidaemia type 1 identified following neonatal screening

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.

Testing following diagnostic metabolic testing should use code R449 and follow the routing for specialist metabolic tests

Where in Pathway

Following neonatal screening

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neonatology
- Obstetrics
- Paediatrics

Specialist Service Group

- Screening

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R275.1	GCDH Single gene sequencing	Singleton	Small variants	Single gene(s)	GCDH (1339)	Single gene sequencing >=10 amplicons

Part XIV. Mitochondrial

R64 MELAS or MIDD

Testing Criteria

Adult onset sensorineural hearing loss and diabetes or family history suggestive of a diagnosis of maternally inherited diabetes and deafness OR

A clinical presentation compatible with MELAS ((Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes)

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
- Endocrinology
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R64.1	MTTL1 3243A>G Targeted variant testing	Singleton	Small variants	Single interval	MTTL1 3243A>G	Targeted variant testing

R299 Possible mitochondrial disorder - mitochondrial DNA rearrangement testing

Testing Criteria

Possible mitochondrial disorder caused by mitochondrial DNA rearrangements including individuals with clinical features suggestive of CPEO, Kearns-Sayre syndrome or Pearson syndrome

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.

Affected tissue, such as muscle, preferred

Where in Pathway

At presentation following assessment by a Consultant in Metabolic Medicine, Neurology, Paediatric Neurology, Clinical Genetics or Haematology

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R299.1	Possible Mitochondrial disorder - Mitochondrial DNA rearrangement testing	Singleton	CNVs	Single interval	Mitochondrial genome	Other
R299.2	Possible mitochondrial disorder - mitochondrial DNA rearrangement testing	Singleton	CNVs and structural variants	Single interval	Heteroplasmy assessment - mitochondrial genome	Other
R299.3	Possible mitochondrial disorder - mitochondrial DNA rearrangement testing	Singleton	CNVs and structural variants	Single interval	Breakpoint mapping - mitochondrial genome	Other

R300 Possible mitochondrial disorder - whole mitochondrial genome sequencing

Testing Criteria

Clinical features strongly suggestive of a mitochondrial disorder and/or biochemical evidence of a mitochondrial DNA disorder

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 assessment by a Consultant in Metabolic Medicine, Neurology, Paediatric Neurology or Clinical Genetics, or following biochemical studies

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R300.1	Mitochondrial genome Whole mitochondrial genome sequencing	Singleton	Small variants	Single interval	Mitochondrial genome	Other

R301 Possible mitochondrial disorder - mitochondrial DNA depletion testing

Testing Criteria

Clinical features suggestive of a mitochondrial DNA depletion syndrome

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.

Muscle or liver tissue required

Where in Pathway

Following findings on biopsy sample

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R301.1	Mitochondrial genome Mitochondrial DNA depletion testing	Singleton	Complex variants	Single interval	Mitochondrial genome	Other

R315 POLG-related disorder

Testing Criteria

Clinical features suggestive of a POLG-related disorder (including status epilepticus and other severe intractable epilepsy with other suggestive features)

Overlapping indications

- R59 Early onset or syndromic epilepsy, R29 Intellectual disability or other relevant broader tests should be used instead where clinical features are not strongly suggestive of POLG-related disorder and a broader differential diagnosis is under consideration

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 assessment by a Consultant in Metabolic Medicine, Neurology, Paediatric Neurology or Clinical Genetics, or following evidence of mtDNA depletion or multiple mtDNA deletions

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Please note all the tests below will be undertaken for R315 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R315.1	Common POLG variants Targeted variant testing	Singleton	Small variants	Single interval	Common POLG variants	Targeted variant testing
R315.2	POLG Single gene sequencing	Singleton	Small variants	Single gene(s)	POLG (1379)	Single gene sequencing >=10 amplicons

R316 Pyruvate dehydrogenase (PDH) deficiency

Testing Criteria

Clinical features and laboratory features strongly suggestive of pyruvate dehydrogenase deficiency

Overlapping indications

- R63 Possible mitochondrial disorder - nuclear genes test should be considered where a broader range of mitochondrial nuclear genes are potentially causative

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 assessment by a Consultant in Metabolic Medicine, Neurology, Paediatric Neurology or Clinical Genetics, or following skin biopsy and biochemical PDH assay in fibroblasts

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R316.1	Pyruvate dehydrogenase PDH deficiency WES or Medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Pyruvate dehydrogenase (PDH) deficiency (531)	WES or Medium panel

R317 Mitochondrial liver disease, including transient infantile liver failure

Testing Criteria

Infants (aged <2 years) with acute liver failure of unknown aetiology, or individuals with liver dysfunction suspected to be related to mitochondrial dysfunction

Where in Pathway

At presentation following assessment by a Consultant in Hepatology or Paediatric Hepatology, or following liver/muscle biopsy with evidence of respiratory chain deficiency and/or mtDNA depletion

Requesting Specialties

- Clinical Genetics
- Hepatology
- Metabolic Medicine

Specialist Service Group

- Mitochondrial

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R317.1	Mitochondrial liver disease Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Mitochondrial liver disease (532)	Small panel

R350 MERRF syndrome

Testing Criteria

Clinical features suggestive of MERRF syndrome

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 assessment by a Consultant in Metabolic Medicine, Neurology, Paediatric Neurology or Clinical Genetics

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R350.1	Common MERRF variants Targeted variant testing	Singleton	Small variants	Single interval	Common MERRF variants	Targeted variant testing

R351 NARP syndrome or maternally inherited Leigh syndrome

Testing Criteria

Clinical features suggestive of NARP syndrome (neuropathy, ataxia and retinitis pigmentosa) or MILS (maternally inherited Leigh syndrome)

Where in Pathway

At presentation following assessment by a Consultant in Metabolic Medicine, Neurology, Paediatric Neurology or Clinical Genetics

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology
- Ophthalmology

Specialist Service Group

- Mitochondrial

Associated Tests

Please note all the tests below will be undertaken for R351 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R351.1	MT-ATP6;	Singleton	Small variants	Small panel	MT-ATP6; (1368)	Single gene sequencing <10 amplicons
R351.2	m.8993T>C/G Targeted variant testing	Singleton	Small variants	Single interval	m.8993T>C/G	Targeted variant testing

R352 Mitochondrial DNA maintenance disorder

Testing Criteria

Clinical features suggestive of mtDNA maintenance disorder and/or evidence of mtDNA depletion or multiple mtDNA deletions

Overlapping indications

- R63 Possible mitochondrial disorder - nuclear genes test should be considered where a broader range of mitochondrial nuclear genes are potentially causative

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 assessment by a Consultant in Metabolic Medicine, Neurology, Paediatric Neurology or Clinical Genetics, or following evidence of mtDNA depletion or multiple mtDNA deletions

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R352.1	Mitochondrial DNA maintenance disorder WES or medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Mitochondrial DNA maintenance disorder (533)	WES or Medium Panel

R353 Mitochondrial disorder with complex I deficiency

Testing Criteria

Clinical features and laboratory features strongly suggestive of mitochondrial complex I deficiency

Overlapping indications

- R63 Possible mitochondrial disorder - nuclear genes test should be considered where a broader range of mitochondrial nuclear genes are potentially causative

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

Following laboratory or clinical assessment by a mitochondrial highly specialised service

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R353.1	Mitochondrial disorder with complex I deficiency WES or medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Mitochondrial disorder with complex I deficiency (534)	WES or Medium Panel

R354 Mitochondrial disorder with complex II deficiency

Testing Criteria

Clinical features and laboratory features strongly suggestive of mitochondrial complex II deficiency

Overlapping indications

- R63 Possible mitochondrial disorder - nuclear genes test should be considered where a broader range of mitochondrial nuclear genes are potentially causative

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

Following laboratory or clinical assessment by a mitochondrial highly specialised service

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R354.1	Mitochondrial disorder with complex II deficiency WES or small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Mitochondrial disorder with complex II deficiency (535)	WES or Small Panel

R355 Mitochondrial disorder with complex III deficiency

Testing Criteria

Clinical features and laboratory features strongly suggestive of mitochondrial complex III deficiency

Overlapping indications

- R63 Possible mitochondrial disorder - nuclear genes test should be considered where a broader range of mitochondrial nuclear genes are potentially causative

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

Following laboratory or clinical assessment by a mitochondrial highly specialised service

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R355.1	Mitochondrial disorder with complex III deficiency WES or small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Mitochondrial disorder with complex III deficiency (536)	WES or Small Panel

R356 Mitochondrial disorder with complex IV deficiency

Testing Criteria

Clinical features and laboratory features strongly suggestive of mitochondrial complex IV deficiency

Overlapping indications

- R63 Possible mitochondrial disorder - nuclear genes test should be considered where a broader range of mitochondrial nuclear genes are potentially causative

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

Following laboratory or clinical assessment by a mitochondrial highly specialised service

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R356.1	Mitochondrial disorder with complex IV deficiency WES or small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Mitochondrial disorder with complex IV deficiency (537)	WES or Small Panel

R357 Mitochondrial disorder with complex V deficiency

Testing Criteria

Clinical features and laboratory features strongly suggestive of mitochondrial complex V deficiency

Overlapping indications

- R63 Possible mitochondrial disorder - nuclear genes test should be considered where a broader range of mitochondrial nuclear genes are potentially causative

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

Following laboratory or clinical assessment by a mitochondrial highly specialised service

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R357.1	Mitochondrial disorder with complex V deficiency WES or small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Mitochondrial disorder with complex V deficiency (538)	WES or Small Panel

R63 Possible mitochondrial disorder - nuclear genes

Testing Criteria

Individuals with clinical features suggestive of a mitochondrial disorder requiring examination of nuclear genes where more targeted testing is not possible.

Overlapping indications

- Examination of the mitochondrial genome using one or more of the following indications should be considered first where possible based on clinical or biochemical/enzyme results:
  a. R42 Leber hereditary optic neuropathy
  b. R64 MELAS or MIDD
  c. R350 MERRF syndrome
  d. R351 NARP syndrome or maternally inherited Leigh syndrome
  e. R317 Mitochondrial liver disease, including transient infantile liver failure
  f. R299 Possible mitochondrial disorder - mitochondrial DNA rearrangement testing
  g. R300 Possible mitochondrial disorder - whole mitochondrial genome sequencing
  h. R301 Possible mitochondrial disorder - mitochondrial DNA depletion testing
- Targeted examination of nuclear genes should be considered first where possible based on clinical or biochemical/enzyme results:
  i. R315 POLG-related disorder
  j. R352 Mitochondrial DNA maintenance disorder
  k. R353 Mitochondrial disorder with complex I deficiency
  l. R354 Mitochondrial disorder with complex II deficiency
  m. R355 Mitochondrial disorder with complex III deficiency
  n. R356 Mitochondrial disorder with complex IV deficiency
  o. R356 Mitochondrial disorder with complex V deficiency
  p. R316 Pyruvate dehydrogenase (PDH) deficiency

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

Following assessment by a Consultant in Metabolic Medicine, Neurology, Paediatric Neurology or Clinical Genetics

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R63.1	Possible mitochondrial disorder - nuclear genes WES or large panel	Singleton	Small variants, CNVs	Panel of genes or loci	Possible mitochondrial disorder - nuclear genes (539)	WES or Large Panel

R394 Mitochondrial neurogastrointestinal encephalopathy

Testing Criteria

Clinical features suggestive of mitochondrial neurogastrointestinal encephalopathy (MNGIE) with elevated thymidine and deoxyuridine levels in blood and/or urine

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

Following laboratory or clinical assessment by a mitochondrial highly specialised service

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R394.1	TYMP Single gene sequencing	Singleton	Small variants	Single gene(s)	TYMP (1357)	Single gene sequencing >=10 amplicons

R395 Thiamine metabolism dysfunction syndrome 2

Testing Criteria

Clinical features and characteristic brain MRI changes suggestive of thiamine metabolism dysfunction syndrome 2 (also known as Biotin-responsive basal ganglia disease / thiamine responsive encephalopathy)

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

Following laboratory or clinical assessment by a mitochondrial highly specialised service

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R395.1	SLC19A3 Single gene sequencing	Singleton	Small variants	Single gene(s)	SLC19A3 (1399)	Single gene sequencing <10 amplicons

R396 Mitochondrial Complex V deficiency, TMEM70 type

Testing Criteria

Infantile/paediatric onset hypertrophic cardiomyopathy, raised lactate and raised 3-methylglutaconic acid

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

Following laboratory or clinical assessment by a mitochondrial highly specialised service

Requesting Specialties

- Cardiology
- Clinical Genetics
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R396.1	TMEM70 Single gene sequencing	Singleton	Small variants	Single gene(s)	TMEM70 (1356)	Single gene sequencing <10 amplicons

R397 Maternally inherited cardiomyopathy

Testing Criteria

Maternally inherited hypertrophic cardiomyopathy

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

Following laboratory or clinical assessment by a mitochondrial highly specialised service

Requesting Specialties

- Cardiology
- Clinical Genetics

Specialist Service Group

- Mitochondrial

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R397.1	m.4300A>G Targeted variant testing	Singleton	Small variants	Single interval	m.4300A>G	Targeted variant testing

R42 Leber hereditary optic neuropathy

Testing Criteria

Likely or possible clinical diagnosis of Leber hereditary optic neuropathy

Where in Pathway

At presentation following assessment by a Consultant Ophthalmologist, Neurologist or Clinical Geneticist

Requesting Specialties

- Clinical Genetics
- Neurology
- Ophthalmology

Specialist Service Group

- Mitochondrial

Associated Tests

Please note all the tests below will be undertaken for R42 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R42.1	Three common LHON variants Targeted variant testing	Singleton	Small variants	Single interval	Three common LHON variants	Targeted variant testing
R42.2	Mitochondrial genome Whole mitochondrial genome sequencing	Singleton	Small variants	Mitochondrial Genome	Mitochondrial Genome	Mitochondrial Genome

Part XV. Mosaic and structural chromosomal disorders

R297 Possible structural chromosomal rearrangement – karyotype or Targeted Chromosomal Analysis

Testing Criteria

Possible structural chromosomal rearrangement requiring karyotype **including one of the following**:

1. Possible Robertsonian translocation, reciprocal translocation, ring chromosome or other microscopically visible structural rearrangement indicated by findings from microarray, WGS or other laboratory technique.

2. Recurrent miscarriage (defined as three or more miscarriages):

- where testing of the pregnancy loss has not been possible due to an unsuitable/failed sample e.g. no fetal material/MCC/fixed in formalin, and no previous losses have been successfully tested and reported.

Note that although parental karyotype analysis is available following a failed test, this is of limited utility and the most informative pathway is to test any subsequent pregnancy loss.

- with five or more pregnancy losses where none of the previous losses has been successfully tested and reported e.g. biochemical pregnancies, no products available for testing

3. A family history suggestive of familial balanced translocation.
4. Unexplained infertility who are going to undergo infertility treatment.
5. Patient with ambiguous genitalia potentially caused by a sex chromosome rearrangement not detectable via other tests.
6. Egg/sperm donors prior to acceptance.

Where in Pathway

As appropriate or where IVF centres with HFEA license are performing treatment with egg or sperm donation.

Requesting Specialties

- Clinical Genetics
- Genomics laboratory
- Fetal Medicine

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R297.1	Genomewide Karyotype	Singleton	copy number variant detection to genomewide resolution and structural variants or TCA	Genomewide or TCA	As determined by indication	Karyotype/TCA

R298 Possible structural or mosaic chromosomal abnormality - FISH

Testing Criteria

Possible structural or mosaic chromosomal abnormality requiring FISH

Testing for Y chromosome microdeletions should not routinely be performed before ICSI
https://www.nice.org.uk/guidance/cg156/chapter/Recommendations

Overlapping indications

- R26 Likely common aneuploidy, test should be used for common aneuploidy testing, which may be delivered by FISH
- R297 Possible structural chromosomal rearrangement – karyotype, is available where karyotype alone is required
- R265 Chromosomal mosaicism – karyotype, is available where extended karyotype is required
- R411 Y chromosome microdeletions is available where surgical sperm retrieval is considered

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

Following discussion with laboratory

Requesting Specialties

- Clinical Genetics
- Genomics laboratory

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R298.1	Specific target FISH	Singleton	Balanced rearrangements	Single interval	As determined by indication	FISH

R265 Chromosomal mosaicism - karyotype

Testing Criteria

Individuals with possible mosaic chromosome abnormality requiring extended count karyotype including:

1. possible mosaic chromosome abnormality indicated by findings from conventional karyotype, microarray, WGS or other laboratory technique, OR
2. clinical features strongly suggestive of a specific chromosomal phenotype, for example Down syndrome, in whom conventional testing is negative

Overlapping indications

- R343 Chromosomal mosaicism - microarray should be used where a microarray is indicated

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

N/A

Requesting Specialties

- Clinical Genetics
- Dermatology
- Genomics laboratory

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R265.1	Genomewide Karyotype - mosaicism	Singleton	Aneuploidy	Genomewide	Genomewide	Karyotype

R343 Chromosomal mosaicism - microarray

Testing Criteria

Hyper- or hypo- pigmentation following Blaschkos lines (Hypomelanosis of Ito), with associated abnormalities such as neurodevelopmental delay, seizures or asymmetry

Overlapping indications

- R327 Mosaic skin disorders – deep sequencing test should be used where the mosaicism is likely to be caused by a single gene

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.

NOTE: Sample submitted for this test can be either a skin biopsy or a blood sample

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Dermatology

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R343.1	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray

R411 Y Chromosome microdeletions

Testing Criteria

Patients with non-obstructive azoospermia or severe oligospermia where testicular sperm extraction (TESE)/microdissection TESE (mTESE) is considered and outcome of testing will inform eligibility for (m)TESE and success of sperm retrieval (https://www.england.nhs.uk/wp-content/uploads/2018/07/Surgical-sperm-retrieval-for-male-infertility.pdf)

Testing for Y chromosome microdeletions should not routinely be performed before ICSI (https://www.nice.org.uk/guidance/cg156/chapter/Recommendations)

Testing for this clinical indication is performed by designated GLHs on behalf of the national genomic testing network

Overlapping indications

- R298 - Possible structural or mosaic chromosomal abnormality requiring FISH

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

Following review by a urologist with an interest in infertility or specialist fertility MDT

Requesting Specialties

- Clinical Genetics
- Urology / gynaecology

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R411.1	Y chromosome microdeletions	Singleton	CNVs to exon level	Single interval	Y chromosome AZF regions	Targeted variant testing or equivalent

Part XVI. Musculoskeletal

R52 Short stature - SHOX deficiency

Testing Criteria

Disproportionate short stature with features in the patient or relatives suggestive of SHOX deficiency, e.g. Madelung deformity,

Overlapping indications

- R382 Hypochondroplasia and R24 Achondroplasia
- R104 Skeletal dysplasia to be used where clinical features indicative of a likely monogenic skeletal dysplasia

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
- Endocrinology
- Paediatrics

Specialist Service Group

- Musculoskeletal

Associated Tests

Please note all the tests below will be undertaken for R52 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R52.1	SHOX MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	SHOX (1390)	MLPA or equivalent
R52.2	SHOX Single gene sequencing	Singleton	Small variants	Single gene(s)	SHOX (1390)	Single gene sequencing <10 amplicons

R24 Achondroplasia

Testing Criteria

Clinical features strongly suggestive of achondroplasia

Overlapping clinical indications:

- R309 NIPD for FGFR3-related skeletal dysplasias - variant testing
- R104 Skeletal dysplasia test should be used where features are atypical and a broader range of genes are likely to be causative
- R382 Hypochondroplasia testing may also be indicated if clinically relevant

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
- Neonatology
- Paediatrics

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R24.1	FGFR3 c.1138 Targeted variant testing	Singleton	Small variants	Single interval	FGFR3 c.1138	Targeted variant testing

R382 Hypochondroplasia

Testing Criteria

Clinical features strongly suggestive of hypochondroplasia

Overlapping clinical indications:

- R309 NIPD for FGFR3-related skeletal dysplasias - variant testing
- R24 Achondroplasia testing may also be indicated if clinically relevant
- R52 Short stature – SHOX deficiency
- R104 Skeletal dysplasia test should be used where features are atypical and a broader range of genes are likely to be causative

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
- Endocrinology

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R382.1	FGFR3 c.1620 Targeted variant testing	Singleton	Small variants	Single interval	FGFR3 c.1620	Targeted variant testing

R25 Thanatophoric dysplasia

Testing Criteria

Clinical features strongly suggestive of thanatophoric dysplasia.

Overlapping clinical indications:

- R309 NIPD for FGFR3-related skeletal dysplasias - variant testing
- R104 Skeletal dysplasia test should be used where features are atypical and a broader range of genes are likely to be causative

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
- Fetal Medicine

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R25.1	FGFR3 Single gene sequencing	Singleton	Small variants	Single gene(s)	FGFR3 (1398)	Single gene sequencing >=10 amplicons

R104 Skeletal dysplasia

Testing Criteria

Clinical features indicative of a likely monogenic skeletal dysplasia

Patients with suspected severe congenital autosomal recessive malignant osteopetrosis where rapid genetic diagnosis is required for urgent patient management (e.g. curative stem cell transplantation) are eligible for urgent testing via R104.4

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.

Overlapping indications

Where in Pathway

Following review of clinical features and x-rays by a Clinical Geneticist or Radiologist expert in skeletal dysplasias

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Musculoskeletal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R104.3	Skeletal dysplasia WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants	Panel of genes or loci	Skeletal dysplasia (309)	WGS
R104.4	Osteopetrosis WES or large panel (urgent testing only)	Singleton	Small variants	Panel of genes or loci	Osteopetrosis (943)	WES or large panel

R415 Cleidocranial Dysplasia (CCD)

Testing Criteria

Radiographic and/or clinical features of CCD

CCD features include:

- Large anterior fontanelle
- hypoplastic clavicles
- macrocephaly
- dental features (permanent primary dentition, supernumerary teeth)

Overlapping indications

- R104 Skeletal dysplasia

Where in Pathway

At presentation. Testing is indicated following clinical and radiographic diagnosis and following discussion with a consultant in clinical genetics or paediatric endocrinology or another specialist approved by the GLH.

Requesting Specialties

- Clinical Genetics
- Paediatrics
- Neonatology
- Endocrinology

Specialist Service Group

- Musculoskeletal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R415.1	Cleidocranial Dysplasia	Singleton	small variant detection	Single gene (s)	RUNX2 (1315)	Single gene sequencing < 10 amplicons
R415.2	Cleidocranial Dysplasia	Singleton	Exon level CNVs	Single gene (s)	RUNX2 (1315)	MLPA or equivalent

R99 Common craniosynostosis syndromes

Testing Criteria

Recognisable multisuture craniosynostosis syndromes consistent with variants in EFNB1, ERF, FGFR1 common hot spots, FGFR2 common hot spots, FGFR3 common hot spots, TCF12 or TWIST1 or with unicoronal or bicoronal craniosynostosis

Overlapping indications

- R100 Rare syndromic craniosynostosis or isolated multisuture synostosis test should be used where features are not consistent with variants in EFNB1, ERF, FGFR1 common hot spots, FGFR2 common hot spots, FGFR3 common hot spots, TCF12 or TWIST1

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

Specialist Service Group

- Musculoskeletal

Associated Tests

Please note all the tests below will be undertaken for R99 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R99.1	Common craniosynostosis syndromes Small panel	Singleton	Small variants	Panel of genes or loci	Common craniosynostosis syndromes (507)	Small panel
R99.2	Common craniosynostosis syndromes MLPA or equivalent	Singleton	Exon level CNVs	Panel of genes or loci	Common craniosynostosis syndromes (507)	MLPA or equivalent

R100 Rare syndromic craniosynostosis or isolated multisuture synostosis

Testing Criteria

Rare syndromic craniosynostosis syndrome or isolated multisuture synostosis, confirmed by skull scan where possible

Variants in EFNB1, ERF, FGFR1 common hot spots, FGFR2 common hot spots, FGFR3 common hot spots, TCF12 or TWIST1 must have been excluded on targeted genetic testing (R99 Common craniosynostosis syndromes)

Overlapping indications

- R99 Common craniosynostosis syndromes should be used where features are consistent with variants in EFNB1, ERF, FGFR1 common hot spots, FGFR2 common hot spots, FGFR3 common hot spots, TCF12 or TWIST1

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.

NOTE: If the SMO gene is suspected as causative, a tissue sample will be required for testing

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Musculoskeletal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R100.3	Craniosynostosis WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants	Panel of genes or loci	Craniosynostosis (168)	WGS

R416 Syndromic & non-syndromic craniosynostosis involving midline sutures

Testing Criteria

1. Patients presenting with confirmed craniosynostosis involving/including the metopic suture (trigonocephaly), OR

2. Sagittal suture, OR

3. both sagittal and metopic sutures.

Overlapping indications

- R100 Rare syndromic craniosynostosis or isolated multisuture synostosis

Where in Pathway

At presentation and following discussion with a consultant in clinical genetics or craniofacial neurosurgeon or another specialist approved by the GLH.

Requesting Specialties

- Clinical Genetics
- Neurosurgery

Specialist Service Group

- Musculoskeletal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R416.1	Syndromic & non-syndromic craniosynostosis involving midline sutures	Singleton	Small variant detection	Single gene(s)	SMAD6 (1395)	Single gene sequencing < 10 amplicons

R340 Amelogenesis imperfecta

Testing Criteria

1. Significant developmental abnormalities of enamel quality and/or quantity affecting all or nearly all teeth of both dentitions (primary and secondary), AND
2. Environmental factors excluded

NOTE: Enamel abnormalities affecting unerupted permanent teeth can be detected on dental radiographs meaning that information about both dentitions is available well before eruption of the first permanent tooth

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

Following review by dentist expert in developmental dental disorders

Requesting Specialties

- Clinical Genetics
- Surgical Dentistry

Specialist Service Group

- Musculoskeletal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R340.1	Amelogenesis imperfecta WES or Medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Amelogenesis imperfecta (269)	WES or Medium panel

R23 Apert syndrome

Testing Criteria

Clinical features strongly suggestive of Apert syndrome, including both craniosynostosis and syndactyly of the hands and feet, with or without additional features

Overlapping indications

- R306 NIPD for Apert syndrome - variant testing
- R99 Common craniosynostosis syndromes or R100 Rare syndromic craniosynostosis or isolated multisuture synostosis should be used where features are atypical and a broader range of genes are likely to be causative

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

Specialist Service Group

- Musculoskeletal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R23.1	FGFR2 c.755 and c.758 Targeted variant testing	Singleton	Small variants	Single interval	FGFR2 c.755 and c.758	Targeted variant testing

R101 Ehlers Danlos syndrome with a likely monogenic cause

Testing Criteria

Clinical features indicative of a likely monogenic Ehlers Danlos syndrome:

- Classical EDS (cEDS)
- Classical-like EDS (clEDS)
- Cardiac-valvular EDS (cvEDS)
- Vascular EDS (vEDS)
- Arthrochalasia EDS (aEDS)
- Dermatosparaxis EDS (dEDS)
- Kyphoscoliotic EDS (kEDS)
- Brittle Cornea Syndrome (BCS)
- Spondylodysplastic EDS (spEDS)
- Musculocontractural EDS (mcEDS)
- Myopathic EDS (mEDS)
- Periodontal EDS (pEDS)

Testing should only be used where it will impact on clinical management

Overlapping indications

- R89 Ultra-rare and atypical monogenic disorders or R27 Paediatric disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations not typical of disorders covered by the panel

Where in Pathway

Following assessment by a Clinical Geneticist or other expert in a highly specialised Ehlers Danlos service

Requesting Specialties

- Clinical Genetics
- Rheumatology

Specialist Service Group

- Musculoskeletal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R101.1	Ehlers Danlos syndromes WES or medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Ehlers Danlos syndromes (53)	WES or Medium Panel

R102 Osteogenesis imperfecta

Testing Criteria

Clinical features indicative of a likely monogenic bone fragility disorder / rare and atypical forms of osteogenesis imperfecta

In adults, testing is only routinely recommended where it will impact on reproductive choices

Testing should only be used where it will impact on clinical management

Overlapping indications

- R89 Ultra-rare and atypical monogenic disorders or R27 Paediatric disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations not typical of disorders covered by the panel

Where in Pathway

Following assessment by a Clinical Geneticist or other expert in highly specialised osteogenesis imperfecta service

Requesting Specialties

- Clinical Genetics
- Endocrinology
- Rheumatology
- Metabolic medicine

Specialist Service Group

- Musculoskeletal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R102.1	Osteogenesis imperfecta WES or medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Osteogenesis imperfecta (196)	WES or Medium Panel

R390 Multiple exostoses

Testing Criteria

Individuals with multiple exostoses (osteochondromas) where a monogenic cause is likely and a molecular diagnosis will contribute to management or advice

Where in Pathway

At presentation or when a molecular diagnosis becomes necessary for management or advice

Requesting Specialties

- Clinical Genetics
- Orthopaedics
- Rheumatology

Specialist Service Group

- Musculoskeletal

Associated Tests

Please note all the tests below will be undertaken for R390 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R390.1	EXT1; EXT2	Singleton	Small variants	Small panel	EXT1; EXT2 (1367)	Small panel
R390.2	EXT1; EXT2 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	EXT1; EXT2 (1367)	MLPA or equivalent

R284 Van der Woude syndrome

Testing Criteria

Clinical features strongly suggestive of van der Woude syndrome.

Overlapping indications

- R27 Paediatric disorders test should be used in individuals with cleft palate with a likely complex syndromic cause

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

Specialist Service Group

- Musculoskeletal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R284.1	IRF6 Single gene sequencing	Singleton	Small variants	Single gene(s)	IRF6 (1401)	Single gene sequencing <10 amplicons

Part XVII. Neurology

R70 Spinal muscular atrophy type 1 diagnostic test

Testing Criteria

Clinical features suggestive of spinal muscular atrophy type 1

NOTE: pre symptomatic testing of siblings of individuals with a molecularly confirmed diagnosis of SMA, where testing may inform treatment decisions, should use R242

Overlapping indications

- R69 Hypotonic infant with a likely central cause test should be used in floppy babies where the clinical picture is suggestive of a central cause, i.e. particularly where the baby is not alert, but lethargic or sleepy

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
- Neonatology
- Neurology
- Paediatrics

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R70.1	SMN1, SMN2 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	SMN1; SMN2	MLPA or equivalent

R71 Spinal muscular atrophy type 1 rare variant testing

Testing Criteria

Individuals in whom a rare variant in the SMN1 gene is likely. This will mainly be used for individuals with clinical features of spinal muscular atrophy (SMA) type 1 and monoallelic copy number variant of SMN1

NOTE: pre symptomatic testing of siblings of individuals with a molecularly confirmed diagnosis of SMA, where testing may inform treatment decisions, should use R242

Overlapping indications

- R70 Spinal muscular atrophy type 1 diagnostic test should be used first where clinical features are suggestive of spinal muscular atrophy type 1 and SMN1 copy number has not been tested.

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

After SMN1 copy number analysis

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R71.1	SMN1 Single gene sequencing	Singleton	Small variants	Single gene(s)	SMN1 (1393)	Single gene sequencing >=10 amplicons

R72 Myotonic dystrophy type 1

Testing Criteria

Clinical features strongly suggestive of myotonic dystrophy type 1

Overlapping indications

- R69 Hypotonic infant with a likely central cause test should be used in floppy babies where the clinical picture is suggestive of a central cause
- R381 Other rare neuromuscular disorders should be used where clinical features are atypical and a broader range of genes are potentially causative
- R410 Myotonic dystrophy type 2 should be used where there is clinical suspicion of myotonic dystrophy type 2 or where myotonic dystrophy type 1 has been excluded

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
- Neurology

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R72.1	DMPK STR testing	Singleton	Methylation	Single gene(s)	DMPK STR	STR testing

R77 Hereditary neuropathy - PMP22 copy number

Testing Criteria

Hereditary neuropathy where PMP22 copy number abnormalities are possible

Overlapping indications

- R78 Hereditary neuropathy or pain disorder test should be used where PMP22 copy number abnormalities are clinically unlikely or have already been excluded
- R89 Ultra-rare and atypical monogenic disorders or R27 Paediatric disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

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
- Neurology
- Paediatrics

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R77.1	PMP22 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	PMP22	MLPA or equivalent

R68 Huntington disease

Testing Criteria

Clinical features that indicate a likely diagnosis of Huntington disease

- Specialties other than those listed in Requesting Specialties may request tests in certain settings following discussion with their local laboratory-clinical team

Overlapping indications

- R56 Adult onset dystonia, chorea or related movement disorder or other relevant broader test should be used where clinical features are not strongly suggestive of Huntington disease

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
- Neurology
- Psychiatry

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R68.1	HTT STR testing	Singleton	STRs	Single gene(s)	HTT STR	STR testing

R383 Linkage testing for Huntington disease

Testing Criteria

Families with a confirmed diagnosis of Huntington disease who require linkage testing to guide management or advice

Where in Pathway

As appropriate

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R383.1	HTT Linkage testing	Multiple affected individuals	Other	Single gene(s)	HTT	Other

R252 SMA carrier testing at population risk for partners of known carriers

Testing Criteria

Testing in partners of known carriers of SMA where management of a current or future pregnancy depends on the result

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 the time of reproductive planning

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R252.1	SMN1 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	SMN1	MLPA or equivalent

R54 Hereditary ataxia with onset in adulthood

Testing Criteria

Unexplained ataxia with onset in adulthood including where differential diagnosis encompasses STR loci.

Overlapping indications

R60 Adult onset hereditary spastic paraplegia

Where in Pathway

At presentation following assessment by a Neurologist

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Please note R54.4 (RFC1 STR) will not be included unless specifically requested

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R54.3	Hereditary ataxia - adult onset WGS (phase 1)	Singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Hereditary ataxia - adult onset (466)	WGS
R54.4	*RFC1* STR	Singleton	STRs	Panel of genes or loci	*RFC1* STR	STR testing
R54.5	Hereditary ataxia adult onset confirmatory STR testing	Singleton	STRs	Panel of genes or loci	Hereditary ataxia - adult onset (466)	STR testing

R55 Hereditary ataxia with onset in childhood

Testing Criteria

Unexplained hereditary ataxia with onset in childhood including where differential diagnosis encompasses STR loci

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 assessment by a Neurologist

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R55.4	Hereditary ataxia and cerebellar anomalies - childhood onset WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Hereditary ataxia and cerebellar anomalies - childhood onset (488)	WGS
R55.5	Hereditary ataxia and cerebellar anomalies - childhood onset confirmatory STR testing.	Singleton	STRs	Panel of genes or loci	Hereditary ataxia and cerebellar anomalies - childhood onset (488)	STR testing

R56 Adult onset dystonia, chorea or related movement disorder

Testing Criteria

One of the following:

1. Unexplained isolated dystonia, chorea or related movement disorder with onset before age of 30, or familial
2. Unexplained complex dystonia, chorea or related movement disorder with onset before age of 45, or familial
3. HD-like (regardless of age or dystonia type), following a negative R68 HD test

Overlapping indications

- R68 Huntington disease test should be used where clinical features indicate a likely diagnosis of Huntington disease

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 assessment by a Neurologist

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R56.3	Adult onset dystonia, chorea, or related movement disorder WGS (phase 2)	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Adult onset movement disorder (540)	WGS
R56.4	Adult onset dystonia, chorea, or related movement disorder confirmatory STR testing	Singleton	STRs	Panel of genes or loci	Adult onset movement disorder (540)	STR testing

R57 Childhood onset dystonia, chorea or related movement disorder

Testing Criteria

Unexplained dystonia, chorea or related movement disorder with onset in childhood with a likely monogenic cause

Overlapping indications

- R61 Childhood onset hereditary spastic paraplegia – if the patient has spastic paraplegia
- R55 Hereditary ataxia with onset in childhood – if the patient has ataxia
- R27 Paediatric disorders
- R29 Intellectual disability
- R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with complex or syndromic presentations

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 assessment by a Neurologist

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R57.5	Childhood onset dystonia or chorea or related movement disorder WGS (phase 2)	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Childhood onset dystonia or chorea or related movement disorder (847)	WGS
R57.6	Childhood onset dystonia or chorea or related movement disorder confirmatory STR testing	Singleton	STRs	Panel of genes or loci	Childhood onset dystonia or chorea or related movement disorder (847)	STR testing

R58 Adult onset neurodegenerative disorder

Testing Criteria

Young onset or familial neurodegeneration starting in adulthood with a likely monogenic cause, including:

1. Unexplained dementia where acquired causes (e.g. stroke, tumour) have been excluded AND
   a. Age at onset <55 years, OR
   b. First or second degree relative with MND/ALS (cross reference to point 3 below), OR
   c. Neurological features suggestive of a monogenic disorder where cognitive impairment is part of a wider phenotype, OR
   d. Family history highly suggestive of a monogenic cause for dementia for example one or more first or second degree relatives with dementia onset <65y where the type of dementia is the same as the proband. NOTE a family history of dementia of uncertain or mixed type where onset is predominantly over 65y is unlikely to represent a monogenic disorder.
2. Parkinson's disease or complex Parkinsonism
   a. Age at onset <50 years, OR
   b. First degree relative affected at <50 years, OR
   c. Complex features such as spasticity, gaze palsy, early dementia, early bulbar failure, dyspraxia, ataxia, postural hypotension, cortical sensory loss, brain iron accumulation on MRI brain
3. Amyotrophic lateral sclerosis (ALS) with or without frontotemporal dementia
   a. Evidence of lower motor neuron (LMN) degeneration by clinical, electrophysiologic or neuropathologic examination, AND
   b. Evidence of upper motor neuron (UMN) degeneration by clinical examination, AND
   c. Progressive course, AND
   e. No evidence of other aetiology
4. Cerebral amyloid angiopathy (CAA)
   a. Age of onset < 50 years OR
   b. Family history of haemorrhagic stroke (intracerebral haemorrhage or convexity subarachnoid haemorrhage) or dementia AND
   c. Clinical presentation in keeping with CAA i.e. transient focal neurological episodes ("amyloid spells"), intracerebral haemorrhage, convexity subarachnoid haemorrhage, cognitive impairment, dementia AND
   d. Radiological features consistent with CAA i.e. two or more strictly lobar haemorrhagic lesions on blood sensitive MRI, which can include intracerebral haemorrhage, cerebral microbleeds, cortical superficial siderosis or convexity subarachnoid haemorrhage OR
   e. Other investigations supportive of amyloid-beta deposition within the central nervous system e.g. amyloid-PET imaging, CSF amyloid-beta measures, brain biopsy

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 assessment by a Neurologist

Requesting Specialties

- Clinical Genetics
- Neurology
- Psychiatry

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R58.4	Adult onset neurodegenerative disorder WGS (phase 2)	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Neurodegenerative disorders - adult onset (474)	WGS
R58.5	Adult onset neurodegenerative disorder confirmatory STR testing	Singleton	STRs	Panel of genes or loci	Neurodegenerative disorders - adult onset (474)	STR testing

R59 Early onset or syndromic epilepsy

Testing Criteria

Unexplained epilepsy with clinical suspicion of a monogenic cause including:

1. Onset under 2 years, OR
2. Clinical features suggestive of specific genetic epilepsy, for example Dravet syndrome, OR
3. 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

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
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

R60 Adult onset hereditary spastic paraplegia

Testing Criteria

Unexplained spastic paraplegia of likely monogenic aetiology with onset in adulthood

STR testing of spinocerebellar ataxia loci will be included as a component test where spinocerebellar ataxia is considered plausible clinically.

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 assessment by a Neurologist or Clinical Geneticist

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R60.3	Adult onset hereditary spastic paraplegia WGS (phase 2)	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Hereditary spastic paraplegia - adult onset (567)	WGS
R60.4	Adult onset hereditary spastic paraplegia confirmatory STR testing	Singleton	STRs	Panel of genes or loci	Hereditary spastic paraplegia - adult onset (567)	STR testing

R61 Childhood onset hereditary spastic paraplegia

Testing Criteria

Unexplained spastic paraplegia of likely monogenic aetiology with onset in childhood

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 assessment by a Neurologist or Clinical Geneticist

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R61.4	Hereditary spastic paraplegia - child onset WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants; STRs	Panel of genes or loci	Hereditary spastic paraplegia - Childhood onset (568)	WGS
R61.5	Hereditary spastic paraplegia - child onset confirmatory STR testing	Singleton	STRs	Panel of genes or loci	Hereditary spastic paraplegia - Childhood onset (568)	STR testing

R62 Adult onset leukodystrophy

Testing Criteria

Individuals with unexplained leukodystrophy on neuroimaging with onset in adulthood

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 review of neuroimaging by Neuroradiologist

Referrals can be arranged via the Highly Specialised Service for Inherited White Matter Disorders, or directly by the specialties below. The HSS service supports centres in establishing diagnoses for patients, including via remote review MDTs. It also maintains a IWMD patient Registry and provides treatment and management advice to clinicians. Please contact uclh.iwmd@nhs.net or see https://www.uclh.nhs.uk/our-services/find-service/neurology-and-neurosurgery/inherited-white-matter-disorders for more details.

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R62.2	Adult onset leukodystrophy WGS (phase 2)	Trio or singleton	Exon level CNVs, Small variants	Panel of genes or loci	White matter disorders - adult onset (579)	WGS

R66 Paroxysmal central nervous system disorders

Testing Criteria

Paroxysmal central nervous system disorder that is likely to be monogenic in aetiology

Overlapping indications

- R56 Adult onset dystonia, chorea or related movement disorder or R57 Childhood onset dystonia, chorea or related movement disorder tests should be used in individuals with dystonia
- R89 Ultra-rare and atypical monogenic disorders or other relevant broader tests should be used in individuals with complex or syndromic presentations

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 assessment by a Consultant Neurologist or Paediatric Neurologist

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R66.1	Paroxysmal central nervous system disorders WES or medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Paroxysmal central nervous system disorders (541)	WES or Medium Panel

R73 Duchenne or Becker muscular dystrophy

Testing Criteria

1. Individuals with clinical features strongly suggestive of Duchenne or Becker muscular dystrophy AND elevated creatine kinase
2. Testing a female family member of an affected male known to have or likely to have had Duchenne or Becker muscular dystrophy, but without confirmed molecular diagnosis.

Overlapping indications

- R79 Congenital muscular dystrophy test should be considered following discussion with Neuromuscular specialist in atypical cases
- R381 Other rare neuromuscular disorders should be used where clinical features are atypical and a broader range of genes are potentially causative

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
- Community Paediatrics
- Neurology
- Paediatrics

Specialist Service Group

- Neurology

Associated Tests

Please note all the tests below will be undertaken for R73 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R73.1	DMD Single gene sequencing	Singleton	Small variants	Single gene(s)	DMD (1321)	Single gene sequencing >=10 amplicons
R73.2	DMD MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	DMD (1321)	MLPA or equivalent

R378 Linkage testing for Duchenne or Becker muscular dystrophy

Testing Criteria

Families with a confirmed diagnosis of Duchenne or Becker muscular dystrophy with no detectable variant in dystrophin who require linkage testing to guide management or advice

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

As appropriate

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R378.1	Dystrophin Linkage testing	Multiple affected individuals	Other	Single gene(s)	Dystrophin	Other

R74 Facioscapulohumeral muscular dystrophy

Testing Criteria

Clinical features strongly suggestive of facioscapulohumeral muscular dystrophy (FSHD) in whom a DUX4 contraction has not been excluded

Overlapping indications

- R82 Limb girdle muscular dystrophies, myofibrillar myopathies and distal myopathies and broader tests such as R89 Ultra-rare and atypical monogenic disorders should be considered where features are atypical
- R345 Facioscapulohumeral muscular dystrophy (FSHD) extended testing should be considered in cases negative for the test where clinical features are strongly suggestive of FSHD
- R381 Other rare neuromuscular disorders should be used where clinical features are atypical and a broader range of genes are potentially causative

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
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R74.1	DUX4 Contraction testing	Singleton	STRs	Single interval	DUX4 STR	Other

R345 Facioscapulohumeral muscular dystrophy - extended testing

Testing Criteria

Clinical features strongly suggestive of facioscapulohumeral muscular dystrophy (FSHD) in whom a DUX4 contraction has been excluded

Overlapping indications

- R74 Facioscapulohumeral muscular dystrophy test should be used where DUX4 contraction has not been excluded
- R82 Limb girdle muscular dystrophies, myofibrillar myopathies and distal myopathies and broader tests such as R381 Other rare neuromuscular disorders should be considered where features are atypical

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

Following discussion with Neuromuscular consultant and/or testing laboratory

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R345.1	DUX4 Methylation testing	Singleton	Methylation	Single interval	DUX4	Methylation testing
R345.2	SMCHD1 Single gene sequencing	Singleton	Small variants	Single gene(s)	SMCHD1 (1324)	Single gene sequencing >=10 amplicons
R345.3	4q Extended testing	Singleton	Complex variants	Single interval	4q	Other

R75 Oculopharyngeal muscular dystrophy

Testing Criteria

Clinical features strongly suggestive of oculopharyngeal muscular dystrophy

Overlapping indications

- R89 Ultra-rare and atypical monogenic disorders test should be considered where features are atypical
- R381 Other rare neuromuscular disorders should be used where clinical features are atypical and a broader range of genes are potentially causative

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
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R75.1	PABPN1 STR testing	Singleton	STRs	Single gene(s)	PABPN1 STR	STR testing

R76 Skeletal muscle channelopathy

Testing Criteria

Clinical features strongly suggestive of a skeletal muscle channelopathy including myotonia congenita or paramyotonia congenita

Overlapping indications

- R89 Ultra-rare and atypical monogenic disorders should be used where features are atypical
- R381 Other rare neuromuscular disorders should be used where clinical features are atypical and a broader range of genes are potentially causative

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 or following clinical assessment as part of the rare neuromuscular highly specialised service

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R76.1	Skeletal muscle channelopathy Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Skeletal muscle channelopathy (542)	Small panel

R78 Hereditary neuropathy or pain disorder

Testing Criteria

Clinical features that indicate a likely hereditary neuropathy or pain disorder in whom PMP22 copy number abnormalities are clinically unlikely or have already been excluded

Overlapping indications

- R77 Hereditary neuropathy - PMP22 copy number test should be used where PMP22 copy number abnormalities are possible
- R89 Ultra-rare and atypical monogenic disorders or R27 Paediatric disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

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
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Please note R78.5 (RFC1 STR) will not be included unless specifically requested.

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R78.4	Hereditary neuropathy or pain disorder number WGS (phase 2)	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Hereditary neuropathy (846)	WGS
R78.5	*RFC1* STR	Singleton	STR	Single gene(s)	*RFC1 STR*	STR testing
R78.6	Hereditary neuropathy or pain disorder confirmatory STR testing	Singleton	STR	Single gene(s)	Hereditary neuropathy (846)	STR testing

R79 Congenital muscular dystrophy

Testing Criteria

Individuals with clinical features that indicate a likely congenital muscular dystrophy:

1. Muscle biopsy results indicative of congenital muscular dystrophy, OR
2. Muscle and/or brain MRI findings indicative of congenital muscular dystrophy

Overlapping indications

- R89 Ultra-rare and atypical monogenic disorders or R27 Paediatric disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations not typical of disorders covered by the panel

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 assessment by a Neurologist or following clinical assessment as part of the rare neuromuscular highly specialised service

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R79.1	Congenital muscular dystrophy WES or medium panel	Singleton	Small variants	Panel of genes or loci	Congenital muscular dystrophy (207)	WES or Medium Panel

R80 Congenital myaesthenic syndrome

Testing Criteria

Clinical features that indicate a likely monogenic congenital myaesthenia

Overlapping indications

- R89 Ultra-rare and atypical monogenic disorders or R27 Paediatric disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations not typical of disorders covered by the panel

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 assessment by a Neurologist, typically in parallel to maternal anti-AChR antibody testing or following clinical assessment as part of the rare neuromuscular highly specialised service

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R80.1	Congenital myaesthenic syndrome WES or medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Congenital myaesthenic syndrome (232)	WES or Medium Panel

R81 Congenital myopathy

Testing Criteria

Clinical or histopathological features that indicate a likely monogenic congenital myopathy

Overlapping indications

- R89 Ultra-rare and atypical monogenic disorders or R27 Paediatric disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations not typical of disorders covered by the panel

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 assessment by a Neurologist or following clinical assessment as part of the rare neuromuscular highly specialised service

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R81.1	Congenital myopathy WES or medium panel	Singleton	Small variants	Panel of genes or loci	Congenital myopathy (225)	WES or Medium Panel

R82 Limb girdle muscular dystrophies, myofibrillar myopathies and distal myopathies

Testing Criteria

Clinical features that indicate a likely limb girdle muscular dystrophy or a genetic condition with overlapping phenotype such as distal myopathy or myofibrillar myopathy.

Overlapping indications

- R79 Congenital muscular dystrophy or R89 Ultra-rare and atypical monogenic disorders tests should be used where features are atypical

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 assessment by a Neurologist or following clinical assessment as part of the rare neuromuscular highly specialised service

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R82.1	Limb girdle muscular dystrophies, myofibrillar myopathies and distal myopathies WES or medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Limb girdle muscular dystrophies, myofibrillar myopathies and distal myopathies (185)	WES or Medium Panel

R371 Malignant hyperthermia

Testing Criteria

Confident clinical diagnosis of malignant hyperthermia; anaesthetic history reviewed by MH investigation unit as appropriate. Reasons for referral:

1. Family history of malignant hyperthermia.
2. Adverse reaction to general anaesthesia where a trigger agent has been used, involving any combination of signs of increased metabolism (unexplained increase in carbon dioxide production, tachycardia, temperature increase, muscle rigidity, rhabdomyolysis, disseminated intravascular coagulation and/or death). Initial signs should be evident during anaesthesia or within 60 minutes of discontinuation of anaesthesia.
3. Family history of unexplained perioperative death suggestive of malignant hyperthermia.
4. Postoperative rhabdomyolysis after clinical exclusion of other myopathies.
5. Exertional rhabdomyolysis / recurrent rhabdomyolysis or persistently raised serum creatine kinase concentration of unknown cause (idiopathic hyperCKaemia) where no cause has been identified following neurological work-up.
6. Exertional heat stroke requiring hospital admission, where known predisposing factors have been excluded.

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

Following discussion with national specialist service

Requesting Specialties

- Clinical Genetics
- Other

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R371.1	Malignant hyperthermia small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Malignant hyperthermia (1076)	Small panel

R83 Arthrogryposis

Testing Criteria

Clinical features that indicate arthrogryposis of monogenic aetiology

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 assessment by a Neurologist or Clinical Geneticist and following serum CK estimation

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R83.3	Arthrogryposis - broad panel WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants	Panel of genes or loci	Arthrogryposis (258)	WGS

R381 Other rare neuromuscular disorders

Testing Criteria

Clinical features of rare neuromuscular disorder not covered by more specific indications

Overlapping indications

- Targeted tests for specific neuromuscular indications where relevant

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
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R381.2	Neuromuscular disorders WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants; STRs	Panel of genes or loci	Neuromuscular disorders (465)	WGS
R381.4	Neuromuscular disorders confirmatory STR testing	Singleton	STRs	Single gene(s)	Neuromuscular disorders (465)	STR testing

R84 Cerebellar anomalies

Testing Criteria

Likely monogenic cerebellar malformation, cerebellar or pontocerebellar hypoplasia or childhood-onset cerebellar atrophy

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 MRI brain and assessment by a Neurologist or Clinical Geneticist

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R84.4	Hereditary ataxia and cerebellar anomalies - childhood onset WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Hereditary ataxia and cerebellar anomalies - childhood onset (488)	WGS
R84.5	Hereditary ataxia and cerebellar anomalies - childhood onset confirmatory STR testing	Singleton	STRs	Panel of genes or loci	Hereditary ataxia and cerebellar anomalies - childhood onset (488)	STR testing

R85 Holoprosencephaly - NOT chromosomal

Testing Criteria

Liveborn individuals with unexplained holoprosencephaly in whom a chromosomal cause has been excluded by microarray or equivalent

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 chromosome microarray (which may have followed rapid aneuploidy screening)

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R85.2	Holoprosencephaly WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants	Panel of genes or loci	Holoprosencephaly (78)	WGS

R86 Hydrocephalus

Testing Criteria

Unexplained hydrocephalus with a likely monogenic cause, i.e. where secondary causes such as congenital infection and intraventricular haemorrhage are unlikely to be causative

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 after relevant acquired causes have been excluded where feasible

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R86.3	Hydrocephalus WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants	Panel of genes or loci	Hydrocephalus (179)	WGS

R87 Cerebral malformation

Testing Criteria

Cerebral malformation such as cortical malformation or porencephaly with features suggestive of a monogenic cause.

Overlapping indications

- R110 Segmental overgrowth disorders – Deep sequencing test should be used where megalencephaly is present to allow detection of mosaic variants

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
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R87.3	Cerebral malformations WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants	Panel of genes or loci	Cerebral malformations (491)	WGS

R88 Severe microcephaly

Testing Criteria

Individuals with severe microcephaly* of likely monogenic aetiology.

*Severe microcephaly is defined as having an occipitofrontal circumference (OFC) beyond 3 standard deviations below the mean for age

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
- Neurology
- Paediatrics

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R88.3	Severe microcephaly WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants	Panel of genes or loci	Severe microcephaly (162)	WGS

R109 Childhood onset leukodystrophy

Testing Criteria

Unexplained leukodystrophy on neuroimaging with onset in childhood

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 review of neuroimaging by Neuroradiologist

Referrals can be arranged via the Highly Specialised Service for Inherited White Matter Disorders, or directly by the specialties below. The HSS service supports centres in establishing diagnoses for patients, including via remote review MDTs. It also maintains a IWMD patient Registry and provides treatment and management advice to clinicians. Please contact gst-tr.gosh-iwmdr@nhs.net for clinics at Guys and St Thomas' and Great Ormond Street Hospitals in London, bwc.neurologysecretaries@nhs.net for clinics in Birmingham and Leedsth-tr.north-IWMD@nhs.net for clinics in Leeds.

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R109.3	White matter disorders - childhood onset WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	White matter disorders - childhood onset (496)	WGS

R221 Familial tumours of the nervous system

Testing Criteria

1. Individual +/- family history fulfils clinical criteria for Neurofibromatosis Type 2

a. Bilateral vestibular schwannomas, OR

b. Unilateral vestibular schwannoma AND ≥2 NF2 associated features (meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities/cataract) OR

c. ≥ 1 of unilateral vestibular schwannoma, meningioma, schwannoma, glioma, neurofibroma, multiple meningiomas, posterior subcapsular lenticular opacities/cataract AND ≥ 1 first / second degree relative with a vestibular schwannoma OR

d. Multiple Meningiomas AND ≥2 NF2 associated features (schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities/cataract) OR

e. Unilateral Vestibular Schwannoma AND multiple meningiomas

f. Meninogioma diagnosed <20 years

g. Childhood retinal hamartoma

2. Unilateral Vestibular Schwannoma AND a non-intradermal schwannoma without other NF2-features

3. Schwannomatosis:

a. Two or more non-intradermal schwannomas (at least one biopsy-confirmed) OR

b. One pathologically confirmed schwannoma, unilateral vestibular schwannoma, or intracranial meningioma AND ≥1 FDR with Schwannomatosis

4. Schwannoma diagnosed <30years

5. ≥2 meningiomas

6. Any clear Cell Meningioma

Extent of testing

1. Patients fulfilling criterion 1 should have NF2 testing only
2. Patients fulfilling criterion 2 should have testing of NF2 AND LZTR1
3. Patients fulfilling criterion 3 should have testing of NF2, LZTR1, SMARCB1 and DGCR8
4. Patients fulfilling criterion 4 should have testing of NF2, LZTR1, SMARCB1
5. Patients fulfilling criterion 5 should have testing of NF2, SMARCE1, SUFU
6. Patients fulfilling criterion 6 should have testing of SMARCE1

Note

Tumour-based testing of NF2 checking for mosaicism should be offered in the following circumstances:

1. Patients fulfilling criterion 1 in whom germline NF2 testing is uninformative
2. Patients with two or more NF2-related tumours not otherwise fulfilling criteria 1-6
3. Patients fulfilling criterion 3 in whom testing of NF2, LZTR1, SMARCB1 and DGCR8 is uninformative

NOTE: All tumours should be histologically confirmed

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 and/or following consultation with the NF2 highly specialised service

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Neurology

Associated Tests

Please note all the tests below will be undertaken for R221 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R221.1	Familial tumours of the nervous system	Singleton	Small variants	Single genes	Familial tumours of the nervous system (1334)	Small panel
R221.2	Familial tumours of the nervous system	Singleton	Exon level CNVs	Single genes	Familial tumours of the nervous system (1334)	MLPA or equivalent

R222 Neurofibromatosis type 1

Testing Criteria

Clinical diagnosis of NF1, as defined below, AND molecular diagnosis is required for management of the proband or for reproductive planning

Diagnosis requires two of:

1. At least 6 café au lait macules (at least 0.5cm in a child and 1.5cm in an adult)
2. At least 2 subcutaneous or cutaneous neurofibromas
3. Plexiform neurofibroma
4. Optic glioma
5. At least 2 Lisch nodules
6. Bony dysplasia (sphenoid wing, long bone bowing, pseudarthrosis)
7. Family history of NF1

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.

Overlapping indications

- R236 Pigmentary skin disorders test should be used where clinical features are atypical and a broader range of genes is potentially causative
- R27 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

Where in Pathway

At a point where clinical management or reproductive planning require a molecular diagnosis

Requesting Specialties

- Clinical Genetics
- Dermatology
- Neurology
- Paediatrics

Specialist Service Group

- Neurology

Associated Tests

Please note all the tests below will be undertaken for R222 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R222.1	NF1; SPRED1 Single gene sequencing	Singleton	Small variants	Single gene(s)	NF1; SPRED1 (1370)	Small panel
R222.2	NF1; SPRED1 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	NF1; SPRED1 (1370)	MLPA or equivalent

R376 Segmental or atypical neurofibromatosis type 1 testing

Testing Criteria

Clinical features suggestive of segmental or atypical neurofibromatosis type 1 or individuals with classical neurofibromatosis who have tested negative on gDNA analysis requiring cDNA analysis following discussion with highly specialised service

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

Following consultation with highly specialised service

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Please note all the tests below will be undertaken for R376 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R376.1	NF1 Single gene sequencing – mosaic	Singleton	Small variants	Single gene(s)	NF1 (1387)	Single gene sequencing >=10 amplicons
R376.2	NF1 MLPA or equivalent – mosaic	Singleton	Exon level CNVs	Single gene(s)	NF1 (1387)	MLPA or equivalent

R228 Tuberous sclerosis

Testing Criteria

Clinical features suggestive of tuberous sclerosis requiring molecular testing

Testing should typically be targeted at those with one or more major features or two or more minor features:

1. Major features:
    a. Hypomelanotic macules (at least 3 of at least 5 mm in diameter)
    b. Angiofibromas (at least three) or fibrous cephalic plaque
    c. Ungual fibromas (at least two)
    d. Shagreen patch
    e. Multiple retinal hamartomas
    f. Cortical dysplasias characteristic of tuberous sclerosis such as tubers and cerebral white matter radial migration lines
    g. Subependymal nodules
    h. Subependymal giant cell astrocytoma
    i. Cardiac rhabdomyomas
    j. Lymphangioleiomyomatosis (LAM)
    k. Angiomyolipomas (at least two)
2. Minor features:
    a. Confetti skin lesions
    b. Dental enamel pits (>3)
    c. Intraoral fibromas (at least two)
    d. Retinal achromic patch
    e. Multiple renal cysts
    f. Non- renal hamartomas

Overlapping indications

- R27 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

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
- Fetal Medicine
- Nephrology
- Neurology
- Respiratory Medicine

Specialist Service Group

- Neurology

Associated Tests

Please note R228.1 and R228.2 will be undertaken for all R228 Clinical Indication requests and R228.3 will only be undertaken where a pathogenic variant has not been found on R228.1 and R228.2

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R228.1	TSC1; TSC2	Singleton	Small variants	Small panel	TSC1; TSC2 (1400)	Small panel

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R228.2	TSC1; TSC2 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	TSC1; TSC2 (1400)	MLPA or equivalent
R228.3	TSC1; TSC2 – Small panel deep sequencing	Singleton	Small variants	Small panel	TSC1; TSC2 (1400)	Small panel – deep sequencing

R294 Ataxia telangiectasia – DNA repair testing

Testing Criteria

1. Clinical features strongly suggestive of ataxia telangiectasia including elevated serum AFP levels, AND one or more of the following:
    a. Progressive gait and truncal ataxia with onset between one and four years of age, OR
    b. Ocular motor apraxia, OR
    c. Ocular telangiectasia, OR
    d. Chorea and dysarthria, OR
    e. Immunodeficiency with frequent infections, OR
    f. Malignancy (e.g. leukaemia and lymphoma, breast cancer, ovarian cancer gastric cancer, leiomyoma, sarcoma or melanoma), OR
2. Molecular findings suggestive of Fanconi anaemia or Bloom syndrome from genome, exome or other genomic analysis

Overlapping indications

- R27 Paediatric disorders, R89 Ultra-rare and atypical monogenic disorders or other broad genomic tests should typically be used except where the above criteria are fulfilled
- Prenatal diagnosis or cascade testing by chromosome breakage testing will be requested via R240 Diagnostic testing for known familial variant(s)

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

- Oncology
- Clinical Genetics
- Haematology
- Immunology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R294.1	Genomewide DNA repair defect testing	Singleton	DNA repair	Genomewide	Genomewide	DNA repair defect testing

R295 Ataxia telangiectasia – variant testing

Testing Criteria

Confirmed diagnosis of ataxia telangiectasia requiring variant testing

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

After DNA repair testing

Requesting Specialties

- Oncology
- Clinical Genetics
- Haematology
- Immunology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R295.1	ATM Single gene sequencing	Singleton	Small variants	Single gene(s)	ATM (1213)	Single gene sequencing >=10 amplicons

R336 Cerebral vascular malformations

Testing Criteria

1. Multiple cerebral vascular malformations, OR
2. Cerebral vascular malformation AND family history of cerebral vascular malformation

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

Following neuroimaging

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R336.1	Cerebral vascular malformations WES or medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Cerebral vascular malformations (147)	WES or Medium Panel

R337 CADASIL

Testing Criteria

A confident clinical diagnosis of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) including:

Cerebral ischaemic event below age of 50 or >50 if with a family history of dementia/migraine, AND one or more of:

1. Cognitive impairment with recurrent ischaemic attacks, OR
2. Subcortical lacunar lesions on MRI scan in white matter

Overlapping indications

- R58 Adult onset neurodegenerative disorder test should be used in atypical cases where a broader differential diagnosis is under consideration

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
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R337.1	NOTCH3 Single gene sequencing	Singleton	Small variants	Single gene(s)	NOTCH3 (1311)	Single gene sequencing >=10 amplicons

R410 Myotonic dystrophy type 2 (DM2)

Testing Criteria

1. Adult with muscle weakness, usually proximal, and one of the following:
   a. Clinical Myotonia: of grip or on percussion
   b. EMG evidence of myotonic discharges
   c. Cataracts (fine dust like opacities on the outer layers of the lens that are highly coloured and iridescent, producing a “Christmas Tree” appearance)
   d. Three or more supportive features (from list below)
   e. Family History suggestive of autosomal dominant inheritance

2. **AND** DM1 excluded first if the clinical presentation/Family history could easily fit DM1
3. **OR** Family history of variant positive DM2

Additional supportive features:

- Elevated serum CK
- Insulin-insensitive type 2 diabetes
- Testicular failure
- Cardiac conduction defects
- Low serum IgG or IgM
- Muscle biopsy showing atrophic fibres and proliferation of fibres with central nuclei
- Excessive daytime sleepiness
- Mildly elevated liver function tests (LFT)
- Muscle pain

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.

Overlapping indications

- R72 Myotonic dystrophy type 1 should be used prior to this indication unless there is clinical suspicion of myotonic dystrophy type 2
- R381 Other rare neuromuscular disorders should be used where clinical features are atypical and a broader range of genes are potentially causative

Where in Pathway

At presentation, following a normal test for Myotonic dystrophy type 1, unless there is clinical suspicion of myotonic dystrophy type 2

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R410.1	CNBP (ZNF9) STR testing	Singleton	Short tandem repeats	Single gene(s)	CNBP (ZNF9)	STR testing

R419 Acute Rhabdomyolysis

Testing Criteria

Any patient (including children) presenting with an acute rise in skeletal muscle CK>20,000 iu/l regardless of the trigger, unless this occurs following a single episode of unaccustomed exercise not requiring hospital admission e.g. following weight lifting, a personal trainer session, spin class, marathon etc. However, a second similar episode should trigger testing.

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.

Overlapping indications

- R371 Malignant hyperthermia

Where in Pathway

At presentation or following clinical assessment as part of the McArdle Disease and related disorders highly specialised service

Requesting Specialties

- Neurology
- Intensive Care
- Clinical genetics
  Metabolic medicine
- Nephrology

Specialist Service Group

Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R419.1	Acute Rhabdomyolysis Medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Panel is being created in PanelApp	Medium panel

Part XVIII. Renal

R193 Cystic renal disease

Testing Criteria

1. Patients with non-syndromic cystic renal disease (excluding acquired cystic disease due to chronic or end stage kidney disease) which is EITHER
2. Clinically not characteristic of ADPKD and underlying diagnosis is required for management purposes, OR
3. Clinically symptomatic disease presenting before the age of 18, OR
4. Clinical diagnosis of ADPKD where a genetic diagnosis is required to influence management

Overlapping indications

- R27 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

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, or when clinical management decision depending on molecular diagnosis is required

Requesting Specialties

- Clinical Genetics
- Nephrology

Specialist Service Group

- Renal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R193.4	Cystic renal disease WGS (phase 1)	Singleton	Exon level CNVs, Small variants	Panel of genes or loci	Cystic renal disease (487)	WGS

R194 Haematuria

Testing Criteria

Proband with haematuria and ONE of:

1. A first degree relative with haematuria or unexplained chronic renal failure, OR
2. Histological evidence following electron microscopy on renal biopsy of EITHER Alport syndrome (thickening and splitting of glomerular basement membrane +/- electron lucent areas) OR thin basement membrane disease (TBMD), OR
3. Clinical features of Alport syndrome (high tone sensorineural hearing loss or characteristic ophthalmic signs such as perimacular flecks or anterior lenticonus)

Overlapping indications

- R27 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations
- R196 CFHR5 nephropathy test should be used as a first line test in patients of Cypriot ancestry with haematuria

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

- Audiology
- Clinical Genetics
- Nephrology
- Ophthalmology
- Paediatrics

Specialist Service Group

- Renal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R194.1	Haematuria Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Haematuria (99)	Small panel

R195 Proteinuric renal disease

Testing Criteria

1. Steroid-resistant nephrotic syndrome presenting at any age, OR
2. Proteinuria with a histological picture of focal segmental glomerulosclerosis (FSGS) or diffuse mesangial sclerosis (DMS) on biopsy, with no identifiable cause, where a transplant or immunosuppression is planned

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, or at a time when management requires a molecular diagnosis

Requesting Specialties

- Clinical Genetics
- Nephrology

Specialist Service Group

- Renal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R195.3	Proteinuric renal disease	Singleton	Small variants, CNVs	Panel of genes or loci	Proteinuric renal disease (106)	WGS

R196 CFHR5 nephropathy

Testing Criteria

C3 glomerulopathy or unexplained haematuria or renal failure in a patient of Cypriot ancestry

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
- Nephrology

Specialist Service Group

- Renal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R196.1	CFHR5 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	CFHR5	MLPA or equivalent

R197 Membranoproliferative glomerulonephritis including C3 glomerulopathy

Testing Criteria

Idiopathic membranoproliferative glomerulonephritis (MPGN) or C3 glomerulopathy with onset before the age of 18, together with one of:

1. Family history of MPGN or unexplained end-stage renal disease, OR
2. Renal transplant is being considered, OR
3. Patient is being considered for complement inhibitory therapies

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, or at a time when management requires a molecular diagnosis or following assessment as part of the highly specialised atypical haemolytic uraemic syndrome service

Requesting Specialties

- Clinical Genetics
- Nephrology

Specialist Service Group

- Renal

Associated Tests

Please note all the tests below will be undertaken for R197 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R197.1	Membranoproliferative glomerulonephritis Small panel	Singleton	Small variants	Panel of genes or loci	Membranoproliferative glomerulonephritis (83)	Small panel
R197.2	Membranoproliferative glomerulonephritis MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	Membranoproliferative glomerulonephritis (83)	MLPA or equivalent

R198 Renal tubulopathies

Testing Criteria

Patients with a primary renal tubulopathy presenting as one of the following conditions:

1. Hypokalaemic alkalosis with normal or low blood pressure (e.g. Bartter/Gitelman syndromes), OR
2. Hypokalaemic alkalosis with elevated blood pressure (e.g. Liddle syndrome), OR
3. Hyperkalaemic acidosis with low/normal BP (PHA type 1), OR
4. Hyperkalaemic acidosis with elevated BP (PHA type 2), OR
5. Hypokalaemic acidosis (pRTA and renal Fanconi syndromes), OR
6. Hypomagnesaemia, OR
7. Nephrogenic diabetes insipidus, OR
8. Other rare types of renal tubulopathy seen in an expert center

NOTE: Patients with electrolyte imbalance secondary to non-renal processes should not be tested under this indication

Overlapping indications

- R183 Glucocorticoid-remediable aldosteronism (GRA)
- R344 Primary hyperaldosteronism – KCNJ5
- R256 Nephrocalcinosis or nephrolithiasis

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
- Nephrology

Specialist Service Group

- Renal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R198.1	Renal tubulopathies WES or medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Renal tubulopathies (292)	WES or Medium Panel

R199 Congenital anomalies of the kidney and urinary tract – familial

Testing Criteria

Clinically significant non-syndromic congenital anomalies of the kidney and urinary tract (CAKUT), with a first degree relative with CAKUT or unexplained end-stage renal disease

Families in which there are only minor forms of CAKUT are unlikely to benefit from genetic testing (e.g. isolated vesico-ureteric reflux, duplex kidney, posterior urethral valves)

Overlapping conditions:

- R141 Monogenic diabetes test should be used where there is a personal or family history of diabetes or renal cysts
- R27 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

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
- Nephrology
- Paediatrics

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R199.1	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray

R201 Atypical haemolytic uraemic syndrome

Testing Criteria

Acute renal failure AND thrombocytopenia AND microangiopathic haemolytic anaemia (Coombs test negative), in a patient being considered for complement inhibitory therapies

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 or following assessment as part of the highly specialized atypical haemolytic uraemic syndrome service

Requesting Specialties

- Clinical Genetics
- Haematology
- Nephrology

Specialist Service Group

- Renal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R201.1	Atypical haemolytic uraemic syndrome Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Atypical haemolytic uraemic syndrome (139)	Small panel

R202 Tubulointerstitial kidney disease

Testing Criteria

1. Renal impairment caused by tubulointerstitial fibrosis with no glomerular lesion, with no identifiable cause, often associated with medullary cysts, hyperuricaemia or gout, AND
2. A first degree relative with TIKD or unexplained end-stage renal disease. Exceptions may be made for patients where the clinical presentation is highly suggestive of a monogenic aetiology, but family history is unknown eg. the patient was adopted

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
- Nephrology

Specialist Service Group

- Renal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R202.1	Tubulointerstitial kidney disease Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Tubulointerstitial kidney disease (548)	Small panel

R204 Hereditary systemic amyloidosis

Testing Criteria

Clinical features suggestive of hereditary amyloidosis which may include restrictive cardiomyopathy, autonomic and peripheral neuropathy, renal impairment or GI symptoms.

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

- Cardiology
- Clinical Genetics
- Nephrology
- Neurology
- Haematology
- Gastroenterology

Specialist Service Group

- Renal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R204.1	Hereditary systemic amyloidosis Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Amyloidosis (502)	Small panel

R256 Nephrocalcinosis or nephrolithiasis

Testing Criteria

Nephrocalcinosis or nephrolithiasis where acquired causes have been excluded

Overlapping indications

- Where a primary endocrine disturbance of calcium homeostasis is identified, the appropriate specific test should be used
- In individuals with an identifiable primary renal disorder, the specific test for that disorder should be used where genetic testing is appropriate
- Individuals with nephrocalcinosis likely to be caused by Bartter syndrome can be tested using this indication; individuals with a different presentation of Bartter syndrome should be tested using R198 Renal tubulopathies

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, after exclusion of acquired causes

Requesting Specialties

- Clinical Genetics
- Endocrinology
- Nephrology

Specialist Service Group

- Renal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R256.1	Nephrocalcinosis or nephrolithiasis WES or medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Nephrocalcinosis or nephrolithiasis (149)	WES or Medium Panel

R257 Unexplained young onset end-stage renal disease

Testing Criteria

End-stage renal disease developing under the age of 36, with no identifiable cause detectable by renal biopsy, biochemistry, imaging or clinical assessment

Use of this test in young adults over the age of 36 may be appropriate after expert clinical review, if there is strong clinical suspicion of a monogenic disorder

Overlapping conditions:

- R27 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

Testing Criteria for Semi-Rapid Testing

- Acutely unwell children or adults where monogenic young onset end-stage renal disease is considered highly likely to be the primary cause of the phenotype in the patient.

- Cases should meet the standard eligibility criteria for R257, AND

- Where testing will provide an immediate change to treatment or clinical management for the patient eg. To inform a decision about renal transplant, therapeutic intervention or prenatal testing for an ongoing at risk pregnancy.

- The patient is either not eligible for the R14 pathway or Rapid R257 is considered to be the more appropriate test.

Where in Pathway

At presentation

Where in Pathway for Semi-Rapid Testing

At presentation following clinically relevant, rapidly available investigations. All cases must be agreed in advance with the testing laboratory.

Requesting Specialties

- Clinical Genetics
- Nephrology

Requesting Specialties for Semi-Rapid Testing

- Clinical Genetics
- Renal
- Neonatology

Specialist Service Group

- Renal

Associated Tests

R257.3 is only for semi urgent testing

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R257.2	Unexplained end-stage renal disease WGS (phase 2)	Trio or singleton	Exon level CNVs, Small variants	Panel of genes or loci	Unexplained end-stage renal disease (678)	WGS
R257.3	Unexplained end-stage renal disease WES	Trio	Small variants	Panel of genes or loci	Unexplained end-stage renal disease (678)	WES

R446 APOL1 kidney donor testing

Testing Criteria

Testing for potential living donors, where ALL the following criteria are met:

1. The individual is being assessed for living kidney donation AND
2. Both the individual's parents have (or are likely to have) African, African-American, Caribbean or Brazilian heritage AND
3. Individual has undergone counselling and understands the indications and implications of testing and has provided consent.

Where in Pathway

Testing should be performed by transplant specialists after a potential donor has undergone basic biochemical, tissue type and antibody testing but before exposing the donor to ionising radiation e.g. CT renal angiogram.

Requesting Specialties

- Clinical genetics
- Nephrology

Specialist Service Group

- Renal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R446.1	APOL1 kidney donor testing	Singleton	Targeted variant testing	Single gene	APOL1	Single gene sequencing < 10 amplicons

Part XIX. Respiratory

R184 Cystic fibrosis diagnostic test

Testing Criteria

Test in an individual clinically likely to be affected with cystic fibrosis:

1. Child with clinical suspicion of CF (e.g. recurrent chest infections, failure to thrive, fat malabsorption, neonatal history of meconium ileus), AND
    a. A not normal sweat test performed in a recognised experienced test centre/laboratory (i.e. sweat chloride ≥30mM with sufficient sweat obtained), OR
    b. An additional urgent prenatal situation for the parents or for a close relative, but urgent sweat testing not accessible
2. Adult with CT-proven bronchiectasis, AND
    a. A not normal sweat test performed in a recognised experienced test centre/laboratory (i.e. sweat chloride ≥30mM with sufficient sweat obtained), OR
    b. Chronic suppurative chest infection with colonisation by Pseudomonas and Staph aureus, OR
    c. Additional exocrine pancreatic dysfunction
3. Idiopathic chronic pancreatitis with exocrine dysfunction (fat malabsorption) with other obvious and acquired causes excluded, AND
    a. A not normal sweat test performed in a recognised experienced test centre/laboratory (i.e. sweat chloride ≥30mM with sufficient sweat obtained), OR
    b. Sweat testing not practical, and all other causes excluded
4. Infertility associated with obstructive azoospermia, AND
    a. CBAVD (or isolated CUAVD) diagnosed from expert clinical examination, OR
    b. CBAVD identified at incidental herniotomy
5. Fetal echogenic bowel as bright as bone on 2nd trimester scan or dilated fetal bowel on 2nd or 3rd trimester scan with echogenic bowel as bright as bone, AND
    a. both parents not available for carrier testing [if both parents are available, Cystic fibrosis carrier testing should be used instead of an invasive prenatal test], AND
    b. Other more common causes excluded (e.g. IUGR, placental failure, earlier bleeding, infection, raised aneuploidy markers)

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

Initial population-specific targeted test sufficient to exclude CF as the likely diagnosis in the absence of a clear clinical diagnosis

Proceed to a full gene test if the targeted test is negative and there is a high clinical suspicion of a diagnosis of Cystic Fibrosis

Requesting Specialties

For R184.1 CFTR Targeted variant testing

- Clinical Genetics
- Fetal Medicine
- Gastroenterology
- Genomics laboratory
- Gynaecology
- Obstetrics
- Paediatrics
- Respiratory Medicine

For R184.2 and R184.3 Single gene sequencing and MLPA

- CF service,
- Clinical Genetics
- Respiratory medicine

Specialist Service Group

- Core

Associated Tests

Please note all the tests below will be undertaken for R184 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

R65 “Aminoglycoside exposure posing risk to hearing” testing will be carried out in any patient with a confirmed diagnosis of Cystic Fibrosis as a result of the R184 test.

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R184.1	CFTR Targeted variant testing	Singleton	Small variants	Single gene(s)	CFTR (1318)	Targeted variant testing
R184.2	CFTR Single gene sequencing	Singleton	Small variants	Single gene(s)	CFTR (1318)	Single gene sequencing >=10 amplicons
R184.3	CFTR MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	CFTR (1318)	MLPA or equivalent

R185 Cystic fibrosis carrier testing

Testing Criteria

1. Prospective egg or sperm donor
2. Family history of CF in close relative (up to 4th degree, i.e. in 1st cousin's child or closer relative), or in a similar close relative of partner
3. Partner of a known CF carrier
4. Close consanguineous couple (1st cousins), AND from an ethnic group with a high carrier frequency
5. Both parents of a fetus with echogenic bowel (where both parents are available)
6. Both parents of a fetus with dilated bowel (where both parents are available)

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.

Overlapping indications

R184 Cystic fibrosis diagnostic test should be used where a fetus has echogenic bowel and BOTH parents are not available for testing

Where in Pathway

At time of reproductive planning

Requesting Specialties

- Clinical Genetics
- Fetal Medicine
- Gynaecology
- Respiratory medicine
- General practice

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R185.1	CFTR Targeted variant testing	Singleton	Small variants	Single gene(s)	CFTR	Targeted variant testing

R253 Cystic fibrosis newborn screening follow-up

Testing Criteria

Positive IRT test on newborn screening, according to definition in the National Standard Protocol for Cystic Fibrosis

Where in Pathway

According to the National Standard Protocol for Cystic Fibrosis

Requesting Specialties

- Appropriate specialist referring clinician

Specialist Service Group

- Screening

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R253.1	CFTR 4 commonest variants Targeted variant testing	Singleton	Small variants	Single interval	CFTR 4 commonest variants	Targeted variant testing

R333 Central congenital hypoventilation

Testing Criteria

Clinical features suggestive of congenital central hypoventilation syndrome:

1. Central alveolar hypoventilation, AND
2. Absence of primary lung, cardiac or neuromuscular cause or identifiable brainstem lesion, WITH OR WITHOUT the following additional PHOX2B-reated features:
   a. Hirschsprung disease, OR
   b. Neuroblastoma or other neural crest tumour, OR
   c. Autonomic dysfunction, for example affecting the cardiovascular system, gastrointestinal tract, sweating or temperature control

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
- Neonatology
- Neurology
- Respiratory Medicine

Specialist Service Group

- Respiratory

Associated Tests

Please note all the tests below will be undertaken for R333 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary.

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R333.1	PHOX2B STR testing	Singleton	STRs	Single gene(s)	PHOX2B (1314)	STR testing
R333.2	PHOX2B Single gene sequencing	Singleton	Small variants, CNVs	Single gene(s)	PHOX2B (1314)	Single gene sequencing >=10 amplicons

R139 Laterality disorders and isomerism

Testing Criteria

1. Classical heterotaxy affecting more than one body system, OR
2. Non-classical heterotaxy (an isolated heterotaxy-type malformation), OR
3. Combination of malformations which may occur in heterotaxy but which are not diagnostic of heterotaxy (e.g. oesophageal atresia with intestinal malrotation)

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

- Cardiology
- Clinical Genetics

Specialist Service Group

- Respiratory

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R139.1	Laterality disorders and isomerism WES or medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Laterality disorders and isomerism (549)	WES or Medium Panel

R186 Hereditary haemorrhagic telangiectasia

Testing Criteria

Test where any THREE of the following criteria are met:

1. Epistaxis: spontaneous, recurrent nose bleeds
2. Telangiectases: multiple, at characteristic sites (lips, oral cavity, fingers, nose)
3. Visceral lesions such as gastrointestinal telangiectasia (with or without bleeding), pulmonary arteriovenous malformation (AVM), hepatic AVM, cerebral AVMs, spinal AVM
4. Family history: a first degree relative with HHT according to these criteria (as above) or an autosomal dominant family history of nosebleeds or first degree relative with cerebral AVM / cerebral haemorrhage / pulmonary or hepatic AVM.

Alternatively, test where any ONE of the following criteria are met:

A) Personal history of at least one pulmonary AVM*

B) Personal history of two or more AVMs at one or more characteristic sites (pulmonary*, cerebral, hepatic or spinal)

C) Personal history of at least one AVM and severe epistaxis or characteristic telangiectasia or family history

D) Personal history of telangiectasia, and refractory or severe epistaxis (e.g. requiring recurrent transfusions) *

*Pulmonary AVM only if confirmed by cross sectional imaging (usually thoracic CT scan), and/or later therapeutic angiography/surgery. Do not diagnose if only supported by a positive right-to-left shunt study ("bubble echo") or chest x-ray.

To Note: if there is no antecedent family history implying a "first in family" case more likely to be mosaic.

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
- Dermatology
- Gastroenterology
- Neurology
- Respiratory Medicine

Specialist Service Group

- Respiratory

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R186.1	Hereditary haemorrhagic telangiectasia Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Hereditary haemorrhagic telangiectasia (123)	Small panel

R188 Pulmonary arterial hypertension

Testing Criteria

Idiopathic PAH or suspected Familial/Heritable Pulmonary Arterial Hypertension (PAH).

Overlapping indications

- R186 Hereditary haemorrhagic telangiectasia test should be used in patients with PAH and HHT

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
- Respiratory Medicine

Specialist Service Group

- Respiratory

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R188.1	Pulmonary arterial hypertension Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Pulmonary arterial hypertension (193)	Small panel

R189 Respiratory ciliopathies including non-CF bronchiectasis

Testing Criteria

1. Neonatal presentation with at least one of:
    a. Situs inversus plus lower airway or nasal symptoms, OR
    b. Persistent respiratory distress where other causes have been excluded, OR
    c. Persistent rhinorrhea and cough where other causes have been excluded, OR
2. Testing in childhood with at least one of:
    a. Persistent life-long wet cough (CF excluded)
    b. Unexplained bronchiectasis (CF excluded)
    c. Serous otitis media in association with lower and upper airway symptoms
3. Testing in adults who have had symptoms as above since early childhood, often associated with infertility or subfertility

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
- Respiratory Medicine

Specialist Service Group

- Respiratory

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R189.1	Respiratory ciliopathies including non-CF bronchiectasis WES or medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Respiratory ciliopathies including non-CF bronchiectasis (550)	WES or Medium Panel

R190 Pneumothorax – familial

Testing Criteria

Primary spontaneous pneumothorax with no identifiable cause, AND one of:

- A first degree relative with primary spontaneous pneumothorax, OR
- Characteristic radiological features of Birt-Hogg-Dubé syndrome on chest imaging

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
- Respiratory Medicine

Specialist Service Group

- Respiratory

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R190.1	Pneumothorax – familial Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Pneumothorax – familial (105)	Small panel

R191 Alpha-1-antitrypsin deficiency

Testing Criteria

Plasma concentration of alpha-1-antitrypsin below normal range, AND

1. Prolonged neonatal jaundice with an inconclusive alpha-1-antitrypsin phenotyping result, OR
2. Variant analysis will inform reproductive choice, OR
3. Adult with cirrhosis or emphysema where a genetic diagnosis would influence management following an inconclusive alpha-1-antitrypsin phenotyping result

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

In most patients, an alpha-1-antitrypsin phenotyping test will be sufficient to establish the diagnosis

Genetic testing can be used for diagnostic confirmation in the situations specified in the Eligibility Criteria

Cascade testing of relatives is rarely indicated.

Requesting Specialties

- Clinical Genetics
- Gastroenterology
- Hepatology
- Respiratory Medicine
- General practice

Specialist Service Group

- Respiratory

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R191.1	SERPINA1 common variants Targeted variant testing	Singleton	Small variants	Single interval	SERPINA1 common variants	Targeted variant testing

R192 Surfactant deficiency

Testing Criteria

1. Neonatal respiratory insufficiency of disproportionate severity for advanced gestation, with clinical and X-ray features consistent with pulmonary surfactant deficiency, AND
2. No other obvious cause for respiratory distress e.g. no difficult delivery, no infection, no prematurity

With or without a known family history of surfactant deficiency

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
- Neonatology
- Respiratory Medicine

Specialist Service Group

- Respiratory

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R192.1	Surfactant deficiency Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Surfactant deficiency (551)	Small panel

R330 Alveolar capillary dysplasia with misalignment of pulmonary veins

Testing Criteria

1. Respiratory distress and severe pulmonary hypertension presenting within the first two days of life, and without any sustained response to supportive measures, AND
2. Additional malformations affecting cardiac, gastrointestinal and genitourinary systems

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
- Neonatology
- Respiratory Medicine

Specialist Service Group

- Respiratory

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R330.1	FOXF1 Single gene sequencing	Singleton	Small variants, CNVs	Single gene(s)	FOXF1 (1211)	Single gene sequencing >=10 amplicons

R421 Pulmonary Fibrosis Familial

Testing Criteria

Interstitial Lung Disease (ILD) and **ONE** of the following:

1. ILD, no identifiable cause or association, and age <50 years.
2. Family history of ILD regardless of identifiable cause or association
3. For suspected telomerase complex variants, testing to be considered in the absence of 1. and 2. above if one or more of the following are present in addition to ILD:
    - unexplained haematological abnormalities including macrocytosis, anaemia, thrombocytopenia, leukopenia and/or isolated lymphopenia;
    - unexplained haematological abnormalities including macrocytosis, anaemia, thrombocytopenia, leukopenia and/or isolated lymphopenia; premature greying,
    - or unexplained liver function abnormalities.
    - Consideration of lung transplantation

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
- Respiratory Medicine
- Haematology
- Hepatology

Specialist Service Group

- Respiratory

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R421.1	Pulmonary Fibrosis Familial	Singleton	Small variants, CNVs	Panel of genes or loci	Medium panel to be created in PanelApp	WES or medium panel

R426 Pulmonary alveolar microlithiasis

Testing Criteria

Individuals with a clinical suspicion/diagnosis of PAM including presence of diffuse intra-alveolar microliths, typically with widespread nodular calcification, on chest imaging.

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
- Genomic laboratory
- Respiratory medicine

Specialist Service Group

- Respiratory

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R426.1	Pulmonary alveolar microlithiasis Single gene sequencing	Singleton	Small variants, CNVs	Single gene(s)	SLC34A2 (1383)	Single gene sequencing >=10 amplicons

Part XX. Dermatology

R110 Segmental overgrowth disorders – Deep sequencing

Testing Criteria

Clinical features suggestive of a segmental overgrowth disorder. Features may include:

1. Congenital or early onset segmental overgrowth (which may affect the brain only, i.e. megalencephaly)
2. Confirmed Vascular malformations (capillary, venous, lymphatic or combinations) following discussion with a specialist
3. Characteristic cutaneous features (for example epidermal naevi or connective tissue naevi)
4. Brain malformations (for example hydrocephalus or cortical malformations)
5. Additional dysmorphism (for example polydactyly)

Overlapping indications

- R27 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be considered in overlapping features are present but germline variant is considered likely

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.

NOTE: Many of these disorders are anticipated to be mosaic and sample type and test technology must take account of this. An assay capable of detecting mosaicism below 10% should be used, e.g high read depth sequencing and an appropriate bioinformatic pipeline.

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Dermatology
- Surgery*

*plastic

Specialist Service Group

- Dermatology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R110.1	Segmental overgrowth disorders – Deep sequencing Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Segmental overgrowth disorders – Deep sequencing (98)	Small panel

R163 Ectodermal dysplasia

Testing Criteria

Individuals with a clinical diagnosis of ectodermal dysplasia who have one or more of:

1. Abnormalities of hair (hypotrichosis, sparse hair, sparse/missing eyebrows)
2. Abnormalities of teeth (hypodontia, conical incisors)
3. Abnormalities of skin (hypohidrosis, episodes of hyperthermia)

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
- Dermatology
- Surgical Dentistry

Specialist Service Group

- Dermatology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R163.1	Ectodermal dysplasia WES or Medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Ectodermal dysplasia (553)	WES or Medium panel

R164 Epidermolysis bullosa and congenital skin fragility

Testing Criteria

Individuals with a clinical diagnosis of epidermolysis bullosa or other forms of unexplained skin fragility including peeling skin syndrome

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

For most patients, the test will be arranged as part of assessment in the highly specialised epidermolysis bullosa service

Requesting Specialties

- Clinical Genetics
- Dermatology

Specialist Service Group

- Dermatology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R164.1	Epidermolysis bullosa and congenital skin fragility WES or medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Epidermolysis bullosa and congenital skin fragility (554)	WES or Medium Panel

R165 Ichthyosis and erythrokeratoderma

Testing Criteria

Individuals with at least TWO features from the list below:

1. Born with collodion membrane
2. Erythroderma
3. Dark plate-like scales or fine white scaling
4. Ectropium/eclabium
5. Hyperkeratosis

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
- Dermatology
- Neonatology

Specialist Service Group

- Dermatology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R165.1	Ichthyosis and erythrokeratoderma WES or Medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Ichthyosis and erythrokeratoderma (555)	WES or Medium panel

R166 Palmoplantar keratodermas

Testing Criteria

Individuals with unexplained isolated or syndromic keratodermas, including those occurring as part of generalised skin disease.

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
- Dermatology

Specialist Service Group

- Dermatology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R166.1	Palmoplantar keratodermas WES or Medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Palmoplantar keratodermas (556)	WES or Medium panel

R167 Autosomal recessive primary hypertrophic osteoarthropathy

Testing Criteria

Individuals with unexplained digital clubbing, AND either periostosis OR pachydermia

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
- Dermatology
- Respiratory Medicine
- Rheumatology

Specialist Service Group

- Dermatology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R167.1	Autosomal recessive primary hypertrophic osteoarthropathy Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Autosomal recessive primary hypertrophic osteoarthropathy (557)	Small panel

R227 Xeroderma pigmentosum, Trichothiodystrophy or Cockayne syndrome

Testing Criteria

1. Confident clinical diagnosis of xeroderma pigmentosum plus specific XP-related features in the eye, neurological system or a related cancer, OR
2. Confident clinical diagnosis of trichothiodystrophy, OR
3. Confident clinical diagnosis of Cockayne syndrome

Overlapping indications

- R27 Paediatric disorders or
- R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or less recognisable presentations

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

Skin biopsy for complementation testing (specialist DNA repair test) is likely to be required in many patients to confirm the results of the panel test; this can be carried out in parallel with or after the genetic panel test, usually as part of assessment in the Highly Specialised service for xeroderma pigmentosum.

Requesting Specialties

- Clinical Genetics
- Dermatology

Specialist Service Group

- Dermatology

Associated Tests

Please note that the following tests below will be undertaken for R227 dependent on the clinical presentation and/or initial results.

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R227.1	Xeroderma pigmentosum, Trichothiodystrophy or Cockayne syndrome Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Xeroderma pigmentosum, Trichothiodystrophy or Cockayne syndrome (77)	Small panel
R227.2	Genomewide DNA repair defect testing	Singleton	DNA repair	Genomewide	Genomewide	DNA repair defect testing

R230 Multiple monogenic benign skin tumours

Testing Criteria

Three or more benign skin tumours suggesting a diagnosis of any of the following conditions, with at least two histologically confirmed:

1. Familial cylindromatosis, OR
2. Brooke-Spiegler syndrome, OR
3. Multiple Familial Trichoepithelioma, OR
4. Muir-Torre syndrome, OR
5. Buschke-Ollendorff syndrome*, OR
6. Birt-Hogg-Dubé syndrome

*One skin biopsy may be sufficient to make a confident diagnosis

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
- Dermatology

Specialist Service Group

- Dermatology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R230.1	Multiple monogenic benign skin tumours Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Multiple monogenic benign skin tumours (558)	Small panel

R236 Pigmentary skin disorders

Testing Criteria

1. Multiple café-au-lait macules where neurofibromatosis type 1 (NF1) has been excluded either clinically or on genetic testing, OR
2. Poikiloderma with a likely genetic cause, OR
3. Other forms of reticulate, patchy or speckled hypo- or hyperpigmentation with a likely genetic cause

Overlapping indications

- R222 Neurofibromatosis type 1 test should be used where features are typical of this condition
- R343 Chromosomal mosaicism – microarray test should be used where this is the likely diagnosis
- R327 Mosaic skin disorders – deep sequencing test should be used where the likely cause is a mosaic genetic change, as the technology applied to the mosaic disorders will be more sensitive to these than the panel test designed to detect germline disorders

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
- Dermatology

Specialist Service Group

- Dermatology

Associated Tests

Please note all the tests below will be undertaken for R236 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R236.1	Pigmentary skin disorders WES or Large panel	Singleton	Small variants	Panel of genes or loci	Pigmentary skin disorders (559)	WES or Large panel
R236.2	SPRED1 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	SPRED1	MLPA or equivalent

R237 Cutaneous photosensitivity with a likely genetic cause

Testing Criteria

Clinical diagnosis of a genetic condition causing cutaneous photosensitivity, for example Rothmund-Thompson syndrome, hydroa vacciniforme

Overlapping indications

- Porphyria (cutaneous presentation, R168 or R170) should be tested using the appropriate porphyria test
- R227 Xeroderma pigmentosum, Trichothiodystrophy or Cockayne syndrome test should be used where there is a high likelihood that this is the diagnosis

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
- Dermatology

Specialist Service Group

- Dermatology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R237.1	Cutaneous photosensitivity with a likely genetic cause Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Cutaneous photosensitivity with a likely genetic cause (560)	Small panel

R239 Incontinentia pigmenti

Testing Criteria

Confident clinical diagnosis of incontinentia pigmenti

Overlapping indications

- If the presentation is not specific to incontinentia pigmenti, please use one of the broader tests, for example the R165 Ichthyosis and erythrokeratoderma, R163 Ectodermal dysplasia or R236 Pigmentary skin disorders tests

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
- Dermatology
- Neonatology
- Neurology
- Ophthalmology

Specialist Service Group

- Dermatology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R239.1	IKBKG Single gene sequencing	Singleton	Small variants	Single gene(s)	IKBKG (1347)	Single gene sequencing >=10 amplicons
R239.2	IKBKG common deletion	Singleton	CNVs	Common deletion	IKBKG (1347)	Targeted variant testing

R255 Epidermodysplasia verruciformis

Testing Criteria

Severe widespread infection with human papillomavirus in the absence of detectable immunodeficiency, with or without squamous cell carcinoma

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
- Dermatology

Specialist Service Group

- Dermatology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R255.1	Epidermodysplasia verruciformis Small panel	Singleton	Small variants, CNVs	Panel of genes or loci	Epidermodysplasia verruciformis (562)	Small panel

R326 Vascular skin disorders

Testing Criteria

Vascular skin disorders with a likely germline genetic cause

Overlapping indications

- R327 Mosaic skin disorders – deep sequencing test should be used where a mosaic cause is likely, as the technology used for this test will be more sensitive to detect mosaicism
- R110 Segmental overgrowth disorders test should be used where relevant

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
- Dermatology

Specialist Service Group

- Dermatology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R326.1	Vascular skin disorders WES or Medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Vascular skin disorders (563)	WES or Medium panel

R327 Mosaic skin disorders – deep sequencing

Testing Criteria

Dermatological abnormality likely to have a mosaic single gene cause

Overlapping indications

- R110 Segmental overgrowth disorders test should be used where relevant
- R343 Chromosomal mosaicism – microarray test should be used where a microarray is required

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.

NOTE: Many of these disorders are anticipated to be mosaic and sample type and test technology need to take account of this e.g. in planning coverage of NGS assay

Testing for McCune-Albright syndrome is eligible under this clinical indication – appropriate sample type (e.g. diseased tissue) should be considered for this phenotype

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Dermatology

Specialist Service Group

- Dermatology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R327.1	Mosaic skin disorders – deep sequencing Medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Mosaic skin disorders – deep sequencing (564)	Medium panel

R332 Rare genetic inflammatory skin disorders

Testing Criteria

Clinical diagnosis of a rare inflammatory skin disorder of probably genetic origin, including autoinflammatory disease (e.g. early onset urticaria, recurrent febrile erythemas), infantile pustular psoriasis, likely genetic forms of pityriasis rubra pilaris

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
- Dermatology
- Rheumatology

Specialist Service Group

- Dermatology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R332.1	Rare genetic inflammatory skin disorders WES or Medium panel	Singleton	Small variants, CNVs	Panel of genes or loci	Rare genetic inflammatory skin disorders (565)	WES or Medium panel

R424 Subcutaneous panniculitis T-cell lymphoma (SPTCL)

Testing Criteria

1. New diagnosis of SPTCL (to guide therapeutic management)
2. Suspected SPTCL (to aid diagnosis)

Detection of the germline HAVCR2 variant is associated with the life-threatening complication of haemophagocytic lymphohistiocytosis (HLH) in a subset of SPTCL patients and also indicates which patients may benefit from immunosuppressive therapy (eg Cyclosporin) as opposed to chemotherapy

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
- Dermatology
- Oncology

Specialist Service Group

- Dermatology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R424.1	Subcutaneous panniculitis T-cell lymphoma (SPTCL)	Singleton	Small variants	Single gene	HAVCR2 (1394) HAVCR2 c.245A>G (p.Tyr82Cys) and c.219A>G (p.Ile97Met)	Single gene sequencing <=10 amplicons

Part XXI. Ultra-rare and atypical monogenic disorders

R89 Ultra-rare and atypical monogenic disorders

Testing Criteria

- This clinical indication should be used for patients with ultra-rare disorders or atypical manifestations of recognised monogenic disorders that make broad analysis of multiple gene panels that potentially cross different clinical indications the optimal approach. (e.g. for patients where two or more potential genetic disorders are suspected and the patient is eligible for more than one non-WGS test, WGS via R89 could be used).

- **R89 should not be used if appropriate testing is available via another single test in the test directory** (e.g. if testing for monogenic hearing loss only is required this should be requested by the test available for R67).

- **If the patient meets the eligibility criteria for another WGS clinical indication then that indication should be requested as the primary reason for referral but additional panels can be requested, as appropriate,** (e.g. R29 intellectual disability).

- Gene panels must be selected for clinical indication R89. These should be entered into the 'Additional panel(s)' box on the WGS test order form.

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

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R89.3	Relevant panels in PanelApp WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Relevant panel(s) in PanelApp	WGS

Part XXII. Multi-purpose tests

R240 Diagnostic testing for known variant(s)

Testing Criteria

1. Patient clinically affected with specific disorder where:
   a. the familial variant(s) have already been identified in a relative, OR
   b. there is a recurrent variant for the disorder that is likely to be causative, OR
   c. there is a founder variant for the disorder that is likely to be causative, OR
   d. a variant has been identified in the patient during somatic testing that is likely to be germline origin and causative
2. Molecular confirmation of the diagnosis is required to guide management

This indication is relevant for prenatal and postnatal diagnosis

Where in Pathway

As dictated by clinical situation

Requesting Specialties

- Clinical Genetics
- Other

Specialist Service Group

- Core or Specialised; depending on the clinical scenario

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R240.1	Specific target Targeted variant testing	Singleton	Small variants	Single interval	Specific Target	Targeted variant testing

R242 Predictive testing for known familial variant(s)

Testing Criteria

Patient requiring predictive testing for specific disorder where the familial variant(s) have already been identified in a relative

Where in Pathway

As dictated by clinical situation

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Core or Specialised; depending on the clinical scenario

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R242.1	Specific target Targeted variant testing	Singleton	Small variants	Single interval	Specific Target	Targeted variant testing

R244 Carrier testing for known familial variant(s)

Testing Criteria

Patient requiring carrier testing for specific disorder where the familial variant(s) have already been identified in a relative

The range of specialties who will request this test will depend on the disorder in question

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

As dictated by clinical situation

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Core or Specialised; depending on the clinical scenario

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R244.1	Specific target Targeted variant testing	Singleton	Small variants	Single interval	Specific Target	Targeted variant testing

R246 Carrier testing at population risk for partners of known carriers of nationally agreed autosomal recessive disorders

Testing Criteria

This Clinical Indication relates to carrier testing in partners of individuals who are affected with, or are known carriers with a family history of, an autosomal recessive condition, where:

- management of a current or future pregnancy would be impacted by the result, and the couple would be eligible either for PGD, or for prenatal diagnosis under the clinical indication R448 Prenatal Testing

or

- carrier testing of a partner is feasible and will inform/determine clinical management (including surveillance) for their children.

This Clinical Indication is not intended to influence decision making, related to reporting of incidental carrier findings in genes associated with autosomal recessive disorders, in individuals without a personal or family history. It is only relevant to partners of affected individuals or partners of carriers detected through targeted testing due to family history.

In most autosomal recessive conditions, cascade testing of wider family members and unrelated partners is NOT indicated. Clinicians wishing to request a test under this indication should check with their GLH whether the test is feasible prior to offering testing to patients.

Testing is not usually indicated in this context because the test results have a minimal impact on the risk of health problems in pregnancies beyond the parents and siblings of the affected individual:

1. For most genes, interpreting the results of population risk carrier testing is complex, and the proportion of detected variants which can be confidently used for reproductive purposes is low
2. Carrier testing at population risk is not able to rule out an unrelated partner being a carrier of the condition, only reduce the likelihood
3. The carrier frequency of most autosomal recessive conditions is low, such that the marginal gain from genetic testing of an unrelated partner has limited impact on the prenatal decision-making process

However, there are circumstances in which the chance of a baby being affected is more substantial, and/or there are early detection/screening strategies available to biallelic offspring and carrier testing is feasible. Testing is more likely to be considered appropriate where the following criteria are met:

1. Presence of a homozygous or compound heterozygous genotype in a baby would have a sufficiently predictable effect to permit reproductive choices to be made; for example, carrier testing for haemochromatosis or alpha-1-antitrypsin deficiency is NOT appropriate as it is not possible to predict from the genotype whether an affected baby will ever develop medical problems
2. The associated gene is well-understood and does not contain a high level of novel, benign variation, such that it is likely to be possible to interpret variants found on full gene testing in individuals at population risk; in this context only likely pathogenic or pathogenic variants according to the ACGS / ACMG classification will be reported
3. Presence of a biallelic genotype in the couple's offspring would result inform/determine clinical management e.g. early detection and/or prevention strategies.

PLUS one of the following:

1. The carrier frequency of the condition is higher than 1 in 70 (in the relevant population(s) for the patient to be tested)
2. The couple are consanguineous (second cousins or closer); where this is the only criterion that is met, testing will be limited to the known familial variant.

In exceptional circumstances and after discussion with the home GLH, testing may be considered appropriate in situations where the gene is suitable for testing and there are known pathogenic variant(s), that can be tested for, that account for the majority of cases in the relevant population(s) for the patient to be tested; in this context, the test will primarily target the pathogenic variants that account for the majority of cases in the relevant population(s).

NOTE: The following specific clinical indications should be used instead for the relevant disorders:

- R181 Congenital adrenal hyperplasia carrier testing
- R361 Haemoglobinopathy trait or carrier testing
- R362 Carrier testing for sickle cell disease
- R252 SMA carrier testing at population risk for partners of known carriers
- R185 Cystic fibrosis carrier testing

Table 1. Example autosomal recessive conditions with a carrier frequency higher than 1 in 70 in these example populations, which would be covered by this clinical indication. Note these are examples only and the indication covers a much wider range of conditions and populations where evidence of high carrier frequency is available and the criteria above are met.

Disease	Gene	Carrier frequency
Deafness, autosomal recessive 1A	*GJB2*	1 in 50 in European populations
Gaucher disease	*GBA*	1 in 25 in Ashkenazi population
Phenylketonuria	*PAH*	1 in 50 in European populations
Tay-Sachs disease	*HEXA*	1 in 30 in Ashkenazi population

Where in Pathway

As dictated by clinical situation

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Core or Specialised; depending on the autosomal disorder being investigated

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R246.1	Specific target Single gene sequencing	Singleton	Small variants	Single gene(s)	Relevant single gene	Single gene sequencing >=10 amplicons

R321 Maternal cell contamination testing

Testing Criteria

Pregnancy requiring maternal cell contamination to inform interpretation of other testing, for example invasive prenatal testing, tests on fetal tissues or tests performed on cord blood

Testing will often be initiated by the testing laboratory but relevant samples will be required in advance of testing

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

As appropriate

Requesting Specialties

- Clinical Genetics
- Genomics laboratory

Specialist Service Group

- Core or Specialised; depending on the clinical scenario

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R321.1	Genomewide Identity testing	Multiple affected individuals	Identity	Genomewide	Genomewide	Identity testing

R320 Invasive prenatal diagnosis requiring fetal sexing

Testing Criteria

Pregnancy requiring sexing on invasive prenatal sample to inform management

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

As appropriate

Requesting Specialties

- Clinical Genetics
- Genomics laboratory

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R320.1	Sex determination testing	Singleton	Aneuploidy	Genomewide	Other	Common aneuploidy testing

R263 Confirmation of uniparental disomy

Testing Criteria

Confirmation of probable UPD identified by methylation testing at imprinted loci and UPD identified via other routes, for example SNP array, exome or genome sequencing. This could include testing for mosaic genome-wide UPD

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

As appropriate

Requesting Specialties

- Clinical Genetics
- Genomics laboratory

Specialist Service Group

- Core or Specialised; depending on the clinical scenario

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R263.1	Specific target UPD testing	Trio	Small variants	Single interval	As relevant to clinical setting	UPD testing

R264 Identity testing

Testing Criteria

Where biological relationships need to be determined to guide diagnostic interpretation or alter advice

Where in Pathway

N/A

Requesting Specialties

- Clinical Genetics
- Genomics laboratory

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R264.1	Identity testing	Singleton	Identity	Other	Other	Identity testing

R111 X-inactivation testing

Testing Criteria

Clinical setting where X-inactivation testing will alter clinical management and/or assist reclassification of variant using the ACGS / ACMG guidelines

Where in Pathway

After MDT discussion

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Core or Specialised; depending on the clinical scenario

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R111.1	X-inactivation testing	Singleton	Methylation	Single interval	Other	X-inactivation testing

R370 Validation test

Testing Criteria

Validation using a second test or technique when required for diagnostic reporting.

Examples of settings in which this indication may be used include

- Variants detected outside of an accredited process where the accuracy of the result needs to be validated.
- where the sample has passed outside an accredited pipeline and confirmation of sample identity is required

Where in Pathway

Following primary test where required

Requesting Specialties

- Clinical Genetics
- Genomics laboratory

Specialist Service Group

- Core or Specialised; depending on the clinical scenario

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R370.1	Specific target Targeted variant testing	Singleton	Small variants	Single interval	Specific Target	Targeted variant testing

R443 Confirmation test

Testing Criteria

Confirmation using a second technique where required to provide diagnostic reporting.

Where in Pathway

Following primary test where required

Requesting Specialties

- Clinical Genetics
- Genomics laboratory

Specialist Service Group

- Core or Specialised; depending on the clinical scenario

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R443.1	Specific target Targeted variant testing	Singleton	Small variants, CNVs and STRs	Single interval	Specific Target	Targeted variant testing

R442 Variant Re-interpretation

Testing Criteria

Interpretation of a known variant to determine if the pathogenic status has changed since primary analysis and reporting or a previous re-interpretation. Re-interpretation of a variant may be performed as a result of;

- A request from a clinician responsible for a patient with a reported variant of uncertain significance,

OR

- new evidence available that will likely change the classification of a variant. For example, the identification of additional patient(s) with the same genetic variant or new functional evidence,

AND

- where either; there is new clinical information related to the patient or their family, or sufficient time has passed that there may be additional published evidence or knowledge, that could result in a change to the classification of the variant.

Where in Pathway

Following primary test where required

Requesting Specialties

- Clinical Genetics
- Genomics laboratory

Specialist Service Group

- Core or Specialised; depending on the clinical scenario

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R442.1	Specific target Targeted variant testing	Singleton	Small variants	Single interval	Specific Target	Targeted variant testing

R375 Family follow-up testing to aid variant interpretation

Testing Criteria

Family follow-up testing to aid variant interpretation

Where in Pathway

Where requested by the laboratory

Requesting Specialties

- Clinical Genetics
- Other

Specialist Service Group

- Core or Specialised; depending on the clinical scenario

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R375.1	Specific target Targeted variant testing	Singleton	Small variants	Single interval	Specific Target	Targeted variant testing

R387 Reanalysis of existing data

Testing Criteria

Reanalysis of data which has previously been interpreted and reported is required, due to:

1. New clinical information or clinical events which would substantially change the relevant genomic target, OR
2. Sufficient time has passed since the initial analysis that new gene discovery will have substantially increased the relevant genomic target, OR
3. A technical or scientific advance requires reanalysis of a group of tests to detect an important new source of actionable diagnoses

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

Following discussion with the genomics laboratory to ensure stored data is suitable for reanalysis and that the request is aligned to the national guidance for reanalysis (https://future.nhs.uk/NHSgenomics/view?objectId=154355365).

The R387 request form should be used to provide all required information. This can be obtained from the Genomic Laboratory Hub or via NHS Futures for those with access (https://future.nhs.uk/NHSgenomics/view?objectId=156197061).

Requesting Specialties

- Clinical Genetics
- Genomics laboratory

Specialist Service Group

- Core or Specialised; depending on the clinical scenario

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R387.1	Reanalysis of existing data	Multiple affected individuals	Other	Other	As per updated indication	Other

R296 RNA analysis of variants

Testing Criteria

Variant(s) requiring RNA analysis to aid interpretation where a molecular diagnosis will guide management or alter advice through reclassification of a variant from ACGS / ACMG variant of uncertain significance to likely pathogenic or pathogenic.

Testing should be discussed in advance with the laboratory

Where in Pathway

Following MDT discussion of candidate splice variant

Requesting Specialties

- Clinical Genetics
- Genomics laboratory

Specialist Service Group

- Core or Specialised; depending on the disorder and associated variant being investigated
-

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R296.1	Specific target RNA analysis	Singleton	Complex variants	Other	As dictated by variant under investigation	Other

R346 DNA to be stored

Testing Criteria

To be requested where genetic testing is likely to be required in future, but further information or discussion is needed before a test request is made

Where in Pathway

At any time, including where a sample is available e.g. because phlebotomy is being undertaken for other investigations and a future genetic test is likely to be required

Requesting Specialties

- Clinical Genetics
- Other

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R346.1	DNA Storage	Singleton	Other	Other	No target identified at this stage	Other

R373 RNA to be stored

Testing Criteria

To be requested where RNA testing is likely to be required in future, but further information or discussion is needed before a test request is made

Where in Pathway

Following discussion with the laboratory

Requesting Specialties

- Clinical Genetics
- Other

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R373.1	RNA Storage	Singleton	Other	Other	No target identified at this stage	Other

R322 Skin fibroblasts to be cultured and stored

Testing Criteria

Skin fibroblast sample requiring culture and storage for potential future testing

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

As appropriate

Requesting Specialties

- Clinical Genetics
- Dermatology
- Metabolic Medicine
- Neurology
- Other

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R322.1	Skin fibroblast culture and storage	Singleton	Other	Other	No target identified at this stage	Other

R374 Other sample to be stored

Testing Criteria

To be requested where testing of other sample types (for example, lymphocyte culture) is likely to be required in future, but further information or discussion is needed before a test request is made

Overlapping indications

- R346 DNA to be stored, R373 RNA to be stored and R322 Skin fibroblasts to be cultured and stored should be used instead where relevant

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

Following discussion with the laboratory

Requesting Specialties

- Clinical Genetics
- Other

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R374.1	Other sample storage	Singleton	Other	Other	No target identified at this stage	Other

R428 Patient receiving solid organ transplantation (only in cases where passenger lymphocyte syndrome is suspected)

Testing Criteria

Patient is post-solid organ transplant and the treating clinician has concerns they have developed passenger lymphocyte syndrome based on their clinical presentation; i.e. they have developed cytopenias not wholly explainable via other causes.

Allogeneic transplant where chimerism knowledge will aid patient management.

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.

Overlapping indications

- M242 Any patient receiving solid organ transplantation – same test duplicated in the cancer Test Directory

Where in Pathway

As dictated by clinical situation

Requesting Specialties

- Oncology
- Appropriate specialist referring clinician

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R428.1	Patient undergoing allogeneic solid organ transplantation STR testing	Singleton	Short tandem repeats	Targeted variant testing	Relevant gene(s) or loci	STR testing
R428.2	Patient undergoing allogeneic solid organ transplantation CNV testing	Singleton	CNVs	Targeted variant testing	Sex chromosomes	FISH

R409 Linkage testing for other recognisable Mendelian disorders

Testing Criteria

Patients with a recognisable mendelian disorder where linkage testing will guide patient management (if informative), where linkage testing is not facilitated via an alternative 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

As dictated by clinical situation

Requesting Specialties

- Clinical Genetics
- Other

Specialist Service Group

- Core or Specialised; depending on the clinical scenario

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R409.1	Linkage testing for other recognisable Mendelian disorders	Multiple affected individuals	Other	Single gene(s) or loci	Relevant gene(s) or loci	Linkage analysis

R447 Diagnostic discovery - validation/confirmation of findings

Testing Criteria

Validation and/or confirmation of putative diagnostic findings returned from whole genome sequencing data from 100,000 genome project or GMS patients, through the NHS Diagnostic discovery pathways. This will involve analytical validation and interpretation of the genomic variant(s) with or without confirmatory testing by an orthogonal test as required.

Overlapping indications

R370 validation testing should be used for the validation of potential diagnostic findings identified outside of the WGS Diagnostic Discovery pathway.

Where in Pathway

Following primary test where required

Requesting Specialties

- Genomics laboratory

Specialist Service Group

- Core or Specialised; depending on the clinical scenario

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R447.1	Diagnostic discovery – validation/confirmation of findings	Singleton	Small variants, CNVs, STRs	Single interval	Specific Target	Targeted variant testing

R448 Prenatal testing

Testing Criteria

Ongoing pregnancy requiring prenatal testing for a specific disorder where the familial variant(s) have already been identified in a relative

Where in Pathway

As dictated by clinical situation

Requesting Specialties

Clinical Genetics

Specialist Service Group

- Core or Specialised; depending on the clinical scenario.

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R448.1	Prenatal testing	Singleton	Small variants, CNVs, STRs	Single interval	Specific Target	Targeted variant testing

R431 Genome-wide DNA Methylation Profiling to Aid Variant Interpretation

Testing Criteria

Patients must have a plausibly significant variant of uncertain significance in a gene which is covered by this test (see below).

The list of disorders/genes is available at: https://mft.nhs.uk/app/uploads/2023/08/Methylation-Array-Panel-content-for-EpiSign.pdf.

Patients can be referred by clinical genetics or from an appropriate specialty via consultation with clinical genetics.

Please note that this test requires DNA extracted from peripheral blood preferably obtained at more than 6 months of age.

Where in Pathway

Following discussion with Clinical Genetics and the testing laboratory

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Multi specialty

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R431.1	Genome-wide DNA Methylation Profiling to Aid Variant Interpretation	Singleton	Methylation signature	Genomewide	Genomewide	Methylation microarray

Change Log

Date	Document Name	Version	Summary of Changes
January 2025	Rare and inherited disease eligibility criteria January 2025	January 2025 v7.1	R137 Congenital heart disease – microarray: amendment to the eligibility criteria to provide clarity on when this testing should not be requested.
January 2025	Rare and inherited disease eligibility criteria January 2025	January 2025 v7.1	R56 Adult onset dystonia, chorea or related movement disorder: amended eligibility criteria to provide clarity on when it is appropriate to request this testing.
January 2025	Rare and inherited disease eligibility criteria January 2025	January 2025 v7.1	R53 Fragile X: removal of this Clinical Indication
January 2025	Rare and inherited disease eligibility criteria January 2025	January 2025 v7.1	R59.2 Epilepsy R69.3 Hypotonic infant R83.2 Arthrogryposis R84.2 Cerebellar anomalies R86.2 Hydrocephalus R87.2 Cerebral malformation R88.2 Severe microcephaly R89.2 Ultra-rare disorders R100.2 Craniosynostosis Removal of these Clinical Indication Test Types that are all for array testing.
January 2025	Rare and inherited disease eligibility criteria January 2025	January 2025 v7.1	R27 Paediatric disorders: amended criteria for clarity on when to request this testing and included some exclusion criteria. Addition of requesting specialties
January 2025	Rare and inherited disease eligibility criteria January 2025	January 2025 v7.1	R28 Congenital malformation and dysmorphism syndromes (microarray): amended criteria to provide clarity that clinical requestors need to specify the suspected chromosomal disorder for their patient.
January 2025	Rare and inherited disease eligibility criteria January 2025	January 2025 v7.1	R29 Intellectual disability: updated the overlapping Clinical Indications
January 2025	Rare and inherited disease eligibility criteria January 2025	January 2025 v7.1	R377 Intellectual disability – microarray only: minor amendments to the criteria.
January 2025	Rare and inherited disease eligibility criteria January 2025	January 2025 v7.1	R454 Mavacamten for treating symptomatic obstructive hypertrophic cardiomyopathy: New Clinical Indication
January 2025	Rare and inherited disease eligibility criteria January 2025	January 2025 v7.1	R297 Possible structural chromosomal rearrangement – karyotype: updated criteria for recurrent miscarriages and updated the name of the Clinical Indication to include Targeted Chromosome Analysis
January 2025	Rare and inherited disease eligibility criteria January 2025	January 2025 v7.1	R146 Differences in sex development: amended criteria to provide clarity that a karyotype does not need to have been done before testing to determine the chromosomal sex. The requirement is to know the chromosomal sex by any testing method that can provide this information.

Date	Document Name	Version	Summary of Changes
January 2025	Rare and inherited disease eligibility criteria January 2025	January 2025 v7.1	R176 Gilbert Syndrome: added general practice as a requesting specialty
January 2025	Rare and inherited disease eligibility criteria January 2025	January 2025 v7.1	R58 Adult onset neurodegenerative disorder: amendment to criteria related to dementia
January 2025	Rare and inherited disease eligibility criteria January 2025	January 2025 v7.1	R69 Hypotonic infant: addition to the overlapping Clinical Indications to provide clarity.
January 2025	Rare and inherited disease eligibility criteria January 2025	January 2025 v7.1	R402 Premature ovarian insufficiency: removal of Fragile X as an overlapping Clinical Indication.
January 2025	Rare and inherited disease eligibility criteria January 2025	January 2025 v7.1	R210 Inherited MMR deficiency (Lynch syndrome): Amendment to criteria for deceased affected individuals to provide clarity, confirming MLH1 is in relation to somatic variants and added to list of types of lynch cancers: urothelial cancers, upper gastrointestinal cancer.
January 2025	Rare and inherited disease eligibility criteria January 2025	January 2025 v7.1	R211 Inherited polyposis and early onset colorectal cancer - germline test: Amendment to criteria for deceased affected individuals to provide clarity and addition of criteria: 2) Any small bowel cancer diagnosis under 40 years 3) Proband has endometrial or colorectal cancer (CRC) with ≥2 siblings with CRC/LRC, where at least 1 diagnosed <50.
January 2025	Rare and inherited disease eligibility criteria January 2025	January 2025 v7.1	R414 APC Associated polyposis: Amendment to criteria to include people of any age that meet GAPP criteria and not restricted to children and young adults, plus amendment for deceased affected individuals for clarity.
January 2025	Rare and inherited disease eligibility criteria January 2025	January 2025 v7.1	R224 Inherited renal cancer: Amendment to criteria: increased age of proband who has renal cancer form under 40 years to under 46 years, changed 2nd criterion and removed age threshold of less than 50 years, raised age threshold for proband with a 1st degree relative affected for both from 50 years to 60 years, but kept requirement if proband has 2nd degree relative affected to 50 years or lower plus amends for deceased affected to provide clarity.
January 2025	Rare and inherited disease eligibility criteria January 2025	January 2025 v7.1	R367 Inherited pancreatic cancer: amendment to criterion 1c plus amendment to the criteria for deceased affected individuals to provide clarity
January 2025	Rare and inherited disease eligibility criteria January 2025	January 2025 v7.1	R430 Inherited prostate cancer: amendment to criteria and addition of R207 to overlapping Clinical Indications.
January 2025	Rare and inherited disease eligibility criteria January 2025	January 2025 v7.1	Various inherited cancer CIs: updating the criteria for deceased affected individuals to provide clarity (R207, R211, R212,R213, R214, R215, R216, R219, R220, R358, R359, R225, R254, R422, R363, R364, R365.
January 2025	Rare and inherited disease eligibility criteria January 2025	January 2025 v7.1	R63 Possible mitochondrial disorder - nuclear genes: amendment to overlapping clinical indications to correct an error.

Date	Document Name	Version	Summary of Changes
January 2025	Rare and inherited disease eligibility criteria January 2025	January 2025 v7.1	R69 Hypotonic infant: R69.1 was removed from the July 2024 publication from the eligibility criteria document but in error was not removed from the Excel part of the Test Directory. This has been corrected in the January 2025 publication.
January 2025	Rare and inherited disease eligibility criteria January 2025	January 2025 v7.1	R411 Y Chromosome microdeletions testing: added gynaecology as a requesting specialty.
January 2025	Rare and inherited disease eligibility criteria January 2025	January 2025 v7.1	R449 Diagnostic testing for Glutaric acidaemia I: Correction to the CITT on the associated tests table from R275.1 to R449.1
January 2025	Rare and inherited disease eligibility criteria January 2025	January 2025 v7.1	R381 Other rare neuromuscular disorders: correction in the CITT code in the associated tests table from R81.4 to R381.4
January 2025	Rare and inherited disease eligibility criteria January 2025	January 2025 v7.1	R131 Hypertrophic cardiomyopathy: added information to the overlapping clinical indication to provide clarity.
January 2025	Rare and inherited disease eligibility criteria January 2025	January 2025 v7.1	R15 Primary immunodeficiency or monogenic inflammatory bowel disease: added R239 Incontinentia pigmenti as an overlapping Clinical Indication
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R62: addition of information referring to the Highly Specialised Service
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R109: addition of information referring to the Highly Specialised Service
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R65: addition of two variants to test m.1095T>C m.1494C>T
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R147: removal of Clinical Indication and replaced with R452 Silver Russell Syndrome and Temple Syndrome and R453 Monogenic short stature
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R195: CI moved to WGS
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R246: removal of R105 from the exceptions list and additional text added to the criteria to provide clarity.
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R445: Removed the yellow box from the criteria that requested referrers contact the testing laboratories before sending samples. Removed the line stating that the GLH will triage the requests Added in an exclusion for egg donors Added in additional text in the “Where in the pathway” to indicate that samples should be routed as per FASP
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R446: New CI APOL1 kidney donor testing

Date	Document Name	Version	Summary of Changes
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R351: removal of MT-ND6 target from R351.1
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R211: criteria tightened for serrated polyposis but expanded to include endometrial cancer in addition to colon cancer.
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R221: addition of criteria f. and g.
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R151, R217, R218 & R226: addition of Surgeons (head/neck/endocrine) and oncologists to requesting specialties.
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R207: expand testing criteria to include serous tubal intraepithelial carcinoma (STIC)
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R223: addition of metastatic phaeochromocytoma to the testing criteria
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R208: age threshold for bilateral breast cancer raised from < 50 years to < 60 years and addition of testing for people affected and with Orkney and Shetland ancestry. R430: addition of testing for people affected and with Shetland ancestry
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R213: amendment in the testing criteria
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R422: amendment in the testing criteria
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R215: amendments in testing criteria. 1h lowering the age threshold from <70 years to < 50 years Adding a new 1i for bilateral lobular breast cancer < 70 years Re label 1i to 1j but remains as is: diffuse gastric cancer in any individual of Maori ethnicity
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R225: adding spinal to 1b in the testing criteria
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R254: addition of ≥1 melanoma < 18 years to the testing criteria
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R377: amendment to testing criteria including removal of autism and addition of overlapping CI for Fragile X
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R275: amendments to criteria as this code to be used following newborn screening only
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R449: new CI for diagnostic testing glutaric acidaeemia type 1
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R105 & R403: amendments to criteria as these codes to be used following newborn screening only

Date	Document Name	Version	Summary of Changes
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R451: new CI for diagnostic testing MCADD
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R279: amendments to criteria as this code to be used following newborn screening only
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R450: new CI for diagnostic testing isovaleric acidaemia
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R365: added overlapping CI M246 Uterine smooth muscle tumours
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R364: added overlapping CI M245 Ovarian sex cord stromal tumours
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R239: added a new test type R239.2 Exon level CNV detection by MLPA or equivalent
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R444: addition to criteria to allow g*BRCA* testing for people with breast cancer to access Talazoparib. Test targets for R444.1 confirmed as *BRCA1* and *BRCA2* only.
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R210: amendment to criterion 5a for clarification
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R407: removal of this test code from the RD Test Directory as it is duplicated in the Cancer Test Directory
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	Various: removal of test type for Exon level CNVs by MLPA or equivalent / MLPA or equivalent and including in the panel test type
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	Removal of array test type for: R27 and R29
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R239: addition of a test type for the common deletion testing
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R423: corrected CI name by including “haplotype testing” in the title
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	Various: amended CI name to change word “mutation” to “variant”.
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R69, R59, R83, R84, R86, R87, R88 and R89: added note: “It is not a requirement to perform microarray testing in addition to WGS but microarray testing can be performed where appropriate”.
June 2024	Rare and inherited disease eligibility criteria January 2024	July 2024 v7	R98 change in CI name from Likely inborn errors of metabolism – targeted testing not possible to Likely inborn errors of metabolism.