National Genomic Test Directory

Testing Criteria for Rare and Inherited Disease

Version 6, January 2024 (Official)

Summary

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

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

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

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

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

Document overview

Clinical Indications

The following elements are presented for each clinical indication:

- **Clinical Indication Name**: name of the clinical indication, preceded by unique clinical indication code.
- **Testing Criteria**: description of the patients who should receive the test. 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
- Requesting specialties have been nationally agreed as appropriate specialties for referrals for testing. The list of requesting specialties is not designed to operate at a very specific level or to limit test requests to just those clinical specialities listed, as pathways will differ across the country, e.g. a specialist with the job title 'paediatric craniofacial surgeon' would potentially be grouped within 'Surgery' or 'Paediatrics'.

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

Associated Tests

The associated tests contain information about the tests which routinely constitute the target for the clinical indication. It is expected that all tests listed under a particular clinical indication will be routinely performed, unless there is clear clinical rationale not to do so. Where a test has not been undertaken this will be clearly communicated to the requesting clinician.

Information provided includes:

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

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

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

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

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

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

Target Name: names of the gene(s), 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 variant 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

Test Ordering

Clinicians wishing to request genomic tests can do so by;

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

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.

Glossary

- Where the term ‘maternal’ is used this refers to the genetic contribution, from parent to offspring, from an ovum and the term ‘paternal’ refers to the parental contribution from a sperm.
- Singleton – the patient
- Duo – patient with one biological parent
- Trio – patient and both biological parents

Find Text in Document

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

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

Change Log

Date	Document Name	Version	Summary of Changes
January 2024	Rare and inherited disease eligibility criteria June 2023	January 2024 v6	R445 Common aneuploidy testing – NIPT: New clinical indication
January 2024	Rare and inherited disease eligibility criteria June 2023	January 2024 v6	R447 Diagnostic discovery – validation/confirmation of findings: New clinical indication
January 2024	Rare and inherited disease eligibility criteria June 2023	January 2024 v6	R448 Prenatal testing: New clinical indication
January 2024	Rare and inherited disease eligibility criteria June 2023	January 2024 v6	R431 Genome-wide DNA Methylation Profiling to Aid Variant Interpretation: New Clinical Indication
January 2024	Rare and inherited disease eligibility criteria June 2023	January 2024 v6	R27: Clinical indication name changed to Paediatric disorders and added 2 further criteria in the testing criteria
January 2024	Rare and inherited disease eligibility criteria June 2023	January 2024 v6	R29 Intellectual disability: R53 Fragile X removed as an overlapping indication and amendment to the testing criteria
January 2024	Rare and inherited disease eligibility criteria June 2023	January 2024 v6	R83 Arthrogryposis: R266 Neuromuscular arthrogryposis removed as an overlapping indication
January 2024	Rare and inherited disease eligibility criteria June 2023	January 2024 v6	R260 Fanconi anaemia or Bloom syndrome - chromosome breakage testing: Moved to Haematology from Endocrinology in contents
January 2024	Rare and inherited disease eligibility criteria June 2023	January 2024 v6	R191: requesting specialties changed Primary Care to General Practitioners
January 2024	Rare and inherited disease eligibility criteria June 2023	January 2024 v6	Panelapp panel IDs added for small panels and single gene tests
January 2024	Rare and inherited disease eligibility criteria June 2023	January 2024 v6	Renamed the clinical specialty NIPD to pre natal
January 2024	Rare and inherited disease eligibility criteria June 2023	January 2024 v6	Review of criteria to promote gender inclusivity.
January 2024	Rare and inherited disease eligibility criteria June 2023	January 2024 v6	R14: updated link to Guidance
January 2024	Rare and inherited disease eligibility criteria June 2023	January 2024 v6	Introduced a “Multi specialty” specialist test group for R441 and R431
January 2024	Rare and inherited disease eligibility criteria June 2023	January 2024 v6	R318 & R297: Amended criteria removing the need for recurrent miscarriages to be consecutive.
January 2024	Rare and inherited disease eligibility criteria June 2023	January 2024 v6	R215: Added *CTNNA1* gene and renamed the CI to Hereditary diffuse gastric cancer.

Content

Part V. Ophthalmology

Part VI. Fetal (including NIPD)

Part VII. Gastrohepatology

Part VIII. Haematology

Part XII. Lipids

Part XIII. Metabolic

Part XIV. Mitochondrial

Part XV. Mosaic and structural chromosomal disorders

Part XVI. Musculoskeletal

Part XVII. Neurology

Part XVIII. Renal

Part XIX. Respiratory

Part XX. Dermatology

Part XXI. Ultra-rare and atypical monogenic disorders

Part XXII. Multi-purpose tests

Part I. Acutely unwell children

R14 Acutely unwell children with a likely monogenic disorder

Testing Criteria

Acutely unwell children with a likely monogenic disorder

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

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

Overlapping indications

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

Where in Pathway

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

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Multi specialty

Associated Tests

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

Part II. Cardiology

R137 Congenital heart disease - microarray

Testing Criteria

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

Overlapping indications

- R26 Likely common aneuploidy test should be used for patients with coarctation of the aorta and features suggestive of Turner syndrome
- R27 Paediatric disorders – likely monogenic or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

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

Where in Pathway

At presentation

Requesting Specialties

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

Specialist Service Group

- Core

Associated Tests

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

R125 Thoracic aortic aneurysm or dissection

Testing Criteria

1. Thoracic aortic aneurysm* or dissection with onset before age 50, OR
2. Thoracic aortic aneurysm* or dissection with onset before age 60 with a first degree relative with thoracic aortic aneurysm or dissection, OR
3. Thoracic aortic aneurysm* or dissection before age 60 with no classical cardiovascular risk factors, OR
4. Thoracic aortic aneurysm* or dissection before age 60 with features suggestive of aortopathy, e.g. arterial tortuosity, OR
5. Clinical features suggestive of Loeys-Dietz syndrome, OR
6. Features of Marfan syndrome giving a systemic Ghent score of ≥7, following assessment by a clinical geneticist or specialist with expertise in aortopathy, OR
7. High clinical suspicion of a condition predisposing to aortic/arterial disease AND diagnostic testing for other conditions such as Ehlers Danlos syndrome (where indicated) has not identified a causative 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 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

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

Where in Pathway

At presentation

Requesting Specialties

- Cardiology
- Clinical Genetics

Specialist Service Group

- Cardiology

Associated Tests

Please note all the tests below will be undertaken for R125 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary.

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

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

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

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

Where in Pathway

At presentation

Requesting Specialties

- Cardiology
- Clinical Genetics

Specialist Service Group

- Cardiology

Associated Tests

Please note all the tests below will be undertaken for R127 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary.

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R127.1	Long QT syndrome Small panel	Singleton	Small variants	Panel of genes or loci	Long QT syndrome (76)	Small panel
R127.2	Long QT syndrome	Singleton	Exon level CNVs	Panel of genes or loci	Long QT syndrome (76)	Exon level CNV detection by MLPA or equivalent

R128 Brugada syndrome and cardiac sodium channel disease

Testing Criteria

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

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

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

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

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

Where in Pathway

At presentation

Requesting Specialties

- Cardiology
- Clinical Genetics

Specialist Service Group

- Cardiology

Associated Tests

Please note all the tests below will be undertaken for R128 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary.

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R128.1	Brugada syndrome and cardiac sodium channel disease Small panel	Singleton	Small variants	Panel of genes or loci	Brugada syndrome (13)	Small panel
R128.2	Brugada syndrome and cardiac sodium channel disease	Singleton	Exon level CNVs	Panel of genes or loci	Brugada syndrome (13)	Exon level CNV detection by MLPA or equivalent

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

Please note all the tests below will be undertaken for R129 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R129.1	Catecholaminergic polymorphic VT Small panel	Singleton	Small variants	Panel of genes or loci	Catecholaminergic polymorphic VT (214)	Small panel
R129.2	Catecholaminergic polymorphic VT	Singleton	Exon level CNVs	Panel of genes or loci	Catecholaminergic polymorphic VT (214)	Exon level CNV detection by MLPA or equivalent

R130 Short QT syndrome

Testing Criteria

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

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

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

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

Where in Pathway

At presentation

Requesting Specialties

- Cardiology
- Clinical Genetics

Specialist Service Group

- Cardiology

Associated Tests

Please note all the tests below will be undertaken for R130 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R130.1	Short QT syndrome Small panel	Singleton	Small variants	Panel of genes or loci	Short QT syndrome (224)	Small panel
R130.2	Short QT syndrome	Singleton	Exon level CNVs	Panel of genes or loci	Short QT syndrome (224)	Exon level CNV detection by MLPA or equivalent

R131 Hypertrophic cardiomyopathy

Testing Criteria

A firm clinical diagnosis of hypertrophic cardiomyopathy as indicated by:

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

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

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

Overlapping indications

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

Where in Pathway

At presentation

Requesting Specialties

- Cardiology
- Clinical Genetics

Specialist Service Group

- Cardiology

Associated Tests

Please note all the tests below will be undertaken for R131 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
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
R131.2	Hypertrophic cardiomyopathy	Singleton	Exon level CNVs	Panel of genes or loci	Hypertrophic cardiomyopathy - teen and adult (49)	Exon level CNV detection by MLPA or equivalent

R132 Dilated and arrhythmogenic cardiomyopathy

Testing Criteria

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

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

OR

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

OR

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

OR

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

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

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

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

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

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

Overlapping indications

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

Where in Pathway

At presentation

Requesting Specialties

- Cardiology
- Clinical Genetics

Specialist Service Group

- Cardiology

Associated Tests

Please note all the tests below will be undertaken for R132 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

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

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R132.2	Dilated and arrhythmogenic cardiomyopathy	Singleton	Exon level CNVs	Panel of genes or loci	Dilated cardiomyopathy - teen and adult (652)	Exon level CNV detection by MLPA or equivalent

R391 Barth syndrome

Testing Criteria

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

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

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

Where in Pathway

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

Requesting Specialties

- Cardiology
- Clinical Genetics
- Neonatology
- Neurology
- Paediatrics

Specialist Service Group

- Cardiology

Associated Tests

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

R133 Arrhythmogenic right ventricular cardiomyopathy

Testing Criteria

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

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

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

Overlapping indications

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

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

Where in Pathway

At presentation

Requesting Specialties

- Cardiology
- Clinical Genetics

Specialist Service Group

- Cardiology

Associated Tests

Please note all the tests below will be undertaken for R133 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R133.1	Arrhythmogenic right ventricular cardiomyopathy Small panel	Singleton	Small variants	Panel of genes or loci	Arrhythmogenic cardiomyopathy (134)	Small panel
R133.2	Arrhythmogenic right ventricular cardiomyopathy	Singleton	Exon level CNVs	Panel of genes or loci	Arrhythmogenic cardiomyopathy (134)	Exon level CNV detection by MLPA or equivalent

R135 Paediatric or syndromic cardiomyopathy

Testing Criteria

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

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

Testing Criteria for Semi-Rapid Testing

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

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

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

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

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

Overlapping indications

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

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

Where in Pathway

At presentation

Where in Pathway for Semi-Rapid Testing

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

Requesting Specialties

- Cardiology
- Clinical Genetics

Requesting Specialties for Semi-Rapid Testing

- Clinical Genetics
- Cardiology
- Neonatology

Specialist Service Group

- Cardiology

Associated Tests (see next page)

R135.3 is only for semi urgent testing

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

R136 Primary lymphoedema

Testing Criteria

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

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Other

Specialist Service Group

- Cardiology

Associated Tests

Please note all the tests below will be undertaken for R136 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R136.1	Primary lymphoedema WES or medium panel	Singleton	Small variants	Panel of genes or loci	Primary lymphoedema (65)	WES or Medium Panel
R136.2	Primary lymphoedema	Singleton	Exon level CNVs	Panel of genes or loci	Primary lymphoedema (65)	Exon level CNV detection by MLPA or equivalent

R138 Sudden unexplained death or survivors of a cardiac event

Testing Criteria

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

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

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

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

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

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

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

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

Where in Pathway

At presentation

Requesting Specialties

- Cardiology
- Clinical Genetics

Specialist Service Group

- Cardiology

Associated Tests

Please note all the tests below will be undertaken for R138 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R138.1	Sudden unexplained death or survivors of a cardiac event WES or medium panel	Singleton	Small variants	Panel of genes or loci	Sudden cardiac death (841)	WES or Medium Panel
R138.2	Sudden unexplained death or survivors of a cardiac event	Singleton	Exon level CNVs	Panel of genes or loci	Sudden cardiac death (841)	Exon level CNV detection by MLPA or equivalent

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

Please note all the tests below will be undertaken for R328 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
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
R328.2	Progressive cardiac conduction disease	Singleton	Exon level CNVs	Panel of genes or loci	Progressive cardiac conduction disease (506)	Exon level CNV detection by MLPA or equivalent

R384 Generalised arterial calcification in infancy

Testing Criteria

Generalised arterial calcification with onset in the neonatal period

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Neonatology

Specialist Service Group

- Cardiology

Associated Tests

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

R140 Elastin-related phenotypes

Testing Criteria

1. Congenital heart disease of a type associated with Elastin 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 Paediatric disorders test should be used for individuals with syndromic forms of cutis laxaR125 Thoracic aortic aneurysm or dissection test should be used for individuals with primarily aortic/large arterial involvement, with some features of cutis laxa

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

Where in Pathway

At presentation

Requesting Specialties

- Cardiology
- Clinical Genetics

Specialist Service Group

- Cardiology

Associated Tests

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

R441 Unexplained death in infancy and sudden unexplained death in childhood

Testing Criteria

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

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

3. DNA available from proband and one biological parent only

Where in Pathway

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

Requesting Specialties

- Clinical Genetics
- Paediatrics

Specialist Service Group

- Multi specialty

Associated Tests

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

Part III. Developmental disorders

R26 Likely common aneuploidy

Testing Criteria

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

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

Overlapping indications

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Community Paediatrics
- Neonatology
- Paediatrics

Specialist Service Group

- Core

Associated Tests

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

R27 Paediatric disorders

Testing Criteria

- Congenital malformations and/or dysmorphism 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
- Testing of adults with congenital malformation and dysmorphism syndromes would also be appropriate under this clinical indication
- This clinical indication can be used for a fetus from a demised/non-continued pregnancy, with multiple major structural abnormalities detected on fetal ultrasound or post-mortem examination and where a monogenic malformation disorder is considered highly likely

Overlapping indications

- R14 Acutely unwell infants with a likely monogenic disorder test should be used instead where relevant where a rapid result is required
- R412 Fetal anomalies with a likely genetic cause – non urgent can be used in a fetus where insufficient DNA is available for R27

Referrals for testing will be triaged by the Genomic Laboratory; testing 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

Where microarray has not been performed, this will be undertaken in advance of WGS testing unless the requestor specifies that this is not required

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R27.2	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray
R27.3	Paediatric disorders (486) by WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Paediatric disorders (486)	WGS

R28 Congenital malformation and dysmorphism syndromes – microarray only

Testing Criteria

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

Overlapping indications

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

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

Where in Pathway

At presentation, following discussion with a Clinical Geneticist to consider whether broader testing is more appropriate

Requesting Specialties

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

Specialist Service Group

- Core

Associated Tests

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

R29 Intellectual disability

Testing Criteria

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

Microarray 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

Where microarray has not been performed, this will be undertaken in advance of WGS testing unless the requestor specifies that this is not required

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R29.2	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray
R29.4	Intellectual disability WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Intellectual disability (285)	WGS

R377 Intellectual disability - microarray only

Testing Criteria

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Community Paediatrics
- Neurology
- Paediatrics
- Psychiatry

Specialist Service Group

- Core

Associated Tests

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

R47 Angelman syndrome

Testing Criteria

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

Overlapping indications

- R29 Intellectual disability or other relevant broader tests should be used in preference individuals where Angelman syndrome is plausible but not highly likely
- R263 Confirmation of uniparental disomy test should be used to confirm likely UPD detected on methylation and copy number testing

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

Where in Pathway

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

Requesting Specialties

- Clinical Genetics
- Genomics laboratory
- Neurology
- Community paediatrics

Specialist Service Group

- Core

Associated Tests

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

R48 Prader-Willi syndrome

Testing Criteria

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

Overlapping indications

- R29 Intellectual disability or other relevant broader tests should be used in preference individuals where Prader-Willi syndrome is plausible but not highly likely.
- R263 Confirmation of uniparental disomy test should be used to confirm likely UPD detected on methylation and copy number testing

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

Where in Pathway

Following assessment by a Consultant Clinical Geneticist

Requesting Specialties

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

Specialist Service Group

- Core

Associated Tests

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

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
- 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	Optimal 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
- **R14 Acutely unwell children with a likely monogenic disorder, should be used for acutely unwell neonates with hypotonia.**

Referrals for testing will be triaged by the Genomic Laboratory; testing 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

Please note that initially only WGS testing (plus microarray where indicated) will be undertaken for R69 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are necessary.

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R69.1	SNRPN DMR Methylation testing	Singleton	Methylation	Single gene(s)	SNRPN DMR	Methylation testing
R69.3	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray
R69.5	Hypotonic infant WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Hypotonic infant (490)	WGS
R69.6	Hypotonic infant STR confirmatory testing	As appropriate	STRs	Single gene(s)	Hypotonic infant (490) STR	STR testing

R312 Parental sequencing for lethal autosomal recessive disorders

Testing Criteria

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

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

Where in Pathway

As appropriate

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Other

Associated Tests

Please note all the tests below will be undertaken for R312 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R312.1	Relevant panels in PanelApp or gene agnostic WES or large panel	Parents only	Small variants	Panel of genes or loci	Relevant panel(s) in PanelApp	WES or large panel
R312.2	Relevant panels in PanelApp or gene agnostic	Singleton	Exon level CNVs	Panel of genes or loci	Relevant panel(s) in PanelApp	Exon level CNV detection by MLPA or equivalent

Part IV. Endocrinology

R402 Premature ovarian insufficiency

Testing Criteria

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

Overlapping indications

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

R314 Ambiguous genitalia presenting neonatally

Testing Criteria

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

Overlapping indications

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

Where in Pathway

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

Requesting Specialties

- Clinical Genetics
- Endocrinology
- Neonatology

Specialist Service Group

- Core

Associated Tests

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

R106 Alstrom syndrome

Testing Criteria

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

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

Overlapping indications

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

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

Where in Pathway

At presentation

Requesting Specialties

- Cardiology
- Clinical Genetics
- Endocrinology
- Ophthalmology

Specialist Service Group

- Endocrinology

Associated Tests

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

R141 Monogenic diabetes

Testing Criteria

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

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

AND

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

AND

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

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

- Diabetes diagnosed young

AND

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

AND

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

3. **Diabetes with severe insulin resistance**

- Patients have features of severe insulin resistance in the absence of obesity:
  - Acanthosis nigricans

  OR

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

  AND

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

Overlapping indications

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

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

Where in Pathway

At presentation; HbA1C testing is required prior to genetic testing

Requesting Specialties

- Clinical Genetics
- Endocrinology
- Nephrology

Specialist Service Group

- Endocrinology

Associated Tests

Please note all the tests below will be undertaken for R141 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
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

Fasting glucose noted to be raised ≤35 years

AND

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

OR

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

In pregnancy

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

AND

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

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

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

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

Where in Pathway

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

Requesting Specialties

- Clinical Genetics
- Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

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

R143 Neonatal diabetes

Testing Criteria

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

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

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

Order of testing

Start with treatment response screen for sulphonylurea-sensitive genes by 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

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

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

R145 Congenital hypothyroidism

Testing Criteria

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

Please note all the tests below will be undertaken for R145 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R145.1	Congenital hypothyroidism WES or Medium panel	Singleton	Small variants	Panel of genes or loci	Congenital hypothyroidism (31)	WES or Medium panel
R145.2	Congenital hypothyroidism	Singleton	Exon level CNVs	Panel of genes or loci	Congenital hypothyroidism (31)	Exon level CNV detection by MLPA or equivalent

R329 Familial dysalbuminaemic hyperthyroxinaemia

Testing Criteria

Raised serum T4 with inappropriately non-suppressed serum TSH

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

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

R182 Hyperthyroidism

Testing Criteria

Hyperthyroidism where common causes have been excluded:

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

Please note all the tests below will be undertaken for R182 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R182.1	Hyperthyroidism Small panel	Singleton	Small variants	Panel of genes or loci	Hyperthyroidism (236)	Small panel
R182.2	Hyperthyroidism	Singleton	Exon level CNVs	Panel of genes or loci	Hyperthyroidism (236)	Exon level CNV detection by MLPA or equivalent

R146 Differences in 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 an individual assigned male at birth
5. Virilisation in an individual assigned female at birth
6. Urine steroid profile suggestive of DSD
7. Pubertal failure
8. Precocious puberty
9. Primary amenorrhea
10. Very early onset hypertension with evidence of pubertal or electrolyte disturbance

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

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

Overlapping indications

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

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

Where in Pathway

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

Requesting Specialties

- Clinical Genetics
- Endocrinology
- Gynaecology

Specialist Service Group

- Endocrinology

Associated Tests

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

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

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R146.3	Differences in sex development	Singleton	Exon level CNVs	Panel of genes or loci	Differences in sex development (9)	Exon level CNV detection by MLPA or equivalent

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 **in the absence of microcephaly**, **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): ≤−2 SDS for gestational age
2. Postnatal growth failure: Height at 24 ± 1 months ≤−2 SDS or height ≤−2 SDS below mid-parental target height
3. Relative macrocephaly at birth: Head circumference at birth ≥1.5 SDS above birth weight and/or length 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 ≥0.5 cm or arm asymmetry or leg length discrepancy <0.5 cm with at least two other asymmetrical body parts (one non-face)
6. Feeding difficulties and/or low BMI: BMI ≤−2 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

- R88 Severe microcephaly test should be used for patients with primary microcephaly – microcephalic dwarfism spectrum.
- 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 should be considered if overlapping features are present and should be used where clinical features indicative of a likely monogenic skeletal dysplasia
- R28 Congenital malformation and dysmorphism syndromes – microarray only

Referrals for testing will be triaged by the Genomic 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

Please note all the tests below will be undertaken for R147 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

If Silver Russell Syndrome is strongly suspected testing for Silver Russell Syndrome will be undertaken first using R147.2 and array CGH (R147.3)

Code	Name	Optimal 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	Growth failure in early childhood	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray
R147.4	Growth failure in early childhood	Singleton	Exon level CNVs	Panel of genes or loci	Growth failure in early childhood (473)	Exon level CNV detection by MLPA or equivalent

R49 Beckwith-Wiedemann syndrome

Testing Criteria

Clinical features suggestive of Beckwith-Wiedemann syndrome defined as:

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

Cardinal features

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

Suggestive features:

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

*See Brioude et al 2018, PMID: 29377879

Overlapping indications

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

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

Where in Pathway

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

Requesting Specialties

- Cancer
- Clinical Genetics
- Endocrinology
- Neonatology
- Paediatrics

Specialist Service Group

- Endocrinology

Associated Tests

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

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

R50 Isolated hemihypertrophy or macroglossia

Testing Criteria

Isolated hemihypertrophy, OR

Isolated macroglossia

Overlapping indications

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

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

Where in Pathway

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

Requesting Specialties

- Clinical Genetics
- Paediatrics

Specialist Service Group

- Endocrinology

Associated Tests

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

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

R267 Temple syndrome – maternal uniparental disomy 14

Testing Criteria

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Endocrinology

Associated Tests

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

R268 Kagami-Ogata syndrome – paternal uniparental disomy 14

Testing Criteria

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Endocrinology

Associated Tests

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

R149 Severe early-onset obesity

Testing Criteria

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

Overlapping indications

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Endocrinology
- Paediatrics

Specialist Service Group

- Endocrinology

Associated Tests

Please note all the tests below will be undertaken for R149 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R149.1	Severe early-onset obesity WES or Medium panel	Singleton	Small variants	Panel of genes or loci	Severe early-onset obesity (130)	WES or Medium panel
R149.2	Severe early-onset obesity	Singleton	Exon level CNVs	Panel of genes or loci	Severe early-onset obesity (130)	Exon level CNV detection by MLPA or equivalent

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

Please note all the tests below will be undertaken for R150 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R150.1	Congenital adrenal hypoplasia Small panel	Singleton	Small variants	Panel of genes or loci	Congenital adrenal hypoplasia (145)	Small panel
R150.2	Congenital adrenal hypoplasia	Singleton	Exon level CNVs	Panel of genes or loci	Congenital adrenal hypoplasia (145)	Exon level CNV detection by MLPA or equivalent

R180 Congenital adrenal hyperplasia diagnostic test

Testing Criteria

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

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

Overlapping indications

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Endocrinology
- Neonatology
- Paediatrics

Specialist Service Group

- Endocrinology

Associated Tests

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

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

R388 Linkage testing for congenital adrenal hyperplasia

Testing Criteria

Families with a confirmed diagnosis of 21-hydroxylase congenital adrenal hyperplasia with no detectable 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	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R388.1	CYP21A2 Linkage testing	Multiple affected individuals	Other	Single gene(s)	CYP21A2	Linkage Analysis

R181 Congenital adrenal hyperplasia carrier testing

Testing Criteria

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

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

Where in Pathway

At the time of reproductive planning

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Endocrinology

Associated Tests

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

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

R183 Glucocorticoid-remediable aldosteronism (GRA)

Testing Criteria

Primary hyperaldosteronism with one of:

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Endocrinology
- Nephrology

Specialist Service Group

- Endocrinology

Associated Tests

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

R344 Primary hyperaldosteronism - KCNJ5

Testing Criteria

Primary hyperaldosteronism presenting under the age of 10 years

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Endocrinology
- Nephrology

Specialist Service Group

- Endocrinology

Associated Tests

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

R160 Primary pigmented nodular adrenocortical disease

Testing Criteria

Primary pigmented nodular adrenocortical disease, OR

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

Please note all the tests below will be undertaken for R160 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
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
R160.2	Primary pigmented nodular adrenocortical disease	Singleton	Exon level CNVs	Panel of genes or loci	Primary pigmented nodular adrenocortical disease (566)	Exon level CNV detection by MLPA or equivalent

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

Testing Criteria

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

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

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R293.1	GNAS, PRKAR1A and PDE4D Small panel	Singleton	Small variants	Panel of genes or loci	GNAS, PRKAR1A, PDE4D (1209)	Small panel
R293.2	GNAS DMRs Methylation testing	Singleton	Methylation	Single interval	GNAS DMRs	Methylation testing
R293.3	STX16 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	STX16	MLPA or equivalent

R151 Familial hyperparathyroidism or Hypocalciuric hypercalcaemia

Testing Criteria

Familial Primary Hyperparathyroidism

i) <50y,

OR

ii) any age with

a) a confirmed or relevant family history, OR

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

c) parathyroid carcinoma or atypical or cystic adenoma, OR

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

Hypocalciuric hypercalcaemia

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

Overlapping indications

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

Please note all the tests below will be undertaken for R151 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary.

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R151.1	Familial hyperparathyroidism or Hypocalciuric hypercalcaemia Small panel	Singleton	Small variants	Panel of genes or loci	Familial hyperparathyroidism or Hypocalciuric hypercalcaemia (480)	Small panel
R151.2	Familial hyperparathyroidism or Hypocalciuric hypercalcaemia	Singleton	Exon level CNVs	Panel of genes or loci	Familial hyperparathyroidism or Hypocalciuric hypercalcaemia (480)	Exon level CNV detection by MLPA or equivalent

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

Please note all the tests below will be undertaken for R153 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
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

Please note all the tests below will be undertaken for R154 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R154.1	Hypophosphataemia or rickets Small panel	Singleton	Small variants	Panel of genes or loci	Hypophosphataemia or rickets (482)	Small panel
R154.2	Hypophosphataemia or rickets	Singleton	Exon level CNVs	Panel of genes or loci	Hypophosphataemia or rickets (482)	Exon level CNV detection by MLPA or equivalent

R319 Calcium-sensing receptor phenotypes

Testing Criteria

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

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

R157 IPEX - Immunodysregulation Polyendocrinopathy and Enteropathy, X-Linked

Testing Criteria

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

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

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Endocrinology
- Gastroenterology
- Immunology

Specialist Service Group

- Endocrinology

Associated Tests

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

R156 Carney complex

Testing Criteria

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

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

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Dermatology
- Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

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

R148 Hypogonadotropic hypogonadism

Testing Criteria

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Endocrinology
- Gynaecology

Specialist Service Group

- Endocrinology

Associated Tests

Please note all the tests below will be undertaken for R148 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R148.1	Hypogonadotropic hypogonadism Small panel	Singleton	Small variants	Panel of genes or loci	Hypogonadotropic hypogonadism idiopathic (650)	Small panel
R148.2	Hypogonadotropic hypogonadism	Singleton	Exon level CNVs	Panel of genes or loci	Hypogonadotropic hypogonadism idiopathic (650)	Exon level CNV detection by MLPA or equivalent

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

Please note all the tests below will be undertaken for R159 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R159.1	Pituitary hormone deficiency WES or Medium panel	Singleton	Small variants	Panel of genes or loci	Pituitary hormone deficiency (483)	WES or Medium panel
R159.2	Pituitary hormone deficiency	Singleton	Exon level CNVs	Panel of genes or loci	Pituitary hormone deficiency (483)	Exon level CNV detection by MLPA or equivalent

R217 Endocrine neoplasia

Testing Criteria

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

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

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

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

2. Familial isolated pituitary adenoma (FIPA)

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

3. X-linked acrogigantism

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

NOTE: All cancers should be histologically confirmed

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

Please note all the tests below will be undertaken for R217 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R217.1	Endocrine neoplasia Small panel	Singleton	Small variants	Panel of genes or loci	Endocrine neoplasms (648)	Small panel
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 excluding NF1

Testing Criteria

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

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

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

NOTE: Testing under this clinical indication does not include NF1

Overlapping indications

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

Please note all the tests below will be undertaken for R223 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R223.1	Inherited phaeochromocytoma and paraganglioma excluding NF1 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

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

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R144.1	ABCC8; KCNJ11	Singleton	Small variants	Small panel	ABCC8; KCNJ11	Small panel
R144.2	Congenital hyperinsulinism Small panel	Singleton	Small variants	Panel of genes or loci	Congenital hyperinsulinism (308)	Small panel
R144.3	Congenital hyperinsulinism	Singleton	Exon level CNVs	Panel of genes or loci	Congenital hyperinsulinism (308)	Exon level CNV detection by MLPA or equivalent

R158 Lipodystrophy - childhood onset

Testing Criteria

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

AND

Acquired causes have been excluded

OR

Individuals with the following features of severe insulin resistance:

• Acanthosis nigricans

OR

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

AND

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

Overlapping indications

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

Please note all the tests below will be undertaken for R158 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R158.1	Lipodystrophy - childhood onset Small panel	Singleton	Small variants	Panel of genes or loci	Lipodystrophy - childhood onset (546)	Small panel
R158.2	Lipodystrophy - childhood onset	Singleton	Exon level CNVs	Panel of genes or loci	Lipodystrophy - childhood onset (546)	Exon level CNV detection by MLPA or equivalent

R218 Multiple endocrine neoplasia type 2

Testing Criteria

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

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

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

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

Overlapping indications

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

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

R226 Inherited parathyroid cancer

Testing Criteria

Testing of individual (proband) affected with parathyroid carcinoma

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

Overlapping indications

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

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

R162 Familial tumoral calcinosis

Testing Criteria

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

Please note all the tests below will be undertaken for R162 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R162.1	Familial tumoral calcinosis Small panel	Singleton	Small variants	Panel of genes or loci	Familial tumoral calcinosis (552)	Small panel
R162.2	Familial tumoral calcinosis	Singleton	Exon level CNVs	Panel of genes or loci	Familial tumoral calcinosis (552)	Exon level CNV detection by MLPA or equivalent

R417 Multi Locus Imprinting Disorder (MLID)

Testing Criteria

R417.1

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

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

R417.2

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

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

Overlapping indications

- R143 Neonatal diabetes (ZFP57)

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Endocrinology
- Paediatrics
- Genomics Laboratory

Specialist Service Group

- Endocrinology

Associated Tests

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

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

R440 Hereditary isolated diabetes insipidus

Testing Criteria

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

Overlapping indications

- R198 Renal tubulopathies

Where in Pathway

At presentation

Requesting Specialties

- Nephrology
- Clinical Genetics

  Endocrinology

Specialist Service Group

- Endocrinology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R440.1	Hereditary isolated diabetes Insipidus small panel	Singleton	Small variants	Panel of genes or loci	AVP, AVPR2, AQP2	Small panel
R440.2	Hereditary isolated diabetes Insipidus	Singleton	Exon level CNVs	Panel of genes or loci	AVP, AVPR2, AQP2	Exon level CNV detection by MLPA or equivalent

Part V. Ophthalmology

R107 Bardet Biedl syndrome

Testing Criteria

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

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

Overlapping indications

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Nephrology
- Ophthalmology

Specialist Service Group

- Ophthalmology

Associated Tests

Please note all the tests below will be undertaken for R107 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
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
R107.2	Bardet Biedl syndrome	Singleton	Exon level CNVs	Panel of genes or loci	Bardet Biedl syndrome (543)	Exon level CNV detection by MLPA or equivalent

R31 Bilateral congenital or childhood onset cataracts

Testing Criteria

Unexplained bilateral congenital or childhood onset cataracts

Overlapping indications

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

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

Where in Pathway

At presentation, after urine reducing substances

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

Requesting Specialties

- Clinical Genetics
- Ophthalmology

Specialist Service Group

- Ophthalmology

Associated Tests

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

R32 Retinal disorders

Testing Criteria

Unexplained retinal disease that is likely to be monogenic

Overlapping indications

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

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

Where in Pathway

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

Requesting Specialties

- Clinical Genetics
- Ophthalmology

Specialist Service Group

- Ophthalmology

Associated Tests

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

R33 Possible X-linked retinitis pigmentosa

Testing Criteria

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

Order of testing

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

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

Where in Pathway

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

Requesting Specialties

- Clinical Genetics
- Ophthalmology

Specialist Service Group

- Ophthalmology

Associated Tests

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

R36 Structural eye disease

Testing Criteria

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

Overlapping indications

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

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

Where in Pathway

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

Requesting Specialties

- Clinical Genetics
- Ophthalmology

Specialist Service Group

- Ophthalmology

Associated Tests

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

R38 Sporadic aniridia

Testing Criteria

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

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

Where in Pathway

At presentation

Requesting Specialties

- Oncology
- Clinical Genetics
- Ophthalmology
- Paediatrics

Specialist Service Group

- Ophthalmology

Associated Tests

Please note all the tests below will be undertaken for R38 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
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

- Ophthalmology

Associated Tests

Please note all the tests below will be undertaken for R39 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R39.1	Albinism or congenital nystagmus WES or Medium panel	Singleton	Small variants	Panel of genes or loci	Albinism or congenital nystagmus (511)	WES or Medium panel
R39.2	Albinism or congenital nystagmus	Singleton	Exon level CNVs	Panel of genes or loci	Albinism or congenital nystagmus (511)	Exon level CNV detection by MLPA or equivalent

R41 Optic neuropathy

Testing Criteria

Unexplained optic neuropathy

Overlapping indications

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

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

Where in Pathway

At presentation following expert by a Consultant Ophthalmologist

Requesting Specialties

- Clinical Genetics
- Ophthalmology

Specialist Service Group

- Ophthalmology

Associated Tests

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

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R41.1	Optic neuropathy WES or Medium panel	Singleton	Small variants	Panel of genes or loci	Optic neuropathy (186)	WES or Medium panel
R41.2	Optic neuropathy	Singleton	Exon level CNVs	Panel of genes or loci	Optic neuropathy (186)	Exon level CNV detection by MLPA or equivalent
R41.3	Optic neuropathy	Singleton	Targeted variant testing	Three common LHON variants	Three common LHON variants	Targeted variant testing

R43 Blepharophimosis ptosis and epicanthus inversus

Testing Criteria

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Ophthalmology

Specialist Service Group

- Ophthalmology

Associated Tests

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

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

R46 Congenital fibrosis of the extraocular muscles

Testing Criteria

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Neurology
- Ophthalmology

Specialist Service Group

- Ophthalmology

Associated Tests

Please note all the tests below will be undertaken for R46 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
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
R46.2	Congenital fibrosis of the extraocular muscles	Singleton	Exon level CNVs	Panel of genes or loci	Congenital fibrosis of the extraocular muscles (512)	Exon level CNV detection by MLPA or equivalent

R262 Corneal dystrophy

Testing Criteria

Corneal dystrophy of likely monogenic aetiology

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

Where in Pathway

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

Requesting Specialties

- Clinical Genetics
- Ophthalmology

Specialist Service Group

- Ophthalmology

Associated Tests

Please note all the tests below will be undertaken for R262 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R262.1	Corneal dystrophy WES or Medium panel	Singleton	Small variants	Panel of genes or loci	Corneal dystrophies (658)	WES or Medium panel
R262.2	Corneal dystrophy	Singleton	Exon level CNVs	Panel of genes or loci	Corneal dystrophies (658)	Exon level CNV detection by MLPA or equivalent

R45 Stickler syndrome

Testing Criteria

Clinical features indicative of likely Stickler syndrome

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

Where in Pathway

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

Requesting Specialties

- Clinical Genetics
- Ophthalmology

Specialist Service Group

- Ophthalmology

Associated Tests

Please note all the tests below will be undertaken for R45 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
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

R420 Pseudoxanthoma elasticum

Testing Criteria

Individuals who have characteristic features of Pseudoxanthoma elasticum:

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

Overlapping indications

- R384 Generalised arterial calcification in infancy

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Ophthalmology

Specialist Service Group

- Ophthalmology

Associated Tests

Please note all the tests below will be undertaken for R420 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R420.1	Pseudoxanthoma elasticum	Singleton	Small variants	Panel of genes or loci	ABCC6, ENPP1 (1381)	Small panel
R420.2	Pseudoxanthoma elasticum	Singleton	Exon level CNVs	Single gene(s)	ABCC6, ENPP1 (1381)	Exon level CNV detection by MLPA or equivalent

Part VI. Fetal (including NIPD)

R401 Common aneuploidy testing - prenatal

Testing Criteria

Prenatal findings requiring common aneuploidy testing including:

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

Overlapping indications

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

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

Where in Pathway

N/A

Requesting Specialties

- Clinical Genetics
- Fetal Medicine
- Obstetrics

Specialist Service Group

- Core

Associated Tests

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

R445 Common aneuploidy testing - NIPT

Testing Criteria

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

Inclusion:

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

Exclusion:

- Maternal cancer (unless in remission)
- Blood transfusion in the last 4 months (whole blood or plasma)
- Bone marrow or organ transplant recipient
- Vanished twin pregnancy (an empty second pregnancy sac or a second pregnancy sac containing non-viable fetus)
- Maternal T21
- Maternal balanced translocation or mosaicism of T21, T18 or T13
- Immunotherapy in the current pregnancy, excluding IVIg treatment
- Stem cell therapy
- Previous pregnancy was not a full trisomy (reciprocal translocation or partial trisomy)

To note: Currently not available in all regions. Requestors to check with the testing laboratory before sending samples. Service will be available across the Network from April 2024

Overlapping indications

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

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

Where in Pathway

Samples to be taken by trained midwife or Clinical Genetics Unit.

Requesting Specialties

- Clinical Genetics
- Specialist Midwifery

Specialist Service Group

- Prenatal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R445.1	Common aneuploidy testing NIPT	Singleton or duo	Aneuploidy	Genomewide	Genomewide	NIPT

R318 Recurrent miscarriage with products of conception available for testing

Testing Criteria

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

Overlapping indications

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Fetal Medicine
- Gynaecology
- Obstetrics

Specialist Service Group

- Core

Associated Tests

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

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

R22 Fetus with a likely chromosomal abnormality

Testing Criteria

This indication is relevant to:

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

Overlapping indications

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Fetal Medicine
- Pathology

Specialist Service Group

- Core

Associated Tests

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

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

R21 Fetal anomalies with a likely genetic cause

Testing Criteria

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

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

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

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

Clinical examples

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

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

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

Exclusion criteria

• Confirmed aneuploidy or pathogenic copy number variant consistent with fetal anomalies detected by microarray
• Fetuses with confirmed thanatophoric dysplasia, achondroplasia or Apert syndrome on other relevant rapid tests (R23, R24, R25, R306 or R309) are excluded.
• Cases where familial causative variant(s) are known - targeted testing should be performed
• For cases where sonographic findings indicate a specific monogenic disorder, targeted testing should be

applied where appropriate
• Where termination of pregnancy has already been decided or when fetal demise has occurred or is imminent then rapid exome sequencing will not be performed. Appropriate testing should be implemented postnatally using the R27 clinical indication (Paediatric disorders).

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

Overlapping indications

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

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

Where in Pathway

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

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

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Prenatal

Associated Tests

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

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R21.1	Genomewide Common aneuploidy testing - prenatal	Singleton	Aneuploidy	Genomewide	Genomewide	Common aneuploidy testing
R21.2	Fetal anomalies WES or large panel	Trio	Small variants	Panel of genes or loci	Fetal anomalies (478)	WES or Large Panel
R21.3	Genomewide Microarray	Singleton	Genomewide	Genomewide	Genomewide	Microarray
R21.4	Fetal anomalies	Singleton	Exon level CNVs	Panel of genes or loci	Fetal anomalies (478)	Exon level CNV detection by MLPA or equivalent

R412 Fetal anomalies with a likely genetic cause – non urgent

Testing Criteria

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

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

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

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

Overlapping indications

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

Where in Pathway

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

Requesting Specialties

- Clinical Genetics and/or other appropriate specialist referring clinician

Specialist Service Group

- Prenatal

Associated Tests

Please note all the tests below will be undertaken for R412 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R412.1	Fetal anomalies WES or Large Panel	Trio	Small variants	Panel of genes or loci	Fetal anomalies (478)	WES or Large Panel
R412.2	Fetal anomalies	Singleton	Exon level CNVs	Panel of genes or loci	Fetal anomalies (478)	Exon level CNV detection by MLPA or equivalent

R251 Non-invasive prenatal sexing

Testing Criteria

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

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

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

Where in Pathway

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

Requesting Specialties

- Clinical Genetics
- Fetal Medicine

Specialist Service Group

- Prenatal

Associated Tests

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

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

- Prenatal

Associated Tests

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

R250 NIPD for congenital adrenal hyperplasia - CYP21A2 haplotype testing

Testing Criteria

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

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

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

Testing is not currently possible for consanguineous couples

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

Where in Pathway

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

Requesting Specialties

- Clinical Genetics
- Fetal Medicine

Specialist Service Group

- Prenatal

Associated Tests

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

- Prenatal

Associated Tests

Code	Name	Optimal 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

- Prenatal

Associated Tests

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

R306 NIPD for Apert syndrome - 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

- Prenatal

Associated Tests

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

R307 NIPD for Crouzon syndrome with acanthosis nigricans - 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

- Prenatal

Associated Tests

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

R308 NIPD for FGFR2-related craniosynostosis syndromes - 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

- Prenatal

Associated Tests

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

R309 NIPD for FGFR3-related skeletal dysplasias - 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 fingers

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

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

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

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

Where in Pathway

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

Requesting Specialties

- Clinical Genetics
- Fetal Medicine

Specialist Service Group

- Prenatal

Associated Tests

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

R310 NIPD for Duchenne and Becker muscular dystrophy - haplotype testing

Testing Criteria

Pregnancy at risk of Duchenne or Becker muscular dystrophy due to known 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 XY fetus

Requesting Specialties

- Clinical Genetics
- Fetal Medicine

Specialist Service Group

- Prenatal

Associated Tests

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

- Prenatal

Associated Tests

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

R423 NIPD for Retinoblastoma

Testing Criteria

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

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

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

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

Testing is not possible in multiple pregnancies.

Where in Pathway

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

Requesting Specialties

- Clinical Genetics
- Fetal Medicine

Specialist Service Group

- Prenatal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R423.1	NIPD for Retinoblastoma	Singleton	Small variants (SNVs and CNVs)	Single gene(s)	RB1	NIPD

R389 NIPD - pre-pregnancy test work-up

Testing Criteria

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

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

Where in Pathway

Prior to the pregnancy in which NIPD is planned

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- NIPD

Associated Tests

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

R433 NIPD for Monogenic diabetes, subtype glucokinase

Testing Criteria

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

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

Overlapping indications

- R142 Glucokinase-related fasting hyperglycaemia
- R141 Monogenic diabetes

Where in Pathway

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

Requesting Specialties

- Clinical Genetics
- Endocrinology
- Obstetrics
- Specialist Diabetes Clinics

Specialist Service Group

- Prenatal

Associated Tests

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

Part VII. Gastrohepatology

R168 Non-acute porphyrias

Testing Criteria

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

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

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

Where in Pathway

At presentation or after clinical assessment by a highly specialised service

Requesting Specialties

- Dermatology
- Haematology
- Hepatology
- Neurology

Specialist Service Group

- Gastrohepatology

Associated Tests

Please note all the tests below will be undertaken for R168 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R168.1	Non-acute porphyrias Small panel	Singleton	Small variants	Panel of genes or loci	Non-acute porphyrias (513)	Small panel
R168.2	Non-acute porphyrias	Singleton	Exon level CNVs	Panel of genes or loci	Non-acute porphyrias (513)	Exon level CNV detection by MLPA or equivalent

R169 Acute intermittent porphyria

Testing Criteria

Clinical features of acute intermittent porphyria (AIP), AND

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

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

Where in Pathway

At presentation or after clinical assessment by a highly specialised service

Requesting Specialties

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

Specialist Service Group

- Gastrohepatology

Associated Tests

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

R170 Variegate porphyria

Testing Criteria

Clinical features of variegate porphyria, AND

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Dermatology
- Gastroenterology
- Hepatology
- Neurology

Specialist Service Group

- Gastrohepatology

Associated Tests

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

R171 Cholestasis

Testing Criteria

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

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

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

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

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

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

Where in Pathway

At presentation

Requesting Specialties

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

Specialist Service Group

- Gastrohepatology

Associated Tests

Please note all the tests below will be undertaken for R171 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R171.1	Cholestasis WES or Medium panel	Singleton	Small variants	Panel of genes or loci	Cholestasis (544)	WES or Medium Panel
R171.2	Cholestasis	Singleton	Exon level CNVs	Panel of genes or loci	Cholestasis (544)	Exon level CNV detection by MLPA or equivalent

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 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with atypical features in whom a broader differential diagnosis is under consideration

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Hepatology
- Metabolic Medicine
- Neurology
- Psychiatry
- Paediatrics

Specialist Service Group

- Gastrohepatology

Associated Tests

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

R173 Polycystic liver disease

Testing Criteria

Patients with multiple hepatic cysts with no explanation

Overlapping indications

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Hepatology

Specialist Service Group

- Gastrohepatology

Associated Tests

Please note all the tests below will be undertaken for R173 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
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
R173.2	Polycystic liver disease	Singleton	Exon level CNVs	Panel of genes or loci	Polycystic liver disease interim (653)	Exon level CNV detection by MLPA or equivalent

R175 Pancreatitis

Testing Criteria

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

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Gastroenterology
- Hepatology

Specialist Service Group

- Gastrohepatology

Associated Tests

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

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R175.1	Pancreatitis Small panel	Singleton	Small variants	Panel of genes or loci	Pancreatitis (386)	Small panel
R175.2	PRSS1	Singleton	Small variants	Single interval	PRSS1	Single gene testing (<10 amplicons)
R175.3	Pancreatitis	Singleton	Exon level CNVs	Panel of genes or loci	Pancreatitis (386)	Exon level CNV detection by MLPA or equivalent

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

R177 Hirschsprung disease

Testing Criteria

Diagnosis of Hirschsprung disease

Overlapping indications

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Gastroenterology
- Neonatology
- Paediatrics (including Paediatric surgeons)

Specialist Service Group

- Gastrohepatology

Associated Tests

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

R331 Intestinal failure or congenital diarrhoea

Testing Criteria

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

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

Overlapping indications

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Gastroenterology
- Neonatology
- Paediatrics

Specialist Service Group

- Gastrohepatology

Associated Tests

Please note all the tests below will be undertaken for R331 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R331.1	Intestinal failure WES or small panel	Singleton	Small variants	Panel of genes or loci	Intestinal failure (514)	WES or Small Panel
R331.2	Intestinal failure	Singleton	Exon level CNVs	Panel of genes or loci	Intestinal failure (514)	Exon level CNV detection by MLPA or equivalent

R438 Paediatric pseudo-obstruction syndrome

Testing Criteria

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

Overlapping indications

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

Where in Pathway

At presentation or following assessment by the highly specialised service.

Requesting Specialties

- Clinical Genetics
- Gastroenterology
- Neonatology
- Paediatrics

Specialist Service Group

- Gastrohepatology

Associated Tests

Please note all the tests below will be undertaken for R438 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R438.1	Paediatric pseudo-obstruction syndrome WES or medium panel	Singleton	Small variants	Panel of genes or loci	Paediatric pseudo-obstruction syndrome (1217)	WES or Medium Panel
R438.2	Paediatric pseudo-obstruction syndrome	Singleton	Exon level CNVs	Panel of genes or loci	Paediatric pseudo-obstruction syndrome (1217)	Exon level CNV detection by MLPA or equivalent

Part VIII. Haematology

R361 Haemoglobinopathy trait or carrier testing

Testing Criteria

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

Overlapping indications

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

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

Where in Pathway

Following haemoglobin electrophoresis

Requesting Specialties

- Clinical Genetics
- Haematology
- Obstetrics

Specialist Service Group

- Haematology

Associated Tests

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

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

R362 Carrier testing for sickle cell disease

Testing Criteria

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

Overlapping indications

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

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

Where in Pathway

Following haemoglobin electrophoresis

Requesting Specialties

- Clinical Genetics
- Haematology
- Obstetrics

Specialist Service Group

- Haematology

Associated Tests

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

R90 Bleeding and platelet disorders

Testing Criteria

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

Overlapping indications

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

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

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

Where in Pathway

At presentation following consultation with Consultant Haematologist and following relevant functional haemostasis testing

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

Please note all the tests below will be undertaken for R90 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
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; ; 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

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

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

R94 HbSS sickle cell anaemia

Testing Criteria

Likely HbSS sickle cell anaemia on haemoglobin electrophoresis

Overlapping indications

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Fetal Medicine
- Haematology
- Obstetrics
- Paediatrics

Specialist Service Group

- Haematology

Associated Tests

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

R372 Newborn screening for sickle cell disease in a transfused baby

Testing Criteria

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

Where in Pathway

As per protocol

Requesting Specialties

- Appropriate specialist referring clinician

Specialist Service Group

- Screening

Associated Tests

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

R95 Iron overload - hereditary haemochromatosis testing

Testing Criteria

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

Overlapping indications

- R96 Iron metabolism disorders - not common HFE 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
- General practice

Specialist Service Group

- Core

Associated Tests

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

R96 Iron metabolism disorders - NOT common HFE mutations

Testing Criteria

Iron overload (with raised transferrin saturation and/or 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

Please note all the tests below will be undertaken for R96 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
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

Please note all the tests below will be undertaken for R97 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

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

R115 Factor V deficiency

Testing Criteria

Clinical features characteristic of factor V deficiency

Overlapping indications

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

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

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

Where in Pathway

At presentation following functional haemostasis testing

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

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

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

R116 Factor VII deficiency

Testing Criteria

Clinical features characteristic of factor VII deficiency

Overlapping indications

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

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

Where in Pathway

At presentation following functional haemostasis testing

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

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

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

R117 Factor VIII deficiency

Testing Criteria

Clinical features characteristic of factor VIII deficiency

Overlapping indications

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

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

Where in Pathway

At presentation following functional haemostasis testing

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

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

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

R118 Factor IX deficiency

Testing Criteria

Clinical features characteristic of factor IX deficiency

Overlapping indications

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

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

Where in Pathway

At presentation following functional haemostasis testing

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

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

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

R119 Factor X deficiency

Testing Criteria

Clinical features characteristic of factor X deficiency

Overlapping indications

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

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

Where in Pathway

At presentation following functional haemostasis testing

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

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

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

R120 Factor XI deficiency

Testing Criteria

Clinical features characteristic of factor XI deficiency

Overlapping indications

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

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

Where in Pathway

At presentation following functional haemostasis testing

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

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

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

R121 von Willebrand disease

Testing Criteria

Clinical features characteristic of von Willebrand disease

Overlapping indications

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

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

Where in Pathway

At presentation following functional haemostasis testing

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

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

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

R122 Factor XIII deficiency

Testing Criteria

Clinical features characteristic of factor XIII deficiency

Overlapping indications

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

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

Where in Pathway

At presentation following functional haemostasis testing

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

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

R123 Combined vitamin K-dependent clotting factor deficiency

Testing Criteria

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

Overlapping indications

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

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

Where in Pathway

At presentation following functional haemostasis testing

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

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

R124 Combined factor V and VIII deficiency

Testing Criteria

Clinical features characteristic of combined factor V and VIII deficiency

Overlapping indications

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

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

Where in Pathway

At presentation following functional haemostasis testing

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

Please note all the tests below will be undertaken for R124 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
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
R124.2	Combined factor V and VIII deficiency	Singleton	Exon level CNVs	Panel of genes or loci	Combined factor V and VIII deficiency (517)	Exon level CNV detection by MLPA or equivalent

R92 Rare anaemia

Testing Criteria

Rare anaemias of likely monogenic aetiology

Overlapping indications:

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

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

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

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

Where in Pathway

At presentation following exclusion of likely acquired causes

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

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

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R92.1	HBA1; HBA2; HBG1; HBG2; HBB; RPL11; RPL35A; RPS17; RPS19; RPS26; RPL5; PKLR MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	HBA1; HBA2; HBG1; HBG2; HBB; RPL11; RPL35A; RPS17; RPS19; RPS26; RPL5; PKLR	MLPA or equivalent
R92.2	HBA1; HBA2; HBG1; HBG2; HBB	Singleton	Small variants	Small panel	HBA1; HBA2; HBG1; HBG2; HBB	Small panel
R92.3	Rare anaemia WES or medium panel	Singleton	Small variants	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 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

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

Where in Pathway

At presentation following exclusion of acquired causes including relevant auto-antibodies

Requesting Specialties

- Clinical Genetics
- Haematology
- Immunology

Specialist Service Group

- Haematology

Associated Tests

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

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

R258 Cytopenia - Fanconi breakage testing indicated

Testing Criteria

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

Overlapping indications

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Haematology
- Immunology

Specialist Service Group

- Haematology

Associated Tests

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

R259 Nijmegen breakage syndrome

Testing Criteria

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

Overlapping indications

- R27 Paediatric disorders, R89 Ultra-rare and atypical monogenic disorders or other broad tests should be used except where clinical features are characteristic of Nijmegen breakage syndrome
- Prenatal diagnosis or cascade testing by chromosome breakage testing will be requested via R240 Diagnostic testing for known familial 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	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R259.1	Nijmegen breakage DNA repair defect testing	Singleton	DNA repair	Genomewide	Nijmegen breakage	DNA repair defect testing
R259.2	NBN Single gene sequencing	Singleton	Small variants	Single gene(s)	NBN (1376)	Single gene sequencing >=10 amplicons

R229 Confirmed Fanconi anaemia or Bloom syndrome - 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, R27Paediatric disorders , R89 Ultra-rare and atypical monogenic disorders or other broad genomic tests should typically be used except where clinical features are strongly suggestive of Fanconi anaemia or Bloom syndrome

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

Where in Pathway

Following chromosome breakage analysis

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

Please note all the tests below will be undertaken for R229 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
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

R260 Fanconi anaemia or Bloom syndrome - chromosome breakage testing

Testing Criteria

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

Overlapping indications

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

- In other cases where testing is based on clinical features, R27 Paediatric disorders, R89 Ultra-rare and atypical monogenic disorders or other broad genomic tests should typically be used except where clinical features are strongly suggestive of Fanconi anaemia or Bloom syndrome
- Prenatal diagnosis or cascade testing by chromosome breakage testing will be requested via R240 Diagnostic testing for known familial 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	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R260.1	Fanconi breakage DNA repair defect testing	Singleton	DNA repair	Genomewide	Fanconi breakage	DNA repair defect testing

R313 Neutropaenia consistent with ELANE 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 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

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

Where in Pathway

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

Requesting Specialties

- Clinical Genetics
- Haematology
- Immunology

Specialist Service Group

- Haematology

Associated Tests

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

R338 Monitoring for G(M)CSF escape 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	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R338.1	CSF3R Single gene sequencing	Singleton	Small variants	Single gene(s)	CSF3R (1358)	Single gene sequencing >=10 amplicons

R347 Inherited predisposition to acute myeloid leukaemia (AML)

Testing Criteria

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

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

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

Overlapping indications

- M80 Acute myeloid leukaemia should be used for somatic testing

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

Please note all the tests below will be undertaken for R347 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
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	Inherited predisposition to acute myeloid leukaemia AML	Singleton	Exon level CNVs	Single gene(s)	Inherited predisposition to acute myeloid leukaemia (AML) (525)	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 Leukaemia (ALL), AND

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

NOTE: All diagnoses must be medically documented

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

Overlapping indications

- M91 Acute lymphoblastic leukaemia should be used for somatic testing

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

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

R405 Hereditary Erythrocytosis

Testing Criteria

1. Clinical features of a likely erythrocytosis of monogenic aetiology

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

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

Overlapping Indications

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Haematology

Specialist Service Group

- Haematology

Associated Tests

Please note all the tests below will be undertaken for R405 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R405.1	Hereditary Erythrocytosis Small panel	Singleton	Small variants	Panel of genes or loci	Hereditary Erythrocytosis (157)	Small panel
R405.2	Hereditary Erythrocytosis	Singleton	Exon level CNVs	Panel of genes or loci	Hereditary Erythrocytosis (157)	Exon level CNV detection by MLPA or equivalent

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

Please note all the tests below will be undertaken for R406 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R406.1	Thrombocythaemia Small panel	Singleton	Small variants	Panel of genes or loci	Thrombocythaemia (945)	Small panel
R406.2	Thrombocythaemia	Singleton	Exon level CNVs	Panel of genes or loci	Thrombocythaemia (945)	Exon level CNV detection by MLPA or equivalent

Part IX. Audiology

R65 Aminoglycoside exposure posing risk to hearing

Testing Criteria

Significant exposure to aminoglycosides posing risk of ototoxicity

This indication would be relevant to:

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

Overlapping indications

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

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

Where in Pathway

As appropriate

Requesting Specialties

- Appropriate specialist referring clinician

Specialist Service Group

- Core

Associated Tests

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

R67 Monogenic hearing loss

Testing Criteria

Likely or possible monogenic hearing loss

Hearing loss should be confirmed and bilateral

Cases of unilateral hearing loss are accepted IF there are:

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

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

Overlapping indications

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

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

Where in Pathway

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

Requesting Specialties

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

Specialist Service Group

- Audiology

Associated Tests

Please note all the tests below will be undertaken for R67 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
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

R155 Autoimmune Polyendocrine Syndrome

Testing Criteria

Individuals with a clinical diagnosis of autoimmune polyendocrine syndrome

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Endocrinology
- Immunology

Specialist Service Group

- Immunology

Associated Tests

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

R15 Primary immunodeficiency or monogenic Inflammatory Bowel Disease

Testing Criteria

Suspected primary immunodeficiency diagnosed by a consultant immunologist

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

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

OR

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

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

Testing Criteria for Semi-Rapid Testing

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

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

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

Notes:

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

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

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

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

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

Overlapping indications

- R16 Severe combined immunodeficiency with adenosine deaminase deficiency test should be used in individuals with ADA deficiency
- R234 Severe combined immunodeficiency with PNP deficiency test should be used in individuals with PNP deficiency

- R235 Severe combined immunodeficiency with gamma chain deficiency test should be used in individuals with low or absent gamma chain or low or absent STAT5 pTyr to IL-2,7, and 15
- R17 Lymphoproliferative syndrome with low or absent SAP expression test should be used in individuals with absent SAP expression
- R232 Lymphoproliferative syndrome with low or absent perforin expression test should be used in individuals with absent perforin expression
- R18 Lymphoproliferative syndrome with low or absent XIAP expression test should be used in individuals with absent XIAP expression
- R19 Autoimmune lymphoproliferative syndrome with defective apoptosis test should be used in individuals with defective Fas-mediated apoptosis, elevated alpha double negative T cells, elevated sFAS or elevated vitamin B12
- R233 Agammaglobulinaemia with low or absent BTK expression test should be used in individuals with absent BTK expression
- R20 Wiskott-Aldrich syndrome test should be used in individuals with a likely diagnosis of WAS
- R204 Amyloidosis with no identifiable cause test should be used in cases with confirmed amyloidosis

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

Where in Pathway

N/A

Where in Pathway for Semi-Rapid Testing

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

Requesting Specialties

- Clinical Genetics
- Haematology
- Immunology

  Gastroenterology

Requesting Specialties for Semi-Rapid Testing

- Clinical Genetics
- Immunology
- Neonatology

Specialist Service Group

- Immunology

Associated Tests

R15.5 is only for semi urgent testing

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

R413 Autoinflammatory Disorders

Testing Criteria

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

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

Overlapping indications

- R15 Primary immunodeficiency or monogenic Inflammatory Bowel Disease

Where in Pathway

At presentation

Requesting Specialties

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

Specialist Service Group

- Immunology

Associated Tests

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

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

R16 Severe combined immunodeficiency with adenosine deaminase deficiency

Testing Criteria

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

Overlapping indications

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

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

Where in Pathway

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

Requesting Specialties

- Clinical Genetics
- Immunology

Specialist Service Group

- Immunology

Associated Tests

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

R235 SCID with features of gamma chain deficiency

Testing Criteria

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

Overlapping indications

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

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

Where in Pathway

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

Requesting Specialties

- Clinical Genetics
- Immunology

Specialist Service Group

- Immunology

Associated Tests

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

R234 Severe combined immunodeficiency with PNP deficiency

Testing Criteria

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

Overlapping indications

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

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

Where in Pathway

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

Requesting Specialties

- Clinical Genetics
- Immunology

Specialist Service Group

- Immunology

Associated Tests

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

R17 Lymphoproliferative syndrome with absent SAP expression

Testing Criteria

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

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

Overlapping indications

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

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

Where in Pathway

At presentation, following SAP expression analysis

Requesting Specialties

- Clinical Genetics
- Haematology
- Immunology

Specialist Service Group

- Immunology

Associated Tests

Please note all the tests below will be undertaken for R17 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R17.1	SH2D1A Single gene sequencing	Singleton	Small variants	Single gene(s)	SH2D1A (1353)	Single gene sequencing <10 amplicons
R17.2	SH2D1A MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	SH2D1A (1353)	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

Please note all the tests below will be undertaken for R18 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R18.1	XIAP Single gene sequencing	Singleton	Small variants	Single gene(s)	XIAP (1344)	Single gene sequencing >=10 amplicons
R18.2	XIAP MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	XIAP (1344)	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	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R232.1	PRF1 Single gene sequencing	Singleton	Small variants	Single gene(s)	PRF1 (1343)	Single gene sequencing <10 amplicons

R19 Autoimmune lymphoproliferative syndrome with defective apoptosis

Testing Criteria

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

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

Overlapping indications

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

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

Where in Pathway

At presentation, following analysis of Fas-mediated apoptosis

Requesting Specialties

- Clinical Genetics
- Haematology
- Immunology

Specialist Service Group

- Immunology

Associated Tests

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

R233 Agammaglobulinaemia with absent BTK expression

Testing Criteria

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

Overlapping indications

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

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

Where in Pathway

At presentation, following BTK expression analysis

Requesting Specialties

- Clinical Genetics
- Immunology

Specialist Service Group

- Immunology

Associated Tests

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

R20 Wiskott-Aldrich syndrome

Testing Criteria

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

The diagnosis should be considered in any male with small platelets

Overlapping indications

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

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

Where in Pathway

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

Requesting Specialties

- Clinical Genetics
- Haematology
- Immunology

Specialist Service Group

- Immunology

Associated Tests

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

R341 Hereditary angioedema types I and II

Testing Criteria

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

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

Where in Pathway

Following C1INH testing

Requesting Specialties

- Clinical Genetics
- Dermatology
- Immunology

Specialist Service Group

- Immunology

Associated Tests

Please note all the tests below will be undertaken for R341 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R341.1	SERPING1 Single gene sequencing	Singleton	Small variants	Single gene(s)	SERPING1 (1345)	Single gene sequencing >=10 amplicons
R341.2	SERPING1 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	SERPING1 (1345)	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	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R368.1	F12 hotspot Targeted variant testing	Singleton	Small variants	Single interval	F12 hotspot	Targeted variant testing

R436 Hereditary alpha tryptasaemia

Testing Criteria

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

Where in Pathway

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

Requesting Specialties

- Immunology
- Haematology
- Paediatrics
- Allergy specialists
- Dermatology

Specialist Service Group

- Immunology

Associated Tests

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

Part XI. Inherited cancer

R207 Inherited ovarian cancer (without breast cancer)

Testing Criteria

1. High grade non mucinous epithelial ovarian cancer (EOC) at any age

OR

2. Epithelial ovarian cancer (EOC) AND

a. ≥1 first degree relative with EOC, OR

b. ≥1 second degree relative with EOC (intervening relative without ovaries or deceased) OR

c. ≥2 second / third degree relatives with EOC

3. Deceased affected individual (proband) where criteria 2 are reached (or family Manchester score of 20) and:

a. Appropriate tissue is available (tumour or normal) AND

b. No living affected individual is available for genetic testing

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

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

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

Overlapping indications

- M2 Ovarian carcinoma should be used for somatic testing

Where in Pathway

At presentation

Requesting Specialties

- Oncology
- Clinical Genetics
- Gynaecology

Specialist Service Group

- Core

Associated Tests

Please note all the tests below will be undertaken for R207 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R207.1	Inherited ovarian cancer without breast cancer Small panel	Singleton	SNVs	Panel of genes or loci	Inherited ovarian cancer (without breast cancer) (143)	Small panel
R207.2	BRCA1; BRCA2; BRIP1; MLH1; MSH2; MSH6; PALB2; RAD51C; RAD51D MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	BRCA1; BRCA2; BRIP1; MLH1; MSH2; MSH6; PALB2; RAD51C; RAD51D	MLPA or equivalent

R208 Inherited breast cancer and ovarian cancer

Testing Criteria

1. **Living affected individual (proband)** with breast* or high grade ovarian cancer where the individual +/- family history meets one of the criteria. The proband has:
   a. Breast cancer (age <40 years), OR
   b. Bilateral breast cancer (age < 50 years), OR
   c. Triple negative breast cancer (age < 60 years), OR
   d. Assigned male at birth and affected with breast cancer (any age), OR
   e. Breast cancer (age <45 years) and a first degree relative with breast cancer (age <45 years), OR
   f. Combined pathology-adjusted Manchester score ≥15 or single gene pathology adjusted score of ≥10 or BOADICEA/CanRisk score ≥10% OR
   g. Ashkenazi Jewish ancestry and breast cancer at any age
2. **Living affected individual with pancreatic cancer** AND family history of breast*/high grade ovarian/prostate cancer with a pathology adjusted Manchester score of ≥ 15/CanRisk score of 10%.
3. **Living affected individual with prostate cancer** AND a family history of breast/ovarian/pancreatic cancer with a pathology adjusted Manchester score of ≥ 15/CanRisk score of 10%.
4. **Deceased affected individual** with breast* or high grade ovarian cancer with:
   a. A stored DNA, blood or tissue sample available for DNA extraction, AND
   b. Pathology-adjusted Manchester score ≥17 or CanRisk score ≥15%, AND
   c. No living affected individual is available for genetic testing
5. **Living unaffected** individual with:
   a. first degree relative affected by breast* or serous ovarian cancer, AND
   b. Combined pathology-adjusted Manchester score ≥20 or BOADICEA/CanRisk score of ≥20% for affected relative or BOADICEA/CanRisk score of ≥10% for unaffected relative AND
   c. No living affected individual is available for genetic testing, AND
   d. No deceased affected individual with tumour material available for testing

   Note for living unaffected individuals:

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

NOTES

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

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

Overlapping indications

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

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

Where in Pathway

At presentation

Requesting Specialties

- Oncology
- Clinical Genetics
- Surgery

Specialist Service Group

- Core

Associated Tests

Please note all the tests below will be undertaken for R208 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R208.1	Inherited breast and ovarian cancer	Singleton	Small variants	Small panel of genes	Inherited breast and ovarian cancer (635)	Small panel
R208.2	Inherited breast and ovarian cancer	Singleton	Exon level CNVs	Single gene(s)	Inherited breast and ovarian cancer (635)	MLPA or equivalent

R210 Inherited MMR deficiency (Lynch syndrome)

Testing Criteria

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

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

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

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

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

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

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

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

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

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

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

Overlapping indications

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

Where in Pathway

At presentation following tumour studies (IHC/MSI)

Requesting Specialties

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

* Surgery to cover colorectal and gynecological surgeons

Specialist Service Group

- Core

Associated Tests

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

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R210.2	Inherited MMR deficiency Lynch syndrome Small panel	Singleton	Small variants	Panel of genes or loci	Inherited MMR deficiency (Lynch syndrome) (503)	Small panel
R210.4	Germline MLH1 promotor methylation	Singleton	Methylation	Single gene(s)	MLH1	Methylation testing
R210.5	MLH1; MSH2; MSH6; PMS2 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	MLH1; MSH2; MSH6; PMS2	MLPA or equivalent

R211 Inherited polyposis and early onset colorectal cancer - 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. Any colorectal cancer diagnosis under 40 years
2. ≥5 adenomatous polyps and colorectal cancer, OR
3. ≥5 adenomatous polyps (age <40 years), OR
4. ≥10 adenomatous polyps (age <60 years, OR
5. ≥20 adenomatous polyps (age ≥ 60 years), OR
6. ≥5 adenomatous polyps (age <60 years) and first degree relative with ≥5 adenomatous polyps or CRC (age <60 years), OR
7. Serrated polyposis:
    a. Five or more serrated lesions/polyps proximal to the rectum all being at least 5 mm in size with two or more being at least 10mm in size,
    b. More than 20 serrated lesions/polyps of any size distributed through the large bowel with at least five being proximal to the rectum.
8. Hamartomatous polyposis syndromes:
    a. ≥ 5 hamartomatous polyps of the colorectum, OR
    b. ≥ 2 hamartomatous polyps throughout the GI tract, OR
    c. ≥ 1 hamartomatous polyp and a first / second degree relative has hamartomatous polyp.

NOTE: The majority of polyps are histologically confirmed

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

Overlapping indications

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Gastroenterology
- Surgery*

*Surgery to cover colorectal surgeons

Specialist Service Group

- Core

Associated Tests

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

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

R414 APC Associated Polyposis

Testing Criteria

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

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

*Footnote: Diagnostic criteria of GAPPS (Worthley et al. Gut. 2012 May;61(5):774-9)

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

Overlapping indications

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

R359 Childhood solid tumor panel

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Surgery
- Oncology*
  *including paediatrics

Specialist Service Group

- Core

Associated Tests

Please note all the tests below will be undertaken for R414 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R414.1	APC Associated Polyposis	Singleton	small variant detection	Single gene	APC (1212)	Single gene sequencing ≥ 10 amplicons
R414.2	APC Associated Polyposis	Singleton	Exon level CNVs	Single gene	APC (1212)	Exon level CNV detection by MLPA or equivalent

R212 Peutz Jeghers Syndrome

Testing Criteria

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

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

Deceased affected individual (proband) where (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

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

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

Where in Pathway

At presentation/at follow-up

Requesting Specialties

- Clinical Genetics
- Dermatology
- Gastroenterology
- Surgery

Specialist Service Group

- Inherited cancer

Associated Tests

Please note all the tests below will be undertaken for R212 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R212.1	STK11 Single gene sequencing	Singleton	Small variants	Single gene(s)	STK11 (1377)	Single gene sequencing >=10 amplicons
R212.2	STK11 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	STK11 (1377)	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 one of the following:
   a. ≥ 6 facial papules, of which ≥ 3 are trichilemmoma,
   b. Cutaneous facial papules AND oral mucosal papillomatosis,
   c. Oral mucosal papillomatosis AND acral keratosis,
   d. ≥6 palmoplantar keratosis,
2. Cerebellar dysplastic gangliocytoma (Adult Lhermitte-Duclos disease (LDD)),
3. ≥2 major criteria, of which one should be macrocephaly
4. ≥1 major criteria and ≥ 1 PTEN-HTS-related mucocutaneous lesion,
5. ≥1 major and ≥ 3 minor criteria, OR
6. Macrocephaly ≥97th centile, AND
   a. ≥ 1 minor criteria, OR
   . b ≥ 1 PTEN-HTS-related mucocutaneous lesion, OR
7. ≥ 4 minor criteria, OR
8. ≥ 1 major criteria, AND ≥ 2 first / second degree relatives each with one of the following:
   a. ≥ 1 major criteria,
   b. ≥ 1 PTEN-HTS-related mucocutaneous lesion,
   c. ≥ 2 minor criteria (multiple cases of breast cancer are not eligible for inclusion)
9. Cleveland Clinic PTEN risk calculator score corresponding to probability of pathogenic/likely pathogenic variant of 10%

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 ≥97th percentile)
- Endometrial carcinoma

Minor criteria:

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

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

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

Where in Pathway

At presentation/at follow-up

Requesting Specialties

- Clinical Genetics
- Dermatology
- Neurology

Specialist Service Group

- Inherited cancer

Associated Tests

Please note all the tests below will be undertaken for R213 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R213.1	PTEN Single gene sequencing	Singleton	Small variants	Single gene(s)	PTEN (1382)	Single gene sequencing >=10 amplicons
R213.2	PTEN MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	PTEN (1382)	MLPA or equivalent

R214 Nevoid Basal Cell Carcinoma Syndrome or Gorlin syndrome

Testing Criteria

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

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

3. Minor criteria:

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

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

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

Where in Pathway

At presentation/at follow-up

Requesting Specialties

- Clinical Genetics
- Dermatology

Specialist Service Group

- Inherited cancer

Associated Tests

Please note all the tests below will be undertaken for R214 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R214.1	PTCH1; SUFU	Singleton	Small variants	Small panel	PTCH1; SUFU (1373)	Small panel
R214.2	PTCH1; SUFU MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	PTCH1; SUFU (1373)	MLPA or equivalent

R215 Hereditary diffuse gastric cancer

Testing Criteria

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

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: At least one cancer should be histologically confirmed

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

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

Where in Pathway

At presentation/at follow-up

Requesting Specialties

- Clinical Genetics
- Gastroenterology
- Surgery*

*Surgery to cover upper gastro-intestinal surgeons

Specialist Service Group

- Inherited cancer

Associated Tests

Please note all the tests below will be undertaken for R215 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R215.1	Hereditary diffuse gastric cancer	Singleton	Small variants	Small panel	CDH1; CTNNA1 (1221)	Small panel
R215.2	Hereditary diffuse gastric cancer - MLPA or equivalent	Singleton	Exon level CNVs	Small panel	CDH1; CTNNA1 (1221)	MLPA or equivalent

R216 Li Fraumeni Syndrome

Testing Criteria

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

The proband has:

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

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

Deceased affected individual (proband) where (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: soft tissue sarcomas, osteosarcomas, adrenocortical carcinoma, central nervous system tumours and breast cancers.

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

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

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

Overlapping indications

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

Where in Pathway

At presentation/at follow-up

Requesting Specialties

- Clinical Genetics
- Oncology*

  *including paediatrics

Specialist Service Group

- Inherited cancer

Associated Tests

Please note all the tests below will be undertaken for R216 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R216.1	Li Fraumeni Syndrome (1222) - small panel	Singleton	Small variants	Small panel	TP53, POT1(1222)	Small panel
R216.2	Li Fraumeni Syndrome (1222) MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	TP53, POT1(1222)	Exon level CNVs detected by MLPA or equivalent

R219 Retinoblastoma

Testing Criteria

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

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

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

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

Overlapping indications

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

Where in Pathway

At presentation/at follow-up

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Inherited cancer

Associated Tests

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

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

R220 Wilms tumour with features suggestive of predisposition

Testing Criteria

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

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

Overlapping indications

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

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

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

Where in Pathway

At presentation/at follow-up

Requesting Specialties

- Clinical Genetics
- Oncology*

  including paediatrics

Specialist Service Group

- Inherited cancer

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R220.1	Wilms tumour with features suggestive of predisposition	Singleton	Small variants	Small panel	Wilms tumour with features suggestive of predisposition (1108)	Small panel
R220.2	Wilms tumour with features suggestive of predisposition	Singleton	Exon level CNVs	Single gene(s)	Wilms tumour with features suggestive of predisposition (1108)	MLPA or equivalent
R220.3	Wilms tumour with features suggestive of predisposition	Singleton	Methylation	Single interval	11p15 imprinted growth regulatory region	Methylation testing
R220.4	Wilms tumour with features suggestive of predisposition	Singleton	CNVs	Single interval	11p15 imprinted growth regulatory region	MLPA or equivalent

R358 Familial rhabdoid tumours

Testing Criteria

Living affected individual (proband) where the proband has atypical teratoid/rhabdoid tumour (any age) OR

Small cell carcinoma of the ovary, hypercalcaemic type (SCCOHT) (any age)

NOTE: The proband's cancer should have been confirmed

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

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

Likely to need to specify high coverage depth to detect mosaic SMARCB1 and SMARCA4 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
- Oncology*

  * including paediatrics

Specialist Service Group

- Inherited cancer

Associated Tests

Please note all the tests below will be undertaken for R358 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R358.1	Familial rhabdoid tumours Small panel	Singleton	Small variants	Panel of genes or loci	Rhabdoid tumour predisposition (600)	Small panel
R358.2	Familial rhabdoid tumours	Singleton	Exon level CNVs	Panel of genes or loci	Rhabdoid tumour predisposition (600)	Exon level CNV detection by MLPA or equivalent

R359 Childhood solid tumours

Testing Criteria

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

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

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

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

Overlapping indications

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

Where in Pathway

At presentation/at follow-up

Requesting Specialties

- Oncology
- Clinical Genetics

Specialist Service Group

- Inherited cancer

Associated Tests

Please note all the tests below will be undertaken for R359 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R359.1	Childhood solid tumours WES or Medium panel	Singleton	Small variants	Panel of genes or loci	Tumour predisposition - childhood onset (243)	WES or Medium panel
R359.2	Childhood solid tumours	Singleton	Exon level CNVs	Panel of genes or loci	Tumour predisposition - childhood onset (243)	Exon level CNV detection by MLPA or equivalent

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

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

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

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

Overlapping indications

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

Where in Pathway

At presentation/at follow-up

Requesting Specialties

- Clinical Genetics
- Urology
- Nephrology

Specialist Service Group

- Inherited cancer

Associated Tests

Please note all the tests below will be undertaken for R224 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
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. ≥2 VHL-related tumours (any age), OR
   d. ≥1 VHL-related tumour and a first degree relative with ≥1 VHL-related tumour (where one of the tumours is retinal angioma / hemangioblastoma)
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

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

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

Where in Pathway

At presentation/at follow-up

Requesting Specialties

- Clinical Genetics
- Endocrinology
- Nephrology
- Neurology
- Ophthalmology
- Urology
- Neurosurgery

Specialist Service Group

- Inherited cancer

Associated Tests

Please note all the tests below will be undertaken for R225 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R225.1	VHL Single gene sequencing	Singleton	Small variants	Single gene(s)	VHL (1403)	Single gene sequencing >=10 amplicons
R225.2	VHL MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	VHL (1403)	MLPA or equivalent

R254 Familial melanoma

Testing Criteria

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

a. ≥2 melanomas and/or melanomas in situ age <30 years, OR
b. ≥3 melanoma and/or melanomas in situ at any age, OR
c. Melanoma and/or melanoma in situ AND ≥2 relatives (first / second / third degree relatives) with melanoma and/or melanoma in situ, OR
d. Melanoma and/or melanoma in situ AND ≥1 first degree relative with melanoma and/or melanoma in situ; one individual has multiple melanomas and/or melanomas in situ, OR
e. ≥1 Melanoma and/or melanoma in situ OR melanoma and/or melanoma in situ and atypical moles AND ≥1 first degree relative with pancreatic cancer aged <60, OR
f. Atypical moles AND ≥2 relatives (first / second degree relatives) with melanoma and/or melanoma in situ, OR
g. 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.

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

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

Overlapping indications

- M7 Melanoma (adult) and M187 Uveal melanoma should be used for somatic testing

Where in Pathway

At presentation/at follow-up

Requesting Specialties

- Clinical Genetics
- Dermatology

Specialist Service Group

- Inherited cancer

Associated Tests

Please note all the tests below will be undertaken for R254 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R254.1	Familial melanoma Small panel	Singleton	Small variants	Panel of genes or loci	Familial melanoma (522)	Small panel
R254.2	Familial melanoma	Singleton	Exon level CNVs	Panel of genes or loci	Familial melanoma (522)	Exon level CNV detection by MLPA or equivalent

R422 BAP1 associated tumour predisposition syndrome

Testing Criteria

Individual (proband) affected with either:

1. BAP1 deficient mesothelioma or mesothelioma diagnosed under 50 years if BAP1 status unknown OR,
2. BAP1-inactivated melanocytic tumors (BIMT) (Also known as BAPoma, atypical Spitz naevus, Melanocytic BAP1-associated intradermal tumor (MBAIT) or nevoid melanoma-like melanocytic proliferation (NEMMP) OR
3. Personal history of two or more BAP1 associated tumours* OR
4. Individual affected with BAP1 associated tumour and FDR affected with BAP1 related tumour*

* Excluding combination of basal cell cancers and/or cutaneous melanomas alone, given their high frequency in the general population

BAP1 associated tumours= uveal melanoma, cutaneous melanoma, basal cell cancer, BAP1-inactivated melanocytic tumors (BIMT), malignant mesothelioma (lung or peritoneal), renal cell carcinoma, meningioma, cholangiocarcinoma or hepatocellular carcinoma.

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

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

Overlapping indications

R254 Familial melanoma

R214 Nevoid Basal Cell Carcinoma Syndrome or Gorlin syndrome

R224 Inherited renal cancer

Where in Pathway

At presentation/at follow-up

Requesting Specialties

- Clinical Genetics
- Dermatology
- Oncology

Specialist Service Group

- Inherited cancer

Associated Tests

Please note all the tests below will be undertaken for R422 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R422.1	BAP1 associated tumour predisposition syndrome	Singleton	Small variants	Single gene	BAP1 (1216)	Single gene sequencing >=10 amplicons
R422.2	BAP1 associated tumour predisposition syndrome	Singleton	Exon level CNVs	Single gene	BAP1 (1216)	Exon level CNV detection by MLPA or equivalent

R363 Inherited predisposition to GIST

Testing Criteria

Testing of affected individual (proband) where the individual +/- family history meets the following criteria:
The proband has GIST (gastrointestinal stromal tumour):

1. Diagnosed age before age 50, OR
2. With ≥1 relative (first / second / third degree relative) with GIST, phaeochromocytoma / paraganglioma

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

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

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

Overlapping indications

- M8 Gastrointestinal stromal tumour should be used for somatic testing
- R223 Inherited phaeochromocytoma and paraganglioma excluding NF1

Where in Pathway

At presentation/at follow-up

Requesting Specialties

- Clinical Genetics
- Endocrinology
- Gastroenterology

Specialist Service Group

- Inherited cancer

Associated Tests

Please note all the tests below will be undertaken for R363 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
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	SDHB; 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

1. Testing of affected individual (proband) where the individual has one of the following diagnoses:

Pleuropulmonary blastoma or Lung cyst(s) in childhood, especially if multi-septated, multiple or bilateral; Thoracic, uterine, cervical or ovarian embryonal rhabdomyosarcoma; Cystic nephroma; Genitourinary sarcoma including undifferentiated sarcoma in childhood; Ovarian Sertoli Leydig tumour; Gynandroblastoma; Genitourinary/gynaecologic neuroendocrine tumors; Childhood-onset multinodular goitre or differentiated thyroid cancer (papillary or follicular); Ciliary body medulloepithelioma; Nasal chondromesenchymal hamartoma; Pineoblastoma; Pituitary blastoma, OR

2. Testing of affected individual where there is a combination of two of the following diagnoses, either both in one affected individual or in two affected first degree relatives;

Lung cyst(s) in adults; Wilms tumor; Multinodular goiter or differentiated thyroid cancer; Embryonal rhabdomyosarcoma other than thoracic or gynaecologic; Poorly differentiated neuroendocrine tumour; Undifferentiated sarcoma; Macrocephaly

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

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

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

Where in Pathway

At presentation/at follow-up

Requesting Specialties

- Clinical Genetics
- Paediatric oncology
- Paediatric endocrinology

Specialist Service Group

- Inherited cancer

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R364.1	DICER1 related cancer predisposition Single gene sequencing	Singleton	Small variants	Single gene(s)	DICER1 (1320)	Single gene sequencing >=10 amplicons
R364.2	DICER1 related cancer predisposition	Singleton	Exon level CNVs	Single gene	DICER1 (1320)	Exon level CNV detection by MLPA or equivalent

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, HLRCC associated RCC (WHO pathology definition) OR tubulo-papillary renal tumour at any age, OR
   b. Two of: cutaneous leiomyomata, renal tumour (any histology) , OR uterine leiomyomata with classic histological features < 40 years OR
   c. Cutaneous leiomyomata AND one first / second / third degree relative with renal tumour, OR
   d. Cutaneous leiomyomata AND two first / second / third degree relatives with cutaneous leiomyomata OR uterine leiomyomata with classic histological features < 40 years, OR
   e. Uterine leiomyomata with classic histological features (age <40) OR
   f. Multiple cutaneous leiomyomata
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

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

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

Overlapping indications

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

Where in Pathway

At presentation/at follow-up

Requesting Specialties

- Clinical Genetics
- Dermatology
- Urology
- Nephrology

Specialist Service Group

- Inherited cancer

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R365.1	FH Single gene sequencing	Singleton	Small variants	Single gene(s)	FH (1335)	Single gene sequencing >=10 amplicons

R367 Inherited pancreatic cancer

Testing Criteria

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

1. Pancreatic cancer age <60, OR
2. Pancreatic cancer age <70, AND
   a. Breast cancer age <60, melanoma age <60, OR ovarian cancer, OR
   b. One first / second degree relative with pancreatic cancer age <60, OR
   c. Two first / second degree relatives with any of breast cancer age <60, melanoma age <60, OR ovarian cancer OR

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

NOTE: The proband's cancer and majority of reported cancers in the family should have been confirmed. Pancreatic cancer is adenocarcinoma and not neuroendocrine tumour.

If there is a family history of BRCA related cancers (breast, ovarian, prostate and pancreatic), please consider if R208 Inherited Breast Cancer panel testing is required.

If there is a family history of melanoma, please consider if R254 Familial Melanoma panel testing is required.

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

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

Overlapping indications

- M219 Pancreatic cancer should be used for somatic testing

Where in Pathway

At presentation/at follow-up

Requesting Specialties

- Clinical Genetics
- Gastroenterology
- Oncology

Specialist Service Group

- Inherited cancer

Associated Tests

Please note all the tests below will be undertaken for R367 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R367.1	Inherited pancreatic cancer Small panel	Singleton	Small variants	Panel of genes or loci	Inherited pancreatic cancer (524)	Small panel
R367.2	Inherited pancreatic cancer	Singleton	Exon level CNVs	Panel of genes or loci	Inherited pancreatic cancer (524)	Exon level CNV detection by MLPA or equivalent

R404 Testing of unaffected individuals for inherited cancer predisposition syndromes

Testing Criteria

Germline testing of unaffected individuals for specific inherited cancer predisposition syndromes where the following criteria are met:

1. There are no living affected relatives available for testing, AND
2. Any applicable somatic testing on deceased relatives tumour samples has been performed first, AND
3. The individual to be tested is deemed to have ≥10% chance of having a mutation (deceased first degree relative with ≥20% chance), AND
4. This is agreed by specialist cancer genetics MDT

For testing for hereditary breast and ovarian cancer and inherited MMR deficiency (Lynch syndrome), unaffected individuals must meet criteria as specified under relevant indications R208/R215

NOTE: All cancers must be confirmed

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Core and Inherited cancer; depending on the cancer of suspicion

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R404.1	Inherited cancer predisposition gene sequencing	Singleton	Small variants	Single gene(s)	As dictated by clinical indication	Single gene sequencing >=10 amplicons
R404.2	Inherited cancer predisposition gene	Singleton	Exon level CNVs	Panel of genes or loci	As per appropriate inherited cancer indication	Exon level CNV detection by 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

R430 Inherited prostate cancer

Testing Criteria

- Proband diagnosed with prostate cancer at <50 years
- Ashkenazi Jewish ancestry and prostate cancer at any age
- Proband diagnosed with metastatic prostate cancer <60 years
- Proband diagnosed with prostate cancer with a family history of prostate cancer where estimated likelihood of identifying a pathogenic variant in the relevant target genes is at least 10%

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

Overlapping indications

- R208 Inherited breast cancer and ovarian cancer - Proband affected with prostate cancer who has a personal/family history of other BRCA related cancers see R208 (BRCA related cancers = breast, ovarian, pancreatic, prostate).
- R210 Inherited MMR deficiency (Lynch syndrome) - For prostate cancer with personal/family history of other Lynch related cancers see R210 (See list of Lynch related cancers in R210).
- R444 NICE approved PARP inhibitor treatment
- M218 prostate cancer should be used for somatic testing

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Oncology
- Urology

Specialist Service Group

- Core

Associated Tests

Please note all the tests below will be undertaken for R430 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R430.1	Inherited prostate cancer	Singleton	Small variants	Small panel of genes	Inherited prostate cancer (1223)	Small panel
R430.2	Inherited prostate cancer	Singleton	Exon level CNVs	Small panel of genes	Inherited prostate cancer (1223)	Exon level CNV detection by MLPA or equivalent

R444 NICE approved PARP inhibitor treatment

Testing Criteria

Testing Criteria only applies to patients not meeting R208/R430 criteria AND with current cancer diagnosis for treatment decisions.

R444.1 Breast Cancer

1. For people with triple negative breast cancer who have received neo-adjuvant chemotherapy:
    - residual invasive cancer in the breast, the resected lymph nodes (non-pathological complete response) or both at the time of surgery
2. For people with triple-negative breast cancer having adjuvant chemotherapy:
    - node-positive OR
    - node-negative cancer with a primary tumour ≥ 2 cm
3. For people with hormone receptor-positive, HER2-negative breast cancer who have received neoadjuvant chemotherapy:
    - residual invasive cancer in the breast, the resected lymph nodes (non-pathologic complete response) or both at the time of surgery, AND a CPS + EG score of ≥3 based on pre-treatment clinical and posttreatment pathological stage, receptor status and histological grade
4. For people with hormone receptor-positive, HER2-negative breast cancer having adjuvant chemotherapy:
    - 4 or more pathologically confirmed positive lymph nodes.

R444.2 Prostate Cancer

Metastatic, castration-resistant prostate cancer where somatic tumour testing (M218.1) has failed.

Overlapping indications

- R208 Inherited breast cancer and ovarian cancer
- R430 Inherited prostate cancer
- M3 breast cancer should be used for somatic testing
- M218 prostate cancer should be used for somatic testing

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

Where in Pathway

At earliest stage, either at primary surgery or after neo-adjuvant chemotherapy

Requesting Specialties

- Clinical Genetics
- Surgery
- Oncology

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R444.1	NICE approved PARP inhibitor treatment – breast cancer	Singleton	Small variants	Small panel of genes	BRCA1; BRCA2; PALB2; RAD51C; RAD51D; ATM; CHEK2	Small panel
R444.2	NICE approved PARP inhibitor treatment – prostate cancer	Singleton	Small variants	Small panel of genes	BRCA1, BRCA2	Small panel
R444.3	NICE approved PARP inhibitor treatment – breast or prostate	Singleton	Exon level CNVs	Single gene(s)	As dictated by relevant test ID	MLPA or equivalent