

# **National Genomic Test Directory**

**Testing Criteria for Rare  
and Inherited Disease**

**v3 April 2022 (Official)**

# Summary

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

<https://www.england.nhs.uk/publication/national-genomic-test-directories/>

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

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

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

If you have any questions about the genomic testing available in your area, please contact your local Genomic Laboratory Hub. More information about the Genomic Laboratory Hubs can be found here:

<https://www.england.nhs.uk/genomics/genomic-laboratory-hubs/>

# Document overview

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## Clinical Indications

The following elements are presented for each clinical indication:

- **Clinical Indication Name:** name of the clinical indication, preceded by unique clinical indication code.
- **Testing Criteria:** description of the patients who should receive the test. Where a clinical indication has multiple individual test items and testing is expected to be performed in a specific order, this is specified. Details of commonly overlapping clinical indications are also provided.
- **Overlapping Indications:** pointers to other clinical indications with overlapping presentations or genomic targets.
- **Where in Pathway:** guidance as to where the genetic test should usually sit in the patient pathway, particularly with respect to other diagnostic investigations
- **Requesting Specialties:** specialties that will be routinely permitted to request the test
- Requesting specialties have been nationally agreed as appropriate specialties for referrals for testing. The list of requesting specialties is not designed to operate at a very specific level or to limit test requests to just those clinical specialties listed, as pathways will differ across the country, e.g. a specialist with the job title 'paediatric craniofacial surgeon' would potentially be grouped within 'Surgery' or 'Paediatrics'.

If GLHs receive test requests from clinicians whose role doesn't fall neatly within a single requesting specialty, or whose clinical specialty is not listed for that clinical indication, the GLH can process that test if it is appropriate as per their agreed local pathways and the eligibility criteria for the clinical indication is being met.

- **Specialist Service Group:** specialist service group that covers the clinical indication. The options are:
  - Core;
  - Cardiology;
  - Audiology;
  - Endocrinology;
  - Ophthalmology;
  - Gastrohepatology;
  - Haematology;
  - Immunology;
  - Inherited cancer;
  - Metabolic;
  - Mitochondrial;
  - Musculoskeletal;
  - Neurology;
  - Renal;
  - Respiratory;
  - Dermatology;
  - NIPT;
  - NIPD; and
  - Screening

## Associated Tests

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

Information provided includes:

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

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

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

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

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

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

**Target Name:** names of the gene(s), interval(s) or panels at which the variant type should be detected

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

- |                              |                               |
|------------------------------|-------------------------------|
| – WGS;                       | – FISH;                       |
| – WES;                       | – DNA repair testing;         |
| – Large panel;               | – Methylation testing;        |
| – Medium panel;              | – UPD testing;                |
| – Small panel;               | – X-inactivation testing;     |
| – Single gene sequencing;    | – Identity testing;           |
| – Targeted mutation testing; | – Microsatellite instability; |
| – STR testing;               | – NIPT;                       |
| – MLPA or equivalent;        | – NIPD;                       |
| – Microarray;                | – Other                       |
| – Common aneuploidy testing; |                               |
| – Karyotype;                 |                               |

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

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

This document incorporates the feedback received; subsequent changes to the Test Directory are managed through NHS England's test evaluation process.

## Test Ordering

Clinicians wishing to request genomic tests can do so by;

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

Clinicians should follow local process to request genomic tests. All referrals for testing will be triaged by the local Genomic Laboratory Hub to ensure the most appropriate test is performed. In instances where testing is requested by the clinical indication, the Genomic Laboratory Hub will review the test request and relevant clinical information and select the most appropriate constituent test(s) to facilitate the test request. Testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

## Change Log

| Date       | Document Name  | Version       | Summary of Changes   |
|------------|--|---------------|--|
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R424: New CI   |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R398: removed this CI  |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R34 and R35: removed these two CIs as the testing for Sorbys and Doyne are now encompassed in the scope of R32. Removed R34 and R35 as overlapping CIs for R32.  |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | Various CIs: changed test method from single gene sanger sequencing to small panel:<br>R208.1 Inherited breast cancer and ovarian cancer<br>R384.1 Generalised arterial calcification in infancy<br>R143.1 Neonatal diabetes<br>R144.1 Congenital hyperinsulinism<br>R361.1 Haemoglobinopathy trait or carrier testing<br>R93.2 Thalassaemia and other haemoglobinopathies<br>R122.1 Factor XIII deficiency<br>R123.1 Combined vitamin K-dependent clotting factor deficiency<br>R92.2 Rare anaemia<br>R366.1 Inherited susceptibility to acute lymphoblastoid leukaemia (ALL)<br>R214.1 Nevroid Basal Cell Carcinoma Syndrome or Gorlin syndrome<br>R380.1 Niemann Pick disease type C<br>R323.1 Sitosterolaemia<br>R351.1 NARP syndrome or maternally inherited Leigh syndrome<br>R390.1 Multiple exostoses<br>R228.1 Tuberous sclerosis |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | Amended tag line above the associated tests table for all CIs where there is more than one associated test from: "Please note all the tests below will be undertaken for RXX Clinical Indication requests" to "Please note all the tests below will be undertaken for RXX Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary" For some of the WGS CIs the tag line has been further expanded.  |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R42: Removed R42.3 test type and added R42.4 single gene test type for DNAJC30   |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R78: removed MLPA GJB1 test type   |

| Date       | Document Name  | Version       | Summary of Changes  |
|------------|--|---------------|---|
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R61: removed MLPA SPAST test type   |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R60: removed MLPA test type   |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R57: added overlapping CIs:<br>R61 Childhood onset hereditary spastic paraplegia – if the patient has spastic paraplegia<br>R55 Hereditary ataxia with onset in childhood – if the patient has ataxia<br>And removed MLPA test type   |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R54: added note:<br>Please note testing R54 does not include testing for Fragile X (Clinical Indication number R53) and this should be requested in addition if required.   |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R65: amended testing criteria from:<br>1. individuals in whom aminoglycoside therapy may be required, OR<br>2.individuals who have been exposed to aminoglycosides in whom mt.1555A>G status needs to be determined because of concern regarding hearing loss<br><br>To:<br>1.individuals with a predisposition to gram negative infections due to known respiratory disease for example: bronchiectasis, cystic fibrosis or due to structural or voiding genitourinary tract disorders, OR<br>2.individuals with hearing loss who have been exposed to aminoglycosides |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R147: amended testing criteria to include “in the absence of microcephaly” and added R88 as an overlapping CI. Also re-instated test type R147.3 microarray.  |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R347: amendments to test type 2   |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R423: new CI  |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R299: added two new test types 1) Heteroplasmy assessment - mitochondrial genome and 2) Breakpoint mapping - mitochondrial genome   |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R221: Merged R393 with this Clinical Indication, added 3 new gene targets (SMARCE1, SUFU and DGCR8), changed test method to small panel and added Specialised to the commissioning category as this test could be for patients being seen as part of the HSS or through other specialised testing routes. NWGLH national provider.  |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R254: removed reference to BAP1-oma now that there is a new separate CI for BAP1 and included melanoma in addition to melanoma in situ  |

| Date       | Document Name  | Version       | Summary of Changes   |
|------------|--|---------------|--|
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R220: Amended testing criteria, added to requesting specialties and amended the test types to add four more gene targets   |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R216: Amended testing criteria and added to requesting specialties   |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R215: amended testing criteria and added gastric surgeons to the requesting specialties  |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R422 BAP1 associated tumour predisposition syndrome – new CI   |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R188: Amendment to the testing criteria  |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R421 Pulmonary Fibrosis Familial – new CI  |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R420 Pseudoxanthoma elasticum – new CI   |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R222: Added paediatrics to referring specialties   |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R73: Amended eligibility criteria  |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R58: amended criteria 1b to include “and/or family history of MND” and 3d age threshold from < 40 years to < 50 years.   |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R419: added new CI   |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | <p>R331: added to the test name “congenital diarrhoea” and added to the criteria</p> <p>Infants presenting with severe and persistent diarrhoea that arises in the neonatal period (first 28 days of life). Severity is defined as requirement for critical care input or parenteral nutrition at any point and persistence for at least 14 days. The disease must be unrelated to surgical short bowel OR</p> <p>Congenital Short Bowel Syndrome (approx. 50cm in length compared to ~250cm).</p> <p>as additional genes related to congenital diarrhoea, have been added to the panel.</p> |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | <p>R175: Amended test target and test method for R175.2 from CFTR common mutations</p> <p>Targeted mutation testing to PRSS1</p>   |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | <p>R171: Added to criteria:</p> <p>Persistence of unexplained cholestasis beyond 3 months or recurrence of otherwise unexplained cholestasis, including those with a suspected precipitating drug OR</p> <p>Cholestasis of pregnancy onset in the second trimester or serum bile acids &gt;42umol/mL in the third trimester</p> <p>Testing may occasionally be appropriate outside these criteria following discussion at the national gastrohepatology genomics MDT. and to the requesting specialties</p> <p>Added paediatrics to the requesting specialties.</p>                          |

| Date       | Document Name  | Version       | Summary of Changes   |
|------------|--|---------------|--|
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R209: Removed CI. Amended criteria for R211 and R210 to cover the patients that would have been tested using R209.   |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R211: Changed name of CI, amended the criteria and added gene targets to the panel RNF43 & GREM1 and added colorectal surgeons to requesting specialties.  |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R210: removed methylation test type as this is in the Cancer TD.   |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R208: Moved criteria 1e to R207. Added new criterions, new numbers 2. And 3.. Changed BOADICEA score to CanRisk scores. Changed age threshold from <30 years to < 40 years for 1a. Added new test targets to small panel ATM and CHEK2 truncating variants   |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R207: Amended criteria and added PALB2 gene target to the panel  |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R185: Added to criteria "Both parents of a fetus with dilated bowel (where both parents are available)" and changed requesting specialties   |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R184: Added to criteria "Dilated fetal bowel on 2nd trimester scan" and changed requesting specialties   |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | <p>R297: Amendment to criteria to add inclusion of egg/sperm donors prior to acceptance and added to the pathway to include "or where IVF centres with HFEA license are performing treatment with egg or sperm donation".</p> <p>Also clarified point 2. By adding:</p> <p>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:</p> <p>Where an attempt to provide pregnancy loss samples has been unsuccessful;</p> <ul style="list-style-type: none"> <li>o unsuitable sample (eg. no fetal material/MCC)</li> <li>o failed sample (eg. fixed in formalin)</li> <li>• Where the intention has been to collect the next pregnancy loss but this has not been possible due to the nature of the loss</li> <li>• Five or more biochemical pregnancy losses.</li> </ul> |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R151 & R152: merged the clinical indications into a single indication for R151 and updated criteria  |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | R417 added new CI for MLID   |
| April 2022 | Rare and inherited disease eligibility criteria April 2022 | April 2022 v3 | <p>R293: Changed CI name from "Albright hereditary osteodystrophy, pseudohypoparathyroidism and pseudopseudohypoparathyroidism" to "Albright hereditary osteodystrophy, pseudohypoparathyroidism, pseudopseudohypoparathyroidism, acrodysostosis and osteoma cutis"</p> <p>R293.1: added test targets PRKAR1A and PDE4D &amp; changed test method to small panel</p>   |



| Date         | Document Name   | Version         | Summary of Changes  |
|--------------|---|-----------------|---|
| April 2022   | Rare and inherited disease eligibility criteria April 2022      | April 2022 v3   | R272: Changed CI name to Gaucher Disease amended criteria to "Clinical features and glucocerebrosidase activity indicative of Gaucher disease types 1, 2, or 3, including the perinatal lethal and cardiovascular subtypes". Added requesting specialties: Neurology and Cardiology.  |
| April 2022   | Rare and inherited disease eligibility criteria April 2022      | April 2022 v3   | R133: Added criterion "Identification of a mutation would complete diagnostic task force criteria for ARVC"   |
| April 2022   | Rare and inherited disease eligibility criteria April 2022      | April 2022 v3   | R132: Added criterion "Patients with D/ACM at any age if they have a first degree relative with confirmed diagnosis of D/ACM"   |
| April 2022   | Rare and inherited disease eligibility criteria April 2022      | April 2022 v3   | R14.1 updated the panel name in the associated tests tabel to Acutely unwell children with a likely monogenic disorder in the associated tests table and updated the target name to Trio gene agnostic or appropriate panels in singletons or duos  |
| April 2022   | Rare and inherited disease eligibility criteria April 2022      | April 2022 v3   | R127: changed criteria from LQTS risk score >3.5 to LQTS risk score ≥ 3.5   |
| January 2022 | Rare and inherited disease eligibility criteria October 2021 v2 | October 2021 v2 | <p>Changed test type from single gene to small panel for the following Clinical Indications:</p> <p>R384.1 Generalised arterial calcification in infancy</p> <p>R143.1 Neonatal diabetes</p> <p>R144.1 Congenital hyperinsulinism</p> <p>R361.1 Haemoglobinopathy trait or carrier testing</p> <p>R93.2 Thalassaemia and other haemoglobinopathies</p> <p>R122.1 Factor XIII deficiency</p> <p>R123.1 Combined vitamin K-dependent clotting factor deficiency</p> <p>R92.2 Rare anaemia</p> <p>R366.1 Inherited susceptibility to acute lymphoblastoid leukaemia (ALL)</p> <p>R214.1 Nevoid Basal Cell Carcinoma Syndrome or Gorlin syndrome</p> <p>R393.1 Schwannomatosis</p> <p>R380.1 Niemann Pick disease type C</p> <p>R323.1 Sitosterolaemia</p> <p>R351.1 NARP syndrome or maternally inherited Leigh syndrome</p> <p>R390.1 Multiple exostoses</p> <p>R228.1 Tuberous sclerosis</p> |
| January 2022 | Rare and inherited disease eligibility criteria October 2021 v2 | October 2021 v2 | R409: changed test method from "other" to "linkage analysis"  |
| January 2022 | Rare and inherited disease eligibility criteria October 2021 v2 | October 2021 v2 | R388: changed test method from "other" to "linkage analysis"  |
| January 2022 | Rare and inherited disease eligibility criteria October 2021 v2 | October 2021 v2 | R331: removal from the test name "congenital diarrhoea" and removal of the criteria related to congenital diarrhoea, as GLHs are not ready until April 2022 to add the additional genes.  |

| Date         | Document Name   | Version         | Summary of Changes   |
|--------------|---|-----------------|--|
| January 2022 | Rare and inherited disease eligibility criteria October 2021 v2 | October 2021 v2 | R276: corrected test target for CNV analysis   |
| January 2022 | Rare and inherited disease eligibility criteria October 2021 v2 | October 2021 v2 | R208: changed test type single gene to small panel   |
| January 2022 | Rare and inherited disease eligibility criteria October 2021 v2 | October 2021 v2 | R414: Specialist Service Group, changed from inherited cancer to core  |
| January 2022 | Rare and inherited disease eligibility criteria October 2021 v2 | October 2021 v2 | R33: removed test type R33.3 WGS as if R33.1 is uninformative GLH to inform clinician to request R32 WGS. The WGS panel for R32 is the same as R33. Also added to the sentence in "order of testing" section.  |
| January 2022 | Rare and inherited disease eligibility criteria October 2021 v2 | October 2021 v2 | R35: removed test type R35.1 EFEMP1 hotspot Targeted mutation testing  |
| January 2022 | Rare and inherited disease eligibility criteria October 2021 v2 | October 2021 v2 | R34: removed test type R34.1 targeted mutation testing TIMP3 hotspot exon  |
| January 2022 | Rare and inherited disease eligibility criteria October 2021 v2 | October 2021 v2 | R283: changed specialist group from screening to metabolic and updated criteria in line with NICE recommendation and NHSE position to test all patients with PKU (except those who are pregnant and those who have previously proven responsiveness) for sapropterin responsiveness. |
| January 2022 | Rare and inherited disease eligibility criteria October 2021 v2 | October 2021 v2 | R59: Added: "Testing may occasionally be appropriate where age of onset is between 2 and 3 years and following clinical agreement by a specialist MDT"   |
| January 2022 | Rare and inherited disease eligibility criteria October 2021 v2 | October 2021 v2 | All inherited cancer CIs: Added tag line "Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present"  |
| January 2022 | Rare and inherited disease eligibility criteria October 2021 v2 | October 2021 v2 | All WGS CIs: display those in phase 1 and those in phase 2   |
| January 2022 | Rare and inherited disease eligibility criteria October 2021 v2 | October 2021 v2 | R416: made correction in error to the criteria   |
| January 2022 | Rare and inherited disease eligibility criteria October 2021 v2 | October 2021 v2 | R211: removed R385 CI in overlapping CIs as it no longer exists  |
| January 2022 | Rare and inherited disease eligibility criteria October 2021 v2 | October 2021 v2 | R210: Removed 1b from criteria as incorrect  |
| January 2022 | Rare and inherited disease eligibility criteria October 2021 v2 | October 2021 v2 | R208: removed R386 CI in overlapping CIs as it no longer exists  |

| Date           | Document Name   | Version         | Summary of Changes   |
|----------------|---|-----------------|--|
| January 2022   | Rare and inherited disease eligibility criteria October 2021 v2 | October 2021 v2 | R209: Changed age threshold to <40   |
| January 2022   | Rare and inherited disease eligibility criteria October 2021 v2 | October 2021 v2 | R246: Updated wording of criteria for clarity  |
| September 2021 | Rare and inherited disease eligibility criteria October 2021    | TD              | As noted in column H of GLH facing Test Directory spreadsheet PLUS name changes for specialty groups & requesting specialties:<br>Eyes > Ophthalmology<br>Cancer > Oncology<br>Hearing > Audiology<br>Skin > Dermatology<br>Plus, removed from scope of R49, R50 and R220 "exon level" in relation to CNVs |
| 21 August 2020 | Rare and inherited disease eligibility criteria August 2020     | TD5             | As noted in column L of GLH-facing Test Directory spreadsheet  |
| 15 March 2019  | TD4 for Rare Disease Section                                    | TD4             | R201. Removal of clinical indication test type R201.2  |
| 05 March 2019  | TD3b for Rare Disease Section                                   | TD3b            | R66. Minor amendments to eligibility criteria  |
| 04 March 2019  | TD3a for Rare Disease Section                                   | TD3a            | R193. Updated requesting specialties, ages and where in pathway  |
| 01 March 2019  | TD3 for Rare Disease Section                                    | TD3             | All. Initial release with roman numeral section parts  |

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# Part I. Acutely unwell children

## R14 Acutely unwell children with a likely monogenic disorder

### Testing Criteria

Acutely unwell children with a likely monogenic disorder

For more detailed guidance for R14 outlined in “Guidance Document - Rapid Exome Sequencing for NICU-PICU Referrals” please contact your local Genomic Laboratory Hub.

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

### Overlapping indications

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics

### Specialist Service Group

- Core

### Associated Tests

| Code  | Name   | Optional Family Structure | Scope(s)                | Target Type            | Target Name  | Method |
|-------|--|---------------------------|-------------------------|------------------------|--|--------|
| R14.1 | Acutely unwell children with a likely monogenic disorder | Trio or singleton         | Small variants and CNVs | Panel of genes or loci | Trio gene agnostic or appropriate panels in singletons or duos | WES    |

## Part II. Cardiology

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### R137 Congenital heart disease - microarray

#### Testing Criteria

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

#### Overlapping indications

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

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

#### Where in Pathway

At presentation

#### Requesting Specialties

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

#### Specialist Service Group

- Core

#### Associated Tests

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

## R125 Thoracic aortic aneurysm or dissection

### Testing Criteria

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

\*Thoracic aortic aneurysm defined as:

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

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

### Overlapping Indications

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Cardiology
- Clinical Genetics

### Specialist Service Group

- Cardiology

### Associated Tests

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

| Code   | Name   | Optional Family Structure | Scope(s)        | Target Type            | Target Name                                  | Method              |
|--------|--|---------------------------|-----------------|------------------------|--|---------------------|
| R125.1 | Thoracic aortic aneurysm or dissection WES or medium panel | Singleton                 | Small variants  | Panel of genes or loci | Thoracic aortic aneurysm or dissection (700) | WES or Medium Panel |
| R125.2 | Thoracic aortic aneurysm or dissection MLPA or equivalent  | Singleton                 | Exon level CNVs | Panel of genes or loci | Thoracic aortic aneurysm or dissection (700) | MLPA or equivalent  |

## R127 Long QT syndrome

### Testing Criteria

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

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

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

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Cardiology
- Clinical Genetics

### Specialist Service Group

- Cardiology

### Associated Tests

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

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



## R128 Brugada syndrome and cardiac sodium channel disease

### Testing Criteria

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

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

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

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Cardiology
- Clinical Genetics

### Specialist Service Group

- Cardiology

### Associated Tests

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

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

## R129 Catecholaminergic polymorphic VT

### Testing Criteria

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

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

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Cardiology
- Clinical Genetics

### Specialist Service Group

- Cardiology

### Associated Tests

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

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

## R130 Short QT syndrome

### Testing Criteria

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

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

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Cardiology
- Clinical Genetics

### Specialist Service Group

- Cardiology

### Associated Tests

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

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

## R131 Hypertrophic cardiomyopathy

### Testing Criteria

A firm clinical diagnosis of hypertrophic cardiomyopathy as indicated by:

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

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

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

### Overlapping indications

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

### Where in Pathway

At presentation

### Requesting Specialties

- Cardiology
- Clinical Genetics

### Specialist Service Group

- Cardiology

### Associated Tests

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

| Code   | Name  | Optional Family Structure | Scope(s)        | Target Type            | Target Name                                       | Method   |
|--------|---|---------------------------|-----------------|------------------------|---|--|
| R131.1 | Hypertrophic cardiomyopathy WES or medium panel | Singleton                 | Small variants  | Panel of genes or loci | Hypertrophic cardiomyopathy - teen and adult (49) | WES or Medium Panel                            |
| R131.2 | Hypertrophic cardiomyopathy                     | Singleton                 | Exon level CNVs | Panel of genes or loci | Hypertrophic cardiomyopathy - teen and adult (49) | Exon level CNV detection by MLPA or equivalent |

## R132 Dilated and arrhythmogenic cardiomyopathy

### Testing Criteria

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

1. Left ventricular end diastolic diameter (LVEDD) greater than 2 standard deviations, AND
  - a. Reduced ejection fraction (EF) to less than 45%, adjusted for age and sex, AND
  - b. Age of onset below 50 years, OR
  - c. DCM with conduction defects, with age of onset below 65 years

OR

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

OR

3. A deceased individual with pathologically confirmed DCM or ACM and age of onset below 50 years suitable for post-mortem DNA analysis.

OR

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

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

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

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

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

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

### Overlapping indications

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

### Where in Pathway

At presentation

### Requesting Specialties

- Cardiology
- Clinical Genetics

### Specialist Service Group

- Cardiology

### Associated Tests

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

| Code   | Name   | Optional Family Structure | Scope(s)        | Target Type            | Target Name                                   | Method   |
|--------|--|---------------------------|-----------------|------------------------|---|--|
| R132.1 | Dilated and arrhythmogenic cardiomyopathy<br>WES or medium panel | Singleton                 | Small variants  | Panel of genes or loci | Dilated cardiomyopathy - teen and adult (652) | WES or Medium Panel                            |
| R132.2 | Dilated and arrhythmogenic cardiomyopathy                        | Singleton                 | Exon level CNVs | Panel of genes or loci | Dilated cardiomyopathy - teen and adult (652) | Exon level CNV detection by MLPA or equivalent |

## R391 Barth syndrome

### Testing Criteria

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

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Cardiology
- Clinical Genetics
- Neonatology
- Neurology
- Paediatrics

### Specialist Service Group

- Cardiology

### Associated Tests

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

## R133 Arrhythmogenic right ventricular cardiomyopathy

### Testing Criteria

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

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

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

### Overlapping indications

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Cardiology
- Clinical Genetics

### Specialist Service Group

- Cardiology

### Associated Tests

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

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



## R135 Paediatric or syndromic cardiomyopathy

### Testing Criteria

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

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

### Overlapping indications

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Cardiology
- Clinical Genetics

### Specialist Service Group

- Cardiology

### Associated Tests

| Code   | Name   | Optional Family Structure | Scope(s)                        | Target Type            | Target Name  | Method |
|--------|--|---------------------------|---------------------------------|------------------------|--|--------|
| R135.1 | Paediatric or syndromic cardiomyopathy WGS (phase 2) | Trio or Singleton         | Exon level CNVs, Small variants | Panel of genes or loci | Cardiomyopathies - including childhood onset (749) | WGS    |

## R136 Primary lymphoedema

### Testing Criteria

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

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Other

### Specialist Service Group

- Cardiology

### Associated Tests

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

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

## R138 Sudden unexplained death or survivors of a cardiac event

### Testing Criteria

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

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

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

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

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

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

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

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

### Overlapping Indications

#### Where in Pathway

At presentation

#### Requesting Specialties

- Cardiology
- Clinical Genetics

#### Specialist Service Group

- Cardiology

### Associated Tests

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

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

## R328 Progressive cardiac conduction disease

### Testing Criteria

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Cardiology
- Clinical Genetics

### Specialist Service Group

- Cardiology

### Associated Tests

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

| Code   | Name  | Optional Family Structure | Scope(s)        | Target Type            | Target Name                                  | Method   |
|--------|---|---------------------------|-----------------|------------------------|--|--|
| R328.1 | Progressive cardiac conduction disease WES or small panel | Singleton                 | Small variants  | Panel of genes or loci | Progressive cardiac conduction disease (506) | WES or Small Panel                             |
| R328.2 | Progressive cardiac conduction disease                    | Singleton                 | Exon level CNVs | Panel of genes or loci | Progressive cardiac conduction disease (506) | Exon level CNV detection by MLPA or equivalent |

## R384 Generalised arterial calcification in infancy

### Testing Criteria

Generalised arterial calcification with onset in the neonatal period

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Neonatology

### Specialist Service Group

- Cardiology

### Associated Tests

| Code   | Name         | Optional Family Structure | Scope(s)       | Target Type | Target Name  | Method      |
|--------|--------------|---------------------------|----------------|-------------|--------------|-------------|
| R384.1 | ABCC6; ENPP1 | Singleton                 | Small variants | Small panel | ABCC6; ENPP1 | Small panel |

## R140 Elastin-related phenotypes

### Testing Criteria

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

### Overlapping indications

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

R125 Thoracic aortic aneurysm or dissection test should be used for individuals with primarily aortic/large arterial involvement, with some features of cutis laxa

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

### Where in Pathway

At presentation

### Requesting Specialties

- Cardiology
- Clinical Genetics

### Specialist Service Group

- Cardiology

### Associated Tests

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

## Part III. Developmental disorders

### R26 Likely common aneuploidy

#### Testing Criteria

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

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

#### Overlapping indications

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

#### Where in Pathway

At presentation

#### Requesting Specialties

- Clinical Genetics
- Community Paediatrics
- Neonatology
- Paediatrics

#### Specialist Service Group

- Core

#### Associated Tests

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

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

### Testing Criteria

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

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

### Overlapping indications

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

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics

### Specialist Service Group

- Core

### Associated Tests

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

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



## R28 Congenital malformation and dysmorphism syndromes – microarray only

### Testing Criteria

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

### Overlapping indications

- R27 Congenital malformation and dysmorphism syndromes – likely monogenic test should be used instead where the likelihood of a chromosomal cause is lower
- R26 Likely common aneuploidy test should be used where clinical features are strongly suggestive of trisomy 13, 18 or 21, Turner syndrome or other sex chromosome aneuploidy

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

### Where in Pathway

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

### Requesting Specialties

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

### Specialist Service Group

- Core

### Associated Tests

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

## R29 Intellectual disability - microarray, and sequencing

### Testing Criteria

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

Microarray can be deselected if not relevant, for example if they have already been performed

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

### Overlapping indications

**R53 Fragile X – if clinical features are suggestive of Fragile X syndrome then this test should also be requested.**

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology
- Paediatrics

### Specialist Service Group

- Core

### Associated Tests

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

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

## R377 Intellectual disability - microarray only

### Testing Criteria

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

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

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

### Overlapping indications

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Community Paediatrics
- Neurology
- Paediatrics

### Specialist Service Group

- Core

### Associated Tests

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

## R47 Angelman syndrome

### Testing Criteria

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

### Overlapping indications

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

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Genomics laboratory
- Neurology
- Community paediatrics

### Specialist Service Group

- Core

### Associated Tests

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

## R48 Prader-Willi syndrome

### Testing Criteria

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

### Overlapping indications

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

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

### Where in Pathway

Following assessment by a Consultant Clinical Geneticist

### Requesting Specialties

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

### Specialist Service Group

- Core

### Associated Tests

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

## R53 Fragile X

### Testing Criteria

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

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

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

### Overlapping indications

- R29 Intellectual disability – microarray, and sequencing
- R54 Hereditary ataxia with onset in adulthood test should be used in preference in individuals with adult onset ataxia given the broad range of possible causes
- R402 Premature ovarian insufficiency test should be used where this is the relevant clinical context

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Community Paediatrics
- Paediatrics

### Specialist Service Group

- Core

### Associated Tests

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

## R69 Hypotonic infant

### Testing Criteria

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

### Overlapping indications

- R70 Spinal muscular atrophy type 1 diagnostic test and other tests for peripheral or neuromuscular causes should be used where clinical features point to a peripheral cause, i.e. particularly where the baby is alert and responsive and the floppiness appears static over a period of days
- **R14 Acutely unwell children with a likely monogenic disorder, should be used for acutely unwell neonates with hypotonia.**

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

### Where in Pathway

At presentation after exclusion of sepsis or hypoglycaemia as causes

### Requesting Specialties

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

### Specialist Service Group

- Core

### Associated Tests

Please note that initially only WGS testing (plus microarray where indicated) will be undertaken for R69 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are necessary. Whilst this includes testing of all STRs in the gene panel, analysis is currently not optimal and therefore if a specific STR is suspected this should be stated at referral to prompt additional testing where necessary

| Code  | Name                           | Optional Family Structure | Scope(s)                              | Target Type            | Target Name            | Method              |
|-------|--------------------------------|---------------------------|---------------------------------------|------------------------|------------------------|---------------------|
| R69.1 | SNRPN DMR Methylation testing  | Singleton                 | Methylation                           | Single gene(s)         | SNRPN DMR              | Methylation testing |
| R69.3 | Genomewide Microarray          | Singleton                 | Genomewide CNVs                       | Genomewide             | Genomewide             | Microarray          |
| R69.4 | DMPK STR testing               | Singleton                 | Methylation                           | Single gene(s)         | DMPK STR               | STR testing         |
| R69.5 | Hypotonic infant WGS (phase 1) | Trio or singleton         | Exon level CNVs, Small variants, STRs | Panel of genes or loci | Hypotonic infant (490) | WGS                 |

## R312 Parental sequencing for lethal autosomal recessive disorders

### Testing Criteria

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

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

### Where in Pathway

As appropriate

### Requesting Specialties

- Clinical Genetics

### Specialist Service Group

- Other

### Associated Tests

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



## Part IV. Endocrinology

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### R402 Premature ovarian insufficiency

#### Testing Criteria

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

#### Overlapping indications

- R53 Fragile X syndrome should be used for individuals with suspected fragile X syndrome
- R54 Hereditary ataxia with onset in adulthood test should be used in preference in individuals with adult onset ataxia given the broad range of possible causes

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

#### Where in Pathway

N/A

#### Requesting Specialties

- Clinical Genetics
- Endocrinology
- Gynaecology

#### Specialist Service Group

- Core

#### Associated Tests

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

## R314 Ambiguous genitalia presenting neonatally

### Testing Criteria

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

### Overlapping indications

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Endocrinology
- Neonatology

### Specialist Service Group

- Core

### Associated Tests

| Code   | Name   | Optional Family Structure | Scope(s)                | Target Type | Target Name     | Method                    |
|--------|--|---------------------------|-------------------------|-------------|-----------------|---------------------------|
| R314.1 | Sex chromosomes<br>Common aneuploidy testing | Singleton                 | Aneuploidy              | Genomewide  | Sex chromosomes | Common aneuploidy testing |
| R314.2 | Sex chromosomes<br>Karyotype                 | Singleton                 | Karyotype or equivalent | Genomewide  | Sex chromosomes | Karyotype                 |

## R106 Alstrom syndrome

### Testing Criteria

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

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

### Overlapping indications

- R27 Congenital malformation and dysmorphism syndromes – likely monogenic or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals overlapping or atypical presentations where features are not characteristic of Alstrom syndrome specifically

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

### Where in Pathway

At presentation

### Requesting Specialties

- Cardiology
- Clinical Genetics
- Endocrinology
- Ophthalmology

### Specialist Service Group

- Endocrinology

### Associated Tests

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

## R141 Monogenic diabetes

### Testing Criteria

1. **Patients with isolated diabetes** should be tested if they have:
  - a. **Diabetes diagnosed young** ( $\leq 35$  years in White Europeans and  $\leq 30$  years in high prevalence ethnic groups).

**AND**

- b. **Unlikely to have Type 1 diabetes** because:

They are not on insulin treatment.

**OR**

They are on insulin treatment with all autoantibodies tested negative (minimum testing of GADA and IA2A) and a random non-fasting C peptide value  $\geq 200$  pmol/l

**AND**

- c. **Have features suggestive of MODY:**

An HbA1c at diagnosis of diabetes  $< 7.5\%$  (58 mmol/mol), if diagnosed under 18 years of age,

**OR**

BMI  $< 30$  kg/m<sup>2</sup> adult (child BMI  $< 95^{\text{th}}$  centile) **and** a parent with diabetes (if White) or BMI  $< 27$  kg/m<sup>2</sup> (child BMI  $< 95^{\text{th}}$  centile) **and** a parent with diabetes (if high prevalence type 2 diabetes ethnic group).

**OR**

Have a MODY probability score  $\geq 20\%$  if not insulin treated and  $\geq 10\%$  if insulin treated (see <https://www.diabetesgenes.org/exeter-diabetes-app/ModyCalculator>)

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

- Diabetes diagnosed young

**AND**

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

**AND**

- Non-autoimmune extra pancreatic features suggestive of syndromic monogenic diabetes e.g.

- Cystic renal disease and/or congenital anomaly of kidney or urinary tract
- Bilateral sensorineural deafness
- Developmental delay
- Developmental defects
- Cardiomyopathy
- Optic atrophy
- Microcephaly

3. **Diabetes with severe insulin resistance**

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

- Acanthosis nigricans

**OR**

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

**AND**

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

### Overlapping indications

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

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

### Where in Pathway

At presentation; HbA1C testing is required prior to genetic testing

### Requesting Specialties

- Clinical Genetics
- Endocrinology
- Nephrology

### Specialist Service Group

- Endocrinology

### Associated Tests

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

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

## R142 Glucokinase-related fasting hyperglycaemia

### Testing Criteria

Fasting glucose noted to be raised  $\leq 35$  years

**AND**

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

**OR**

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

#### In pregnancy

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

**AND**

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

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

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

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Endocrinology

### Specialist Service Group

- Endocrinology

### Associated Tests

| Code   | Name                       | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                     |
|--------|----------------------------|---------------------------|----------------|----------------|-------------|--|
| R142.1 | GCK Single gene sequencing | Singleton                 | Small variants | Single gene(s) | GCK         | Single gene sequencing $\geq 10$ amplicons |

## R143 Neonatal diabetes

### Testing Criteria

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

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

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

### Order of testing

Start with treatment response screen for sulphonylurea-sensitive genes by Sanger sequencing

Continue to panel test if negative

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Endocrinology
- Genomics laboratory
- Neonatology

### Specialist Service Group

- Endocrinology

### Associated Tests

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

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

## R145 Congenital hypothyroidism

### Testing Criteria

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Endocrinology

### Specialist Service Group

- Endocrinology

### Associated Tests

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

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



## R329 Familial dysalbuminaemic hyperthyroxinaemia

### Testing Criteria

Raised serum T4 with inappropriately non-suppressed serum TSH

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Endocrinology

### Specialist Service Group

- Endocrinology

### Associated Tests

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

## R182 Hyperthyroidism

### Testing Criteria

Hyperthyroidism where common causes have been excluded:

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Endocrinology

### Specialist Service Group

- Endocrinology

### Associated Tests

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

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

## R146 Disorders of sex development

### Testing Criteria

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

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

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

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

### Overlapping indications

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

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Endocrinology
- Gynaecology

### Specialist Service Group

- Endocrinology

### Associated Tests

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

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

|        |                              |           |                 |                        |                                  |  |
|--------|------------------------------|-----------|-----------------|------------------------|----------------------------------|--|
| R146.3 | Disorders of sex development | Singleton | Exon level CNVs | Panel of genes or loci | Disorders of sex development (9) | Exon level CNV detection by MLPA or equivalent |
|--------|------------------------------|-----------|-----------------|------------------------|----------------------------------|--|

## R147 Growth failure in early childhood

### Testing Criteria

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

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

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

\*See Wakeling et al 2017, PMID: 27585961

### Overlapping indications

- R88 Severe microcephaly test should be used for patients with primary microcephaly – microcephalic dwarfism spectrum.
- R52 Short stature – SHOX deficiency test should be used where only a microarray is required
- R159 Pituitary hormone deficiency test should be used where more than one pituitary hormone is deficient as the cause of growth failure
- R104 Skeletal dysplasia should be considered if overlapping features are present and should be used where clinical features indicative of a likely monogenic skeletal dysplasia
- R28 Congenital malformation and dysmorphism syndromes – microarray only

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Endocrinology
- Paediatrics

### Specialist Service Group

- Endocrinology

### Associated Tests

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

| Code   | Name   | Optional Family Structure | Scope(s)       | Target Type            | Target Name                             | Method              |
|--------|--|---------------------------|----------------|------------------------|---|---------------------|
| R147.1 | Growth failure in early childhood<br>WES or medium panel | Singleton                 | Small variants | Panel of genes or loci | Growth failure in early childhood (473) | WES or Medium Panel |

|        |  |           |                 |                        |   |  |
|--------|--|-----------|-----------------|------------------------|---|--|
| R147.2 | 11p15 imprinted growth regulatory region and UPD7 growth regulatory critical region<br>Methylation testing | Singleton | Methylation     | Single interval        | 11p15 imprinted growth regulatory region and UPD7 growth regulatory critical region | Methylation testing                            |
| R147.3 | Growth failure in early childhood  | Singleton | Genomewide CNVs | Genomewide             | Genomewide  | Microarray                                     |
| R147.4 | Growth failure in early childhood  | Singleton | Exon level CNVs | Panel of genes or loci | Growth failure in early childhood (473)   | Exon level CNV detection by MLPA or equivalent |

## R49 Beckwith-Wiedemann syndrome

### Testing Criteria

Clinical features suggestive of Beckwith-Wiedemann syndrome defined as:

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

Cardinal features

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

Suggestive features:

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

\*See Brioude et al 2018, PMID: 29377879

### Overlapping indications

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

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

### Where in Pathway

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

### Requesting Specialties

- Cancer
- Clinical Genetics
- Endocrinology
- Neonatology
- Paediatrics

### Specialist Service Group

- Endocrinology

### Associated Tests

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

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



## R50 Isolated hemihypertrophy or macroglossia

### Testing Criteria

Isolated hemihypertrophy, OR  
Isolated macroglossia

### Overlapping indications

- R49 Beckwith-Wiedemann syndrome test should be used where additional features suggestive of Beckwith-Wiedemann syndrome are present
- R147 Growth failure in early childhood test should be used where additional features suggestive of Silver-Russell syndrome are present
- R26 Likely common aneuploidy test should be used where macroglossia occurs in the presence of features suggestive of Down syndrome
- R27 Congenital malformation and dysmorphism syndromes – likely monogenic or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with complex or syndromic presentations not suggestive of Beckwith-Wiedemann syndrome, Silver-Russell syndrome or Down syndrome.
- R263 Confirmation of uniparental disomy test should be used to confirm likely UPD detected on methylation and copy number testing

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Paediatrics

### Specialist Service Group

- Endocrinology

### Associated Tests

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

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

## R267 Temple syndrome - maternal uniparental disomy 14

### Testing Criteria

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics

### Specialist Service Group

- Endocrinology

### Associated Tests

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

## R268 Kagami-Ogata syndrome - paternal uniparental disomy 14

### Testing Criteria

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics

### Specialist Service Group

- Endocrinology

### Associated Tests

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

## R149 Severe early-onset obesity

### Testing Criteria

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

### Overlapping indications

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Endocrinology
- Paediatrics

### Specialist Service Group

- Endocrinology

### Associated Tests

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

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

## R150 Congenital adrenal hypoplasia

### Testing Criteria

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

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Endocrinology

### Specialist Service Group

- Endocrinology

### Associated Tests

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

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

## R180 Congenital adrenal hyperplasia diagnostic test

### Testing Criteria

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

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

### Overlapping indications

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Endocrinology
- Neonatology
- Paediatrics

### Specialist Service Group

- Endocrinology

### Associated Tests

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

| Code   | Name                           | Optional Family Structure | Scope(s)        | Target Type    | Target Name | Method                                     |
|--------|--------------------------------|---------------------------|-----------------|----------------|-------------|--|
| R180.1 | CYP21A2 Single gene sequencing | Singleton                 | Small variants  | Single gene(s) | CYP21A2     | Single gene sequencing $\geq 10$ amplicons |
| R180.2 | CYP21A2 MLPA or equivalent     | Singleton                 | Exon level CNVs | Single gene(s) | CYP21A2     | MLPA or equivalent                         |

## R388 Linkage testing for congenital adrenal hyperplasia

### Testing Criteria

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

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

### Where in Pathway

As appropriate

### Requesting Specialties

- Clinical Genetics

### Specialist Service Group

- Endocrinology

### Associated Tests

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

## R181 Congenital adrenal hyperplasia carrier testing

### Testing Criteria

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

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

### Where in Pathway

At the time of reproductive planning

### Requesting Specialties

- Clinical Genetics

### Specialist Service Group

- Endocrinology

### Associated Tests

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

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



## R183 Glucocorticoid-remediable aldosteronism (GRA)

### Testing Criteria

Primary hyperaldosteronism with one of:

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Endocrinology
- Nephrology

### Specialist Service Group

- Endocrinology

### Associated Tests

| Code   | Name   | Optional Family Structure | Scope(s)                  | Target Type     | Target Name                 | Method                    |
|--------|--|---------------------------|---------------------------|-----------------|-----------------------------|---------------------------|
| R183.1 | CYP11B1/CYP11B2 gene fusion<br>Targeted mutation testing | Singleton                 | Complex variant detection | Single interval | CYP11B1/CYP11B2 gene fusion | Targeted mutation testing |

## R344 Primary hyperaldosteronism - KCNJ5

### Testing Criteria

Primary hyperaldosteronism presenting under the age of 10 years

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Endocrinology
- Nephrology

### Specialist Service Group

- Endocrinology

### Associated Tests

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

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

### Testing Criteria

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

### Overlapping indications

- R91 Cytopenia - NOT Fanconi anaemia test should be used where exclusion of Fanconi anaemia using chromosome breakage testing is clinically indicated
- R260 Fanconi anaemia or Bloom syndrome - chromosome breakage testing test should be used instead where clinical features strongly suggestive of Fanconi anaemia or Bloom syndrome
- In other cases where testing is based on clinical features, R27 Congenital malformation and dysmorphism syndromes – likely monogenic, R89 Ultra-rare and atypical monogenic disorders or other broad genomic tests should typically be used except where clinical features are strongly suggestive of Fanconi anaemia or Bloom syndrome

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

### Where in Pathway

Following chromosome breakage analysis

### Requesting Specialties

- Clinical Genetics
- Haematology

### Specialist Service Group

- Haematology

### Associated Tests

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

| Code   | Name  | Optional Family Structure | Scope(s)        | Target Type            | Target Name                                       | Method             |
|--------|---|---------------------------|-----------------|------------------------|---|--------------------|
| R229.1 | Confirmed Fanconi anaemia or Bloom syndrome Small panel | Singleton                 | Small variants  | Panel of genes or loci | Confirmed Fanconi anaemia or Bloom syndrome (508) | Small panel        |
| R229.2 | FANCA; FANCB; FANCD2; PALB2 MLPA or equivalent          | Singleton                 | Exon level CNVs | Single gene(s)         | FANCA; FANCB; FANCD2; PALB2                       | MLPA or equivalent |

## R160 Primary pigmented nodular adrenocortical disease

### Testing Criteria

Primary pigmented nodular adrenocortical disease, OR

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Endocrinology

### Specialist Service Group

- Endocrinology

### Associated Tests

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

| Code   | Name   | Optional Family Structure | Scope(s)        | Target Type            | Target Name  | Method   |
|--------|--|---------------------------|-----------------|------------------------|--|--|
| R160.1 | Primary pigmented nodular adrenocortical disease Small panel | Singleton                 | Small variants  | Panel of genes or loci | Primary pigmented nodular adrenocortical disease (566) | Small panel                                    |
| R160.2 | Primary pigmented nodular adrenocortical disease             | Singleton                 | Exon level CNVs | Panel of genes or loci | Primary pigmented nodular adrenocortical disease (566) | Exon level CNV detection by MLPA or equivalent |

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

### Testing Criteria

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Endocrinology

### Specialist Service Group

- Endocrinology

### Associated Tests

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

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

## R151 Familial hyperparathyroidism or Hypocalciuric hypercalcaemia

### Testing Criteria

#### Familial Primary Hyperparathyroidism

- i) <50y,  
OR
- ii) any age with
  - a) a confirmed or relevant family history, OR
  - b) multiglandular disease or hyperplasia in the presence of relevant family history, OR
  - c) parathyroid carcinoma or atypical or cystic adenoma, OR
  - d) ossifying fibroma(s) of the maxilla and /or mandible.

#### Hypocalciuric hypercalcaemia

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

### Overlapping indications

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Endocrinology

### Specialist Service Group

- Endocrinology

### Associated Tests

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

| Code   | Name  | Optional Family Structure | Scope(s)        | Target Type            | Target Name  | Method   |
|--------|---|---------------------------|-----------------|------------------------|--|--|
| R151.1 | Familial hyperparathyroidism or Hypocalciuric hypercalcaemia<br>Small panel | Singleton                 | Small variants  | Panel of genes or loci | Familial hyperparathyroidism (480) and<br>Hypocalciuric hypercalcaemia (481) | Small panel                                    |
| R151.2 | Familial hyperparathyroidism or Hypocalciuric hypercalcaemia                | Singleton                 | Exon level CNVs | Panel of genes or loci | Familial hyperparathyroidism (480) and<br>Hypocalciuric hypercalcaemia (481) | Exon level CNV detection by MLPA or equivalent |

## R153 Familial hypoparathyroidism

### Testing Criteria

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

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

### Overlapping indications

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Endocrinology

### Specialist Service Group

- Endocrinology

### Associated Tests

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

| Code   | Name                                       | Optional Family Structure | Scope(s)        | Target Type            | Target Name                       | Method             |
|--------|--|---------------------------|-----------------|------------------------|-----------------------------------|--------------------|
| R153.1 | Familial hypoparathyroidism<br>Small panel | Singleton                 | Small variants  | Panel of genes or loci | Familial hypoparathyroidism (312) | Small panel        |
| R153.2 | GATA3 MLPA or equivalent                   | Singleton                 | Exon level CNVs | Single gene(s)         | GATA3                             | MLPA or equivalent |

## R154 Hypophosphataemia or rickets

### Testing Criteria

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Endocrinology

### Specialist Service Group

- Endocrinology

### Associated Tests

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

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



## R319 Calcium-sensing receptor phenotypes

### Testing Criteria

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Endocrinology

### Specialist Service Group

- Endocrinology

### Associated Tests

| Code   | Name                        | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                     |
|--------|-----------------------------|---------------------------|----------------|----------------|-------------|--|
| R319.1 | CASR Single gene sequencing | Singleton                 | Small variants | Single gene(s) | CASR        | Single gene sequencing $\geq 10$ amplicons |

## R157 IPEX - Immunodysregulation Polyendocrinopathy and Enteropathy, X-Linked

### Testing Criteria

Males with type 1 diabetes mellitus in early infancy or childhood, AND ANY TWO of the features below, OR  
Males with absent regulatory T cells, AND ONE of the features below:

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Endocrinology
- Gastroenterology
- Immunology

### Specialist Service Group

- Endocrinology

### Associated Tests

| Code   | Name                         | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                     |
|--------|------------------------------|---------------------------|----------------|----------------|-------------|--|
| R157.1 | FOXP3 Single gene sequencing | Singleton                 | Small variants | Single gene(s) | FOXP3       | Single gene sequencing $\geq 10$ amplicons |

## R156 Carney complex

### Testing Criteria

Two or more of the features from the list below (with histological confirmation where relevant), OR  
One feature from the list below (with histological confirmation where relevant) and an affected first degree relative:

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Dermatology
- Endocrinology

### Specialist Service Group

- Endocrinology

### Associated Tests

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

## R148 Hypogonadotropic hypogonadism

### Testing Criteria

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Endocrinology
- Gynaecology

### Specialist Service Group

- Endocrinology

### Associated Tests

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

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

## R159 Pituitary hormone deficiency

### Testing Criteria

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Endocrinology

### Specialist Service Group

- Endocrinology

### Associated Tests

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

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

## R217 Endocrine neoplasia

### Testing Criteria

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

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

MEN1-related endocrine abnormalities include:

  - Parathyroid hyperplasia/multiglandular adenomas
  - Pituitary tumors
  - Endocrine tumors of the gastro-entero-pancreatic (GEP) tract
  - Carcinoid tumors
  - Adrenocortical tumors

MEN1-related non-endocrine tumours include:

  - facial angiofibromas
  - collagenomas
  - meningioma
2. Familial isolated pituitary adenoma (FIPA)
  - Isolated pituitary adenoma developing under the age of 35, with at least one first degree relative with an isolated pituitary adenoma
3. X-linked acrogigantism
  - Onset of excess of growth hormone diagnosed by age 20 years in male patients, with increased growth velocity and/or tall stature (height  $>2$  standard deviations above the mean, or  $>3$  standard deviations over mid-parental height)
  - If testing on blood is negative and clinical suspicion of this diagnosis is strong, please contact the testing laboratory to discuss sending a fresh frozen tissue or skin biopsy sample to identify a mosaic form of the condition

**NOTE: All cancers should be histologically confirmed**

Where a patient doesn't meet the stated criteria but there is strong clinical suspicion of a monogenic predisposition to endocrine neoplasia, testing can go ahead after discussion in a specialist MDT meeting. Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Endocrinology

### Specialist Service Group

- Endocrinology

### Associated Tests

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

| Code   | Name  | Optional Family Structure | Scope(s)        | Target Type            | Target Name               | Method             |
|--------|---|---------------------------|-----------------|------------------------|---------------------------|--------------------|
| R217.1 | Endocrine neoplasia Small panel             | Singleton                 | Small variants  | Panel of genes or loci | Endocrine neoplasms (648) | Small panel        |
| R217.2 | MEN1; AIP; CDKN1B; CDC73 MLPA or equivalent | Singleton                 | Exon level CNVs | Single gene(s)         | MEN1; AIP; CDKN1B; CDC73  | MLPA or equivalent |

## R223 Inherited pheochromocytoma and paraganglioma excluding NF1

### Testing Criteria

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

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

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

**NOTE: Testing under this clinical indication does not include NF1**

### Overlapping indications

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Endocrinology

### Specialist Service Group

- Endocrinology

### Associated Tests

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

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



## R144 Congenital hyperinsulinism

### Testing Criteria

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

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

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

### Order of testing

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Endocrinology

### Specialist Service Group

- Endocrinology

### Associated Tests

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

| Code   | Name                                      | Optional Family Structure | Scope(s)        | Target Type            | Target Name                      | Method   |
|--------|---|---------------------------|-----------------|------------------------|----------------------------------|--|
| R144.1 | ABCC8; KCNJ11                             | Singleton                 | Small variants  | Small panel            | ABCC8; KCNJ11                    | Small panel                                    |
| R144.2 | Congenital hyperinsulinism<br>Small panel | Singleton                 | Small variants  | Panel of genes or loci | Congenital hyperinsulinism (308) | Small panel                                    |
| R143.3 | Congenital hyperinsulinism                | Singleton                 | Exon level CNVs | Panel of genes or loci | Congenital hyperinsulinism (308) | Exon level CNV detection by MLPA or equivalent |

## R158 Lipodystrophy - childhood onset

### Testing Criteria

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

AND

Acquired causes have been excluded

OR

**Individuals with the following features of severe insulin resistance:**

- Acanthosis nigricans

OR

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

AND

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

### Overlapping indications

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Endocrinology

### Specialist Service Group

- Endocrinology

### Associated Tests

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

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

## R218 Multiple endocrine neoplasia type 2

### Testing Criteria

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

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

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

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

### Overlapping indications

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Endocrinology

### Specialist Service Group

- Endocrinology

### Associated Tests

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

## R226 Inherited parathyroid cancer

### Testing Criteria

Testing of individual (proband) affected with parathyroid carcinoma

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

### Overlapping indications

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Endocrinology

### Specialist Service Group

- Endocrinology

### Associated Tests

| Code   | Name                         | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                     |
|--------|------------------------------|---------------------------|----------------|----------------|-------------|--|
| R226.1 | CDC73 Single gene sequencing | Singleton                 | Small variants | Single gene(s) | CDC73       | Single gene sequencing $\geq 10$ amplicons |

## R162 Familial tumoral calcinosis

### Testing Criteria

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Endocrinology

### Specialist Service Group

- Endocrinology

### Associated Tests

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

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

## R417 Multi Locus Imprinting Disorder (MLID)

### Testing Criteria

#### **R417.1**

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

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

#### **R417.2**

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

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

### Overlapping indications

- R143 Neonatal diabetes (ZFP57)

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Endocrinology
- Paediatrics
- Genomics Laboratory

### Specialist Service Group

- Endocrinology

### Associated Tests

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

| Code   | Name   | Optional Family Structure | Scope(s)        | Target Type            | Target Name  | Method      |
|--------|--|---------------------------|-----------------|------------------------|--|-------------|
| R417.1 | Multi Locus Imprinting Disorder<br>MLPA        | Singleton                 | Exon level CNVs | Panel of genes or loci | genes on chromosomes: 6, 7, 11, 14, 15, 19, 20. (PLAGL1, GRB10, MEST, H19, KCNQ1, GTL2, SNRPN, PEG3, GNAS) | MS-MLPA     |
| R417.2 | Multi Locus Imprinting Disorder<br>Small panel | Singleton                 | Small variants  | Panel of genes or loci | NLRP5, NLRP7, NLRP2, PAD16, KHDC3L   | Small panel |

## Part V. Ophthalmology

### R107 Bardet-Biedl syndrome

#### Testing Criteria

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

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

#### Overlapping indications

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

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

#### Where in Pathway

At presentation

#### Requesting Specialties

- Clinical Genetics
- Nephrology
- Ophthalmology

#### Specialist Service Group

- Ophthalmology

#### Associated Tests

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

| Code   | Name                                     | Optional Family Structure | Scope(s)        | Target Type            | Target Name                 | Method   |
|--------|--|---------------------------|-----------------|------------------------|-----------------------------|--|
| R107.1 | Bardet Biedl syndrome WES or large panel | Singleton                 | Small variants  | Panel of genes or loci | Bardet Biedl syndrome (543) | WES or Large Panel                             |
| R107.2 | Bardet Biedl syndrome                    | Singleton                 | Exon level CNVs | Panel of genes or loci | Bardet Biedl syndrome (543) | Exon level CNV detection by MLPA or equivalent |

## R31 Bilateral congenital or childhood onset cataracts

### Testing Criteria

Unexplained bilateral congenital or childhood onset cataracts

### Overlapping indications

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

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

### Where in Pathway

At presentation, after urine reducing substances

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

### Requesting Specialties

- Clinical Genetics
- Ophthalmology

### Specialist Service Group

- Ophthalmology

### Associated Tests

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



## R32 Retinal disorders

### Testing Criteria

Unexplained retinal disease that is likely to be monogenic

### Overlapping indications

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

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Ophthalmology

### Specialist Service Group

- Ophthalmology

### Associated Tests

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

## R33 Possible X-linked retinitis pigmentosa

### Testing Criteria

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

### Order of testing

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

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Ophthalmology

### Specialist Service Group

- Ophthalmology

### Associated Tests

| Code  | Name   | Optional Family Structure | Scope(s)       | Target Type     | Target Name     | Method                    |
|-------|--|---------------------------|----------------|-----------------|-----------------|---------------------------|
| R33.1 | RPGR exon ORF15<br>Targeted mutation testing | Singleton                 | Small variants | Single interval | RPGR exon ORF15 | Targeted mutation testing |

## R36 Structural eye disease

### Testing Criteria

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

### Overlapping indications

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

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Ophthalmology

### Specialist Service Group

- Ophthalmology

### Associated Tests

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

## R38 Sporadic aniridia

### Testing Criteria

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Oncology
- Clinical Genetics
- Ophthalmology
- Paediatrics

### Specialist Service Group

- Ophthalmology

### Associated Tests

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

| Code  | Name                         | Optional Family Structure | Scope(s)        | Target Type            | Target Name    | Method             |
|-------|------------------------------|---------------------------|-----------------|------------------------|----------------|--------------------|
| R38.1 | PAX6; WT1 MLPA or equivalent | Singleton                 | Exon level CNVs | Single gene(s)         | PAX6; WT1      | MLPA or equivalent |
| R38.2 | Aniridia Small panel         | Singleton                 | Small variants  | Panel of genes or loci | Aniridia (510) | Small panel        |

## R39 Albinism or congenital nystagmus

### Testing Criteria

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

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Dermatology
- Ophthalmology

### Specialist Service Group

- Ophthalmology

### Associated Tests

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

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

## R41 Optic neuropathy

### Testing Criteria

Unexplained optic neuropathy

### Overlapping indications

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

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

### Where in Pathway

At presentation following expert by a Consultant Ophthalmologist

### Requesting Specialties

- Clinical Genetics
- Ophthalmology

### Specialist Service Group

- Ophthalmology

### Associated Tests

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

| Code  | Name                                 | Optional Family Structure | Scope(s)        | Target Type            | Target Name            | Method   |
|-------|--------------------------------------|---------------------------|-----------------|------------------------|------------------------|--|
| R41.1 | Optic neuropathy WES or Medium panel | Singleton                 | Small variants  | Panel of genes or loci | Optic neuropathy (186) | WES or Medium panel                            |
| R41.2 | Optic neuropathy                     | Singleton                 | Exon level CNVs | Panel of genes or loci | Optic neuropathy (186) | Exon level CNV detection by MLPA or equivalent |

## R43 Blepharophimosis ptosis and epicanthus inversus

### Testing Criteria

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Ophthalmology

### Specialist Service Group

- Ophthalmology

### Associated Tests

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

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

## R46 Congenital fibrosis of the extraocular muscles

### Testing Criteria

Individuals with a suspected clinical diagnosis of congenital fibrosis of the extraocular muscles  
Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Neurology
- Ophthalmology

### Specialist Service Group

- Ophthalmology

### Associated Tests

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

| Code  | Name   | Optional Family Structure | Scope(s)        | Target Type            | Target Name  | Method   |
|-------|--|---------------------------|-----------------|------------------------|--|--|
| R46.1 | Congenital fibrosis of the extraocular muscles Small panel | Singleton                 | Small variants  | Panel of genes or loci | Congenital fibrosis of the extraocular muscles (512) | Small panel                                    |
| R46.2 | Congenital fibrosis of the extraocular muscles             | Singleton                 | Exon level CNVs | Panel of genes or loci | Congenital fibrosis of the extraocular muscles (512) | Exon level CNV detection by MLPA or equivalent |



## R262 Corneal dystrophy

### Testing Criteria

Corneal dystrophy of likely monogenic aetiology

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Ophthalmology

### Specialist Service Group

- Ophthalmology

### Associated Tests

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

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

## R45 Stickler syndrome

### Testing Criteria

Clinical features indicative of likely Stickler syndrome

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Ophthalmology

### Specialist Service Group

- Ophthalmology

### Associated Tests

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

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

## R420 Pseudoxanthomaelasticum

### Testing Criteria

Individuals who have characteristic features of Pseudoxanthoma elasticum:

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

### Overlapping indications

- R384 Generalised arterial calcification in infancy

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Ophthalmology

### Specialist Service Group

- Ophthalmology

### Associated Tests

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

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

## Part VI. Fetal (including NIPD)

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### R401 Common aneuploidy testing - prenatal

#### Testing Criteria

Prenatal findings requiring common aneuploidy testing including:

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

#### Overlapping indications

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

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

#### Where in Pathway

N/A

#### Requesting Specialties

- Clinical Genetics
- Fetal Medicine
- Obstetrics

#### Specialist Service Group

- Core

#### Associated Tests

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

## R318 Recurrent miscarriage with products of conception available for testing

### Testing Criteria

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

### Overlapping indications

- R297 Possible structural chromosomal rearrangement - karyotype test should be used in parents of recurrent miscarriage where products of conception are not available for testing
- R22 Fetus with a likely chromosomal abnormality or R21 Fetal anomalies with a likely genetic cause should be used in cases of second or third trimester intrauterine death or stillbirth
- R318 Recurrent miscarriage with products of conception available for testing can be used where there has been recurrent miscarriage in the absence of additional features suggestive of chromosomal abnormality

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Fetal Medicine
- Gynaecology
- Obstetrics

### Specialist Service Group

- Core

### Associated Tests

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

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

## R22 Fetus with a likely chromosomal abnormality

### Testing Criteria

Fetus with a likely chromosomal abnormality

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

### Overlapping indications

- R26 Likely common aneuploidy should be used where only common aneuploidy testing is indicated
- R21 Fetal anomalies with a likely genetic cause test should be used instead following discussion with a Clinical Geneticist where it is considered more appropriate
- R318 Recurrent miscarriage with products of conception available for testing can be used where there has been recurrent miscarriage in the absence of additional features suggestive of chromosomal abnormality

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Fetal Medicine
- Pathology

### Specialist Service Group

- Core

### Associated Tests

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

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

## R21 Fetal anomalies with a likely genetic cause

### Testing Criteria

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

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

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

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

### Clinical examples

- Fetuses with multiple anomalies, suspected skeletal dysplasias (IUGR should be excluded), large echogenic kidneys with a normal bladder, major CNS abnormalities (excluding neural tube defects), multiple contractures (excluding isolated bilateral talipes).
- Nuchal translucency of greater than 6.5mm plus another anomaly (that can include a minor finding) with a normal array CGH
- Isolated non-immune fetal hydrops (detected at or after the routine 18-20-week scan in the second or third trimesters), defined as fluid/oedema in at least two compartments (e.g. skin, pleural, pericardial or ascites) with a normal array CGH
- Persistent nuchal translucency (>3.5mm) can only be considered in the presence of other structural abnormalities in two or more systems.
- Minor 'markers of aneuploidy' – choroid plexus cysts, echogenic foci, mild renal pelvis dilation, small nasal bone, long bones on 3rd centile etc are excluded.
- Mild ventriculomegaly should only be considered as an abnormality if the posterior horn is persistently >11mm. Under these circumstances it is not considered a major CNS abnormality in isolation.

### Exclusion criteria

- Confirmed aneuploidy or pathogenic copy number variant consistent with fetal anomalies detected by microarray
- Fetuses with confirmed thanatophoric dysplasia, achondroplasia or Apert syndrome on other relevant rapid tests (R23, R24, R25, R306 or R309) are excluded.
- Cases where familial causative variant(s) are known - targeted testing should be performed
- For cases where sonographic findings indicate a specific monogenic disorder, targeted testing should be applied where appropriate
- Where termination of pregnancy has already been decided or when fetal demise has occurred or is imminent then rapid exome sequencing will not be performed. Appropriate testing should be implemented postnatally using the R27 clinical indication (Congenital malformation and dysmorphism syndromes - microarray and sequencing).

### Overlapping indications

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

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

### Where in Pathway

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

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

### Requesting Specialties

- Clinical Genetics

## Specialist Service Group

- Core

### Associated Tests

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

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



## R412 Fetal anomalies with a likely genetic cause – non urgent

### Testing Criteria

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

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

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

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

### Overlapping indications

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics and/or other appropriate specialist referring clinician

### Specialist Service Group

- Specialised

### Associated Tests

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

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

## R251 Non-invasive prenatal sexing

### Testing Criteria

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

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

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Fetal Medicine

### Specialist Service Group

- NIPD

### Associated Tests

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

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

### Testing Criteria

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

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

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

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

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics

### Specialist Service Group

- NIPD

### Associated Tests

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

## R250 NIPD for congenital adrenal hyperplasia - CYP21A2 haplotype testing

### Testing Criteria

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

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

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

Testing is not currently possible for consanguineous couples

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Fetal Medicine

### Specialist Service Group

- NIPD

### Associated Tests

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

## R304 NIPD for cystic fibrosis - haplotype testing

### Testing Criteria

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

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

Testing is not currently possible for consanguineous couples

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Fetal Medicine

### Specialist Service Group

- NIPD

### Associated Tests

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

## R305 NIPD for cystic fibrosis - mutation testing

### Testing Criteria

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

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Fetal Medicine
- Obstetrics

### Specialist Service Group

- NIPD

### Associated Tests

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

## R306 NIPD for Apert syndrome - mutation testing

### Testing Criteria

Pregnancy in which NIPD for Apert syndrome is required

Either:

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

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Fetal Medicine

### Specialist Service Group

- NIPD

### Associated Tests

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

## R307 NIPD for Crouzon syndrome with acanthosis nigricans - mutation testing

### Testing Criteria

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

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Fetal Medicine

### Specialist Service Group

- NIPD

### Associated Tests

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



## R308 NIPD for FGFR2-related craniosynostosis syndromes - mutation testing

### Testing Criteria

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Fetal Medicine

### Specialist Service Group

- NIPD

### Associated Tests

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

## R309 NIPD for FGFR3-related skeletal dysplasias - mutation testing

### Testing Criteria

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

1. Abnormal ultrasound findings compatible with sonographic diagnosis of achondroplasia or other rare FGFR3-related skeletal dysplasia including Muenke syndrome, hypochondroplasia or hypochondroplasia with acanthosis nigricans:
  - a. Femoral length within the normal range at the routine 18-20-week scan, AND
  - b. Femur length and all long bones below the 3rd percentile after 25 weeks gestation, AND
  - c. Head circumference on or above 95th percentile or above the normal range for gestation at diagnosis and/or frontal bossing present, AND
  - d. Fetal and maternal dopplers should be normal
  - e. Other features may include polyhydramnios or short fingersOR
2. Abnormal ultrasound findings compatible with sonographic diagnosis of thanatophoric dysplasia or severe achondroplasia with developmental delay:
  - a. All long bones below the 3rd percentile from early pregnancy, AND
  - b. Small chest with short ribs, AND
  - c. At least one of: bowed femora, frontal bossing, cloverleaf skull, short fingersOR
3. At risk pregnancy due to paternal FGFR3-related skeletal disorder OR a previous pregnancy with confirmed FGFR3-related skeletal disorder

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

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Fetal Medicine

### Specialist Service Group

- NIPD

### Associated Tests

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

## R310 NIPD for Duchenne and Becker muscular dystrophy - haplotype testing

### Testing Criteria

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

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

Testing is not currently possible for consanguineous couples

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Fetal Medicine

### Specialist Service Group

- NIPD

### Associated Tests

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

## R311 NIPD for spinal muscular atrophy - mutation testing

### Testing Criteria

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

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

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

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Fetal Medicine

### Specialist Service Group

- NIPD

### Associated Tests

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

## R423 NIPD for Retinoblastoma

### Testing Criteria

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

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

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

Testing is not possible in multiple pregnancies.

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Fetal Medicine

### Specialist Service Group

- NIPD

### Associated Tests

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

## R389 NIPD - pre-pregnancy test work-up

### Testing Criteria

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

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

### Where in Pathway

Prior to the pregnancy in which NIPD is planned

### Requesting Specialties

- Clinical Genetics

### Specialist Service Group

- NIPD

### Associated Tests

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

## Part VII. Gastrohepatology

### R168 Non-acute porphyrias

#### Testing Criteria

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

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

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

#### Where in Pathway

At presentation or after clinical assessment by a highly specialised service

#### Requesting Specialties

- Dermatology
- Haematology
- Hepatology
- Neurology

#### Specialist Service Group

- Gastrohepatology

#### Associated Tests

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

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

## R169 Acute intermittent porphyria

### Testing Criteria

Clinical features of acute intermittent porphyria (AIP), AND

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

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

### Where in Pathway

At presentation or after clinical assessment by a highly specialised service

### Requesting Specialties

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

### Specialist Service Group

- Gastrohepatology

### Associated Tests

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



## R170 Variegate porphyria

### Testing Criteria

Clinical features of variegate porphyria, AND

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Dermatology
- Gastroenterology
- Hepatology
- Neurology

### Specialist Service Group

- Gastrohepatology

### Associated Tests

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

## R171 Cholestasis

### Testing Criteria

Neonatal conjugated hyperbilirubinaemia where multifactorial and infective causes have been excluded, OR  
Unexplained cholestasis developing below the age of 18 (It may occasionally be appropriate to test individuals presenting over the 18 under this indication following expert review) OR

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

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

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

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

### Where in Pathway

At presentation

### Requesting Specialties

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

### Specialist Service Group

- Gastrohepatology

### Associated Tests

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

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

## R172 Wilson disease

### Testing Criteria

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

### Overlapping indications

- R98 Likely inborn error of metabolism - targeted testing is not possible, R27 Congenital malformation and dysmorphism syndromes – likely monogenic or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with atypical features in whom a broader differential diagnosis is under consideration

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

### Where in Pathway

At presentation

### Requesting Specialties

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

### Specialist Service Group

- Gastrohepatology

### Associated Tests

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

## R173 Polycystic liver disease

### Testing Criteria

Patients with multiple hepatic cysts with no explanation

### Overlapping indications

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Hepatology

### Specialist Service Group

- Gastrohepatology

### Associated Tests

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

| Code   | Name  | Optional Family Structure | Scope(s)        | Target Type            | Target Name                            | Method   |
|--------|---|---------------------------|-----------------|------------------------|--|--|
| R173.1 | Polycystic liver disease WES or small panel | Singleton                 | Small variants  | Panel of genes or loci | Polycystic liver disease interim (653) | WES or Small Panel                             |
| R173.2 | Polycystic liver disease                    | Singleton                 | Exon level CNVs | Panel of genes or loci | Polycystic liver disease interim (653) | Exon level CNV detection by MLPA or equivalent |

## R175 Pancreatitis

### Testing Criteria

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

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Gastroenterology
- Hepatology

### Specialist Service Group

- Gastrohepatology

### Associated Tests

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

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

## R176 Gilbert syndrome

### Testing Criteria

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Hepatology

### Specialist Service Group

- Gastrohepatology

### Associated Tests

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

## R177 Hirschsprung disease

### Testing Criteria

Diagnosis of Hirschsprung disease

### Overlapping indications

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

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

### Where in Pathway

At presentation

### Requesting Specialties

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

### Specialist Service Group

- Gastrohepatology

### Associated Tests

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

## R331 Intestinal failure or congenital diarrhoea

### Testing Criteria

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

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

### Overlapping indications

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Gastroenterology
- Neonatology
- Paediatrics

### Specialist Service Group

- Gastrohepatology

### Associated Tests

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

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



## Part VIII. Haematology

### R361 Haemoglobinopathy trait or carrier testing

#### Testing Criteria

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

#### Overlapping indications

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

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

#### Where in Pathway

Following haemoglobin electrophoresis

#### Requesting Specialties

- Clinical Genetics
- Haematology
- Obstetrics

#### Specialist Service Group

- Haematology

#### Associated Tests

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

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

## R362 Carrier testing for sickle cell disease

### Testing Criteria

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

### Overlapping indications

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

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

### Where in Pathway

Following haemoglobin electrophoresis

### Requesting Specialties

- Clinical Genetics
- Haematology
- Obstetrics

### Specialist Service Group

- Haematology

### Associated Tests

| Code   | Name                                     | Optional Family Structure | Scope(s)       | Target Type     | Target Name | Method                    |
|--------|--|---------------------------|----------------|-----------------|-------------|---------------------------|
| R362.1 | HbS variant<br>Targeted mutation testing | Singleton                 | Small variants | Single interval | HbS variant | Targeted mutation testing |

## R90 Bleeding and platelet disorders

### Testing Criteria

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

### Overlapping indications

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

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

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Haematology

### Specialist Service Group

- Haematology

### Associated Tests

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

| Code  | Name  | Optional Family Structure | Scope(s)        | Target Type            | Target Name   | Method              |
|-------|---|---------------------------|-----------------|------------------------|---|---------------------|
| R90.1 | Bleeding and platelet disorders<br>WES or medium panel                | Singleton                 | Small variants  | Panel of genes or loci | Bleeding and platelet disorders (545)                   | WES or Medium Panel |
| R90.2 | F5; F11; MYH9; ENG; ACVRL1; ; F7; F8; F9; F10; VWF MLPA or equivalent | Singleton                 | Exon level CNVs | Single gene(s)         | F5; F11; MYH9; ENG; ACVRL1; BMPR2; F7; F8; F9; F10; VWF | MLPA or equivalent  |

## R93 Thalassaemia and other haemoglobinopathies

### Testing Criteria

Clinical features indicative of likely thalassaemia or other clinically significant haemoglobinopathy

### Overlapping indications

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

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

### Where in Pathway

At presentation

### Requesting Specialties

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

### Specialist Service Group

- Haematology

### Associated Tests

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

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

## R94 HbSS sickle cell anaemia

### Testing Criteria

Likely HbSS sickle cell anaemia on haemoglobin electrophoresis

### Overlapping indications

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

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

### Where in Pathway

At presentation

### Requesting Specialties

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

### Specialist Service Group

- Haematology

### Associated Tests

| Code  | Name                                     | Optional Family Structure | Scope(s)       | Target Type     | Target Name | Method                    |
|-------|--|---------------------------|----------------|-----------------|-------------|---------------------------|
| R94.1 | HbS variant<br>Targeted mutation testing | Singleton                 | Small variants | Single interval | HbS variant | Targeted mutation testing |

## R372 Newborn screening for sickle cell disease in a transfused baby

### Testing Criteria

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

### Where in Pathway

As per protocol

### Requesting Specialties

- Other

### Specialist Service Group

- Screening

### Associated Tests

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

## R95 Iron overload - hereditary haemochromatosis testing

### Testing Criteria

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

### Overlapping indications

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Cardiology
- Clinical Genetics
- Haematology
- Hepatology
- Primary Care

### Specialist Service Group

- Core

### Associated Tests

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

## R96 Iron metabolism disorders - NOT common HFE mutations

### Testing Criteria

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

### Overlapping indications

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Cardiology
- Clinical Genetics
- Haematology
- Hepatology

### Specialist Service Group

- Haematology

### Associated Tests

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

| Code  | Name   | Optional Family Structure | Scope(s)        | Target Type            | Target Name                           | Method             |
|-------|--|---------------------------|-----------------|------------------------|---------------------------------------|--------------------|
| R96.1 | Iron metabolism disorders Small panel                    | Singleton                 | Small variants  | Panel of genes or loci | Iron metabolism disorders (515)       | Small panel        |
| R96.2 | HFE; SLC40A1; TFR2; HFE2; HAMP; ATP7B MLPA or equivalent | Singleton                 | Exon level CNVs | Single gene(s)         | HFE; SLC40A1; TFR2; HFE2; HAMP; ATP7B | MLPA or equivalent |



## R97 Thrombophilia with a likely monogenic cause

### Testing Criteria

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

### Where in Pathway

At presentation following consultation with Consultant Haematologist

### Requesting Specialties

- Clinical Genetics
- Haematology

### Specialist Service Group

- Haematology

### Associated Tests

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

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

## R112 Factor II deficiency

### Testing Criteria

Clinical features characteristic of factor II deficiency

### Overlapping indications

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

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

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

### Where in Pathway

At presentation following functional haemostasis testing

### Requesting Specialties

- Clinical Genetics
- Haematology

### Specialist Service Group

- Haematology

### Associated Tests

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

## R115 Factor V deficiency

### Testing Criteria

Clinical features characteristic of factor V deficiency

### Overlapping indications

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

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

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

### Where in Pathway

At presentation following functional haemostasis testing

### Requesting Specialties

- Clinical Genetics
- Haematology

### Specialist Service Group

- Haematology

### Associated Tests

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

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

## R116 Factor VII deficiency

### Testing Criteria

Clinical features characteristic of factor VII deficiency

### Overlapping indications

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

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

### Where in Pathway

At presentation following functional haemostasis testing

### Requesting Specialties

- Clinical Genetics
- Haematology

### Specialist Service Group

- Haematology

### Associated Tests

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

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

## R117 Factor VIII deficiency

### Testing Criteria

Clinical features characteristic of factor VIII deficiency

### Overlapping indications

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

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

### Where in Pathway

At presentation following functional haemostasis testing

### Requesting Specialties

- Clinical Genetics
- Haematology

### Specialist Service Group

- Haematology

### Associated Tests

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

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

## R118 Factor IX deficiency

### Testing Criteria

Clinical features characteristic of factor IX deficiency

### Overlapping indications

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

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

### Where in Pathway

At presentation following functional haemostasis testing

### Requesting Specialties

- Clinical Genetics
- Haematology

### Specialist Service Group

- Haematology

### Associated Tests

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

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

## R119 Factor X deficiency

### Testing Criteria

Clinical features characteristic of factor X deficiency

### Overlapping indications

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

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

### Where in Pathway

At presentation following functional haemostasis testing

### Requesting Specialties

- Clinical Genetics
- Haematology

### Specialist Service Group

- Haematology

### Associated Tests

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

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

## R120 Factor XI deficiency

### Testing Criteria

Clinical features characteristic of factor XI deficiency

### Overlapping indications

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

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

### Where in Pathway

At presentation following functional haemostasis testing

### Requesting Specialties

- Clinical Genetics
- Haematology

### Specialist Service Group

- Haematology

### Associated Tests

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

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



## R121 von Willebrand disease

### Testing Criteria

Clinical features characteristic of von Willebrand disease

### Overlapping indications

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

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

### Where in Pathway

At presentation following functional haemostasis testing

### Requesting Specialties

- Clinical Genetics
- Haematology

### Specialist Service Group

- Haematology

### Associated Tests

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

| Code   | Name                       | Optional Family Structure | Scope(s)        | Target Type    | Target Name | Method                                     |
|--------|----------------------------|---------------------------|-----------------|----------------|-------------|--|
| R121.1 | VWF Single gene sequencing | Singleton                 | Small variants  | Single gene(s) | VWF         | Single gene sequencing $\geq 10$ amplicons |
| R121.2 | VWF MLPA or equivalent     | Singleton                 | Exon level CNVs | Single gene(s) | VWF         | MLPA or equivalent                         |

## R122 Factor XIII deficiency

### Testing Criteria

Clinical features characteristic of factor XIII deficiency

### Overlapping indications

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

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

### Where in Pathway

At presentation following functional haemostasis testing

### Requesting Specialties

- Clinical Genetics
- Haematology

### Specialist Service Group

- Haematology

### Associated Tests

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

## R123 Combined vitamin K-dependent clotting factor deficiency

### Testing Criteria

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

### Overlapping indications

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

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

### Where in Pathway

At presentation following functional haemostasis testing

### Requesting Specialties

- Clinical Genetics
- Haematology

### Specialist Service Group

- Haematology

### Associated Tests

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

## R124 Combined factor V and VIII deficiency

### Testing Criteria

Clinical features characteristic of combined factor V and VIII deficiency

### Overlapping indications

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

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

### Where in Pathway

At presentation following functional haemostasis testing

### Requesting Specialties

- Clinical Genetics
- Haematology

### Specialist Service Group

- Haematology

### Associated Tests

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

| Code   | Name   | Optional Family Structure | Scope(s)        | Target Type            | Target Name                                 | Method   |
|--------|--|---------------------------|-----------------|------------------------|---|--|
| R124.1 | Combined factor V and VIII deficiency<br>Small panel | Singleton                 | Small variants  | Panel of genes or loci | Combined factor V and VIII deficiency (517) | Small panel                                    |
| R124.2 | Combined factor V and VIII deficiency                | Singleton                 | Exon level CNVs | Panel of genes or loci | Combined factor V and VIII deficiency (517) | Exon level CNV detection by MLPA or equivalent |

## R92 Rare anaemia

### Testing Criteria

Rare anaemias of likely monogenic aetiology

### Overlapping indications:

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

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

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

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

### Where in Pathway

At presentation following exclusion of likely acquired causes

### Requesting Specialties

- Clinical Genetics
- Haematology

### Specialist Service Group

- Haematology

### Associated Tests

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

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

## R91 Cytopenia - NOT Fanconi anaemia

### Testing Criteria

Persistent or recurrent cytopenia or pancytopenia of unknown cause where Fanconi anaemia is unlikely  
This includes unexplained isolated aplastic anaemia, thrombocytopenia or neutropenia

### Overlapping indications

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

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Haematology
- Immunology

### Specialist Service Group

- Haematology

### Associated Tests

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

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

## R258 Cytopenia - Fanconi breakage testing indicated

### Testing Criteria

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

### Overlapping indications

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Haematology
- Immunology

### Specialist Service Group

- Haematology

### Associated Tests

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

## R259 Nijmegen breakage syndrome

### Testing Criteria

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

### Overlapping indications

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

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

### Where in Pathway

N/A

### Requesting Specialties

- Clinical Genetics

### Specialist Service Group

- Haematology

### Associated Tests

| Code   | Name  | Optional Family Structure | Scope(s)       | Target Type    | Target Name       | Method                                     |
|--------|---|---------------------------|----------------|----------------|-------------------|--|
| R259.1 | Nijmegen breakage DNA repair defect testing | Singleton                 | DNA repair     | Genomewide     | Nijmegen breakage | DNA repair defect testing                  |
| R259.2 | NBN Single gene sequencing                  | Singleton                 | Small variants | Single gene(s) | NBN               | Single gene sequencing $\geq 10$ amplicons |



## R260 Fanconi anaemia or Bloom syndrome - chromosome breakage testing

### Testing Criteria

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

### Overlapping indications

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

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

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

### Where in Pathway

N/A

### Requesting Specialties

- Clinical Genetics
- Haematology

### Specialist Service Group

- Haematology

### Associated Tests

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

## R313 Neutropaenia consistent with ELANE mutations

### Testing Criteria

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

### Overlapping indications

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

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Haematology
- Immunology

### Specialist Service Group

- Haematology

### Associated Tests

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

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

### Testing Criteria

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

### Where in Pathway

As per relevant clinical protocol

### Requesting Specialties

- Haematology
- Immunology

### Specialist Service Group

- Haematology

### Associated Tests

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

## R347 Inherited predisposition to acute myeloid leukaemia (AML)

### Testing Criteria

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

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

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

### Overlapping indications

- M80 Acute myeloid leukaemia should be used for somatic testing

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Haematology

### Specialist Service Group

- Haematology

### Associated Tests

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

| Code   | Name  | Optional Family Structure | Scope(s)        | Target Type            | Target Name   | Method             |
|--------|---|---------------------------|-----------------|------------------------|---|--------------------|
| R347.1 | Inherited predisposition to acute myeloid leukaemia AML Small panel | Singleton                 | Small variants  | Panel of genes or loci | Inherited predisposition to acute myeloid leukaemia (AML) (525) | Small panel        |
| R347.2 | Inherited predisposition to acute myeloid leukaemia AML             | Singleton                 | Exon level CNVs | Single gene(s)         | Inherited predisposition to acute myeloid leukaemia (AML) (525) | MLPA or equivalent |

## R366 Inherited susceptibility to acute lymphoblastoid leukaemia (ALL)

### Testing Criteria

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

The proband has:

Acute Lymphoblastic Leukemia (ALL), AND

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

**NOTE: All diagnoses must be medically documented**

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

### Overlapping indications

- M91 Acute lymphoblastic leukaemia should be used for somatic testing

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Haematology

### Specialist Service Group

- Haematology

### Associated Tests

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

## R405 Hereditary Erythrocytosis

### Testing Criteria

1. Clinical features of a likely erythrocytosis of monogenic aetiology
2. Exclusion of secondary causes of erythrocytosis and acquired bone marrow disorders such as myeloproliferative neoplasm

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

### Overlapping Indications

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Haematology

### Specialist Service Group

- Haematology

### Associated Tests

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

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

## R406 Thrombocythaemia

### Testing Criteria

1. Clinical features of a likely thrombocythaemia of monogenic aetiology
2. Exclusion of secondary causes of thrombocythaemia and acquired bone marrow disorders such as myeloproliferative neoplasm

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

### Overlapping Indications

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Haematology

### Specialist Service Group

- Haematology

### Associated Tests

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

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

## Part IX. Audiology

### R65 Aminoglycoside exposure posing risk to hearing

#### Testing Criteria

Significant exposure to aminoglycosides posing risk of ototoxicity

This indication would be relevant to:

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

#### Overlapping indications

- R67 Non-syndromic hearing loss should be used in individuals with unexplained hearing loss

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

#### Where in Pathway

As appropriate

#### Requesting Specialties

- Other

#### Specialist Service Group

- Core

#### Associated Tests

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



## R67 Monogenic hearing loss

### Testing Criteria

Likely or possible monogenic hearing loss

Hearing loss should be confirmed and bilateral

Cases of unilateral hearing loss are accepted IF there are:

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

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

### Overlapping indications

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

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

### Where in Pathway

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

### Requesting Specialties

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

### Specialist Service Group

- Audiology

### Associated Tests

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

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

## Part X. Immunology

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### R155 Autoimmune Polyendocrine Syndrome

#### Testing Criteria

Individuals with a clinical diagnosis of autoimmune polyendocrine syndrome

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

#### Where in Pathway

At presentation

#### Requesting Specialties

- Clinical Genetics
- Endocrinology
- Immunology

#### Specialist Service Group

- Immunology

#### Associated Tests

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

## R15 Primary immunodeficiency or monogenic Inflammatory Bowel Disease

### Testing Criteria

Suspected primary immunodeficiency diagnosed by a consultant immunologist

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

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

OR

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

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

### Overlapping indications

- R16 Severe combined immunodeficiency with adenosine deaminase deficiency test should be used in individuals with ADA deficiency
- R234 Severe combined immunodeficiency with PNP deficiency test should be used in individuals with PNP deficiency
- R235 Severe combined immunodeficiency with gamma chain deficiency test should be used in individuals with low or absent gamma chain or low or absent STAT5 pTyr to IL-2,7, and 15
- R17 Lymphoproliferative syndrome with low or absent SAP expression test should be used in individuals with absent SAP expression
- R232 Lymphoproliferative syndrome with low or absent perforin expression test should be used in individuals with absent perforin expression
- R18 Lymphoproliferative syndrome with low or absent XIAP expression test should be used in individuals with absent XIAP expression
- R19 Autoimmune lymphoproliferative syndrome with defective apoptosis test should be used in individuals with defective Fas-mediated apoptosis, elevated alpha double negative T cells, elevated sFAS or elevated vitamin B12
- R233 Agammaglobulinaemia with low or absent BTK expression test should be used in individuals with absent BTK expression
- R20 Wiskott-Aldrich syndrome test should be used in individuals with a likely diagnosis of WAS
- R204 Amyloidosis with no identifiable cause test should be used in cases with confirmed amyloidosis

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

## Where in Pathway

N/A

## Requesting Specialties

- Clinical Genetics
- Haematology
- Immunology
- Gastroenterology

## Specialist Service Group

- Immunology

## Associated Tests

| Code  | Name                                   | Optional Family Structure | Scope(s)                        | Target Type            | Target Name                    | Method |
|-------|--|---------------------------|---------------------------------|------------------------|--------------------------------|--------|
| R15.4 | Primary immunodeficiency WGS (phase 2) | Trio or singleton         | Exon level CNVs, Small variants | Panel of genes or loci | Primary immunodeficiency (398) | WGS    |

## R413 Autoinflammatory Disorders

### Testing Criteria

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

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

### Overlapping indications

- R15 Primary immunodeficiency or monogenic Inflammatory Bowel Disease

### Where in Pathway

At presentation

### Requesting Specialties

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

### Specialist Service Group

- Immunology

### Associated Tests

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

| Code   | Name                                    | Optional Family Structure | Scope(s)                | Target Type            | Target Name                      | Method   |
|--------|---|---------------------------|-------------------------|------------------------|----------------------------------|--|
| R413.1 | Autoinflammatory Disorders medium panel | Singleton                 | Small variant detection | Panel of genes or loci | Autoinflammatory Disorders (TBC) | Medium Panel                                   |
| R413.2 | Autoinflammatory Disorders              | Singleton                 | Exon level CNVs         | Panel of genes or loci | Autoinflammatory Disorders (TBC) | Exon level CNV detection by MLPA or equivalent |

## R16 Severe combined immunodeficiency with adenosine deaminase deficiency

### Testing Criteria

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

### Overlapping indications

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

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Immunology

### Specialist Service Group

- Immunology

### Associated Tests

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

## R235 SCID with features of gamma chain deficiency

### Testing Criteria

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

### Overlapping indications

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

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Immunology

### Specialist Service Group

- Immunology

### Associated Tests

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

## R234 Severe combined immunodeficiency with PNP deficiency

### Testing Criteria

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

### Overlapping indications

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

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Immunology

### Specialist Service Group

- Immunology

### Associated Tests

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



## R17 Lymphoproliferative syndrome with absent SAP expression

### Testing Criteria

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

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

### Overlapping indications

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

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

### Where in Pathway

At presentation, following SAP expression analysis

### Requesting Specialties

- Clinical Genetics
- Haematology
- Immunology

### Specialist Service Group

- Immunology

### Associated Tests

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

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

## R18 Haemophagocytic syndrome with absent XIAP expression

### Testing Criteria

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

Typical features include inflammatory bowel disease or colitis

### Overlapping indications

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

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

### Where in Pathway

At presentation, following XIAP expression analysis

### Requesting Specialties

- Clinical Genetics
- Haematology
- Immunology

### Specialist Service Group

- Immunology

### Associated Tests

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

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

## R232 Haemophagocytic syndrome with absent perforin expression

### Testing Criteria

Haemophagocytic syndrome with low or absent perforin expression

### Overlapping indications

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

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

### Where in Pathway

At presentation, following perforin expression analysis

### Requesting Specialties

- Clinical Genetics
- Haematology
- Immunology

### Specialist Service Group

- Immunology

### Associated Tests

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

## R19 Autoimmune lymphoproliferative syndrome with defective apoptosis

### Testing Criteria

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

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

### Overlapping indications

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

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

### Where in Pathway

At presentation, following analysis of Fas-mediated apoptosis

### Requesting Specialties

- Clinical Genetics
- Haematology
- Immunology

### Specialist Service Group

- Immunology

### Associated Tests

| Code  | Name                       | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                     |
|-------|----------------------------|---------------------------|----------------|----------------|-------------|--|
| R19.1 | FAS Single gene sequencing | Singleton                 | Small variants | Single gene(s) | FAS         | Single gene sequencing $\geq 10$ amplicons |

## R233 Agammaglobulinaemia with absent BTK expression

### Testing Criteria

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

### Overlapping indications

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

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

### Where in Pathway

At presentation, following BTK expression analysis

### Requesting Specialties

- Clinical Genetics
- Immunology

### Specialist Service Group

- Immunology

### Associated Tests

| Code   | Name                       | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                     |
|--------|----------------------------|---------------------------|----------------|----------------|-------------|--|
| R233.1 | BTK Single gene sequencing | Singleton                 | Small variants | Single gene(s) | BTK         | Single gene sequencing $\geq 10$ amplicons |

## R20 Wiskott-Aldrich syndrome

### Testing Criteria

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

The diagnosis should be considered in any male with small platelets

### Overlapping indications

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

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

### Where in Pathway

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

### Requesting Specialties

- Clinical Genetics
- Haematology
- Immunology

### Specialist Service Group

- Immunology

### Associated Tests

| Code  | Name                       | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                     |
|-------|----------------------------|---------------------------|----------------|----------------|-------------|--|
| R20.1 | WAS Single gene sequencing | Singleton                 | Small variants | Single gene(s) | WAS         | Single gene sequencing $\geq 10$ amplicons |

## R341 Hereditary angioedema types I and II

### Testing Criteria

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

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

### Where in Pathway

Following C1INH testing

### Requesting Specialties

- Clinical Genetics
- Dermatology
- Immunology

### Specialist Service Group

- Immunology

### Associated Tests

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

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

## R368 Hereditary angioedema type III

### Testing Criteria

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

Normal serum C1INH concentration or function

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

### Where in Pathway

Following complement testing

### Requesting Specialties

- Clinical Genetics
- Dermatology
- Immunology

### Specialist Service Group

- Immunology

### Associated Tests

| Code   | Name                                     | Optional Family Structure | Scope(s)       | Target Type     | Target Name | Method                    |
|--------|--|---------------------------|----------------|-----------------|-------------|---------------------------|
| R368.1 | F12 hotspot<br>Targeted mutation testing | Singleton                 | Small variants | Single interval | F12 hotspot | Targeted mutation testing |



## Part XI. Inherited cancer

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

#### Testing Criteria

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

OR

2. Epithelial ovarian cancer (EOC) AND

- ≥1 first degree relative with EOC, OR
- ≥1 second degree relative with EOC (intervening relative is male, OR female with BSO, OR female deceased) OR
- ≥2 second / third degree relatives with EOC

3. Deceased affected individual (proband) where:

- Appropriate tissue is available (tumour or normal) AND
- No living affected individual is available for genetic testing

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

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

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

#### Overlapping indications

- M2 Ovarian carcinoma should be used for somatic testing

#### Where in Pathway

At presentation

#### Requesting Specialties

- Oncology
- Clinical Genetics
- Gynaecology

#### Specialist Service Group

- Core

#### Associated Tests

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

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

## R208 Inherited breast cancer and ovarian cancer

### Testing Criteria

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

#### NOTES

- The proband's cancer and majority of reported cancers in the family should have been confirmed
- The pathology adjusted Manchester score involved incorporation of pathology data for the tested proband alone, i.e. pathology need not be sought for other family members.
- Ovarian cancer: Fallopian Tube and Primary Peritoneal cancers can be included
- BRCA1/BRCA2 testing has not previously been performed
- Testing of unaffected and deceased individuals can only be offered by Clinical Genetics

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

### Overlapping indications

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Oncology
- Clinical Genetics

### Specialist Service Group

- Core

## Associated Tests

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

| Code   | Name   | Optional Family Structure | Scope(s)        | Target Type          | Target Name  | Method             |
|--------|--|---------------------------|-----------------|----------------------|--|--------------------|
| R208.1 | BRCA1; BRCA2; PALB2; ATM and CHEK2 truncating variants | Singleton                 | Small variants  | Small panel of genes | BRCA1; BRCA2; PALB2; ATM and CHEK2 truncating variants | Small panel        |
| R208.2 | BRCA1; BRCA2; PALB2 MLPA or equivalent                 | Singleton                 | Exon level CNVs | Single gene(s)       | BRCA1; BRCA2; PALB2                                    | MLPA or equivalent |

## R210 Inherited MMR deficiency (Lynch syndrome)

### Testing Criteria

All new diagnoses of colorectal and endometrial cancer should have tumour MSI / IHC as outlined in the cancer test directory and the Lynch syndrome handbook for Alliances in order to identify dMMR tumours

#### 1. Clinical Criteria for germline testing in an affected individual

- a. The proband has a dMMR tumour where results of BRAF and/or MLH1 hypermethylation testing suggest Lynch syndrome
- b. The affected proband comes from a modified Amsterdam criteria positive family irrespective of the dMMR status of the tumour
- c. Personal or family history suggestive of Constitutional Mismatch Repair Deficiency (CMMRD) with Wimmer score  $\geq 3$

#### 2. Clinical criteria for MSI /IHC testing on a stored tumour sample prior to germline testing

- a. Personal/family history of colorectal cancers reaching Modified Amsterdam Criteria ( $\geq 3$  cases of Lynch related cancer over  $\geq 2$  generations with  $\geq 1$  case diagnosed  $\leq 50$  years) OR
- b. Any lynch-related cancer\* ( $\leq 50$  years)
- c. Two Lynch-related cancers (any age, one is colorectal or endometrial), OR
- d. Lynch-related cancer and  $\geq 1$  first degree relative has Lynch-related cancer (both occurred  $\leq 60$  years, one is colorectal or endometrial), OR
- e. Lynch-related cancer and  $\geq 2$  relatives (first / second / third degree relatives) have Lynch-related cancer (all occurring  $\leq 75$  years, one is colorectal or endometrial), OR
- f. Lynch-related cancer and  $\geq 3$  relatives (first / second / third degree relatives) have Lynch-related cancer (occurring any age, one is colorectal or endometrial)

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

#### 3. Clinical Criteria for somatic (tumour)Lynch syndrome panel testing

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

#### 4. Clinical Criteria for germline testing in an unaffected individual

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

#### 5. Criteria for germline MLH1 promoter methylation

- a. Families where MLH1 promoter methylation has been identified in  $>1$  affected individual with colorectal cancer  $\leq 60$

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

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

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

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

### Where in Pathway

At presentation following tumour studies (IHC/MSI)

### Requesting Specialties

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

\* Surgery to cover colorectal and gynecological surgeons

### Specialist Service Group

- Core

### Associated Tests

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

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

## R211 Inherited polyposis and early onset colorectal cancer - germline test

### Testing Criteria

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

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

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

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

### Overlapping indications

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

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

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Gastroenterology
- Surgery\*

\*Surgery to cover colorectal surgeons

### Specialist Service Group

- Core

### Associated Tests

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

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

## R414 APC Associated Polyposis

### Testing Criteria

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

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

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

### Overlapping indications

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

R359 Childhood solid tumor panel

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
  - Oncology\*
- \*including paediatrics

### Specialist Service Group

- Core

### Associated Tests

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

| Code   | Name                     | Optional Family Structure | Scope(s)                | Target Type | Target Name | Method   |
|--------|--------------------------|---------------------------|-------------------------|-------------|-------------|--|
| R414.1 | APC Associated Polyposis | Singleton                 | small variant detection | Single gene | APC         | Single gene sequencing $\geq 10$ amplicons     |
| R414.2 | APC Associated Polyposis | Singleton                 | Exon level CNVs         | Single gene | APC         | Exon level CNV detection by MLPA or equivalent |



## R212 Peutz Jegher Syndrome

### Testing Criteria

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

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

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

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

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

**NOTE: The majority of polyps should be histologically confirmed**

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

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

### Where in Pathway

At presentation/at follow-up

### Requesting Specialties

- Clinical Genetics
- Dermatology
- Gastroenterology

### Specialist Service Group

- Inherited cancer

### Associated Tests

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

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

## R213 PTEN Hamartoma Tumor Syndrome

### Testing Criteria

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

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

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

PTEN-HTS-related mucocutaneous lesions comprise:

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

Major criteria:

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

Minor criteria:

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

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

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

### Where in Pathway

At presentation/at follow-up

## Requesting Specialties

- Clinical Genetics
- Dermatology
- Neurology

## Specialist Service Group

- Inherited cancer

## Associated Tests

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

| Code   | Name                        | Optional Family Structure | Scope(s)        | Target Type    | Target Name | Method                                     |
|--------|-----------------------------|---------------------------|-----------------|----------------|-------------|--|
| R213.1 | PTEN Single gene sequencing | Singleton                 | Small variants  | Single gene(s) | PTEN        | Single gene sequencing $\geq 10$ amplicons |
| R213.2 | PTEN MLPA or equivalent     | Singleton                 | Exon level CNVs | Single gene(s) | PTEN        | MLPA or equivalent                         |

## R214 Nevroid Basal Cell Carcinoma Syndrome or Gorlin syndrome

### Testing Criteria

1. Living individual affected (proband) where the individual history meets:
  - a.  $\geq 1$  major OR
  - b.  $\geq 2$  minor criteria
2. Major criteria:
  - Lamellar (sheet-like) calcification of the falx or clear evidence of calcification in an individual younger than age 20 years
  - Jaw keratocyst: odontogenic keratocyst histologically
  - Palmar/plantar pits (two or more)
  - SHH medulloblastoma, confirmed on tumour testing
  - Multiple basal cell carcinomas (BCCs) ( $>5$  under 50)
  -
3. Minor criteria:
  - Childhood medulloblastoma where SHH pathway in tumour has not been investigated (also called primitive neuroectodermal tumor [PNET])
  - Lympho-mesenteric or pleural cysts
  - Macrocephaly (OFC  $>97$ th centile)
  - Cleft lip/palate
  - Vertebral/rib anomalies observed on chest x-ray and/or spinal x-ray; bifid/splayed/extra ribs; bifid vertebrae
  - Preaxial or postaxial polydactyly
  - Ovarian/cardiac fibromas
  - Ocular anomalies (cataract, developmental defects, and pigmentary changes of the retinal epithelium)

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

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

### Where in Pathway

At presentation/at follow-up

### Requesting Specialties

- Clinical Genetics
- Dermatology

### Specialist Service Group

- Inherited cancer

### Associated Tests

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

| Code   | Name                              | Optional Family Structure | Scope(s)        | Target Type    | Target Name | Method             |
|--------|-----------------------------------|---------------------------|-----------------|----------------|-------------|--------------------|
| R214.1 | PTCH1; SUFU                       | Singleton                 | Small variants  | Small panel    | PTCH1; SUFU | Small panel        |
| R214.2 | PTCH1; SUFU<br>MLPA or equivalent | Singleton                 | Exon level CNVs | Single gene(s) | PTCH1; SUFU | MLPA or equivalent |

## R215 CDH1-related cancer syndrome

### Testing Criteria

1. Living affected individual (proband) where the individual +/- family history **meets one of the criteria**.  
The proband has:
  - a. Diffuse gastric cancer ( <50 years).
  - b. gastric in situ signet ring cells or pagetoid spread of signet ring cells under 50 years
  - c. diffuse gastric cancer at any age with a personal history or FDR with cleft lip or cleft palate.
  - d. double primary diffuse gastric cancer and lobular breast cancer (both <70 years).
  - e. diffuse gastric cancer and  $\geq 1$  FDR/SDR with diffuse gastric cancer at any age.
  - f. diffuse gastric cancer at any age and  $\geq 1$  FDR/SDR with lobular breast cancer <70 years.
  - g. Lobular breast cancer and  $\geq$ FDR/SDR has diffuse gastric cancer ( $\geq 1$  case occurred < 70 years).
  - h. 2 cases of lobular breast cancer<50 years e.g. bilateral or multiple ipsilateral tumours
2. Deceased affected individual (proband) where (i) the individual +/- family history meets one of the above criteria, (ii) appropriate tissue is available (tumour or normal), and (iii) no living affected individual is available for genetic testing

**NOTE: At least one cancer should be histologically confirmed**

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

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

### Where in Pathway

At presentation/at follow-up

### Requesting Specialties

- Clinical Genetics
- Gastroenterology
- Surgery\*

\*Surgery to cover upper gastro-intestinal surgeons

### Specialist Service Group

- Inherited cancer

### Associated Tests

Please note all the tests below will be undertaken for R215 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

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

## R216 Li Fraumeni Syndrome

### Testing Criteria

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

The proband has:

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

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

LFS-related cancers comprise: soft tissue sarcomas, osteosarcomas, adrenocortical carcinoma, central nervous system tumours and very early onset female breast cancers under 31 years.

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

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

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

### Overlapping indications

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

### Where in Pathway

At presentation/at follow-up

### Requesting Specialties

- Clinical Genetics
  - Oncology\*
- \*including paediatrics

### Specialist Service Group

- Inherited cancer

### Associated Tests

Please note all the tests below will be undertaken for R216 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

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

## R219 Retinoblastoma

### Testing Criteria

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

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

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

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

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

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

### Overlapping indications

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

### Where in Pathway

At presentation/at follow-up

### Requesting Specialties

- Clinical Genetics

### Specialist Service Group

- Inherited cancer

### Associated Tests

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

| Code   | Name                       | Optional Family Structure | Scope(s)        | Target Type    | Target Name | Method                                     |
|--------|----------------------------|---------------------------|-----------------|----------------|-------------|--|
| R219.1 | RB1 Single gene sequencing | Singleton                 | Small variants  | Single gene(s) | RB1         | Single gene sequencing $\geq 10$ amplicons |
| R219.2 | RB1 MLPA or equivalent     | Singleton                 | Exon level CNVs | Single gene(s) | RB1         | MLPA or equivalent                         |



## R220 Wilms tumour with features suggestive of predisposition

### Testing Criteria

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

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

### Overlapping indications

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

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

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

### Where in Pathway

At presentation/at follow-up

### Requesting Specialties

- Clinical Genetics
- Oncology\*  
including paediatrics

### Specialist Service Group

- Inherited cancer

### Associated Tests

| Code   | Name  | Optional Family Structure | Scope(s)        | Target Type     | Target Name                              | Method              |
|--------|---|---------------------------|-----------------|-----------------|--|---------------------|
| R220.1 | Wilms tumour with features suggestive of predisposition | Singleton                 | Small variants  | Small panel     | WT1, CDKN1C; TRIM28; REST; CTR9          | Small panel         |
| R220.2 | Wilms tumour with features suggestive of predisposition | Singleton                 | Exon level CNVs | Single gene(s)  | WT1, CDKN1C; TRIM28; REST; CTR9          | MLPA or equivalent  |
| R220.3 | Wilms tumour with features suggestive of predisposition | Singleton                 | Methylation     | Single interval | 11p15 imprinted growth regulatory region | Methylation testing |
| R220.4 | Wilms tumour with features suggestive of predisposition | Singleton                 | CNVs            | Single interval | 11p15 imprinted growth regulatory region | MLPA or equivalent  |

## R358 Familial rhabdoid tumours

### Testing Criteria

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

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

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

Likely to need to specify high coverage depth to detect mosaic SMARCB1 and SMARCA4 mutations

### Overlapping indications

- M120 Atypical teratoid/rhabdoid tumour (ATRT) should be used for somatic testing

### Where in Pathway

At presentation/at follow-up

### Requesting Specialties

- Clinical Genetics
    - Oncology\*
- \* including paediatrics

### Specialist Service Group

- Inherited cancer

### Associated Tests

Please note all the tests below will be undertaken for R358 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

| Code   | Name                                  | Optional Family Structure | Scope(s)        | Target Type            | Target Name                          | Method   |
|--------|---------------------------------------|---------------------------|-----------------|------------------------|--------------------------------------|--|
| R358.1 | Familial rhabdoid tumours Small panel | Singleton                 | Small variants  | Panel of genes or loci | Rhabdoid tumour predisposition (600) | Small panel                                    |
| R358.2 | Familial rhabdoid tumours             | Singleton                 | Exon level CNVs | Panel of genes or loci | Rhabdoid tumour predisposition (600) | Exon level CNV detection by MLPA or equivalent |

## R359 Childhood solid tumours

### Testing Criteria

Any presentation of an invasive solid tumour diagnosed at age  $\leq 18$ , where no other Testing Criteria are met, OR other test did not identify pathogenic variant, AND the patient has NOT been investigated through:

1. Tumour WGS, OR
2. Another large germline cancer susceptibility panel, OR
3. Exome test through GMS or an alternative route

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Overlapping indications

- The associated paediatric cancer clinical indication (M coded) should be used for somatic testing

### Where in Pathway

At presentation/at follow-up

### Requesting Specialties

- Oncology
- Clinical Genetics

### Specialist Service Group

- Inherited cancer

### Associated Tests

Please note all the tests below will be undertaken for R359 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

| Code   | Name  | Optional Family Structure | Scope(s)        | Target Type            | Target Name                                   | Method   |
|--------|---|---------------------------|-----------------|------------------------|---|--|
| R359.1 | Tumour predisposition - childhood onset WES or Medium panel | Singleton                 | Small variants  | Panel of genes or loci | Tumour predisposition - childhood onset (243) | WES or Medium panel                            |
| R359.2 | Tumour predisposition - childhood onset                     | Singleton                 | Exon level CNVs | Panel of genes or loci | Tumour predisposition - childhood onset (243) | Exon level CNV detection by MLPA or equivalent |

## R224 Inherited renal cancer

### Testing Criteria

Testing of individual (proband) affected with renal cancer where the individual +/- family history meets one of the following criteria. The proband has

1. Renal cancer ( $\leq 40$  years), OR
2. Type 2 papillary renal cancer ( $\leq 50$  years), OR
3. Bilateral/multifocal renal cancer (any age), OR
4. Renal cancer AND first / second degree relative with renal cancer, both cases diagnosed under 50 years of age
5. Renal cancer and features of inherited cancer syndrome such as:
  - Cerebellar/spinal haemangioblastoma
  - Retinal angioma
  - Pheochromocytoma/paraganglioma
  - Spontaneous pneumothorax
  - Fibrofolliculomas
  - Trichodiscomas
  - Cutaneous Leiomyomata
  - Uterine leiomyomas (under 40 years of age with pathology suggesting FH mutation)
  - Mesothelioma
  - Uveal melanoma

Deceased affected individual (proband) where (i) the individual +/- family history meets one of the above criteria, (ii) appropriate tissue is available (tumour or normal), and (iii) no living affected individual is available for genetic testing

**NOTE: The proband's cancer and majority of reported cancers in the family should have been confirmed**

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Overlapping indications

- M18 Renal cell carcinoma or the associated pediatric cancer clinical indication (M173, M180, M165, M212) should be used for somatic testing

### Where in Pathway

At presentation/at follow-up

### Requesting Specialties

- Clinical Genetics
- Urology
- Nephrology

### Specialist Service Group

- Inherited cancer

### Associated Tests

Please note all the tests below will be undertaken for R224 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

| Code   | Name                               | Optional Family Structure | Scope(s)       | Target Type            | Target Name                  | Method      |
|--------|------------------------------------|---------------------------|----------------|------------------------|------------------------------|-------------|
| R224.1 | Inherited renal cancer Small panel | Singleton                 | Small variants | Panel of genes or loci | Inherited renal cancer (521) | Small panel |

|        |                                 |           |                    |                |           |                       |
|--------|---------------------------------|-----------|--------------------|----------------|-----------|-----------------------|
| R224.2 | FLCN; VHL MLPA<br>or equivalent | Singleton | Exon level<br>CNVs | Single gene(s) | FLCN; VHL | MLPA or<br>equivalent |
|--------|---------------------------------|-----------|--------------------|----------------|-----------|-----------------------|

## R225 Von Hippel Lindau syndrome

### Testing Criteria

1. Testing of individual (proband) affected with VHL-related tumours where the individual/family history meets one of the following criteria:
  - a. Retinal angioma, spinal or endolymphatic sac tumour (<40 years), OR
  - b. Cerebellar haemangioblastoma (<60 years), OR
  - c.  $\geq 2$  VHL-related tumours (any age), OR
  - d.  $\geq 1$  VHL-related tumour and a first degree relative with  $\geq 1$  VHL-related tumour (where one of the tumours is retinal angioma / hemangioblastoma)
2. Deceased affected individual (proband) where (i) the individual +/- family history meets one of the above criteria, (ii) appropriate tissue is available (tumour or normal), and (iii) no living affected individual is available for genetic testing

VHL-related tumours comprise: Retinal angioma, Spinal or cerebellar hemangioblastoma, adrenal or extra-adrenal pheochromocytoma, Renal cell carcinoma, multiple renal and/or pancreatic cysts, endolymphatic sac tumors, papillary cystadenomas of the epididymis or broad ligament, neuroendocrine tumour of the pancreas

**NOTE: The proband's cancer and majority of reported cancers in the family should have been confirmed**

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation/at follow-up

### Requesting Specialties

- Clinical Genetics
- Endocrinology
- Nephrology
- Neurology
- Ophthalmology
- Urology
- Neurosurgery

### Specialist Service Group

- Inherited cancer

### Associated Tests

Please note all the tests below will be undertaken for R225 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

| Code   | Name                       | Optional Family Structure | Scope(s)        | Target Type    | Target Name | Method                                     |
|--------|----------------------------|---------------------------|-----------------|----------------|-------------|--|
| R225.1 | VHL Single gene sequencing | Singleton                 | Small variants  | Single gene(s) | VHL         | Single gene sequencing $\geq 10$ amplicons |
| R225.2 | VHL MLPA or equivalent     | Singleton                 | Exon level CNVs | Single gene(s) | VHL         | MLPA or equivalent                         |

## R254 Familial melanoma

### Testing Criteria

Testing of phenotypically affected individual (proband) where the individual +/- family history meets **ONE** of the following criteria. The proband has:

- ≥2 melanomas and/or melanomas in situ age <30 years, OR
- Melanoma and/or melanoma in situ AND ≥2 relatives (first / second / third degree relatives) with melanoma in situ, OR
- Melanoma and/or melanoma in situ AND ≥1 first degree relative with melanoma in situ; one individual has multiple melanomas in situ, OR
- ≥1 Melanoma and/or melanoma in situ OR melanoma in situ and atypical moles AND ≥1 first degree relative with pancreatic cancer aged <60, OR
- Atypical moles AND ≥2 relatives (first / second degree relatives) with melanoma and/or melanoma in situ, OR

Deceased affected individual (proband) where (i) the individual +/- family history meets one of the above criteria, (ii) appropriate tissue is available (tumour or normal), and (iii) no living affected individual is available for genetic testing.

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Overlapping indications

- M7 Melanoma (adult) and M187 Uveal melanoma should be used for somatic testing

### Where in Pathway

At presentation/at follow-up

### Requesting Specialties

- Clinical Genetics
- Dermatology

### Specialist Service Group

- Inherited cancer

### Associated Tests

Please note all the tests below will be undertaken for R254 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

| Code   | Name                             | Optional Family Structure | Scope(s)        | Target Type            | Target Name             | Method   |
|--------|----------------------------------|---------------------------|-----------------|------------------------|-------------------------|--|
| R254.1 | Familial melanoma<br>Small panel | Singleton                 | Small variants  | Panel of genes or loci | Familial melanoma (522) | Small panel                                    |
| R254.2 | Familial melanoma                | Singleton                 | Exon level CNVs | Panel of genes or loci | Familial melanoma (522) | Exon level CNV detection by MLPA or equivalent |

## R422 BAP1 associated tumour predisposition syndrome

### Testing Criteria

Individual (proband) affected with either:

1. BAP1 deficient mesothelioma or mesothelioma diagnosed under 50 years if BAP1 status unknown OR,
2. BAP1-inactivated melanocytic tumors (BIMT) (Also known as BAPoma, atypical Spitz naevus, Melanocytic BAP1-associated intradermal tumor (MBAIT) or nevoid melanoma-like melanocytic proliferation (NEMMP) OR
3. Personal history of two or more BAP1 associated tumours\* OR
4. Individual affected with BAP1 associated tumour and FDR affected with BAP1 related tumour\*

\* Excluding combination of basal cell cancers and/or cutaneous melanomas alone, given their high frequency in the general population

BAP1 associated tumours= uveal melanoma, cutaneous melanoma, basal cell cancer, BAP1-inactivated melanocytic tumors (BIMT), malignant mesothelioma (lung or peritoneal), renal cell carcinoma, meningioma, cholangiocarcinoma or hepatocellular carcinoma.

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Overlapping indications

R254 Familial melanoma

R214 Nevoid Basal Cell Carcinoma Syndrome or Gorlin syndrome

R224 Inherited renal cancer

### Where in Pathway

At presentation/at follow-up

### Requesting Specialties

- Clinical Genetics
- Dermatology
- Oncology

### Specialist Service Group

- Inherited cancer

### Associated Tests

Please note all the tests below will be undertaken for R422 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

| Code   | Name   | Optional Family Structure | Scope(s)        | Target Type | Target Name | Method   |
|--------|--|---------------------------|-----------------|-------------|-------------|--|
| R422.1 | BAP1 associated tumour predisposition syndrome | Singleton                 | Small variants  | Single gene | BAP1        | Single gene sequencing $\geq 10$ amplicons     |
| R422.2 | BAP1 associated tumour predisposition syndrome | Singleton                 | Exon level CNVs | Single gene | BAP1        | Exon level CNV detection by MLPA or equivalent |



## R363 Inherited predisposition to GIST

### Testing Criteria

Testing of affected individual (proband) where the individual +/- family history meets the following criteria:  
The proband has GIST (gastrointestinal stromal tumour) :

1. Diagnosed age before age 50, OR
2. With  $\geq 1$  relative (first / second / third degree relative) with GIST, phaeochromocytoma / paraganglioma

**NOTE: The proband's cancer and majority of reported cancers in the family should have been confirmed**

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Overlapping indications

- M8 Gastrointestinal stromal tumour should be used for somatic testing

### R223 Inherited phaeochromocytoma and paraganglioma excluding NF1 Where in Pathway

At presentation/at follow-up

### Requesting Specialties

- Clinical Genetics
- Endocrinology
- Gastroenterology

### Specialist Service Group

- Inherited cancer

### Associated Tests

Please note all the tests below will be undertaken for R363 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

| Code   | Name   | Optional Family Structure | Scope(s)        | Target Type            | Target Name                            | Method             |
|--------|--|---------------------------|-----------------|------------------------|--|--------------------|
| R363.1 | Inherited predisposition to GIST Small panel | Singleton                 | Small variants  | Panel of genes or loci | Inherited predisposition to GIST (523) | Small panel        |
| R363.2 | SDHB; SDHC; SDHD MLPA or equivalent          | Singleton                 | Exon level CNVs | Single gene(s)         | SDHA; SDHC; SDHD                       | MLPA or equivalent |

## R364 DICER1-related cancer predisposition

### Testing Criteria

1. Testing of affected individual (proband) where the individual has one of the following diagnoses:  
Pleuropulmonary blastoma or Lung cyst(s) in childhood, especially if multi-septated, multiple or bilateral;  
Thoracic, uterine, cervical or ovarian embryonal rhabdomyosarcoma; Cystic nephroma; Genitourinary sarcoma including undifferentiated sarcoma in childhood; Ovarian Sertoli Leydig tumour;  
Gynandroblastoma; Genitourinary/gynaecologic neuroendocrine tumors; Childhood-onset multinodular goitre or differentiated thyroid cancer (papillary or follicular); Ciliary body medulloepithelioma; Nasal chondromesenchymal hamartoma; Pineoblastoma; Pituitary blastoma, OR
2. Testing of affected individual where there is a combination of two of the following diagnoses, either both in one affected individual or in two affected first degree relatives;  
Lung cyst(s) in adults; Wilms tumor; Multinodular goiter or differentiated thyroid cancer; Embryonal rhabdomyosarcoma other than thoracic or gynaecologic; Poorly differentiated neuroendocrine tumour; Undifferentiated sarcoma; Macrocephaly

**NOTE: The proband's cancer and majority of reported cancers in the family should have been confirmed**

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation/at follow-up

### Requesting Specialties

- Clinical Genetics

### Specialist Service Group

- Inherited cancer

### Associated Tests

| Code   | Name                          | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                |
|--------|-------------------------------|---------------------------|----------------|----------------|-------------|---------------------------------------|
| R364.1 | DICER1 Single gene sequencing | Singleton                 | Small variants | Single gene(s) | DICER1      | Single gene sequencing >=10 amplicons |

## R365 Fumarate hydratase-related tumour syndromes

### Testing Criteria

1. Testing of affected individual (proband) with hereditary leiomyomatosis and renal cell cancer (HLRCC) or other FH deficiency disorder where the individual +/- family history meets one of the following criteria. The proband has:
  - a. Type 2 papillary, HLRCC associated RCC (WHO pathology definition) OR tubulo-papillary renal tumour at any age, OR
  - b. Two of: cutaneous leiomyomata, renal tumour (any histology) , OR uterine leiomyomata with classic histological features < 40 years OR
  - c. Cutaneous leiomyomata AND one first / second / third degree relative with renal tumour, OR
  - d. Cutaneous leiomyomata AND two first / second / third degree relatives with cutaneous leiomyomata OR uterine leiomyomata with classic histological features < 40 years, OR
  - e. Uterine leiomyomata with classic histological features (age <40) OR
  - f. Multiple cutaneous leiomyomata
2. Deceased affected individual (proband) where (i) the individual +/- family history meets one of the above criteria, (ii) appropriate tissue is available (tumour or normal), and (iii) no living affected individual is available for genetic testing

**NOTE: Cutaneous leiomyomata should be histologically confirmed; uterine leiomyomata and renal tumours should be medically documented**

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Overlapping indications

- M18 Renal cell carcinoma or the associated pediatric cancer clinical indication (M173, M180, M165, M212) should be used for somatic testing

### Where in Pathway

At presentation/at follow-up

### Requesting Specialties

- Clinical Genetics
- Dermatology
- Urology
- Nephrology

### Specialist Service Group

- Inherited cancer

### Associated Tests

| Code   | Name                      | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                |
|--------|---------------------------|---------------------------|----------------|----------------|-------------|---------------------------------------|
| R365.1 | FH Single gene sequencing | Singleton                 | Small variants | Single gene(s) | FH          | Single gene sequencing >=10 amplicons |

## R367 Inherited pancreatic cancer

### Testing Criteria

1. Testing of affected individual (proband) where the individual +/- family history meets one of the following criteria. The proband has:
2. Pancreatic cancer age <60, OR
3. Pancreatic cancer age <70, AND
  - a. Breast cancer age <60, melanoma age <60, OR ovarian cancer, OR
  - b. One first / second degree relative with pancreatic cancer age <60, OR
  - c. Two first / second degree relatives with any of breast cancer age <60, melanoma age <60, OR ovarian cancer

Deceased affected individual (proband) where (i) the individual +/- family history meets one of the above criteria, (ii) appropriate tissue is available (tumour or normal), and (iii) no living affected individual is available for genetic testing

**NOTE: The proband's cancer and majority of reported cancers in the family should have been confirmed. Pancreatic cancer is adenocarcinoma and not neuroendocrine tumour.**

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Overlapping indications

- M219 Pancreatic cancer should be used for somatic testing

### Where in Pathway

At presentation/at follow-up

### Requesting Specialties

- Clinical Genetics
- Gastroenterology
- Oncology

### Specialist Service Group

- Inherited cancer

### Associated Tests

Please note all the tests below will be undertaken for R367 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

| Code   | Name                                    | Optional Family Structure | Scope(s)        | Target Type            | Target Name                       | Method   |
|--------|---|---------------------------|-----------------|------------------------|-----------------------------------|--|
| R367.1 | Inherited pancreatic cancer Small panel | Singleton                 | Small variants  | Panel of genes or loci | Inherited pancreatic cancer (524) | Small panel                                    |
| R367.2 | Inherited pancreatic cancer             | Singleton                 | Exon level CNVs | Panel of genes or loci | Inherited pancreatic cancer (524) | Exon level CNV detection by MLPA or equivalent |

## R404 Testing of unaffected individuals for inherited cancer predisposition syndromes

### Testing Criteria

Germline testing of unaffected individuals for specific inherited cancer predisposition syndromes where the following criteria are met:

1. There are no living affected relatives available for testing, AND
2. Any applicable somatic testing on deceased relatives tumour samples has been performed first, AND
3. The individual to be tested is deemed to have  $\geq 10\%$  chance of having a mutation (deceased first degree relative with  $\geq 20\%$  chance), AND
4. This is agreed by specialist cancer genetics MDT

**NOTE: All cancers must be confirmed**

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

### Overlapping indications:

- For testing for hereditary breast and ovarian cancer and inherited MMR deficiency (Lynch syndrome), unaffected individuals must meet criteria as specified under relevant indications R208/R215

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics

### Specialist Service Group

- Core and Inherited cancer; depending on the cancer of suspicion

### Associated Tests

| Code   | Name  | Optional Family Structure | Scope(s)        | Target Type            | Target Name                                    | Method   |
|--------|---|---------------------------|-----------------|------------------------|--|--|
| R404.1 | Inherited cancer predisposition gene sequencing | Singleton                 | Small variants  | Single gene(s)         | As dictated by clinical indication             | Single gene sequencing $\geq 10$ amplicons     |
| R404.2 | Inherited cancer predisposition gene            | Singleton                 | Exon level CNVs | Panel of genes or loci | As per appropriate inherited cancer indication | Exon level CNV detection by MLPA or equivalent |
| R404.3 | Relevant inherited cancer panel Small panel     | Singleton                 | Small variants  | Panel of genes or loci | Relevant inherited cancer panel                | Small panel                                    |

## 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  | Optional Family Structure | Scope(s)        | Target Type            | Target Name   | Method             |
|--------|---|---------------------------|-----------------|------------------------|---|--------------------|
| R134.1 | Familial hypercholesterolaemia<br>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  | Optional Family Structure | Scope(s)        | Target Type            | Target Name                         | Method   |
|--------|---|---------------------------|-----------------|------------------------|-------------------------------------|--|
| R324.1 | Familial Chylomicronaemia Syndrome (FCS)<br>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                          | Optional Family Structure | Scope(s)        | Target Type    | Target Name | Method             |
|--------|-------------------------------|---------------------------|-----------------|----------------|-------------|--------------------|
| R380.1 | NPC1; NPC2                    | Singleton                 | Small variants  | Small panel    | NPC1; NPC2  | Small panel        |
| R380.2 | NPC1; NPC2 MLPA or equivalent | Singleton                 | Exon level CNVs | Single gene(s) | NPC1; NPC2  | MLPA or equivalent |



## R98 Likely inborn error of metabolism - targeted testing not possible

### Testing Criteria

Clinical feature of a likely inborn error of metabolism where targeted testing is not possible

### Overlapping indications

- Targeted tests for specific metabolic disorders should be used where clinical features or biochemical/enzyme testing results are rapidly available and strongly suggestive of the relevant disorder(s)

### Where in Pathway

At presentation following clinically relevant, rapidly available investigations

### Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

### Specialist Service Group

- Metabolic

### Associated Tests

| Code  | Name                                      | Optional Family Structure | Scope(s)                              | Target Type            | Target Name                       | Method |
|-------|---|---------------------------|---------------------------------------|------------------------|-----------------------------------|--------|
| R98.2 | 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    |

## R270 Smith-Lemli-Opitz syndrome

### Testing Criteria

Clinical and biochemical features characteristic of Smith-Lemli-Opitz syndrome

### Overlapping indications

- R98 Likely inborn error of metabolism - targeted testing is not possible, R27 Congenital malformation and dysmorphism syndromes – likely monogenic or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with atypical features in whom a broader differential diagnosis is under consideration

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation following biochemical testing

### Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

### Specialist Service Group

- Metabolic

### Associated Tests

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                         | Optional Family Structure | Scope(s)        | Target Type    | Target Name | Method                                     |
|--------|------------------------------|---------------------------|-----------------|----------------|-------------|--|
| R270.1 | DHCR7 Single gene sequencing | Singleton                 | Small variants  | Single gene(s) | DHCR7       | Single gene sequencing $\geq 10$ amplicons |
| R270.2 | DHCR7 MLPA or equivalent     | Singleton                 | Exon level CNVs | Single gene(s) | DHCR7       | MLPA or equivalent                         |

## R231 Neuronal ceroid lipofuscinosis

### Testing Criteria

Clinical and laboratory features characteristic of Neuronal ceroid lipofuscinosis including presence of vacuolate lymphocytes, presence of pathological inclusions on tissue biopsy or enzyme deficiency

### Overlapping indications

- R271 Neuronal ceroid lipofuscinosis type 2 test should be considered where clinical features are specific to CLN2
- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation following histological analysis and/or enzyme testing

### Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

### Specialist Service Group

- Metabolic

### Associated Tests

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                                       | Optional Family Structure | Scope(s)        | Target Type            | Target Name                          | Method             |
|--------|--|---------------------------|-----------------|------------------------|--------------------------------------|--------------------|
| R231.1 | CLN3 MLPA or equivalent                    | Singleton                 | Exon level CNVs | Single gene(s)         | CLN3                                 | MLPA or equivalent |
| R231.2 | Neuronal ceroid lipofuscinosis Small panel | Singleton                 | Small variants  | Panel of genes or loci | Neuronal ceroid lipofuscinosis (526) | Small panel        |

## R271 Neuronal ceroid lipofuscinosis type 2

### Testing Criteria

Clinical and laboratory features characteristic of neuronal ceroid lipofuscinosis type 2

### Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation following histological analysis and/or enzyme testing

### Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

### Specialist Service Group

- Metabolic

### Associated Tests

| Code   | Name                        | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                     |
|--------|-----------------------------|---------------------------|----------------|----------------|-------------|--|
| R271.1 | TPP1 Single gene sequencing | Singleton                 | Small variants | Single gene(s) | TPP1        | Single gene sequencing $\geq 10$ 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                        | Optional Family Structure | Scope(s)        | Target Type    | Target Name | Method                                |
|--------|-----------------------------|---------------------------|-----------------|----------------|-------------|---------------------------------------|
| R334.1 | CTNS Single gene sequencing | Singleton                 | Small variants  | Single gene(s) | CTNS        | Single gene sequencing >=10 amplicons |
| R334.2 | CTNS MLPA or equivalent     | Singleton                 | Exon level CNVs | Single gene(s) | CTNS        | MLPA or equivalent                    |

## R335 Fabry disease

### Testing Criteria

- In males: clinical and laboratory features characteristic of Fabry disease following alpha-galactosidase A enzyme testing
- In females: clinical features characteristic of Fabry disease

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

Following alpha-galactosidase A enzyme testing

### Requesting Specialties

- Cardiology
- Clinical Genetics
- Dermatology
- Metabolic Medicine
- Nephrology
- Ophthalmology

### Specialist Service Group

- Metabolic

### Associated Tests

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                       | Optional Family Structure | Scope(s)        | Target Type    | Target Name | Method                               |
|--------|----------------------------|---------------------------|-----------------|----------------|-------------|--------------------------------------|
| R335.1 | GLA Single gene sequencing | Singleton                 | Small variants  | Single gene(s) | GLA         | Single gene sequencing <10 amplicons |
| R335.2 | GLA MLPA or equivalent     | Singleton                 | Exon level CNVs | Single gene(s) | GLA         | MLPA or equivalent                   |

## R325 Lysosomal acid lipase deficiency

### Testing Criteria

Biochemically established lysosomal acid lipase deficiency

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation

### Requesting Specialties

- Chemical Pathology
- Clinical Genetics
- Metabolic Medicine

### Specialist Service Group

- Metabolic

### Associated Tests

| Code   | Name                        | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                     |
|--------|-----------------------------|---------------------------|----------------|----------------|-------------|--|
| R325.1 | LIPA Single gene sequencing | Singleton                 | Small variants | Single gene(s) | LIPA        | Single gene sequencing $\geq 10$ amplicons |

## R323 Sitosterolaemia

### Testing Criteria

Elevated plasma beta-sitosterol with development of xanthomata before the age of 30

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation

### Requesting Specialties

- Cardiology
- Chemical Pathology
- Clinical Genetics
- Metabolic Medicine

### Specialist Service Group

- Metabolic

### Associated Tests

| Code   | Name         | Optional Family Structure | Scope(s)       | Target Type | Target Name  | Method      |
|--------|--------------|---------------------------|----------------|-------------|--------------|-------------|
| R323.1 | ABCG5; ABCG8 | Singleton                 | Small variants | Small panel | ABCG5; ABCG8 | 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                        | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                     |
|--------|-----------------------------|---------------------------|----------------|----------------|-------------|--|
| R286.1 | HEXA Single gene sequencing | Singleton                 | Small variants | Single gene(s) | HEXA        | Single gene sequencing $\geq 10$ amplicons |

## R272 Gaucher disease

### 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                       | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                |
|--------|----------------------------|---------------------------|----------------|----------------|-------------|---------------------------------------|
| R272.1 | GBA Single gene sequencing | Singleton                 | Small variants | Single gene(s) | GBA         | Single gene sequencing >=10 amplicons |

## R273 Glycogen storage disease V

### Testing Criteria

Clinical and laboratory features characteristic of Glycogen storage disease type V including:

1. Elevated baseline serum CK, AND
2. Characteristic lactate/lactate:ammonia profile after exercise

### Overlapping indications

- Broader R274 Glycogen storage disease panel test should be used where a broader differential diagnosis of glycogen storage diseases is under consideration
- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation following laboratory testing

### Requesting Specialties

- Cardiology
- Clinical Genetics
- Hepatology
- Metabolic Medicine
- Neurology
- Paediatrics

### Specialist Service Group

- Metabolic

### Associated Tests

| Code   | Name                        | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                     |
|--------|-----------------------------|---------------------------|----------------|----------------|-------------|--|
| R273.1 | PYGM Single gene sequencing | Singleton                 | Small variants | Single gene(s) | PYGM        | Single gene sequencing $\geq 10$ amplicons |

## R274 Glycogen storage disease

### Testing Criteria

Clinical and laboratory features characteristic of Glycogen storage disease:

1. Persistent hypoglycaemia with other metabolic disorders excluded, AND one or more of the following
  - a. Persistent hepatomegaly in childhood, OR
  - b. Liver biopsy suggestive of glycogen storage disease, OR
  - c. Neuromuscular presentation suggestive of glycogen storage disease, OR
  - d. Affected first degree relative

OR

1. Glycogen accumulation in the relevant tissue, AND one or more of the following:
  - a. Evidence of liver involvement: hepatomegaly OR hypoglycaemia with other metabolic disorders excluded, OR
  - b. Evidence of muscle involvement: myalgia OR rhabdomyolysis OR muscle weakness, OR
  - c. Evidence of cardiac involvement: cardiomegaly OR cardiomyopathy, OR
  - d. Other general evidence - at least two of: myopathy, cardiomyopathy, respiratory weakness, vacuolar myopathy on muscle biopsy, pathological pattern on oligosaccharides

### Overlapping indications

- R273 Glycogen storage disease V test should be considered where clinical features are specific to Glycogen storage disease V (McArdle disease)
- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation following laboratory testing

### Requesting Specialties

- Cardiology
- Clinical Genetics
- Hepatology
- Metabolic Medicine
- Neurology
- Paediatrics

### Specialist Service Group

- Metabolic

### Associated Tests

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   | Optional Family Structure | Scope(s)        | Target Type            | Target Name                    | Method   |
|--------|--|---------------------------|-----------------|------------------------|--------------------------------|--|
| R274.1 | Glycogen storage disease WES or medium panel | Singleton                 | Small variants  | Panel of genes or loci | Glycogen storage disease (528) | WES or Medium Panel                            |
| 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   | Optional Family Structure | Scope(s)        | Target Type            | Target Name                      | Method   |
|--------|--|---------------------------|-----------------|------------------------|----------------------------------|--|
| R276.1 | Lysosomal storage disorder WES or medium panel | Singleton                 | Small variants  | Panel of genes or loci | Lysosomal storage disorder (529) | WES or Medium Panel                            |
| 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                        | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                |
|--------|-----------------------------|---------------------------|----------------|----------------|-------------|---------------------------------------|
| R288.1 | GLB1 Single gene sequencing | Singleton                 | Small variants | Single gene(s) | GLB1        | Single gene sequencing >=10 amplicons |

## R277 Mucopolysaccharidosis type IH/S

### Testing Criteria

Clinical and laboratory features characteristic of Mucopolysaccharidosis type IH/S (Hurler-Scheie syndrome)

### Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation following laboratory testing

### Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

### Specialist Service Group

- Metabolic

### Associated Tests

| Code   | Name                        | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                     |
|--------|-----------------------------|---------------------------|----------------|----------------|-------------|--|
| R277.1 | IDUA Single gene sequencing | Singleton                 | Small variants | Single gene(s) | IDUA        | Single gene sequencing $\geq 10$ 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                        | Optional Family Structure | Scope(s)        | Target Type    | Target Name | Method                                     |
|--------|-----------------------------|---------------------------|-----------------|----------------|-------------|--|
| R280.1 | GALC Single gene sequencing | Singleton                 | Small variants  | Single gene(s) | GALC        | Single gene sequencing $\geq 10$ amplicons |
| R280.2 | GALC MLPA or equivalent     | Singleton                 | Exon level CNVs | Single gene(s) | GALC        | MLPA or equivalent                         |



## R281 Krabbe disease - Saposin A deficiency

### Testing Criteria

Clinical and laboratory features characteristic of atypical Krabbe disease due to Saposin A deficiency

### Overlapping indications

- R280 Krabbe disease – GALC deficiency should be used in individuals with clinical and laboratory features characteristic of atypical Krabbe disease due to GALC deficiency
- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation following laboratory testing

### Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

### Specialist Service Group

- Metabolic

### Associated Tests

| Code   | Name                        | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                |
|--------|-----------------------------|---------------------------|----------------|----------------|-------------|---------------------------------------|
| R281.1 | PSAP Single gene sequencing | Singleton                 | Small variants | Single gene(s) | PSAP        | Single gene sequencing >=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                          | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                     |
|--------|-------------------------------|---------------------------|----------------|----------------|-------------|--|
| R278.1 | IDS Single gene sequencing    | Singleton                 | Small variants | Single gene(s) | IDS         | Single gene sequencing $\geq 10$ amplicons |
| R278.2 | IDS Targeted mutation testing | Singleton                 | Small variants | Single gene(s) | IDS         | Targeted mutation testing                  |

## R287 Mucopolysaccharidosis type IVA

### Testing Criteria

Clinical and laboratory features characteristic of Mucopolysaccharidosis type IVA

### Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation following laboratory testing

### Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

### Specialist Service Group

- Metabolic

### Associated Tests

| Code   | Name                         | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                     |
|--------|------------------------------|---------------------------|----------------|----------------|-------------|--|
| R287.1 | GALNS Single gene sequencing | Singleton                 | Small variants | Single gene(s) | GALNS       | Single gene sequencing $\geq 10$ amplicons |

## R289 Mucopolidosis II and III Alpha/Beta

### Testing Criteria

Clinical and laboratory features characteristic of Mucopolidosis II or Mucopolidosis III Alpha/Beta

### Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation following laboratory testing

### Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

### Specialist Service Group

- Metabolic

### Associated Tests

| Code   | Name                          | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                |
|--------|-------------------------------|---------------------------|----------------|----------------|-------------|---------------------------------------|
| R289.1 | GNPTAB Single gene sequencing | Singleton                 | Small variants | Single gene(s) | GNPTAB      | Single gene sequencing >=10 amplicons |

## R290 Mucopolysaccharidosis type VI

### Testing Criteria

Clinical and laboratory features characteristic of Mucopolysaccharidosis type VI

### Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation following laboratory testing

### Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

### Specialist Service Group

- Metabolic

### Associated Tests

| Code   | Name                        | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                     |
|--------|-----------------------------|---------------------------|----------------|----------------|-------------|--|
| R290.1 | ARSB Single gene sequencing | Singleton                 | Small variants | Single gene(s) | ARSB        | Single gene sequencing $\geq 10$ amplicons |

## R291 Mucopolysaccharidosis type IIIA

### Testing Criteria

Clinical and laboratory features characteristic of Mucopolysaccharidosis type IIIA

### Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation following laboratory testing

### Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

### Specialist Service Group

- Metabolic

### Associated Tests

| Code   | Name                        | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                     |
|--------|-----------------------------|---------------------------|----------------|----------------|-------------|--|
| R291.1 | SGSH Single gene sequencing | Singleton                 | Small variants | Single gene(s) | SGSH        | Single gene sequencing $\geq 10$ amplicons |

## R292 Mucopolysaccharidosis type IIIB

### Testing Criteria

Clinical and laboratory features characteristic of Mucopolysaccharidosis type IIIB

### Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation following laboratory testing

### Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

### Specialist Service Group

- Metabolic

### Associated Tests

| Code   | Name                         | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                |
|--------|------------------------------|---------------------------|----------------|----------------|-------------|---------------------------------------|
| R292.1 | NAGLU Single gene sequencing | Singleton                 | Small variants | Single gene(s) | NAGLU       | Single gene sequencing >=10 amplicons |

## R282 Niemann-Pick disease type A or B

### Testing Criteria

Clinical and laboratory features characteristic of Niemann-Pick disease type A or B

### Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation following laboratory testing

### Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

### Specialist Service Group

- Metabolic

### Associated Tests

| Code   | Name                         | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                     |
|--------|------------------------------|---------------------------|----------------|----------------|-------------|--|
| R282.1 | SMPD1 Single gene sequencing | Singleton                 | Small variants | Single gene(s) | SMPD1       | Single gene sequencing $\geq 10$ amplicons |



## R285 Sandhoff disease

### Testing Criteria

Clinical and laboratory features characteristic of Sandhoff disease

### Overlapping indications

- It is anticipated that many specific metabolic diagnoses will be made through use of broad genomic testing via the R98 Likely inborn error of metabolism - targeted testing is not possible early in the investigative pathway and in cases with atypical features where a broader differential diagnosis is under consideration

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation following laboratory testing

### Requesting Specialties

- Clinical Genetics
- Metabolic Medicine

### Specialist Service Group

- Metabolic

### Associated Tests

| Code   | Name                        | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                     |
|--------|-----------------------------|---------------------------|----------------|----------------|-------------|--|
| R285.1 | HEXB Single gene sequencing | Singleton                 | Small variants | Single gene(s) | HEXB        | Single gene sequencing $\geq 10$ amplicons |

## R283 Phenylketonuria

### Testing Criteria

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                       | Optional Family Structure | Scope(s)        | Target Type    | Target Name | Method                                     |
|--------|----------------------------|---------------------------|-----------------|----------------|-------------|--|
| R283.1 | PAH Single gene sequencing | Singleton                 | Small variants  | Single gene(s) | PAH         | Single gene sequencing $\geq 10$ amplicons |
| R283.2 | PAH MLPA or equivalent     | Singleton                 | Exon level CNVs | Single gene(s) | PAH         | MLPA or equivalent                         |

## R279 Isovaleric acidaemia

### Testing Criteria

Likely isovaleric acidaemia identified following neonatal screening or diagnostic metabolic testing

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family. In the case of isovaleric acidaemia, this means that testing is almost exclusively used at those in whom biochemical results indicate a likely pseudodeficiency allele is present.

Testing following newborn screening should follow the established sample and testing pathways set out in the newborn screening protocol

### Where in Pathway

Following neonatal screening or diagnostic metabolic testing

### Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neonatology
- Obstetrics
- Paediatrics

### Specialist Service Group

- Screening

### Associated Tests

| Code   | Name  | Optional Family Structure | Scope(s)       | Target Type     | Target Name                         | Method                    |
|--------|---|---------------------------|----------------|-----------------|-------------------------------------|---------------------------|
| R279.1 | IVD common pseudodeficiency variant Targeted mutation testing | Singleton                 | Small variants | Single interval | IVD common pseudodeficiency variant | Targeted mutation testing |

## R105 MCADD - Medium-chain acyl-CoA dehydrogenase deficiency – common variant

### Testing Criteria

Likely MCADD identified following neonatal screening or diagnostic metabolic testing requiring testing of the common ACADM c.985G>A variant

Testing following newborn screening should follow the established sample and testing pathways set out in the newborn screening protocol

### Where in Pathway

Following neonatal screening or diagnostic metabolic testing

### Requesting Specialties

- Clinical Genetics
- Neonatology
- Obstetrics
- Paediatrics

### Specialist Service Group

- Screening

### Associated Tests

| Code   | Name  | Optional Family Structure | Scope(s)       | Target Type     | Target Name                      | Method                    |
|--------|---|---------------------------|----------------|-----------------|----------------------------------|---------------------------|
| R105.1 | ACADM common pathogenic variants<br>Targeted mutation testing | Singleton                 | Small variants | Single interval | ACADM common pathogenic variants | Targeted mutation testing |

## R403 MCADD - Medium-chain acyl-CoA dehydrogenase deficiency – full ACADM sequencing

### Testing Criteria

Likely MCADD identified following neonatal screening or diagnostic metabolic testing requiring testing of the full ACADM gene

### Overlapping indications:

- R105 MCADD - Medium-chain acyl-CoA dehydrogenase deficiency – common variant test should be used in the first instance except where the testing laboratory specifically guides otherwise

Testing following newborn screening should follow the established sample and testing pathways set out in the newborn screening protocol

### Where in Pathway

N/A

### Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neonatology
- Paediatrics

### Specialist Service Group

- Screening

### Associated Tests

| Code   | Name                         | Optional Family Structure | Scope(s)       | Target Type | Target Name | Method                               |
|--------|------------------------------|---------------------------|----------------|-------------|-------------|--------------------------------------|
| R403.1 | MCADD Single gene sequencing | Singleton                 | Small variants | Other       | ACADM       | Single gene sequencing <10 amplicons |

## R275 Glutaric acidaemia I

### Testing Criteria

Likely glutaric acidaemia type 1 identified following neonatal screening or diagnostic metabolic testing

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

Testing following newborn screening should follow the established sample and testing pathways set out in the newborn screening protocol

### Where in Pathway

Following neonatal screening or diagnostic metabolic testing

### Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neonatology
- Obstetrics
- Paediatrics

### Specialist Service Group

- Screening

### Associated Tests

| Code   | Name                        | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                     |
|--------|-----------------------------|---------------------------|----------------|----------------|-------------|--|
| R275.1 | GCDH Single gene sequencing | Singleton                 | Small variants | Single gene(s) | GCDH        | Single gene sequencing $\geq 10$ amplicons |

## Part XIV. Mitochondrial

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### R64 MELAS or MIDD

#### Testing Criteria

Adult onset sensorineural hearing loss and diabetes or family history suggestive of a diagnosis of maternally inherited diabetes and deafness

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

#### Where in Pathway

At presentation

#### Requesting Specialties

- Clinical Genetics
- Endocrinology
- Neurology

#### Specialist Service Group

- Mitochondrial

#### Associated Tests

| Code  | Name                                       | Optional Family Structure | Scope(s)       | Target Type     | Target Name   | Method                    |
|-------|--|---------------------------|----------------|-----------------|---------------|---------------------------|
| R64.1 | MTTL1 3243A>G<br>Targeted mutation testing | Singleton                 | Small variants | Single interval | MTTL1 3243A>G | Targeted mutation testing |

## R299 Possible mitochondrial disorder - mitochondrial DNA rearrangement testing

### Testing Criteria

Possible mitochondrial disorder caused by mitochondrial DNA rearrangements including individuals with clinical features suggestive of CPEO, Kearns-Sayre syndrome or Pearson syndrome

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

Affected tissue, such as muscle, preferred

### Where in Pathway

At presentation following assessment by a Consultant in Metabolic Medicine, Neurology, Paediatric Neurology, Clinical Genetics or Haematology

### Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

### Specialist Service Group

- Mitochondrial

### Associated Tests

| Code   | Name   | Optional Family Structure | Scope(s)                     | Target Type     | Target Name                                    | Method |
|--------|--|---------------------------|------------------------------|-----------------|--|--------|
| R299.1 | Possible Mitochondrial disorder<br>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   | Optional Family Structure | Scope(s)       | Target Type     | Target Name          | Method |
|--------|--|---------------------------|----------------|-----------------|----------------------|--------|
| R300.1 | Mitochondrial genome Whole mitochondrial genome sequencing | Singleton                 | Small variants | Single interval | Mitochondrial genome | Other  |

## R301 Possible mitochondrial disorder - mitochondrial DNA depletion testing

### Testing Criteria

Clinical features suggestive of a mitochondrial DNA depletion syndrome

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

Muscle or liver tissue required

### Where in Pathway

Following findings on biopsy sample

### Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

### Specialist Service Group

- Mitochondrial

### Associated Tests

| Code   | Name  | Optional Family Structure | Scope(s)         | Target Type     | Target Name          | Method |
|--------|---|---------------------------|------------------|-----------------|----------------------|--------|
| R301.1 | Mitochondrial genome<br>Mitochondrial DNA depletion testing | Singleton                 | Complex variants | Single interval | Mitochondrial genome | Other  |

## R315 POLG-related disorder

### Testing Criteria

Clinical features suggestive of a POLG-related disorder (including status epilepticus and other severe intractable epilepsy with other suggestive features)

### Overlapping indications

- R59 Early onset or syndromic epilepsy, R29 Intellectual disability – microarray, fragile X and sequencing or other relevant broader tests should be used instead where clinical features are not strongly suggestive of POLG-related disorder and a broader differential diagnosis is under consideration

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation following assessment by a Consultant in Metabolic Medicine, Neurology, Paediatric Neurology or Clinical Genetics, or following evidence of mtDNA depletion or multiple mtDNA deletions

### Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

### Specialist Service Group

- Mitochondrial

### Associated Tests

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  | Optional Family Structure | Scope(s)       | Target Type     | Target Name           | Method                                     |
|--------|---|---------------------------|----------------|-----------------|-----------------------|--|
| R315.1 | Common POLG mutations Targeted mutation testing | Singleton                 | Small variants | Single interval | Common POLG mutations | Targeted mutation testing                  |
| R315.2 | POLG Single gene sequencing                     | Singleton                 | Small variants | Single gene(s)  | POLG                  | Single gene sequencing $\geq 10$ 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  | Optional 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                                    | Optional Family Structure | Scope(s)        | Target Type            | Target Name                       | Method   |
|--------|---|---------------------------|-----------------|------------------------|-----------------------------------|--|
| R317.1 | Mitochondrial liver disease Small panel | Singleton                 | Small variants  | Panel of genes or loci | Mitochondrial liver disease (532) | Small panel                                    |
| 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   | Optional Family Structure | Scope(s)       | Target Type     | Target Name            | Method                    |
|--------|--|---------------------------|----------------|-----------------|------------------------|---------------------------|
| R350.1 | Common MERRF mutations Targeted mutation testing | Singleton                 | Small variants | Single interval | Common MERRF mutations | Targeted mutation testing |

## R351 NARP syndrome or maternally inherited Leigh syndrome

### Testing Criteria

Clinical features suggestive of NARP syndrome (neuropathy, ataxia and retinitis pigmentosa) or MILS (maternally inherited Leigh syndrome)

### Where in Pathway

At presentation following assessment by a Consultant in Metabolic Medicine, Neurology, Paediatric Neurology or Clinical Genetics

### Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology
- Ophthalmology

### Specialist Service Group

- Mitochondrial

### Associated Tests

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                                     | Optional Family Structure | Scope(s)       | Target Type     | Target Name     | Method                    |
|--------|--|---------------------------|----------------|-----------------|-----------------|---------------------------|
| R351.1 | MT-ATP6; MT-ND6                          | Singleton                 | Small variants | Small panel     | MT-ATP6; MT-ND6 | Small panel               |
| R351.2 | m.8993T>C/G<br>Targeted mutation testing | Singleton                 | Small variants | Single interval | m.8993T>C/G     | Targeted mutation testing |

## R352 Mitochondrial DNA maintenance disorder

### Testing Criteria

Clinical features suggestive of mtDNA maintenance disorder and/or evidence of mtDNA depletion or multiple mtDNA deletions

### Overlapping indications

- R63 Possible mitochondrial disorder - nuclear genes test should be considered where a broader range of mitochondrial nuclear genes are potentially causative

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation following assessment by a Consultant in Metabolic Medicine, Neurology, Paediatric Neurology or Clinical Genetics, or following evidence of mtDNA depletion or multiple mtDNA deletions

### Requesting Specialties

- Clinical Genetics
- Neurology

### Specialist Service Group

- Mitochondrial

### Associated Tests

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   | Optional Family Structure | Scope(s)        | Target Type            | Target Name                                  | Method   |
|--------|--|---------------------------|-----------------|------------------------|--|--|
| R352.1 | Mitochondrial DNA maintenance disorder WES or medium panel | Singleton                 | Small variants  | Panel of genes or loci | Mitochondrial DNA maintenance disorder (533) | WES or Medium Panel                            |
| 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   | Optional Family Structure | Scope(s)        | Target Type            | Target Name  | Method   |
|--------|--|---------------------------|-----------------|------------------------|--|--|
| R353.1 | Mitochondrial disorder with complex I deficiency WES or medium panel | Singleton                 | Small variants  | Panel of genes or loci | Mitochondrial disorder with complex I deficiency (534) | WES or Medium Panel                            |
| 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   | Optional Family Structure | Scope(s)        | Target Type            | Target Name   | Method   |
|--------|--|---------------------------|-----------------|------------------------|---|--|
| R354.1 | Mitochondrial disorder with complex II deficiency WES or small panel | Singleton                 | Small variants  | Panel of genes or loci | Mitochondrial disorder with complex II deficiency (535) | WES or Small Panel                             |
| 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  | Optional Family Structure | Scope(s)        | Target Type            | Target Name  | Method   |
|--------|---|---------------------------|-----------------|------------------------|--|--|
| R355.1 | Mitochondrial disorder with complex III deficiency WES or small panel | Singleton                 | Small variants  | Panel of genes or loci | Mitochondrial disorder with complex III deficiency (536) | WES or Small Panel                             |
| 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   | Optional Family Structure | Scope(s)        | Target Type            | Target Name   | Method   |
|--------|--|---------------------------|-----------------|------------------------|---|--|
| R356.1 | Mitochondrial disorder with complex IV deficiency WES or small panel | Singleton                 | Small variants  | Panel of genes or loci | Mitochondrial disorder with complex IV deficiency (537) | WES or Small Panel                             |
| 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  | Optional Family Structure | Scope(s)        | Target Type            | Target Name  | Method   |
|--------|---|---------------------------|-----------------|------------------------|--|--|
| R357.1 | Mitochondrial disorder with complex V deficiency WES or small panel | Singleton                 | Small variants  | Panel of genes or loci | Mitochondrial disorder with complex V deficiency (538) | WES or Small Panel                             |
| 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   | Optional Family Structure | Scope(s)       | Target Type            | Target Name   | Method             |
|-------|--|---------------------------|----------------|------------------------|---|--------------------|
| R63.1 | Possible mitochondrial disorder - nuclear genes WES or large panel | Singleton                 | Small variants | Panel of genes or loci | Possible mitochondrial disorder - nuclear genes (539) | WES or Large Panel |

|       |   |           |                 |                        |   |  |
|-------|---|-----------|-----------------|------------------------|---|--|
| 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                        | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                     |
|--------|-----------------------------|---------------------------|----------------|----------------|-------------|--|
| R394.1 | TYMP Single gene sequencing | Singleton                 | Small variants | Single gene(s) | TYMP        | Single gene sequencing $\geq 10$ 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                           | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                               |
|--------|--------------------------------|---------------------------|----------------|----------------|-------------|--------------------------------------|
| R395.1 | SLC19A3 Single gene sequencing | Singleton                 | Small variants | Single gene(s) | SLC19A3     | Single gene sequencing <10 amplicons |

## R396 Mitochondrial Complex V deficiency, TMEM70 type

### Testing Criteria

Infantile/paediatric onset hypertrophic cardiomyopathy, raised lactate and raised 3-methylglutaconic acid  
Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

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                          | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                               |
|--------|-------------------------------|---------------------------|----------------|----------------|-------------|--------------------------------------|
| R396.1 | TMEM70 Single gene sequencing | Singleton                 | Small variants | Single gene(s) | TMEM70      | Single gene sequencing <10 amplicons |

## R397 Maternally inherited cardiomyopathy

### Testing Criteria

Maternally inherited hypertrophic cardiomyopathy

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

Following laboratory or clinical assessment by a mitochondrial highly specialised service

### Requesting Specialties

- Cardiology
- Clinical Genetics

### Specialist Service Group

- Mitochondrial

### Associated Tests

| Code   | Name                                   | Optional Family Structure | Scope(s)       | Target Type     | Target Name | Method                    |
|--------|--|---------------------------|----------------|-----------------|-------------|---------------------------|
| R397.1 | m.4300A>G<br>Targeted mutation testing | Singleton                 | Small variants | Single interval | m.4300A>G   | Targeted mutation testing |

## R42 Leber hereditary optic neuropathy

### Testing Criteria

Likely or possible clinical diagnosis of Leber hereditary optic neuropathy

### Where in Pathway

At presentation following assessment by a Consultant Ophthalmologist, Neurologist or Clinical Geneticist

### Requesting Specialties

- Clinical Genetics
- Neurology
- Ophthalmology

### Specialist Service Group

- Mitochondrial

### Associated Tests

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   | Optional Family Structure | Scope(s)       | Target Type          | Target Name                | Method                                |
|-------|--|---------------------------|----------------|----------------------|----------------------------|---------------------------------------|
| R42.1 | Three common LHON variants<br>Targeted mutation testing    | Singleton                 | Small variants | Single interval      | Three common LHON variants | Targeted mutation testing             |
| R42.2 | Mitochondrial genome Whole mitochondrial genome sequencing | Singleton                 | Small variants | Mitochondrial Genome | Mitochondrial Genome       | Mitochondrial Genome                  |
| R42.4 | DNAJC30  | Singleton                 | Small variants | Single interval      | DNAJC30                    | single gene sequencing < 10 amplicons |

## 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 consecutive 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                 | Optional 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                 | Optional Family Structure | Scope(s)                | Target Type     | Target Name                 | Method |
|--------|----------------------|---------------------------|-------------------------|-----------------|-----------------------------|--------|
| R298.1 | Specific target FISH | Singleton                 | Balanced rearrangements | Single interval | As determined by indication | FISH   |

## R265 Chromosomal mosaicism - karyotype

### Testing Criteria

Individuals with possible mosaic chromosome abnormality requiring extended count karyotype including:

1. possible mosaic chromosome abnormality indicated by findings from conventional karyotype, microarray, WGS or other laboratory technique, OR
2. clinical features strongly suggestive of a specific chromosomal phenotype, for example Down syndrome, in whom conventional testing is negative

### Overlapping indications

- R343 Chromosomal mosaicism - microarray should be used where a microarray is indicated

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

N/A

### Requesting Specialties

- Clinical Genetics
- Dermatology
- Genomics laboratory

### Specialist Service Group

- Core

### Associated Tests

| Code   | Name                             | Optional Family Structure | Scope(s)   | Target Type | Target Name | Method    |
|--------|----------------------------------|---------------------------|------------|-------------|-------------|-----------|
| R265.1 | Genomewide Karyotype - mosaicism | Singleton                 | Aneuploidy | Genomewide  | Genomewide  | Karyotype |

## R343 Chromosomal mosaicism - microarray

### Testing Criteria

Hyper- or hypo- pigmentation following Blaschkos lines (Hypomelanosis of Ito), with associated abnormalities such as neurodevelopmental delay, seizures or asymmetry

### Overlapping indications

- R327 Mosaic skin disorders – deep sequencing test should be used where the mosaicism is likely to be caused by a single gene

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

**NOTE: Sample submitted for this test can be either a skin biopsy or a blood sample**

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Dermatology

### Specialist Service Group

- Core

### Associated Tests

| Code   | Name                  | Optional Family Structure | Scope(s)        | Target Type | Target Name | Method     |
|--------|-----------------------|---------------------------|-----------------|-------------|-------------|------------|
| R343.1 | Genomewide Microarray | Singleton                 | Genomewide CNVs | Genomewide  | Genomewide  | Microarray |



## R411 Y Chromosome microdeletions

### Testing Criteria

Patients with non-obstructive azoospermia or severe oligospermia where testicular sperm extraction (TESE)/microdissection TESE (mTESE) is considered and outcome of testing will inform eligibility for (m)TESE and success of sperm retrieval (<https://www.england.nhs.uk/wp-content/uploads/2018/07/Surgical-sperm-retrieval-for-male-infertility.pdf>)

Testing for Y chromosome microdeletions should not routinely be performed before ICSI (<https://www.nice.org.uk/guidance/cg156/chapter/Recommendations>)

Testing for this clinical indication is performed by designated GLHs on behalf of the national genomic testing network

### Overlapping indications

- R298 - Possible structural or mosaic chromosomal abnormality requiring FISH

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

Following review by a urologist with an interest in male infertility or specialist fertility MDT

### Requesting Specialties

- Clinical Genetics
- Urology

### Specialist Service Group

- Core

### Associated Tests

| Code   | Name                        | Optional Family Structure | Scope(s)           | Target Type     | Target Name              | Method                                  |
|--------|-----------------------------|---------------------------|--------------------|-----------------|--------------------------|---|
| R411.1 | Y chromosome microdeletions | Singleton                 | CNVs to exon level | Single interval | Y chromosome AZF regions | Targeted mutation testing or equivalent |

## Part XVI. Musculoskeletal

### R52 Short stature - SHOX deficiency

#### Testing Criteria

Disproportionate short stature with features in the patient or relatives suggestive of SHOX deficiency, e.g. Madelung deformity,

#### Overlapping indications

- R147 Growth failure in early childhood to be used for more significant/earlier onset short stature, including where Silver-Russell syndrome is the likely diagnosis
- R382 Hypochondroplasia and R24 Achondroplasia
- R104 Skeletal dysplasia to be used where clinical features indicative of a likely monogenic skeletal dysplasia

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

#### Where in Pathway

At presentation

#### Requesting Specialties

- Clinical Genetics
- Endocrinology
- Paediatrics

#### Specialist Service Group

- Musculoskeletal

#### Associated Tests

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                        | Optional Family Structure | Scope(s)        | Target Type    | Target Name | Method                               |
|-------|-----------------------------|---------------------------|-----------------|----------------|-------------|--------------------------------------|
| R52.1 | SHOX MLPA or equivalent     | Singleton                 | Exon level CNVs | Single gene(s) | SHOX        | MLPA or equivalent                   |
| R52.2 | SHOX Single gene sequencing | Singleton                 | Small variants  | Single gene(s) | SHOX        | Single gene sequencing <10 amplicons |

## R24 Achondroplasia

### Testing Criteria

Clinical features strongly suggestive of achondroplasia

#### Overlapping clinical indications:

- R309 NIPD for FGFR3-related skeletal dysplasias - mutation testing
- R104 Skeletal dysplasia test should be used where features are atypical and a broader range of genes are likely to be causative
- R382 Hypochondroplasia testing may also be indicated if clinically relevant

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Neonatology
- Paediatrics

### Specialist Service Group

- Core

### Associated Tests

| Code  | Name                                   | Optional Family Structure | Scope(s)       | Target Type     | Target Name  | Method                    |
|-------|--|---------------------------|----------------|-----------------|--------------|---------------------------|
| R24.1 | FGFR3 c.1138 Targeted mutation testing | Singleton                 | Small variants | Single interval | FGFR3 c.1138 | Targeted mutation testing |

## R382 Hypochondroplasia

### Testing Criteria

Clinical features strongly suggestive of hypochondroplasia

Overlapping clinical indications:

- R309 NIPD for FGFR3-related skeletal dysplasias - mutation testing
- R24 Achondroplasia testing may also be indicated if clinically relevant
- R52 Short stature – SHOX deficiency
- R104 Skeletal dysplasia test should be used where features are atypical and a broader range of genes are likely to be causative

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Endocrinology

### Specialist Service Group

- Core

### Associated Tests

| Code   | Name                                      | Optional Family Structure | Scope(s)       | Target Type     | Target Name  | Method                    |
|--------|---|---------------------------|----------------|-----------------|--------------|---------------------------|
| R382.1 | FGFR3 c.1620<br>Targeted mutation testing | Singleton                 | Small variants | Single interval | FGFR3 c.1620 | Targeted mutation testing |

## R25 Thanatophoric dysplasia

### Testing Criteria

Clinical features strongly suggestive of thanatophoric dysplasia

Overlapping clinical indications:

- R309 NIPD for FGFR3-related skeletal dysplasias - mutation testing
- R104 Skeletal dysplasia test should be used where features are atypical and a broader range of genes are likely to be causative

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Fetal Medicine

### Specialist Service Group

- Core

### Associated Tests

| Code  | Name                         | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                     |
|-------|------------------------------|---------------------------|----------------|----------------|-------------|--|
| R25.1 | FGFR3 Single gene sequencing | Singleton                 | Small variants | Single gene(s) | FGFR3       | Single gene sequencing $\geq 10$ amplicons |

## R104 Skeletal dysplasia

### Testing Criteria

Clinical features indicative of a likely monogenic skeletal dysplasia

Patients with suspected severe congenital autosomal recessive malignant osteopetrosis where rapid genetic diagnosis is required for urgent patient management (e.g. curative stem cell transplantation) are eligible for urgent testing via R104.4

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### 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   | Optional Family Structure | Scope(s)                        | Target Type            | Target Name              | Method             |
|--------|--|---------------------------|---------------------------------|------------------------|--------------------------|--------------------|
| R104.2 | 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                    | Optional Family Structure | Scope(s)                | Target Type     | Target Name | Method   |
|--------|-------------------------|---------------------------|-------------------------|-----------------|-------------|--|
| R415.1 | Cleidocranial Dysplasia | Singleton                 | small variant detection | Single gene (s) | RUNX2       | Single gene sequencing < 10 amplicons          |
| R415.2 | Cleidocranial Dysplasia | Singleton                 | Exon level CNVs         | Single gene (s) | RUNX2       | 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   | Optional Family Structure | Scope(s)        | Target Type            | Target Name                             | Method   |
|-------|--|---------------------------|-----------------|------------------------|---|--|
| R99.1 | Common craniosynostosis syndromes Small panel        | Singleton                 | Small variants  | Panel of genes or loci | Common craniosynostosis syndromes (507) | Small panel                                    |
| R99.2 | Common craniosynostosis syndromes MLPA or equivalent | Singleton                 | Exon level CNVs | Panel of genes or loci | 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                           | Optional 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 only

### 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  | Optional Family Structure | Scope(s)                | Target Type    | Target Name | Method                                |
|--------|---|---------------------------|-------------------------|----------------|-------------|---------------------------------------|
| R416.1 | Syndromic & non-syndromic craniosynostosis involving midline sutures only | Singleton                 | Small variant detection | Single gene(s) | SMAD6       | 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  | Optional 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  | Optional Family Structure | Scope(s)       | Target Type     | Target Name           | Method                    |
|-------|---|---------------------------|----------------|-----------------|-----------------------|---------------------------|
| R23.1 | FGFR2 c.755 and c.758 Targeted mutation testing | Singleton                 | Small variants | Single interval | FGFR2 c.755 and c.758 | Targeted mutation testing |

## R101 Ehlers Danlos syndrome with a likely monogenic cause

### Testing Criteria

Clinical features indicative of a likely monogenic Ehlers Danlos syndrome:

- Classical EDS (cEDS)
- Classical-like EDS (clEDS)
- Cardiac-valvular EDS (cvEDS)
- Vascular EDS (vEDS)
- Arthrochalasia EDS (aEDS)
- Dermatosparaxis EDS (dEDS)
- Kyphoscoliotic EDS (kEDS)
- Brittle Cornea Syndrome (BCS)
- Spondylodysplastic EDS (spEDS)
- Musculocontractural EDS (mcEDS)
- Myopathic EDS (mEDS)
- Periodontal EDS (pEDS)

Testing should only be used where it will impact on clinical management

### Overlapping indications

- R89 Ultra-rare and atypical monogenic disorders or R27 Congenital malformation and dysmorphism syndromes – likely monogenic tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations not typical of disorders covered by the panel

### Where in Pathway

Following assessment by a Clinical Geneticist or other expert in a highly specialised Ehlers Danlos service

### Requesting Specialties

- Clinical Genetics
- Rheumatology

### Specialist Service Group

- Musculoskeletal

### Associated Tests

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  | Optional Family Structure | Scope(s)        | Target Type            | Target Name                  | Method   |
|--------|---|---------------------------|-----------------|------------------------|------------------------------|--|
| R101.1 | Ehlers Danlos syndromes WES or medium panel | Singleton                 | Small variants  | Panel of genes or loci | Ehlers Danlos syndromes (53) | WES or Medium Panel                            |
| 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 Congenital malformation and dysmorphism syndromes – likely monogenic tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations not typical of disorders covered by the panel

### Where in Pathway

Following assessment by a Clinical Geneticist or other expert in highly specialised osteogenesis imperfecta service

### Requesting Specialties

- Clinical Genetics
- 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  | Optional Family Structure | Scope(s)        | Target Type            | Target Name                   | Method   |
|--------|---|---------------------------|-----------------|------------------------|-------------------------------|--|
| R102.1 | Osteogenesis imperfecta WES or medium panel | Singleton                 | Small variants  | Panel of genes or loci | Osteogenesis imperfecta (196) | WES or Medium Panel                            |
| 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                          | Optional Family Structure | Scope(s)        | Target Type    | Target Name | Method             |
|--------|-------------------------------|---------------------------|-----------------|----------------|-------------|--------------------|
| R390.1 | EXT1; EXT2                    | Singleton                 | Small variants  | Small panel    | EXT1; EXT2  | Small panel        |
| R390.2 | EXT1; EXT2 MLPA or equivalent | Singleton                 | Exon level CNVs | Single gene(s) | EXT1; EXT2  | MLPA or equivalent |

## R284 Van der Woude syndrome

### Testing Criteria

Clinical features strongly suggestive of van der Woude syndrome.

### Overlapping indications

- R27 Congenital malformation and dysmorphism syndromes – likely monogenic test should be used in individuals with cleft palate with a likely complex syndromic cause

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics

### Specialist Service Group

- Musculoskeletal

### Associated Tests

| Code   | Name                        | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                               |
|--------|-----------------------------|---------------------------|----------------|----------------|-------------|--------------------------------------|
| R284.1 | IRF6 Single gene sequencing | Singleton                 | Small variants | Single gene(s) | IRF6        | Single gene sequencing <10 amplicons |



## Part XVII. Neurology

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### R70 Spinal muscular atrophy type 1 diagnostic test

#### Testing Criteria

Clinical features suggestive of spinal muscular atrophy type 1

#### Overlapping indications

- R69 Hypotonic infant with a likely central cause test should be used in floppy babies where the clinical picture is suggestive of a central cause, i.e. particularly where the baby is not alert, but lethargic or sleepy

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

#### Where in Pathway

At presentation

#### Requesting Specialties

- Clinical Genetics
- Neonatology
- Neurology
- Paediatrics

#### Specialist Service Group

- Core

#### Associated Tests

| Code  | Name                    | Optional Family Structure | Scope(s)        | Target Type    | Target Name | Method             |
|-------|-------------------------|---------------------------|-----------------|----------------|-------------|--------------------|
| R70.1 | SMN1 MLPA or equivalent | Singleton                 | Exon level CNVs | Single gene(s) | SMN1        | MLPA or equivalent |

## R72 Myotonic dystrophy type 1

### Testing Criteria

Clinical features strongly suggestive of myotonic dystrophy type 1

### Overlapping indications

- R69 Hypotonic infant with a likely central cause test should be used in floppy babies where the clinical picture is suggestive of a central cause
- R381 Other rare neuromuscular disorders should be used where clinical features are atypical and a broader range of genes are potentially causative
- R410 Myotonic dystrophy type 2 should be used where there is clinical suspicion of myotonic dystrophy type 2 or where myotonic dystrophy type 1 has been excluded

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Neurology

### Specialist Service Group

- Core

### Associated Tests

| Code  | Name             | Optional Family Structure | Scope(s)    | Target Type    | Target Name | Method      |
|-------|------------------|---------------------------|-------------|----------------|-------------|-------------|
| R72.1 | DMPK STR testing | Singleton                 | Methylation | Single gene(s) | DMPK STR    | STR testing |

## R77 Hereditary neuropathy - PMP22 copy number

### Testing Criteria

Hereditary neuropathy where PMP22 copy number abnormalities are possible

### Overlapping indications

- R78 Hereditary neuropathy or pain disorder – NOT PMP22 copy number test should be used where PMP22 copy number abnormalities are clinically unlikely or have already been excluded
- R89 Ultra-rare and atypical monogenic disorders or R27 Congenital malformation and dysmorphism syndromes – likely monogenic tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Neurology
- Paediatrics

### Specialist Service Group

- Core

### Associated Tests

| Code  | Name                     | Optional Family Structure | Scope(s)        | Target Type    | Target Name | Method             |
|-------|--------------------------|---------------------------|-----------------|----------------|-------------|--------------------|
| R77.1 | PMP22 MLPA or equivalent | Singleton                 | Exon level CNVs | Single gene(s) | PMP22       | MLPA or equivalent |

## R68 Huntington disease

### Testing Criteria

Clinical features that indicate a likely diagnosis of Huntington disease

- Specialties other than those listed in Requesting Specialties may request tests in certain settings following discussion with their local laboratory-clinical team

### Overlapping indications

- R56 Adult onset dystonia, chorea or related movement disorder or other relevant broader test should be used where clinical features are not strongly suggestive of Huntington disease

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Neurology
- Psychiatry

### Specialist Service Group

- Core

### Associated Tests

| Code  | Name            | Optional Family Structure | Scope(s) | Target Type    | Target Name | Method      |
|-------|-----------------|---------------------------|----------|----------------|-------------|-------------|
| R68.1 | HTT STR testing | Singleton                 | STRs     | Single gene(s) | HTT         | STR testing |

## R383 Linkage testing for Huntington disease

### Testing Criteria

Families with a confirmed diagnosis of Huntington disease who require linkage testing to guide management or advice

### Where in Pathway

As appropriate

### Requesting Specialties

- Clinical Genetics

### Specialist Service Group

- Neurology

### Associated Tests

| Code   | Name                | Optional Family Structure     | Scope(s) | Target Type    | Target Name | Method |
|--------|---------------------|-------------------------------|----------|----------------|-------------|--------|
| R383.1 | HTT Linkage testing | Multiple affected individuals | Other    | Single gene(s) | HTT         | Other  |

## R252 SMA carrier testing at population risk for partners of known carriers

### Testing Criteria

Testing in partners of known carriers of SMA where management of a current or future pregnancy depends on the result

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At the time of reproductive planning

### Requesting Specialties

- Clinical Genetics

### Specialist Service Group

- Core

### Associated Tests

| Code   | Name                    | Optional Family Structure | Scope(s)        | Target Type    | Target Name | Method             |
|--------|-------------------------|---------------------------|-----------------|----------------|-------------|--------------------|
| R252.1 | SMN1 MLPA or equivalent | Singleton                 | Exon level CNVs | Single gene(s) | SMN1        | MLPA or equivalent |

## R54 Hereditary ataxia with onset in adulthood

### Testing Criteria

Unexplained ataxia with onset in adulthood including where differential diagnosis encompasses STR loci

### Overlapping indications

R53 Fragile X – if clinical features are suggestive of Fragile X ataxia then this test should also be requested.

### Where in Pathway

At presentation following assessment by a Neurologist

### Requesting Specialties

- Clinical Genetics
- Neurology

### Specialist Service Group

- Neurology

### Associated Tests

Please note that initially only WGS testing will be undertaken for R54 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are necessary. Whilst this includes testing of all STRs in the gene panel, analysis is currently not optimal and therefore if a specific STR is suspected this should be stated at referral to prompt additional testing where necessary.

Please note testing R54 does not include testing for Fragile X (Clinical Indication number R53) and this should be requested in addition if required.

| Code  | Name  | Optional Family Structure | Scope(s)                              | Target Type            | Target Name                           | Method      |
|-------|---|---------------------------|---------------------------------------|------------------------|---------------------------------------|-------------|
| R54.2 | Hereditary ataxia - adult onset STR testing   | Singleton                 | STRs                                  | Panel of genes or loci | Hereditary ataxia - adult onset (466) | STR testing |
| R54.3 | Hereditary ataxia - adult onset WGS (phase 1) | Singleton                 | Exon level CNVs, Small variants, STRs | Panel of genes or loci | Hereditary ataxia - adult onset (466) | WGS         |

## R55 Hereditary ataxia with onset in childhood

### Testing Criteria

Unexplained hereditary ataxia with onset in childhood including where differential diagnosis encompasses STR loci

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation following assessment by a Neurologist

### Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

### Specialist Service Group

- Neurology

### Associated Tests

Please note that initially only WGS testing will be undertaken for R55 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are necessary. Whilst this includes testing of all STRs in the gene panel, analysis is currently not optimal and therefore if a specific STR is suspected this should be stated at referral to prompt additional testing where necessary.

| Code  | Name   | Optional Family Structure | Scope(s)                              | Target Type            | Target Name  | Method      |
|-------|--|---------------------------|---------------------------------------|------------------------|--|-------------|
| R55.3 | Hereditary ataxia and cerebellar anomalies - childhood onset STR testing   | Singleton                 | STRs                                  | Panel of genes or loci | Hereditary ataxia and cerebellar anomalies - childhood onset (488) | STR testing |
| R55.4 | Hereditary ataxia and cerebellar anomalies - childhood onset WGS (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         |



## 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

Please note that initially only WGS testing will be undertaken for R56 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are necessary. Whilst this includes testing of all STRs in the gene panel, analysis is currently not optimum and therefore if a specific STR is suspected this should be stated at referral to prompt additional testing where necessary.

| Code  | Name   | Optional Family Structure | Scope(s)                              | Target Type            | Target Name                         | Method      |
|-------|--|---------------------------|---------------------------------------|------------------------|-------------------------------------|-------------|
| R56.2 | Adult onset movement disorder STR testing                                | Singleton                 | STRs                                  | Panel of genes or loci | Adult onset movement disorder (540) | STR testing |
| 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         |

## 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 Congenital malformation and dysmorphism syndromes – likely monogenic,
- R29 Intellectual disability – microarray, fragile X and sequencing,
- R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with complex or syndromic presentations

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation following assessment by a Neurologist

### Requesting Specialties

- Clinical Genetics
- Metabolic Medicine
- Neurology

### Specialist Service Group

- Neurology

### Associated Tests

Please note all the tests below will be undertaken for R57 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary.

| Code  | Name   | Optional Family Structure | Scope(s)                              | Target Type            | Target Name   | Method      |
|-------|--|---------------------------|---------------------------------------|------------------------|---|-------------|
| R57.3 | Childhood onset dystonia or chorea or related movement disorder (847)<br>STR testing | Singleton                 | STRs                                  | Panel of genes or loci | Childhood onset dystonia or chorea or related movement disorder (847) | STR testing |
| 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         |

## 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
  - d. Age of onset <50 years or family history of ALS or frontotemporal dementia, AND
  - e. No evidence of other aetiology

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation following assessment by a Neurologist

### Requesting Specialties

- Clinical Genetics
- Neurology

### Specialist Service Group

- Neurology

### Associated Tests

Please note that initially only WGS testing will be undertaken for R58 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are necessary. Whilst this includes testing of all STRs in the gene panel, analysis is currently not optimal and therefore if a specific STR is suspected this should be stated at referral to prompt additional testing where necessary.

| Code  | Name  | Optional Family Structure | Scope(s)                              | Target Type            | Target Name                                     | Method      |
|-------|---|---------------------------|---------------------------------------|------------------------|---|-------------|
| R58.3 | Neurodegenerative disorders - adult onset STR testing | Singleton                 | STRs                                  | Panel of genes or loci | Neurodegenerative disorders - adult onset (474) | STR testing |
| 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         |

## 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 test should be used where megalencephaly is present to allow detection of somatic mosaic mutations

**NOTE: If a metabolic disorder is suspected, testing should be carried 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  | Optional 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

Please note that initially only WGS testing will be undertaken for R60 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are necessary. Whilst this includes testing of all STRs in the gene panel, analysis is currently not optimal and therefore if a specific STR is suspected this should be stated at referral to prompt additional testing where necessary.

| Code  | Name  | Optional Family Structure | Scope(s)                              | Target Type            | Target Name                                       | Method      |
|-------|---|---------------------------|---------------------------------------|------------------------|---|-------------|
| R60.2 | Hereditary spastic paraplegia - adult onset STR testing | Singleton                 | STRs                                  | Panel of genes or loci | Hereditary spastic paraplegia - adult onset (567) | STR testing |
| 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         |

## 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

Please note that initially only WGS testing (plus SPAST CNVs where indicated) will be undertaken for R61 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are necessary. Whilst this includes testing of all STRs in the gene panel, analysis is currently not optimal and therefore if a specific STR is suspected this should be stated at referral to prompt additional testing where necessary.

| Code  | Name  | Optional Family Structure | Scope(s)                              | Target Type            | Target Name   | Method      |
|-------|---|---------------------------|---------------------------------------|------------------------|---|-------------|
| R61.3 | Hereditary spastic paraplegia - child onset STR testing   | Singleton                 | STRs                                  | Panel of genes or loci | Hereditary spastic paraplegia - Childhood onset (568) | STR testing |
| R61.4 | Hereditary spastic paraplegia - child onset WGS (phase 1) | Trio or singleton         | Exon level CNVs, Small variants; STRs | Panel of genes or loci | Hereditary spastic paraplegia - Childhood onset (568) | WGS         |

## R62 Adult onset leukodystrophy

### Testing Criteria

Individuals with unexplained leukodystrophy on neuroimaging with onset in adulthood

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation following review of neuroimaging by Neuroradiologist

### Requesting Specialties

- Clinical Genetics
- Neurology

### Specialist Service Group

- Neurology

### Associated Tests

| Code  | Name                                     | Optional Family Structure | Scope(s)                        | Target Type            | Target Name                                | Method |
|-------|--|---------------------------|---------------------------------|------------------------|--|--------|
| R62.2 | 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  | Optional Family Structure | Scope(s)        | Target Type            | Target Name   | Method   |
|-------|---|---------------------------|-----------------|------------------------|---|--|
| R66.1 | Paroxysmal neurological disorders, pain disorders and sleep disorders WES or medium panel | Singleton                 | Small variants  | Panel of genes or loci | Paroxysmal neurological disorders, pain disorders and sleep disorders (541) | WES or Medium Panel                            |
| R66.2 | Paroxysmal central nervous system disorders   | Singleton                 | Exon level CNVs | Panel of genes or loci | Paroxysmal neurological disorders, pain disorders and sleep disorders (541) | Exon level CNV detection by 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

### Overlapping indications

- R70 Spinal muscular atrophy type 1 diagnostic test should be used first where clinical features are suggestive of spinal muscular atrophy type 1 and SMN1 copy number has not been tested.

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

After SMN1 copy number analysis

### Requesting Specialties

- Clinical Genetics
- Neurology

### Specialist Service Group

- Neurology

### Associated Tests

| Code  | Name                        | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                     |
|-------|-----------------------------|---------------------------|----------------|----------------|-------------|--|
| R71.1 | SMN1 Single gene sequencing | Singleton                 | Small variants | Single gene(s) | SMN1        | Single gene sequencing $\geq 10$ amplicons |

## R73 Duchenne or Becker muscular dystrophy

### Testing Criteria

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                       | Optional Family Structure | Scope(s)        | Target Type    | Target Name | Method                                     |
|-------|----------------------------|---------------------------|-----------------|----------------|-------------|--|
| R73.1 | DMD Single gene sequencing | Singleton                 | Small variants  | Single gene(s) | DMD         | Single gene sequencing $\geq 10$ amplicons |
| R73.2 | DMD MLPA or equivalent     | Singleton                 | Exon level CNVs | Single gene(s) | DMD         | MLPA or equivalent                         |

## R378 Linkage testing for Duchenne or Becker muscular dystrophy

### Testing Criteria

Families with a confirmed diagnosis of Duchenne or Becker muscular dystrophy with no detectable mutation in dystrophin who require linkage testing to guide management or advice

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

As appropriate

### Requesting Specialties

- Clinical Genetics

### Specialist Service Group

- Neurology

### Associated Tests

| Code   | Name                       | Optional Family Structure     | Scope(s) | Target Type    | Target Name | Method |
|--------|----------------------------|-------------------------------|----------|----------------|-------------|--------|
| R378.1 | Dystrophin Linkage testing | Multiple affected individuals | Other    | Single gene(s) | Dystrophin  | Other  |

## R74 Facioscapulohumeral muscular dystrophy

### Testing Criteria

Clinical features strongly suggestive of facioscapulohumeral muscular dystrophy (FSHD) in whom a DUX4 contraction has not been excluded

### Overlapping indications

- R82 Limb girdle muscular dystrophy and broader tests such as R89 Ultra-rare and atypical monogenic disorders should be considered where features are atypical
- R345 Facioscapulohumeral muscular dystrophy (FSHD) extended testing should be considered in cases negative for the test where clinical features are strongly suggestive of FSHD
- R381 Other rare neuromuscular disorders should be used where clinical features are atypical and a broader range of genes are potentially causative

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Neurology

### Specialist Service Group

- Neurology

### Associated Tests

| Code  | Name                     | Optional Family Structure | Scope(s) | Target Type     | Target Name | Method |
|-------|--------------------------|---------------------------|----------|-----------------|-------------|--------|
| R74.1 | DUX4 Contraction testing | Singleton                 | STRs     | Single interval | DUX4        | Other  |

## R345 Facioscapulohumeral muscular dystrophy - extended testing

### Testing Criteria

Clinical features strongly suggestive of facioscapulohumeral muscular dystrophy (FSHD) in whom a DUX4 contraction has been excluded

### Overlapping indications

- R74 Facioscapulohumeral muscular dystrophy test should be used where DUX4 contraction has not been excluded
- R82 Limb girdle muscular dystrophy and broader tests such as R381 Other rare neuromuscular disorders should be considered where features are atypical

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

Following discussion with Neuromuscular consultant and/or testing laboratory

### Requesting Specialties

- Clinical Genetics
- Neurology

### Specialist Service Group

- Neurology

### Associated Tests

| Code   | Name                          | Optional Family Structure | Scope(s)         | Target Type     | Target Name | Method                                |
|--------|-------------------------------|---------------------------|------------------|-----------------|-------------|---------------------------------------|
| R345.1 | DUX4 Methylation testing      | Singleton                 | Methylation      | Single interval | DUX4        | Methylation testing                   |
| R345.2 | SMCHD1 Single gene sequencing | Singleton                 | Small variants   | Single gene(s)  | SMCHD1      | Single gene sequencing >=10 amplicons |
| R345.3 | 4q Extended testing           | Singleton                 | Complex variants | Single interval | 4q          | Other                                 |

## R75 Oculopharyngeal muscular dystrophy

### Testing Criteria

Clinical features strongly suggestive of oculopharyngeal muscular dystrophy

### Overlapping indications

- R89 Ultra-rare and atypical monogenic disorders test should be considered where features are atypical
- R381 Other rare neuromuscular disorders should be used where clinical features are atypical and a broader range of genes are potentially causative

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Neurology

### Specialist Service Group

- Neurology

### Associated Tests

| Code  | Name               | Optional Family Structure | Scope(s) | Target Type    | Target Name | Method      |
|-------|--------------------|---------------------------|----------|----------------|-------------|-------------|
| R75.1 | PABPN1 STR testing | Singleton                 | STRs     | Single gene(s) | PABPN1 STR  | STR testing |

## R76 Skeletal muscle channelopathy

### Testing Criteria

Clinical features strongly suggestive of a skeletal muscle channelopathy including myotonia congenita or paramyotonia congenita

### Overlapping indications

- R89 Ultra-rare and atypical monogenic disorders should be used where features are atypical
- R381 Other rare neuromuscular disorders should be used where clinical features are atypical and a broader range of genes are potentially causative

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation 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   | Optional Family Structure | Scope(s)        | Target Type            | Target Name                         | Method   |
|-------|--|---------------------------|-----------------|------------------------|-------------------------------------|--|
| R76.1 | Skeletal muscle channelopathy<br>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 – NOT PMP22 copy number

### Testing Criteria

Clinical features that indicate a likely hereditary neuropathy or pain disorder in whom PMP22 copy number abnormalities are clinically unlikely or have already been excluded

### Overlapping indications

- R77 Hereditary neuropathy - PMP22 copy number test should be used where PMP22 copy number abnormalities are possible
- R89 Ultra-rare and atypical monogenic disorders or R27 Congenital malformation and dysmorphism syndromes – likely monogenic tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Neurology

### Specialist Service Group

- Neurology

### Associated Tests

Please note that initially only WGS testing will be undertaken for R78 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are necessary.

Whilst this includes testing of SMAX1 STR, analysis is currently not optimal and therefore if this specific STR is suspected this should be stated at referral to prompt additional testing where necessary.

| Code  | Name   | Optional Family Structure | Scope(s)                              | Target Type            | Target Name                                       | Method |
|-------|--|---------------------------|---------------------------------------|------------------------|---|--------|
| R78.2 | SMAX1 (AR_CAG); STR  | Singleton                 | STR                                   | Single gene(s)         | SMAX1 (AR_CAG);                                   | STR    |
| R78.4 | Hereditary neuropathy or pain disorder – NOT PMP22 copy number WGS (phase 2) | Trio or singleton         | Exon level CNVs, Small variants, STRs | Panel of genes or loci | Hereditary neuropathy NOT PMP22 copy number (846) | WGS    |



## R79 Congenital muscular dystrophy

### Testing Criteria

Individuals with clinical features that indicate a likely congenital muscular dystrophy:

1. Muscle biopsy results indicative of congenital muscular dystrophy, OR
2. Muscle and/or brain MRI findings indicative of congenital muscular dystrophy

### Overlapping indications

- R89 Ultra-rare and atypical monogenic disorders or R27 Congenital malformation and dysmorphism syndromes – likely monogenic tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations not typical of disorders covered by the panel

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation following assessment by a Neurologist 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  | Optional Family Structure | Scope(s)        | Target Type            | Target Name                         | Method   |
|-------|---|---------------------------|-----------------|------------------------|-------------------------------------|--|
| R79.1 | Congenital muscular dystrophy WES or medium panel | Singleton                 | Small variants  | Panel of genes or loci | Congenital muscular dystrophy (207) | WES or Medium Panel                            |
| 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 myaesthetic syndrome

### Testing Criteria

Clinical features that indicate a likely monogenic congenital myaesthesia

### Overlapping indications

- R89 Ultra-rare and atypical monogenic disorders or R27 Congenital malformation and dysmorphism syndromes – likely monogenic tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations not typical of disorders covered by the panel

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation following assessment by a Neurologist, typically in parallel to maternal anti-AChR antibody testing 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  | Optional Family Structure | Scope(s)        | Target Type            | Target Name                           | Method   |
|-------|---|---------------------------|-----------------|------------------------|---------------------------------------|--|
| R80.1 | Congenital myaesthetic syndrome WES or medium panel | Singleton                 | Small variants  | Panel of genes or loci | Congenital myaesthetic syndrome (232) | WES or Medium Panel                            |
| R80.2 | Congenital myaesthetic syndrome                     | Singleton                 | Exon level CNVs | Panel of genes or loci | Congenital myaesthetic 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 Congenital malformation and dysmorphism syndromes – likely monogenic tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations not typical of disorders covered by the panel

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation following assessment by a Neurologist 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                                    | Optional Family Structure | Scope(s)        | Target Type            | Target Name               | Method   |
|-------|---|---------------------------|-----------------|------------------------|---------------------------|--|
| R81.1 | Congenital myopathy WES or medium panel | Singleton                 | Small variants  | Panel of genes or loci | Congenital myopathy (225) | WES or Medium Panel                            |
| 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 dystrophy

### Testing Criteria

Clinical features that indicate a likely limb girdle muscular dystrophy

### Overlapping indications

- R79 Congenital muscular dystrophy or R89 Ultra-rare and atypical monogenic disorders tests should be used where features are atypical

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation following assessment by a Neurologist 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   | Optional Family Structure | Scope(s)        | Target Type            | Target Name                          | Method   |
|-------|--|---------------------------|-----------------|------------------------|--------------------------------------|--|
| R82.1 | Limb girdle muscular dystrophy WES or medium panel | Singleton                 | Small variants  | Panel of genes or loci | Limb girdle muscular dystrophy (185) | WES or Medium Panel                            |
| R82.2 | Limb girdle muscular dystrophy                     | Singleton                 | Exon level CNVs | Panel of genes or loci | Limb girdle muscular dystrophy (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                               | Optional Family Structure | Scope(s)        | Target Type            | Target Name          | Method   |
|--------|------------------------------------|---------------------------|-----------------|------------------------|----------------------|--|
| R371.1 | Malignant hyperthermia small panel | Singleton                 | Small variants  | Panel of genes or loci | RYR1, CACNA1S, STAC3 | Small panel (PanelApp number TBC)              |
| R371.2 | Malignant hyperthermia             | Singleton                 | Exon level CNVs | Panel of genes or loci | RYR1, CACNA1S, STAC3 | Exon level CNV detection by MLPA or equivalent |

## R83 Arthrogryposis

### Testing Criteria

Clinical features that indicate arthrogryposis of monogenic aetiology

### Overlapping indications

- R266 Neuromuscular arthrogryposis test should be used where a neuromuscular cause is confirmed

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation following assessment by a Neurologist or Clinical Geneticist and following serum CK estimation

### Requesting Specialties

- Clinical Genetics
- Neurology

### Specialist Service Group

- Neurology

### Associated Tests

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                                       | Optional 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

Please note that initially only WGS testing will be undertaken for R381 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are necessary.

Whilst this includes testing of 2 STRs, analysis is currently not optimal and therefore if these specific STRs are suspected this should be stated at referral to prompt additional testing where necessary

| Code   | Name                                  | Optional Family Structure | Scope(s)                              | Target Type            | Target Name                   | Method      |
|--------|---------------------------------------|---------------------------|---------------------------------------|------------------------|-------------------------------|-------------|
| R381.2 | Neuromuscular disorders WGS (phase 1) | Trio or singleton         | Exon level CNVs, Small variants; STRs | Panel of genes or loci | Neuromuscular disorders (465) | WGS         |
| R381.3 | AR_CAG; DMPK_CTG STR testing          | Singleton                 | STRs                                  | Single gene(s)         | AR_CAG; DPMK_CTG              | STR testing |

## R84 Cerebellar anomalies

### Testing Criteria

Likely monogenic cerebellar malformation, cerebellar or pontocerebellar hypoplasia or childhood-onset cerebellar atrophy

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation following MRI brain and assessment by a Neurologist or Clinical Geneticist

### Requesting Specialties

- Clinical Genetics
- Neurology

### Specialist Service Group

- Neurology

### Associated Tests

Please note that initially only WGS testing (plus microarray where indicated) will be undertaken for R84 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are necessary.

Whilst this includes testing of all STRs in the gene panel, analysis is currently not optimal and therefore if a specific STR is suspected this should be stated at referral to prompt additional testing where necessary

| Code  | Name   | Optional Family Structure | Scope(s)                              | Target Type            | Target Name  | Method      |
|-------|--|---------------------------|---------------------------------------|------------------------|--|-------------|
| R84.2 | Genomewide Microarray  | Singleton                 | Genomewide CNVs                       | Genomewide             | Genomewide   | Microarray  |
| R84.3 | Hereditary ataxia and cerebellar anomalies - childhood onset STR testing   | Singleton                 | STRs                                  | Panel of genes or loci | Hereditary ataxia and cerebellar anomalies - childhood onset (488) | STR testing |
| R84.4 | Hereditary ataxia and cerebellar anomalies - childhood onset WGS (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         |



## R85 Holoprosencephaly - NOT chromosomal

### Testing Criteria

Liveborn individuals with unexplained holoprosencephaly in whom a chromosomal cause has been excluded by microarray or equivalent

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation following chromosome microarray (which may have followed rapid aneuploidy screening)

### Requesting Specialties

- Clinical Genetics
- Neurology

### Specialist Service Group

- Neurology

### Associated Tests

| Code  | Name                            | Optional Family Structure | Scope(s)                        | Target Type            | Target Name            | Method |
|-------|---------------------------------|---------------------------|---------------------------------|------------------------|------------------------|--------|
| R85.2 | 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                        | Optional 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 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                                 | Optional 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                              | Optional 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   | Optional 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  $\geq 2$  NF2 associated features (meningioma, schwannoma, glioma, neurofibroma, posterior subcapsular lenticular opacities/cataract) OR
  - c.  $\geq 1$  of unilateral vestibular schwannoma, meningioma, schwannoma, glioma, neurofibroma, multiple meningiomas, posterior subcapsular lenticular opacities/cataract AND  $\geq 1$  first / second degree relative with a vestibular schwannoma OR
  - d. Multiple Meningiomas AND  $\geq 2$  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  $\geq 1$  FDR with Schwannomatosis
4. Schwannoma diagnosed <30years
5.  $\geq 2$  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                                   | Optional Family Structure | Scope(s)        | Target Type                                   | Target Name                           | Method             |
|--------|--|---------------------------|-----------------|---|---------------------------------------|--------------------|
| R221.1 | Familial tumours of the nervous system | Singleton                 | Small variants  | NF2, SMARCB1, LZTFL1, SMARCE1, SUFU and DGCR8 | Small panel to be created in PanelApp | Small panel        |
| R221.2 | Familial tumours of the nervous system | Singleton                 | Exon level CNVs | Single gene(s)                                | Small panel to be created in PanelApp | MLPA or equivalent |

## R222 Neurofibromatosis type 1

### Testing Criteria

Clinical diagnosis of NF1, as defined below, AND molecular diagnosis is required for management of the proband or for reproductive planning

Diagnosis requires two of:

1. At least 6 café au lait macules (at least 0.5cm in a child and 1.5cm in an adult)
2. At least 2 subcutaneous or cutaneous neurofibromas
3. Plexiform neurofibroma
4. Optic glioma
5. At least 2 Lisch nodules
6. Bony dysplasia (sphenoid wing, long bone bowing, pseudarthrosis)
7. Family history of NF1

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Overlapping indications

- R236 Pigmentary skin disorders test should be used where clinical features are atypical and a broader range of genes is potentially causative
- R27 Congenital malformation and dysmorphism syndromes – likely monogenic or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

### Where in Pathway

At a point where clinical management or reproductive planning require a molecular diagnosis

### Requesting Specialties

- Clinical Genetics
- Dermatology
- Neurology
- 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                       | Optional Family Structure | Scope(s)        | Target Type    | Target Name | Method                                     |
|--------|----------------------------|---------------------------|-----------------|----------------|-------------|--|
| R222.1 | NF1 Single gene sequencing | Singleton                 | Small variants  | Single gene(s) | NF1         | Single gene sequencing $\geq 10$ amplicons |
| R222.2 | NF1 MLPA or equivalent     | Singleton                 | Exon level CNVs | Single gene(s) | NF1         | MLPA or equivalent                         |



## R376 Segmental or atypical neurofibromatosis type 1 testing

### Testing Criteria

Clinical features suggestive of segmental or atypical neurofibromatosis type 1 or individuals with classical neurofibromatosis who have tested negative on gDNA analysis requiring cDNA analysis following discussion with highly specialised service

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

Following consultation with highly specialised service

### Requesting Specialties

- Clinical Genetics
- Neurology

### Specialist Service Group

- Neurology

### Associated Tests

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                                | Optional Family Structure | Scope(s)        | Target Type    | Target Name | Method                                |
|--------|-------------------------------------|---------------------------|-----------------|----------------|-------------|---------------------------------------|
| R376.1 | NF1 Single gene sequencing - mosaic | Singleton                 | Small variants  | Single gene(s) | NF1         | Single gene sequencing >=10 amplicons |
| R376.2 | NF1 MLPA or equivalent - mosaic     | Singleton                 | Exon level CNVs | Single gene(s) | NF1         | MLPA or equivalent                    |

## R228 Tuberous sclerosis

### Testing Criteria

Clinical features suggestive of tuberous sclerosis requiring molecular testing

Testing should be typically be targeted at those with one or more major features or two or more minor features:

1. Major features:
  - a. Hypomelanotic macules (at least 3 of at least 5 mm in diameter)
  - b. Angiofibromas (at least three) or fibrous cephalic plaque
  - c. Ungual fibromas (at least two)
  - d. Shagreen patch
  - e. Multiple retinal hamartomas
  - f. Cortical dysplasias characteristic of tuberous sclerosis such as tubers and cerebral white matter radial migration lines
  - g. Subependymal nodules
  - h. Subependymal giant cell astrocytoma
  - i. Cardiac rhabdomyomas
  - j. 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 Congenital malformation and dysmorphism syndromes – likely monogenic or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Fetal Medicine
- Nephrology
- Neurology
- Respiratory Medicine

### Specialist Service Group

- Neurology

### Associated Tests

Please note all the tests below will be undertaken for R228 Clinical Indication requests, unless clinical presentation and/or initial results indicate all tests are not necessary

| Code   | Name       | Optional Family Structure | Scope(s)       | Target Type | Target Name | Method      |
|--------|------------|---------------------------|----------------|-------------|-------------|-------------|
| R228.1 | TSC1; TSC2 | Singleton                 | Small variants | Small panel | TSC1; TSC2  | Small panel |

|        |                               |           |                 |                |            |                    |
|--------|-------------------------------|-----------|-----------------|----------------|------------|--------------------|
| R228.2 | TSC1; TSC2 MLPA or equivalent | Singleton | Exon level CNVs | Single gene(s) | TSC1; TSC2 | MLPA or equivalent |
|--------|-------------------------------|-----------|-----------------|----------------|------------|--------------------|

## R294 Ataxia telangiectasia - DNA repair testing

### Testing Criteria

1. Clinical features strongly suggestive of ataxia telangiectasia including elevated serum AFP levels, AND one or more of the following:
  - a. Progressive gait and truncal ataxia with onset between one and four years of age, OR
  - b. Ocular motor apraxia, OR
  - c. Ocular telangiectasia, OR
  - d. Chorea and dysarthria, OR
  - e. Immunodeficiency with frequent infections, OR
  - f. Malignancy (e.g. leukaemia and lymphoma, breast cancer, ovarian cancer gastric cancer, leiomyoma, sarcoma or melanoma), OR
2. Molecular findings suggestive of Fanconi anaemia or Bloom syndrome from genome, exome or other genomic analysis

### Overlapping indications

- R27 Congenital malformation and dysmorphism syndromes – likely monogenic, R89 Ultra-rare and atypical monogenic disorders or other broad genomic tests should typically be used except where the above criteria are fulfilled
- Prenatal diagnosis or cascade testing by chromosome breakage testing will be requested via R240 Diagnostic testing for known familial mutation(s)

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation

### Requesting Specialties

- Oncology
- Clinical Genetics
- Haematology
- Immunology

### Specialist Service Group

- Neurology

### Associated Tests

| Code   | Name                                 | Optional Family Structure | Scope(s)   | Target Type | Target Name | Method                    |
|--------|--------------------------------------|---------------------------|------------|-------------|-------------|---------------------------|
| R294.1 | Genomewide DNA repair defect testing | Singleton                 | DNA repair | Genomewide  | Genomewide  | DNA repair defect testing |

## R295 Ataxia telangiectasia - mutation testing

### Testing Criteria

Confirmed diagnosis of ataxia telangiectasia requiring mutation testing

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

After DNA repair testing

### Requesting Specialties

- Oncology
- Clinical Genetics
- Haematology
- Immunology

### Specialist Service Group

- Neurology

### Associated Tests

| Code   | Name                       | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                |
|--------|----------------------------|---------------------------|----------------|----------------|-------------|---------------------------------------|
| R295.1 | ATM Single gene sequencing | Singleton                 | Small variants | Single gene(s) | ATM         | Single gene sequencing >=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  | Optional Family Structure | Scope(s)        | Target Type            | Target Name                           | Method   |
|--------|---|---------------------------|-----------------|------------------------|---------------------------------------|--|
| R336.1 | Cerebral vascular malformations WES or medium panel | Singleton                 | Small variants  | Panel of genes or loci | Cerebral vascular malformations (147) | WES or Medium Panel                            |
| 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                          | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                |
|--------|-------------------------------|---------------------------|----------------|----------------|-------------|---------------------------------------|
| R337.1 | NOTCH3 Single gene sequencing | Singleton                 | Small variants | Single gene(s) | NOTCH3      | Single gene sequencing >=10 amplicons |

## R410 Myotonic dystrophy type 2 (DM2)

### Testing Criteria

1. Adult with muscle weakness, usually proximal, and one of the following:
  - a. Clinical Myotonia: of grip or on percussion
  - b. EMG evidence of myotonic discharges
  - c. Cataracts (fine dust like opacities on the outer layers of the lens that are highly coloured and iridescent, producing a “Christmas Tree” appearance)
  - d. Three or more supportive features (from list below)
  - e. Family History suggestive of autosomal dominant inheritance
2. **AND** DM1 excluded first if the clinical presentation/Family history could easily fit DM1
3. **OR** Family history of mutation positive DM2

Additional supportive features:

- Elevated serum CK
- Insulin-insensitive type 2 diabetes
- Testicular failure
- Cardiac conduction defects
- Low serum IgG or IgM
- Muscle biopsy showing atrophic fibres and proliferation of fibres with central nuclei
- Excessive daytime sleepiness
- Mildly elevated liver function tests (LFT)
- Muscle pain

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Overlapping indications

- R72 Myotonic dystrophy type 1 should be used prior to this indication unless there is clinical suspicion of myotonic dystrophy type 2
- R381 Other rare neuromuscular disorders should be used where clinical features are atypical and a broader range of genes are potentially causative

### Where in Pathway

At presentation, following a normal test for Myotonic dystrophy type 1, unless there is clinical suspicion of myotonic dystrophy type 2

### Requesting Specialties

- Clinical Genetics
- Neurology

### Specialist Service Group

- Neurology

### Associated Tests

| Code   | Name                    | Optional Family Structure | Scope(s)             | Target Type    | Target Name | Method      |
|--------|-------------------------|---------------------------|----------------------|----------------|-------------|-------------|
| R410.1 | CNBP (ZNF9) STR testing | Singleton                 | Short tandem repeats | Single gene(s) | CNBP (ZNF9) | STR testing |



## 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                                 | Optional Family Structure | Scope(s)        | Target Type            | Target Name                        | Method   |
|--------|--------------------------------------|---------------------------|-----------------|------------------------|------------------------------------|--|
| R419.1 | Acute Rhabdomyolysis<br>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 conditions:

- R27 Congenital malformation and dysmorphism syndromes – likely monogenic or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

#### Where in Pathway

At presentation, or when clinical management decision depending on molecular diagnosis is required

#### Requesting Specialties

- Clinical Genetics
- Nephrology

#### Specialist Service Group

- Renal

#### Associated Tests

| Code   | Name                               | Optional Family Structure | Scope(s)                        | Target Type            | Target Name                | Method |
|--------|------------------------------------|---------------------------|---------------------------------|------------------------|----------------------------|--------|
| R193.4 | 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 Congenital malformation and dysmorphism syndromes – likely monogenic or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations
- R196 CFHR5 nephropathy test should be used as a first line test in patients of Cypriot ancestry with haematuria

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation

### Requesting Specialties

- Audiology
- Clinical Genetics
- Nephrology
- Ophthalmology
- 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                   | Optional Family Structure | Scope(s)        | Target Type            | Target Name     | Method   |
|--------|------------------------|---------------------------|-----------------|------------------------|-----------------|--|
| R194.1 | Haematuria Small panel | Singleton                 | Small variants  | Panel of genes or loci | Haematuria (99) | Small panel                                    |
| 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  | Optional Family Structure | Scope(s)        | Target Type            | Target Name                     | Method   |
|--------|---|---------------------------|-----------------|------------------------|---------------------------------|--|
| R195.1 | Proteinuric renal disease WES or medium panel | Singleton                 | Small variants  | Panel of genes or loci | Proteinuric renal disease (106) | WES or Medium Panel                            |
| 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                     | Optional Family Structure | Scope(s)        | Target Type    | Target Name | Method             |
|--------|--------------------------|---------------------------|-----------------|----------------|-------------|--------------------|
| R196.1 | CFHR5 MLPA or equivalent | Singleton                 | Exon level CNVs | Single gene(s) | CFHR5       | MLPA or equivalent |

## R197 Membranoproliferative glomerulonephritis including C3 glomerulopathy

### Testing Criteria

Idiopathic membranoproliferative glomerulonephritis (MPGN) or C3 glomerulopathy with onset before the age of 18, together with one of:

1. Family history of MPGN or unexplained end-stage renal disease, OR
2. Renal transplant is being considered, OR
3. Patient is being considered for complement inhibitory therapies

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation, or at a time when management requires a molecular diagnosis 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  | Optional Family Structure | Scope(s)        | Target Type            | Target Name                                   | Method             |
|--------|---|---------------------------|-----------------|------------------------|---|--------------------|
| R197.1 | Membranoproliferative glomerulonephritis<br>Small panel | Singleton                 | Small variants  | Panel of genes or loci | Membranoproliferative glomerulonephritis (83) | Small panel        |
| R197.2 | CFH; CFHR MLPA or equivalent                            | Singleton                 | Exon level CNVs | Single gene(s)         | CFH; CFHR                                     | MLPA or equivalent |

## R198 Renal tubulopathies

### Testing Criteria

Patients with a primary renal tubulopathy presenting as one of the following conditions:

1. Hypokalaemic alkalosis with normal or low blood pressure (e.g. Bartter/Gitelman syndromes), OR
2. Hypokalaemic alkalosis with elevated blood pressure (e.g. Liddle syndrome), OR
3. Hyperkalaemic acidosis with low/normal BP (PHA type 1), OR
4. Hyperkalaemic acidosis with elevated BP (PHA type 2), OR
5. Hypokalaemic acidosis (pRTA and renal Fanconi syndromes), OR
6. Hypomagnesaemia, OR
7. Nephrogenic diabetes insipidus, OR
8. Other rare types of renal tubulopathy seen in an expert center

**NOTE: Patients with electrolyte imbalance secondary to non-renal processes should not be tested under this indication**

### Overlapping indications

- R183 Glucocorticoid-remediable aldosteronism (GRA)
- R344 Primary hyperaldosteronism – KCNJ5
- R256 Nephrocalcinosis or nephrolithiasis

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Nephrology

### Specialist Service Group

- Renal

### Associated Tests

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                                    | Optional Family Structure | Scope(s)        | Target Type            | Target Name               | Method   |
|--------|---|---------------------------|-----------------|------------------------|---------------------------|--|
| R198.1 | Renal tubulopathies WES or medium panel | Singleton                 | Small variants  | Panel of genes or loci | Renal tubulopathies (292) | WES or Medium Panel                            |
| 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 Congenital malformation and dysmorphism syndromes – likely monogenic or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Nephrology
- Paediatrics

### Specialist Service Group

- Core

### Associated Tests

| Code   | Name                  | Optional Family Structure | Scope(s)        | Target Type | Target Name | Method     |
|--------|-----------------------|---------------------------|-----------------|-------------|-------------|------------|
| R199.1 | Genomewide Microarray | Singleton                 | Genomewide CNVs | Genomewide  | Genomewide  | Microarray |



## R201 Atypical haemolytic uraemic syndrome

### Testing Criteria

Acute renal failure AND thrombocytopenia AND microangiopathic haemolytic anaemia (Coombs test negative), in a patient being considered for complement inhibitory therapies

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation 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  | Optional Family Structure | Scope(s)           | Target Type            | Target Name                                | Method                |
|--------|---|---------------------------|--------------------|------------------------|--|-----------------------|
| R201.1 | Atypical haemolytic uraemic syndrome<br>Small panel   | Singleton                 | Small variants     | Panel of genes or loci | Atypical haemolytic uraemic syndrome (139) | Small panel           |
| R201.3 | CFH; CFHR1;<br>CFHR3; CD46; CFI<br>MLPA or equivalent | Singleton                 | Exon level<br>CNVs | Single gene(s)         | CFH; CFHR1; CFHR3; CD46;<br>CFI            | MLPA or<br>equivalent |

## R202 Tubulointerstitial kidney disease

### Testing Criteria

1. Renal impairment caused by tubulointerstitial fibrosis with no glomerular lesion, with no identifiable cause, often associated with medullary cysts, hyperuricaemia or gout, AND
  2. A first degree relative with TIKD or unexplained end-stage renal disease
- Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Nephrology

### Specialist Service Group

- Renal

### Associated Tests

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   | Optional Family Structure | Scope(s)        | Target Type            | Target Name                             | Method   |
|--------|--|---------------------------|-----------------|------------------------|---|--|
| R202.1 | Tubulointerstitial kidney disease<br>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  | Optional Family Structure | Scope(s)        | Target Type            | Target Name       | Method   |
|--------|---|---------------------------|-----------------|------------------------|-------------------|--|
| R204.1 | Hereditary systemic amyloidosis Small panel | Singleton                 | Small variants  | Panel of genes or loci | Amyloidosis (502) | Small panel                                    |
| 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   | Optional Family Structure | Scope(s)        | Target Type            | Target Name                               | Method   |
|--------|--|---------------------------|-----------------|------------------------|---|--|
| R256.1 | Nephrocalcinosis or nephrolithiasis<br>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 paediatric onset end-stage renal disease

### Testing Criteria

End-stage renal disease developing under the age of 18, with no identifiable cause detectable by renal biopsy, biochemistry, imaging or clinical assessment

Use of this test in young adults over the age of 18 may be appropriate after expert clinical review, if there is strong clinical suspicion of a monogenic disorder

Overlapping conditions:

- R27 Congenital malformation and dysmorphism syndromes – likely monogenic or R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or syndromic presentations

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Nephrology

### Specialist Service Group

- Renal

### Associated Tests

| Code   | Name   | Optional Family Structure | Scope(s)                        | Target Type            | Target Name  | Method |
|--------|--|---------------------------|---------------------------------|------------------------|--|--------|
| R257.2 | Unexplained paediatric onset end-stage renal disease WGS (phase 2) | Trio or singleton         | Exon level CNVs, Small variants | Panel of genes or loci | Unexplained paediatric onset end-stage renal disease (678) | WGS    |

## Part XIX. Respiratory

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### R184 Cystic fibrosis diagnostic test

#### Testing Criteria

Test in an individual clinically likely to be affected with cystic fibrosis:

1. Child with clinical suspicion of CF (e.g. recurrent chest infections, failure to thrive, fat malabsorption, neonatal history of meconium ileus), AND
  - a. A not normal sweat test performed in a recognised experienced test centre/laboratory (i.e. sweat chloride  $\geq 30\text{mM}$  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  $\geq 30\text{mM}$  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  $\geq 30\text{mM}$  with sufficient sweat obtained), OR
  - b. Sweat testing not practical, and all other causes excluded
4. Male infertility associated with obstructive azoospermia, AND
  - a. CBAVD (or isolated CUAVD) diagnosed from expert clinical examination, OR
  - b. CBAVD identified at incidental herniotomy
5. Fetal echogenic bowel as bright as bone on 2<sup>nd</sup> trimester scan, AND
  - a. Both parents not available for carrier testing [if both parents are available, Cystic fibrosis carrier testing should be used instead of an invasive prenatal test], AND
  - b. Isolated anomaly or <2 other common fetal markers, AND
  - c. Other more common causes excluded (e.g. IUGR, placental failure, earlier bleeding, infection, raised aneuploidy markers)
6. Dilated fetal bowel on 2<sup>nd</sup> trimester scan

Referrals for testing will be triaged by the Genomic 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 mutation 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

| Code   | Name                           | Optional Family Structure | Scope(s)        | Target Type    | Target Name | Method                                     |
|--------|--------------------------------|---------------------------|-----------------|----------------|-------------|--|
| R184.1 | CFTR Targeted mutation testing | Singleton                 | Small variants  | Single gene(s) | CFTR        | Targeted mutation testing                  |
| R184.2 | CFTR Single gene sequencing    | Singleton                 | Small variants  | Single gene(s) | CFTR        | Single gene sequencing $\geq 10$ amplicons |
| R184.3 | CFTR MLPA or equivalent        | Singleton                 | Exon level CNVs | Single gene(s) | CFTR        | MLPA or equivalent                         |

## R185 Cystic fibrosis carrier testing

### Testing Criteria

1. Prospective egg or sperm donor
2. Family history of CF in close relative (up to 4<sup>th</sup> degree, i.e. in 1<sup>st</sup> 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 (1<sup>st</sup> 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

### Specialist Service Group

- Core

### Associated Tests

| Code   | Name                           | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                    |
|--------|--------------------------------|---------------------------|----------------|----------------|-------------|---------------------------|
| R185.1 | CFTR Targeted mutation testing | Singleton                 | Small variants | Single gene(s) | CFTR        | Targeted mutation testing |



## R253 Cystic fibrosis newborn screening follow-up

### Testing Criteria

Positive IRT test on newborn screening, according to definition in the National Standard Protocol for Cystic Fibrosis

### Where in Pathway

According to the National Standard Protocol for Cystic Fibrosis

### Requesting Specialties

- Other

### Specialist Service Group

- Screening

### Associated Tests

| Code   | Name   | Optional Family Structure | Scope(s)       | Target Type     | Target Name                | Method                    |
|--------|--|---------------------------|----------------|-----------------|----------------------------|---------------------------|
| R253.1 | CFTR 4 commonest mutations Targeted mutation testing | Singleton                 | Small variants | Single interval | CFTR 4 commonest mutations | Targeted mutation testing |

## R333 Central congenital hypoventilation

### Testing Criteria

Clinical features suggestive of congenital central hypoventilation syndrome:

1. Central alveolar hypoventilation, AND
2. Absence of primary lung, cardiac or neuromuscular cause or identifiable brainstem lesion, WITH OR WITHOUT the following additional PHOX2B-related features:
  - a. Hirschsprung disease, OR
  - b. Neuroblastoma or other neural crest tumour, OR
  - c. Autonomic dysfunction, for example affecting the cardiovascular system, gastrointestinal tract, sweating or temperature control

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Neonatology
- Neurology
- Respiratory Medicine

### Specialist Service Group

- Respiratory

### Associated Tests

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                          | Optional Family Structure | Scope(s)        | Target Type    | Target Name | Method   |
|--------|-------------------------------|---------------------------|-----------------|----------------|-------------|--|
| R333.1 | PHOX2B STR testing            | Singleton                 | STRs            | Single gene(s) | PHOX2B      | STR testing                                    |
| R333.2 | PHOX2B Single gene sequencing | Singleton                 | Small variants  | Single gene(s) | PHOX2B      | Single gene sequencing $\geq 10$ amplicons     |
| 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  | Optional Family Structure | Scope(s)        | Target Type            | Target Name                              | Method   |
|--------|---|---------------------------|-----------------|------------------------|--|--|
| R139.1 | Laterality disorders and isomerism<br>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   | Optional Family Structure | Scope(s)        | Target Type            | Target Name                                  | Method   |
|--------|--|---------------------------|-----------------|------------------------|--|--|
| R186.1 | Hereditary haemorrhagic telangiectasia Small panel | Singleton                 | Small variants  | Panel of genes or loci | Hereditary haemorrhagic telangiectasia (123) | Small panel                                    |
| 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  | Optional Family Structure | Scope(s)        | Target Type            | Target Name                                   | Method   |
|--------|---|---------------------------|-----------------|------------------------|---|--|
| R188.1 | Pulmonary arterial hypertension Small panel | Singleton                 | Small variants  | Panel of genes or loci | Pulmonary arterial hypertension (193)         | Small panel                                    |
| R188.2 | Pulmonary arterial hypertension             | Singleton                 | Exon level CNVs | Panel of genes or loci | Pulmonary arterial hypertension (193) & BMPR2 | 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   | Optional Family Structure | Scope(s)        | Target Type            | Target Name  | Method   |
|--------|--|---------------------------|-----------------|------------------------|--|--|
| R189.1 | Respiratory ciliopathies including non-CF bronchiectasis WES or medium panel | Singleton                 | Small variants  | Panel of genes or loci | Respiratory ciliopathies including non-CF bronchiectasis (550) | WES or Medium Panel                            |
| 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                                | Optional Family Structure | Scope(s)        | Target Type            | Target Name                   | Method   |
|--------|-------------------------------------|---------------------------|-----------------|------------------------|-------------------------------|--|
| R190.1 | Pneumothorax – familial Small panel | Singleton                 | Small variants  | Panel of genes or loci | Pneumothorax – familial (105) | Small panel                                    |
| R190.2 | 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
- Primary Care

### Specialist Service Group

- Respiratory

### Associated Tests

| Code   | Name   | Optional Family Structure | Scope(s)       | Target Type     | Target Name               | Method                    |
|--------|--|---------------------------|----------------|-----------------|---------------------------|---------------------------|
| R191.1 | SERPINA1 common mutations<br>Targeted mutation testing | Singleton                 | Small variants | Single interval | SERPINA1 common mutations | Targeted mutation testing |



## R192 Surfactant deficiency

### Testing Criteria

1. Neonatal respiratory insufficiency of disproportionate severity for advanced gestation, with clinical and X-ray features consistent with pulmonary surfactant deficiency, AND
  2. No other obvious cause for respiratory distress e.g. no difficult delivery, no infection, no prematurity
- With or without a known family history of surfactant deficiency

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Neonatology
- Respiratory Medicine

### Specialist Service Group

- Respiratory

### Associated Tests

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                              | Optional Family Structure | Scope(s)        | Target Type            | Target Name                 | Method   |
|--------|-----------------------------------|---------------------------|-----------------|------------------------|-----------------------------|--|
| R192.1 | Surfactant deficiency Small panel | Singleton                 | Small variants  | Panel of genes or loci | Surfactant deficiency (551) | Small panel                                    |
| 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                         | Optional Family Structure | Scope(s)        | Target Type            | Target Name | Method   |
|--------|------------------------------|---------------------------|-----------------|------------------------|-------------|--|
| R330.1 | FOXF1 Single gene sequencing | Singleton                 | Small variants  | Single gene(s)         | FOXF1       | Single gene sequencing $\geq 10$ amplicons     |
| R330.2 | FOXF1                        | Singleton                 | Exon level CNVs | Panel of genes or loci | FOXF1       | 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.

### Overlapping indications

### 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                        | Optional 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 |

## Part XX. Dermatology

### R110 Segmental overgrowth disorders

#### Testing Criteria

Clinical features suggestive of a segmental overgrowth disorder. Features may include:

1. Congenital or early onset segmental overgrowth (which may affect the brain only, i.e. megalencephaly)
2. Vascular malformations (capillary, venous, lymphatic or combinations)
3. Characteristic cutaneous features (for example epidermal naevi or connective tissue naevi)
4. Brain malformations (for example hydrocephalus or cortical malformations)
5. Additional dysmorphism (for example polydactyly)

#### Overlapping indications

- R27 Congenital malformation and dysmorphism syndromes – likely monogenic or R89 Ultra-rare and atypical monogenic disorders tests should be considered in overlapping features are present but germline mutation is considered likely

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

**NOTE:** Many of these disorders are anticipated to be mosaic and sample type and test technology need to take account of this e.g. in planning coverage of NGS assay

#### Where in Pathway

At presentation

#### Requesting Specialties

- Clinical Genetics

#### Specialist Service Group

- 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                                       | Optional Family Structure | Scope(s)        | Target Type            | Target Name                         | Method   |
|--------|--|---------------------------|-----------------|------------------------|-------------------------------------|--|
| R110.1 | Segmental overgrowth disorders Small panel | Singleton                 | Small variants  | Panel of genes or loci | Segmental overgrowth disorders (98) | Small panel                                    |
| R110.2 | Segmental overgrowth disorders             | Singleton                 | Exon level CNVs | Panel of genes or loci | Segmental overgrowth disorders (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                                     | Optional 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  | Optional Family Structure | Scope(s)        | Target Type            | Target Name   | Method   |
|--------|---|---------------------------|-----------------|------------------------|---|--|
| R164.1 | Epidermolysis bullosa and congenital skin fragility WES or medium panel | Singleton                 | Small variants  | Panel of genes or loci | Epidermolysis bullosa and congenital skin fragility (554) | WES or Medium Panel                            |
| 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  | Optional 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  | Optional 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  | Optional Family Structure | Scope(s)        | Target Type            | Target Name   | Method   |
|--------|---|---------------------------|-----------------|------------------------|---|--|
| R167.1 | Autosomal recessive primary hypertrophic osteoarthropathy Small panel | Singleton                 | Small variants  | Panel of genes or loci | Autosomal recessive primary hypertrophic osteoarthropathy (557) | Small panel                                    |
| 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 Congenital malformation and dysmorphism syndromes – likely monogenic or
- R89 Ultra-rare and atypical monogenic disorders tests should be used in individuals with congenital malformations, dysmorphism or other complex or less recognisable presentations

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

Skin biopsy for complementation testing (specialist DNA repair test) is likely to be required in many patients to confirm the results of the panel test; this can be carried out in parallel with or after the genetic panel test, usually as part of assessment in the Highly Specialised service for xeroderma pigmentosum.

### Requesting Specialties

- Clinical Genetics
- Dermatology

### Specialist Service Group

- 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  | Optional Family Structure | Scope(s)        | Target Type            | Target Name  | Method   |
|--------|---|---------------------------|-----------------|------------------------|--|--|
| R227.1 | Xeroderma pigmentosum, Trichothiodystrophy or Cockayne syndrome Small panel | Singleton                 | Small variants  | Panel of genes or loci | Xeroderma pigmentosum, Trichothiodystrophy or Cockayne syndrome (77) | Small panel                                    |
| R227.2 | Genomewide DNA repair defect testing  | Singleton                 | DNA repair      | Genomewide             | Genomewide   | DNA repair defect testing                      |
| 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   | Optional Family Structure | Scope(s)        | Target Type            | Target Name                                  | Method             |
|--------|--|---------------------------|-----------------|------------------------|--|--------------------|
| R230.1 | Multiple monogenic benign skin tumours Small panel | Singleton                 | Small variants  | Panel of genes or loci | Multiple monogenic benign skin tumours (558) | Small panel        |
| R230.2 | FLCN MLPA or equivalent                            | Singleton                 | Exon level CNVs | Single gene(s)         | FLCN   | MLPA or equivalent |

## R236 Pigmentary skin disorders

### Testing Criteria

1. Multiple café-au-lait macules where neurofibromatosis type 1 (NF1) has been excluded either clinically or on genetic testing, OR
2. Poikiloderma with a likely genetic cause, OR
3. Other forms of reticulate, patchy or speckled hypo- or hyperpigmentation with a likely genetic cause

### Overlapping indications

- R222 Neurofibromatosis type 1 test should be used where features are typical of this condition
- R343 Chromosomal mosaicism – microarray test should be used where this is the likely diagnosis
- R327 Mosaic skin disorders – deep sequencing test should be used where the likely cause is a mosaic genetic change, as the technology applied to the mosaic disorders will be more sensitive to these than the panel test designed to detect germline disorders

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Dermatology

### Specialist Service Group

- 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   | Optional 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   | Optional Family Structure | Scope(s)        | Target Type            | Target Name  | Method   |
|--------|--|---------------------------|-----------------|------------------------|--|--|
| R237.1 | Cutaneous photosensitivity with a likely genetic cause Small panel | Singleton                 | Small variants  | Panel of genes or loci | Cutaneous photosensitivity with a likely genetic cause (560) | Small panel                                    |
| 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                         | Optional Family Structure | Scope(s)       | Target Type    | Target Name | Method                                     |
|--------|------------------------------|---------------------------|----------------|----------------|-------------|--|
| R239.1 | IKBKG Single gene sequencing | Singleton                 | Small variants | Single gene(s) | IKBKG       | Single gene sequencing $\geq 10$ amplicons |

## R255 Epidermodysplasia verruciformis

### Testing Criteria

Severe widespread infection with human papillomavirus in the absence of detectable immunodeficiency, with or without squamous cell carcinoma

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

At presentation

### Requesting Specialties

- Clinical Genetics
- Dermatology

### Specialist Service Group

- 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  | Optional Family Structure | Scope(s)        | Target Type            | Target Name                           | Method   |
|--------|---|---------------------------|-----------------|------------------------|---------------------------------------|--|
| R255.1 | Epidermodysplasia verruciformis Small panel | Singleton                 | Small variants  | Panel of genes or loci | Epidermodysplasia verruciformis (562) | Small panel                                    |
| 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  | Optional 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  | Optional Family Structure | Scope(s)        | Target Type            | Target Name                                   | Method   |
|--------|---|---------------------------|-----------------|------------------------|---|--|
| R327.1 | Mosaic skin disorders – deep sequencing<br>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   | Optional 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                                      | Optional Family Structure | Scope(s)        | Target Type | Target Name | Method   |
|--------|---|---------------------------|-----------------|-------------|-------------|--|
| R424.1 | Subcutaneous panniculitis T-cell lymphoma | Singleton                 | Small variants  | Single gene | HAVCR2      | Single gene sequencing <=10 amplicons          |
| R424.2 | Subcutaneous panniculitis T-cell lymphoma | Singleton                 | Exon level CNVs | Single gene | HAVCR2      | Exon level CNV detection by MLPA or equivalent |

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 non-syndromic 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                                      | Optional 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   | Optional Family Structure | Scope(s)       | Target Type     | Target Name     | Method                    |
|--------|--|---------------------------|----------------|-----------------|-----------------|---------------------------|
| R240.1 | Specific target<br>Targeted mutation testing | Singleton                 | Small variants | Single interval | Specific Target | Targeted mutation testing |

## R242 Predictive testing for known familial mutation(s)

### Testing Criteria

Patient requiring predictive testing for specific disorder where the familial mutation(s) have already been identified in a relative

### Where in Pathway

As dictated by clinical situation

### Requesting Specialties

- Clinical Genetics

### Specialist Service Group

- Core or Specialised; depending on the clinical scenario

### Associated Tests

| Code   | Name                                      | Optional Family Structure | Scope(s)       | Target Type     | Target Name     | Method                    |
|--------|---|---------------------------|----------------|-----------------|-----------------|---------------------------|
| R242.1 | Specific target Targeted mutation testing | Singleton                 | Small variants | Single interval | Specific Target | Targeted mutation testing |

## R244 Carrier testing for known familial mutation(s)

### Testing Criteria

Patient requiring carrier testing for specific disorder where the familial mutation(s) have already been identified in a relative

The range of specialties who will request this test will depend on the disorder in question

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

As dictated by clinical situation

### Requesting Specialties

- Clinical Genetics

### Specialist Service Group

- Core or Specialised; depending on the clinical scenario

### Associated Tests

| Code   | Name   | Optional Family Structure | Scope(s)       | Target Type     | Target Name     | Method                    |
|--------|--|---------------------------|----------------|-----------------|-----------------|---------------------------|
| R244.1 | Specific target<br>Targeted mutation testing | Singleton                 | Small variants | Single interval | Specific Target | Targeted mutation testing |

## R246 Carrier testing at population risk for partners of known carriers of nationally agreed autosomal recessive disorders

### 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 | <i>GJB2</i> | 1 in 50 in European populations |
| Gaucher disease                  | <i>GBA</i>  | 1 in 25 in Ashkenazi population |
| Phenylketonuria                  | <i>PAH</i>  | 1 in 50 in European populations |
| Tay-Sachs disease                | <i>HEXA</i> | 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                                      | Optional Family Structure | Scope(s)       | Target Type    | Target Name          | Method                                     |
|--------|---|---------------------------|----------------|----------------|----------------------|--|
| R246.1 | Specific target<br>Single gene sequencing | Singleton                 | Small variants | Single gene(s) | Relevant single gene | Single gene sequencing $\geq 10$ 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                        | Optional Family Structure     | Scope(s) | Target Type | Target Name | Method           |
|--------|-----------------------------|-------------------------------|----------|-------------|-------------|------------------|
| R321.1 | Genomewide Identity testing | Multiple affected individuals | Identity | Genomewide  | Genomewide  | Identity testing |

## R320 Invasive prenatal diagnosis requiring fetal sexing

### Testing Criteria

Pregnancy requiring sexing on invasive prenatal sample to inform management

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

As appropriate

### Requesting Specialties

- Clinical Genetics
- Genomics laboratory

### Specialist Service Group

- Core

### Associated Tests

| Code   | Name                      | Optional Family Structure | Scope(s)   | Target Type | Target Name | Method                    |
|--------|---------------------------|---------------------------|------------|-------------|-------------|---------------------------|
| R320.1 | Sex determination testing | Singleton                 | Aneuploidy | Genomewide  | Other       | Common aneuploidy testing |

## R263 Confirmation of uniparental disomy

### Testing Criteria

Confirmation of probable UPD identified by methylation testing at imprinted loci and UPD identified via other routes, for example SNP array, exome or genome sequencing. This could include testing for mosaic genome-wide UPD

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

As appropriate

### Requesting Specialties

- Clinical Genetics
- Genomics laboratory

### Specialist Service Group

- Core or Specialised; depending on the clinical scenario

### Associated Tests

| Code   | Name                        | Optional Family Structure | Scope(s)       | Target Type     | Target Name                     | Method      |
|--------|-----------------------------|---------------------------|----------------|-----------------|---------------------------------|-------------|
| R263.1 | Specific target UPD testing | Trio                      | Small variants | Single interval | As relevant to clinical setting | UPD testing |

## R264 Identity testing

### Testing Criteria

Where biological relationships need to be determined to guide diagnostic interpretation or alter advice

### Where in Pathway

N/A

### Requesting Specialties

- Clinical Genetics
- Genomics laboratory

### Specialist Service Group

- Core

### Associated Tests

| Code   | Name             | Optional Family Structure | Scope(s) | Target Type | Target Name | Method           |
|--------|------------------|---------------------------|----------|-------------|-------------|------------------|
| R264.1 | Identity testing | Singleton                 | Identity | Other       | Other       | Identity testing |

## R111 X-inactivation testing

### Testing Criteria

Clinical setting where X-inactivation testing will alter clinical management and/or assist reclassification of variant using the ACMG guidelines

### Where in Pathway

After MDT discussion

### Requesting Specialties

- Clinical Genetics

### Specialist Service Group

- Core or Specialised; depending on the clinical scenario

### Associated Tests

| Code   | Name                   | Optional Family Structure | Scope(s)    | Target Type     | Target Name | Method                 |
|--------|------------------------|---------------------------|-------------|-----------------|-------------|------------------------|
| R111.1 | X-inactivation testing | Singleton                 | Methylation | Single interval | Other       | X-inactivation testing |

## R370 Validation test

### Testing Criteria

Confirmation using a second technique where required for diagnostic reporting.

Examples of settings in which this indication may be used include

- variants where QC metrics indicate that confirmation with a second technique are necessary
- variant where the sample has passed outside an accredited pipeline and confirmation of sample identify is required

### Where in Pathway

Following primary test where required

### Requesting Specialties

- Clinical Genetics
- Genomics laboratory

### Specialist Service Group

- Core or Specialised; depending on the clinical scenario

### Associated Tests

| Code   | Name                                      | Optional Family Structure | Scope(s)       | Target Type     | Target Name     | Method                    |
|--------|---|---------------------------|----------------|-----------------|-----------------|---------------------------|
| R370.1 | Specific target Targeted mutation testing | Singleton                 | Small variants | Single interval | Specific Target | Targeted mutation testing |

## R375 Family follow-up testing to aid variant interpretation

### Testing Criteria

Family follow-up testing to aid variant interpretation

### Where in Pathway

Where requested by the laboratory

### Requesting Specialties

- Clinical Genetics
- Other

### Specialist Service Group

- Core or Specialised; depending on the clinical scenario

### Associated Tests

| Code   | Name   | Optional Family Structure | Scope(s)       | Target Type     | Target Name     | Method                    |
|--------|--|---------------------------|----------------|-----------------|-----------------|---------------------------|
| R375.1 | Specific target<br>Targeted mutation testing | Singleton                 | Small variants | Single interval | Specific Target | Targeted mutation testing |



## R387 Reanalysis of existing data

### Testing Criteria

Reanalysis of data which has previously been interpreted and reported is required, due to:

1. New clinical information or clinical events which would substantially change the relevant genomic target, OR
2. Sufficient time has passed since the initial analysis that new gene discovery will have substantially increased the relevant genomic target (national approach to be confirmed), OR
3. A technical or scientific advance requires reanalysis of a group of tests to detect an important new source of actionable diagnoses (national approach to be confirmed)

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

Following discussion with the genomics laboratory to ensure stored data is suitable for reanalysis; the national approach to defining events which should trigger analysis remains to be confirmed

### Requesting Specialties

- Clinical Genetics
- Genomics laboratory

### Specialist Service Group

- Core or Specialised; depending on the clinical scenario

### Associated Tests

| Code   | Name                        | Optional 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                         | Optional Family Structure | Scope(s)         | Target Type | Target Name                                | Method |
|--------|------------------------------|---------------------------|------------------|-------------|--|--------|
| R296.1 | Specific target RNA analysis | Singleton                 | Complex variants | Other       | As dictated by variant under investigation | Other  |

## R346 DNA to be stored

### Testing Criteria

To be requested where genetic testing is likely to be required in future, but further information or discussion is needed before a test request is made

### Where in Pathway

At any time, including where a sample is available e.g. because phlebotomy is being undertaken for other investigations and a future genetic test is likely to be required

### Requesting Specialties

- Clinical Genetics
- Other

### Specialist Service Group

- Core

### Associated Tests

| Code   | Name        | Optional Family Structure | Scope(s) | Target Type | Target Name                        | Method |
|--------|-------------|---------------------------|----------|-------------|------------------------------------|--------|
| R346.1 | DNA Storage | Singleton                 | Other    | Other       | No target identified at this stage | Other  |

## R373 RNA to be stored

### Testing Criteria

To be requested where RNA testing is likely to be required in future, but further information or discussion is needed before a test request is made

### Where in Pathway

Following discussion with the laboratory

### Requesting Specialties

- Clinical Genetics
- Other

### Specialist Service Group

- Core

### Associated Tests

| Code   | Name        | Optional Family Structure | Scope(s) | Target Type | Target Name                        | Method |
|--------|-------------|---------------------------|----------|-------------|------------------------------------|--------|
| R373.1 | RNA Storage | Singleton                 | Other    | Other       | No target identified at this stage | Other  |

## R322 Skin fibroblasts to be cultured and stored

### Testing Criteria

Skin fibroblast sample requiring culture and storage for potential future testing

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

As appropriate

### Requesting Specialties

- Clinical Genetics
- Dermatology
- Metabolic Medicine
- Neurology
- Other

### Specialist Service Group

- Core

### Associated Tests

| Code   | Name                                | Optional Family Structure | Scope(s) | Target Type | Target Name                        | Method |
|--------|-------------------------------------|---------------------------|----------|-------------|------------------------------------|--------|
| R322.1 | Skin fibroblast culture and storage | Singleton                 | Other    | Other       | No target identified at this stage | Other  |

## R374 Other sample to be stored

### Testing Criteria

To be requested where testing of other sample types (for example, lymphocyte culture) is likely to be required in future, but further information or discussion is needed before a test request is made

### Overlapping indications

- R346 DNA to be stored, R373 RNA to be stored and R322 Skin fibroblasts to be cultured and stored should be used instead where relevant

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

Following discussion with the laboratory

### Requesting Specialties

- Clinical Genetics
- Other

### Specialist Service Group

- Core

### Associated Tests

| Code   | Name                 | Optional Family Structure | Scope(s) | Target Type | Target Name                        | Method |
|--------|----------------------|---------------------------|----------|-------------|------------------------------------|--------|
| R374.1 | Other sample storage | Singleton                 | Other    | Other       | No target identified at this stage | Other  |

## 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   | Optional Family Structure | Scope(s)             | Target Type    | Target Name              | Method      |
|--------|--|---------------------------|----------------------|----------------|--------------------------|-------------|
| R407.1 | Patient undergoing allogeneic haematopoietic stem cell transplantation STR testing | Singleton                 | Short tandem repeats | Single gene(s) | Relevant gene(s) or loci | STR testing |

## R409 Linkage testing for other recognisable Mendelian disorders

### Testing Criteria

Patients with a recognisable mendelian disorder where linkage testing will guide patient management (if informative), where linkage testing is not facilitated via an alternative clinical indication.

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

### Where in Pathway

As dictated by clinical situation

### Requesting Specialties

- Clinical Genetics
- Other

### Specialist Service Group

- Core or Specialised; depending on the clinical scenario

### Associated Tests

| Code   | Name   | Optional Family Structure     | Scope(s) | Target Type            | Target Name              | Method           |
|--------|--|-------------------------------|----------|------------------------|--------------------------|------------------|
| R409.1 | Linkage testing for other recognisable Mendelian disorders | Multiple affected individuals | Other    | Single gene(s) or loci | Relevant gene(s) or loci | Linkage analysis |



