Part XII. Lipids

R134 Familial hypercholesterolaemia

Testing Criteria

Dutch (or Welsh) lipid clinic score >5, OR

Simon Broome criteria indicate possible FH (following assessment in a specialist Lipid Clinic or Familial Hypercholesterolaemia service)

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

Where in Pathway

At presentation

Requesting Specialties

- Cardiology
- Chemical Pathology
- Clinical Genetics
- Metabolic Medicine
- Paediatrics

Specialist Service Group

- Core

Associated Tests

Please note all the tests below will be undertaken for R134 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
R134.1	Familial hypercholesterolaemia Small panel	Singleton	Small variants	Panel of genes or loci	Familial hypercholesterolaemia – targeted panel (772)	Small panel
R134.2	LDLR MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	LDLR	MLPA or equivalent

R324 Familial Chylomicronaemia Syndrome (FCS)

Testing Criteria

1. Fasting triglycerides >20mmol/L, AND
2. Exclusion of secondary causes of hypertriglyceridaemia e.g. excess alcohol, uncontrolled diabetes

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

Where in Pathway

At presentation

Requesting Specialties

- Cardiology
- Chemical Pathology
- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Please note all the tests below will be undertaken for R324 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
R324.1	Familial Chylomicronaemia Syndrome (FCS) Small panel	Singleton	Small variants	Panel of genes or loci	Lipoprotein lipase deficiency (527)	Small panel
R324.2	Familial Chylomicronaemia Syndrome (FCS)	Singleton	Exon level CNVs	Panel of genes or loci	Lipoprotein lipase deficiency (527)	Exon level CNV detection by MLPA or equivalent

Part XIII. Metabolic

R380 Niemann Pick disease type C

Testing Criteria

Clinical and laboratory features characteristic of Niemann-Pick disease type C

Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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

Where in Pathway

At presentation following laboratory testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Please note all the tests below will be undertaken for R380 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R380.1	NPC1; NPC2	Singleton	Small variants	Small panel	NPC1; NPC2 (1347)	Small panel
R380.2	NPC1; NPC2 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	NPC1; NPC2 (1347)	MLPA or equivalent

R98 Likely inborn error of metabolism - targeted testing not possible

Testing Criteria

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

Testing Criteria for Semi-Rapid Testing

- Children or adults with a suspected likely inborn error of metabolism, where a rapid diagnosis will direct immediate treatment or medical care of the patient, and:

- Biochemical testing and/or enzyme analysis specifically points to one particular gene and condition, or to a subset of genes and conditions for which specific testing can be provided using a “slice” or small subset of genes of the R98.2 gene panel.

- This testing pathway is not intended as an exclusion test for patients with a broad differential diagnosis, and without a specific diagnosis from biochemical testing/enzyme analyses. These referrals will not be accepted and will be directed to the WGS route.

- The patient is either not eligible for the R14 pathway or Rapid R98 is considered to be the more appropriate test.

Overlapping indications

- Targeted tests for specific metabolic disorders should be used where clinical features or biochemical/enzyme testing results are rapidly available and strongly suggestive of the relevant disorder(s)

Where in Pathway

At presentation following clinically relevant, rapidly available investigations

Where in Pathway for Semi-Rapid Testing

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

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Requesting Specialties for Semi-Rapid Testing

- Clinical Genetics
- Metabolic Medicine
- Neurology
- Neonatology

Specialist Service Group

- Metabolic

Associated Tests

R98.3 is only for semi urgent testing

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R98.2	Inborn errors of metabolism WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Inborn errors of metabolism (467)	WGS
R98.3	Inborn errors of metabolism WES	Trio	Exon level CNVs, Small variants	Panel of genes or loci	Inborn errors of metabolism (467)	WES

R270 Smith-Lemli-Opitz syndrome

Testing Criteria

Clinical and biochemical features characteristic of Smith-Lemli-Opitz syndrome

Overlapping indications

- R98 Likely inborn error of metabolism - 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 following biochemical testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Please note all the tests below will be undertaken for R270 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R270.1	DHCR7 Single gene sequencing	Singleton	Small variants	Single gene(s)	DHCR7 (1392)	Single gene sequencing >=10 amplicons
R270.2	DHCR7 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	DHCR7 (1392)	MLPA or equivalent

R231 Neuronal ceroid lipofuscinosis

Testing Criteria

Clinical and laboratory features characteristic of Neuronal ceroid lipofuscinosis including presence of vacuolate lymphocytes, presence of pathological inclusions on tissue biopsy or enzyme deficiency

Overlapping indications

- R271 Neuronal ceroid lipofuscinosis type 2 test should be considered where clinical features are specific to CLN2
- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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

Where in Pathway

At presentation following histological analysis and/or enzyme testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Metabolic

Associated Tests

Please note all the tests below will be undertaken for R231 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
R231.1	CLN3 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	CLN3	MLPA or equivalent
R231.2	Neuronal ceroid lipofuscinosis Small panel	Singleton	Small variants	Panel of genes or loci	Neuronal ceroid lipofuscinosis (526)	Small panel

R271 Neuronal ceroid lipofuscinosis type 2

Testing Criteria

Clinical and laboratory features characteristic of neuronal ceroid lipofuscinosis type 2

Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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

Where in Pathway

At presentation following histological analysis and/or enzyme testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R271.1	TPP1 Single gene sequencing	Singleton	Small variants	Single gene(s)	TPP1 (1371)	Single gene sequencing >=10 amplicons

R334 Cystinosis

Testing Criteria

1. Paediatric presentation with nephropathic cystinosis, OR
2. Adult presentation with non-nephropathic cystinosis

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Gastroenterology
- Metabolic Medicine
- Nephrology
- Neurology
- Ophthalmology

Specialist Service Group

- Metabolic

Associated Tests

Please note all the tests below will be undertaken for R334 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
R334.1	CTNS Single gene sequencing	Singleton	Small variants	Single gene(s)	CTNS (1319)	Single gene sequencing >=10 amplicons
R334.2	CTNS MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	CTNS (1319)	MLPA or equivalent

R335 Fabry disease

Testing Criteria

- In males: clinical and laboratory features characteristic of Fabry disease following alpha-galactosidase A enzyme testing
- In females: clinical features characteristic of Fabry disease

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

Where in Pathway

Following alpha-galactosidase A enzyme testing

Requesting Specialties

- Cardiology
- Clinical Genetics
- Dermatology
- Metabolic Medicine
- Nephrology
- Ophthalmology

Specialist Service Group

- Metabolic

Associated Tests

Please note all the tests below will be undertaken for R335 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R335.1	GLA Single gene sequencing	Singleton	Small variants	Single gene(s)	GLA (1323)	Single gene sequencing <10 amplicons
R335.2	GLA MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	GLA (1323)	MLPA or equivalent

R325 Lysosomal acid lipase deficiency

Testing Criteria

Biochemically established lysosomal acid lipase deficiency

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

Where in Pathway

At presentation

Requesting Specialties

- Chemical Pathology
- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R325.1	LIPA Single gene sequencing	Singleton	Small variants	Single gene(s)	LIPA (1354)	Single gene sequencing >=10 amplicons

R323 Sitosterolaemia

Testing Criteria

Elevated plasma beta-sitosterol with development of xanthomata before the age of 30

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

Where in Pathway

At presentation

Requesting Specialties

- Cardiology
- Chemical Pathology
- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R323.1	ABCG5; ABCG8	Singleton	Small variants	Small panel	ABCG5; ABCG8 (1391)	Small panel

R286 Tay-Sachs disease

Testing Criteria

Clinical and laboratory features characteristic of Tay-Sachs disease

Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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

Where in Pathway

At presentation following laboratory testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R286.1	HEXA Single gene sequencing	Singleton	Small variants	Single gene(s)	HEXA (1396)	Single gene sequencing >=10 amplicons

R272 Gaucher disease

Testing Criteria

Clinical features and glucocerebrosidase activity indicative of Gaucher disease types 1, 2, or 3, including the perinatal lethal and cardiovascular subtypes.

Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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

Where in Pathway

At presentation following enzyme testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology
- Cardiology

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R272.1	GBA Single gene sequencing	Singleton	Small variants	Single gene(s)	GBA (1336)	Single gene sequencing >=10 amplicons

R273 Glycogen storage disease V

Testing Criteria

Clinical and laboratory features characteristic of Glycogen storage disease type V including:

1. Elevated baseline serum CK, AND
2. Characteristic lactate/lactate:ammonia profile after exercise

Overlapping indications

- Broader R274 Glycogen storage disease panel test should be used where a broader differential diagnosis of glycogen storage diseases is under consideration
- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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

Where in Pathway

At presentation following laboratory testing

Requesting Specialties

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

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R273.1	PYGM Single gene sequencing	Singleton	Small variants	Single gene(s)	PYGM (1340)	Single gene sequencing >=10 amplicons

R274 Glycogen storage disease

Testing Criteria

Clinical and laboratory features characteristic of Glycogen storage disease:

1. Persistent hypoglycaemia with other metabolic disorders excluded, AND one or more of the following
   a. Persistent hepatomegaly in childhood, OR
   b. Liver biopsy suggestive of glycogen storage disease, OR
   c. Neuromuscular presentation suggestive of glycogen storage disease, OR
   d. Affected first degree relative

OR

2. Glycogen accumulation in the relevant tissue, AND one or more of the following:
   a. Evidence of liver involvement: hepatomegaly OR hypoglycaemia with other metabolic disorders excluded, OR
   b. Evidence of muscle involvement: myalgia OR rhabdomyolysis OR muscle weakness, OR
   c. Evidence of cardiac involvement: cardiomegaly OR cardiomyopathy, OR
   d. Other general evidence - at least two of: myopathy, cardiomyopathy, respiratory weakness, vacuolar myopathy on muscle biopsy, pathological pattern on oligosaccharides

Overlapping indications

- R273 Glycogen storage disease V test should be considered where clinical features are specific to Glycogen storage disease V (McArdle disease)
- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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

Where in Pathway

At presentation following laboratory testing

Requesting Specialties

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

Specialist Service Group

- Metabolic

Associated Tests

Please note all the tests below will be undertaken for R274 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
R274.1	Glycogen storage disease WES or medium panel	Singleton	Small variants	Panel of genes or loci	Glycogen storage disease (528)	WES or Medium Panel
R274.2	Glycogen storage disease	Singleton	Exon level CNVs	Panel of genes or loci	Glycogen storage disease (528)	Exon level CNV detection by MLPA or equivalent

R276 Lysosomal storage disorder

Testing Criteria

1. Clinical phenotype or radiological signs suggesting a lysosomal storage disorder, AND
2. Abnormal urine MPS or oligosaccharides screen or white cell enzymes analysis that are indicative of lysosomal storage disorder but do not allow more targeted testing

Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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

Where in Pathway

At presentation following laboratory testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Metabolic

Associated Tests

Please note all the tests below will be undertaken for R276 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
R276.1	Lysosomal storage disorder WES or medium panel	Singleton	Small variants	Panel of genes or loci	Lysosomal storage disorder (529)	WES or Medium Panel
R276.2	Lysosomal storage disorder	Singleton	Exon level CNVs	Panel of genes or loci	Lysosomal storage disorder (529)	Exon level CNV detection by MLPA or equivalent

R288 GM1 Gangliosidosis and Mucopolysaccharidosis Type IVB

Testing Criteria

Clinical and laboratory features characteristic of GM1 Gangliosidosis or Mucopolysaccharidosis Type IVB

Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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

Where in Pathway

At presentation following laboratory testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R288.1	GLB1 Single gene sequencing	Singleton	Small variants	Single gene(s)	GLB1 (1341)	Single gene sequencing >=10 amplicons

R277 Mucopolysaccharidosis type IH/S

Testing Criteria

Clinical and laboratory features characteristic of Mucopolysaccharidosis type IH/S (Hurler-Scheie syndrome)

Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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

Where in Pathway

At presentation following laboratory testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R277.1	IDUA Single gene sequencing	Singleton	Small variants	Single gene(s)	IDUA (1360)	Single gene sequencing >=10 amplicons

R280 Krabbe disease – GALC deficiency

Testing Criteria

Clinical and laboratory features characteristic of Krabbe disease due to GALC deficiency

Overlapping indications

- R281 Krabbe disease - Saposin A deficiency should be used in individuals with clinical and laboratory features characteristic of atypical Krabbe disease due to Saposin A deficiency
- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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

Where in Pathway

At presentation following laboratory testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Please note all the tests below will be undertaken for R280 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R280.1	GALC Single gene sequencing	Singleton	Small variants	Single gene(s)	GALC (1351)	Single gene sequencing >=10 amplicons
R280.2	GALC MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	GALC (1351)	MLPA or equivalent

R281 Krabbe disease - Saposin A deficiency

Testing Criteria

Clinical and laboratory features characteristic of atypical Krabbe disease due to Saposin A deficiency

Overlapping indications

- R280 Krabbe disease – GALC deficiency should be used in individuals with clinical and laboratory features characteristic of atypical Krabbe disease due to GALC deficiency
- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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

Where in Pathway

At presentation following laboratory testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R281.1	PSAP Single gene sequencing	Singleton	Small variants	Single gene(s)	PSAP (1352)	Single gene sequencing >=10 amplicons

R278 Mucopolysaccharidosis type II

Testing Criteria

Clinical and laboratory features characteristic of Mucopolysaccharidosis type II

Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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

Where in Pathway

At presentation following laboratory testing

Requesting Specialties

- Cleft clinics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Please note all the tests below will be undertaken for R278 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R278.1	IDS Single gene sequencing	Singleton	Small variants	Single gene(s)	IDS (1361)	Single gene sequencing >=10 amplicons
R278.2	IDS Targeted variant testing	Singleton	Small variants	Single gene(s)	IDS (1361)	Targeted variant testing

R287 Mucopolysaccharidosis type IVA

Testing Criteria

Clinical and laboratory features characteristic of Mucopolysaccharidosis type IVA

Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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

Where in Pathway

At presentation following laboratory testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R287.1	GALNS Single gene sequencing	Singleton	Small variants	Single gene(s)	GALNS (1364)	Single gene sequencing >=10 amplicons

R289 Mucolipidosis II and III Alpha/Beta

Testing Criteria

Clinical and laboratory features characteristic of Mucolipidosis II or Mucolipidosis III Alpha/Beta

Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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

Where in Pathway

At presentation following laboratory testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R289.1	GNPTAB Single gene sequencing	Singleton	Small variants	Single gene(s)	GNPTAB (1359)	Single gene sequencing >=10 amplicons

R290 Mucopolysaccharidosis type VI

Testing Criteria

Clinical and laboratory features characteristic of Mucopolysaccharidosis type VI

Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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

Where in Pathway

At presentation following laboratory testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R290.1	ARSB Single gene sequencing	Singleton	Small variants	Single gene(s)	ARSB (1365)	Single gene sequencing >=10 amplicons

R291 Mucopolysaccharidosis type IIIA

Testing Criteria

Clinical and laboratory features characteristic of Mucopolysaccharidosis type IIIA

Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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

Where in Pathway

At presentation following laboratory testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R291.1	SGSH Single gene sequencing	Singleton	Small variants	Single gene(s)	SGSH (1362)	Single gene sequencing >=10 amplicons

R292 Mucopolysaccharidosis type IIIB

Testing Criteria

Clinical and laboratory features characteristic of Mucopolysaccharidosis type IIIB

Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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

Where in Pathway

At presentation following laboratory testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R292.1	NAGLU Single gene sequencing	Singleton	Small variants	Single gene(s)	NAGLU (1363)	Single gene sequencing >=10 amplicons

R282 Niemann-Pick disease type A or B

Testing Criteria

Clinical and laboratory features characteristic of Niemann-Pick disease type A or B

Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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

Where in Pathway

At presentation following laboratory testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R282.1	SMPD1 Single gene sequencing	Singleton	Small variants	Single gene(s)	SMPD1 (1375)	Single gene sequencing >=10 amplicons

R285 Sandhoff disease

Testing Criteria

Clinical and laboratory features characteristic of Sandhoff disease

Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

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

Where in Pathway

At presentation following laboratory testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R285.1	HEXB Single gene sequencing	Singleton	Small variants	Single gene(s)	HEXB (1385)	Single gene sequencing >=10 amplicons

R283 Phenylketonuria

Testing Criteria

1. Likely phenylketonuria identified following diagnostic metabolic testing **OR**
2. Testing patients diagnosed with PKU to indicate sapropterin responsiveness

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

Where in Pathway

Following neonatal screening or diagnostic metabolic testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

Specialist Service Group

- Metabolic

Associated Tests

Please note all the tests below will be undertaken for R283 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
R283.1	PAH Single gene sequencing	Singleton	Small variants	Single gene(s)	PAH (1378)	Single gene sequencing >=10 amplicons
R283.2	PAH MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	PAH (1378)	MLPA or equivalent

R279 Isovaleric acidaemia

Testing Criteria

Likely isovaleric acidaemia identified following neonatal screening or diagnostic metabolic testing

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family. In the case of isovaleric acidaemia, this means that testing is almost exclusively used at those in whom biochemical results indicate a likely pseudodeficiency allele is present.

Testing following newborn screening should follow the established sample and testing pathways set out in the newborn screening protocol

Where in Pathway

Following neonatal screening or diagnostic metabolic testing

Requesting Specialties

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

Specialist Service Group

- Screening

Associated Tests

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

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

Testing Criteria

Likely MCADD identified following neonatal screening or diagnostic metabolic testing requiring testing of the common ACADM c.985G>A variant

Testing following newborn screening should follow the established sample and testing pathways set out in the newborn screening protocol

Where in Pathway

Following neonatal screening or diagnostic metabolic testing

Requesting Specialties

- Clinical Genetics
- Neonatology
- Obstetrics
- Paediatrics

Specialist Service Group

- Screening

Associated Tests

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

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

Testing Criteria

Likely MCADD identified following neonatal screening or diagnostic metabolic testing requiring testing of the full ACADM gene

Overlapping indications:

- R105 MCADD - Medium-chain acyl-CoA dehydrogenase deficiency – common variant test should be used in the first instance except where the testing laboratory specifically guides otherwise

Testing following newborn screening should follow the established sample and testing pathways set out in the newborn screening protocol

Where in Pathway

N/A

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neonatology
- Paediatrics

Specialist Service Group

- Screening

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R403.1	MCADD Single gene sequencing	Singleton	Small variants	Other	ACADM (1355)	Single gene sequencing <10 amplicons

R275 Glutaric acidaemia I

Testing Criteria

Likely glutaric acidaemia type 1 identified following neonatal screening or diagnostic metabolic testing

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

Testing following newborn screening should follow the established sample and testing pathways set out in the newborn screening protocol

Where in Pathway

Following neonatal screening or diagnostic metabolic testing

Requesting Specialties

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

Specialist Service Group

- Screening

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R275.1	GCDH Single gene sequencing	Singleton	Small variants	Single gene(s)	GCDH (1339)	Single gene sequencing >=10 amplicons

Part XIV. Mitochondrial

R64 MELAS or MIDD

Testing Criteria

Adult onset sensorineural hearing loss and diabetes or family history suggestive of a diagnosis of maternally inherited diabetes and deafness

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Endocrinology
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R64.1	MTTL1 3243A>G Targeted variant testing	Singleton	Small variants	Single interval	MTTL1 3243A>G	Targeted variant testing

R299 Possible mitochondrial disorder - mitochondrial DNA rearrangement testing

Testing Criteria

Possible mitochondrial disorder caused by mitochondrial DNA rearrangements including individuals with clinical features suggestive of CPEO, Kearns-Sayre syndrome or Pearson syndrome

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

Affected tissue, such as muscle, preferred

Where in Pathway

At presentation following assessment by a Consultant in Metabolic Medicine, Neurology, Paediatric Neurology, Clinical Genetics or Haematology

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R299.1	Possible Mitochondrial disorder - Mitochondrial DNA rearrangement testing	Singleton	CNVs	Single interval	Mitochondrial genome	Other
R299.2	Possible mitochondrial disorder - mitochondrial DNA rearrangement testing	Singleton	CNVs and structural variants	Single interval	Heteroplasmy assessment - mitochondrial genome	Other
R299.3	Possible mitochondrial disorder - mitochondrial DNA rearrangement testing	Singleton	CNVs and structural variants	Single interval	Breakpoint mapping - mitochondrial genome	Other

R300 Possible mitochondrial disorder - whole mitochondrial genome sequencing

Testing Criteria

Clinical features strongly suggestive of a mitochondrial disorder and/or biochemical evidence of a mitochondrial DNA disorder

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

Where in Pathway

At presentation following assessment by a Consultant in Metabolic Medicine, Neurology, Paediatric Neurology or Clinical Genetics, or following biochemical studies

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R300.1	Mitochondrial genome Whole mitochondrial genome sequencing	Singleton	Small variants	Single interval	Mitochondrial genome	Other

R301 Possible mitochondrial disorder - mitochondrial DNA depletion testing

Testing Criteria

Clinical features suggestive of a mitochondrial DNA depletion syndrome

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

Muscle or liver tissue required

Where in Pathway

Following findings on biopsy sample

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R301.1	Mitochondrial genome Mitochondrial DNA depletion testing	Singleton	Complex variants	Single interval	Mitochondrial genome	Other

R315 POLG-related disorder

Testing Criteria

Clinical features suggestive of a POLG-related disorder (including status epilepticus and other severe intractable epilepsy with other suggestive features)

Overlapping indications

- R59 Early onset or syndromic epilepsy, R29 Intellectual disability or other relevant broader tests should be used instead where clinical features are not strongly suggestive of POLG-related disorder and a broader differential diagnosis is under consideration

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

Where in Pathway

At presentation following assessment by a Consultant in Metabolic Medicine, Neurology, Paediatric Neurology or Clinical Genetics, or following evidence of mtDNA depletion or multiple mtDNA deletions

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Please note all the tests below will be undertaken for R315 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R315.1	Common POLG mutations Targeted variant testing	Singleton	Small variants	Single interval	Common POLG mutations	Targeted variant testing
R315.2	POLG Single gene sequencing	Singleton	Small variants	Single gene(s)	POLG (1379)	Single gene sequencing >=10 amplicons

R316 Pyruvate dehydrogenase (PDH) deficiency

Testing Criteria

Clinical features and laboratory features strongly suggestive of pyruvate dehydrogenase deficiency

Overlapping indications

- R63 Possible mitochondrial disorder - nuclear genes test should be considered where a broader range of mitochondrial nuclear genes are potentially causative

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

Where in Pathway

At presentation following assessment by a Consultant in Metabolic Medicine, Neurology, Paediatric Neurology or Clinical Genetics, or following skin biopsy and biochemical PDH assay in fibroblasts

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Please note all the tests below will be undertaken for R316 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
R316.1	Pyruvate dehydrogenase PDH deficiency WES or Medium panel	Singleton	Small variants	Panel of genes or loci	Pyruvate dehydrogenase (PDH) deficiency (531)	WES or Medium panel
R316.2	Pyruvate dehydrogenase PDH deficiency	Singleton	Exon level CNVs	Panel of genes or loci	Pyruvate dehydrogenase (PDH) deficiency (531)	Exon level CNV detection by MLPA or equivalent

R317 Mitochondrial liver disease, including transient infantile liver failure

Testing Criteria

Infants (aged <2 years) with acute liver failure of unknown aetiology, or individuals with liver dysfunction suspected to be related to mitochondrial dysfunction

Where in Pathway

At presentation following assessment by a Consultant in Hepatology or Paediatric Hepatology, or following liver/muscle biopsy with evidence of respiratory chain deficiency and/or mtDNA depletion

Requesting Specialties

- Clinical Genetics
- Hepatology
- Metabolic Medicine

Specialist Service Group

- Mitochondrial

Associated Tests

Please note all the tests below will be undertaken for R317 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
R317.1	Mitochondrial liver disease Small panel	Singleton	Small variants	Panel of genes or loci	Mitochondrial liver disease (532)	Small panel
R317.2	Mitochondrial liver disease	Singleton	Exon level CNVs	Panel of genes or loci	Mitochondrial liver disease (532)	Exon level CNV detection by MLPA or equivalent

R350 MERRF syndrome

Testing Criteria

Clinical features suggestive of MERRF syndrome

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

Where in Pathway

At presentation following assessment by a Consultant in Metabolic Medicine, Neurology, Paediatric Neurology or Clinical Genetics

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R350.1	Common MERRF mutations Targeted variant testing	Singleton	Small variants	Single interval	Common MERRF mutations	Targeted variant testing

R351 NARP syndrome or maternally inherited Leigh syndrome

Testing Criteria

Clinical features suggestive of NARP syndrome (neuropathy, ataxia and retinitis pigmentosa) or MILS (maternally inherited Leigh syndrome)

Where in Pathway

At presentation following assessment by a Consultant in Metabolic Medicine, Neurology, Paediatric Neurology or Clinical Genetics

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology
- Ophthalmology

Specialist Service Group

- Mitochondrial

Associated Tests

Please note all the tests below will be undertaken for R351 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R351.1	MT-ATP6; MT-ND6	Singleton	Small variants	Small panel	MT-ATP6; MT-ND6 (1368)	Small panel
R351.2	m.8993T>C/G Targeted variant testing	Singleton	Small variants	Single interval	m.8993T>C/G	Targeted variant testing

R352 Mitochondrial DNA maintenance disorder

Testing Criteria

Clinical features suggestive of mtDNA maintenance disorder and/or evidence of mtDNA depletion or multiple mtDNA deletions

Overlapping indications

- R63 Possible mitochondrial disorder - nuclear genes test should be considered where a broader range of mitochondrial nuclear genes are potentially causative

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

Where in Pathway

At presentation following assessment by a Consultant in Metabolic Medicine, Neurology, Paediatric Neurology or Clinical Genetics, or following evidence of mtDNA depletion or multiple mtDNA deletions

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Please note all the tests below will be undertaken for R352 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
R352.1	Mitochondrial DNA maintenance disorder WES or medium panel	Singleton	Small variants	Panel of genes or loci	Mitochondrial DNA maintenance disorder (533)	WES or Medium Panel
R352.2	Mitochondrial DNA maintenance disorder	Singleton	Exon level CNVs	Panel of genes or loci	Mitochondrial DNA maintenance disorder (533)	Exon level CNV detection by MLPA or equivalent

R353 Mitochondrial disorder with complex I deficiency

Testing Criteria

Clinical features and laboratory features strongly suggestive of mitochondrial complex I deficiency

Overlapping indications

- R63 Possible mitochondrial disorder - nuclear genes test should be considered where a broader range of mitochondrial nuclear genes are potentially causative

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

Where in Pathway

Following laboratory or clinical assessment by a mitochondrial highly specialised service

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Please note all the tests below will be undertaken for R353 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
R353.1	Mitochondrial disorder with complex I deficiency WES or medium panel	Singleton	Small variants	Panel of genes or loci	Mitochondrial disorder with complex I deficiency (534)	WES or Medium Panel
R353.2	Mitochondrial disorder with complex I deficiency	Singleton	Exon level CNVs	Panel of genes or loci	Mitochondrial disorder with complex I deficiency (534)	Exon level CNV detection by MLPA or equivalent

R354 Mitochondrial disorder with complex II deficiency

Testing Criteria

Clinical features and laboratory features strongly suggestive of mitochondrial complex II deficiency

Overlapping indications

- R63 Possible mitochondrial disorder - nuclear genes test should be considered where a broader range of mitochondrial nuclear genes are potentially causative

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

Where in Pathway

Following laboratory or clinical assessment by a mitochondrial highly specialised service

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Please note all the tests below will be undertaken for R354 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
R354.1	Mitochondrial disorder with complex II deficiency WES or small panel	Singleton	Small variants	Panel of genes or loci	Mitochondrial disorder with complex II deficiency (535)	WES or Small Panel
R354.2	Mitochondrial disorder with complex II deficiency	Singleton	Exon level CNVs	Panel of genes or loci	Mitochondrial disorder with complex II deficiency (535)	Exon level CNV detection by MLPA or equivalent

R355 Mitochondrial disorder with complex III deficiency

Testing Criteria

Clinical features and laboratory features strongly suggestive of mitochondrial complex III deficiency

Overlapping indications

- R63 Possible mitochondrial disorder - nuclear genes test should be considered where a broader range of mitochondrial nuclear genes are potentially causative

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

Where in Pathway

Following laboratory or clinical assessment by a mitochondrial highly specialised service

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Please note all the tests below will be undertaken for R355 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
R355.1	Mitochondrial disorder with complex III deficiency WES or small panel	Singleton	Small variants	Panel of genes or loci	Mitochondrial disorder with complex III deficiency (536)	WES or Small Panel
R355.2	Mitochondrial disorder with complex III deficiency	Singleton	Exon level CNVs	Panel of genes or loci	Mitochondrial disorder with complex III deficiency (536)	Exon level CNV detection by MLPA or equivalent

R356 Mitochondrial disorder with complex IV deficiency

Testing Criteria

Clinical features and laboratory features strongly suggestive of mitochondrial complex IV deficiency

Overlapping indications

- R63 Possible mitochondrial disorder - nuclear genes test should be considered where a broader range of mitochondrial nuclear genes are potentially causative

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

Where in Pathway

Following laboratory or clinical assessment by a mitochondrial highly specialised service

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Please note all the tests below will be undertaken for R356 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
R356.1	Mitochondrial disorder with complex IV deficiency WES or small panel	Singleton	Small variants	Panel of genes or loci	Mitochondrial disorder with complex IV deficiency (537)	WES or Small Panel
R356.2	Mitochondrial disorder with complex IV deficiency	Singleton	Exon level CNVs	Panel of genes or loci	Mitochondrial disorder with complex IV deficiency (537)	Exon level CNV detection by MLPA or equivalent

R357 Mitochondrial disorder with complex V deficiency

Testing Criteria

Clinical features and laboratory features strongly suggestive of mitochondrial complex V deficiency

Overlapping indications

- R63 Possible mitochondrial disorder - nuclear genes test should be considered where a broader range of mitochondrial nuclear genes are potentially causative

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

Where in Pathway

Following laboratory or clinical assessment by a mitochondrial highly specialised service

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Please note all the tests below will be undertaken for R357 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
R357.1	Mitochondrial disorder with complex V deficiency WES or small panel	Singleton	Small variants	Panel of genes or loci	Mitochondrial disorder with complex V deficiency (538)	WES or Small Panel
R357.2	Mitochondrial disorder with complex V deficiency	Singleton	Exon level CNVs	Panel of genes or loci	Mitochondrial disorder with complex V deficiency (538)	Exon level CNV detection by MLPA or equivalent

R63 Possible mitochondrial disorder - nuclear genes

Testing Criteria

Individuals with clinical features suggestive of a mitochondrial disorder requiring examination of nuclear genes where more targeted testing is not possible.

Overlapping indications

- Examination of the mitochondrial genome using one or more of the following indications should be considered first where possible based on clinical or biochemical/enzyme results:
  a. R42 Leber hereditary optic neuropathy
  b. R64 Maternally inherited diabetes and deafness
  c. R349 MELAS syndrome
  d. R350 MERRF syndrome
  e. R351 NARP syndrome or maternally inherited Leigh syndrome
  f. R317 Mitochondrial liver disease, including transient infantile liver failure
  g. R299 Possible mitochondrial disorder - mitochondrial DNA rearrangement testing
  h. R300 Possible mitochondrial disorder - whole mitochondrial genome sequencing
  i. R301 Possible mitochondrial disorder - mitochondrial DNA depletion testing
- Targeted examination of nuclear genes should be considered first where possible based on clinical or biochemical/enzyme results:
  j. R315 POLG-related disorder
  k. R352 Mitochondrial DNA maintenance disorder
  l. R353 Mitochondrial disorder with complex I deficiency
  m. R354 Mitochondrial disorder with complex II deficiency
  n. R355 Mitochondrial disorder with complex III deficiency
  o. R356 Mitochondrial disorder with complex IV deficiency
  p. R356 Mitochondrial disorder with complex V deficiency
  q. R316 Pyruvate dehydrogenase (PDH) deficiency

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

Where in Pathway

Following assessment by a Consultant in Metabolic Medicine, Neurology, Paediatric Neurology or Clinical Genetics

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Please note all the tests below will be undertaken for R63 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
R63.1	Possible mitochondrial disorder - nuclear genes WES or large panel	Singleton	Small variants	Panel of genes or loci	Possible mitochondrial disorder - nuclear genes (539)	WES or Large Panel

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R63.2	Possible mitochondrial disorder - nuclear genes	Singleton	Exon level CNVs	Panel of genes or loci	Possible mitochondrial disorder - nuclear genes (539)	Exon level CNV detection by MLPA or equivalent

R394 Mitochondrial neurogastrointestinal encephalopathy

Testing Criteria

Clinical features suggestive of mitochondrial neurogastrointestinal encephalopathy (MNGIE) with elevated thymidine and deoxyuridine levels in blood and/or urine

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

Where in Pathway

Following laboratory or clinical assessment by a mitochondrial highly specialised service

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R394.1	TYMP Single gene sequencing	Singleton	Small variants	Single gene(s)	TYMP (1357)	Single gene sequencing >=10 amplicons

R395 Thiamine metabolism dysfunction syndrome 2

Testing Criteria

Clinical features and characteristic brain MRI changes suggestive of thiamine metabolism dysfunction syndrome 2 (also known as Biotin-responsive basal ganglia disease / thiamine responsive encephalopathy)

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

Where in Pathway

Following laboratory or clinical assessment by a mitochondrial highly specialised service

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R395.1	SLC19A3 Single gene sequencing	Singleton	Small variants	Single gene(s)	SLC19A3 (1399)	Single gene sequencing <10 amplicons

R396 Mitochondrial Complex V deficiency, TMEM70 type

Testing Criteria

Infantile/paediatric onset hypertrophic cardiomyopathy, raised lactate and raised 3-methylglutaconic acid

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

Where in Pathway

Following laboratory or clinical assessment by a mitochondrial highly specialised service

Requesting Specialties

- Cardiology
- Clinical Genetics
- Neurology

Specialist Service Group

- Mitochondrial

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R396.1	TMEM70 Single gene sequencing	Singleton	Small variants	Single gene(s)	TMEM70 (1356)	Single gene sequencing <10 amplicons

R397 Maternally inherited cardiomyopathy

Testing Criteria

Maternally inherited hypertrophic cardiomyopathy

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

Where in Pathway

Following laboratory or clinical assessment by a mitochondrial highly specialised service

Requesting Specialties

- Cardiology
- Clinical Genetics

Specialist Service Group

- Mitochondrial

Associated Tests

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

R42 Leber hereditary optic neuropathy

Testing Criteria

Likely or possible clinical diagnosis of Leber hereditary optic neuropathy

Where in Pathway

At presentation following assessment by a Consultant Ophthalmologist, Neurologist or Clinical Geneticist

Requesting Specialties

- Clinical Genetics
- Neurology
- Ophthalmology

Specialist Service Group

- Mitochondrial

Associated Tests

Please note all the tests below will be undertaken for R42 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R42.1	Three common LHON variants Targeted variant testing	Singleton	Small variants	Single interval	Three common LHON variants	Targeted variant testing
R42.2	Mitochondrial genome Whole mitochondrial genome sequencing	Singleton	Small variants	Mitochondrial Genome	Mitochondrial Genome	Mitochondrial Genome

Part XV. Mosaic and structural chromosomal disorders

R297 Possible structural chromosomal rearrangement - karyotype

Testing Criteria

Possible structural chromosomal rearrangement requiring karyotype **including one of the following**:

1. Possible Robertsonian translocation, reciprocal translocation, ring chromosome or other microscopically visible structural rearrangement indicated by findings from microarray, WGS or other laboratory technique.
2. Recurrent miscarriage (defined as three or more miscarriages) in whom testing of products of conception has not been possible. Note: this should not be performed routinely nor retrospectively where products of conception have not been provided, but may be used in exceptional circumstances, detailed below;

- Where an attempt to provide pregnancy loss samples has been unsuccessful;
  - o unsuitable sample (eg. no fetal material/MCC)
  - o failed sample (eg. fixed in formalin)
- Where the intention has been to collect the next pregnancy loss but this has not been possible due to the nature of the loss
- Five or more biochemical pregnancy losses.

3. A family history suggestive of familial balanced translocation.
4. Unexplained infertility who are going to undergo infertility treatment.
5. Patient with ambiguous genitalia potentially caused by a sex chromosome rearrangement not detectable via other tests.
6. Egg/sperm donors prior to acceptance.

Where in Pathway

As appropriate or where IVF centres with HFEA license are performing treatment with egg or sperm donation.

Requesting Specialties

- Clinical Genetics
- Genomics laboratory
- Fetal Medicine

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R297.1	Genomewide Karyotype	Singleton	copy number variant detection to genomewide resolution and structural variants	Genomewide	As determined by indication	Karyotype

R298 Possible structural or mosaic chromosomal abnormality - FISH

Testing Criteria

Possible structural or mosaic chromosomal abnormality requiring FISH

Testing for Y chromosome microdeletions should not routinely be performed before ICSI
https://www.nice.org.uk/guidance/cg156/chapter/Recommendations

Overlapping indications

- R26 Likely common aneuploidy, test should be used for common aneuploidy testing, which may be delivered by FISH
- R297 Possible structural chromosomal rearrangement – karyotype, is available where karyotype alone is required
- R265 Chromosomal mosaicism – karyotype, is available where extended karyotype is required
- R411 Y chromosome microdeletions is available where surgical sperm retrieval is considered

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

Where in Pathway

Following discussion with laboratory

Requesting Specialties

- Clinical Genetics
- Genomics laboratory

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R298.1	Specific target FISH	Singleton	Balanced rearrangements	Single interval	As determined by indication	FISH

R265 Chromosomal mosaicism - karyotype

Testing Criteria

Individuals with possible mosaic chromosome abnormality requiring extended count karyotype including:

1. possible mosaic chromosome abnormality indicated by findings from conventional karyotype, microarray, WGS or other laboratory technique, OR
2. clinical features strongly suggestive of a specific chromosomal phenotype, for example Down syndrome, in whom conventional testing is negative

Overlapping indications

- R343 Chromosomal mosaicism - microarray should be used where a microarray is indicated

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

Where in Pathway

N/A

Requesting Specialties

- Clinical Genetics
- Dermatology
- Genomics laboratory

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R265.1	Genomewide Karyotype - mosaicism	Singleton	Aneuploidy	Genomewide	Genomewide	Karyotype

R343 Chromosomal mosaicism - microarray

Testing Criteria

Hyper- or hypo- pigmentation following Blaschkos lines (Hypomelanosis of Ito), with associated abnormalities such as neurodevelopmental delay, seizures or asymmetry

Overlapping indications

- R327 Mosaic skin disorders – deep sequencing test should be used where the mosaicism is likely to be caused by a single gene

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

NOTE: Sample submitted for this test can be either a skin biopsy or a blood sample

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Dermatology

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R343.1	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray

R411 Y Chromosome microdeletions

Testing Criteria

Patients with non-obstructive azoospermia or severe oligospermia where testicular sperm extraction (TESE)/microdissection TESE (mTESE) is considered and outcome of testing will inform eligibility for (m)TESE and success of sperm retrieval (https://www.england.nhs.uk/wp-content/uploads/2018/07/Surgical-sperm-retrieval-for-male-infertility.pdf)

Testing for Y chromosome microdeletions should not routinely be performed before ICSI (https://www.nice.org.uk/guidance/cg156/chapter/Recommendations)

Testing for this clinical indication is performed by designated GLHs on behalf of the national genomic testing network

Overlapping indications

- R298 - Possible structural or mosaic chromosomal abnormality requiring FISH

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

Where in Pathway

Following review by a urologist with an interest in infertility or specialist fertility MDT

Requesting Specialties

- Clinical Genetics
- Urology

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R411.1	Y chromosome microdeletions	Singleton	CNVs to exon level	Single interval	Y chromosome AZF regions	Targeted variant testing or equivalent

Part XVI. Musculoskeletal

R52 Short stature - SHOX deficiency

Testing Criteria

Disproportionate short stature with features in the patient or relatives suggestive of SHOX deficiency, e.g. Madelung deformity,

Overlapping indications

- R147 Growth failure in early childhood to be used for more significant/earlier onset short stature, including where Silver-Russell syndrome is the likely diagnosis
- R382 Hypochondroplasia and R24 Achondroplasia
- R104 Skeletal dysplasia to be used where clinical features indicative of a likely monogenic skeletal dysplasia

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Endocrinology
- Paediatrics

Specialist Service Group

- Musculoskeletal

Associated Tests

Please note all the tests below will be undertaken for R52 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R52.1	SHOX MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	SHOX (1390)	MLPA or equivalent
R52.2	SHOX Single gene sequencing	Singleton	Small variants	Single gene(s)	SHOX (1390)	Single gene sequencing <10 amplicons

R24 Achondroplasia

Testing Criteria

Clinical features strongly suggestive of achondroplasia

Overlapping clinical indications:

- R309 NIPD for FGFR3-related skeletal dysplasias - mutation testing
- R104 Skeletal dysplasia test should be used where features are atypical and a broader range of genes are likely to be causative
- R382 Hypochondroplasia testing may also be indicated if clinically relevant

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Neonatology
- Paediatrics

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R24.1	FGFR3 c.1138 Targeted variant testing	Singleton	Small variants	Single interval	FGFR3 c.1138	Targeted variant testing

R382 Hypochondroplasia

Testing Criteria

Clinical features strongly suggestive of hypochondroplasia

Overlapping clinical indications:

- R309 NIPD for FGFR3-related skeletal dysplasias - mutation testing
- R24 Achondroplasia testing may also be indicated if clinically relevant
- R52 Short stature – SHOX deficiency
- R104 Skeletal dysplasia test should be used where features are atypical and a broader range of genes are likely to be causative

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Endocrinology

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R382.1	FGFR3 c.1620 Targeted variant testing	Singleton	Small variants	Single interval	FGFR3 c.1620	Targeted variant testing

R25 Thanatophoric dysplasia

Testing Criteria

Clinical features strongly suggestive of thanatophoric dysplasia.

Overlapping clinical indications:

- R309 NIPD for FGFR3-related skeletal dysplasias - mutation testing
- R104 Skeletal dysplasia test should be used where features are atypical and a broader range of genes are likely to be causative

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Fetal Medicine

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R25.1	FGFR3 Single gene sequencing	Singleton	Small variants	Single gene(s)	FGFR3 (1398)	Single gene sequencing >=10 amplicons

R104 Skeletal dysplasia

Testing Criteria

Clinical features indicative of a likely monogenic skeletal dysplasia

Patients with suspected severe congenital autosomal recessive malignant osteopetrosis where rapid genetic diagnosis is required for urgent patient management (e.g. curative stem cell transplantation) are eligible for urgent testing via R104.4

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

Overlapping indications

R147 Growth failure in early childhood**,** should be considered if overlapping features are present

Where in Pathway

Following review of clinical features and x-rays by a Clinical Geneticist or Radiologist expert in skeletal dysplasias

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Musculoskeletal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R104.3	Skeletal dysplasia WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants	Panel of genes or loci	Skeletal dysplasia (309)	WGS
R104.4	Osteopetrosis WES or large panel (urgent testing only)	Singleton	Small variants	Panel of genes or loci	Osteopetrosis (943)	WES or large panel

R415 Cleidocranial Dysplasia (CCD)

Testing Criteria

Radiographic and/or clinical features of CCD

CCD features include:

- Large anterior fontanelle
- hypoplastic clavicles
- macrocephaly
- dental features (permanent primary dentition, supernumerary teeth)

Overlapping indications

- R104 Skeletal dysplasia

Where in Pathway

At presentation. Testing is indicated following clinical and radiographic diagnosis and following discussion with a consultant in clinical genetics or paediatric endocrinology or another specialist approved by the GLH.

Requesting Specialties

- Clinical Genetics
- Paediatrics
- Neonatology
- Endocrinology

Specialist Service Group

- Musculoskeletal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R415.1	Cleidocranial Dysplasia	Singleton	small variant detection	Single gene (s)	RUNX2 (1315)	Single gene sequencing < 10 amplicons
R415.2	Cleidocranial Dysplasia	Singleton	Exon level CNVs	Single gene (s)	RUNX2 (1315)	Exon level CNV detection by MLPA or equivalent

R99 Common craniosynostosis syndromes

Testing Criteria

Recognisable multisuture craniosynostosis syndromes consistent with mutations in EFNB1, ERF, FGFR1 common hot spots, FGFR2 common hot spots, FGFR3 common hot spots, TCF12 or TWIST1 or with unicoronal or bicoronal craniosynostosis

Overlapping indications

- R100 Rare syndromic craniosynostosis or isolated multisuture synostosis test should be used where features are not consistent with mutations in EFNB1, ERF, FGFR1 common hot spots, FGFR2 common hot spots, FGFR3 common hot spots, TCF12 or TWIST1

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Musculoskeletal

Associated Tests

Please note all the tests below will be undertaken for R99 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R99.1	Common craniosynostosis syndromes Small panel	Singleton	Small variants	Panel of genes or loci	Common craniosynostosis syndromes (507)	Small panel
R99.2	Common craniosynostosis syndromes MLPA or equivalent	Singleton	Exon level CNVs	Panel of genes or loci	Common craniosynostosis syndromes (507)	Exon level CNV detection by MLPA or equivalent

R100 Rare syndromic craniosynostosis or isolated multisuture synostosis

Testing Criteria

Rare syndromic craniosynostosis syndrome or isolated multisuture synostosis, confirmed by skull scan where possible

Mutations in EFNB1, ERF, FGFR1 common hot spots, FGFR2 common hot spots, FGFR3 common hot spots, TCF12 or TWIST1 must have been excluded on targeted genetic testing (R99 Common craniosynostosis syndromes)

Overlapping indications

- R99 Common craniosynostosis syndromes should be used where features are consistent with mutations in EFNB1, ERF, FGFR1 common hot spots, FGFR2 common hot spots, FGFR3 common hot spots, TCF12 or TWIST1

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

NOTE: If the SMO gene is suspected as causative, a tissue sample will be required for testing

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Musculoskeletal

Associated Tests

Please note all the tests below will be undertaken for R100 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
R100.2	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray
R100.3	Craniosynostosis WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants	Panel of genes or loci	Craniosynostosis (168)	WGS

R416 Syndromic & non-syndromic craniosynostosis involving midline sutures

Testing Criteria

1. Patients presenting with confirmed craniosynostosis involving/including the metopic suture (trigonocephaly), OR

2. Sagittal suture, OR

3. both sagittal and metopic sutures.

Overlapping indications

- R100 Rare syndromic craniosynostosis or isolated multisuture synostosis

Where in Pathway

At presentation and following discussion with a consultant in clinical genetics or craniofacial neurosurgeon or another specialist approved by the GLH.

Requesting Specialties

- Clinical Genetics
- Neurosurgery

Specialist Service Group

- Musculoskeletal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R416.1	Syndromic & non-syndromic craniosynostosis involving midline sutures	Singleton	Small variant detection	Single gene(s)	SMAD6 (1395)	Single gene sequencing < 10 amplicons

R340 Amelogenesis imperfecta

Testing Criteria

1. Significant developmental abnormalities of enamel quality and/or quantity affecting all or nearly all teeth of both dentitions (primary and secondary), AND
2. Environmental factors excluded

NOTE: Enamel abnormalities affecting unerupted permanent teeth can be detected on dental radiographs meaning that information about both dentitions is available well before eruption of the first permanent tooth

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

Where in Pathway

Following review by dentist expert in developmental dental disorders

Requesting Specialties

- Clinical Genetics
- Surgical Dentistry

Specialist Service Group

- Musculoskeletal

Associated Tests

Please note all the tests below will be undertaken for R340 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
R340.1	Amelogenesis imperfecta WES or Medium panel	Singleton	Small variants	Panel of genes or loci	Amelogenesis imperfecta (269)	WES or Medium panel
R340.2	Amelogenesis imperfecta	Singleton	Exon level CNVs	Panel of genes or loci	Amelogenesis imperfecta (269)	Exon level CNV detection by MLPA or equivalent

R23 Apert syndrome

Testing Criteria

Clinical features strongly suggestive of Apert syndrome, including both craniosynostosis and syndactyly of the hands and feet, with or without additional features

Overlapping indications

- R306 NIPD for Apert syndrome - mutation testing
- R99 Common craniosynostosis syndromes or R100 Rare syndromic craniosynostosis or isolated multisuture synostosis should be used where features are atypical and a broader range of genes are likely to be causative

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Musculoskeletal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R23.1	FGFR2 c.755 and c.758 Targeted variant testing	Singleton	Small variants	Single interval	FGFR2 c.755 and c.758	Targeted variant testing

R101 Ehlers Danlos syndrome with a likely monogenic cause

Testing Criteria

Clinical features indicative of a likely monogenic Ehlers Danlos syndrome:

- Classical EDS (cEDS)
- Classical-like EDS (clEDS)
- Cardiac-valvular EDS (cvEDS)
- Vascular EDS (vEDS)
- Arthrochalasia EDS (aEDS)
- Dermatosparaxis EDS (dEDS)
- Kyphoscoliotic EDS (kEDS)
- Brittle Cornea Syndrome (BCS)
- Spondylodysplastic EDS (spEDS)
- Musculocontractural EDS (mcEDS)
- Myopathic EDS (mEDS)
- Periodontal EDS (pEDS)

Testing should only be used where it will impact on clinical management

Overlapping indications

- R89 Ultra-rare and atypical monogenic disorders or R27 Paediatric disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations not typical of disorders covered by the panel

Where in Pathway

Following assessment by a Clinical Geneticist or other expert in a highly specialised Ehlers Danlos service

Requesting Specialties

- Clinical Genetics
- Rheumatology

Specialist Service Group

- Musculoskeletal

Associated Tests

Please note all the tests below will be undertaken for R101 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
R101.1	Ehlers Danlos syndromes WES or medium panel	Singleton	Small variants	Panel of genes or loci	Ehlers Danlos syndromes (53)	WES or Medium Panel
R101.2	Ehlers Danlos syndromes	Singleton	Exon level CNVs	Panel of genes or loci	Ehlers Danlos syndromes (53)	Exon level CNV detection by MLPA or equivalent

R102 Osteogenesis imperfecta

Testing Criteria

Clinical features indicative of a likely monogenic bone fragility disorder / rare and atypical forms of osteogenesis imperfecta

In adults, testing is only routinely recommended where it will impact on reproductive choices

Testing should only be used where it will impact on clinical management

Overlapping indications

- R89 Ultra-rare and atypical monogenic disorders or R27 Paediatric disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations not typical of disorders covered by the panel

Where in Pathway

Following assessment by a Clinical Geneticist or other expert in highly specialised osteogenesis imperfecta service

Requesting Specialties

- Clinical Genetics
- Endocrinology
- Rheumatology
- Metabolic medicine

Specialist Service Group

- Musculoskeletal

Associated Tests

Please note all the tests below will be undertaken for R102 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
R102.1	Osteogenesis imperfecta WES or medium panel	Singleton	Small variants	Panel of genes or loci	Osteogenesis imperfecta (196)	WES or Medium Panel
R102.2	Osteogenesis imperfecta	Singleton	Exon level CNVs	Panel of genes or loci	Osteogenesis imperfecta (196)	Exon level CNV detection by MLPA or equivalent

R390 Multiple exostoses

Testing Criteria

Individuals with multiple exostoses (osteochondromas) where a monogenic cause is likely and a molecular diagnosis will contribute to management or advice

Where in Pathway

At presentation or when a molecular diagnosis becomes necessary for management or advice

Requesting Specialties

- Clinical Genetics
- Orthopaedics
- Rheumatology

Specialist Service Group

- Musculoskeletal

Associated Tests

Please note all the tests below will be undertaken for R390 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R390.1	EXT1; EXT2	Singleton	Small variants	Small panel	EXT1; EXT2 (1367)	Small panel
R390.2	EXT1; EXT2 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	EXT1; EXT2 (1367)	MLPA or equivalent

R284 Van der Woude syndrome

Testing Criteria

Clinical features strongly suggestive of van der Woude syndrome.

Overlapping indications

- R27 Paediatric disorders test should be used in individuals with cleft palate with a likely complex syndromic cause

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Musculoskeletal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R284.1	IRF6 Single gene sequencing	Singleton	Small variants	Single gene(s)	IRF6 (1401)	Single gene sequencing <10 amplicons

Part XVII. Neurology

R70 Spinal muscular atrophy type 1 diagnostic test

Testing Criteria

Clinical features suggestive of spinal muscular atrophy type 1

NOTE: pre symptomatic testing of siblings of individuals with a molecularly confirmed diagnosis of SMA, where testing may inform treatment decisions, should use R242

Overlapping indications

- R69 Hypotonic infant with a likely central cause test should be used in floppy babies where the clinical picture is suggestive of a central cause, i.e. particularly where the baby is not alert, but lethargic or sleepy

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Neonatology
- Neurology
- Paediatrics

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R70.1	SMN1, SMN2 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	SMN1; SMN2	MLPA or equivalent

R71 Spinal muscular atrophy type 1 rare mutation testing

Testing Criteria

Individuals in whom a rare mutation in the SMN1 gene is likely. This will mainly be used for individuals with clinical features of spinal muscular atrophy (SMA) type 1 and monoallelic copy number mutation of SMN1

NOTE: pre symptomatic testing of siblings of individuals with a molecularly confirmed diagnosis of SMA, where testing may inform treatment decisions, should use R242

Overlapping indications

- R70 Spinal muscular atrophy type 1 diagnostic test should be used first where clinical features are suggestive of spinal muscular atrophy type 1 and SMN1 copy number has not been tested.

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

Where in Pathway

After SMN1 copy number analysis

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R71.1	SMN1 Single gene sequencing	Singleton	Small variants	Single gene(s)	SMN1 (1393)	Single gene sequencing >=10 amplicons

R72 Myotonic dystrophy type 1

Testing Criteria

Clinical features strongly suggestive of myotonic dystrophy type 1

Overlapping indications

- R69 Hypotonic infant with a likely central cause test should be used in floppy babies where the clinical picture is suggestive of a central cause
- R381 Other rare neuromuscular disorders should be used where clinical features are atypical and a broader range of genes are potentially causative
- R410 Myotonic dystrophy type 2 should be used where there is clinical suspicion of myotonic dystrophy type 2 or where myotonic dystrophy type 1 has been excluded

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R72.1	DMPK STR testing	Singleton	Methylation	Single gene(s)	DMPK STR	STR testing

R77 Hereditary neuropathy - PMP22 copy number

Testing Criteria

Hereditary neuropathy where PMP22 copy number abnormalities are possible

Overlapping indications

- R78 Hereditary neuropathy or pain disorder test should be used where PMP22 copy number abnormalities are clinically unlikely or have already been excluded
- R89 Ultra-rare and atypical monogenic disorders or R27 Paediatric disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Neurology
- Paediatrics

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R77.1	PMP22 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	PMP22	MLPA or equivalent

R68 Huntington disease

Testing Criteria

Clinical features that indicate a likely diagnosis of Huntington disease

- Specialties other than those listed in Requesting Specialties may request tests in certain settings following discussion with their local laboratory-clinical team

Overlapping indications

- R56 Adult onset dystonia, chorea or related movement disorder or other relevant broader test should be used where clinical features are not strongly suggestive of Huntington disease

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Neurology
- Psychiatry

Specialist Service Group

- Core

Associated Tests

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

R383 Linkage testing for Huntington disease

Testing Criteria

Families with a confirmed diagnosis of Huntington disease who require linkage testing to guide management or advice

Where in Pathway

As appropriate

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R383.1	HTT Linkage testing	Multiple affected individuals	Other	Single gene(s)	HTT	Other

R252 SMA carrier testing at population risk for partners of known carriers

Testing Criteria

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

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

Where in Pathway

At the time of reproductive planning

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R252.1	SMN1 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	SMN1	MLPA or equivalent

R54 Hereditary ataxia with onset in adulthood

Testing Criteria

Unexplained ataxia with onset in adulthood including where differential diagnosis encompasses STR loci.

Overlapping indications

R60 Adult onset hereditary spastic paraplegia

Where in Pathway

At presentation following assessment by a Neurologist

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Please note R54.4 (RFC1 STR) will not be included unless specifically requested

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R54.3	Hereditary ataxia - adult onset WGS (phase 1)	Singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Hereditary ataxia - adult onset (466)	WGS
R54.4	*RFC1* STR	Singleton	STRs	Panel of genes or loci	*RFC1* STR	STR testing
R54.5	Hereditary ataxia adult onset confirmatory STR testing	Singleton	STRs	Panel of genes or loci	Hereditary ataxia - adult onset (466)	STR testing

R55 Hereditary ataxia with onset in childhood

Testing Criteria

Unexplained hereditary ataxia with onset in childhood including where differential diagnosis encompasses STR loci

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

Where in Pathway

At presentation following assessment by a Neurologist

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R55.4	Hereditary ataxia and cerebellar anomalies - childhood onset WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Hereditary ataxia and cerebellar anomalies - childhood onset (488)	WGS
R55.5	Hereditary ataxia and cerebellar anomalies - childhood onset confirmatory STR testing.	Singleton	STRs	Panel of genes or loci	Hereditary ataxia and cerebellar anomalies - childhood onset (488)	STR testing

R56 Adult onset dystonia, chorea or related movement disorder

Testing Criteria

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

Overlapping indications

- R68 Huntington disease test should be used where clinical features indicate a likely diagnosis of Huntington disease
- R89 Ultra-rare and atypical monogenic disorders or other relevant broader tests should be used in individuals with complex or syndromic presentations

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

Where in Pathway

At presentation following assessment by a Neurologist

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R56.3	Adult onset dystonia, chorea, or related movement disorder WGS (phase 2)	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Adult onset movement disorder (540)	WGS
R56.4	Adult onset dystonia, chorea, or related movement disorder confirmatory STR testing	Singleton	STRs	Panel of genes or loci	Adult onset movement disorder (540)	STR testing

R57 Childhood onset dystonia, chorea or related movement disorder

Testing Criteria

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

Overlapping indications

- R61 Childhood onset hereditary spastic paraplegia – if the patient has spastic paraplegia
- R55 Hereditary ataxia with onset in childhood – if the patient has ataxia
- R27 Paediatric disorders
- R29 Intellectual disability
- R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with complex or syndromic presentations

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

Where in Pathway

At presentation following assessment by a Neurologist

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R57.5	Childhood onset dystonia or chorea or related movement disorder WGS (phase 2)	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Childhood onset dystonia or chorea or related movement disorder (847)	WGS
R57.6	Childhood onset dystonia or chorea or related movement disorder confirmatory STR testing	Singleton	STRs	Panel of genes or loci	Childhood onset dystonia or chorea or related movement disorder (847)	STR testing

R58 Adult onset neurodegenerative disorder

Testing Criteria

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

1. Unexplained dementia
    a. Age at onset <55 years where acquired causes (e.g. stroke, tumour) have been excluded, OR
    b. Family history of dementia of the same type and/or family history of MND in a first / second degree relative
2. Parkinson's disease or complex Parkinsonism
    a. Age at onset <50 years, OR
    b. First degree relative affected at <50 years, OR
    c. Complex features such as spasticity, gaze palsy, early dementia, early bulbar failure, dyspraxia, ataxia, postural hypotension, cortical sensory loss, brain iron accumulation on MRI brain
3. Amyotrophic lateral sclerosis (ALS) with or without frontotemporal dementia
    a. Evidence of lower motor neuron (LMN) degeneration by clinical, electrophysiologic or neuropathologic examination, AND
    b. Evidence of upper motor neuron (UMN) degeneration by clinical examination, AND
    c. Progressive course, AND
    e. No evidence of other aetiology
4. Cerebral amyloid angiopathy (CAA)
    a. Age of onset < 50 years OR
    b. Family history of haemorrhagic stroke (intracerebral haemorrhage or convexity subarachnoid haemorrhage) or dementia AND
    c. Clinical presentation in keeping with CAA i.e. transient focal neurological episodes ("amyloid spells"), intracerebral haemorrhage, convexity subarachnoid haemorrhage, cognitive impairment, dementia AND
    d. Radiological features consistent with CAA i.e. two or more strictly lobar haemorrhagic lesions on blood sensitive MRI, which can include intracerebral haemorrhage, cerebral microbleeds, cortical superficial siderosis or convexity subarachnoid haemorrhage OR
    e. Other investigations supportive of amyloid-beta deposition within the central nervous system e.g. amyloid-PET imaging, CSF amyloid-beta measures, brain biopsy

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

Where in Pathway

At presentation following assessment by a Neurologist

Requesting Specialties

- Clinical Genetics
- Neurology
- Psychiatry

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R58.4	Adult onset neurodegenerative disorder WGS (phase 2)	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Neurodegenerative disorders - adult onset (474)	WGS

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R58.5	Adult onset neurodegenerative disorder confirmatory STR testing	Singleton	STRs	Panel of genes or loci	Neurodegenerative disorders - adult onset (474)	STR testing

R59 Early onset or syndromic epilepsy

Testing Criteria

Unexplained epilepsy with clinical suspicion of a monogenic cause including:

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

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

Overlapping indications

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

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Please note all the tests below will be undertaken for R59 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
R59.2	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray
R59.3	Epilepsy - early onset or syndromic WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Genetic epilepsy syndromes (402)	WGS

R60 Adult onset hereditary spastic paraplegia

Testing Criteria

Unexplained spastic paraplegia of likely monogenic aetiology with onset in adulthood

STR testing of spinocerebellar ataxia loci will be included as a component test where spinocerebellar ataxia is considered plausible clinically.

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

Where in Pathway

At presentation following assessment by a Neurologist or Clinical Geneticist

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R60.3	Adult onset hereditary spastic paraplegia WGS (phase 2)	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Hereditary spastic paraplegia - adult onset (567)	WGS
R60.4	Adult onset hereditary spastic paraplegia confirmatory STR testing	Singleton	STRs	Panel of genes or loci	Hereditary spastic paraplegia - adult onset (567)	STR testing

R61 Childhood onset hereditary spastic paraplegia

Testing Criteria

Unexplained spastic paraplegia of likely monogenic aetiology with onset in childhood

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

Where in Pathway

At presentation following assessment by a Neurologist or Clinical Geneticist

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R61.4	Hereditary spastic paraplegia - child onset WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants; STRs	Panel of genes or loci	Hereditary spastic paraplegia - Childhood onset (568)	WGS
R61.5	Hereditary spastic paraplegia - child onset confirmatory STR testing	Singleton	STRs	Panel of genes or loci	Hereditary spastic paraplegia - Childhood onset (568)	STR testing

R62 Adult onset leukodystrophy

Testing Criteria

Individuals with unexplained leukodystrophy on neuroimaging with onset in adulthood

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

Where in Pathway

At presentation following review of neuroimaging by Neuroradiologist

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R62.2	Adult onset leukodystrophy WGS (phase 2)	Trio or singleton	Exon level CNVs, Small variants	Panel of genes or loci	White matter disorders - adult onset (579)	WGS

R66 Paroxysmal central nervous system disorders

Testing Criteria

Paroxysmal central nervous system disorder that is likely to be monogenic in aetiology

Overlapping indications

- R56 Adult onset dystonia, chorea or related movement disorder or R57 Childhood onset dystonia, chorea or related movement disorder tests should be used in individuals with dystonia
- R89 Ultra-rare and atypical monogenic disorders or other relevant broader tests should be used in individuals with complex or syndromic presentations

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

Where in Pathway

At presentation following assessment by a Consultant Neurologist or Paediatric Neurologist

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Please note all the tests below will be undertaken for R66 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
R66.1	Paroxysmal central nervous system disorders WES or medium panel	Singleton	Small variants	Panel of genes or loci	Paroxysmal central nervous system disorders (541)	WES or Medium Panel
R66.2	Paroxysmal central nervous system disorders	Singleton	Exon level CNVs	Panel of genes or loci	Paroxysmal central nervous system disorders (541)	Exon level CNV detection by MLPA or equivalent

R73 Duchenne or Becker muscular dystrophy

Testing Criteria

1. Individuals with clinical features strongly suggestive of Duchenne or Becker muscular dystrophy AND elevated creatine kinase
2. Testing a female family member of an affected male known to have or likely to have had Duchenne or Becker muscular dystrophy, but without confirmed molecular diagnosis.

Overlapping indications

- R79 Congenital muscular dystrophy test should be considered following discussion with Neuromuscular specialist in atypical cases
- R381 Other rare neuromuscular disorders should be used where clinical features are atypical and a broader range of genes are potentially causative

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Community Paediatrics
- Neurology
- Paediatrics

Specialist Service Group

- Neurology

Associated Tests

Please note all the tests below will be undertaken for R73 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R73.1	DMD Single gene sequencing	Singleton	Small variants	Single gene(s)	DMD (1321)	Single gene sequencing >=10 amplicons
R73.2	DMD MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	DMD (1321)	MLPA or equivalent

R378 Linkage testing for Duchenne or Becker muscular dystrophy

Testing Criteria

Families with a confirmed diagnosis of Duchenne or Becker muscular dystrophy with no detectable mutation in dystrophin who require linkage testing to guide management or advice

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

Where in Pathway

As appropriate

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R378.1	Dystrophin Linkage testing	Multiple affected individuals	Other	Single gene(s)	Dystrophin	Other

R74 Facioscapulohumeral muscular dystrophy

Testing Criteria

Clinical features strongly suggestive of facioscapulohumeral muscular dystrophy (FSHD) in whom a DUX4 contraction has not been excluded

Overlapping indications

- R82 Limb girdle muscular dystrophies, myofibrillar myopathies and distal myopathies and broader tests such as R89 Ultra-rare and atypical monogenic disorders should be considered where features are atypical
- R345 Facioscapulohumeral muscular dystrophy (FSHD) extended testing should be considered in cases negative for the test where clinical features are strongly suggestive of FSHD
- R381 Other rare neuromuscular disorders should be used where clinical features are atypical and a broader range of genes are potentially causative

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R74.1	DUX4 Contraction testing	Singleton	STRs	Single interval	DUX4 STR	Other

R345 Facioscapulohumeral muscular dystrophy - extended testing

Testing Criteria

Clinical features strongly suggestive of facioscapulohumeral muscular dystrophy (FSHD) in whom a DUX4 contraction has been excluded

Overlapping indications

- R74 Facioscapulohumeral muscular dystrophy test should be used where DUX4 contraction has not been excluded
- R82 Limb girdle muscular dystrophies, myofibrillar myopathies and distal myopathies and broader tests such as R381 Other rare neuromuscular disorders should be considered where features are atypical

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

Where in Pathway

Following discussion with Neuromuscular consultant and/or testing laboratory

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R345.1	DUX4 Methylation testing	Singleton	Methylation	Single interval	DUX4	Methylation testing
R345.2	SMCHD1 Single gene sequencing	Singleton	Small variants	Single gene(s)	SMCHD1 (1324)	Single gene sequencing >=10 amplicons
R345.3	4q Extended testing	Singleton	Complex variants	Single interval	4q	Other

R75 Oculopharyngeal muscular dystrophy

Testing Criteria

Clinical features strongly suggestive of oculopharyngeal muscular dystrophy

Overlapping indications

- R89 Ultra-rare and atypical monogenic disorders test should be considered where features are atypical
- R381 Other rare neuromuscular disorders should be used where clinical features are atypical and a broader range of genes are potentially causative

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R75.1	PABPN1 STR testing	Singleton	STRs	Single gene(s)	PABPN1 STR	STR testing

R76 Skeletal muscle channelopathy

Testing Criteria

Clinical features strongly suggestive of a skeletal muscle channelopathy including myotonia congenita or paramyotonia congenita

Overlapping indications

- R89 Ultra-rare and atypical monogenic disorders should be used where features are atypical
- R381 Other rare neuromuscular disorders should be used where clinical features are atypical and a broader range of genes are potentially causative

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

Where in Pathway

At presentation or following clinical assessment as part of the rare neuromuscular highly specialised service

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Please note all the tests below will be undertaken for R76 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
R76.1	Skeletal muscle channelopathy Small panel	Singleton	Small variants	Panel of genes or loci	Skeletal muscle channelopathy (542)	Small panel
R76.2	Skeletal muscle channelopathy	Singleton	Exon level CNVs	Panel of genes or loci	Skeletal muscle channelopathy (542)	Exon level CNV detection by MLPA or equivalent

R78 Hereditary neuropathy or pain disorder

Testing Criteria

Clinical features that indicate a likely hereditary neuropathy or pain disorder in whom PMP22 copy number abnormalities are clinically unlikely or have already been excluded

Overlapping indications

- R77 Hereditary neuropathy - PMP22 copy number test should be used where PMP22 copy number abnormalities are possible
- R89 Ultra-rare and atypical monogenic disorders or R27 Paediatric disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Please note R78.5 (RFC1 STR) will not be included unless specifically requested.

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R78.4	Hereditary neuropathy or pain disorder number WGS (phase 2)	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Hereditary neuropathy (846)	WGS
R78.5	*RFC1* STR	Singleton	STR	Single gene(s)	*RFC1 STR*	STR testing
R78.6	Hereditary neuropathy or pain disorder confirmatory STR testing	Singleton	STR	Single gene(s)	Hereditary neuropathy (846)	STR testing

R79 Congenital muscular dystrophy

Testing Criteria

Individuals with clinical features that indicate a likely congenital muscular dystrophy:

1. Muscle biopsy results indicative of congenital muscular dystrophy, OR
2. Muscle and/or brain MRI findings indicative of congenital muscular dystrophy

Overlapping indications

- R89 Ultra-rare and atypical monogenic disorders or R27 Paediatric disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations not typical of disorders covered by the panel

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

Where in Pathway

At presentation following assessment by a Neurologist or following clinical assessment as part of the rare neuromuscular highly specialised service

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Please note all the tests below will be undertaken for R79 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
R79.1	Congenital muscular dystrophy WES or medium panel	Singleton	Small variants	Panel of genes or loci	Congenital muscular dystrophy (207)	WES or Medium Panel
R79.2	Congenital muscular dystrophy	Singleton	Exon level CNVs	Panel of genes or loci	Congenital muscular dystrophy (207)	Exon level CNV detection by MLPA or equivalent

R80 Congenital myaesthenic syndrome

Testing Criteria

Clinical features that indicate a likely monogenic congenital myaesthenia

Overlapping indications

- R89 Ultra-rare and atypical monogenic disorders or R27 Paediatric disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations not typical of disorders covered by the panel

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

Where in Pathway

At presentation following assessment by a Neurologist, typically in parallel to maternal anti-AChR antibody testing or following clinical assessment as part of the rare neuromuscular highly specialised service

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Please note all the tests below will be undertaken for R80 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
R80.1	Congenital myaesthenic syndrome WES or medium panel	Singleton	Small variants	Panel of genes or loci	Congenital myaesthenic syndrome (232)	WES or Medium Panel
R80.2	Congenital myaesthenic syndrome	Singleton	Exon level CNVs	Panel of genes or loci	Congenital myaesthenic syndrome (232)	Exon level CNV detection by MLPA or equivalent

R81 Congenital myopathy

Testing Criteria

Clinical or histopathological features that indicate a likely monogenic congenital myopathy

Overlapping indications

- R89 Ultra-rare and atypical monogenic disorders or R27 Paediatric disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations not typical of disorders covered by the panel

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

Where in Pathway

At presentation following assessment by a Neurologist or following clinical assessment as part of the rare neuromuscular highly specialised service

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Please note all the tests below will be undertaken for R81 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
R81.1	Congenital myopathy WES or medium panel	Singleton	Small variants	Panel of genes or loci	Congenital myopathy (225)	WES or Medium Panel
R81.2	Congenital myopathy	Singleton	Exon level CNVs	Panel of genes or loci	Congenital myopathy (225)	Exon level CNV detection by MLPA or equivalent

R82 Limb girdle muscular dystrophies, myofibrillar myopathies and distal myopathies

Testing Criteria

Clinical features that indicate a likely limb girdle muscular dystrophy or a genetic condition with overlapping phenotype such as distal myopathy or myofibrillar myopathy.

Overlapping indications

- R79 Congenital muscular dystrophy or R89 Ultra-rare and atypical monogenic disorders tests should be used where features are atypical

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

Where in Pathway

At presentation following assessment by a Neurologist or following clinical assessment as part of the rare neuromuscular highly specialised service

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Please note all the tests below will be undertaken for R82 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
R82.1	Limb girdle muscular dystrophies, myofibrillar myopathies and distal myopathies WES or medium panel	Singleton	Small variants	Panel of genes or loci	Limb girdle muscular dystrophies, myofibrillar myopathies and distal myopathies (185)	WES or Medium Panel
R82.2	Limb girdle muscular dystrophies, myofibrillar myopathies and distal myopathies	Singleton	Exon level CNVs	Panel of genes or loci	Limb girdle muscular dystrophies, myofibrillar myopathies and distal myopathies (185)	Exon level CNV detection by MLPA or equivalent

R371 Malignant hyperthermia

Testing Criteria

Confident clinical diagnosis of malignant hyperthermia; anaesthetic history reviewed by MH investigation unit as appropriate. Reasons for referral:

1. Family history of malignant hyperthermia.
2. Adverse reaction to general anaesthesia where a trigger agent has been used, involving any combination of signs of increased metabolism (unexplained increase in carbon dioxide production, tachycardia, temperature increase, muscle rigidity, rhabdomyolysis, disseminated intravascular coagulation and/or death). Initial signs should be evident during anaesthesia or within 60 minutes of discontinuation of anaesthesia.
3. Family history of unexplained perioperative death suggestive of malignant hyperthermia.
4. Postoperative rhabdomyolysis after clinical exclusion of other myopathies.
5. Exertional rhabdomyolysis / recurrent rhabdomyolysis or persistently raised serum creatine kinase concentration of unknown cause (idiopathic hyperCKaemia) where no cause has been identified following neurological work-up.
6. Exertional heat stroke requiring hospital admission, where known predisposing factors have been excluded.

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

Where in Pathway

Following discussion with national specialist service

Requesting Specialties

- Clinical Genetics
- Other

Specialist Service Group

- Neurology

Associated Tests

Please note all the tests below will be undertaken for R371 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
R371.1	Malignant hyperthermia small panel	Singleton	Small variants	Panel of genes or loci	Malignant hyperthermia (1076)	Small panel
R371.2	Malignant hyperthermia	Singleton	Exon level CNVs	Panel of genes or loci	Malignant hyperthermia (1076)	Exon level CNV detection by MLPA or equivalent

R83 Arthrogryposis

Testing Criteria

Clinical features that indicate arthrogryposis of monogenic aetiology

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

Where in Pathway

At presentation following assessment by a Neurologist or Clinical Geneticist and following serum CK estimation

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Please note all the tests below will be undertaken for R83 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
R83.2	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray
R83.3	Arthrogryposis - broad panel WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants	Panel of genes or loci	Arthrogryposis (258)	WGS

R381 Other rare neuromuscular disorders

Testing Criteria

Clinical features of rare neuromuscular disorder not covered by more specific indications

Overlapping indications

- Targeted tests for specific neuromuscular indications where relevant

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R381.2	Neuromuscular disorders WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants; STRs	Panel of genes or loci	Neuromuscular disorders (465)	WGS
R81.4	Neuromuscular disorders confirmatory STR testing	Singleton	STRs	Single gene(s)	Neuromuscular disorders (465)	STR testing

R84 Cerebellar anomalies

Testing Criteria

Likely monogenic cerebellar malformation, cerebellar or pontocerebellar hypoplasia or childhood-onset cerebellar atrophy

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

Where in Pathway

At presentation following MRI brain and assessment by a Neurologist or Clinical Geneticist

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Please note all the tests below will be undertaken for R84 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
R84.2	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray
R84.4	Hereditary ataxia and cerebellar anomalies - childhood onset WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Hereditary ataxia and cerebellar anomalies - childhood onset (488)	WGS
R84.5	Hereditary ataxia and cerebellar anomalies - childhood onset confirmatory STR testing	Singleton	STRs	Panel of genes or loci	Hereditary ataxia and cerebellar anomalies - childhood onset (488)	STR testing

R85 Holoprosencephaly - NOT chromosomal

Testing Criteria

Liveborn individuals with unexplained holoprosencephaly in whom a chromosomal cause has been excluded by microarray or equivalent

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

Where in Pathway

At presentation following chromosome microarray (which may have followed rapid aneuploidy screening)

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R85.2	Holoprosencephaly WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants	Panel of genes or loci	Holoprosencephaly (78)	WGS

R86 Hydrocephalus

Testing Criteria

Unexplained hydrocephalus with a likely monogenic cause, i.e. where secondary causes such as congenital infection and intraventricular haemorrhage are unlikely to be causative

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

Where in Pathway

At presentation after relevant acquired causes have been excluded where feasible

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Please note all the tests below will be undertaken for R86 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
R86.2	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray
R86.3	Hydrocephalus WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants	Panel of genes or loci	Hydrocephalus (179)	WGS

R87 Cerebral malformation

Testing Criteria

Cerebral malformation such as cortical malformation or porencephaly with features suggestive of a monogenic cause.

Overlapping indications

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Please note all the tests below will be undertaken for R87 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
R87.2	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray
R87.3	Cerebral malformations WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants	Panel of genes or loci	Cerebral malformations (491)	WGS

R88 Severe microcephaly

Testing Criteria

Individuals with severe microcephaly* of likely monogenic aetiology.

*Severe microcephaly is defined as having an occipitofrontal circumference (OFC) beyond 3 standard deviations below the mean for age

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Neurology
- Paediatrics

Specialist Service Group

- Neurology

Associated Tests

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
R88.2	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray
R88.3	Severe microcephaly WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants	Panel of genes or loci	Severe microcephaly (162)	WGS

R109 Childhood onset leukodystrophy

Testing Criteria

Unexplained leukodystrophy on neuroimaging with onset in childhood

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

Where in Pathway

At presentation following review of neuroimaging by Neuroradiologist

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R109.3	White matter disorders - childhood onset WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	White matter disorders - childhood onset (496)	WGS

R221 Familial tumours of the nervous system

Testing Criteria

1. Individual +/- family history fulfils clinical criteria for Neurofibromatosis Type 2

a. Bilateral vestibular schwannomas, OR

b. Unilateral vestibular schwannoma AND ≥2 NF2 associated features (meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities/cataract) OR

c. ≥ 1 of unilateral vestibular schwannoma, meningioma, schwannoma, glioma, neurofibroma, multiple meningiomas, posterior subcapsular lenticular opacities/cataract AND ≥ 1 first / second degree relative with a vestibular schwannoma OR

d. Multiple Meningiomas AND ≥2 NF2 associated features (schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities/cataract) OR

e. Unilateral Vestibular Schwannoma AND multiple meningiomas

2. Unilateral Vestibular Schwannoma AND a non-intradermal schwannoma without other NF2-features

3. Schwannomatosis:

a. Two or more non-intradermal schwannomas (at least one biopsy-confirmed) OR

b. One pathologically confirmed schwannoma, unilateral vestibular schwannoma, or intracranial meningioma AND ≥1 FDR with Schwannomatosis

4. Schwannoma diagnosed <30years

5. ≥2 meningiomas

6. Any clear Cell Meningioma

Extent of testing

1. Patients fulfilling criterion 1 should have NF2 testing only
2. Patients fulfilling criterion 2 should have testing of NF2 AND LZTR1
3. Patients fulfilling criterion 3 should have testing of NF2, LZTR1, SMARCB1 and DGCR8
4. Patients fulfilling criterion 4 should have testing of NF2, LZTR1, SMARCB1
5. Patients fulfilling criterion 5 should have testing of NF2, SMARCE1, SUFU
6. Patients fulfilling criterion 6 should have testing of SMARCE1

Note

Tumour-based testing of NF2 checking for mosaicism should be offered in the following circumstances:

1. Patients fulfilling criterion 1 in whom germline NF2 testing is uninformative
2. Patients with two or more NF2-related tumours not otherwise fulfilling criteria 1-6
3. Patients fulfilling criterion 3 in whom testing of NF2, LZTR1, SMARCB1 and DGCR8 is uninformative

NOTE: All tumours should be histologically confirmed

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

Where in Pathway

At presentation and/or following consultation with the NF2 highly specialised service

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Neurology

Associated Tests

Please note all the tests below will be undertaken for R221 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R221.1	Familial tumours of the nervous system	Singleton	Small variants	Single genes	Familial tumours of the nervous system (1334)	Small panel
R221.2	Familial tumours of the nervous system	Singleton	Exon level CNVs	Single genes	Familial tumours of the nervous system (1334)	MLPA or equivalent

R222 Neurofibromatosis type 1

Testing Criteria

Clinical diagnosis of NF1, as defined below, AND molecular diagnosis is required for management of the proband or for reproductive planning

Diagnosis requires two of:

1. At least 6 café au lait macules (at least 0.5cm in a child and 1.5cm in an adult)
2. At least 2 subcutaneous or cutaneous neurofibromas
3. Plexiform neurofibroma
4. Optic glioma
5. At least 2 Lisch nodules
6. Bony dysplasia (sphenoid wing, long bone bowing, pseudarthrosis)
7. Family history of NF1

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

Overlapping indications

- R236 Pigmentary skin disorders test should be used where clinical features are atypical and a broader range of genes is potentially causative
- R27 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

Where in Pathway

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

Requesting Specialties

- Clinical Genetics
- Dermatology
- Neurology
- Paediatrics

Specialist Service Group

- Neurology

Associated Tests

Please note all the tests below will be undertaken for R222 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R222.1	NF1; SPRED1 Single gene sequencing	Singleton	Small variants	Single gene(s)	NF1; SPRED1 (1370)	Small panel
R222.2	NF1; SPRED1 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	NF1; SPRED1 (1370)	MLPA or equivalent

R376 Segmental or atypical neurofibromatosis type 1 testing

Testing Criteria

Clinical features suggestive of segmental or atypical neurofibromatosis type 1 or individuals with classical neurofibromatosis who have tested negative on gDNA analysis requiring cDNA analysis following discussion with highly specialised service

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

Where in Pathway

Following consultation with highly specialised service

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Please note all the tests below will be undertaken for R376 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R376.1	NF1 Single gene sequencing – mosaic	Singleton	Small variants	Single gene(s)	NF1 (1387)	Single gene sequencing >=10 amplicons
R376.2	NF1 MLPA or equivalent – mosaic	Singleton	Exon level CNVs	Single gene(s)	NF1 (1387)	MLPA or equivalent

R228 Tuberous sclerosis

Testing Criteria

Clinical features suggestive of tuberous sclerosis requiring molecular testing

Testing should typically be targeted at those with one or more major features or two or more minor features:

1. Major features:
    a. Hypomelanotic macules (at least 3 of at least 5 mm in diameter)
    b. Angiofibromas (at least three) or fibrous cephalic plaque
    c. Ungual fibromas (at least two)
    d. Shagreen patch
    e. Multiple retinal hamartomas
    f. Cortical dysplasias characteristic of tuberous sclerosis such as tubers and cerebral white matter radial migration lines
    g. Subependymal nodules
    h. Subependymal giant cell astrocytoma
    i. Cardiac rhabdomyomas
    j. Lymphangioleiomyomatosis (LAM)
    k. Angiomyolipomas (at least two)
2. Minor features:
    a. Confetti skin lesions
    b. Dental enamel pits (>3)
    c. Intraoral fibromas (at least two)
    d. Retinal achromic patch
    e. Multiple renal cysts
    f. Non- renal hamartomas

Overlapping indications

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Fetal Medicine
- Nephrology
- Neurology
- Respiratory Medicine

Specialist Service Group

- Neurology

Associated Tests

Please note R228.1 and R228.2 will be undertaken for all R228 Clinical Indication requests and R228.3 will only be undertaken where a pathogenic variant has not been found on R228.1 and R228.2

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R228.1	TSC1; TSC2	Singleton	Small variants	Small panel	TSC1; TSC2 (1400)	Small panel

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R228.2	TSC1; TSC2 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	TSC1; TSC2 (1400)	MLPA or equivalent
R228.3	TSC1; TSC2 – Small panel deep sequencing	Singleton	Small variants	Small panel	TSC1; TSC2 (1400)	Small panel – deep sequencing

R294 Ataxia telangiectasia – DNA repair testing

Testing Criteria

1. Clinical features strongly suggestive of ataxia telangiectasia including elevated serum AFP levels, AND one or more of the following:
    a. Progressive gait and truncal ataxia with onset between one and four years of age, OR
    b. Ocular motor apraxia, OR
    c. Ocular telangiectasia, OR
    d. Chorea and dysarthria, OR
    e. Immunodeficiency with frequent infections, OR
    f. Malignancy (e.g. leukaemia and lymphoma, breast cancer, ovarian cancer gastric cancer, leiomyoma, sarcoma or melanoma), OR
2. Molecular findings suggestive of Fanconi anaemia or Bloom syndrome from genome, exome or other genomic analysis

Overlapping indications

- R27 Paediatric disorders, R89 Ultra-rare and atypical monogenic disorders or other broad genomic tests should typically be used except where the above criteria are fulfilled
- Prenatal diagnosis or cascade testing by chromosome breakage testing will be requested via R240 Diagnostic testing for known familial mutation(s)

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

Where in Pathway

At presentation

Requesting Specialties

- Oncology
- Clinical Genetics
- Haematology
- Immunology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R294.1	Genomewide DNA repair defect testing	Singleton	DNA repair	Genomewide	Genomewide	DNA repair defect testing

R295 Ataxia telangiectasia – mutation testing

Testing Criteria

Confirmed diagnosis of ataxia telangiectasia requiring mutation testing

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

Where in Pathway

After DNA repair testing

Requesting Specialties

- Oncology
- Clinical Genetics
- Haematology
- Immunology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R295.1	ATM Single gene sequencing	Singleton	Small variants	Single gene(s)	ATM (1213)	Single gene sequencing >=10 amplicons

R336 Cerebral vascular malformations

Testing Criteria

1. Multiple cerebral vascular malformations, OR
2. Cerebral vascular malformation AND family history of cerebral vascular malformation

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

Where in Pathway

Following neuroimaging

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Please note all the tests below will be undertaken for R336 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
R336.1	Cerebral vascular malformations WES or medium panel	Singleton	Small variants	Panel of genes or loci	Cerebral vascular malformations (147)	WES or Medium Panel
R336.2	Cerebral vascular malformations	Singleton	Exon level CNVs	Panel of genes or loci	Cerebral vascular malformations (147)	Exon level CNV detection by MLPA or equivalent

R337 CADASIL

Testing Criteria

A confident clinical diagnosis of CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) including:

Cerebral ischaemic event below age of 50 or >50 if with a family history of dementia/migraine, AND one or more of:

1. Cognitive impairment with recurrent ischaemic attacks, OR
2. Subcortical lacunar lesions on MRI scan in white matter

Overlapping indications

- R58 Adult onset neurodegenerative disorder test should be used in atypical cases where a broader differential diagnosis is under consideration

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R337.1	NOTCH3 Single gene sequencing	Singleton	Small variants	Single gene(s)	NOTCH3 (1311)	Single gene sequencing >=10 amplicons

R410 Myotonic dystrophy type 2 (DM2)

Testing Criteria

1. Adult with muscle weakness, usually proximal, and one of the following:
   a. Clinical Myotonia: of grip or on percussion
   b. EMG evidence of myotonic discharges
   c. Cataracts (fine dust like opacities on the outer layers of the lens that are highly coloured and iridescent, producing a “Christmas Tree” appearance)
   d. Three or more supportive features (from list below)
   e. Family History suggestive of autosomal dominant inheritance

2. **AND** DM1 excluded first if the clinical presentation/Family history could easily fit DM1
3. **OR** Family history of mutation positive DM2

Additional supportive features:

- Elevated serum CK
- Insulin-insensitive type 2 diabetes
- Testicular failure
- Cardiac conduction defects
- Low serum IgG or IgM
- Muscle biopsy showing atrophic fibres and proliferation of fibres with central nuclei
- Excessive daytime sleepiness
- Mildly elevated liver function tests (LFT)
- Muscle pain

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

Overlapping indications

- R72 Myotonic dystrophy type 1 should be used prior to this indication unless there is clinical suspicion of myotonic dystrophy type 2
- R381 Other rare neuromuscular disorders should be used where clinical features are atypical and a broader range of genes are potentially causative

Where in Pathway

At presentation, following a normal test for Myotonic dystrophy type 1, unless there is clinical suspicion of myotonic dystrophy type 2

Requesting Specialties

- Clinical Genetics
- Neurology

Specialist Service Group

- Neurology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R410.1	CNBP (ZNF9) STR testing	Singleton	Short tandem repeats	Single gene(s)	CNBP (ZNF9)	STR testing

R419 Acute Rhabdomyolysis

Testing Criteria

Any patient (including children) presenting with an acute rise in skeletal muscle CK>20,000 iu/l regardless of the trigger, unless this occurs following a single episode of unaccustomed exercise not requiring hospital admission e.g. following weight lifting, a personal trainer session, spin class, marathon etc. However, a second similar episode should trigger testing.

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

Overlapping indications

- R371 Malignant hyperthermia

Where in Pathway

At presentation or following clinical assessment as part of the McArdle Disease and related disorders highly specialised service

Requesting Specialties

- Neurology
- Intensive Care
- Clinical genetics
  Metabolic medicine
- Nephrology

Specialist Service Group

Neurology

Associated Tests

Please note all the tests below will be undertaken for R419 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
R419.1	Acute Rhabdomyolysis Medium panel	Singleton	Small variants	Panel of genes or loci	Panel is being created in PanelApp	Medium panel
R419.2	Acute Rhabdomyolysis	Singleton	Exon level CNVs	Panel of genes or loci	Panel is being created in PanelApp	Exon level CNV detection by MLPA or equivalent

Part XVIII. Renal

R193 Cystic renal disease

Testing Criteria

1. Patients with non-syndromic cystic renal disease (excluding acquired cystic disease due to chronic or end stage kidney disease) which is EITHER
2. Clinically not characteristic of ADPKD and underlying diagnosis is required for management purposes, OR
3. Clinically symptomatic disease presenting before the age of 18, OR
4. Clinical diagnosis of ADPKD where a genetic diagnosis is required to influence management

Overlapping indications

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

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

Where in Pathway

At presentation, or when clinical management decision depending on molecular diagnosis is required

Requesting Specialties

- Clinical Genetics
- Nephrology

Specialist Service Group

- Renal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R193.4	Cystic renal disease WGS (phase 1)	Singleton	Exon level CNVs, Small variants	Panel of genes or loci	Cystic renal disease (487)	WGS

R194 Haematuria

Testing Criteria

Proband with haematuria and ONE of:

1. A first degree relative with haematuria or unexplained chronic renal failure, OR
2. Histological evidence following electron microscopy on renal biopsy of EITHER Alport syndrome (thickening and splitting of glomerular basement membrane +/- electron lucent areas) OR thin basement membrane disease (TBMD), OR
3. Clinical features of Alport syndrome (high tone sensorineural hearing loss or characteristic ophthalmic signs such as perimacular flecks or anterior lenticonus)

Overlapping indications

- R27 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations
- R196 CFHR5 nephropathy test should be used as a first line test in patients of Cypriot ancestry with haematuria

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

Where in Pathway

At presentation

Requesting Specialties

- Audiology
- Clinical Genetics
- Nephrology
- Ophthalmology
- Paediatrics

Specialist Service Group

- Renal

Associated Tests

Please note all the tests below will be undertaken for R194 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
R194.1	Haematuria Small panel	Singleton	Small variants	Panel of genes or loci	Haematuria (99)	Small panel
R194.2	Haematuria	Singleton	Exon level CNVs	Panel of genes or loci	Haematuria (99)	Exon level CNV detection by MLPA or equivalent

R195 Proteinuric renal disease

Testing Criteria

1. Steroid-resistant nephrotic syndrome presenting at any age, OR
2. Proteinuria with a histological picture of focal segmental glomerulosclerosis (FSGS) or diffuse mesangial sclerosis (DMS) on biopsy, with no identifiable cause, where a transplant or immunosuppression is planned

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

Where in Pathway

At presentation, or at a time when management requires a molecular diagnosis

Requesting Specialties

- Clinical Genetics
- Nephrology

Specialist Service Group

- Renal

Associated Tests

Please note all the tests below will be undertaken for R195 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
R195.1	Proteinuric renal disease WES or medium panel	Singleton	Small variants	Panel of genes or loci	Proteinuric renal disease (106)	WES or Medium Panel
R195.2	Proteinuric renal disease	Singleton	Exon level CNVs	Panel of genes or loci	Proteinuric renal disease (106)	Exon level CNV detection by MLPA or equivalent

R196 CFHR5 nephropathy

Testing Criteria

C3 glomerulopathy or unexplained haematuria or renal failure in a patient of Cypriot ancestry

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Nephrology

Specialist Service Group

- Renal

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R196.1	CFHR5 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	CFHR5	MLPA or equivalent

R197 Membranoproliferative glomerulonephritis including C3 glomerulopathy

Testing Criteria

Idiopathic membranoproliferative glomerulonephritis (MPGN) or C3 glomerulopathy with onset before the age of 18, together with one of:

1. Family history of MPGN or unexplained end-stage renal disease, OR
2. Renal transplant is being considered, OR
3. Patient is being considered for complement inhibitory therapies

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

Where in Pathway

At presentation, or at a time when management requires a molecular diagnosis or following assessment as part of the highly specialised atypical haemolytic uraemic syndrome service

Requesting Specialties

- Clinical Genetics
- Nephrology

Specialist Service Group

- Renal

Associated Tests

Please note all the tests below will be undertaken for R197 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R197.1	Membranoproliferative glomerulonephritis Small panel	Singleton	Small variants	Panel of genes or loci	Membranoproliferative glomerulonephritis (83)	Small panel
R197.2	Membranoproliferative glomerulonephritis MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	Membranoproliferative glomerulonephritis (83)	MLPA or equivalent

R198 Renal tubulopathies

Testing Criteria

Patients with a primary renal tubulopathy presenting as one of the following conditions:

1. Hypokalaemic alkalosis with normal or low blood pressure (e.g. Bartter/Gitelman syndromes), OR
2. Hypokalaemic alkalosis with elevated blood pressure (e.g. Liddle syndrome), OR
3. Hyperkalaemic acidosis with low/normal BP (PHA type 1), OR
4. Hyperkalaemic acidosis with elevated BP (PHA type 2), OR
5. Hypokalaemic acidosis (pRTA and renal Fanconi syndromes), OR
6. Hypomagnesaemia, OR
7. Nephrogenic diabetes insipidus, OR
8. Other rare types of renal tubulopathy seen in an expert center

NOTE: Patients with electrolyte imbalance secondary to non-renal processes should not be tested under this indication

Overlapping indications

- R183 Glucocorticoid-remediable aldosteronism (GRA)
- R344 Primary hyperaldosteronism – KCNJ5
- R256 Nephrocalcinosis or nephrolithiasis

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Nephrology

Specialist Service Group

- Renal

Associated Tests

Please note all the tests below will be undertaken for R198 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
R198.1	Renal tubulopathies WES or medium panel	Singleton	Small variants	Panel of genes or loci	Renal tubulopathies (292)	WES or Medium Panel
R198.2	Renal tubulopathies	Singleton	Exon level CNVs	Panel of genes or loci	Renal tubulopathies (292)	Exon level CNV detection by MLPA or equivalent

R199 Congenital anomalies of the kidney and urinary tract – familial

Testing Criteria

Clinically significant non-syndromic congenital anomalies of the kidney and urinary tract (CAKUT), with a first degree relative with CAKUT or unexplained end-stage renal disease

Families in which there are only minor forms of CAKUT are unlikely to benefit from genetic testing (e.g. isolated vesico-ureteric reflux, duplex kidney, posterior urethral valves)

Overlapping conditions:

- R141 Monogenic diabetes test should be used where there is a personal or family history of diabetes or renal cysts
- R27 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Nephrology
- Paediatrics

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R199.1	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray

R201 Atypical haemolytic uraemic syndrome

Testing Criteria

Acute renal failure AND thrombocytopenia AND microangiopathic haemolytic anaemia (Coombs test negative), in a patient being considered for complement inhibitory therapies

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

Where in Pathway

At presentation or following assessment as part of the highly specialized atypical haemolytic uraemic syndrome service

Requesting Specialties

- Clinical Genetics
- Haematology
- Nephrology

Specialist Service Group

- Renal

Associated Tests

Please note all the tests below will be undertaken for R201 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
R201.1	Atypical haemolytic uraemic syndrome Small panel	Singleton	Small variants	Panel of genes or loci	Atypical haemolytic uraemic syndrome (139)	Small panel
R201.3	CFH; CFHR1; CFHR3; CD46; CFI MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	CFH; CFHR1; CFHR3; CD46; CFI	MLPA or equivalent

R202 Tubulointerstitial kidney disease

Testing Criteria

1. Renal impairment caused by tubulointerstitial fibrosis with no glomerular lesion, with no identifiable cause, often associated with medullary cysts, hyperuricaemia or gout, AND
2. A first degree relative with TIKD or unexplained end-stage renal disease. Exceptions may be made for patients where the clinical presentation is highly suggestive of a monogenic aetiology, but family history is unknown eg. the patient was adopted

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Nephrology

Specialist Service Group

- Renal

Associated Tests

Please note all the tests below will be undertaken for R202 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
R202.1	Tubulointerstitial kidney disease Small panel	Singleton	Small variants	Panel of genes or loci	Tubulointerstitial kidney disease (548)	Small panel
R202.2	Tubulointerstitial kidney disease	Singleton	Exon level CNVs	Panel of genes or loci	Tubulointerstitial kidney disease (548)	Exon level CNV detection by MLPA or equivalent

R204 Hereditary systemic amyloidosis

Testing Criteria

Clinical features suggestive of hereditary amyloidosis which may include restrictive cardiomyopathy, autonomic and peripheral neuropathy, renal impairment or GI symptoms.

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

Where in Pathway

At presentation

Requesting Specialties

- Cardiology
- Clinical Genetics
- Nephrology
- Neurology
- Haematology
- Gastroenterology

Specialist Service Group

- Renal

Associated Tests

Please note all the tests below will be undertaken for R204 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
R204.1	Hereditary systemic amyloidosis Small panel	Singleton	Small variants	Panel of genes or loci	Amyloidosis (502)	Small panel
R204.2	Hereditary systemic amyloidosis	Singleton	Exon level CNVs	Panel of genes or loci	Amyloidosis (502)	Exon level CNV detection by MLPA or equivalent

R256 Nephrocalcinosis or nephrolithiasis

Testing Criteria

Nephrocalcinosis or nephrolithiasis where acquired causes have been excluded

Overlapping indications

- Where a primary endocrine disturbance of calcium homeostasis is identified, the appropriate specific test should be used
- In individuals with an identifiable primary renal disorder, the specific test for that disorder should be used where genetic testing is appropriate
- Individuals with nephrocalcinosis likely to be caused by Bartter syndrome can be tested using this indication; individuals with a different presentation of Bartter syndrome should be tested using R198 Renal tubulopathies

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

Where in Pathway

At presentation, after exclusion of acquired causes

Requesting Specialties

- Clinical Genetics
- Endocrinology
- Nephrology

Specialist Service Group

- Renal

Associated Tests

Please note all the tests below will be undertaken for R256 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
R256.1	Nephrocalcinosis or nephrolithiasis WES or medium panel	Singleton	Small variants	Panel of genes or loci	Nephrocalcinosis or nephrolithiasis (149)	WES or Medium Panel
R256.2	Nephrocalcinosis or nephrolithiasis	Singleton	Exon level CNVs	Panel of genes or loci	Nephrocalcinosis or nephrolithiasis (149)	Exon level CNV detection by MLPA or equivalent

R257 Unexplained young onset end-stage renal disease

Testing Criteria

End-stage renal disease developing under the age of 36, with no identifiable cause detectable by renal biopsy, biochemistry, imaging or clinical assessment

Use of this test in young adults over the age of 36 may be appropriate after expert clinical review, if there is strong clinical suspicion of a monogenic disorder

Overlapping conditions:

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

Testing Criteria for Semi-Rapid Testing

- Acutely unwell children or adults where monogenic young onset end-stage renal disease is considered highly likely to be the primary cause of the phenotype in the patient.

- Cases should meet the standard eligibility criteria for R257, AND

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

- The patient is either not eligible for the R14 pathway or Rapid R257 is considered to be the more appropriate test.

Where in Pathway

At presentation

Where in Pathway for Semi-Rapid Testing

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

Requesting Specialties

- Clinical Genetics
- Nephrology

Requesting Specialties for Semi-Rapid Testing

- Clinical Genetics
- Renal
- Neonatology

Specialist Service Group

- Renal

Associated Tests

R257.3 is only for semi urgent testing

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R257.2	Unexplained young onset end-stage renal disease WGS (phase 2)	Trio or singleton	Exon level CNVs, Small variants	Panel of genes or loci	Unexplained young onset end-stage renal disease (678)	WGS
R257.3	Unexplained young onset end-stage renal disease WES	Trio	Small variants	Panel of genes or loci	Unexplained young onset end-stage renal disease (678)	WES

Part XIX. Respiratory

R184 Cystic fibrosis diagnostic test

Testing Criteria

Test in an individual clinically likely to be affected with cystic fibrosis:

1. Child with clinical suspicion of CF (e.g. recurrent chest infections, failure to thrive, fat malabsorption, neonatal history of meconium ileus), AND
    a. A not normal sweat test performed in a recognised experienced test centre/laboratory (i.e. sweat chloride ≥30mM with sufficient sweat obtained), OR
    b. An additional urgent prenatal situation for the parents or for a close relative, but urgent sweat testing not accessible
2. Adult with CT-proven bronchiectasis, AND
    a. A not normal sweat test performed in a recognised experienced test centre/laboratory (i.e. sweat chloride ≥30mM with sufficient sweat obtained), OR
    b. Chronic suppurative chest infection with colonisation by Pseudomonas and Staph aureus, OR
    c. Additional exocrine pancreatic dysfunction
3. Idiopathic chronic pancreatitis with exocrine dysfunction (fat malabsorption) with other obvious and acquired causes excluded, AND
    a. A not normal sweat test performed in a recognised experienced test centre/laboratory (i.e. sweat chloride ≥30mM with sufficient sweat obtained), OR
    b. Sweat testing not practical, and all other causes excluded
4. Infertility associated with obstructive azoospermia, AND
    a. CBAVD (or isolated CUAVD) diagnosed from expert clinical examination, OR
    b. CBAVD identified at incidental herniotomy
5. Fetal echogenic bowel as bright as bone on 2nd trimester scan or dilated fetal bowel on 2nd or 3rd trimester scan with echogenic bowel as bright as bone, AND
    a. both parents not available for carrier testing [if both parents are available, Cystic fibrosis carrier testing should be used instead of an invasive prenatal test], AND
    b. Other more common causes excluded (e.g. IUGR, placental failure, earlier bleeding, infection, raised aneuploidy markers)

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

Where in Pathway

Initial population-specific targeted test sufficient to exclude CF as the likely diagnosis in the absence of a clear clinical diagnosis

Proceed to a full gene test if the targeted test is negative and there is a high clinical suspicion of a diagnosis of Cystic Fibrosis

Requesting Specialties

For R184.1 CFTR Targeted variant testing

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

For R184.2 and R184.3 Single gene sequencing and MLPA

- CF service,
- Clinical Genetics
- Respiratory medicine

Specialist Service Group

- Core

Associated Tests

Please note all the tests below will be undertaken for R184 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

R65 “Aminoglycoside exposure posing risk to hearing” testing will be carried out in any patient with a confirmed diagnosis of Cystic Fibrosis as a result of the R184 test.

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R184.1	CFTR Targeted variant testing	Singleton	Small variants	Single gene(s)	CFTR (1318)	Targeted variant testing
R184.2	CFTR Single gene sequencing	Singleton	Small variants	Single gene(s)	CFTR (1318)	Single gene sequencing >=10 amplicons
R184.3	CFTR MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	CFTR (1318)	MLPA or equivalent

R185 Cystic fibrosis carrier testing

Testing Criteria

1. Prospective egg or sperm donor
2. Family history of CF in close relative (up to 4th degree, i.e. in 1st cousin's child or closer relative), or in a similar close relative of partner
3. Partner of a known CF carrier
4. Close consanguineous couple (1st cousins), AND from an ethnic group with a high carrier frequency
5. Both parents of a fetus with echogenic bowel (where both parents are available)
6. Both parents of a fetus with dilated bowel (where both parents are available)

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

Overlapping indications

R184 Cystic fibrosis diagnostic test should be used where a fetus has echogenic bowel and BOTH parents are not available for testing

Where in Pathway

At time of reproductive planning

Requesting Specialties

- Clinical Genetics
- Fetal Medicine
- Gynaecology
- Respiratory medicine
- General practice

Specialist Service Group

- Core

Associated Tests

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

R253 Cystic fibrosis newborn screening follow-up

Testing Criteria

Positive IRT test on newborn screening, according to definition in the National Standard Protocol for Cystic Fibrosis

Where in Pathway

According to the National Standard Protocol for Cystic Fibrosis

Requesting Specialties

- Appropriate specialist referring clinician

Specialist Service Group

- Screening

Associated Tests

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

R333 Central congenital hypoventilation

Testing Criteria

Clinical features suggestive of congenital central hypoventilation syndrome:

1. Central alveolar hypoventilation, AND
2. Absence of primary lung, cardiac or neuromuscular cause or identifiable brainstem lesion, WITH OR WITHOUT the following additional PHOX2B-reated features:
   a. Hirschsprung disease, OR
   b. Neuroblastoma or other neural crest tumour, OR
   c. Autonomic dysfunction, for example affecting the cardiovascular system, gastrointestinal tract, sweating or temperature control

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Neonatology
- Neurology
- Respiratory Medicine

Specialist Service Group

- Respiratory

Associated Tests

Please note all the tests below will be undertaken for R333 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary.

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R333.1	PHOX2B STR testing	Singleton	STRs	Single gene(s)	PHOX2B (1314)	STR testing
R333.2	PHOX2B Single gene sequencing	Singleton	Small variants	Single gene(s)	PHOX2B (1314)	Single gene sequencing >=10 amplicons
R333.3	PHOX2B	Singleton	Exon level CNVs	Single gene	PHOX2B	Exon level CNV detection by MLPA or equivalent

R139 Laterality disorders and isomerism

Testing Criteria

1. Classical heterotaxy affecting more than one body system, OR
2. Non-classical heterotaxy (an isolated heterotaxy-type malformation), OR
3. Combination of malformations which may occur in heterotaxy but which are not diagnostic of heterotaxy (e.g. oesophageal atresia with intestinal malrotation)

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

Where in Pathway

At presentation

Requesting Specialties

- Cardiology
- Clinical Genetics

Specialist Service Group

- Respiratory

Associated Tests

Please note all the tests below will be undertaken for R139 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
R139.1	Laterality disorders and isomerism WES or medium panel	Singleton	Small variants	Panel of genes or loci	Laterality disorders and isomerism (549)	WES or Medium Panel
R139.2	Laterality disorders and isomerism	Singleton	Exon level CNVs	Panel of genes or loci	Laterality disorders and isomerism (549)	Exon level CNV detection by MLPA or equivalent

R186 Hereditary haemorrhagic telangiectasia

Testing Criteria

Test where any THREE of the following criteria are met:

1. Epistaxis: spontaneous, recurrent nose bleeds
2. Telangiectases: multiple, at characteristic sites (lips, oral cavity, fingers, nose)
3. Visceral lesions such as gastrointestinal telangiectasia (with or without bleeding), pulmonary arteriovenous malformation (AVM), hepatic AVM, cerebral AVMs, spinal AVM
4. Family history: a first degree relative with HHT according to these criteria (as above) or an autosomal dominant family history of nosebleeds or first degree relative with cerebral AVM / cerebral haemorrhage / pulmonary or hepatic AVM.

Alternatively, test where any ONE of the following criteria are met:

A) Personal history of at least one pulmonary AVM*

B) Personal history of two or more AVMs at one or more characteristic sites (pulmonary*, cerebral, hepatic or spinal)

C) Personal history of at least one AVM and severe epistaxis or characteristic telangiectasia or family history

D) Personal history of telangiectasia, and refractory or severe epistaxis (e.g. requiring recurrent transfusions) *

*Pulmonary AVM only if confirmed by cross sectional imaging (usually thoracic CT scan), and/or later therapeutic angiography/surgery. Do not diagnose if only supported by a positive right-to-left shunt study ("bubble echo") or chest x-ray.

To Note: if there is no antecedent family history implying a "first in family" case more likely to be mosaic.

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Dermatology
- Gastroenterology
- Neurology
- Respiratory Medicine

Specialist Service Group

- Respiratory

Associated Tests

Please note all the tests below will be undertaken for R186 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
R186.1	Hereditary haemorrhagic telangiectasia Small panel	Singleton	Small variants	Panel of genes or loci	Hereditary haemorrhagic telangiectasia (123)	Small panel
R186.2	Hereditary haemorrhagic telangiectasia	Singleton	Exon level CNVs	Panel of genes or loci	Hereditary haemorrhagic telangiectasia (123)	Exon level CNV detection by MLPA or equivalent

R188 Pulmonary arterial hypertension

Testing Criteria

Idiopathic PAH or suspected Familial/Heritable Pulmonary Arterial Hypertension (PAH).

Overlapping indications

- R186 Hereditary haemorrhagic telangiectasia test should be used in patients with PAH and HHT

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Respiratory Medicine

Specialist Service Group

- Respiratory

Associated Tests

Please note all the tests below will be undertaken for R188 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
R188.1	Pulmonary arterial hypertension Small panel	Singleton	Small variants	Panel of genes or loci	Pulmonary arterial hypertension (193)	Small panel
R188.2	Pulmonary arterial hypertension	Singleton	Exon level CNVs	Panel of genes or loci	Pulmonary arterial hypertension (193)	Exon level CNV detection by MLPA or equivalent

R189 Respiratory ciliopathies including non-CF bronchiectasis

Testing Criteria

1. Neonatal presentation with at least one of:
    a. Situs inversus plus lower airway or nasal symptoms, OR
    b. Persistent respiratory distress where other causes have been excluded, OR
    c. Persistent rhinorrhea and cough where other causes have been excluded, OR
2. Testing in childhood with at least one of:
    a. Persistent life-long wet cough (CF excluded)
    b. Unexplained bronchiectasis (CF excluded)
    c. Serous otitis media in association with lower and upper airway symptoms
3. Testing in adults who have had symptoms as above since early childhood, often associated with infertility or subfertility

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Respiratory Medicine

Specialist Service Group

- Respiratory

Associated Tests

Please note all the tests below will be undertaken for R189 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
R189.1	Respiratory ciliopathies including non-CF bronchiectasis WES or medium panel	Singleton	Small variants	Panel of genes or loci	Respiratory ciliopathies including non-CF bronchiectasis (550)	WES or Medium Panel
R189.2	Respiratory ciliopathies including non-CF bronchiectasis	Singleton	Exon level CNVs	Single gene	Respiratory ciliopathies including non-CF bronchiectasis (550)	Exon level CNV detection by MLPA or equivalent

R190 Pneumothorax – familial

Testing Criteria

Primary spontaneous pneumothorax with no identifiable cause, AND one of:

- A first degree relative with primary spontaneous pneumothorax, OR
- Characteristic radiological features of Birt-Hogg-Dubé syndrome on chest imaging

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Respiratory Medicine

Specialist Service Group

- Respiratory

Associated Tests

Please note all the tests below will be undertaken for R190 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
R190.1	Pneumothorax – familial Small panel	Singleton	Small variants	Panel of genes or loci	Pneumothorax – familial (105)	Small panel
R190.2	Pneumothorax – familial	Singleton	Exon level CNVs	Panel of genes or loci	Pneumothorax – familial (105)	Exon level CNV detection by MLPA or equivalent

R191 Alpha-1-antitrypsin deficiency

Testing Criteria

Plasma concentration of alpha-1-antitrypsin below normal range, AND

1. Prolonged neonatal jaundice with an inconclusive alpha-1-antitrypsin phenotyping result, OR
2. Mutation analysis will inform reproductive choice, OR
3. Adult with cirrhosis or emphysema where a genetic diagnosis would influence management following an inconclusive alpha-1-antitrypsin phenotyping result

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

Where in Pathway

In most patients, an alpha-1-antitrypsin phenotyping test will be sufficient to establish the diagnosis

Genetic testing can be used for diagnostic confirmation in the situations specified in the Eligibility Criteria

Cascade testing of relatives is rarely indicated.

Requesting Specialties

- Clinical Genetics
- Gastroenterology
- Hepatology
- Respiratory Medicine
- General practice

Specialist Service Group

- Respiratory

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R191.1	SERPINA1 common mutations Targeted variant testing	Singleton	Small variants	Single interval	SERPINA1 common mutations	Targeted variant testing

R192 Surfactant deficiency

Testing Criteria

1. Neonatal respiratory insufficiency of disproportionate severity for advanced gestation, with clinical and X-ray features consistent with pulmonary surfactant deficiency, AND
2. No other obvious cause for respiratory distress e.g. no difficult delivery, no infection, no prematurity

With or without a known family history of surfactant deficiency

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Neonatology
- Respiratory Medicine

Specialist Service Group

- Respiratory

Associated Tests

Please note all the tests below will be undertaken for R192 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
R192.1	Surfactant deficiency Small panel	Singleton	Small variants	Panel of genes or loci	Surfactant deficiency (551)	Small panel
R192.2	Surfactant deficiency	Singleton	Exon level CNVs	Panel of genes or loci	Surfactant deficiency (551)	Exon level CNV detection by MLPA or equivalent

R330 Alveolar capillary dysplasia with misalignment of pulmonary veins

Testing Criteria

1. Respiratory distress and severe pulmonary hypertension presenting within the first two days of life, and without any sustained response to supportive measures, AND
2. Additional malformations affecting cardiac, gastrointestinal and genitourinary systems

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Neonatology
- Respiratory Medicine

Specialist Service Group

- Respiratory

Associated Tests

Please note all the tests below will be undertaken for R330 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
R330.1	FOXF1 Single gene sequencing	Singleton	Small variants	Single gene(s)	FOXF1 (1211)	Single gene sequencing >=10 amplicons
R330.2	FOXF1	Singleton	Exon level CNVs	Panel of genes or loci	FOXF1 (1211)	Exon level CNV detection by MLPA or equivalent

R421 Pulmonary Fibrosis Familial

Testing Criteria

Interstitial Lung Disease (ILD) and **ONE** of the following:

1. ILD, no identifiable cause or association, and age <50 years.
2. Family history of ILD regardless of identifiable cause or association
3. For suspected telomerase complex mutations, testing to be considered in the absence of 1. and 2. above if one or more of the following are present in addition to ILD:
   - unexplained haematological abnormalities including macrocytosis, anaemia, thrombocytopenia, leukopenia and/or isolated lymphopenia;
   - unexplained haematological abnormalities including macrocytosis, anaemia, thrombocytopenia, leukopenia and/or isolated lymphopenia; premature greying,
   - or unexplained liver function abnormalities.
   - Consideration of lung transplantation

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Respiratory Medicine
- Haematology
- Hepatology

Specialist Service Group

- Respiratory

Associated Tests

Please note all the tests below will be undertaken for R421 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
R421.1	Pulmonary Fibrosis Familial	Singleton	Small variants	Panel of genes or loci	Medium panel to be created in PanelApp	WES or medium panel
R421.2	Pulmonary Fibrosis Familial	Singleton	Exon level CNVs	Panel of genes or loci	Medium panel to be created in PanelApp	Exon level CNV detection by MLPA or equivalent

R426 Pulmonary alveolar microlithiasis

Testing Criteria

Individuals with a clinical suspicion/diagnosis of PAM including presence of diffuse intra-alveolar microliths, typically with widespread nodular calcification, on chest imaging.

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Genomic laboratory
- Respiratory medicine

Specialist Service Group

- Respiratory

Associated Tests

Please note all the tests below will be undertaken for R426 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
R426.1	Pulmonary alveolar microlithiasis Single gene sequencing	Singleton	Small variants	Single gene(s)	SLC34A2 (1383)	Single gene sequencing >=10 amplicons
R426.2	Pulmonary alveolar microlithiasis	Singleton	Exon level CNVs	Single gene	SLC34A2 (1383)	Exon level CNV detection by MLPA or equivalent

Part XX. Dermatology

R110 Segmental overgrowth disorders – Deep sequencing

Testing Criteria

Clinical features suggestive of a segmental overgrowth disorder. Features may include:

1. Congenital or early onset segmental overgrowth (which may affect the brain only, i.e. megalencephaly)
2. Confirmed Vascular malformations (capillary, venous, lymphatic or combinations) following discussion with a specialist
3. Characteristic cutaneous features (for example epidermal naevi or connective tissue naevi)
4. Brain malformations (for example hydrocephalus or cortical malformations)
5. Additional dysmorphism (for example polydactyly)

Overlapping indications

- R27 Paediatric disorders or R89 Ultra-rare and atypical monogenic disorders tests should be considered in overlapping features are present but germline mutation is considered likely

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

NOTE: Many of these disorders are anticipated to be mosaic and sample type and test technology must take account of this. An assay capable of detecting mosaicism below 10% should be used, e.g high read depth sequencing and an appropriate bioinformatic pipeline.

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Dermatology
- Surgery*

*plastic

Specialist Service Group

- Dermatology

Associated Tests

Please note all the tests below will be undertaken for R110 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
R110.1	Segmental overgrowth disorders – Deep sequencing Small panel	Singleton	Small variants	Panel of genes or loci	Segmental overgrowth disorders – Deep sequencing (98)	Small panel
R110.2	Segmental overgrowth disorders – Deep sequencing	Singleton	Exon level CNVs	Panel of genes or loci	Segmental overgrowth disorders – Deep sequencing (98)	Exon level CNV detection by MLPA or equivalent

R163 Ectodermal dysplasia

Testing Criteria

Individuals with a clinical diagnosis of ectodermal dysplasia who have one or more of:

1. Abnormalities of hair (hypotrichosis, sparse hair, sparse/missing eyebrows)
2. Abnormalities of teeth (hypodontia, conical incisors)
3. Abnormalities of skin (hypohidrosis, episodes of hyperthermia)

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Dermatology
- Surgical Dentistry

Specialist Service Group

- Dermatology

Associated Tests

Please note all the tests below will be undertaken for R163 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
R163.1	Ectodermal dysplasia WES or Medium panel	Singleton	Small variants	Panel of genes or loci	Ectodermal dysplasia (553)	WES or Medium panel
R163.2	Ectodermal dysplasia	Singleton	Exon level CNVs	Panel of genes or loci	Ectodermal dysplasia (553)	Exon level CNV detection by MLPA or equivalent

R164 Epidermolysis bullosa and congenital skin fragility

Testing Criteria

Individuals with a clinical diagnosis of epidermolysis bullosa or other forms of unexplained skin fragility including peeling skin syndrome

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

Where in Pathway

For most patients, the test will be arranged as part of assessment in the highly specialised epidermolysis bullosa service

Requesting Specialties

- Clinical Genetics
- Dermatology

Specialist Service Group

- Dermatology

Associated Tests

Please note all the tests below will be undertaken for R164 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
R164.1	Epidermolysis bullosa and congenital skin fragility WES or medium panel	Singleton	Small variants	Panel of genes or loci	Epidermolysis bullosa and congenital skin fragility (554)	WES or Medium Panel
R164.2	Epidermolysis bullosa and congenital skin fragility	Singleton	Exon level CNVs	Panel of genes or loci	Epidermolysis bullosa and congenital skin fragility (554)	Exon level CNV detection by MLPA or equivalent

R165 Ichthyosis and erythrokeratoderma

Testing Criteria

Individuals with at least TWO features from the list below:

1. Born with collodion membrane
2. Erythroderma
3. Dark plate-like scales or fine white scaling
4. Ectropium/eclabium
5. Hyperkeratosis

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Dermatology
- Neonatology

Specialist Service Group

- Dermatology

Associated Tests

Please note all the tests below will be undertaken for R165 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
R165.1	Ichthyosis and erythrokeratoderma WES or Medium panel	Singleton	Small variants	Panel of genes or loci	Ichthyosis and erythrokeratoderma (555)	WES or Medium panel
R165.2	Ichthyosis and erythrokeratoderma	Singleton	Exon level CNVs	Panel of genes or loci	Ichthyosis and erythrokeratoderma (555)	Exon level CNV detection by MLPA or equivalent

R166 Palmoplantar keratodermas

Testing Criteria

Individuals with unexplained isolated or syndromic keratodermas, including those occurring as part of generalised skin disease.

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Dermatology

Specialist Service Group

- Dermatology

Associated Tests

Please note all the tests below will be undertaken for R166 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
R166.1	Palmoplantar keratodermas WES or Medium panel	Singleton	Small variants	Panel of genes or loci	Palmoplantar keratodermas (556)	WES or Medium panel
R166.2	Palmoplantar keratodermas	Singleton	Exon level CNVs	Panel of genes or loci	Palmoplantar keratodermas (556)	Exon level CNV detection by MLPA or equivalent

R167 Autosomal recessive primary hypertrophic osteoarthropathy

Testing Criteria

Individuals with unexplained digital clubbing, AND either periostosis OR pachydermia

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Dermatology
- Respiratory Medicine
- Rheumatology

Specialist Service Group

- Dermatology

Associated Tests

Please note all the tests below will be undertaken for R167 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
R167.1	Autosomal recessive primary hypertrophic osteoarthropathy Small panel	Singleton	Small variants	Panel of genes or loci	Autosomal recessive primary hypertrophic osteoarthropathy (557)	Small panel
R167.2	Autosomal recessive primary hypertrophic osteoarthropathy	Singleton	Exon level CNVs	Panel of genes or loci	Autosomal recessive primary hypertrophic osteoarthropathy (557)	Exon level CNV detection by MLPA or equivalent

R227 Xeroderma pigmentosum, Trichothiodystrophy or Cockayne syndrome

Testing Criteria

1. Confident clinical diagnosis of xeroderma pigmentosum plus specific XP-related features in the eye, neurological system or a related cancer, OR
2. Confident clinical diagnosis of trichothiodystrophy, OR
3. Confident clinical diagnosis of Cockayne syndrome

Overlapping indications

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

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

Where in Pathway

Skin biopsy for complementation testing (specialist DNA repair test) is likely to be required in many patients to confirm the results of the panel test; this can be carried out in parallel with or after the genetic panel test, usually as part of assessment in the Highly Specialised service for xeroderma pigmentosum.

Requesting Specialties

- Clinical Genetics
- Dermatology

Specialist Service Group

- Dermatology

Associated Tests

Please note that the following tests below will be undertaken for R227 dependent on the clinical presentation and/or initial results.

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R227.1	Xeroderma pigmentosum, Trichothiodystrophy or Cockayne syndrome Small panel	Singleton	Small variants	Panel of genes or loci	Xeroderma pigmentosum, Trichothiodystrophy or Cockayne syndrome (77)	Small panel
R227.2	Genomewide DNA repair defect testing	Singleton	DNA repair	Genomewide	Genomewide	DNA repair defect testing
R227.3	Xeroderma pigmentosum, Trichothiodystrophy or Cockayne syndrome	Singleton	Exon level CNVs	Panel of genes or loci	Xeroderma pigmentosum, Trichothiodystrophy or Cockayne syndrome (77)	Exon level CNV detection by MLPA or equivalent

R230 Multiple monogenic benign skin tumours

Testing Criteria

Three or more benign skin tumours suggesting a diagnosis of any of the following conditions, with at least two histologically confirmed:

1. Familial cylindromatosis, OR
2. Brooke-Spiegler syndrome, OR
3. Multiple Familial Trichoepithelioma, OR
4. Muir-Torre syndrome, OR
5. Buschke-Ollendorff syndrome*, OR
6. Birt-Hogg-Dubé syndrome

*One skin biopsy may be sufficient to make a confident diagnosis

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Dermatology

Specialist Service Group

- Dermatology

Associated Tests

Please note all the tests below will be undertaken for R230 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
R230.1	Multiple monogenic benign skin tumours Small panel	Singleton	Small variants	Panel of genes or loci	Multiple monogenic benign skin tumours (558)	Small panel
R230.2	FLCN MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	FLCN	MLPA or equivalent

R236 Pigmentary skin disorders

Testing Criteria

1. Multiple café-au-lait macules where neurofibromatosis type 1 (NF1) has been excluded either clinically or on genetic testing, OR
2. Poikiloderma with a likely genetic cause, OR
3. Other forms of reticulate, patchy or speckled hypo- or hyperpigmentation with a likely genetic cause

Overlapping indications

- R222 Neurofibromatosis type 1 test should be used where features are typical of this condition
- R343 Chromosomal mosaicism – microarray test should be used where this is the likely diagnosis
- R327 Mosaic skin disorders – deep sequencing test should be used where the likely cause is a mosaic genetic change, as the technology applied to the mosaic disorders will be more sensitive to these than the panel test designed to detect germline disorders

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Dermatology

Specialist Service Group

- Dermatology

Associated Tests

Please note all the tests below will be undertaken for R236 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R236.1	Pigmentary skin disorders WES or Large panel	Singleton	Small variants	Panel of genes or loci	Pigmentary skin disorders (559)	WES or Large panel
R236.2	SPRED1 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	SPRED1	MLPA or equivalent

R237 Cutaneous photosensitivity with a likely genetic cause

Testing Criteria

Clinical diagnosis of a genetic condition causing cutaneous photosensitivity, for example Rothmund-Thompson syndrome, hydroa vacciniforme

Overlapping indications

- Porphyria (cutaneous presentation, R168 or R170) should be tested using the appropriate porphyria test
- R227 Xeroderma pigmentosum, Trichothiodystrophy or Cockayne syndrome test should be used where there is a high likelihood that this is the diagnosis

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Dermatology

Specialist Service Group

- Dermatology

Associated Tests

Please note all the tests below will be undertaken for R237 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
R237.1	Cutaneous photosensitivity with a likely genetic cause Small panel	Singleton	Small variants	Panel of genes or loci	Cutaneous photosensitivity with a likely genetic cause (560)	Small panel
R237.1	Cutaneous photosensitivity with a likely genetic cause	Singleton	Exon level CNVs	Panel of genes or loci	Cutaneous photosensitivity with a likely genetic cause (560)	Exon level CNV detection by MLPA or equivalent

R239 Incontinentia pigmenti

Testing Criteria

Confident clinical diagnosis of incontinentia pigmenti

Overlapping indications

- If the presentation is not specific to incontinentia pigmenti, please use one of the broader tests, for example the R165 Ichthyosis and erythrokeratoderma, R163 Ectodermal dysplasia or R236 Pigmentary skin disorders tests

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Dermatology
- Neonatology
- Neurology
- Ophthalmology

Specialist Service Group

- Dermatology

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R239.1	IKBKG Single gene sequencing	Singleton	Small variants	Single gene(s)	IKBKG (1347)	Single gene sequencing >=10 amplicons

R255 Epidermodysplasia verruciformis

Testing Criteria

Severe widespread infection with human papillomavirus in the absence of detectable immunodeficiency, with or without squamous cell carcinoma

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Dermatology

Specialist Service Group

- Dermatology

Associated Tests

Please note all the tests below will be undertaken for R255 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
R255.1	Epidermodysplasia verruciformis Small panel	Singleton	Small variants	Panel of genes or loci	Epidermodysplasia verruciformis (562)	Small panel
R255.2	Epidermodysplasia verruciformis	Singleton	Exon level CNVs	Panel of genes or loci	Epidermodysplasia verruciformis (562)	Exon level CNV detection by MLPA or equivalent

R326 Vascular skin disorders

Testing Criteria

Vascular skin disorders with a likely germline genetic cause

Overlapping indications

- R327 Mosaic skin disorders – deep sequencing test should be used where a mosaic cause is likely, as the technology used for this test will be more sensitive to detect mosaicism
- R110 Segmental overgrowth disorders test should be used where relevant

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Dermatology

Specialist Service Group

- Dermatology

Associated Tests

Please note all the tests below will be undertaken for R326 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
R326.1	Vascular skin disorders WES or Medium panel	Singleton	Small variants	Panel of genes or loci	Vascular skin disorders (563)	WES or Medium panel
R326.2	Vascular skin disorders	Singleton	Exon level CNVs	Panel of genes or loci	Vascular skin disorders (563)	Exon level CNV detection by MLPA or equivalent

R327 Mosaic skin disorders – deep sequencing

Testing Criteria

Dermatological abnormality likely to have a mosaic single gene cause

Overlapping indications

- R110 Segmental overgrowth disorders test should be used where relevant
- R343 Chromosomal mosaicism – microarray test should be used where a microarray is required

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

NOTE: Many of these disorders are anticipated to be mosaic and sample type and test technology need to take account of this e.g. in planning coverage of NGS assay

Testing for McCune-Albright syndrome is eligible under this clinical indication – appropriate sample type (e.g. diseased tissue) should be considered for this phenotype

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Dermatology

Specialist Service Group

- Dermatology

Associated Tests

Please note all the tests below will be undertaken for R327 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
R327.1	Mosaic skin disorders – deep sequencing Medium panel	Singleton	Small variants	Panel of genes or loci	Mosaic skin disorders – deep sequencing (564)	Medium panel
R327.2	Mosaic skin disorders – deep sequencing	Singleton	Exon level CNVs	Panel of genes or loci	Mosaic skin disorders – deep sequencing (564)	Exon level CNV detection by MLPA or equivalent

R332 Rare genetic inflammatory skin disorders

Testing Criteria

Clinical diagnosis of a rare inflammatory skin disorder of probably genetic origin, including autoinflammatory disease (e.g. early onset urticaria, recurrent febrile erythemas), infantile pustular psoriasis, likely genetic forms of pityriasis rubra pilaris

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Dermatology
- Rheumatology

Specialist Service Group

- Dermatology

Associated Tests

Please note all the tests below will be undertaken for R332 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
R332.1	Rare genetic inflammatory skin disorders WES or Medium panel	Singleton	Small variants	Panel of genes or loci	Rare genetic inflammatory skin disorders (565)	WES or Medium panel
R332.2	Rare genetic inflammatory skin disorders	Singleton	Exon level CNVs	Panel of genes or loci	Rare genetic inflammatory skin disorders (565)	Exon level CNV detection by MLPA or equivalent

R424 Subcutaneous panniculitis T-cell lymphoma (SPTCL)

Testing Criteria

1. New diagnosis of SPTCL (to guide therapeutic management)
2. Suspected SPTCL (to aid diagnosis)

Detection of the germline HAVCR2 variant is associated with the life-threatening complication of haemophagocytic lymphohistiocytosis (HLH) in a subset of SPTCL patients and also indicates which patients may benefit from immunosuppressive therapy (eg Cyclosporin) as opposed to chemotherapy

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Dermatology
- Oncology

Specialist Service Group

- Dermatology

Associated Tests

Please note all the tests below will be undertaken for R424 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
R424.1	Subcutaneous panniculitis T-cell lymphoma (SPTCL)	Singleton	Small variants	Single gene	HAVCR2 (1394)	Single gene sequencing <=10 amplicons

Note: two founder point mutations not dosage
HAVCR2 c.245A>G (p.Tyr82Cys) and c.219A>G (p.Ile97Met)

Part XXI. Ultra-rare and atypical monogenic disorders

R89 Ultra-rare and atypical monogenic disorders

Testing Criteria

- This clinical indication should be used for patients with ultra-rare disorders or atypical manifestations of recognised monogenic disorders that make broad analysis of multiple gene panels that potentially cross different clinical indications the optimal approach. (e.g. for patients where two or more potential genetic disorders are suspected and the patient is eligible for more than one non-WGS test, WGS via R89 could be used).

- **R89 should not be used if appropriate testing is available via another test in the test directory** (e.g. if testing for monogenic hearing loss only is required this should be requested by the test available for R67).

- **If the patient meets the eligibility criteria for another WGS clinical indication then that indication should be requested as the primary reason for referral but additional panels can be requested, as appropriate,** (e.g. R29 intellectual disability).

- Gene panels must be selected for clinical indication R89. These should be entered into the 'Additional panel(s)' box on the WGS test order form.

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Core

Associated Tests

Please note all the tests below will be undertaken for R89 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
R89.2	Genomewide Microarray	Singleton	Genomewide CNVs	Genomewide	Genomewide	Microarray
R89.3	Relevant panels in PanelApp WGS (phase 1)	Trio or singleton	Exon level CNVs, Small variants, STRs	Panel of genes or loci	Relevant panel(s) in PanelApp	WGS

Part XXII. Multi-purpose tests

R240 Diagnostic testing for known mutation(s)

Testing Criteria

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

This indication is relevant for prenatal and postnatal diagnosis

Where in Pathway

As dictated by clinical situation

Requesting Specialties

- Clinical Genetics
- Other

Specialist Service Group

- Core or Specialised; depending on the clinical scenario

Associated Tests

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

R242 Predictive testing for known familial mutation(s)

Testing Criteria

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

Where in Pathway

As dictated by clinical situation

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Core or Specialised; depending on the clinical scenario

Associated Tests

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

R244 Carrier testing for known familial mutation(s)

Testing Criteria

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

The range of specialties who will request this test will depend on the disorder in question

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

Where in Pathway

As dictated by clinical situation

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Core or Specialised; depending on the clinical scenario

Associated Tests

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

R246 Carrier testing at population risk for partners of known carriers of nationally agreed autosomal recessive disorders

Testing Criteria

This Clinical Indication relates to carrier testing in partners of individuals who are affected with, or are known carriers of, an autosomal recessive condition, where management of a current or future pregnancy would be impacted by the result, and the couple would be eligible either for PGD, or for prenatal diagnosis under the clinical indication R240 Diagnostic testing for known mutation(s).

In most autosomal recessive conditions, cascade testing of wider family members and unrelated partners is NOT indicated. Clinicians wishing to request a test under this indication should check with their GLH whether the test is feasible prior to offering testing to patients.

Testing is not usually indicated in this context because the test results have a minimal impact on the risk of health problems in pregnancies beyond the parents and siblings of the affected individual:

1. For most genes, interpreting the results of population risk carrier testing is complex, and the proportion of detected variants which can be confidently used for reproductive purposes is low
2. Carrier testing at population risk is not able to rule out an unrelated partner being a carrier of the condition, only reduce the likelihood
3. The carrier frequency of most autosomal recessive conditions is low, such that the marginal gain from genetic testing of an unrelated partner has limited impact on the prenatal decision-making process

However, there are circumstances in which the chance of a baby being affected is more substantial, and carrier testing is possible. Testing is more likely to be considered appropriate where the following criteria are met:

1. Presence of a homozygous or compound heterozygous genotype in a baby would have a sufficiently predictable effect to permit reproductive choices to be made; for example, carrier testing for haemochromatosis or alpha-1-antitrypsin deficiency is NOT appropriate as it is not possible to predict from the genotype whether an affected baby will ever develop medical problems
2. The associated gene is well-understood and does not contain a high level of novel, benign variation, such that it is likely to be possible to interpret variants found on full gene testing in individuals at population risk; in this context only likely pathogenic or pathogenic variants according to the ACGS / ACMG classification will be reported

PLUS one of the following:

1. The carrier frequency of the condition is higher than 1 in 70 (in the relevant population(s) for the patient to be tested)
2. The couple are consanguineous (second cousins or closer); where this is the only criterion that is met, testing will be limited to the known familial variant.

In exceptional circumstances and after discussion with the home GLH, testing may be considered appropriate in situations where the gene is suitable for testing and there are known pathogenic variant(s), that can be tested for, that account for the majority of cases in the relevant population(s) for the patient to be tested; in this context, the test will primarily target the pathogenic variants that account for the majority of cases in the relevant population(s).

NOTE: The following specific clinical indications should be used instead for the relevant disorders:

- R181 Congenital adrenal hyperplasia carrier testing
- R361 Haemoglobinopathy trait or carrier testing
- R362 Carrier testing for sickle cell disease
- R252 SMA carrier testing at population risk for partners of known carriers
- R105 MCADD – Medium-chain acyl-CoA dehydrogenase deficiency – common variant
- R185 Cystic fibrosis carrier testing

Table 1. Example autosomal recessive conditions with a carrier frequency higher than 1 in 70 in these example populations, which would be covered by this clinical indication. Note these are examples only and the indication covers a much wider range of conditions and populations where evidence of high carrier frequency is available and the criteria above are met.

Disease	Gene	Carrier frequency
Deafness, autosomal recessive 1A	*GJB2*	1 in 50 in European populations
Gaucher disease	*GBA*	1 in 25 in Ashkenazi population
Phenylketonuria	*PAH*	1 in 50 in European populations
Tay-Sachs disease	*HEXA*	1 in 30 in Ashkenazi population

Where in Pathway

As dictated by clinical situation

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Core or Specialised; depending on the autosomal disorder being investigated

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R246.1	Specific target Single gene sequencing	Singleton	Small variants	Single gene(s)	Relevant single gene	Single gene sequencing >=10 amplicons

R321 Maternal cell contamination testing

Testing Criteria

Pregnancy requiring maternal cell contamination to inform interpretation of other testing, for example invasive prenatal testing, tests on fetal tissues or tests performed on cord blood

Testing will often be initiated by the testing laboratory but relevant samples will be required in advance of testing

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

Where in Pathway

As appropriate

Requesting Specialties

- Clinical Genetics
- Genomics laboratory

Specialist Service Group

- Core or Specialised; depending on the clinical scenario

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R321.1	Genomewide Identity testing	Multiple affected individuals	Identity	Genomewide	Genomewide	Identity testing

R320 Invasive prenatal diagnosis requiring fetal sexing

Testing Criteria

Pregnancy requiring sexing on invasive prenatal sample to inform management

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

Where in Pathway

As appropriate

Requesting Specialties

- Clinical Genetics
- Genomics laboratory

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R320.1	Sex determination testing	Singleton	Aneuploidy	Genomewide	Other	Common aneuploidy testing

R263 Confirmation of uniparental disomy

Testing Criteria

Confirmation of probable UPD identified by methylation testing at imprinted loci and UPD identified via other routes, for example SNP array, exome ore genome sequencing. This could include testing for mosaic genome-wide UPD

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

Where in Pathway

As appropriate

Requesting Specialties

- Clinical Genetics
- Genomics laboratory

Specialist Service Group

- Core or Specialised; depending on the clinical scenario

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R263.1	Specific target UPD testing	Trio	Small variants	Single interval	As relevant to clinical setting	UPD testing

R264 Identity testing

Testing Criteria

Where biological relationships need to be determined to guide diagnostic interpretation or alter advice

Where in Pathway

N/A

Requesting Specialties

- Clinical Genetics
- Genomics laboratory

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R264.1	Identity testing	Singleton	Identity	Other	Other	Identity testing

R111 X-inactivation testing

Testing Criteria

Clinical setting where X-inactivation testing will alter clinical management and/or assist reclassification of variant using the ACMG guidelines

Where in Pathway

After MDT discussion

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Core or Specialised; depending on the clinical scenario

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R111.1	X-inactivation testing	Singleton	Methylation	Single interval	Other	X-inactivation testing

R370 Validation test

Testing Criteria

Validation using a second test or technique when required for diagnostic reporting.

Examples of settings in which this indication may be used include

- Variants detected outside of an accredited process where the accuracy of the result needs to be validated.
- where the sample has passed outside an accredited pipeline and confirmation of sample identity is required

Where in Pathway

Following primary test where required

Requesting Specialties

- Clinical Genetics
- Genomics laboratory

Specialist Service Group

- Core or Specialised; depending on the clinical scenario

Associated Tests

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

R443 Confirmation test

Testing Criteria

Confirmation using a second technique where required to provide diagnostic reporting.

Where in Pathway

Following primary test where required

Requesting Specialties

- Clinical Genetics
- Genomics laboratory

Specialist Service Group

- Core or Specialised; depending on the clinical scenario

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R443.1	Specific target Targeted variant testing	Singleton	Small variants, CNVs and STRs	Single interval	Specific Target	Targeted variant testing

R442 Variant Re-interpretation

Testing Criteria

Interpretation of a known variant to determine if the pathogenic status has changed since primary analysis and reporting or a previous re-interpretation. Re-interpretation of a variant may be performed as a result of;

- A request from a clinician responsible for a patient with a reported variant of uncertain significance,

OR

- new evidence available that will likely change the classification of a variant. For example, the identification of additional patient(s) with the same genetic variant or new functional evidence,

AND

- where either; there is new clinical information related to the patient or their family, or sufficient time has passed that there may be additional published evidence or knowledge, that could result in a change to the classification of the variant.

Where in Pathway

Following primary test where required

Requesting Specialties

- Clinical Genetics
- Genomics laboratory

Specialist Service Group

- Core or Specialised; depending on the clinical scenario

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R442.1	Specific target Targeted variant testing	Singleton	Small variants	Single interval	Specific Target	Targeted variant testing

R375 Family follow-up testing to aid variant interpretation

Testing Criteria

Family follow-up testing to aid variant interpretation

Where in Pathway

Where requested by the laboratory

Requesting Specialties

- Clinical Genetics
- Other

Specialist Service Group

- Core or Specialised; depending on the clinical scenario

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R375.1	Specific target Targeted variant testing	Singleton	Small variants	Single interval	Specific Target	Targeted variant testing

R387 Reanalysis of existing data

Testing Criteria

Reanalysis of data which has previously been interpreted and reported is required, due to:

1. New clinical information or clinical events which would substantially change the relevant genomic target, OR
2. Sufficient time has passed since the initial analysis that new gene discovery will have substantially increased the relevant genomic target, OR
3. A technical or scientific advance requires reanalysis of a group of tests to detect an important new source of actionable diagnoses

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

Where in Pathway

Following discussion with the genomics laboratory to ensure stored data is suitable for reanalysis and that the request is aligned to the national guidance for reanalysis (https://future.nhs.uk/NHSgenomics/view?objectId=154355365).

The R387 request form should be used to provide all required information. This can be obtained from the Genomic Laboratory Hub or via NHS Futures for those with access (https://future.nhs.uk/NHSgenomics/view?objectId=156197061).

Requesting Specialties

- Clinical Genetics
- Genomics laboratory

Specialist Service Group

- Core or Specialised; depending on the clinical scenario

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R387.1	Reanalysis of existing data	Multiple affected individuals	Other	Other	As per updated indication	Other

R296 RNA analysis of variants

Testing Criteria

Variant(s) requiring RNA analysis to aid interpretation where a molecular diagnosis will guide management or alter advice through reclassification of a variant from ACMG class 3 to class 4 or class 5

Testing should be discussed in advance with the laboratory

Where in Pathway

Following MDT discussion of candidate splice variant

Requesting Specialties

- Clinical Genetics
- Genomics laboratory

Specialist Service Group

- Core or Specialised; depending on the disorder and associated variant being investigated
-

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R296.1	Specific target RNA analysis	Singleton	Complex variants	Other	As dictated by variant under investigation	Other

R346 DNA to be stored

Testing Criteria

To be requested where genetic testing is likely to be required in future, but further information or discussion is needed before a test request is made

Where in Pathway

At any time, including where a sample is available e.g. because phlebotomy is being undertaken for other investigations and a future genetic test is likely to be required

Requesting Specialties

- Clinical Genetics
- Other

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R346.1	DNA Storage	Singleton	Other	Other	No target identified at this stage	Other

R373 RNA to be stored

Testing Criteria

To be requested where RNA testing is likely to be required in future, but further information or discussion is needed before a test request is made

Where in Pathway

Following discussion with the laboratory

Requesting Specialties

- Clinical Genetics
- Other

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R373.1	RNA Storage	Singleton	Other	Other	No target identified at this stage	Other

R322 Skin fibroblasts to be cultured and stored

Testing Criteria

Skin fibroblast sample requiring culture and storage for potential future testing

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

Where in Pathway

As appropriate

Requesting Specialties

- Clinical Genetics
- Dermatology
- Metabolic Medicine
- Neurology
- Other

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R322.1	Skin fibroblast culture and storage	Singleton	Other	Other	No target identified at this stage	Other

R374 Other sample to be stored

Testing Criteria

To be requested where testing of other sample types (for example, lymphocyte culture) is likely to be required in future, but further information or discussion is needed before a test request is made

Overlapping indications

- R346 DNA to be stored, R373 RNA to be stored and R322 Skin fibroblasts to be cultured and stored should be used instead where relevant

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

Where in Pathway

Following discussion with the laboratory

Requesting Specialties

- Clinical Genetics
- Other

Specialist Service Group

- Core

Associated Tests

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

R407 Patient undergoing allogeneic haematopoietic stem cell transplantation

Testing Criteria

Allogeneic transplant where chimerism knowledge will be informative to patient management.

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

Overlapping indications

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

Where in Pathway

As dictated by clinical situation

Requesting Specialties

- Clinical Genetics
- Other

Specialist Service Group

- Core or Specialised; depending on the clinical scenario

Associated Tests

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

R428 Patient receiving solid organ transplantation (only in cases where passenger lymphocyte syndrome is suspected)

Testing Criteria

Patient is post-solid organ transplant and the treating clinician has concerns they have developed passenger lymphocyte syndrome based on their clinical presentation; i.e. they have developed cytopenias not wholly explainable via other causes.

Allogeneic transplant where chimerism knowledge will aid patient management.

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

Overlapping indications

- M242 Any patient receiving solid organ transplantation – same test duplicated in the cancer Test Directory

Where in Pathway

As dictated by clinical situation

Requesting Specialties

- Oncology
- Appropriate specialist referring clinician

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R428.1	Patient undergoing allogeneic solid organ transplantation STR testing	Singleton	Short tandem repeats	Targeted variant testing	Relevant gene(s) or loci	STR testing
R428.2	Patient undergoing allogeneic solid organ transplantation CNV testing	Singleton	CNVs	Targeted variant testing	Sex chromosomes	FISH

R409 Linkage testing for other recognisable Mendelian disorders

Testing Criteria

Patients with a recognisable mendelian disorder where linkage testing will guide patient management (if informative), where linkage testing is not facilitated via an alternative clinical indication.

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

Where in Pathway

As dictated by clinical situation

Requesting Specialties

- Clinical Genetics
- Other

Specialist Service Group

- Core or Specialised; depending on the clinical scenario

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R409.1	Linkage testing for other recognisable Mendelian disorders	Multiple affected individuals	Other	Single gene(s) or loci	Relevant gene(s) or loci	Linkage analysis

R447 Diagnostic discovery - validation/confirmation of findings

Testing Criteria

Validation and/or confirmation of putative diagnostic findings returned from whole genome sequencing data from 100,000 genome project or GMS patients, through the NHS Diagnostic discovery pathways. This will involve analytical validation and interpretation of the genomic variant(s) with or without confirmatory testing by an orthogonal test as required.

Overlapping indications

R370 validation testing should be used for the validation of potential diagnostic findings identified outside of the WGS Diagnostic Discovery pathway.

Where in Pathway

Following primary test where required

Requesting Specialties

- Genomics laboratory

Specialist Service Group

- Core or Specialised; depending on the clinical scenario

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R447.1	Diagnostic discovery – validation/confirmation of findings	Singleton	Small variants, CNVs, STRs	Single interval	Specific Target	Targeted variant testing

R448 Prenatal testing

Testing Criteria

Ongoing pregnancy requiring prenatal testing for a specific disorder where the familial variant(s) have already been identified in a relative

Where in Pathway

As dictated by clinical situation

Requesting Specialties

Clinical Genetics

Specialist Service Group

- Core or Specialised; depending on the clinical scenario.

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R448.1	Prenatal testing	Singleton	Small variants, CNVs, STRs	Single interval	Specific Target	Targeted variant testing

R431 Genome-wide DNA Methylation Profiling to Aid Variant Interpretation

Testing Criteria

Patients must have a plausibly significant VUS in a gene which is covered by this test (see below).

The list of disorders/genes is available at: https://mft.nhs.uk/app/uploads/2023/08/Methylation-Array-Panel-content-for-EpiSign.pdf.

Patients can be referred by clinical genetics or from an appropriate specialty via consultation with clinical genetics.

Please note that this test requires DNA extracted from peripheral blood preferably obtained at more than 6 months of age.

Where in Pathway

Following discussion with Clinical Genetics and the testing laboratory

Requesting Specialties

- Clinical Genetics

Specialist Service Group

- Multi specialty

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R431.1	Genome-wide DNA Methylation Profiling to Aid Variant Interpretation	Singleton	Methylation signature	Genomewide	Genomewide	Methylation microarray