National Genomic Test Directory

Rare and Inherited Disease

Version 1: December 2024

Summary

The HSE established the National Genetics and Genomics Office (NGGO) in 2023 to implement the National Strategy for Accelerating Genetic and Genomic Medicine in Ireland (the Strategy). The Strategy outlines the way forward for the genetics and genomics service in Ireland. The development of a National Genomic Test Directory was identified as a way forward in enhancing genetic and genomic clinical services by promoting evidence based, equitable, and timely access to genetic and genomic tests.

The NGGO evaluated international examples of genomic test directories and identified the UK NHS England version as the most suitable to reference to establish a similar HSE National Genomic Test Directory for Rare and Inherited Disease (the Test Directory). Elements of the Scotland National Genomic Test Directory were also incorporated into the development of the Test Directory.

Through a series of collaborative workshops with clinical specialists and their laboratory colleagues, the NGGO worked to identify the appropriate test, requesting specialties and clinical indications relevant to the population of Ireland and the Irish health care system.

The Test Directory identifies the most appropriate test for each clinical indication and the testing methodology by which it should be delivered. This document includes the eligibility criteria setting out which patients should be considered for testing under that indication, and the requesting specialties is a list of the clinical specialties who would be expected to request the test.

Version 1 of the Test Directory includes tests for clinical indications from the specialties of Cardiology, Lipids, Metabolic, Mitochondrial, and Ophthalmology. The development of a centralised National Genomic Processing Service (NGPS, Genomic Laboratory) in 2025 will enable the operationalisation of the Test Directory by ensuring that the right test is requested for the right patient at the right time in the right laboratory and this will reduce clinical risk associated with genomic testing in Ireland

Only tests included in the Test Directory can be requested through the National Genomic Processing Service.

The Test Directory is available on the NGGO webpage on the HSE website: National Genetics and Genomics - HSE.ie

Document overview

Clinical Indications

The following elements are presented for each clinical indication:

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

Requesting specialties have been determined as appropriate specialties for referrals for testing through consultation with clinical specialists. The list of requesting specialties is not designed to operate at a very specific level or to limit test requests to just those clinical specialties listed if established alternative clinical pathways to testing are in place.

If the National Genomic Processing Service (NGPS, the Genomic Laboratory) receives a test request from a clinician whose role does not fall within a single requesting specialty, or whose clinical specialty is not listed for that clinical indication, the Genomic Laboratory can process that test if it is appropriate, and the eligibility criteria for the clinical indication is being met.

Associated Tests

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

Information provided includes:

Optimal Family Structure: the optimal family structure for testing if relevant relatives are available:

- Singleton;
- Trio or Singleton;

Scope: the type of variation to be detected:

- Small variant detection;
- Copy number variant detection;
- Short tandem repeat analysis;
- Complex variant detection;

Target Type: the type of target at which the variants need to be detected:

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

Target Name: the name(s) of the gene(s) at which the variant type should be detected.

Test Method: the test method(s) to be used:

- WES (Whole Exome Sequencing);
- Large panel;
- Medium panel;
- Small panel;
- Single gene sequencing;
- Targeted variant testing;
- STR (Short Tandem Repeats) testing;
- MLPA (Multiplex Ligation Probe Amplification) or equivalent;
- Other

Test Ordering

Clinicians requesting a genomic test can do so by;

- Requesting the appropriate clinical indication as provided in the Test Directory.
- If the clinician is aware that some of the constituent tests which are offered as part of the clinical indication are not needed, they should specify to the laboratory which constituent tests are required and which are not.
- As much relevant clinical details as possible should be provided to allow the NGPS to efficiently ensure the test selection is appropriate and to aid interpretation of results by the analysing laboratory.

After selecting a genomic test, the NGPS Test Request Form will require completion by the requesting clinician. As a pre-requisite for submission of the sample to the NGPS, completion of the Minimum Data is required. The NGPS Test Request Form will be available on the NGGO webpage on the HSE website: National Genetics and Genomics - HSE.ie from the NGPS 'go-live' date.

In instances where the clinical indication described to the NGPS indicates that a constituent(s) part of a test is more suitable than the requested test, the constituent(s) part will be requested by the NGPS. Testing should be targeted at patients where a genetic or genomic diagnosis will guide management for the proband or family.

Glossary

- Singleton – the patient
- Duo – testing of patient performed simultaneously alongside one of their biological parents
- Trio – testing of patient performed simultaneously alongside both biological parents
- SNVs – Small nucleotide variants
- CNVs – Copy number variants

Find Text in Document

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

1. Press CTRL+F (Windows) or CMD+F (Mac)

2. In text box, enter search term

3. The first match will be highlighted

4. Press Enter or click the arrow keys to navigate between results

Contents

Part I: Cardiology

Arrhythmias Global

Testing Criteria

Cardiac arrest survivors or patients with polymorphic ventricular tachycardia or idiopathic ventricular fibrillation without clear diagnosis of long or short QT syndrome, Brugada syndrome or CPVT

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

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

Overlapping indications

- Specific cardiomyopathy categories should be used where features are typical of Long QT, Brugada syndrome, CPVT or Short QT.

Where in Pathway

At presentation

Requesting Specialties

- Cardiology (should be requested or triaged by an IICCN Cardiologist)
- Clinical Genetics

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Arrhythmias Global	Singleton	Small variants, CNVs	Panel of genes or loci	*CACNA1C, CACNA1D, CALM1, CALM2, CALM3, CASQ2, CAV3, CDH2, DES, DSC2, DSG2, DSP, EMD, FHL1, FLNC, GLA, HCN4, JUP, KCNE1, KCNH2, KCNJ2, KCNQ1, LAMP2, LMNA, MYBPC3, NKX2-5, PKP2, PLN, PRKAG2, RYR2, SCN5A, SLC22A5, TBX5, TECRL, TMEM43, TNNI3K, TRDN, TRPM4, TTR*	WES or Medium Panel

Atrial fibrillation

Testing Criteria

1. Premature onset of Atrial Fibrillation < 30 years of age in the setting of a structurally normal heart and in the absence of a trigger such as alcohol excess, hyperthyroidism or infection
2. Premature onset of Atrial Fibrillation < 40 years of age in the setting of a structurally normal heart with at least one first degree family member < 40 years of age with atrial fibrillation and in the absence of a trigger such as alcohol excess, hyperthyroidism or infection

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

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

Where in Pathway

At presentation

Requesting Specialties

- Cardiology (should be requested or triaged by an IICCN Cardiologist)
- Clinical Genetics

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Atrial fibrillation	Singleton	Small variants, CNVs	Panel of genes or loci	*ACTC1, EMD, GATA4, GJA5, HCN4, KCNA5, KCND3, KCNE1, KCNE2, KCNE3, KCNE5, KCNJ2, KCNQ1, LMNA, NKX2-5, NKX2-6, NPPA, PITX2, RYR2, SCN1B, SCN2B, SCN4B, SCN5A, TBX5, TTR*	WES or Medium Panel

Brugada syndrome and cardiac sodium channel disease

Testing Criteria

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

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

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

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

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

Where in Pathway

At presentation

Requesting Specialties

- Cardiology (should be requested or triaged by an IICCN Cardiologist)
- Clinical Genetics

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Brugada syndrome and cardiac sodium channel disease	Singleton	Small variants, CNVs	Panel of genes or loci	*SCN5A*	Small panel

Cardiomyopathies and Arrhythmias Global

Testing Criteria

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

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

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

OR

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

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

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

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

Where in Pathway

At presentation

Requesting Specialties

- Cardiology (should be requested or triaged by an IICCN Cardiologist)
- Clinical Genetics

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Sudden unexplained death or survivors of a cardiac event	Singleton	Small variants, CNVs	Panel of genes or loci	*ACTC1, ACTN2, ALPK3, BAG3, CACNA1C, CACNA1D, CALM1, CALM2, CALM3, CASQ2, CAV3, CDH2, CSRP3, DES, DMD, DOLK, DSC2, DSG2, DSP, EMD, FHL1, FHOD3, FKTN, FLNC, GLA, HCN4, JPH2, JUP, KCNE1, KCNH2, KCNJ2, KCNQ1, LAMA2, LAMP2, LDB3, LMNA, MYBPC3, MYH6, MYH7, MYL2, MYL3, NEXN, NKX2-5, PKP2, PLN, PRDM16, PRKAG2, RBM20, RYR2, SCN5A, SLC22A5, SLC25A4, TBX5, TBX20, TECRL, TMEM43, TNNC1, TNNI3, TNNI3K, TNNT2, TPM1, TRDN, TRIM63, TRPM4, TTN, TTR, VCL*	WES or Medium Panel

Cardiomyopathies Global

Testing Criteria

Patients with features of Arrhythmogenic or Dilated Cardiomyopathy who also have left ventricular hypertrophy (LV wall thickness ≥ 15mm)

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

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

Overlapping indications

- Specific cardiomyopathy categories should be used where features are typical of non-syndromic hypertrophic, dilated or arrhythmogenic cardiomyopathy in individuals over the age of 12.

Where in Pathway

At presentation

Requesting Specialties

- Cardiology (should be requested or triaged by an IICCN Cardiologist)
- Clinical Genetics

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Cardiomyopathies Global	Singleton	Small variants, CNVs	Panel of genes or loci	*ACTC1, ACTN2, ALPK3, BAG3, CDH2, CSRP3, DES, DMD, DOLK, DSC2, DSG2, DSP, EMD, FHL1, FHOD3, FKTN, FLNC, GLA, JPH2, JUP, LAMA2, LAMP2, LDB3, LMNA, MYBPC3, MYH6, MYH7, MYL2, MYL3, NEXN, NKX2-5, PKP2, PLN, PRDM16, PRKAG2, RBM20, RYR2, SCN5A, TBX20, TMEM43, TNNC1, TNNI3, TNNT2, TPM1, TTN, TTR, VCL, TRIM63*	WES or Medium Panel

Catecholaminergic polymorphic VT

Testing Criteria

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

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

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

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

Where in Pathway

At presentation

Requesting Specialties

- Cardiology (should be requested or triaged by an IICCN Cardiologist)
- Clinical Genetics

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Catecholaminergic polymorphic VT	Singleton	Small variants, CNVs	Panel of genes or loci	*CALM1, CALM2, CALM3, CASQ2, RYR2, TECRL, TRDN*	Small Panel

Dilated and arrhythmogenic cardiomyopathy

Testing Criteria

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

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

OR

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

OR

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

OR

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

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

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

Patients with ventricular dilatation secondary to coronary artery disease or pressure/volume overload should NOT be tested.
Patients with DCM due to other precipitants (such as myocarditis, alcohol, chemotherapy) should only be tested following consultation with an expert or after discussion in an MDT
Testing should be carried out in parallel with expert phenotypic assessment in an Inherited Cardiac Conditions Clinic (ICC), including support from clinical genetics; testing may occasionally be appropriate outside these criteria following discussion in an ICC MDT.

Overlapping indications

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

Where in Pathway

At presentation

Requesting Specialties

- Cardiology (should be requested or triaged by an IICCN Cardiologist)
- Clinical Genetics

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Dilated and arrhythmogenic cardiomyopathy	Singleton	Small variants, CNVs	Panel of genes or loci	*ACTC1, ACTN2, BAG3, CDH2, DES, DMD, DOLK, DSC2, DSG2, DSP, EMD, FLNC, JUP, LAMP2, LMNA, MYBPC3, MYH7, NEXN, NKX2-5, PKP2, PLN, RBM20, SCN5A, TMEM43, TNNC1, TNNI3, TNNI3K, TNNT2, TPM1, TTN, VCL*	WES or Medium Panel

Hypertrophic cardiomyopathy

Testing Criteria

A firm clinical diagnosis of hypertrophic cardiomyopathy as indicated by:

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

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

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

Overlapping indications

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

Where in Pathway

At presentation

Requesting Specialties

- Cardiology (should be requested or triaged by an IICCN Cardiologist)
- Clinical Genetics

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Hypertrophic cardiomyopathy	Singleton	Small variants, CNVs	Panel of genes or loci	*ACTC1, ACTN2, ALPK3, CSRP3, FHL1, FHOD3, FLNC, GLA, JPH2, LAMP2, MYBPC3, MYH7, MYL2, MYL3, PLN, PRKAG2, TNNC1, TNNI3, TNNT2, TPM1, TTR, TRIM63*	WES or Medium Panel

Long QT syndrome

Testing Criteria

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

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

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

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

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

Where in Pathway

At presentation

Requesting Specialties

- Cardiology (should be requested or triaged by an IICCN Cardiologist)
- Clinical Genetics

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Long QT syndrome	Singleton	Small variants, CNVs	Panel of genes or loci	*CACNA1C, CALM1, CALM2, CALM3, KCNE1, KCNH2, KCNJ2, KCNQ1, SCN5A, TRDN*	Small Panel

Paediatric or syndromic cardiomyopathy

Testing Criteria

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

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

Overlapping indications

- In individuals where cardiomyopathy is one of multiple features of a likely multisystem disorder, other tests should be considered to enable testing of broader targets and familial testing where available, after referral to clinical genetics.
- Specific cardiomyopathy panels should be used where features are typical of non-syndromic hypertrophic, dilated or arrhythmogenic cardiomyopathy in individuals over the age of 12.

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

Where in Pathway

At presentation

Requesting Specialties

- Cardiology (should be requested or triaged by an IICCN Cardiologist)
- Clinical Genetics

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Paediatric or syndromic cardiomyopathy	Trio or singleton	Small variants, CNVs	Panel of genes or loci	*AARS2, ABCC9, ACAD9, ACADVL, ACTA1, ACTC1, ACTN2, AGK, ALMS1, ALPK3, BAG3, BRAF, CACNA1C, CAV3, CDH2, COA6, COX10, COX15, CPT2, CSRP3, DES, DMD, DNAJC19, DOLK, DSC2, DSG2, DSP, EMD, EPG5, FHL1, FHOD3, FKRP, FKTN, FLNC, GAA, GLA, GLB1, GUSB, HADHA, HADHB, HRAS, IDH2, IDUA, JPH2, JUP, KRAS, LAMA2, LAMP2, LDB3, LMNA, LMOD2, LZTR1, MAP2K1, MAP2K2, MLYCD, MRAS, MRPL3, MRPL44, MRPS22, MUT, MYBPC3, MYH6, MYH7, MYL2, MYL3, MYLK3, MYPN, NDUFA11, NDUFA2, NDUFAF1, NDUFB11, NDUFS1, NDUFS2, NDUFS4, NDUFS8, NDUFV2, NEXN, NKX2-5, NONO, NRAP, NRAS, PCCA, PCCB, PKP2, PLD1, PLN, PPA2, PPCS, PPP1CB, PPP1R13L, PRDM16, PRKAG2, PTPN11, RAF1, RBM20, RIT1, RRAGC, RRAGD, RYR2, SCN5A, SCO1, SCO2, SHOC2, SLC22A5, SLC25A20, SLC25A3, SLC25A4, SOS1, SOS2, SPEG, SPRED2, TAZ, TBX20, TMEM43, TMEM70, TNNC1, TNNI3, TNNI3K, TNNT2, TPM1, TSFM, TTN, TTR, TRIM63, VCL*	WES

Premature cardiac conduction disease

Testing Criteria

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

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

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

Where in Pathway

At presentation

Requesting Specialties

- Cardiology (should be requested or triaged by an IICCN Cardiologist)
- Clinical Genetics

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Progressive cardiac conduction disease	Singleton	Small variants, CNVs	Panel of genes or loci	*CACNA1D, DES, EMD, GLA, HCN4, KCNJ2, LAMP2, LMNA, NKX2-5, PRKAG2, SCN5A, SLC22A5, TBX5, TNNI3K, TRPM4, TTR*	WES or Small Panel

Short QT syndrome

Testing Criteria

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

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

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

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

Where in Pathway

At presentation

Requesting Specialties

- Cardiology (should be requested or triaged by an IICCN Cardiologist)
- Clinical Genetics

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Short QT syndrome	Singleton	Small variants, CNVs	Panel of genes or loci	*CACNA1C, KCNH2, KCNJ2, KCNQ1, SLC22A5*	Small Panel

Thoracic aortic aneurysm or dissection

Testing Criteria

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

*Thoracic aortic aneurysm defined as:

- In children: Z score > 2 for body surface area
- In adults: Dilatation > 40 mm or Aorta Height Index > 24mm/m

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

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

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Thoracic aortic aneurysm or dissection	Singleton	Small variants, CNVs	Panel of genes or loci	*ABL1, ACTA2, ASPH, BGN, CBS, COL3A1, COL5A1, COL5A2, EFEMP2, ELN, FBLN5, FBN1, FBN2, FKBP14, FLNA, IPO8, LOX, MFAP5, MYH11, MYLK, NOTCH1, PLOD1, PRKG1, SKI, SLC2A10, SMAD2, SMAD3, SMAD4, SMAD6, TGFB2, TGFB3, TGFBR1, TGFBR2*	WES or Medium Panel

Part II: Lipids

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

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Familial Chylomicronaemia Syndrome (FCS)	Singleton	Small variants, CNVs	Panel of genes or loci	*APOA5, APOC2, APOE, CREB3L3, GPD1, GPIHBP1, LMF1, LPL*	Small Panel

Part III: Metabolic

Amino acid disorders & disorders of neurotransmission

Testing Criteria

Clinical and/or biochemical phenotype suggesting an amino acid disorder or disorder of neurotransmission, with supportive biochemical testing. Where biochemical testing indicates a single gene test, please indicate this on the referral 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 following biochemical testing and assessment by a Consultant in Metabolic Medicine/Neurology/Paediatric Neurology or Clinical Genetics.

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Amino acid disorders & disorders of neurotransmission	Singleton	Small variants, Exon level CNVs	Panel of genes or loci	*ABAT, ALDH18A1, ALDH5A1, ALDH7A1, AMT, ASPA, CBS, CTH, D2HGDH, DBH, DDC, FAH, GABRG2, GCDH, GCH1, GLDC, GLRA1, HGD, L2HGDH, MAT1A, OAT, PAH, PCBD1, PNPO, QDPR, SLC25A22, SLC6A19, SLC7A7, SUOX*	WES or Medium Panel

Classical Galactosaemia

Testing Criteria

Clinical and/or biochemical features suggestive of Galactosaemia. Biochemical tests supportive of diagnosis (Increase galactose in blood).

Note: Testing following newborn screening should follow the established sample and testing pathways set out in the National Newborn Bloodspot Screening Programme protocol.

Referrals for testing will be triaged by the Genomic 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 biochemical diagnosis of Galactosaemia and assessment by a Consultant in Metabolic Medicine/Neurology/Paediatric Neurology or Clinical Genetics.

Carrier testing of at-risk expectant parents to guide postnatal feeding decisions.

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Obstetrics

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Target	Method
Classical Galactosaemia	Singleton	Small variants, Exon level CNVs	Single gene(s)	*GALT*	Sanger MLPA

Disorders associated with hyperammonaemia / fatty acid oxidation / ketogenesis / ketolysis

Testing Criteria

Clinical features suggestive of Disorders associated with Hyperammonaemia / Fatty Acid Oxidation / Ketogenesis / Ketolysis (e.g. encephalopathy, severe vomiting or loss of consciousness). Biochemical tests supportive of diagnosis (e.g. Plasma ammonia >150umol/L or Hypoketotic hypoglycaemia or severe ketoacidosis). Where biochemical testing indicates a single gene test, please indicate this on the referral 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 following laboratory testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Disorders associated with hyperammonaemia / fatty acid oxidation / ketogenesis / ketolysis	Singleton	Small variants, Exon level CNVs	Panel of genes or loci	*ACADM, ACADS, ACADVL, ARG1, ASL, ASS1, CPS1, CPT1A, CPT2, ETFA, ETFB, ETFDH, GLUD1, HADHA, HADHB, HMGCL, HMGCS2, IVD, LPIN1, MMAA, MMAB, MMACHC, MMADHC, MUT, NAGS, OAT, OTC, OXCT1, PCCA, PCCB, SLC16A1, SLC22A5, SLC25A13, SLC25A15, SLC25A20, SLC7A7, SLC52A2, SLC52A3*	WES or Large Panel

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

Associated Tests

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

Name	Optimal Family Structure	Scope(s)	Target Type	Target	Method
Fabry disease	Singleton	Small variants	Single gene(s)	*GLA*	Single gene sequencing
Fabry disease	Singleton	Exon level CNVs	Single gene(s)	*GLA*	MLPA or equivalent

Fatty acid oxidation

Testing Criteria

Clinical features suggestive of a Fatty Acid Oxidation disorder. Biochemical tests supportive of diagnosis. Where biochemical testing indicates testing of a single gene, please indicate this on the referral 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

Following laboratory testing and assessment by a Consultant in Metabolic Medicine/Neurology/Paediatric Neurology or Clinical Genetics or Endocrinology.

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology
- Endocrinology

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Fatty acid oxidation	Singleton	Small variants, Exon level CNVs	Panel of genes or loci	*ACADM, ACADS, ACADVL, CPT1A, CPT2, ETFA, ETFB, ETFDH, HADHA, HADHB, HMGCL, HMGCS2, IVD, MMAA, MMAB, MMACHC, MMADHC, OXCT1, SLC22A5, SLC25A20, SLC52A2, SLC52A3*	Medium Panel

Glutaric acidaemia I

Testing Criteria

Clinical and/or biochemical features of Glutaric Acidaemia type 1.

Note: Testing following newborn screening should follow the established sample and testing pathways set out in the National Newborn Bloodspot Screening Programme protocol.

Referrals for testing will be triaged by the Genomic 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 biochemical diagnosis or where GA1 suspected from the clinical presentation (note - classic biochemical findings are not always present)

Requesting Specialties

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

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Target	Method
Glutaric acidaemia I	Singleton	Small variants	Single gene(s)	*GCDH*	Single gene sequencing

Glycogen storage disease

Testing Criteria

Clinical and laboratory features characteristic of Glycogen storage disease.

Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing (Whole Exome Sequencing) 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 a single gene is suspected please indicate this on referring form.

Where in Pathway

At presentation following laboratory testing

Requesting Specialties

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

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Glycogen storage disease	Singleton	Small variants, CNVs	Panel of genes or loci	*AGL, ALDOA, ALDOB, ENO3, EPM2A, FBP1, G6PC, GAA, GBE1, GYG1, GYS1, GYS2, LAMP2, LDHA, NHLRC1, PFKM, PGAM2, PGK1, PGM1, PHKA1, PHKA2, PHKB, PHKG2, PRKAG2, PYGL, PYGM, RBCK1, SLC2A2, SLC37A4*	WES or Medium Panel

Homocystinuria

Testing Criteria

Biochemical tests supportive of diagnosis (High homocysteine levels in blood).

Note: Testing following newborn screening should follow the established sample and testing pathways set out in the National Newborn Bloodspot Screening Programme protocol.

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family. Where single gene is suspected please indicate on referral form.

Where in Pathway

Following laboratory testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Ophthalmology

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Homocystinuria	Singleton	Small variants, Exon level CNVs	Panel of genes or loci	*CBS, MMADHC, MTHFR, MTR, MTRR*	Small Panel

Lysosomal Storage Disease

Testing Criteria

1. Clinical phenotype suggesting a lysosomal storage disorder, AND
2. Abnormal biochemical testing (such as urine MPS/ 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 (Whole Exome Sequencing) early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

Where a single disorder/gene is suspected please indicate on referral 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 following laboratory testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Lysosomal storage disorder	Singleton	Small variants, CNVs	Panel of genes or loci	*AGA, ARSA, ARSB, ARSG, ASAH1, ATP13A2, CLN3, CLN5, CLN6, CLN8, CTNS, CTSA, CTSD, CTSF, CTSK, DNAJC5, FUCA1, GAA, GALC, GALNS, GBA, GLA, GLB1, GM2A, GNE, GNPTAB, GNPTG, GNS, GUSB, HEXA, HEXB, HGSNAT, HYAL1, IDS, IDUA, LAMP2, LIPA, MAN2B1, MANBA, MCOLN1, MFSD8, NAGA, NAGLU, NEU1, NPC1, NPC2, PPT1, PSAP, SGSH, SLC17A5, SMPD1, SUMF1, TPP1, VPS16, VPS33A*	WES or Medium Panel

Maple syrup urine disease (MSUD)

Testing Criteria

Clinical and/or biochemical features suggestive of Maple Syrup Urine Disease.

Note: Testing following newborn screening should follow the established sample and testing pathways set out in the National Newborn Bloodspot Screening Programme protocol.

Referrals for testing will be triaged by the Genomic Laboratory; testing 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 and assessment by a Consultant in Metabolic Medicine/Neurology/Paediatric Neurology or Clinical Genetics.

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Maple syrup urine disease (MSUD)	Singleton	Small variants, Exon level CNVs	Panel of genes or loci	*BCKDHA, BCKDHB, DBT*	Small Panel

MCADD - Medium-chain acyl-CoA dehydrogenase deficiency – common variants

Testing Criteria

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

Note: Testing following newborn screening should follow the established sample and testing pathways set out in the National Newborn Bloodspot Screening Programme protocol.

Where in Pathway

Following biochemical diagnosis

Requesting Specialties

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

Associated Tests

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

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

Testing Criteria

Likely MCADD identified requiring testing of the full ACADM gene.

Overlapping indications

- 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

Note: Testing following newborn screening should follow the established sample and testing pathways set out in the National Newborn Bloodspot Screening Programme protocol.

Where in Pathway

N/A

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neonatology
- Paediatrics

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Target	Method
MCADD	Singleton	Small variants	Other	*ACADM*	Single gene sequencing

Mucopolysaccharidosis (MPS) panel

Testing Criteria

Clinical features suggestive of a Mucopolysaccharidosis disorder. Biochemical tests supportive of diagnosis (Abnormal urine MPS). Where biochemical testing indicates testing of a single gene, please indicate this on the referral 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 following biochemical testing

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Mucopolysaccharidosis	Singleton	Small variants, Exon level CNVs	Panel of genes or loci	*ARSB, ARSK, GALNS, GLB1, GNS, GUSB, HGSNAT, HYAL1, IDS, IDUA, NAGLU, SGSH*	Medium Panel

Neural ceroid lipofuscinosis

Testing Criteria

Clinical and laboratory features characteristic of Neuronal ceroid lipofuscinosis.

Overlapping indications

- 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 (Whole Exome Sequencing) 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 a single gene is suspected please indicate on referral form

Where in Pathway

At presentation following histological analysis and/or enzyme testing.

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Neuronal ceroid lipofuscinosis	Singleton	Small variants, CNVs	Panel of genes or loci	*ATP13A2, CLCN6, CLN3, CLN5, CLN6, CLN8, CTSD, CTSF, DNAJC5, KCTD7, MFSD8, PPT1, TPP1*	Small Panel

Organic acidaemias & cofactor / vitamin disorders

Testing Criteria

Clinical features suggestive of an organic acidaemia or cofactor / vitamin disorder. Biochemical tests supportive of diagnosis (e.g. abnormal results of urine organic acid or amino acid screen, anaemia, unexplained deficiency of a specific vitamin). Where biochemical testing indicates testing of a single gene, please indicate this on the referral 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 following biochemical testing.
At presentation following assessment by a Consultant in Metabolic Medicine/Neurology/Paediatric Neurology or Clinical Genetics.

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Organic acidaemias & cofactor / vitamin disorders	Singleton	Small variants, Exon level CNVs	Panel of genes or loci	*ABCD4, ACSF3, AMN, AUH, BCKDHA, BCKDHB, BTD, CUBN, DBT, DHFR, DNAJC19, FOLR1, GIF, HCFC1, HLCS, IVD, LMBRD1, LPIN1, MCCC1, MCCC2, MCEE, MLYCD, MMAA, MMAB, MMACHC, MMADHC, MTHFD1, MTHFR, MTR, MTRR, MUT, OPA3, PC, PCCA, PCCB, PDHA1, PDHB, PDHX, PRDX1, SLC19A3, SLC46A1, SLC52A3, SUCLA2, SUCLG1, TAZ, TCN2, TMEM70*	WES or Large Panel

Phenylketonuria

Testing Criteria

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

Note: Testing following newborn screening should follow the established sample and testing pathways set out in the National Newborn Bloodspot Screening Programme protocol.

Referrals for testing will be triaged by the Genomic 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 biochemical diagnosis and where result may influence treatment decisions (e.g.use of Sapropterin)

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Target	Method
Phenylketonuria	Singleton	Small variants, CNVs	Single gene(s)	*PAH*	Single gene sequencing

Smith-Lemli-Opitz syndrome

Testing Criteria

Clinical and biochemical features characteristic of Smith-Lemli-Opitz 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 biochemical testing.

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

Associated Tests

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

Name	Optimal Family Structure	Scope(s)	Target Type	Target	Method
Smith-Lemli-Opitz Syndrome	Singleton	Small variants	Single gene(s)	*DHCR7*	Single gene sequencing
Smith-Lemli-Opitz Syndrome	Singleton	Exon level CNVs	Single gene(s)	*DHCR7*	MLPA or equivalent

Part IV: Mitochondrial

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

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Mitochondrial liver disease	Singleton	Small variants, CNVs	Panel of genes or loci	*BCS1L, DGUOK, MPV17, POLG, TRMU, TWNK*	Small Panel

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

- 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
- Metabolic Medicine
- Neurology

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Mitochondrial DNA maintenance disorder	Singleton	Small variants, CNVs	Panel of genes or loci	*ABAT, AFG3L2, DGUOK, DNA2, DNM2, FBXL4, LIG3, MFN2, MGME1, MPV17, OPA1, POLG, POLG2, RNASEH1, RRM2B, SLC25A4, SPG7, SSBP1, SUCLA2, SUCLG1, TFAM, TK2, TOP3A, TWNK, TYMP*	WES or Medium Panel

Mitochondrial disorder with complex I deficiency

Testing Criteria

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

Overlapping indications

- 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 diagnosis of Complex I deficiency and clinical assessment by a metabolic specialist

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Mitochondrial disorder with complex I deficiency	Singleton	Small variants, CNVs	Panel of genes or loci	*ACAD9, FOXRED1, NDUFA1, NDUFA10, NDUFA11, NDUFA12, NDUFA13, NDUFA2, NDUFA6, NDUFA8, NDUFA9, NDUFAF1, NDUFAF2, NDUFAF3, NDUFAF4, NDUFAF5, NDUFAF6, NDUFAF8, NDUFB10, NDUFB11, NDUFB3, NDUFB8, NDUFC2, NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS6, NDUFS7, NDUFS8, NDUFV1, NDUFV2, NUBPL, TIMMDC1, TMEM126B.*	WES or Medium Panel

Mitochondrial disorder with complex II deficiency

Testing Criteria

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

Overlapping indications

- 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 diagnosis of Complex II deficiency and clinical assessment by a metabolic specialist

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Mitochondrial disorder with complex II deficiency	Singleton	Small variants, CNVs	Panel of genes or loci	*SDHA, SDHAF1, SDHB, SDHD*	WES or Small Panel

Mitochondrial disorder with complex III deficiency

Testing Criteria

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

Overlapping indications

- 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 diagnosis of Complex III deficiency and clinical assessment by a metabolic specialist

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Mitochondrial disorder with complex III deficiency	Singleton	Small variants, CNVs	Panel of genes or loci	*ABCS1L, CYC1, LYRM7, TTC19, UQCC2, UQCRB, UQCRC2, UQCRFS1*	WES or Small Panel

Mitochondrial disorder with complex IV deficiency

Testing Criteria

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

Overlapping indications

- 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 diagnosis of Complex IV deficiency and clinical assessment by a metabolic specialist

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Mitochondrial disorder with complex IV deficiency	Singleton	Small variants, CNVs	Panel of genes or loci	*APOPT1, COA6, COA7, COX10, COX14, COX15, COX20, COX4I1, COX6A1, COX6A2, COX6B1, COX7B, LRPPRC, NDUFA4, PET100, SCO1, SCO2, SQOR, SURF1, TACO1.*	WES or Small Panel

Mitochondrial disorder with complex V deficiency

Testing Criteria

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

Overlapping indications

- 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 diagnosis of Complex V deficiency and clinical assessment by a metabolic specialist

Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Mitochondrial disorder with complex V deficiency	Singleton	Small variants, CNVs	Panel of genes or loci	*ATP5A1, ATP5D, ATP5G3, ATPAF2, TMEM70*	WES or Small Panel

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

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Target	Method
Possible mitochondrial disorder - whole mitochondrial genome sequencing	Singleton	Small variants	Single interval	Mitochondrial genome	Other

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.
(Although affected tissue, such as muscle preferred, only blood samples will be processed by National Genomic Processing Service).

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
- Haematology

Associated Tests

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

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. Leber hereditary optic neuropathy
    b. MELAS, or MIDD, or MERRF, or NARP syndrome or maternally inherited Leigh syndrome
    c. Mitochondrial liver disease, including transient infantile liver failure
    d. Possible mitochondrial disorder - mitochondrial DNA rearrangement testing
    e. Possible mitochondrial disorder - whole mitochondrial genome sequencing
    f. Possible mitochondrial disorder – mitochondrially inherited mtDNA depletion disorders

- Targeted examination of nuclear genes should be considered first where possible based on clinical or biochemical/enzyme results:
    g. Mitochondrial DNA maintenance disorder
    h. Mitochondrial disorder with complex I deficiency
    i. Mitochondrial disorder with complex II deficiency
    j. Mitochondrial disorder with complex III deficiency
    k. Mitochondrial disorder with complex IV deficiency
    l. Mitochondrial disorder with complex V deficiency
    m. 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

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Possible mitochondrial disorder - nuclear genes	Singleton	Small variants, CNVs	Panel of genes or loci	*AARS2, ABAT, ABCB7, ACAD9, ACO2, AFG3L2, AGK, AIFM1, APOPT1, APTX, ATAD3A, ATP5A1, ATP5D, ATP5E, ATP5G3, ATP5O, ATPAF2, BCS1L, BOLA3, C12orf65, C19orf70, C1QBP, C2orf69, CA5A, CARS2, CHCHD10, CLPB, CLPP, COA6, COA7, COQ2, COQ4, COQ6, COQ7, COQ8A, COQ8B, COQ9, COX10, COX11, COX15, COX20, COX5A, COX6A1, COX6A2, COX6B1, COX7B, CRLS1, CYC1, CYCS,*	WES or Large Panel

				DARS2, DGUOK, DLAT, DLD, DMPK_CTG STR, DNA2, DNAJC19, DNM1L, DNM2, EARS2, ECHS1, ELAC2, ETFDH, ETHE1, FARS2, FASTKD2, FBXL4, FDX2, FDXR, FH, FLAD1, FOXRED1, GARS, GDAP1, GFER, GFM1, GFM2, GLRX5, GTPBP3, HADHB, HARS2, HCCS, HIBCH, HLCS, HPDL, HSD17B10, HSPD1, HTRA2, IARS2, IBA57, IDH3A, ISCA-37440-Loss 2p21 region (includes PREPL and SLC3A1) Loss region, ISCA1, ISCA2, ISCU, KARS, KIAA0391, LARS2, LETM1, LIAS, LIG3, LIPT1, LIPT2, LONP1, LRPPRC, LYRM4, LYRM7, MARS2, MDH2, MECR, MFF, MFN2, MGME1, MICU1, MIPEP, MPC1, MPV17, MRM2, MRPL3, MRPL44, MRPS2, MRPS22, MRPS34, MSTO1, MT-ATP6, MT-ATP8, MT-CO1, MT-CO2, MT-CO3, MT-CYB, MT-ND1, MT-ND2, MT-ND3, MT-ND4, MT-ND4L, MT-ND5, MT-ND6, MT-RNR1, MT-TA, MT-TC, MT-TD, MT-TE, MT-TF, MT-TG, MT-TH, MT-TI, MT-TK, MT-TL1, MT-TL2, MT-TM, MT-TN, MT-TP, MT-TQ, MT-TR, MT-TS1, MT-TS2, MT-TT, MT-TV, MT-TW, MT-TY, MTFMT, MTO1, MTPAP, NADK2, NARS2, NAXD, NAXE, NDUFA1, NDUFA10, NDUFA11, NDUFA12, NDUFA13, NDUFA2, NDUFA4, NDUFA6, NDUFA8, NDUFA9, NDUFAF1, NDUFAF2, NDUFAF3, NDUFAF4, NDUFAF5, NDUFAF6, NDUFAF8, NDUFB10, NDUFB11, NDUFB3, NDUFB8, NDUFC2, NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS6, NDUFS7, NDUFS8, NDUFV1, NDUFV2, NFS1, NFU1, NSUN3, NUBPL, OPA1, OPA3, OXCT1, PANK2, PARS2, PC, PDHA1, PDHB, PDHX, PDP1, PDSS1, PDSS2, PET100, PITRM1, PLA2G6, PMPCA, PMPCB, PNPLA8, PNPT1, POLG, POLG2, POLRMT, PPA2, PPOX, PTCD3, PUS1, QARS, QRSL1, RARS2, RMND1, RNASEH1, RRM2B, RTN4IP1, SACS, SARS2, SCO1, SCO2, SDHA, SDHAF1, SDHB, SDHD, SERAC1, SFXN4, SLC19A2, SLC19A3, SLC22A5, SLC25A1, SLC25A12, SLC25A19, SLC25A20, SLC25A24, SLC25A26, SLC25A3, SLC25A32, SLC25A36, SLC25A38, SLC25A4, SLC25A42, SLC25A46, SLC52A2, SLC52A3, SPATA5, SPG7, SSBP1, SUCLA2, SUCLG1, SURF1, TACO1, TAMM41, TARS2, TAZ, TEFM, TFAM, TIMM50, TIMM8A, TIMMDC1, TK2, TMEM126B, TMEM70, TOP3A, TPK1, TRIT1, TRMT10C, TRMT5, TRMU, TRNT1, TSFM, TTC19, TUFM, TWNK, TYMP, UQCC2, UQCRB, UQCRC2, UQCRFS1, VARS2, WARS2, YARS2.	

Pyruvate dehydrogenase (PDH) deficiency

Testing Criteria

Clinical features and laboratory features strongly suggestive of pyruvate dehydrogenase deficiency.

Overlapping indications

- 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

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Pyruvate dehydrogenase PDH deficiency	Singleton	Small variants, CNVs	Panel of genes or loci	*BOLA3, DLAT, DLD, ECHS1, FBXL4, GLRX5, HIBCH, IBA57, ISCA1, ISCA2, LIAS, LIPT1, LIPT2, LONP1, NFU1, PDHA1, PDHB, PDHX, PDP1, SLC19A2, SLC19A3, SLC25A19, SLC25A26, TPK1*	WES or Medium panel

Part IV: Ophthalmology

Albinism or congenital nystagmus

Testing Criteria

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

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

Where in Pathway

At presentation following assessment by a Consultant Ophthalmologist (for ophthalmic presentations)

Requesting Specialties

- Clinical Genetics
- Dermatology
- Ophthalmology

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Albinism or congenital nystagmus	Singleton	Small variants, CNVs	Panel of genes or loci	*AP3B1, BLOC1S3, BLOC1S5, BLOC1S6, CACNA1A, CACNA1F, CASK, DCT, FRMD7, GPR143, HPS1, HPS3, HPS4, HPS5, HPS6, LAMA1, LRMDA, LYST, OCA2, PAX6, RAB27A, SACS, SETX, SLC24A5, SLC38A8, SLC45A2, TYR, TYRP1*	WES or Medium panel

Bardet Biedl syndrome

Testing Criteria

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

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Nephrology
- Ophthalmology

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Bardet Biedl syndrome	Singleton	Small variants, CNVs	Panel of genes or loci	*ARL6, BBS1, BBS10, BBS12, BBS2, BBS4, BBS5, BBS7, BBS9, IFT27, IFT74, LZTFL1, MKKS, MKS1, SDCCAG8, TMEM67, TTC8*	WES or Medium Panel

Bilateral congenital or childhood onset cataracts

Testing Criteria

Unexplained bilateral congenital or childhood onset cataracts

Overlapping indications

- Structural eye disease test should be used in individuals with cataract in the context of microphthalmia or other structural eye 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, after urine reducing substances
Where additional features are strongly suggestive of congenital infection, a TORCH screen should be performed before testing.

Requesting Specialties

- Clinical Genetics
- Ophthalmology

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Bilateral congenital or childhood onset cataracts	Trio or singleton	Exon level CNVs, Small variants	Panel of genes or loci	*ABHD12, ADAMTS10, AGK, AGPS, ALDH18A1, ANAPC1, ATAD3A, B3GLCT, BCOR, BFSP1, BFSP2, CDK9, CHMP4B, COG4, COL11A1, COL18A1, COL2A1, COL4A1, CRYAA, CRYAB, CRYBA1, CRYBA4, CRYBB1, CRYBB2, CRYBB3, CRYGC, CRYGD, CRYGS, CYP27A1, CYP51A1, DHCR7, DNMBP, EIF2B2, EPHA2, ERCC2, ERCC3, ERCC6, ERCC8, FAM126A, FAR1, FOXE3, FTL, FYCO1, GALK1, GALT, GCNT2, GFER, GJA3, GJA8, GNPAT, GTF2H5, HMX1, HSF4, HTRA2, INPP5K, INTS1, JAM3, LCAT, LETM1, LIM2, LONP1, LSS, MAF, MAN2B1, MED27, MIP, MIR184, MSMO1, MYH9, NACC1, NDP, NF2, NHS, NUP188, OCRL, OPA3, P3H2, PAX6, PEX1, PEX10, PEX11B, PEX12, PEX13, PEX14, PEX16, PEX19, PEX2, PEX26, PEX3, PEX5, PEX6, PEX7, PIK3C2A, PITX3, PLOD3, POLG, PXDN, RAB18, RAB3GAP1, RAB3GAP2, SC5D, SIL1, SLC16A12, SLC2A1, SLC33A1, SRD5A3, SREBF1, TDRD7, TFAP2A, VIM, VPS4A, VSX2, WFS1, WRN, XYLT2, ZNF526*	WES or Large Panel

Blepharophimosis ptosis and epicanthus inversus

Testing Criteria

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Ophthalmology

Associated Tests

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

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
FOXL2 Single gene sequencing	Singleton	Small variants	Single gene(s)	*FOXL2*	Single gene sequencing
FOXL2 MLPA or equivalent	Singleton	Exon level CNVs	Single gene(s)	*FOXL2*	MLPA or equivalent
FOXL2 STR testing	Singleton	STRs	Single gene(s)	*FOXL2*	STR testing

Congenital fibrosis of the extraocular muscles

Testing Criteria

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

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Nephrology
- Ophthalmology

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Congenital fibrosis of the extraocular muscles	Singleton	Small variants, CNVs	Panel of genes or loci	*KIF21A, PHOX2A, TUBB3*	Small Panel

Corneal dystrophy

Testing Criteria

Corneal dystrophy of likely monogenic aetiology

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

Where in Pathway

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

Requesting Specialties

- Clinical Genetics
- Ophthalmology

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Corneal dystrophy	Singleton	Small variants, CNVs	Panel of genes or loci	*CHST6, COL17A1, COL8A2, DCN, GRHL2, GSN, KERA, KRT12, KRT3, LCAT, OVOL2, PIKFYVE, PRDM5, SLC4A11, STS, TACSTD2, TCF4, TGFBI, UBIAD1, ZEB1, ZNF469*	WES or Medium panel

Optic neuropathy

Testing Criteria

Unexplained optic neuropathy

Overlapping indications

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

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

Where in Pathway

At presentation following expert by a Consultant Ophthalmologist

Requesting Specialties

- Clinical Genetics
- Ophthalmology

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Optic neuropathy	Singleton	Small variants, CNVs	Panel of genes or loci	*ACO2, AFG3L2, ALPK1, ATG7, C12orf65, C19orf12, CISD2, DNAJC30, DNM1L, EPRS, FDXR, ISCA2, MECR, MFF, MFN2, MT-ATP6, MT-ND1, MT-ND4, MT-ND6, NBAS, NDUFA12, NR2F1, OPA1, OPA3, RTN4IP1, SLC25A46, SLC44A1, SLC52A2, SPG7, SSBP1, TFG, TMEM126A, UCHL1, WFS1*	WES or Medium panel

Pseudoxanthoma elasticum

Testing Criteria

Individuals who have characteristic features of Pseudoxanthoma elasticum:

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Ophthalmology

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Pseudoxanthoma elasticum	Singleton	Small variants, CNVs	Panel of genes or loci	*ABCC6, ENPP1*	Small Panel

Retinal disorders

Testing Criteria

Unexplained retinal disease that is likely to be monogenic

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

Where in Pathway

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

Requesting Specialties

- Clinical Genetics
- Ophthalmology

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Retinal disorders	Trio or singleton	Exon level CNVs, Small variants	Panel of genes or loci	*ABCA4, ABCC6, ABHD12, ACBD5, ACO2, ADAM9, ADAMTS18, ADGRV1, AFG3L2, AGLB5, AHI1, AIPL1, AIRE, ALDH3A2, ALMS1, ALPK1, AMACR, ARHGEF18, ARL13B, ARL2BP, ARL3, ARL6, ARSG, ATF6, ATOH7, ATXN7_CAG, BBS1, BBS10, BBS12, BBS2, BBS4, BBS5, BBS7, BBS9, BEST1, C1QTNF5, C21orf2, C2orf71, C8orf37, CABP4, CACNA1F, CACNA2D4, CAPN5, CC2D2A, CDH23, CDH3, CDHR1, CEP164, CEP250, CEP290, CEP78, CERKL, CFAP20, CFH, CHM, CLN3, CLN5, CLN6, CLN8, CLRN1, CNGA1, CNGA3, CNGB1, CNGB3, CNNM4, COL11A1, COL18A1, COL2A1, COL4A1, COL9A1, COL9A2, COL9A3, COQ2, CRB1, CRX, CSPP1, CTC1, CTNNA1, CTNNB1, CTNND1, CTSD, CWC27, CYP4V2, DHDDS, DRAM2, DYNC2H1, EFEMP1, ELOVL4, ERCC6, ERCC8, EYS, FAM161A, FAM57B, FLVCR1, FZD4, GNAT1, GNAT2, GNB3, GNPTG, GPR143, GPR179, GRK1, GRM6, GRN, GUCA1A, GUCA1B, GUCY2D, HCCS, HGSNAT, HK1, HMX1, IDH3A, IDH3B, IFT140, IFT172, IFT27, IFT74, IKBKG, IMPDH1, IMPG1, IMPG2, INPP5E, IQCB1, JAG1, KCNJ13, KCNV2, KIAA1549, KIF11, KIZ, KLHL7, LAMA1, LAMP2, LCA5, LRAT, LRIT3, LRP2, LRP5, LZTFL1, MAK, MCOLN1, MED12, MERTK, MFRP, MFSD8, MIR204, MKKS, MKS1, MMACHC, MPDZ, MSTO1, MT-ATP6, MT-TL1, MTTP, MVK, MYO7A, NBAS, NDP, NEUROD1, NMNAT1, NPHP1, NPHP3, NPHP4, NR2E3, NRL, NYX, OAT, OFD1, OPN1LW, OPN1MW, OTX2, P3H2, PANK2, PAX2, PCDH15, PCYT1A, PDE6A, PDE6B, PDE6C, PDE6G, PDSS1, PEX1, PEX2, PEX6, PEX7, PHYH, PLA2G5, PLK4, PNPLA6, POC1B, POMGNT1, POMT1, PPT1, PQLC2, PRCD, PRDM13, PROM1, PRPF3, PRPF31,*	WES or Large Panel

				PRPF4, PRPF6, PRPF8, PRPH2, PRPS1, PYGM, RAB28, RAX2, RBP3, RBP4, RCBTB1, RD3, RDH12, RDH5, REEP6, RGR, RGS9, RHO, RIMS2, RLBP1, RNU4ATAC, ROM1, RP1, RP1L1, RP2, RP9, RPE65, RPGR, RPGRIP1, RPGRIP1L, RS1, SAG, SAMD7, SCAPER, SDCCAG8, SGSH, SLC24A1, SLC37A3, SLC38A8, SLC6A6, SNRNP200, SPATA7, SRD5A3, SSBP1, STN1, SUMF1, TIMM8A, TIMP3, TINF2, TMEM216, TMEM218, TMEM231, TMEM237, TOPORS, TPP1, TRAF3IP1, TREX1, TRNT1, TRPM1, TSPAN12, TTC21B, TTC8, TTLL5, TUB, TUBB4B, TUBGCP4, TUBGCP6, TULP1, UBAP1L, UNC119, USH1C, USH1G, USH2A, USP45, VCAN, VPS13B, WDPCP, WDR19, WHRN, ZFYVE26, ZNF408, ZNF423	

Sporadic aniridia

Testing Criteria

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

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

Where in Pathway

At presentation

Requesting Specialties

- Oncology
- Clinical Genetics
- Ophthalmology
- Paediatrics

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Sporadic aniridia	Singleton	Small variants, CNVs	Panel of genes or loci	*FOXC1, ISCA-37401-Loss* (associated with the 11p13 WAGR syndrome region loss), *ITPR1, PAX6*	Small Panel

Stickler syndrome

Testing Criteria

Clinical features indicative of likely Stickler syndrome

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

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Ophthalmology

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Stickler syndrome	Singleton	Small variants, CNVs	Panel of genes or loci	*BMP4, COL11A1, COL11A2, COL2A1, COL9A1, COL9A2, COL9A3, GZF1, VCAN*	Small Panel

Structural eye disease

Testing Criteria

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

Overlapping indications

- Sporadic aniridia test should be used instead for sporadic classical aniridia

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

Where in Pathway

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

Requesting Specialties

- Clinical Genetics
- Ophthalmology

Associated Tests

Name	Optimal Family Structure	Scope(s)	Target Type	Targets	Method
Structural eye disease	Trio or singleton	Exon level CNVs, Small variants	Panel of genes or loci	*ABCB6, ACTB, ACTG1, ADAMTS10, ADAMTS17, ADAMTS18, ADAMTSL4, ALDH1A3, ALX1, ANK3, ARHGAP35, ASPH, ATOH7, B3GALNT2, B3GLCT, BCOR, BEST1, BMP4, BMPR1B, C12orf57, CAPN15, CBS, CC2D2A, CDON, CENPF, CEP290, CHD7, CHRDL1, CLDN19, COL18A1, COL4A1, CPAMD8, CREBBP, CRIM1, CRYAA, CRYBB1, CRYBB2, CRYGC, CYP1B1, DDX58, DOCK6, DYRK1A, EPHA2, ESCO2, FAT1, FBN1, FKTN, FOXC1, FOXD3, FOXE3, FRAS1, FREM1, FREM2, FZD5, GDF6, GJA1, GJA8, GRIP1, HCCS, HHAT, HMX1, IFIH1, INPP5E, ISCA-37393-Gain, ISCA-37396-Loss, ISPD, KDM6A, KIAA0586, KIAA1109, KIF11, KMT2D, LAMB2, LMX1B, LRP2, LRP5, LTBP2, MAB21L2, MAF, MAPRE2, MFRP, MIR204, MITF, MYOC, MYRF, NAA10, NDP, NHS, NUP188, OCRL, OFD1, OTX2, PACS1, PAX2, PAX6, PIGL, PITX2, PITX3, POMGNT1, POMT1, POMT2, PORCN, PRR12, PRSS56, PTCH1, PUF60, PXDN, RAB18, RAB3GAP1, RAB3GAP2, RARB, RAX, RBP4, RERE, RHOA, RIPK4, RPGRIP1L, SALL1, SALL4, SBF2, SH3PXD2B, SHH, SIX6, SLC25A24, SLC38A8, SLC4A4, SMCHD1,*	WES or Large Panel

				SMG8, SMO, SMOC1, SOX2, SRD5A3, STRA6, TBC1D20, TEK, TENM3, TFAP2A, TMEM216, TMEM237, TMEM5, TMEM67, TMEM98, TUBGCP4, VSX2, WDR37, WLS, YAP1, ZEB2	