

# **National Genomic Test Directory**

**Testing Criteria for Rare  
and Inherited Disease**

**August 2020**

## Summary

The [National Genomic Test Directory](https://www.england.nhs.uk/publication/national-genomic-test-directories/) 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 panels 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. As part of the future delivery model, each Trust will be mapped to a single Genomic Laboratory Hub for the provision of testing.

During 2020/2021 the Genomic Laboratory Hubs will continue to mobilise the new service, including establishing the capability and capacity to deliver the genomic testing identified in the National Genomic Test Directory. Where testing was not previously available, providers should liaise with their local Genomic Laboratory Hub to confirm the date from which they will be able to requisition new tests.

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. Where a clinical indication has multiple individual test items and testing is expected to be performed in a specific order, this is specified. Details of commonly overlapping clinical indications are also provided.
- **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
- **Specialist Service Group:** specialist service group that covers the clinical indication. The options are:
  - Core;
  - Cardiology;
  - Hearing;
  - Endocrinology;
  - Eyes;
  - Gastrohepatology;
  - Haematology;
  - Immunology;
  - Inherited cancer;
  - Metabolic;
  - Mitochondrial;
  - Musculoskeletal;
  - Neurology;
  - Renal;
  - Respiratory;
  - Skin;
  - NIPT;
  - NIPD; and
  - Screening

### Associated Tests

The associated tests contain information about the tests which routinely constitute the target for the clinical indication, including:

- **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 to exon level resolution;
  - 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), interval(s) or panels at which the variant type should be detected
- **Test Method:** test method to be used. The options are:
  - WGS;
  - WES;
  - Large panel;
  - Medium panel;
  - Small panel;
  - Single gene sequencing;
  - Targeted mutation testing;
  - STR testing;
  - MLPA or equivalent;
  - Microarray;
  - Common aneuploidy testing;
  - Karyotype;
  - FISH;
  - DNA repair testing;
  - Methylation testing;
  - UPD testing;
  - X-inactivation testing;
  - Identity testing;
  - Microsatellite instability;
  - NIPT;
  - NIPD;
  - Other

NHS England has sought feedback regarding the wording of the following components of the testing criteria and scope:

- 'Testing Criteria' including the order of testing
- 'Where In Pathway', 'Requesting Specialties'
- 'Key Locus' components of the 'Test Scope' section

This document incorporates the feedback received; future changes to the Test Directory will be managed through NHS England's evaluation process.

## 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 lab which constituent tests are required and which aren't

Clinicians should follow local process to request genomic tests. All referrals for testing will be triaged by the local Genomic Laboratory Hub to ensure the most appropriate test is performed. In instances where testing is requested by the clinical indication, 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.

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## 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 outlined in “Guidance Document - Rapid Exome Sequencing for NICU-PICU Referrals” please contact your local Genomic Laboratory Hub.

PLEASE NOTE: During 2019/2020 the Genomic Laboratory Hubs will continue to mobilise the new service, including establishing the capability and capacity to deliver the genomic testing identified in the National Genomic Test Directory. Please contact your local Genomic Laboratory Hub to ensure your local pathway is set up BEFORE sending any samples for patients requiring testing under this clinical indication

This rapid Whole Exome Service is being provided by designated GLH(s).

#### 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 only test should be used if the cause is highly likely to be chromosomal, for example where the clinical features are characteristic of Williams syndrome

#### 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

- Core

#### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R14.1	Paediatric disorders WES or large panel	Trio or singleton	Small variants	Panel of genes or loci	Paediatric disorders (486)	WES or Large Panel
R14.2	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray

## Part II. Cardiology

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### 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

#### Overlapping indications

- R26 Likely common aneuploidy test should be used for patients with coarctation of the aorta and features suggestive of Turner syndrome
- R27 Congenital malformation and dysmorphism syndromes – 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

Referrals for testing will be triaged by the Genomic 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	Optional 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  $\geq 7$ , 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 mutation
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 Congenital malformation and dysmorphism syndromes – 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

Referrals for testing will be triaged by the Genomic 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R125.1	Thoracic aortic aneurysm or dissection WES or medium panel	Singleton	Small variants	Panel of genes or loci	Thoracic aortic aneurysm or dissection (700)	WES or Medium Panel
R125.2	Thoracic aortic aneurysm or dissection MLPA or equivalent	Singleton	Exon level CNVs	Panel of genes or loci	Thoracic aortic aneurysm or dissection (700)	MLPA or equivalent

## R127 Long QT syndrome

### Testing Criteria

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

1. QTc  $\geq$ 500ms in repeated 12-lead ECGs, OR
2. LQTS risk score  $>$ 3.5 (Schwartz et al, 2011. PMID: 22083145), OR
3. QTc  $\geq$ 480 ms in repeated 12-lead ECGs AND an unexplained syncopal episode
4. QTc  $\geq$ 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R127.1	Long QT syndrome Small panel	Singleton	Small variants	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  $\geq 2$  mm (0.2 mV) in  $\geq 1$  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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R128.1	Brugada syndrome and cardiac sodium channel disease Small panel	Singleton	Small variants	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R129.1	Catecholaminergic polymorphic VT Small panel	Singleton	Small variants	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  $\leq$  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  $\leq$  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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R130.1	Short QT syndrome Small panel	Singleton	Small variants	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  $\geq 15$  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  $\geq 13$  mm in one or more LV myocardial segments, in a patient with a first degree relative with unequivocal disease (LVH  $\geq 15$  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

### Where in Pathway

At presentation

### Requesting Specialties

- Cardiology
- Clinical Genetics

### Specialist Service Group

- Cardiology

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R131.1	Hypertrophic cardiomyopathy WES or medium panel	Singleton	Small variants	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 or arrhythmogenic cardiomyopathy as indicated by:

1. Left ventricular end diastolic diameter (LVEDD) greater than 2 standard deviations, AND
  - a. Reduced ejection fraction (EF) to less than 45%, adjusted for age and sex, AND
  - b. Age of onset below 50 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 50 years suitable for post-mortem DNA analysis.

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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R132.1	Dilated and arrhythmogenic cardiomyopathy WES or medium panel	Singleton	Small variants	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

### Requesting Specialties

- Cardiology
- Clinical Genetics
- Neonatology
- Neurology
- Paediatrics

### Specialist Service Group

- Cardiology

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R391.1	TAZ Single gene sequencing	Singleton	Small variants	Single gene(s)	TAZ	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.

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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R133.1	Arrhythmogenic right ventricular cardiomyopathy Small panel	Singleton	Small variants	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.

### Overlapping indications

- In individuals where cardiomyopathy is one of multiple features of a likely multisystem disorder R27 Congenital malformation and dysmorphism syndromes - likely monogenic 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

### Requesting Specialties

- Cardiology
- Clinical Genetics

### Specialist Service Group

- Cardiology

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R135.1	Paediatric or syndromic cardiomyopathy WES or large panel	Singleton	Small variants	Panel of genes or loci	Cardiomyopathies - including childhood onset (749)	WES or Large Panel



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

## R138 Molecular autopsy following sudden unexplained death

### 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.

Referrals for testing will be triaged 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

### Overlapping Indications

- R408 Idiopathic ventricular fibrillation should be used for survivors of proven cardiac arrest (idiopathic ventricular fibrillation) as per eligibility criteria

### Where in Pathway

At presentation

### Requesting Specialties

- Cardiology
- Clinical Genetics

### Specialist Service Group

- Cardiology

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R138.1	Molecular autopsy following sudden unexplained death WES or medium panel	Singleton	Small variants	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R328.1	Progressive cardiac conduction disease WES or small panel	Singleton	Small variants	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R384.1	ABCC6; ENPP1 Single gene sequencing	Singleton	Small variants	Single gene(s)	ABCC6; ENPP1	Single gene sequencing >=10 amplicons

## R140 Elastin-related phenotypes

### Testing Criteria

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

### Overlapping indications

- R28 Congenital malformation and dysmorphism syndromes – microarray only should be used for patients with clinical features strongly suggestive of Williams syndrome
- R27 Congenital malformation and dysmorphism syndromes - likely monogenic test should be used for individuals with syndromic forms of cutis laxa

R125 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R140.1	ELN Single gene sequencing	Singleton	Small variants	Single gene(s)	ELN	Single gene sequencing $\geq 10$ amplicons

## R408 Idiopathic ventricular fibrillation

### Testing Criteria

Survivors of proven cardiac arrest (idiopathic ventricular fibrillation) with no phenotype detectable on comprehensive evaluation including coronary assessment, cardiac imaging and ECG provocation testing (idiopathic ventricular fibrillation), 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

### Overlapping indications

R138 Molecular autopsy should be used for deceased patients following sudden unexplained death as per eligibility criteria

### Where in Pathway

At presentation

### Requesting Specialties

- Cardiology
- Clinical Genetics

### Specialist Service Group

- Cardiology

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R408.1	Idiopathic ventricular fibrillation Medium panel	Singleton	Small variants	Panel of genes or loci	Sudden cardiac death (841)	Medium panel

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

## R27 Congenital malformation and dysmorphism syndromes - microarray and sequencing

### Testing Criteria

Congenital malformations and/or dysmorphism suggestive of an underlying monogenic disorder where targeted genetic testing is not possible.

Testing of individuals with syndromic overgrowth or overgrowth in combination with intellectual disability or developmental delay would also be appropriate under this indication

### Overlapping indications

- R14 Acutely unwell infants with a likely monogenic disorder test should be used instead where relevant where a rapid result 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.

### 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

### Specialist Service Group

- Core

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R27.1	Relevant panels in PanelApp WES or large panel	Trio or singleton	Small variants	Panel of genes or loci	Relevant panel(s) in PanelApp	WES or Large Panel
R27.2	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray
R27.3	Relevant panels in PanelApp WGS	Trio or singleton	Exon level CNVs, Genomewide CNVs, Small variants	Panel of genes or loci	Relevant panels in PanelApp	WGS



## R28 Congenital malformation and dysmorphism syndromes – microarray only

### Testing Criteria

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

### Overlapping indications

- R27 Congenital malformation and dysmorphism syndromes – likely monogenic 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R28.1	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray

## R29 Intellectual disability - microarray, fragile X and sequencing

### Testing Criteria

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

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

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology
- Paediatrics

### Specialist Service Group

- Core

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R29.1	Intellectual disability WES or large panel	Trio or singleton	Small variants	Panel of genes or loci	Intellectual disability (285)	WES or Large Panel
R29.2	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray
R29.3	FMR1 STR testing	Singleton	STRs	Single interval	FMR1 STR	STR testing
R29.4	Intellectual disability WGS	Trio or singleton	Exon level CNVs, Genomewide CNVs, Small variants, STRs	Panel of genes or loci	Intellectual disability (285)	WGS

## R377 Intellectual disability - microarray only

### Testing Criteria

Unexplained autism or intellectual disability with clinical features not consistent with fragile X syndrome or where fragile X testing has previously been performed

Typical fragile X syndrome manifestations in females: learning difficulty (usually mild, IQ often 80-85, but can be moderate or severe LD)

Typical fragile X syndrome manifestations in males: moderate to severe developmental delay / learning difficulty (IQ if measured would be 35-70)

### Overlapping indications

- R27 Congenital malformation and dysmorphism syndromes – 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

Referrals for testing will be triaged by the Genomic 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

- Core

### Associated Tests

Code	Name	Optional 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

- R29 Intellectual disability – microarray, fragile X and sequencing 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

### Specialist Service Group

- Core

### Associated Tests

Code	Name	Optional 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	Exon level 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

- R29 Intellectual disability – microarray, fragile X and sequencing 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

### Specialist Service Group

- Core

### Associated Tests

Code	Name	Optional 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	Exon level CNVs	Single interval	AS/PWS critical region	MLPA or equivalent

## R53 Fragile X

### Testing Criteria

Clinical features characteristic of fragile X syndrome or other FMR1-related disorder

Typical fragile X syndrome manifestations in females: learning difficulty (usually mild, IQ often 80-85, but can be moderate or severe LD)

Typical fragile X syndrome manifestations in males: moderate to severe developmental delay / learning difficulty (IQ if measured would be 35-70)

### Overlapping indications

- R29 Intellectual disability – microarray, fragile X and sequencing or other relevant broader tests should be used in preference except where features are characteristic of fragile X syndrome
- 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
- R402 Premature ovarian insufficiency test should be used where this is the relevant clinical context

Referrals for testing will be triaged by the Genomic 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
- Paediatrics

### Specialist Service Group

- Core

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R53.1	FMR1 STR testing	Singleton	STRs	Single interval	FMR1 STR	STR testing

## 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 other tests for peripheral or neuromuscular causes should be used where clinical features point to a peripheral cause, i.e. particularly where the baby is alert and responsive and the floppiness appears static over a period of days

Referrals for testing will be triaged by the Genomic 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R69.1	SNRPN DMR Methylation testing	Singleton	Methylation	Single gene(s)	SNRPN DMR	Methylation testing
R69.2	Hypotonic infant WES or large panel	Trio or singleton	Small variants	Panel of genes or loci	Hypotonic infant (490)	WES or Large Panel
R69.3	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray
R69.4	DMPK STR testing	Singleton	Methylation	Single gene(s)	DMPK STR	STR testing
R69.5	Hypotonic infant WGS	Trio or singleton	Small variants	Panel of genes or loci	Hypotonic infant (490)	WGS

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



## Part IV. Endocrinology

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### 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

- R53 Fragile X syndrome should be used for individuals with suspected fragile X syndrome
- 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	Optional 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 Disorders of 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	Optional 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 Congenital malformation and dysmorphism syndromes – likely monogenic 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R106.1	ALMS1 Single gene sequencing	Singleton	Small variants	Single gene(s)	ALMS1	Single gene sequencing $\geq 10$ amplicons

## R141 Monogenic diabetes

### Testing Criteria

#### Clinical Indication Setting

Diagnostic testing - unknown mutation(s)

#### Eligibility Criteria

1. Minimum two generation family history of diabetes with at least one individual diagnosed under the age of 35 years with BMI less than 30, negative GAD and IA2 autoantibodies and detectable C-peptide, OR
2. High risk of MODY based on MODY calculator <http://www.diabetesgenes.org/content/mody-probability-calculator>, OR
3. Diabetes in conjunction with cystic renal disease and/or congenital anomaly of the kidney or urinary tract (likely HNF1B), OR
4. Post-pubertal children or adults with insulin resistance:
  - a. Severely elevated plasma insulin (typically greater than 150pmol/L in non-diabetic non-obese subject), AND
  - b. Clinical features consistent with severe insulin resistance, e.g. polycystic ovarian syndrome, acanthosis nigricans, diabetes with high insulin requirements, post-prandial hypoglycaemia, OR
  - c. Post-pubertal severe insulin resistance with plasma adiponectin >5mg/l, OR
5. Clinical features of lipodystrophy, including:
  - a. Abnormal fat distribution (with abdominal fat preservation), AND
  - b. Acanthosis nigricans and/or very high insulin requirement, AND
  - c. Impaired glucose tolerance/diabetes

#### 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R141.1	Monogenic diabetes WES or medium panel	Singleton	Small variants	Panel of genes or loci	Monogenic diabetes (472)	WES or Medium Panel
R141.2	GCK; HNF1A; HNF4A; HNF1B MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	GCK; HNF1A; HNF4A; HNF1B	MLPA or equivalent

## R142 Glucokinase-related fasting hyperglycaemia

### Testing Criteria

Asymptomatic fasting hyperglycaemia: fasting glucose 5.5-8mmols/L

Referrals for testing will be triaged by the Genomic 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R142.1	GCK Single gene sequencing	Singleton	Small variants	Single gene(s)	GCK	Single gene sequencing >=10 amplicons

## R143 Neonatal diabetes

### Testing Criteria

Diabetes mellitus diagnosed below the age of 6 months

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 Sanger sequencing

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

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R143.1	ABCC8; KCNJ11 Single gene sequencing	Singleton	Small variants	Single gene(s)	ABCC8; KCNJ11	Single gene sequencing >=10 amplicons
R143.2	Diabetes - neonatal onset WES or medium panel	Trio or singleton	Small variants	Panel of genes or loci	Diabetes - neonatal onset (293)	WES or Medium Panel
R143.3	6q24 Methylation testing	Singleton	Methylation	Single interval	6q24	Methylation testing
R143.4	Diabetes - neonatal onset WGS	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 dysmorphogenesis, 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R145.1	Congenital hypothyroidism Medium panel	Singleton	Small variants	Panel of genes or loci	Congenital hypothyroidism (31)	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R329.1	ALB Single gene sequencing	Singleton	Small variants	Single gene(s)	ALB	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R182.1	Hyperthyroidism Small panel	Singleton	Small variants	Panel of genes or loci	Hyperthyroidism (236)	Small panel

## R146 Disorders of sex development

### Testing Criteria

46,XX or 46,XY karyotype AND one of:

1. Ambiguous genitalia
2. Evidence of gonadal dysgenesis
3. Clinical symptoms of adrenal hypoplasia
4. Under virilisation in a male
5. Virilisation in a female
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

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

## R147 Growth failure in early childhood

### Testing Criteria

Height/length more than 3 standard deviations below the mean at the age of at least 2 years, OR

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. SGA (birth weight and/or birth length):  $\leq -2$  SDS for gestational age
2. Postnatal growth failure: Height at  $24 \pm 1$  months  $\leq -2$  SDS or height  $\leq -2$  SDS below mid-parental target height
3. Relative macrocephaly at birth: Head circumference at birth  $\geq 1.5$  SDS above birth weight and/or length SDS
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  $\geq 0.5$  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  $\leq -2$  SDS at 24 months or current use of a feeding tube or cyproheptadine for appetite stimulation

\*See Wakeling et al 2017, PMID: 27585961

### Overlapping indications

- R52 Short stature – SHOX deficiency test should be used where only a microarray is required
- 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 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

Growth hormone (GH) should be measured prior to the genetic test. In the context of GH deficiency this genetic test will usually not be indicated. However, there may be cases where after consultation with an expert the test should be carried out where there is GH deficiency.

### Requesting Specialties

- Clinical Genetics
- Endocrinology
- Paediatrics

### Specialist Service Group

- Endocrinology

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R147.1	Growth failure in early childhood WES or medium panel	Singleton	Small variants	Panel of genes or loci	Growth failure in early childhood (473)	WES or Medium Panel
R147.2	11p15 imprinted growth regulatory region and UPD7 growth regulatory critical region Methylation testing	Singleton	Methylation	Single interval	11p15 imprinted growth regulatory region and UPD7 growth regulatory critical region	Methylation testing
R147.3	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray

## 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 Congenital malformation and dysmorphism syndromes - likely monogenic 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

Code	Name	Optional 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	Exon level CNVs	Single interval	11p15 imprinted growth regulatory region	MLPA or equivalent
R49.3	CDKN1C Single gene sequencing	Singleton	Small variants	Single gene(s)	CDKN1C	Single gene sequencing $\geq 10$ 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
- R147 Growth failure in early childhood 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 Congenital malformation and dysmorphism syndromes – likely monogenic 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

Code	Name	Optional 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	Exon level 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	Optional 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	Optional 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 Congenital malformation and dysmorphism syndromes – 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

Referrals for testing will be triaged by the Genomic 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R149.1	Severe early-onset obesity Medium panel	Singleton	Small variants	Panel of genes or loci	Severe early-onset obesity (130)	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R150.1	Congenital adrenal hypoplasia Small panel	Singleton	Small variants	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 a female infant 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 Disorders of 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

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R180.1	CYP21A2 Single gene sequencing	Singleton	Small variants	Single gene(s)	CYP21A2	Single gene sequencing $\geq 10$ amplicons
R180.2	CYP21A2 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	CYP21A2	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 mutation 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R388.1	CYP21A2 Linkage testing	Multiple affected individuals	Other	Single gene(s)	CYP21A2	Other

## 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

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R181.1	CYP21A2 Targeted mutation testing	Singleton	Small variants	Single gene(s)	CYP21A2	Targeted mutation 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:

Presentation under the age of 30, OR

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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R183.1	CYP11B1/CYP11B2 gene fusion Targeted mutation testing	Singleton	Other	Single interval	CYP11B1/CYP11B2 gene fusion	Targeted mutation 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R344.1	KCNJ5 Single gene sequencing	Singleton	Small variants	Single gene(s)	KCNJ5	Single gene sequencing <10 amplicons

## R229 Confirmed Fanconi anaemia or Bloom syndrome - mutation testing

### Testing Criteria

Confirmed diagnosis of Fanconi anaemia or Bloom syndrome from chromosome breakage analysis requiring mutation 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, R27 Congenital malformation and dysmorphism syndromes – likely monogenic, 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R229.1	Confirmed Fanconi anaemia or Bloom syndrome Small panel	Singleton	Small variants	Panel of genes or loci	Confirmed Fanconi anaemia or Bloom syndrome (508)	Small panel
R229.2	FANCA; FANCB; FANCD2; PALB2 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	FANCA; FANCB; FANCD2; PALB2	MLPA or equivalent



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

## R293 Albright hereditary osteodystrophy, pseudohypoparathyroidism and pseudopseudohypoparathyroidism

### Testing Criteria

Individuals with a clear clinical diagnosis of Albright hereditary osteodystrophy, pseudohypoparathyroidism or pseudopseudohypoparathyroidism based on clinical and 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

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R293.1	GNAS Single gene sequencing	Singleton	Small variants	Single gene(s)	GNAS	Single gene sequencing $\geq 10$ amplicons
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

### Testing Criteria

Primary hyperparathyroidism (unexplained hypercalcaemia with PTH high or in the upper normal range, and calcium clearance: creatinine clearance ratio > 0.02) which meets ONE of the criteria below:

1. Presenting before the age of 35, OR
2. Presenting before the age of 45 with ONE of:
  - a. Proven multi-glandular involvement, OR
  - b. Hyperplasia on histology, OR
  - c. Ossifying fibroma(s) of the maxilla and / or mandible, OR
  - d. At least one first degree relative with unexplained hyperparathyroidism

### Overlapping indications

- R152 Hypocalciuric hypercalcaemia test should be used where there is hypercalcaemia with hypocalciuria (calcium clearance: creatinine clearance ratio < 0.02)
- R319 Calcium-sensing receptor phenotypes single gene test should be considered in neonatal hyperparathyroidism
- Multiple endocrine neoplasia indications R217 and R218 should be used where there are features of multiple endocrine neoplasia including hypercalcaemia

Referrals for testing will be triaged by the Genomic 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R151.1	Familial hyperparathyroidism Small panel	Singleton	Small variants	Panel of genes or loci	Familial hyperparathyroidism (480)	Small panel

## R152 Hypocalciuric hypercalcaemia

### Testing Criteria

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

### Overlapping indications

- R151 Familial hyperparathyroidism test should be used for hypercalcaemia with calcium clearance: creatinine clearance ratio > 0.02

Referrals for testing will be triaged by the Genomic 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R152.1	Hypocalciuric hypercalcaemia Small panel	Singleton	Small variants	Panel of genes or loci	Hypocalciuric hypercalcaemia (481)	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R153.1	Familial hypoparathyroidism Small panel	Singleton	Small variants	Panel of genes or loci	Familial hypoparathyroidism (312)	Small panel
R153.2	GATA3 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	GATA3	MLPA or equivalent

## 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R154.1	Hypophosphataemia or rickets Small panel	Singleton	Small variants	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R319.1	CASR Single gene sequencing	Singleton	Small variants	Single gene(s)	CASR	Single gene sequencing $\geq 10$ 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R157.1	FOXP3 Single gene sequencing	Singleton	Small variants	Single gene(s)	FOXP3	Single gene sequencing $\geq 10$ 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R156.1	PRKAR1A Single gene sequencing	Singleton	Small variants	Single gene(s)	PRKAR1A	Single gene sequencing $\geq 10$ 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R148.1	Hypogonadotropic hypogonadism Small panel	Singleton	Small variants	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R159.1	Pituitary hormone deficiency Medium panel	Singleton	Small variants	Panel of genes or loci	Pituitary hormone deficiency (483)	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.  $\geq 2$  MEN1-related endocrine abnormalities (any age), OR
  - e.  $\geq 1$  MEN1-related endocrine abnormality and  $\geq 1$  MEN1-related non-endocrine tumours (any age), OR
  - f.  $\geq 1$  MEN1-related endocrine abnormality and a first degree relative has  $\geq 1$  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

### Specialist Service Group

- Endocrinology

### Associated Tests

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

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R217.2	MEN1; AIP; CDKN1B; CDC73 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	MEN1; AIP; CDKN1B; CDC73	MLPA or equivalent

## R223 Inherited phaeochromocytoma and paraganglioma

### 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 / paraganglioma of the head and neck (<60 years), OR
2. Sympathetic, metastatic or abdominal, thoracic, pelvic paraganglioma (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  $\geq 1$  relative (first / second / third degree relative) with phaeochromocytoma / paraganglioma / renal cell cancer (any age)

**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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R223.1	Inherited phaeochromocytoma and paraganglioma Small panel	Singleton	Small variants	Panel of genes or loci	Inherited phaeochromocytoma and paraganglioma excluding NF1 (649)	Small panel
R223.2	SDHB; SDHC; SDHD MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	SDHB; SDHC; SDHD	MLPA or equivalent

## 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

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R144.1	ABCC8; KCNJ11 Single gene sequencing	Singleton	Small variants	Single gene(s)	ABCC8; KCNJ11	Single gene sequencing >=10 amplicons
R144.2	Congenital hyperinsulinism Small panel	Singleton	Small variants	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

### Overlapping indications

- R141 Monogenic diabetes test should be used for adult onset lipodystrophy with insulin resistance or diabetes
- R27 Congenital malformation and dysmorphism syndromes – 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

Referrals for testing will be triaged by the Genomic 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R158.1	Lipodystrophy - childhood onset Small panel	Singleton	Small variants	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.  $\geq 2$  MEN2-related endocrine abnormalities (any age), OR
3.  $\geq 1$  MEN2-related endocrine abnormality and a first degree relative with  $\geq 1$  MEN2-related endocrine abnormality

MEN2-related endocrine abnormalities include: Medullary Thyroid Carcinoma (MTC), Pheochromocytoma/paraganglioma, Parathyroid adenoma/hyperplasia, Hirschsprungs 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

### Specialist Service Group

- Endocrinology

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R218.1	RET Single gene sequencing	Singleton	Small variants	Single gene(s)	RET	Single gene sequencing $\geq 10$ 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

### Specialist Service Group

- Endocrinology

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R226.1	CDC73 Single gene sequencing	Singleton	Small variants	Single gene(s)	CDC73	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R162.1	Familial tumoral calcinosis Small panel	Singleton	Small variants	Panel of genes or loci	Familial tumoral calcinosis (552)	Small panel

## Part V. Eyes

### 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 males
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 Congenital malformation and dysmorphism syndromes – likely monogenic 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

- Eyes

#### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R107.1	Bardet Biedl syndrome WES or large panel	Singleton	Small variants	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 Congenital malformation and dysmorphism syndromes – 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

Referrals for testing will be triaged by the Genomic 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

- Eyes

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R31.1	Cataracts WES or Medium panel	Singleton	Small variants	Panel of genes or loci	Cataracts (230)	WES or Medium Panel
R31.2	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray

## R32 Retinal disorders

### Testing Criteria

Unexplained retinal disease that is likely to be monogenic

### Overlapping indications

- R27 Congenital malformation and dysmorphism syndromes – 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
- R33 X-linked retinitis pigmentosa test should be used where features are consistent with X-linked retinitis pigmentosa
- R35 Doyne retinal dystrophy test should be used where features are strongly suggestive of Doyne retinal dystrophy
- R34 Sorsby retinal dystrophy test should be used where features are strongly suggestive of Sorsby retinal dystrophy

Referrals for testing will be triaged by the Genomic 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

- Eyes

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R32.1	Retinal disorders WES or large panel	Singleton	Small variants	Panel of genes or loci	Retinal disorders (307)	WES or Large Panel

## 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

Referrals for testing will be triaged by the Genomic 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

- Eyes

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R33.1	RPGR exon ORF15 Targeted mutation testing	Singleton	Small variants	Single interval	RPGR exon ORF15	Targeted mutation testing
R33.2	Retinal disorders WES or large panel	Singleton	Small variants	Panel of genes or loci	Retinal disorders (307)	WES or Large Panel

## R34 Sorsby retinal dystrophy

### Testing Criteria

Unexplained retinal disease with features strongly suggestive of Sorsby retinal dystrophy

### Where in Pathway

At presentation following assessment by a Consultant Ophthalmologist expert in inherited eye disease

### Requesting Specialties

- Clinical Genetics
- Ophthalmology

### Specialist Service Group

- Eyes

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R34.1	TIMP3 hotspot exon Targeted mutation testing	Singleton	Small variants	Single interval	TIMP3 hotspot exon	Targeted mutation testing
R34.2	Retinal disorders WES or large panel	Singleton	Small variants	Panel of genes or loci	Retinal disorders (307)	WES or Large Panel



## R35 Doyne retinal dystrophy

### Testing Criteria

Unexplained retinal disease with features strongly suggestive of Doyne retinal dystrophy

### Where in Pathway

At presentation following assessment by a Consultant Ophthalmologist expert in inherited eye disease

### Requesting Specialties

- Clinical Genetics
- Ophthalmology

### Specialist Service Group

- Eyes

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R35.1	EFEMP1 hotspot Targeted mutation testing	Singleton	Small variants	Single interval	EFEMP1 hotspot	Targeted mutation testing
R35.2	Retinal disorders WES or large panel	Singleton	Small variants	Panel of genes or loci	Retinal disorders (307)	WES or Large Panel

## 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 Congenital malformation and dysmorphism syndromes – 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
- 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

- Eyes

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R36.1	Structural eye disease WES or large panel	Singleton	Small variants	Panel of genes or loci	Structural eye disease (509)	WES or Large Panel

## 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

- Cancer
- Clinical Genetics
- Ophthalmology
- Paediatrics

### Specialist Service Group

- Eyes

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R38.1	PAX6; WT1 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	PAX6; WT1	MLPA or equivalent
R38.2	Aniridia Small panel	Singleton	Small variants	Panel of genes or loci	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

- Eyes

### Associated Tests

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

- Eyes

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R41.1	Optic neuropathy Medium panel	Singleton	Small variants	Panel of genes or loci	Optic neuropathy (186)	Medium panel

## 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

- Eyes

### Associated Tests

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

- Eyes

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R46.1	Congenital fibrosis of the extraocular muscles Small panel	Singleton	Small variants	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

- Eyes

### Associated Tests

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

### Requesting Specialties

- Clinical Genetics
- Ophthalmology

### Specialist Service Group

- Eyes

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R45.1	Stickler syndrome Small panel	Singleton	Small variants	Panel of genes or loci	Stickler syndrome (3)	Small panel
R45.2	COL2A1; COL11A1 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	COL2A1; COL11A1	MLPA or equivalent

## Part VI. Fetal (including NIPD)

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### 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R401.1	Genomewide Common aneuploidy testing - prenatal	Singleton	Aneuploidy	Genomewide	Genomewide	Common aneuploidy testing

## 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 consecutive miscarriages.

### Overlapping indications

- R297 Possible structural chromosomal rearrangement - karyotype test should be used in parents of recurrent miscarriage where products of conception are not available for testing
- R22 Fetus with a likely chromosomal abnormality or R21 Fetal anomalies with a likely genetic cause should be used in cases of second or third trimester intrauterine death or stillbirth
- 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

Referrals for testing will be triaged by the Genomic 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

Code	Name	Optional 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

Fetus with a likely chromosomal abnormality

This indication is relevant in ongoing pregnancies and where there has been fetal loss, termination of pregnancy or miscarriage

### Overlapping indications

- 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 instead following discussion with a Clinical Geneticist where it is considered more appropriate
- 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

Referrals for testing will be triaged by the Genomic 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

Code	Name	Optional 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.

PLEASE NOTE: This is a new NHS service and will be rolled out during the transition phase of the Genomic Medicine Service. Please contact your local Genomic Laboratory Hub to ensure your local pathway is set up BEFORE sending any samples for patients requiring testing under this clinical indication

This clinical indication will transition to Whole Genome Sequencing. In the interim a rapid Whole Exome Service is being provided by designated GLH(s).

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 an alternative indication for non-urgent testing

### 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 Congenital malformation and dysmorphism syndromes 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

### Requesting Specialties

- Clinical Genetics

### Specialist Service Group

- Core

### Associated Tests

Code	Name	Optional 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	Panel of genes or loci	Fetal anomalies (478)	WES or Large Panel
R21.3	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray

## 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

- NIPD

### Associated Tests

Code	Name	Optional 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 mutation 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 mutations or where the father has an autosomal dominant mutation or is known mosaic for a mutation. 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

- NIPD

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R249.1	Specific target NIPD	Singleton	All variants	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 female

Referrals for testing will be triaged 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

- NIPD

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R250.1	CYP21A2 NIPD	Singleton	Small variants	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 mutation 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

- NIPD

### Associated Tests

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

## R305 NIPD for cystic fibrosis - mutation testing

### Testing Criteria

1. Pregnancy at risk of cystic fibrosis due to known CFTR mutation(s) for which NIPD by mutation testing is required following discussion with testing laboratory, AND
2. Both parents confirmed to be carriers of a different mutation, AND
3. Father is a carrier of one of the following CFTR mutations 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

- NIPD

### Associated Tests

Code	Name	Optional 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 - mutation 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

- NIPD

### Associated Tests

Code	Name	Optional 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 - mutation 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 mutation is confirmed OR a previous pregnancy with confirmed Crouzon syndrome with acanthosis nigricans with mutation 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

- NIPD

### Associated Tests

Code	Name	Optional 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 - mutation testing

### Testing Criteria

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

- NIPD

### Associated Tests

Code	Name	Optional 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 - mutation 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 fingersOR
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 fingersOR
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

- NIPD

### Associated Tests

Code	Name	Optional 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 mutation for which NIPD by mutation 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 male fetus

### Requesting Specialties

- Clinical Genetics
- Fetal Medicine

### Specialist Service Group

- NIPD

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R310.1	Dystrophin NIPD	Singleton	Small variants	Single gene(s)	Dystrophin	NIPD

## R311 NIPD for spinal muscular atrophy - mutation testing

### Testing Criteria

1. Pregnancy at risk of spinal muscular atrophy due to known SMN1 mutation(s) for which NIPD by mutation 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

- NIPD

### Associated Tests

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

## Part VII. Gastrohepatology

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### 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

#### Requesting Specialties

- Dermatology
- Haematology
- Hepatology
- Neurology

#### Specialist Service Group

- Gastrohepatology

#### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R168.1	Non-acute porphyrias Small panel	Singleton	Small variants	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

### Requesting Specialties

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

### Specialist Service Group

- Gastrohepatology

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R169.1	HMBS Single gene sequencing	Singleton	Small variants	Single gene(s)	HMBS	Single gene sequencing $\geq 10$ 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R170.1	PPOX Single gene sequencing	Singleton	Small variants	Single gene(s)	PPOX	Single gene sequencing $\geq 10$ 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

Referrals for testing will be triaged by the Genomic 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

### Specialist Service Group

- Gastrohepatology

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R171.1	Cholestasis WES or Medium panel	Singleton	Small variants	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 - targeted testing is not possible, R27 Congenital malformation and dysmorphism syndromes – likely monogenic 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

### Specialist Service Group

- Gastrohepatology

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R172.1	ATP7B Single gene sequencing	Singleton	Small variants	Single gene(s)	ATP7B	Single gene sequencing $\geq 10$ 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 Congenital malformation and dysmorphism syndromes – 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

Referrals for testing will be triaged by the Genomic 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R173.1	Polycystic liver disease WES or small panel	Singleton	Small variants	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

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R175.1	Pancreatitis Small panel	Singleton	Small variants	Panel of genes or loci	Pancreatitis (386)	Small panel
R175.2	CFTR common mutations Targeted mutation testing	Singleton	Small variants	Single interval	CFTR common mutations	Targeted mutation testing



## 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

### Specialist Service Group

- Gastrohepatology

### Associated Tests

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

## R177 Hirschsprung disease - familial

### Testing Criteria

Diagnosis of Hirschsprung disease, with a first / second degree relative with a diagnosis of Hirschsprung disease

### Overlapping indications

- R27 Congenital malformation and dysmorphism syndromes – 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

Referrals for testing will be triaged by the Genomic 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

### Specialist Service Group

- Gastrohepatology

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R177.1	RET Single gene sequencing	Singleton	Small variants	Single gene(s)	RET	Single gene sequencing $\geq 10$ amplicons

## R331 Intestinal failure

### 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

Referrals for testing will be triaged 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

### Specialist Service Group

- Gastrohepatology

### Associated Tests

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

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R361.1	HBA1; HBA2; HBG1; HBG2; HBB Single gene sequencing	Singleton	Small variants	Single gene(s)	HBA1; HBA2; HBG1; HBG2; HBB	Single gene sequencing <10 amplicons
R361.2	HBA1; HBA2; HBG1; HBG2; HBB MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	HBA1; HBA2; HBG1; HBG2; HBB	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R362.1	HbS variant Targeted mutation testing	Singleton	Small variants	Single interval	HbS variant	Targeted mutation 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R90.1	Bleeding and platelet disorders WES or medium panel	Singleton	Small variants	Panel of genes or loci	Bleeding and platelet disorders (545)	WES or Medium Panel
R90.2	F5; F11; MYH9; ENG; ACVRL1; BMPR2; F7; F8; F9; F10; VWF MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	F5; F11; MYH9; ENG; ACVRL1; BMPR2; F7; F8; F9; F10; VWF	MLPA or equivalent

## 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

Code	Name	Optional 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	MLPA or equivalent
R93.2	HBA1; HBA2; HBG1; HBG2; HBB Single gene sequencing	Singleton	Small variants	Single gene(s)	HBA1; HBA2; HBG1; HBG2; HBB	Single gene sequencing <10 amplicons

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

- Other

### Specialist Service Group

- Screening

### Associated Tests

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

## R95 Iron overload - hereditary haemochromatosis testing

### Testing Criteria

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

### Overlapping indications

- R96 Iron metabolism disorders - not common HFE mutations should be used instead where hereditary haemochromatosis is not the likely diagnosis, or HFE common mutations 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
- Primary Care

### Specialist Service Group

- Core

### Associated Tests

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

## R96 Iron metabolism disorders - NOT common HFE mutations

### Testing Criteria

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

### Overlapping indications

- R95 Iron overload - hereditary haemochromatosis testing should be used where hereditary haemochromatosis due to common HFE mutations 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R96.1	Iron metabolism disorders Small panel	Singleton	Small variants	Panel of genes or loci	Iron metabolism disorders (515)	Small panel
R96.2	HFE; SLC40A1; TFR2; HFE2; HAMP; ATP7B MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	HFE; SLC40A1; TFR2; HFE2; HAMP; ATP7B	MLPA or equivalent

## 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R97.1	Thrombophilia WES or small panel	Singleton	Small variants	Panel of genes or loci	Thrombophilia (516)	WES or Small Panel
R97.2	PROS1; PROC; SERPINC1 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	PROS1; PROC; SERPINC1	MLPA or equivalent

## 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R112.1	F2 Single gene sequencing	Singleton	Small variants	Single gene(s)	F2	Single gene sequencing $\geq 10$ 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

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R115.1	F5 Single gene sequencing	Singleton	Small variants	Single gene(s)	F5	Single gene sequencing $\geq 10$ amplicons
R115.2	F5 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	F5	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

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

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R117.1	F8 Targeted mutation testing	Singleton	Small variants	Single gene(s)	F8	Targeted mutation testing
R117.2	F8 Single gene sequencing	Singleton	Small variants	Single gene(s)	F8	Single gene sequencing $\geq 10$ amplicons
R117.3	F8 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	F8	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

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

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

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

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R121.1	VWF Single gene sequencing	Singleton	Small variants	Single gene(s)	VWF	Single gene sequencing >=10 amplicons
R121.2	VWF MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	VWF	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R122.1	F13A1; F13B Single gene sequencing	Singleton	Small variants	Single gene(s)	F13A1; F13B	Single gene sequencing >=10 amplicons

## 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R123.1	VKORC1; GGCX Single gene sequencing	Singleton	Small variants	Single gene(s)	VKORC1; GGCX	Single gene sequencing >=10 amplicons

## 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R124.1	Combined factor V and VIII deficiency Small panel	Singleton	Small variants	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 Congenital malformation and dysmorphism syndromes - 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

Referrals for testing will be triaged by the Genomic 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

Code	Name	Optional 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 Single gene sequencing	Singleton	Small variants	Single gene(s)	HBA1; HBA2; HBG1; HBG2; HBB	Single gene sequencing <10 amplicons
R92.3	Rare anaemia WES or medium panel	Singleton	Small variants	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 mutations test should be used in cases of neutropaenia where ELANE mutations are plausible and have not been excluded
- R27 Congenital malformation and dysmorphism syndromes - 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

Referrals for testing will be triaged by the Genomic 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

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R91.1	Cytopenia - NOT Fanconi anaemia WES or medium panel	Singleton	Small variants	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	Optional 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	Panel of genes or loci	Confirmed Fanconi anaemia or Bloom syndrome (508)	WES or Small Panel

## 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 Congenital malformation and dysmorphism syndromes – likely monogenic, 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 mutation(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	Optional 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	Single gene sequencing $\geq 10$ amplicons

## 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 Congenital malformation and dysmorphism syndromes – likely monogenic, 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 mutation(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	Optional 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 mutations

### Testing Criteria

1. Isolated neutropaenia where ELANE mutations 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 mutations
- R27 Congenital malformation and dysmorphism syndromes – 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

Referrals for testing will be triaged by the Genomic 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R313.1	ELANE Single gene sequencing	Singleton	Small variants	Single gene(s)	ELANE	Single gene sequencing <10 amplicons

## R338 Monitoring for G(M)CSF escape mutations

### Testing Criteria

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

### Where in Pathway

As per relevant clinical protocol

### Requesting Specialties

- Haematology
- Immunology

### Specialist Service Group

- Haematology

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R338.1	CSF3R Single gene sequencing	Singleton	Small variants	Single gene(s)	CSF3R	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  $\geq 1$  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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R347.1	Inherited predisposition to acute myeloid leukaemia AML Small panel	Singleton	Small variants	Panel of genes or loci	Inherited predisposition to acute myeloid leukaemia (AML) (525)	Small panel
R347.2	RUNX1 21q22.12; CEBPA 19q13.11; GATA2 3q21.3; TERT 5p15.33; TERC 3q26.2 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	RUNX1 21q22.12; CEBPA 19q13.11; GATA2 3q21.3; TERT 5p15.33; TERC 3q26.2	MLPA or equivalent

## 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 Leukemia (ALL), AND

1. One first / second / third degree relative with AL, 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R366.1	PAX5; ETV6 Single gene sequencing	Singleton	Small variants	Single gene(s)	PAX5; ETV6	Single gene sequencing >=10 amplicons



## 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R405.1	Hereditary Erythrocytosis Small panel	Singleton	Small variants	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R406.1	Thrombocythaemia Small panel	Singleton	Small variants	Panel of genes or loci	Thrombocythaemia (945)	Small panel

## Part IX. Hearing

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### 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 in whom aminoglycoside therapy may be required, OR
2. individuals who have been exposed to aminoglycosides in whom mt.1555A>G status needs to be determined because of concern regarding hearing loss

#### Overlapping indications

- R67 Non-syndromic 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

- Other

#### Specialist Service Group

- Core

#### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R65.1	MT-RNR1 1555A>G Targeted mutation testing	Singleton	Small variants	Single interval	MT-RNR1 1555A>G	Targeted mutation testing

## R67 Non-syndromic hearing loss

### Testing Criteria

Likely or possible monogenic hearing loss

Hearing loss should be confirmed and bilateral

### Overlapping indications

- R27 Congenital malformation and dysmorphism syndromes – 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

Referrals for testing will be triaged by the Genomic 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
- Clinical Genetics
- Ear, Nose and Throat
- Paediatrics

### Specialist Service Group

- Hearing

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R67.1	Hearing loss 126 WES or large panel	Singleton	Small variants	Panel of genes or loci	Hearing loss (126)	WES or Large Panel
R67.2	Hearing loss MLPA or equivalent	Singleton	Exon level CNVs	Panel of genes or loci	Hearing loss (126)	MLPA or equivalent

## Part X. Immunology

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

## R15 Primary immunodeficiency

### 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

### 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

Referrals for testing will be triaged by the Genomic 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
- Immunology

### Specialist Service Group

- Immunology

## Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R15.1	Primary immunodeficiency WES or large panel	Singleton	Small variants	Panel of genes or loci	Primary immunodeficiency (398)	WES or Large Panel
R15.2	Primary immunodeficiency MLPA or equivalent	Singleton	Exon level CNVs	Panel of genes or loci	Primary immunodeficiency (398)	MLPA or equivalent
R15.3	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray

## 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

N/A

### Requesting Specialties

- Clinical Genetics
- Immunology

### Specialist Service Group

- Immunology

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R16.1	ADA Single gene sequencing	Singleton	Small variants	Single gene(s)	ADA	Single gene sequencing $\geq 10$ 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

### Requesting Specialties

- Clinical Genetics
- Immunology

### Specialist Service Group

- Immunology

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R235.1	IL2RG Single gene sequencing	Singleton	Small variants	Single gene(s)	IL2RG	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

### Requesting Specialties

- Clinical Genetics
- Immunology

### Specialist Service Group

- Immunology

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R234.1	PNP Single gene sequencing	Singleton	Small variants	Single gene(s)	PNP	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R17.1	SH2D1A Single gene sequencing	Singleton	Small variants	Single gene(s)	SH2D1A	Single gene sequencing <10 amplicons
R17.2	SH2D1A MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	SH2D1A	MLPA or equivalent

## 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R18.1	XIAP Single gene sequencing	Singleton	Small variants	Single gene(s)	XIAP	Single gene sequencing $\geq 10$ amplicons
R18.2	XIAP MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	XIAP	MLPA or equivalent

## 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R232.1	PRF1 Single gene sequencing	Singleton	Small variants	Single gene(s)	PRF1	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R19.1	FAS Single gene sequencing	Singleton	Small variants	Single gene(s)	FAS	Single gene sequencing $\geq 10$ 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R233.1	BTK Single gene sequencing	Singleton	Small variants	Single gene(s)	BTK	Single gene sequencing $\geq 10$ 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 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 WASP expression analysis

### Requesting Specialties

- Clinical Genetics
- Haematology
- Immunology

### Specialist Service Group

- Immunology

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R20.1	WAS Single gene sequencing	Singleton	Small variants	Single gene(s)	WAS	Single gene sequencing $\geq 10$ 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R341.1	SERPING1 Single gene sequencing	Singleton	Small variants	Single gene(s)	SERPING1	Single gene sequencing $\geq 10$ amplicons
R341.2	SERPING1 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	SERPING1	MLPA or equivalent

## 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R368.1	F12 hotspot Targeted mutation testing	Singleton	Small variants	Single interval	F12 hotspot	Targeted mutation testing

## Part XI. Inherited cancer

### R207 Inherited ovarian cancer (without breast cancer)

#### Testing Criteria

Living affected individual (proband) with high-grade epithelial ovarian cancer (EOC) where the individual +/- family history meet one of the criteria below:

1. EOC AND  $\geq 1$  first degree relative with EOC, OR
2. EOC AND  $\geq 1$  second degree relative with EOC (intervening relative is male, OR female with BSO, OR female deceased <60), OR
3. EOC and  $\geq 2$  second / third degree relatives with EOC
4. Deceased affected individual (proband) where:
  - a. The individual +/- family history meets one of the above criteria AND
  - b. Appropriate tissue is available (tumour or normal) AND
  - c. 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**

Referrals for testing will be triaged 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

- Cancer
- Clinical Genetics
- Gynaecology

#### Specialist Service Group

- Core

#### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R207.1	Inherited ovarian cancer without breast cancer Small panel	Singleton	Exon level CNVs	Panel of genes or loci	Inherited ovarian cancer (without breast cancer) (143)	Small panel
R207.2	BRCA1; BRCA2; MLH1; MSH2; MSH6; PMS2 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	BRCA1; BRCA2; MLH1; MSH2; MSH6; PMS2	MLPA or equivalent

## R208 Inherited breast cancer and ovarian cancer

### Testing Criteria

1. Living affected individual (proband) with breast or ovarian cancer where the individual +/- family history meets one of the criteria. The proband has:
  - a. Breast cancer (age < 30 years), OR
  - b. Bilateral breast cancer (age < 50 years), OR
  - c. Triple negative breast cancer (age < 60 years), OR
  - d. Male breast cancer (any age), OR
  - e. High-grade non mucinous epithelial ovarian cancer at any age, OR
  - f. Breast cancer (age <45 years) and a first degree relative with breast cancer (age <45 years), OR
  - g. Pathology-adjusted Manchester score  $\geq 15$  or BOADICEA score  $\geq 10\%$
  - h. Ashkenazi Jewish ancestry and breast cancer at any age
2. Deceased affected individual with breast or ovarian cancer with:
  - a. A stored DNA, blood or tissue sample available for DNA extraction, AND
  - b. Pathology-adjusted Manchester score  $\geq 17$  or BOADICEA score  $\geq 15\%$ , AND
  - c. No living affected individual is available for genetic testing
3. Living unaffected individual with:
  - a. first degree relative affected by breast or serous ovarian cancer, AND
  - b. Pathology-adjusted Manchester score  $\geq 20$  or BOADICEA score  $\geq 20\%$  (for the first degree relative), AND
  - c. No living affected individual is available for genetic testing, AND
  - d. No deceased affected individual with tumour material available for testing

### NOTES

- 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 has not previously been performed
- Testing of unaffected and deceased individuals can only be offered by Clinical Genetics

### Overlapping indications

- R386 BRCA1 and BRCA2 – somatic test should be used where there is no living affected individual available to test, but tumour material is available from a deceased affected individual
- M2 Ovarian carcinoma should be used for somatic testing
- M3 Breast 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

- Cancer
- Clinical Genetics

### Specialist Service Group

- Core

## Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R208.1	BRCA1; BRCA2; PALB2 Single gene sequencing	Singleton	Small variants	Single gene(s)	BRCA1; BRCA2; PALB2	Single gene sequencing >=10 amplicons
R208.2	BRCA1; BRCA2; PALB2 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	BRCA1; BRCA2; PALB2	MLPA or equivalent

## R209 Inherited colorectal cancer (with or without polyposis)

### Testing Criteria

1. Living affected individual (proband) with colorectal cancer with:
  - a. Diagnosed aged <30 OR
  - b. Personal/family history of colorectal cancers reaching Amsterdam Criteria ( $\geq 3$  cases over  $\geq 2$  generations with  $\geq 1$  case affected at <50 years)
2. Deceased affected individual (proband) where (i) the individual +/- family history meets one of the above criteria, (ii) appropriate tissue is available (tumour or normal) and (iii) 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**

Referrals for testing will be triaged 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 Colorectal carcinoma should be used for somatic testing

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics

### Specialist Service Group

- Core

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R209.1	Inherited colorectal cancer with or without polyposis Small panel	Singleton	Small variants	Panel of genes or loci	Inherited polyposis (504)	Small panel
R209.2	MLH1; MSH2; MSH6; PMS2 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	MLH1; MSH2; MSH6; PMS2	MLPA or equivalent

## R210 Inherited MMR deficiency (Lynch syndrome)

### Testing Criteria

1. Living affected individual (proband) with Lynch-related cancer where the individual +/- family history meets one of the following criteria. The proband has:
  - a. Colorectal cancer (when first diagnosed, any age; as per NICE guidance, OR)
  - b. Any lynch-related cancer\* (<50 years), OR
  - c. Two Lynch-related cancers (any age, one is colorectal or endometrial), OR
  - d. Lynch-related cancer and  $\geq 1$  first degree relative has Lynch-related cancer (both occurred <60 years, one is colorectal or endometrial), OR
  - e. Lynch-related cancer and  $\geq 2$  relatives (first / second / third degree relatives) have Lynch-related cancer (all occurring <75 years, one is colorectal or endometrial), OR
  - f. Lynch-related cancer and  $\geq 3$  relatives (first / second / third degree relatives) have Lynch-related cancer (occurring any age, one is colorectal or endometrial)
2. Deceased affected individual (proband) with:
  - a. Colorectal or endometrial cancer <60 years, AND
  - b.  $\geq 1$  first degree relative with Lynch-related cancer age <60, AND
  - c. Appropriate tissue (tumour or normal) is available, AND
  - d. No living affected individual is available for genetic testing
3. Unaffected individual with:
  - a. First degree relative affected with Lynch-related cancer, AND
  - b. Family history of colorectal cancer/Lynch-related cancers reaches Amsterdam Criteria ( $\geq 3$  cases over  $\geq 2$  generations with  $\geq 1$  case affected <50 years), AND
  - c. Somatic sequencing is not possible, or failed, AND
  - d. No living affected individual is available for genetic testing

\*Lynch-related cancers comprise: Colorectal cancer, Endometrial cancer, Epithelial ovarian cancer, Pancreatic cancer, Ureteric cancer, Transitional cell cancer of renal pelvis, Gastric cancer, Hepatobiliary tract cancer (excluding liver cancer except cholangiocarcinoma), Small bowel cancer, Glioblastoma, pancreatic cancer, prostate cancer, multiple sebaceous adenomata, multiple sebaceous epitheliomas, multiple keratoacanthomas, sebaceous carcinoma, endocervical cancer

### Overlapping indications

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

### Order of testing

1. Microsatellite testing or immunohistochemistry (NOTE: IHC is out of Scope for this test directory)  
If microsatellite stability and/or normal IHC are demonstrated, no further testing is indicated in the individual whose tumour has been tested
2. Exclusion of MMR deficiency due to somatically acquired MLH1 hypermethylation via tumour testing for *BRAF* p.(V600E) OR MLH1 hypermethylation in living proband if:
  - a. Proband has colorectal cancer, AND
  - b. Tumour shows high/intermediate MSI and/or loss of staining of MMR protein(s) on IHCIf acquired MLH1 hypermethylation is demonstrated (i.e. MLH1 hypermethylation in tumour tissue with normal methylation observed in normal tissue) no further testing is indicated in the individual whose tumour has been tested
3. Germline Lynch syndrome panel test in living affected individual (proband) with Lynch-related cancer. The proband has:
  - a. Lynch-related cancer, AND
  - b. Tumour featuring high/intermediate MSI or loss of staining of MMR protein(s) on IHC, AND
  - c. If colorectal or endometrial, tumour which is normal on testing of: *BRAF* p.(V600E) and/or MLH1 hypermethylation analysis (*BRAF* p.(V600E) is not indicated in the endometrial testing pathway)
4. Somatic Lynch syndrome panel test in:
  - a. Living affected individual (proband) with Lynch-related cancer. The proband has:
  - b. Colorectal or endometrial cancer, AND

- c. Tumour featuring high/intermediate MSI or loss of staining of MMR protein(s) on IHC, AND
  - d. Tumour is normal on testing of: *BRAF* p.(V600E) and/or MLH1 hypermethylation analysis (*BRAF* p.(V600E) is not indicated in the endometrial testing pathway), AND
  - e. Germline Lynch panel did not reveal a pathogenic mutation, AND
  - f. Personal/family pattern of disease whereby demonstration of acquired MMR mutations (and therefore exclusion of constitutional MMR abnormality) enables downscaling of surveillance
5. Somatic Lynch syndrome panel test in deceased affected individual with Lynch-related cancer. The individual has:
    - a. Colorectal or endometrial cancer <60 years, AND
    - b. Tumour featuring high/intermediate MSI or loss of staining of MMR protein(s) on IHC, AND
    - c. One first degree relative with Lynch-related cancer at age <60, AND
    - d. No living affected individual is available for genetic testing
  6. Testing of unaffected individual (if none of the options above are available). Germline Lynch gene panel testing in a living unaffected individual with:
    - a. First degree relative affected with Lynch-related cancer, AND
    - b. Family history of colorectal cancer/Lynch-related cancers reaches Amsterdam Criteria ( $\geq 3$  cases over  $\geq 2$  generations with  $\geq 1$  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. Sequencing for somatic Lynch gene panel has been attempted in a sample from an affected relative and is not possible, or failed, AND
    - e. 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**

The order of germline and somatic testing can be determined locally by the laboratory

Living affected individuals from Amsterdam positive families should proceed directly to R209 testing (inherited colorectal cancer).

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

Referrals for testing will be triaged by the Genomic 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
- Surgery\*
- Gastroenterology
- Histopathology

\* Surgery to cover colorectal and gynecological surgeons

## Specialist Service Group

- Core

## Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R210.1	Inherited MMR deficiency Lynch syndrome Microsatellite instability	Singleton	MSI	Panel of genes or loci	Inherited MMR deficiency (Lynch syndrome) (503)	Microsatellite instability



Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R210.2	Inherited MMR deficiency Lynch syndrome Small panel	Singleton	Small variants	Panel of genes or loci	Inherited MMR deficiency (Lynch syndrome) (503)	Small panel
R210.3	BRAF p.(V600E) Targeted mutation testing	Singleton	Small variants	Single interval	BRAF p.(V600E)	Targeted mutation testing
R210.4	MLH1 hypermethylation Methylation testing	Singleton	Methylation	Single interval	MLH1 hypermethylation	Methylation testing
R210.5	MLH1; MSH2; MSH6; PMS2 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	MLH1; MSH2; MSH6; PMS2	MLPA or equivalent

## R211 Inherited polyposis - germline test

### Testing Criteria

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

1. ≥5 adenomatous polyps and colorectal cancer, OR
2. ≥5 adenomatous polyps (age <40 years), OR
3. ≥10 adenomatous polyps (age <60 years), OR
4. ≥20 adenomatous polyps (age ≥ 60 years), OR
5. ≥5 adenomatous polyps (age <60 years) and first degree relative with ≥5 adenomatous polyps (age <60 years), OR
6. Juvenile polyposis syndrome:
  - a. ≥ 5 juvenile polyps of the colorectum, OR
  - b. ≥ 2 juvenile polyps throughout the GI tract, OR
  - c. ≥ 1 juvenile polyp and a first / second degree relative has juvenile polyp, OR
7. Clinical signs indicating potential diagnosis of Familial Adenomatous Polyposis:
  - a. FAP-related CHRPE, OR
  - b. Desmoid tumour (+nuclear  $\beta$ -catenin expression; CTNNB1 WT where testing performed)
  - c. Deceased affected individual (proband) where (i) the individual +/- family history meets one of the above criteria, (ii) appropriate tissue is available (tumour or normal), and (iii) no living affected individual is available for genetic testing.

**NOTE:** The majority of polyps are histologically confirmed

### Overlapping indications

- R385 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

### Specialist Service Group

- Core

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R211.1	Inherited colorectal cancer with or without polyposis Small panel	Singleton	Small variants	Panel of genes or loci	Inherited polyposis (504)	Small panel
R211.2	APC MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	APC	MLPA or equivalent

## R212 Peutz Jegher Syndrome

### Testing Criteria

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

1.  $\geq 2$  PJS-type hamartomatous polyps, OR
2.  $\geq 1$  PJS-type polyp and characteristic mucocutaneous pigmentation, OR
3. Characteristic mucocutaneous pigmentation age  $<10$ , OR
4.  $\geq 1$  PJS-type polyp, AND  $\geq 1$  first / second degree relative with:
  - a.  $\geq 1$  PJS-like feature, OR
  - b.  $\geq 2$  PJS-related cancers (the two cancers can be in the same or different relatives), OR
5. Characteristic mucocutaneous pigmentation, AND  $\geq 1$  first / second degree relative with:
6.  $\geq 1$  PJS-like feature, OR
7.  $\geq 2$  PJS-related cancers (the two cancers can be in the same or different relatives)

Deceased affected individual (proband) where (i) the individual +/- family history meets one of the above criteria, (ii) appropriate tissue is available (tumour or normal), and (iii) no living affected individual is available for genetic testing

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**

Referrals for testing will be triaged by the Genomic 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

### Specialist Service Group

- Inherited cancer

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R212.1	STK11 Single gene sequencing	Singleton	Small variants	Single gene(s)	STK11	Single gene sequencing $\geq 10$ amplicons
R212.2	STK11 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	STK11	MLPA or equivalent

## R213 PTEN Hamartoma Tumor Syndrome

### Testing Criteria

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

1. Mucocutaneous lesions comprising
  - a.  $\geq 6$  facial papules, of which  $\geq 3$  are trichilemmoma, OR
  - b. Cutaneous facial papules AND oral mucosal papillomatosis, OR
  - c. Oral mucosal papillomatosis AND acral keratosis, OR
  - d.  $\geq 6$  palmoplantar keratosis, OR
2. Cerebellar dysplastic gangliocytoma (Adult Lhermitte-Duclos disease (LDD)), OR
3.  $\geq 2$  major criteria, OR
4.  $\geq 1$  major criteria and  $\geq 1$  PTEN-HTS-related mucocutaneous lesion, OR
5.  $\geq 1$  major and  $\geq 3$  minor criteria, OR
6. Macrocephaly  $\geq 99$ th centile, AND
7.  $\geq 1$  minor criteria, OR
8.  $\geq 1$  PTEN-HTS-related mucocutaneous lesion, OR
9.  $\geq 4$  minor criteria, OR
10.  $\geq 1$  major criteria, AND  $\geq 2$  first / second degree relatives each with:
11.  $\geq 1$  major criteria, OR  $\geq 1$  PTEN-HTS-related mucocutaneous lesion, OR
12.  $\geq 2$  minor criteria (multiple cases of breast cancer are not eligible for inclusion)

Deceased affected individual (proband) where (i) the individual +/- family history meets one of the above criteria, (ii) appropriate tissue is available (tumour or normal), and (iii) no living affected individual is available for genetic testing

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  $\geq 97$ th percentile)
- Endometrial carcinoma

Minor criteria:

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

Referrals for testing will be triaged by the Genomic 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R213.1	PTEN Single gene sequencing	Singleton	Small variants	Single gene(s)	PTEN	Single gene sequencing $\geq 10$ amplicons
R213.2	PTEN MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	PTEN	MLPA or equivalent

## R214 Nevroid Basal Cell Carcinoma Syndrome or Gorlin syndrome

### Testing Criteria

1. Living individual affected (proband) where the individual history meets:
  - a.  $\geq 2$  major and  $\geq 1$  minor criteria, OR
  - b.  $\geq 1$  major and  $\geq 3$  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)
  - Multiple basal cell carcinomas (BCCs) ( $>5$  in a lifetime) or BCC before age 30 years
3. Minor criteria:
  - Childhood medulloblastoma (also called primitive neuroectodermal tumor [PNET])
  - Lympho-mesenteric or pleural cysts
  - Macrocephaly (OFC  $>97$ th 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)

Referrals for testing will be triaged by the Genomic 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R214.1	PTCH1; SUFU Single gene sequencing	Singleton	Small variants	Single gene(s)	PTCH1; SUFU	Single gene sequencing $\geq 10$ amplicons
R214.2	PTCH1; SUFU MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	PTCH1; SUFU	MLPA or equivalent

## R215 CDH1-related cancer syndrome

### Testing Criteria

1. Living affected individual (proband) where the individual +/- family history meets one of the criteria. The proband has:
  - a. Diffuse gastric cancer (<40 years), OR
  - b. Diffuse gastric cancer and  $\geq 1$  first / second degree relative has diffuse gastric cancer ( $\geq 1$  case occurred at <50 years), OR
  - c. Diffuse gastric cancer with  $\geq 2$  first / second degree relatives with diffuse gastric cancer (any age), OR
  - d. Diffuse gastric cancer and  $\geq 1$  first / second degree relative has lobular breast cancer ( $\geq 1$  case occurred at <50 years), OR
  - e. Lobular breast cancer and  $\geq 1$  first / second degree relative has diffuse gastric cancer ( $\geq 1$  case occurred at <50 years), OR
2. Deceased affected individual (proband) where (i) the individual +/- family history meets one of the above criteria, (ii) appropriate tissue is available (tumour or normal), and (iii) no living affected individual is available for genetic testing

**NOTE: All cancers 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/at follow-up

### Requesting Specialties

- Clinical Genetics
- Gastroenterology

### Specialist Service Group

- Inherited cancer

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R215.1	CDH1 Single gene sequencing	Singleton	Small variants	Single gene(s)	CDH1	Single gene sequencing $\geq 10$ amplicons
R215.2	CDH1 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	CDH1	MLPA or equivalent

## R216 Li Fraumeni Syndrome

### Testing Criteria

1. Living affected individual (proband) where the individual +/- family history meets one of the criteria. The proband has:
2. Rhabdomyosarcoma ( $\leq 5$  years), OR
  - a. Adrenocortical cancer (any age), OR
  - b. Choroid plexus cancer (any age), OR
  - c. Breast cancer ( $\leq 30$  years), OR
  - d. Triple positive breast cancer ( $\leq 35$  years), OR
  - e.  $\geq 2$  LFS-related cancers (both occurring  $\leq 46$  years; two breast cancers not eligible), OR
  - f.  $\geq 1$  LFS-related cancer with  $\geq 1$  first / second degree relative with  $\geq 1$  LFS-related cancer (one case  $\leq 46$  years, the other case  $\leq 56$  years; two breast cancers not eligible), OR
  - g. Cancer with  $\geq 2$  first / second degree relatives with cancer; across the family there is:
    - i. 1 individual with sarcoma  $\leq 45$  years, AND
    - ii. 1 individual with any cancer  $\leq 45$  years, AND
    - iii. 1 individual with either a sarcoma OR any cancer occurring  $\leq 45$  years
3. Deceased affected individual (proband) where (i) the individual +/- family history meets one of the above criteria, (ii) appropriate tissue is available (tumour or normal), and (iii) no living affected individual is available for genetic testing

LFS-related cancers comprise: Sarcoma of bone/soft tissue, breast cancer, brain cancer, adrenocortical cancer or any childhood cancer (occurring  $\leq 18$  years)

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

### 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

### Specialist Service Group

- Inherited cancer

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R216.1	TP53 Single gene sequencing	Singleton	Small variants	Single gene(s)	TP53	Single gene sequencing $\geq 10$ amplicons
R216.2	TP53 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	TP53	MLPA or equivalent



## R219 Retinoblastoma

### Testing Criteria

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

1. Unilateral unifocal retinoblastoma, OR
2. Bilateral OR multifocal retinoblastoma, OR
3. Retinoblastoma AND  $\geq 1$  relative with retinoblastoma

RB1 somatic test can be undertaken instead in tumour material where indicated

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.

### 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

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R219.1	RB1 Single gene sequencing	Singleton	Small variants	Single gene(s)	RB1	Single gene sequencing $\geq 10$ amplicons
R219.2	RB1 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	RB1	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. Bilateral disease, OR
2. Family history of Wilms tumour, OR
3. Unexplained proteinuria or renal failure, OR
4. Hypospadias, undescended testes or ambiguous genitalia, OR
5. Gonadoblastoma

### 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

Referrals for testing will be triaged by the Genomic 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

### Specialist Service Group

- Inherited cancer

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R220.1	WT1 Single gene sequencing	Singleton	Small variants	Single gene(s)	WT1	Single gene sequencing $\geq 10$ amplicons
R220.2	WT1 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	WT1	MLPA or equivalent
R220.3	11p15 imprinted growth regulatory region Methylation testing	Singleton	Methylation	Single interval	11p15 imprinted growth regulatory region	Methylation testing
R220.4	11p15 imprinted growth regulatory region MLPA or equivalent	Singleton	Exon level 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)

**NOTE: The proband's cancer should have been 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.

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

### 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

### Specialist Service Group

- Inherited cancer

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R358.1	Familial rhabdoid tumours Small panel	Singleton	Small variants	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  $\leq 14$ , 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

Referrals for testing will be triaged 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

- Cancer
- Clinical Genetics

### Specialist Service Group

- Inherited cancer

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R359.1	Tumour predisposition - childhood onset Medium panel	Singleton	Small variants	Panel of genes or loci	Tumour predisposition - childhood onset (243)	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 ( $\leq 40$  years), OR
2. Type 2 papillary renal cancer ( $\leq 50$  years), OR
3. Bilateral/multifocal renal cancer (any age), OR
4. Renal cancer AND first / second degree relative with renal cancer

Deceased affected individual (proband) where (i) the individual +/- family history meets one of the above criteria, (ii) appropriate tissue is available (tumour or normal), and (iii) 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**

Referrals for testing will be triaged 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

### Specialist Service Group

- Inherited cancer

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R224.1	Inherited renal cancer Small panel	Singleton	Small variants	Panel of genes or loci	Inherited renal cancer (521)	Small panel
R224.2	FLCN; VHL MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	FLCN; VHL	MLPA or equivalent

## R225 Von Hippel Lindau syndrome

### Testing Criteria

1. 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 haemangioblastoma (<60 years), OR
  - c.  $\geq 2$  VHL-related tumours (any age), OR
  - d.  $\geq 1$  VHL-related tumour and a first degree relative with  $\geq 1$  VHL-related tumour (where one of the tumours is retinal angioma / hemangioblastoma)
2. Deceased affected individual (proband) where (i) the individual +/- family history meets one of the above criteria, (ii) appropriate tissue is available (tumour or normal), and (iii) no living affected individual is available for genetic testing

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**

Referrals for testing will be triaged by the Genomic 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

### Specialist Service Group

- Inherited cancer

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R225.1	VHL Single gene sequencing	Singleton	Small variants	Single gene(s)	VHL	Single gene sequencing $\geq 10$ amplicons
R225.2	VHL MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	VHL	MLPA or equivalent

## R254 Familial melanoma

### Testing Criteria

1. Testing of phenotypically affected individual (proband) where the individual +/- family history meets one of the following criteria. The proband has:
  - a.  $\geq 2$  melanomas age  $<30$  years, OR
  - b. Melanoma AND  $\geq 2$  relatives (first / second / third degree relatives) with melanoma, OR
  - c. Melanoma AND  $\geq 1$  first degree relative with melanoma; one individual has multiple melanomas, OR
  - d.  $\geq 1$  Melanoma OR melanoma and atypical moles AND  $\geq 1$  first degree relative with pancreatic cancer aged  $<60$ , OR
  - e. Atypical moles AND  $\geq 2$  relatives (first / second degree relatives) with melanoma, OR
  - f. Uveal melanoma OR BAP-oma (atypical spitz naevus with loss of BAP1 on IHC) OR
  - g. Malignant mesothelioma AND  $\geq 1$  first degree relative with malignant mesothelioma OR uveal melanoma OR BAP-oma
2. Deceased affected individual (proband) where (i) the individual +/- family history meets one of the above criteria, (ii) appropriate tissue is available (tumour or normal), and (iii) no living affected individual is available for 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.

### 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R254.1	Familial melanoma Small panel	Singleton	Small variants	Panel of genes or loci	Familial melanoma (522)	Small panel

## 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) somatically wildtype for KIT and PDGFRA:

1. Diagnosed age before age 50, OR
2. With  $\geq 1$  relative (first / second / third degree relative) with GIST, pheochromocytoma / paraganglioma

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

### Overlapping indications

- M8 Gastrointestinal stromal tumour should be used for somatic testing

### Where in Pathway

At presentation/at follow-up

### Requesting Specialties

- Clinical Genetics
- Endocrinology
- Gastroenterology

### Specialist Service Group

- Inherited cancer

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R363.1	Inherited predisposition to GIST Small panel	Singleton	Small variants	Panel of genes or loci	Inherited predisposition to GIST (523)	Small panel
R363.2	SDHA; SDHC; SDHD MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	SDHA; SDHC; SDHD	MLPA or equivalent



## R364 DICER1-related cancer predisposition

### Testing Criteria

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

1. Pleuropulmonary blastoma (PPB) in childhood, OR
2. The proband has ovarian sex cord-stromal tumours OR cystic nephroma, AND a first / second / third degree relative with any solid tumour of childhood or adolescence (age <30) or thyroid gland neoplasia (age <30) [Thyroid gland neoplasia includes multinodular goiter [MNG], adenomas, or differentiated thyroid cancer]

**NOTE: The proband's cancer and majority of reported cancers in the family should have been 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/at follow-up

### Requesting Specialties

- Clinical Genetics

### Specialist Service Group

- Inherited cancer

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R364.1	DICER1 Single gene sequencing	Singleton	Small variants	Single gene(s)	DICER1	Single gene sequencing >=10 amplicons

## R365 Fumarate hydratase-related tumour syndromes

### Testing Criteria

1. 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 OR tubulo-papillary renal tumour at any age, OR
  - b. Two of: cutaneous leiomyomata, renal tumour (any histology) OR uterine leiomyomata at any age, 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, OR
  - e. Uterine leiomyomata with classic histological features (age <40)
2. Deceased affected individual (proband) where (i) the individual +/- family history meets one of the above criteria, (ii) appropriate tissue is available (tumour or normal), and (iii) no living affected individual is available for genetic testing

**NOTE: Cutaneous leiomyomata should be histologically confirmed; uterine leiomyomata and renal tumours should 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

- 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
- Dermatology

### Specialist Service Group

- Inherited cancer

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R365.1	FH Single gene sequencing	Singleton	Small variants	Single gene(s)	FH	Single gene sequencing >=10 amplicons

## R367 Inherited pancreatic cancer

### Testing Criteria

1. Testing of affected individual (proband) where the individual +/- family history meets one of the following criteria. The proband has:
2. Pancreatic cancer age <50, OR
3. Pancreatic cancer age <60, 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 first / second degree relatives with any of breast cancer age <60, melanoma age <60, OR ovarian cancer

Deceased affected individual (proband) where (i) the individual +/- family history meets one of the above criteria, (ii) appropriate tissue is available (tumour or normal), and (iii) 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. Pancreatic cancer is adenocarcinoma and not neuroendocrine tumour.**

Referrals for testing will be triaged 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R367.1	Inherited pancreatic cancer Small panel	Singleton	Small variants	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  $\geq 10\%$  chance of having a mutation (deceased first degree relative with  $\geq 20\%$  chance), AND
4. This is agreed by specialist cancer genetics MDT

**NOTE: All cancers must be confirmed**

### Overlapping indications:

- 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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics

### Specialist Service Group

- Inherited cancer

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R404.1	Inherited cancer predisposition gene sequencing	Singleton	Small variants	Single gene(s)	As dictated by clinical indication	Single gene sequencing $\geq 10$ amplicons
R404.2	Inherited cancer predisposition gene MLPA or equivalent	Singleton	Exon level CNVs	Panel of genes or loci	As per appropriate inherited cancer indication	MLPA or equivalent
R404.3	Relevant inherited cancer panel Small panel	Singleton	Small variants	Panel of genes or loci	Relevant inherited cancer panel	Small panel

## R393 Schwannomatosis

### Testing Criteria

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

1. The proband has:
2.  $\geq 1$  schwannoma under age 25
3.  $\geq 2$  schwannomas at any age
4.  $\geq 1$  schwannoma at any age, AND  $\geq 1$  first / second degree relative with schwannoma

**NOTE: schwannoma does not include vestibular schwannomas or cutaneous plaques**

All individuals must have had a negative test for NF2 mutations in blood DNA

Referrals for testing will be triaged 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 the proband or family

### Where in Pathway

At presentation/at follow-up

### Requesting Specialties

- Clinical Genetics

### Specialist Service Group

- Inherited cancer

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R393.1	SMARCB1; LZTFL1 Single gene sequencing	Singleton	Small variants	Single gene(s)	SMARCB1; LZTFL1	Single gene sequencing $\geq 10$ amplicons
R393.2	SMARCB1; LZTFL1 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	SMARCB1; LZTFL1	MLPA or equivalent

## 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R134.1	Familial hypercholesterolaemia Small panel	Singleton	Small variants	Panel of genes or loci	Familial hypercholesterolaemia – targeted panel (772)	Small panel
R134.2	LDLR MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	LDLR	MLPA or equivalent

## 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R324.1	Familial Chylomicronaemia Syndrome (FCS) Small panel	Singleton	Small variants	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 - targeted testing is not possible 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R380.1	NPC1; NPC2 Single gene sequencing	Singleton	Small variants	Single gene(s)	NPC1; NPC2	Single gene sequencing $\geq 10$ amplicons
R380.2	NPC1; NPC2 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	NPC1; NPC2	MLPA or equivalent



## R98 Likely inborn error of metabolism - targeted testing not possible

### Testing Criteria

Clinical feature of a likely inborn error of metabolism where targeted testing is not possible

### 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

### Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

### Specialist Service Group

- Metabolic

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R98.1	Inborn errors of metabolism WES or large panel	Trio or singleton	Small variants	Panel of genes or loci	Inborn errors of metabolism (467)	WES or Large Panel
R98.2	Inborn errors of metabolism WGS	Trio or singleton	Exon level CNVs, Small variants	Panel of genes or loci	Inborn errors of metabolism (467)	WGS

## 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 - targeted testing is not possible, R27 Congenital malformation and dysmorphism syndromes – likely monogenic 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

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R270.1	DHCR7 Single gene sequencing	Singleton	Small variants	Single gene(s)	DHCR7	Single gene sequencing $\geq 10$ amplicons
R270.2	DHCR7 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	DHCR7	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 - targeted testing is not possible 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R231.1	CLN3 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	CLN3	MLPA or equivalent
R231.2	Neuronal ceroid lipofuscinosis Small panel	Singleton	Small variants	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 - targeted testing is not possible 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R271.1	TPP1 Single gene sequencing	Singleton	Small variants	Single gene(s)	TPP1	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R334.1	CTNS Single gene sequencing	Singleton	Small variants	Single gene(s)	CTNS	Single gene sequencing $\geq 10$ amplicons
R334.2	CTNS MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	CTNS	MLPA or equivalent

## 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

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R335.1	GLA Single gene sequencing	Singleton	Small variants	Single gene(s)	GLA	Single gene sequencing <10 amplicons
R335.2	GLA MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	GLA	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R325.1	LIPA Single gene sequencing	Singleton	Small variants	Single gene(s)	LIPA	Single gene sequencing $\geq 10$ 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R323.1	ABCG5; ABCG8 Single gene sequencing	Singleton	Small variants	Single gene(s)	ABCG5; ABCG8	Single gene sequencing >=10 amplicons



## 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 - targeted testing is not possible 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R286.1	HEXA Single gene sequencing	Singleton	Small variants	Single gene(s)	HEXA	Single gene sequencing $\geq 10$ amplicons

## R272 Gaucher disease type I

### Testing Criteria

Clinical features and glucocerebrosidase activity indicative of Gaucher disease type I

### 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 - targeted testing is not possible 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

### Specialist Service Group

- Metabolic

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R272.1	GBA Single gene sequencing	Singleton	Small variants	Single gene(s)	GBA	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 - targeted testing is not possible 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R273.1	PYGM Single gene sequencing	Singleton	Small variants	Single gene(s)	PYGM	Single gene sequencing $\geq 10$ 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

1. 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 - targeted testing is not possible 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R274.1	Glycogen storage disease WES or medium panel	Singleton	Small variants	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 - targeted testing is not possible 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R276.1	Lysosomal storage disorder WES or medium panel	Singleton	Small variants	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 - targeted testing is not possible 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R288.1	GLB1 Single gene sequencing	Singleton	Small variants	Single gene(s)	GLB1	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 - targeted testing is not possible 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R277.1	IDUA Single gene sequencing	Singleton	Small variants	Single gene(s)	IDUA	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 - targeted testing is not possible 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R280.1	GALC Single gene sequencing	Singleton	Small variants	Single gene(s)	GALC	Single gene sequencing $\geq 10$ amplicons
R280.2	GALC MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	GALC	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 - targeted testing is not possible 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R281.1	PSAP Single gene sequencing	Singleton	Small variants	Single gene(s)	PSAP	Single gene sequencing $\geq 10$ 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 - targeted testing is not possible 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

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R278.1	IDS Single gene sequencing	Singleton	Small variants	Single gene(s)	IDS	Single gene sequencing $\geq 10$ amplicons
R278.2	IDS Targeted mutation testing	Singleton	Small variants	Single gene(s)	IDS	Targeted mutation 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 - targeted testing is not possible 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R287.1	GALNS Single gene sequencing	Singleton	Small variants	Single gene(s)	GALNS	Single gene sequencing $\geq 10$ amplicons

## R289 Mucopolidosis II and III Alpha/Beta

### Testing Criteria

Clinical and laboratory features characteristic of Mucopolidosis II or Mucopolidosis 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 - targeted testing is not possible 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R289.1	GNPTAB Single gene sequencing	Singleton	Small variants	Single gene(s)	GNPTAB	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 - targeted testing is not possible 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R290.1	ARSB Single gene sequencing	Singleton	Small variants	Single gene(s)	ARSB	Single gene sequencing $\geq 10$ 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 - targeted testing is not possible 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R291.1	SGSH Single gene sequencing	Singleton	Small variants	Single gene(s)	SGSH	Single gene sequencing $\geq 10$ 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 - targeted testing is not possible 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R292.1	NAGLU Single gene sequencing	Singleton	Small variants	Single gene(s)	NAGLU	Single gene sequencing $\geq 10$ 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 - targeted testing is not possible 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R282.1	SMPD1 Single gene sequencing	Singleton	Small variants	Single gene(s)	SMPD1	Single gene sequencing $\geq 10$ 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 - targeted testing is not possible 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R285.1	HEXB Single gene sequencing	Singleton	Small variants	Single gene(s)	HEXB	Single gene sequencing $\geq 10$ amplicons

## R283 Phenylketonuria

### Testing Criteria

Likely phenylketonuria 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.

### Where in Pathway

Following neonatal screening or diagnostic metabolic testing

### Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

### Specialist Service Group

- Screening

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R283.1	PAH Single gene sequencing	Singleton	Small variants	Single gene(s)	PAH	Single gene sequencing $\geq 10$ amplicons
R283.2	PAH MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	PAH	MLPA or equivalent

## R279 Isovaleric acidaemia

### Testing Criteria

Likely isovaleric acidaemia identified following neonatal screening or 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

### Where in Pathway

Following neonatal screening or diagnostic metabolic testing

### Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neonatology
- Obstetrics
- Paediatrics

### Specialist Service Group

- Screening

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R279.1	IVD common pseudodeficiency variant Targeted mutation testing	Singleton	Small variants	Single interval	IVD common pseudodeficiency variant	Targeted mutation testing

## R105 MCADD - Medium-chain acyl-CoA dehydrogenase deficiency – common variant

### Testing Criteria

Likely MCADD identified following neonatal screening or diagnostic metabolic testing 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 or diagnostic metabolic testing

### Requesting Specialties

- Clinical Genetics
- Neonatology
- Obstetrics
- Paediatrics

### Specialist Service Group

- Screening

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R105.1	ACADM common pathogenic variants Targeted mutation testing	Singleton	Small variants	Single interval	ACADM common pathogenic variants	Targeted mutation testing

## R403 MCADD - Medium-chain acyl-CoA dehydrogenase deficiency – full ACADM sequencing

### Testing Criteria

Likely MCADD identified following neonatal screening or diagnostic metabolic testing 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R403.1	MCADD Single gene sequencing	Singleton	Small variants	Other	ACADM	Single gene sequencing <10 amplicons

## R275 Glutaric acidaemia I

### Testing Criteria

Likely glutaric acidaemia type 1 identified following neonatal screening or 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

### Where in Pathway

Following neonatal screening or diagnostic metabolic testing

### Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neonatology
- Obstetrics
- Paediatrics

### Specialist Service Group

- Screening

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R275.1	GCDH Single gene sequencing	Singleton	Small variants	Single gene(s)	GCDH	Single gene sequencing >=10 amplicons

## Part XIV. Mitochondrial

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### 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

Referrals for testing will be triaged by the Genomic 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R64.1	MTTL1 3243A>G Targeted mutation testing	Singleton	Small variants	Single interval	MTTL1 3243A>G	Targeted mutation 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R299.1	Mitochondrial genome Mitochondrial DNA rearrangement testing	Singleton	Exon level CNVs	Single interval	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	Optional 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	Optional 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 – microarray, fragile X and sequencing 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

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R315.1	Common POLG mutations Targeted mutation testing	Singleton	Small variants	Single interval	Common POLG mutations	Targeted mutation testing
R315.2	POLG Single gene sequencing	Singleton	Small variants	Single gene(s)	POLG	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R316.1	Pyruvate dehydrogenase PDH deficiency Medium panel	Singleton	Small variants	Panel of genes or loci	Pyruvate dehydrogenase (PDH) deficiency (531)	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R317.1	Mitochondrial liver disease Small panel	Singleton	Small variants	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R350.1	Common MERRF mutations Targeted mutation testing	Singleton	Small variants	Single interval	Common MERRF mutations	Targeted mutation 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

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R351.1	MT-ATP6; MT-ND6 Single gene sequencing	Singleton	Small variants	Single gene(s)	MT-ATP6; MT-ND6	Single gene sequencing <10 amplicons
R351.2	m.8993T>C/G Targeted mutation testing	Singleton	Small variants	Single interval	m.8993T>C/G	Targeted mutation 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R352.1	Mitochondrial DNA maintenance disorder WES or medium panel	Singleton	Small variants	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R353.1	Mitochondrial disorder with complex I deficiency WES or medium panel	Singleton	Small variants	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R354.1	Mitochondrial disorder with complex II deficiency WES or small panel	Singleton	Small variants	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R355.1	Mitochondrial disorder with complex III deficiency WES or small panel	Singleton	Small variants	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R356.1	Mitochondrial disorder with complex IV deficiency WES or small panel	Singleton	Small variants	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R357.1	Mitochondrial disorder with complex V deficiency WES or small panel	Singleton	Small variants	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 Maternally inherited diabetes and deafness
  - c. R349 MELAS syndrome
  - d. R350 MERRF syndrome
  - e. R351 NARP syndrome or maternally inherited Leigh syndrome
  - f. R317 Mitochondrial liver disease, including transient infantile liver failure
  - g. R299 Possible mitochondrial disorder - mitochondrial DNA rearrangement testing
  - h. R300 Possible mitochondrial disorder - whole mitochondrial genome sequencing
  - i. 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:
  - j. R315 POLG-related disorder
  - k. R352 Mitochondrial DNA maintenance disorder
  - l. R353 Mitochondrial disorder with complex I deficiency
  - m. R354 Mitochondrial disorder with complex II deficiency
  - n. R355 Mitochondrial disorder with complex III deficiency
  - o. R356 Mitochondrial disorder with complex IV deficiency
  - p. R356 Mitochondrial disorder with complex V deficiency
  - q. 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R63.1	Possible mitochondrial disorder - nuclear genes WES or large panel	Singleton	Small variants	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

At presentation

### Requesting Specialties

- Clinical Genetics
- Neurology

### Specialist Service Group

- Mitochondrial

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R394.1	TYMP Single gene sequencing	Singleton	Small variants	Single gene(s)	TYMP	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

At presentation

### Requesting Specialties

- Clinical Genetics
- Neurology

### Specialist Service Group

- Mitochondrial

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R395.1	SLC19A3 Single gene sequencing	Singleton	Small variants	Single gene(s)	SLC19A3	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

At presentation

### Requesting Specialties

- Cardiology
- Clinical Genetics
- Neurology

### Specialist Service Group

- Mitochondrial

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R396.1	TMEM70 Single gene sequencing	Singleton	Small variants	Single gene(s)	TMEM70	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

At presentation

### Requesting Specialties

- Cardiology
- Clinical Genetics

### Specialist Service Group

- Mitochondrial

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R397.1	m.4300A>G Targeted mutation testing	Singleton	Small variants	Single interval	m.4300A>G	Targeted mutation 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

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R42.1	Three common LHON variants Targeted mutation testing	Singleton	Small variants	Single interval	Three common LHON variants	Targeted mutation testing
R42.2	Optic neuropathy Medium panel	Singleton	Small variants	Panel of genes or loci	Optic neuropathy (186)	Medium panel

## Part XV. Mosaic and structural chromosomal disorders

### R297 Possible structural chromosomal rearrangement - karyotype

#### Testing Criteria

Possible structural chromosomal rearrangement requiring karyotype including:

1. Possible Robertsonian translocation, reciprocal translocation, ring chromosome or other microscopically visible structural rearrangement indicated by findings from microarray, WGS or other laboratory technique, OR
2. Recurrent miscarriage (defined as three or more consecutive miscarriages) in whom testing of products of conception has not been possible. Note: this should not be performed routinely but can be used in exceptional circumstances where testing of products of conception has not been possible, for example because no testable material has been stored or retained, OR
3. A family history suggestive of familial balanced translocation, OR
4. Unexplained infertility who are going to undergo infertility treatment, OR
5. Patient with ambiguous genitalia potentially caused by a sex chromosome rearrangement not detectable via other tests

#### Where in Pathway

As appropriate

#### Requesting Specialties

- Clinical Genetics
- Genomics laboratory

#### Specialist Service Group

- Core

#### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R297.1	Genomewide Karyotype	Singleton	Other	Genomewide	As determined by indication	Karyotype

## 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	Optional 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	Optional 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	Optional 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 male infertility or specialist fertility MDT

### Requesting Specialties

- Clinical Genetics
- Urology

### Specialist Service Group

- Core

### Associated Tests

Code	Name	Optional 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 mutation 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

- R147 Growth failure in early childhood to be used for more significant/earlier onset short stature, including where Silver-Russell syndrome is the likely diagnosis
- 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

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R52.1	SHOX MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	SHOX	MLPA or equivalent
R52.2	SHOX Single gene sequencing	Singleton	Small variants	Single gene(s)	SHOX	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 - mutation 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R24.1	FGFR3 c.1138 Targeted mutation testing	Singleton	Small variants	Single interval	FGFR3 c.1138	Targeted mutation testing

## R382 Hypochondroplasia

### Testing Criteria

Clinical features strongly suggestive of hypochondroplasia

Overlapping clinical indications:

- R309 NIPD for FGFR3-related skeletal dysplasias - mutation 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R382.1	FGFR3 c.1620 Targeted mutation testing	Singleton	Small variants	Single interval	FGFR3 c.1620	Targeted mutation testing

## R25 Thanatophoric dysplasia

### Testing Criteria

Clinical features strongly suggestive of thanatophoric dysplasia

Overlapping clinical indications:

- R309 NIPD for FGFR3-related skeletal dysplasias - mutation 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R25.1	FGFR3 Single gene sequencing	Singleton	Small variants	Single gene(s)	FGFR3	Single gene sequencing $\geq 10$ 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.

### 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R104.1	Skeletal dysplasia WES or large panel	Trio or singleton	Small variants	Panel of genes or loci	Skeletal dysplasia (309)	WES or Large Panel
R104.2	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray
R104.2	Skeletal dysplasia WGS	Trio or singleton	Exon level CNVs, Genomewide 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

## R99 Common craniosynostosis syndromes

### Testing Criteria

Recognisable multisuture craniosynostosis syndromes consistent with mutations 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 mutations 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

Code	Name	Optional 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	EFNB1; TWIST1; TCF12	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

Mutations 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 mutations 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R100.1	Craniosynostosis WES or medium panel	Trio or singleton	Small variants	Panel of genes or loci	Craniosynostosis (168)	WES or Medium Panel
R100.2	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray
R100.3	Craniosynostosis WGS	Trio or singleton	Exon level CNVs, Genomewide CNVs, Small variants	Panel of genes or loci	Craniosynostosis (168)	WGS

## 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R340.1	Amelogenesis imperfecta Medium panel	Singleton	Small variants	Panel of genes or loci	Amelogenesis imperfecta (269)	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 - mutation 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R23.1	FGFR2 c.755 and c.758 Targeted mutation testing	Singleton	Small variants	Single interval	FGFR2 c.755 and c.758	Targeted mutation 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 Congenital malformation and dysmorphism syndromes – likely monogenic 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R101.1	Ehlers Danlos syndromes WES or medium panel	Singleton	Small variants	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 Congenital malformation and dysmorphism syndromes – likely monogenic 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

### Specialist Service Group

- Musculoskeletal

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R102.1	Osteogenesis imperfecta WES or medium panel	Singleton	Small variants	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

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R390.1	EXT1; EXT2 Single gene sequencing	Singleton	Small variants	Single gene(s)	EXT1; EXT2	Single gene sequencing $\geq 10$ amplicons
R390.2	EXT1; EXT2 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	EXT1; EXT2	MLPA or equivalent

## R284 Van der Woude syndrome

### Testing Criteria

Clinical features strongly suggestive of van der Woude syndrome.

### Overlapping indications

- R27 Congenital malformation and dysmorphism syndromes – likely monogenic 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R284.1	IRF6 Single gene sequencing	Singleton	Small variants	Single gene(s)	IRF6	Single gene sequencing <10 amplicons

## Part XVII. Neurology

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### R70 Spinal muscular atrophy type 1 diagnostic test

#### Testing Criteria

Clinical features suggestive of spinal muscular atrophy 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, 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R70.1	SMN1 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	SMN1	MLPA or equivalent

## 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	Optional 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 – NOT PMP22 copy number 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 Congenital malformation and dysmorphism syndromes – likely monogenic 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

- Core

### Associated Tests

Code	Name	Optional 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

### Specialist Service Group

- Core

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R68.1	HTT STR testing	Singleton	STRs	Single gene(s)	HTT	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	Optional 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	Optional 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

### Where in Pathway

At presentation following assessment by a Neurologist

### Requesting Specialties

- Clinical Genetics
- Neurology

### Specialist Service Group

- Neurology

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R54.1	Hereditary ataxia - adult onset WES or large panel	Singleton	Small variants	Panel of genes or loci	Hereditary ataxia - adult onset (466)	WES or Large Panel
R54.2	Hereditary ataxia - adult onset STR testing	Singleton	STRs	Panel of genes or loci	Hereditary ataxia - adult onset (466)	STR testing
R54.3	Hereditary ataxia - adult onset WGS	Singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Hereditary ataxia - adult onset (466)	WGS

## 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R55.1	Hereditary ataxia and cerebellar anomalies - childhood onset WES or large panel	Trio or singleton	Small variants	Panel of genes or loci	Hereditary ataxia and cerebellar anomalies - childhood onset (488)	WES or Large Panel
R55.2	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray
R55.3	Hereditary ataxia and cerebellar anomalies - childhood onset STR testing	Singleton	STRs	Panel of genes or loci	Hereditary ataxia and cerebellar anomalies - childhood onset (488)	STR testing
R55.4	Hereditary ataxia and cerebellar anomalies - childhood onset WGS	Trio or singleton	Exon level CNVs, Genomewide CNVs, Small variants, STRs	Panel of genes or loci	Hereditary ataxia and cerebellar anomalies - childhood onset (488)	WGS

## R56 Adult onset dystonia, chorea or related movement disorder

### Testing Criteria

Unexplained dystonia, chorea or related movement disorder with onset in adulthood with a likely monogenic cause

### Overlapping indications

R68 Huntington disease test should be used where clinical features indicate a likely diagnosis of Huntington disease

- 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 Neurologist

### Requesting Specialties

- Clinical Genetics
- Neurology

### Specialist Service Group

- Neurology

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R56.1	Adult onset movement disorder WES or medium panel	Singleton	Small variants	Panel of genes or loci	Adult onset movement disorder (540)	WES or Medium Panel
R56.2	Adult onset movement disorder 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

- R27 Congenital malformation and dysmorphism syndromes – likely monogenic, R29 Intellectual disability – microarray, fragile X and sequencing, 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R57.1	Childhood onset dystonia or chorea or related movement disorder (847) WES or large panel	Singleton	Small variants	Panel of genes or loci	Childhood onset dystonia or chorea or related movement disorder (847)	WES or Large Panel
R57.2	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray
R57.3	Childhood onset dystonia or chorea or related movement disorder (847) STR testing	Singleton	STRs	Panel of genes or loci	Childhood onset dystonia or chorea or related movement disorder (847)	STR testing
R57.4	GCH1; SGCE; TH MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	GCH1; SGCE; TH MLPA	MLPA or equivalent

## R58 Adult onset neurodegenerative disorder

### Testing Criteria

Young onset or familial neurodegeneration starting in adulthood with a likely monogenic cause, including:

1. Unexplained dementia
  - a. Age at onset <55 years where acquired causes (e.g. stroke, tumour) have been excluded, OR
  - b. Family history of dementia of the same type in a first / second degree relative
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
  - d. Age of onset <40 years or family history of ALS or frontotemporal dementia, AND
  - e. No evidence of other 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

### Requesting Specialties

- Clinical Genetics
- Neurology

### Specialist Service Group

- Neurology

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R58.1	Neurodegenerative disorders - adult onset WES or large panel	Singleton	Small variants	Panel of genes or loci	Neurodegenerative disorders - adult onset (474)	WES or Large Panel
R58.2	Neurodegenerative disorders - adult onset MLPA or equivalent	Singleton	Exon level CNVs	Panel of genes or loci	Neurodegenerative disorders - adult onset (474)	MLPA or equivalent
R58.3	Neurodegenerative disorders - adult onset 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

### Overlapping indications

- R110 Segmental overgrowth disorders test should be used where megalencephaly is present to allow detection of somatic mosaic mutations

**NOTE: If a metabolic disorder is suspected, testing should be carried out 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R59.1	Epilepsy - early onset or syndromic WES or large panel	Trio or singleton	Small variants	Panel of genes or loci	Genetic epilepsy syndromes (402)	WES or Large Panel
R59.2	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray
R59.3	Epilepsy - early onset or syndromic WGS	Trio or singleton	Small variants, STRs	Panel of genes or loci	Genetic epilepsy syndromes (402)	WGS
R59.4	SLC2A1 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	SLC2A1	MLPA or equivalent

## 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R60.1	Hereditary spastic paraplegia - adult onset WES or medium panel	Singleton	Small variants	Panel of genes or loci	Hereditary spastic paraplegia - adult onset (567)	WES or Medium Panel
R60.2	Hereditary spastic paraplegia - adult onset 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R61.1	Hereditary spastic paraplegia - child onset WES or medium panel	Trio or singleton	Small variants	Panel of genes or loci	Hereditary spastic paraplegia - Childhood onset (568)	WES or Medium Panel
R61.2	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray
R61.3	Hereditary spastic paraplegia - child onset STR testing	Singleton	STRs	Panel of genes or loci	Hereditary spastic paraplegia - Childhood onset (568)	STR testing
R61.4	Hereditary spastic paraplegia - child onset WGS	Trio or singleton	Small variants; STRs	Panel of genes or loci	Hereditary spastic paraplegia - Childhood onset (568)	WGS

## 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

### Requesting Specialties

- Clinical Genetics
- Neurology

### Specialist Service Group

- Neurology

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R62.1	White matter disorders - adult onset WES or medium panel	Singleton	Small variants	Panel of genes or loci	White matter disorders - adult onset (579)	WES or Medium Panel

## 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R66.1	Paroxysmal neurological disorders, pain disorders and sleep disorders WES or medium panel	Singleton	Small variants	Panel of genes or loci	Paroxysmal neurological disorders, pain disorders and sleep disorders (541)	WES or Medium Panel

## R71 Spinal muscular atrophy type 1 rare mutation testing

### Testing Criteria

Individuals in whom a rare mutation 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 mutation of SMN1

### 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R71.1	SMN1 Single gene sequencing	Singleton	Small variants	Single gene(s)	SMN1	Single gene sequencing $\geq 10$ amplicons

## R73 Duchenne or Becker muscular dystrophy

### Testing Criteria

Individuals with clinical features strongly suggestive of Duchenne or Becker muscular dystrophy

### 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

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R73.1	DMD Single gene sequencing	Singleton	Small variants	Single gene(s)	DMD	Single gene sequencing $\geq 10$ amplicons
R73.2	DMD MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	DMD	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 mutation 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	Optional 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 dystrophy 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R74.1	DUX4 Contraction testing	Singleton	STRs	Single interval	DUX4	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 dystrophy 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	Optional 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	Single gene sequencing $\geq 10$ 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	Optional 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

### Requesting Specialties

- Clinical Genetics
- Neurology

### Specialist Service Group

- Neurology

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R76.1	Skeletal muscle channelopathy Small panel	Singleton	Small variants	Panel of genes or loci	Skeletal muscle channelopathy (542)	Small panel

## R78 Hereditary neuropathy or pain disorder – NOT PMP22 copy number

### 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 Congenital malformation and dysmorphism syndromes – likely monogenic 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

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R78.1	Hereditary neuropathy WES or medium panel	Singleton	Small variants	Panel of genes or loci	Hereditary neuropathy NOT PMP22 copy number (846)	WES or Medium Panel
R78.2	SMA1 (AR_CAG); GJB1 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	SMA1 (AR_CAG); GJB1	MLPA or equivalent

## 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 Congenital malformation and dysmorphism syndromes – likely monogenic 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

### Requesting Specialties

- Clinical Genetics
- Neurology

### Specialist Service Group

- Neurology

### Associated Tests

Code	Name	Optional 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 myaesthetic syndrome

### Testing Criteria

Clinical features that indicate a likely monogenic congenital myaesthesia

### Overlapping indications

- R89 Ultra-rare and atypical monogenic disorders or R27 Congenital malformation and dysmorphism syndromes – likely monogenic 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

### Requesting Specialties

- Clinical Genetics
- Neurology

### Specialist Service Group

- Neurology

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R80.1	Congenital myaesthetic syndrome WES or medium panel	Singleton	Small variants	Panel of genes or loci	Congenital myaesthetic 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 Congenital malformation and dysmorphism syndromes – likely monogenic 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

### Requesting Specialties

- Clinical Genetics
- Neurology

### Specialist Service Group

- Neurology

### Associated Tests

Code	Name	Optional 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 dystrophy

### Testing Criteria

Clinical features that indicate a likely limb girdle muscular dystrophy

### 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

### Requesting Specialties

- Clinical Genetics
- Neurology

### Specialist Service Group

- Neurology

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R82.1	Limb girdle muscular dystrophy WES or medium panel	Singleton	Small variants	Panel of genes or loci	Limb girdle muscular dystrophy (185)	WES or Medium Panel

## R371 Malignant hyperthermia

### Testing Criteria

Confident clinical diagnosis of malignant 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

Following discussion with national specialist service

### Requesting Specialties

- Clinical Genetics
- Other

### Specialist Service Group

- Neurology

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R371.1	RYR1 Single gene sequencing	Singleton	Small variants	Single gene(s)	RYR1	Single gene sequencing $\geq 10$ amplicons

## R266 Neuromuscular arthrogryposis

### Testing Criteria

Clinical features indicative of a neuromuscular arthrogryposis

### Overlapping indications

- R83 Arthrogryposis test should be used where a neuromuscular cause is not confirmed and broader testing 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.

### Where in Pathway

N/A

### Requesting Specialties

- Neurology

### Specialist Service Group

- Neurology

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R266.1	Neuromuscular arthrogryposis WES or medium panel	Singleton	Small variants	Panel of genes or loci	Neuromuscular arthrogryposis (547)	WES or Medium Panel

## R83 Arthrogryposis

### Testing Criteria

Clinical features that indicate arthrogryposis of monogenic aetiology

### Overlapping indications

- R266 Neuromuscular arthrogryposis test should be used where a neuromuscular cause is 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 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R83.1	Arthrogryposis - broad panel WES or large panel	Trio or singleton	Small variants	Panel of genes or loci	Arthrogryposis (258)	WES or Large Panel
R83.2	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray
R83.3	Arthrogryposis - broad panel WGS	Trio or singleton	Exon level CNVs, Genomewide 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R381.1	Neuromuscular disorders WES or large panel	Trio or singleton	Small variants	Panel of genes or loci	Neuromuscular disorders (465)	WES or Large Panel
R381.2	Neuromuscular disorders WGS	Trio or singleton	Small variants; STRs	Panel of genes or loci	Neuromuscular disorders (465)	WGS
R381.3	AR_CAG; DMPK_CTG STR testing	Singleton	STRs	Single gene(s)	AR_CAG; DPMK_CTG	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R84.1	Hereditary ataxia and cerebellar anomalies - childhood onset WES or large panel	Trio or singleton	Small variants	Panel of genes or loci	Hereditary ataxia and cerebellar anomalies - childhood onset (488)	WES or Large Panel
R84.2	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray
R84.3	Hereditary ataxia and cerebellar anomalies - childhood onset STR testing	Singleton	STRs	Panel of genes or loci	Hereditary ataxia and cerebellar anomalies - childhood onset (488)	STR testing
R84.4	Hereditary ataxia and cerebellar anomalies - childhood onset WGS	Trio or singleton	Exon level CNVs, Genomewide CNVs, Small variants, STRs	Panel of genes or loci	Hereditary ataxia and cerebellar anomalies - childhood onset (488)	WGS

## 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R85.1	Holoprosencephaly WES or small panel	Trio or singleton	Small variants	Panel of genes or loci	Holoprosencephaly (78)	WES or Small Panel
R85.2	Holoprosencephaly WGS	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R86.1	Hydrocephalus WES or medium panel	Trio or singleton	Small variants	Panel of genes or loci	Hydrocephalus (179)	WES or Medium Panel
R86.2	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray
R86.3	Hydrocephalus WGS	Trio or singleton	Exon level CNVs, Genomewide 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 test should be used where megalencephaly is present to allow detection of mosaic mutations

Referrals for testing will be triaged by the Genomic 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R87.1	Cerebral malformations WES or large panel	Trio or singleton	Small variants	Panel of genes or loci	Cerebral malformations (491)	WES or Large Panel
R87.2	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray
R87.3	Cerebral malformations WGS	Trio or singleton	Exon level CNVs, Genomewide 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R88.1	Severe microcephaly WES or medium panel	Trio or singleton	Small variants	Panel of genes or loci	Severe microcephaly (162)	WES or Medium Panel
R88.2	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray
R88.3	Severe microcephaly WGS	Trio or singleton	Exon level CNVs, Genomewide 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

### Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

### Specialist Service Group

- Neurology

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R109.1	White matter disorders - childhood onset WES or large panel	Trio or singleton	Small variants	Panel of genes or loci	White matter disorders - childhood onset (496)	WES or Large Panel
R109.2	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray
R109.3	White matter disorders - childhood onset WGS	Trio or singleton	Exon level CNVs, Genomewide CNVs, Small variants	Panel of genes or loci	White matter disorders - childhood onset (496)	WGS

## R221 Neurofibromatosis type 2

### Testing Criteria

Testing of individual (proband) affected with NF2-related tumour/schwannoma where the individual +/- family history meets one of the following criteria. The proband has:

1. Bilateral vestibular schwannomas, OR
  2.  $\geq 2$  of unilateral vestibular schwannoma, meningioma, schwannoma, glioma, neurofibroma, multiple meningiomas, posterior subcapsular lenticular opacities/cataract, OR
  3.  $\geq 1$  of unilateral vestibular schwannoma, meningioma, schwannoma, glioma, neurofibroma, multiple meningiomas, posterior subcapsular lenticular opacities/cataract AND  $\geq 1$  first / second degree relative with a vestibular schwannoma, OR
  4.  $\geq 2$  non-vestibular schwannomas, OR
  5.  $\geq 1$  non-vestibular schwannoma AND  $\geq 1$  first / second degree relative with  $\geq 1$  non-vestibular schwannoma, OR
  6. Characteristic ocular features of NF2 including retinal hamartoma and epiretinal membrane
- NF2 somatic test can be undertaken instead in tumour material where indicated

**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

### Requesting Specialties

- Clinical Genetics

### Specialist Service Group

- Neurology

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R221.1	NF2 Single gene sequencing	Singleton	Small variants	Single gene(s)	NF2	Single gene sequencing $\geq 10$ amplicons
R221.2	NF2 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	NF2	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 Congenital malformation and dysmorphism syndromes – 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

### Where in Pathway

At a point where clinical management or reproductive planning require a molecular diagnosis

### Requesting Specialties

- Clinical Genetics
- Dermatology
- Neurology

### Specialist Service Group

- Neurology

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R222.1	NF1 Single gene sequencing	Singleton	Small variants	Single gene(s)	NF1	Single gene sequencing >=10 amplicons
R222.2	NF1 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	NF1	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

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R376.1	NF1 Single gene sequencing - mosaic	Singleton	Small variants	Single gene(s)	NF1	Single gene sequencing >=10 amplicons
R376.2	NF1 MLPA or equivalent - mosaic	Singleton	Exon level CNVs	Single gene(s)	NF1	MLPA or equivalent

## R228 Tuberous sclerosis

### Testing Criteria

Clinical features suggestive of tuberous sclerosis requiring molecular testing

Testing should be 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. Lymphangiomyomatosis (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 Congenital malformation and dysmorphism syndromes – 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

Referrals for testing will be triaged by the Genomic 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

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R228.1	TSC1; TSC2 Single gene sequencing	Singleton	Small variants	Single gene(s)	TSC1; TSC2	Single gene sequencing >=10 amplicons

Code	Name	Optional 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	MLPA or equivalent



## 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 Congenital malformation and dysmorphism syndromes – likely monogenic, 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 mutation(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

- Cancer
- Clinical Genetics
- Haematology
- Immunology

### Specialist Service Group

- Neurology

### Associated Tests

Code	Name	Optional 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 - mutation testing

### Testing Criteria

Confirmed diagnosis of ataxia telangiectasia requiring mutation 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

- Cancer
- Clinical Genetics
- Haematology
- Immunology

### Specialist Service Group

- Neurology

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R295.1	ATM Single gene sequencing	Singleton	Small variants	Single gene(s)	ATM	Single gene sequencing $\geq 10$ 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R336.1	Cerebral vascular malformations WES or medium panel	Singleton	Small variants	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R337.1	NOTCH3 Single gene sequencing	Singleton	Small variants	Single gene(s)	NOTCH3	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 mutation 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	Optional 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

## 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 conditions:

- R27 Congenital malformation and dysmorphism syndromes – 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

Referrals for testing will be triaged by the Genomic 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R193.1	PKD1 Single gene sequencing	Singleton	Small variants	Single gene(s)	PKD1	Single gene sequencing $\geq 10$ amplicons
R193.2	PKD1 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	PKD1	MLPA or equivalent
R193.3	Cystic renal disease WES or Large Panel	Singleton	Small variants	Panel of genes or loci	Cystic renal disease (487)	WES or Large Panel
R193.4	Cystic renal disease WGS	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 Congenital malformation and dysmorphism syndromes – 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
- 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

### Specialist Service Group

- Renal

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R194.1	Haematuria Small panel	Singleton	Small variants	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R195.1	Proteinuric renal disease WES or medium panel	Singleton	Small variants	Panel of genes or loci	Proteinuric renal disease (106)	WES or Medium Panel



## 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	Optional 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

### Requesting Specialties

- Clinical Genetics
- Nephrology

### Specialist Service Group

- Renal

### Associated Tests

Code	Name	Optional 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	CFH; CFHR MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	CFH; CFHR	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R198.1	Renal tubulopathies WES or medium panel	Singleton	Small variants	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 Congenital malformation and dysmorphism syndromes – 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

Referrals for testing will be triaged by the Genomic 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	Optional 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

### Requesting Specialties

- Clinical Genetics
- Haematology
- Nephrology

### Specialist Service Group

- Renal

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R201.1	Atypical haemolytic uraemic syndrome Small panel	Singleton	Small variants	Panel of genes or loci	Atypical haemolytic uraemic syndrome (139)	Small panel
R201.3	CFH; CFHR1; CFHR3; CD46; CFI MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	CFH; CFHR1; CFHR3; CD46; CFI	MLPA or equivalent

## 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

Referrals for testing will be triaged by the Genomic 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R202.1	Tubulointerstitial kidney disease Small panel	Singleton	Small variants	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. Biopsy proven amyloidosis of hereditary type should normally be established 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

At presentation

### Requesting Specialties

- Cardiology
- Clinical Genetics
- Nephrology
- Neurology
- Hepatology

### Specialist Service Group

- Renal

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R204.1	Hereditary systemic amyloidosis Small panel	Singleton	Small variants	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R256.1	Nephrocalcinosis or nephrolithiasis WES or medium panel	Singleton	Small variants	Panel of genes or loci	Nephrocalcinosis or nephrolithiasis (149)	WES or Medium Panel



## R257 Unexplained paediatric onset end-stage renal disease

### Testing Criteria

End-stage renal disease developing under the age of 18, with no identifiable cause detectable by renal biopsy, biochemistry, imaging or clinical assessment

Use of this test in young adults over the age of 18 may be appropriate after expert clinical review, if there is strong clinical suspicion of a monogenic disorder

Overlapping conditions:

- R27 Congenital malformation and dysmorphism syndromes – 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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Nephrology

### Specialist Service Group

- Renal

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R257.1	Unexplained paediatric onset end-stage renal disease WES or large panel	Singleton	Small variants	Panel of genes or loci	Unexplained paediatric onset end-stage renal disease (678)	WES or Large Panel

## Part XIX. Respiratory

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### 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 >40mM with sufficient sweat obtained; >30mM in infants), 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 >40mM 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 >40mM with sufficient sweat obtained), OR
  - b. Sweat testing not practical, and all other causes excluded
4. Male 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, 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. Isolated anomaly or <2 other common fetal markers, AND
  - c. 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 C

#### Requesting Specialties

- Clinical Genetics
- Fetal Medicine
- Gastroenterology
- Genomics laboratory
- Gynaecology
- Obstetrics
- Paediatrics
- Respiratory Medicine

#### Specialist Service Group

- Core

## Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R184.1	CFTR Targeted mutation testing	Singleton	Small variants	Single gene(s)	CFTR	Targeted mutation testing
R184.2	CFTR Single gene sequencing	Singleton	Small variants	Single gene(s)	CFTR	Single gene sequencing $\geq 10$ amplicons
R184.3	CFTR MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	CFTR	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)

Referrals for testing will be triaged 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

### Specialist Service Group

- Core

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R185.1	CFTR Targeted mutation testing	Singleton	Small variants	Single gene(s)	CFTR	Targeted mutation 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

- Other

### Specialist Service Group

- Screening

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R253.1	CFTR 4 commonest mutations Targeted mutation testing	Singleton	Small variants	Single interval	CFTR 4 commonest mutations	Targeted mutation 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-related 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

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R333.1	PHOX2B STR testing	Singleton	STRs	Single gene(s)	PHOX2B	STR testing
R333.2	PHOX2B Single gene sequencing	Singleton	Small variants	Single gene(s)	PHOX2B	Single gene sequencing $\geq 10$ 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R139.1	Laterality disorders and isomerism WES or medium panel	Singleton	Small variants	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

Referrals for testing will be triaged by the Genomic 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R186.1	Hereditary haemorrhagic telangiectasia Small panel	Singleton	Small variants	Panel of genes or loci	Hereditary haemorrhagic telangiectasia (123)	Small panel



## R188 Pulmonary arterial hypertension

### Testing Criteria

Pulmonary arterial hypertension (PAH) AND a first / second degree relative with:

1. PAH, OR
2. Unclassified cardiac-related death compatible with 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R188.1	Pulmonary arterial hypertension Small panel	Singleton	Small variants	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R189.1	Respiratory ciliopathies including non-CF bronchiectasis WES or medium panel	Singleton	Small variants	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R190.1	Pneumothorax - familial Small panel	Singleton	Small variants	Panel of genes or loci	Pneumothorax - familial (105)	Small panel
R190.2	FLCN MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	FLCN	MLPA or equivalent

## 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. Mutation 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

### Requesting Specialties

- Clinical Genetics
- Gastroenterology
- Hepatology
- Respiratory Medicine

### Specialist Service Group

- Respiratory

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R191.1	SERPINA1 common mutations Targeted mutation testing	Singleton	Small variants	Single interval	SERPINA1 common mutations	Targeted mutation 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R192.1	Surfactant deficiency Small panel	Singleton	Small variants	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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R330.1	FOXF1 Single gene sequencing	Singleton	Small variants	Single gene(s)	FOXF1	Single gene sequencing $\geq 10$ amplicons

## Part XX. Skin

### R110 Segmental overgrowth disorders

#### 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. Vascular malformations (capillary, venous, lymphatic or combinations)
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 Congenital malformation and dysmorphism syndromes – likely monogenic or R89 Ultra-rare and atypical monogenic disorders tests should be considered in overlapping features are present but germline mutation 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 need to take account of this e.g. in planning coverage of NGS assay

#### Where in Pathway

At presentation

#### Requesting Specialties

- Clinical Genetics

#### Specialist Service Group

- Skin

#### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R110.1	Segmental overgrowth disorders Small panel	Singleton	Small variants	Panel of genes or loci	Segmental overgrowth disorders (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

- Skin

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R163.1	Ectodermal dysplasia Medium panel	Singleton	Small variants	Panel of genes or loci	Ectodermal dysplasia (553)	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

- Skin

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R164.1	Epidermolysis bullosa and congenital skin fragility WES or medium panel	Singleton	Small variants	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

- Skin

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R165.1	Ichthyosis and erythrokeratoderma Medium panel	Singleton	Small variants	Panel of genes or loci	Ichthyosis and erythrokeratoderma (555)	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

- Skin

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R166.1	Palmoplantar keratodermas Medium panel	Singleton	Small variants	Panel of genes or loci	Palmoplantar keratodermas (556)	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

- Skin

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R167.1	Autosomal recessive primary hypertrophic osteoarthropathy Small panel	Singleton	Small variants	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 Congenital malformation and dysmorphism syndromes – likely monogenic 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

- Skin

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R227.1	Xeroderma pigmentosum, Trichothiodystrophy or Cockayne syndrome Small panel	Singleton	Small variants	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

- Skin

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R230.1	Multiple monogenic benign skin tumours Small panel	Singleton	Small variants	Panel of genes or loci	Multiple monogenic benign skin tumours (558)	Small panel
R230.2	FLCN MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	FLCN	MLPA or equivalent

## 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

- Skin

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R236.1	Pigmentary skin disorders Large panel	Singleton	Small variants	Panel of genes or loci	Pigmentary skin disorders (559)	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

- Skin

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R237.1	Cutaneous photosensitivity with a likely genetic cause Small panel	Singleton	Small variants	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

- Skin

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R239.1	IKBKG Single gene sequencing	Singleton	Small variants	Single gene(s)	IKBKG	Single gene sequencing $\geq 10$ amplicons

## 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

- Skin

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R255.1	Epidermodysplasia verruciformis Small panel	Singleton	Small variants	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

- Skin

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R326.1	Vascular skin disorders Medium panel	Singleton	Small variants	Panel of genes or loci	Vascular skin disorders (563)	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

- Skin

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R327.1	Mosaic skin disorders - deep sequencing Medium panel	Singleton	Small variants	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

- Skin

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R332.1	Rare genetic inflammatory skin disorders Medium panel	Singleton	Small variants	Panel of genes or loci	Rare genetic inflammatory skin disorders (565)	Medium panel

## Part XXI. Ultra-rare and atypical monogenic disorders

### R89 Ultra-rare and atypical monogenic disorders

#### Testing Criteria

PLEASE NOTE: This indication is scheduled to be delivered by whole genome sequencing from 2020; a discussion regarding urgency of the result may be appropriate where WGS would have the potential to provide a more comprehensive analysis than alternative test types

Individuals with ultra-rare disorders or atypical manifestations of recognised monogenic disorders that make broad genomewide analysis the optimal approach

Referrals for testing will be triaged by the Genomic 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R89.1	Relevant panels in PanelApp WES or large panel	Trio or singleton	Small variants	Panel of genes or loci	Relevant panel(s) in PanelApp	WES or Large Panel
R89.2	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray
R89.3	Relevant panels in PanelApp WGS	Trio or singleton	Exon level CNVs, Genomewide CNVs, Small variants	Panel of genes or loci	Relevant panel(s) in PanelApp	WGS

## Part XXII. Multi-purpose tests

### R240 Diagnostic testing for known mutation(s)

#### Testing Criteria

1. Patient clinically affected with specific disorder where:
  - a. the familial mutation(s) have already been identified in a relative, OR
  - b. there is a recurrent mutation for the disorder that is likely to be causative, OR
  - c. there is a founder mutation for the disorder that is likely to be causative, OR
  - d. a mutation has been identified in the patient during somatic testing that is likely to be 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

#### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R240.1	Specific target Targeted mutation testing	Singleton	Small variants	Single interval	Specific Target	Targeted mutation testing

## R242 Predictive testing for known familial mutation(s)

### Testing Criteria

Patient requiring predictive testing for specific disorder where the familial mutation(s) have already been identified in a relative

### Where in Pathway

As dictated by clinical situation

### Requesting Specialties

- Clinical Genetics

### Specialist Service Group

- Core

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R242.1	Specific target Targeted mutation testing	Singleton	Small variants	Single interval	Specific Target	Targeted mutation testing



## R244 Carrier testing for known familial mutation(s)

### Testing Criteria

Patient requiring carrier testing for specific disorder where the familial mutation(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

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R244.1	Specific target Targeted mutation testing	Singleton	Small variants	Single interval	Specific Target	Targeted mutation testing

## **R246 Carrier testing at population risk for partners of known carriers of nationally agreed autosomal recessive disorders (tbc)**

### **Testing Criteria**

Testing under this indication is only available in high risk settings and requests will require multi-disciplinary and/or laboratory discussion before approval. A national approach is in development

### **Where in Pathway**

As dictated by clinical situation

### **Requesting Specialties**

- Clinical Genetics

### **Specialist Service Group**

- Core

### **Associated Tests**

Code	Name	Optional 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

### Associated Tests

Code	Name	Optional 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	Optional 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

### Associated Tests

Code	Name	Optional 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	Optional 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 ACMG guidelines

### Where in Pathway

After MDT discussion

### Requesting Specialties

- Clinical Genetics

### Specialist Service Group

- Core

### Associated Tests

Code	Name	Optional 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

Confirmation using a second technique where required for diagnostic reporting.

Examples of settings in which this indication may be used include

- variants where QC metrics indicate that confirmation with a second technique are necessary
- variant where the sample has passed outside an accredited pipeline and confirmation of sample identify is required

### Where in Pathway

Following primary test where required

### Requesting Specialties

- Clinical Genetics
- Genomics laboratory

### Specialist Service Group

- Core

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R370.1	Specific target Targeted mutation testing	Singleton	Small variants	Single interval	Specific Target	Targeted mutation 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

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R375.1	Specific target Targeted mutation testing	Singleton	Small variants	Single interval	Specific Target	Targeted mutation 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 (national approach to be confirmed), OR
3. A technical or scientific advance requires reanalysis of a group of tests to detect an important new source of actionable diagnoses (national approach to be 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

Following discussion with the genomics laboratory to ensure stored data is suitable for reanalysis; the national approach to defining events which should trigger analysis remains to be confirmed

### Requesting Specialties

- Clinical Genetics
- Genomics laboratory

### Specialist Service Group

- Core

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R387.1	Reanalysis of existing data	Multiple affected individuals	All variants	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 ACMG class 3 to class 4 or class 5

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

### Associated Tests

Code	Name	Optional 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	Optional 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	Optional 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	Optional 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	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R374.1	Other sample storage	Singleton	Other	Other	No target identified at this stage	Other

## R398 INTERIM INDICATION for urgent single gene testing

### Testing Criteria

1. Patient has clinical features indicating a high likelihood of a specific recognisable disorder, AND
2. Molecular confirmation of the diagnosis is required urgently, where the turnaround time of the relevant clinical indication is not quick enough to contribute to management (e.g. in the context of pregnancy), AND
3. A single gene test can be offered by the laboratory for the condition

### Overlapping indications

- The specific clinical indication for the relevant disorder should be used where the turnaround time is sufficient to answer the clinical question

### Where in Pathway

As dictated by clinical situation

### Requesting Specialties

- Clinical Genetics
- Other

### Specialist Service Group

- Core

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R398.1	Specific target Single gene sequencing	Singleton	Small variants	Single gene(s)	Relevant single gene	Single gene sequencing $\geq 10$ amplicons



## R407 Patient undergoing allogeneic haematopoietic stem cell transplantation

### Testing Criteria

Allogeneic transplant where chimerism knowledge will be informative to 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

- M118 patient undergoing allogeneic haematopoietic stem cell transplantation offers the same test for somatic cancer testing

### Where in Pathway

As dictated by clinical situation

### Requesting Specialties

- Clinical Genetics
- Other

### Specialist Service Group

- Core

### Associated Tests

Code	Name	Optional Family Structure	Scope(s)	Target Type	Target Name	Method
R407.1	Patient undergoing allogeneic haematopoietic stem cell transplantation STR testing	Singleton	Short tandem repeats	Single gene(s)	Relevant gene(s) or loci	STR testing

## 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

### Associated Tests

Code	Name	Optional 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	Other

## Change Log

Date	Document Name	Version	Summary of Changes
21 August 2020	Rare and inherited disease eligibility criteria August 2020	TD5	As noted in column L of GLH-facing Test Directory spreadsheet
15 March 2019	TD4 for Rare Disease Section	TD4	R201. Removal of clinical indication test type R201.2
05 March 2019	TD3b for Rare Disease Section	TD3b	R66. Minor amendments to eligibility criteria
04 March 2019	TD3a for Rare Disease Section	TD3a	R193. Updated requesting specialties, ages and where in pathway
01 March 2019	TD3 for Rare Disease Section	TD3	All. Initial release with roman numeral section parts