The 100,000 Genomes Project
The North East and North Cumbria Genomic Medicine Centre

Rare Disease Recruitment
Cardiovascular disorders

Introduction & Eligibility Pack
Genomic Medicine and the 100,000 Genomes Project

New genomic technologies and knowledge – the ability to incorporate information encoded in DNA into clinical practice – is transforming medical practice. For many years this has been a small-scale enterprise, largely focussed on rare diseases and delivered by tertiary Genetics Services. This is changing rapidly, and this change is being driven by the 100,000 Genomes Project delivered by a network of thirteen NHS Genomic Medicine Centres (GMCs) sited within NHS hospital trusts across England.

One key reason for creating a national network of GMCs was to find a way of delivering the 100,000 Genomes Project. This ground-breaking project is currently the Department of Health’s largest and most high-profile development, and aims to deliver 100,000 whole genome sequences (WGSs) into routine clinical practice. It is effectively a world-leading test-case for introducing whole genome sequencing into routine clinical care pathways. This has the chance to revolutionise clinical care, and is driving the development of personalised healthcare.

One large component of the 100,000 Genomes Project is to introduce whole genome sequencing into routine NHS health care in order to improve rare disease diagnosis and detect clinically relevant acquired DNA changes in cancers. Patients participating in the project may be offered a diagnosis where previously one wasn’t available and, in the fullness of time, there is the potential for the development of new and more-effective treatments.

However, not all participating patients and families will receive a meaningful result; the second component of the Project is therefore the collection of comprehensive clinical and laboratory datasets which, in combination with whole genome sequence data, will provide a rich research resource. There is a hope that this resource will drive new medical and scientific research; academic and, potentially, commercial organisations will be able to study how best to use genomics in healthcare and how best to interpret the data to benefit patients. The causes, diagnosis and treatment of disease will be investigated, and there is real push to kick-start the development of a UK genomics industry. It is important to note that this second component is not an NIHR portfolio research project.

The 100,000 Genomes Project is a constantly developing landscape, and changes are happening quickly. The success of the project relies on developing strong links between the NHS GMC teams, NHS consultants and clinical staff, and the patients and families who are invited to participate.

The project itself is divided into two recruitment strands: a ‘rare disease’ and a ‘common cancer’ programme. This introductory pack focuses on the recruitment of patients into the rare disease strand of the project, and provides detailed information on a speciality-specific group of the 193 rare diseases currently open for recruitment.
NHS England commissioned a series of NHS Genomic Medicine Centres (GMCs) to deliver the project. There are currently thirteen GMC sites across England. The contract to found the North East and North Cumbria (NENC) GMC was signed by the Newcastle-upon-Tyne Hospitals NHS Trust in December 2014, and the first members of the project team were employed into post in early 2015. The GMC is situated in the facilities of the Northern Genetics Service, at the International Centre for Life, Newcastle.

Our primary role as a GMC is to coordinate participant recruitment, sample processing, data analysis and clinical reporting. At present, recruitment is undertaken by a small team of dedicated Clinical Genomic Practitioners (CGPs).

As well as co-ordinating patient recruitment the GMCs are effectively being tasked with helping NHS organisations prepare for introduction of genomic technology and there is a strong drive for the GMCs to take charge of NHS ‘transformation’. Some of this transformation is a pivotal requirement to enable patients to be recruited into the 100,000 Genomes Project and includes; the retrieval and export of clinical data in electronic format; the adaptation of tumour processing pathways to enable rapid DNA extraction; and the up-skilling of the wider NHS workforce.

There is also a wider drive, outside of the slightly artificial environment of the 100,000 Genomes Project, to prepare the NHS for the introduction of genomic medicine into routine service. Examples of such develops include somatic tumour testing (already becoming common-place in some tumours); germ-line genetic testing in some cancer patients (e.g. BRCA1/2 testing in women with ovarian cancer); pharmacogenomics (small scale at present, but set to influence prescribing in most specialties); and the migration of microbial diagnostics to rapid DNA-based systems. The GMCs are also tasked with co-ordinating education and training opportunities for NHS staff, and engaging in patient and public involvement (PPI) to increase professional and public awareness of genomic medicine.
Rare Disease Recruitment

Participant recruitment is a multi-step process requiring input from both clinical teams and the NENC GMC project team. The rare disease programme aims to recruit affected patients as part of a wider family group that includes, where appropriate, unaffected close relatives (usually parents or siblings) as part of defined ‘family structures’.

The initial identification of eligible affected patients and the most suitable family structure relies heavily on the patient’s clinical team. Following a referral to the NENC GMC the family is contacted and invited to participate in the project; families who are willing to take part are then asked to attend a dedicated clinic appointment at which our Clinical Genomic Practitioners guide the potential participants through the consent process and collect the required blood samples.

Following successful recruitment, DNA is extracted from the participant’s blood samples by the Molecular Genetics laboratory of the Northern Genetics Service. The extracted DNA, along with accompanying samples for ‘omics analysis, is then dispatched to a national bio-repository for processing. Whole genome sequencing is conducted at a dedicated sequencing centre in Hinxton, Cambridge. Concurrently, a local process of data collection collates an extensive clinical data set for each affected participant to support the analysis of the genome sequencing results.

Ultimately a ‘sequence report’ will be prepared for each participant and any pertinent findings returned to the patient’s care pathway via their clinical teams and genetic specialists. Currently the time frame for the return of the sequence reports is approximately twelve months following the completion of clinical dataset submission; however, it is envisaged that it will improve dramatically as the project develops.
Rare Disease Referral

Patient recruitment into the rare disease programme relies upon clinicians identifying patients affected by an eligible rare disease who meet the disease-specific eligibility criteria.

1. Identify Eligible Disease
2. Identify Eligible Affected Patients
   Affected patients must meet the disease-specific eligibility criteria, which includes meeting defined inclusion and exclusion criteria, and have had the required prior genetic testing to rule out known disease-causing mutations.

The 100,000 Genomes Pilot Project – An Important Note
Anyone already participating in the “100,000 Genomes Pilot Project” cannot be recruited to the main phase of the project. We also cannot recruit relatives of pilot project participants until results from the pilot project have been made available. If in doubt please raise a query directly with the NENC GMC project team.

Bone Marrow Transplant (BMT) Patients
It is important to inform the NENC GMC if a referred patient has had a Bone Marrow Transplant. These patients can still be referred and recruited to the project but a variant DNA collection method is required (a skin biopsy rather than venous blood collection).

3. Identify the appropriate family structure:
   - Isolated case of disease with unaffected parents
   - Multiple Affected (Full) Siblings with unaffected parents
   - Multiple affected family members across more than one generation
   - Multiple affected family members (known consanguineous family)

   Full details of suitable family structures are outlined in the Guidelines for Family Pedigree Selection PDF document.

4. Refer details to NENC GMC team
   (A system for referrals can be tailored to meet the needs of individual clinical teams)

The Current List of Rare Diseases document is a PDF file cataloguing the names of all 193 diseases that are part of the 100,000 Genomes Project at this time. Each disease has a specific set of eligibility criteria and these are listed for every disease in the Rare Disease Conditions Eligibility Criteria PDF document. A speciality-specific list of diseases and details of their accompanying eligibility criteria are included as part of this Introduction and Eligibility Pack. All of the above files and Introduction Packs for other specialist areas are available on the NENC GMC website: www.bit.ly/nencgmc-info

Clinicians are kept up to date with the progress of all of their referrals; if the referred patient declines the invitation the referral is closed and an email generated to inform the clinician. If the referral results in successful recruitment the referring clinician will be informed via email and asked to provide disease-specific input to facilitate the collection of the clinical data set for the participant.

NB. You may need to update your internet browser to access Genomics England documentation - contact IT if you require this service.
# Cardiovascular disorders

## Arteriopathies
- Familial cerebral small vessel disease (40109.1) 20
- Familial Hypercholesterolaemia (28793.5) 18

## Cardiac Arrhythmia
- Brugada syndrome (22550.14) 24
- Catecholaminergic Polymorphic Ventricular Tachycardia (22559.14) 28
- Long QT syndrome (22552.14) 26
- Unexplained sudden death in the young (40116.1) 30

## Cardiomyopathy
- Arrhythmogenic Right Ventricular Cardiomyopathy (22563.14) 31
- Dilated Cardiomyopathy (27973.6) 35
- Dilated Cardiomyopathy and conduction defects (22575.14) 36
- Hypertrophic Cardiomyopathy (22577.14) 38
- Left Ventricular Noncompaction Cardiomyopathy (22569.14) 33

## Congenital heart disease
- Fallots tetralogy (22579.14) 40
- Hypoplastic Left Heart Syndrome (22585.14) 42
- Isomerism and laterality disorders (22589.14) 46
- Left Ventricular Outflow Tract obstruction disorders (22588.14) 45
- Pulmonary atresia (22586.14) 43
- Transposition of the great vessels (22587.14) 44

## Connective Tissues Disorders and Aortopathies
- Familial Thoracic Aortic Aneurysm Disease (22539.14) 22

## Lymphatic disorders
- Lymphoedema distichiasis (40130.1) 50
- Meige disease (28801.5) 47
- Milroy disease (40123.1) 49
### Familial cerebral small vessel disease (40109.1)

#### Familial cerebral small vessel disease eligibility (40110.1)

<table>
<thead>
<tr>
<th>Level 3 Title</th>
<th>Arteriopathies (28792.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 4 Title</td>
<td>Familial cerebral small vessel disease (40109.1)</td>
</tr>
</tbody>
</table>

#### Eligibility Statement

**Familial cerebral small vessel disease inclusion criteria (40111.1)**

- Clinical features consistent with cerebral small vessel disease: either lacunar stroke or vascular cognitive impairment/dementia, AND
- MRI confirmed evidence of cerebral small vessel disease as evidenced by; multiple lacunar infarcts and/or confluent white matter hyperintensities, AND
- Early onset cerebral SVD (<60 years) without cardiovascular risk factors or affected first degree family member

Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease.

In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs.

**Familial cerebral small vessel disease exclusion criteria (40112.1)**

- Causes of white matter disease other than cerebral small vessel disease (e.g. multiple sclerosis, vasculitis, leukodystrophy).
- Cases with NOTCH3 mutations

**Prior genetic testing guidance (22556.14)**

- Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition.
- Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the ‘Genetic investigations’ section of the data capture tool to allow comparison of WGS with current standard testing.

PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.
<table>
<thead>
<tr>
<th>Familial cerebral small vessel disease prior genetic testing genes (40113.1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice:</td>
</tr>
<tr>
<td>NOTCH3</td>
</tr>
</tbody>
</table>

**Closing statement (22558.14)**

These requirements will be kept under continual review during the main programme and may be subject to change.
Rare Disease Conditions Eligibility Criteria

Cardiovascular disorders (22537.14)

Arteriopathies (28792.5)

**Familial Hypercholesterolaemia (28793.5)**

**Familial Hypercholesterolaemia eligibility (28794.5)**

<table>
<thead>
<tr>
<th>Level 3 Title</th>
<th>Arteriopathies (28792.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 4 Title</td>
<td>Familial Hypercholesterolaemia (28793.5)</td>
</tr>
</tbody>
</table>

**Familial Hypercholesterolaemia inclusion criteria (28795.5)**

Lipid levels either pre-treatment or highest on treatment:

- Simon Broome criteria ‘definite familial hypercholesterolaemia’:
  - Abnormal lipids:
    - Total cholesterol > 6.7 mmol/l (260 mg/dl), or LDL cholesterol above 4.0 mmol/l in a child < 16 years, OR
    - Total cholesterol > 7.5 mmol/l (290 mg/dl), or LDL cholesterol above 4.9 mmol/l (190 mg/dl) in an adult
    - Tendon xanthomas (TX) in patient, or in 1st degree relative (parent, sibling, child), or in 2nd degree relative (grandparent, uncle, aunt)
  - OR
  - Abnormal lipids:
    - Total cholesterol > 6.7 mmol/l (260 mg/dl), or LDL cholesterol above 4.0 mmol/l in a child < 16 years, OR
    - Total cholesterol > 8.5 mmol/l, or LDL cholesterol above 5.5 mmol/l in an adult
    - Family history of myocardial infarction below age of 50 in 2nd degree relative or below age 60 in 1st degree relative, OR
    - Family history of raised cholesterol: >7.5 mmol/l in adult 1st or 2nd degree relative or > 6.7 mmol/l in child or sibling under 16
    - Polygenic risk 12-SNP gene score in the bottom two quartiles

Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease.
In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs.

Familial Hypercholesterolaemia exclusion criteria (28796.5)
- Secondary causes of elevated LDL-C. Patients will only be eligible who have elevated LDL-C on measures taken on a fasting blood sample and after secondary causes of hyperlipidaemia have been excluded.
- Recessive inheritance. Families showing a recessive pattern of inheritance will not be recruited
- Individuals with a fasting plasma Triglyceride level of over 2.5mmol/l will be excluded.

Prior genetic testing guidance (22556.14)
- Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition.
- Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the ‘Genetic investigations’ section of the data capture tool to allow comparison of WGS with current standard testing.

PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.

Familial Hypercholesterolaemia prior genetic testing genes (28797.5)
Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice:
- LDLR, APOB and PCSK9
- Polygenic risk 12-SNP gene score

Closing statement (22558.14)
These requirements will be kept under continual review during the main programme and may be subject to change.
## Cardiac arrhythmia (22549.14)

### Brugada syndrome (22550.14)

### Brugada eligibility (27266.7)

<table>
<thead>
<tr>
<th>Level 3 Title</th>
<th>Cardiac arrhythmia (22549.14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 4 Title</td>
<td>Brugada syndrome (22550.14)</td>
</tr>
</tbody>
</table>

#### Relevant diseases:
- Brugada syndrome

#### Brugada inclusion criteria (clinical diagnosis) (40105.1)
Brugada syndrome diagnosed according to criteria*:
- ST segment elevation with type I morphology >= 2 mm in >= 1 lead among the right precordial leads V1,V2 positioned in the 2nd, 3rd, or 4th intercostal space occurring spontaneously.

OR - a type I ECG morphology as above following a provocative drug test with intravenous administration of Class I antiarrhythmic drugs.

AND one or more of the three criteria below:
- a family history of:
  - premature sudden death (<= 40 years old) or autopsy negative sudden death < 65 years old: the sudden arrhythmic death syndrome (SADS)

AND/OR
- other relatives with a diagnosis of BrS (spontaneous or drug-induced; symptomatic or asymptomatic)

AND/OR - survivor of cardiac arrest with a spontaneous type I ECG pattern (constant or intermittent), to be recruited as a trio with parents who have been tested for BrS with normal results

* Heart Rhythm Society/European Heart Rhythm Association

Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GCMs.

#### Brugada exclusion criteria (unclear diagnosis) (40106.1)
- Unclear diagnosis or history suggestive of a non-genetic cause
- Any Brugada syndrome mutation positive (if clearly pathogenic)

**Prior genetic testing guidance (22556.14)**
- Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition.
- Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the ‘Genetic investigations’ section of the data capture tool to allow comparison of WGS with current standard testing.

PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.

**Brugada prior genetic testing genes (27269.7)**
Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice:
SCN5A

**Closing statement (22558.14)**
These requirements will be kept under continual review during the main programme and may be subject to change.
**Catecholaminergic Polymorphic Ventricular Tachycardia (22559.14)**

**Catecholaminergic Polymorphic Ventricular Tachycardia eligibility (22560.14)**

### Level 3 Title
Cardiac arrhythmia (22549.14)

### Level 4 Title
Catecholaminergic Polymorphic Ventricular Tachycardia (22559.14)

### Eligibility Statement

**Relevant diseases:**

- Catecholaminergic polymorphic ventricular tachycardia (CPVT)

**Catecholaminergic Polymorphic Ventricular Tachycardia inclusion criteria (27958.6)**

CPVT diagnosed according to criteria*:

- In the presence of a structurally normal heart, normal ECG, and unexplained exercise or catecholamine induced bidirectional VT or polymorphic ventricular premature beats (VPBs) or VT in an individual younger than 40 years.

**OR**

- In the presence of a structurally normal heart and coronary arteries, normal ECG, and unexplained exercise or catecholamine-induced bidirectional VT or polymorphic VPBs or VT in an individual older than 40 years.

AND either one of the two criteria below:

- A family history for CPVT with other affected family DNA and phenotype available (at least three over three generations) for linkage studies.

**OR**

- Trio of unaffected parents and severely affected child available (sporadic or recessive)

* Heart Rhythm Society/European Heart Rhythm Association

Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease.

In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring.
metrics applied to GMCs.

**Catecholaminergic Polymorphic Ventricular Tachycardia exclusion criteria (27959.6)**
- Unclear diagnosis or history suggestive of a non-genetic cause
- Any CPVT mutation positive (if clearly pathogenic)

**Prior genetic testing guidance (22556.14)**
- Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition.
- Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the ‘Genetic investigations’ section of the data capture tool to allow comparison of WGS with current standard testing.

PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.

**Catecholaminergic Polymorphic Ventricular Tachycardia prior genetic testing genes (22561.14)**
Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice:
CPVT, RYR2

**Closing statement (22558.14)**
These requirements will be kept under continual review during the main programme and may be subject to change.
Long QT syndrome (22552.14)

Long QT Syndrome eligibility (22553.14)

<table>
<thead>
<tr>
<th>Level 3 Title</th>
<th>Cardiac arrhythmia (22549.14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 4 Title</td>
<td>Long QT syndrome (22552.14)</td>
</tr>
</tbody>
</table>

Relevant diseases:
- Long QT syndrome

**Long QT inclusion criteria (27952.6)**

LQTS diagnosed according to criteria*:
- In the presence of an LQTS risk score >= 3.5 in the absence of a secondary cause for QT prolongation

AND/OR
- In the presence of a corrected QT interval for heart rate using Bazett’s formula (QTc) >= 500ms in repeated 12 lead electrocardiogram (ECG) and in the absence of a secondary cause for QT prolongation.

AND/OR
- In the presence of a QTc between 480 and 499ms in repeated 12-lead ECGs in a patient with unexplained syncope in the absence of a secondary cause for QT prolongation in the absence of a pathogenic mutation.

AND either one of the two criteria below:
- A family history for LQTS with other affected family DNA and phenotype available (at least three over three generations) for linkage studies.

OR
- Trio of unaffected parents and severely affected child available (sporadic or recessive)

* Heart Rhythm Society/European Heart Rhythm Association

Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families
should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs.

**Long QT exclusion criteria (27953.6)**
- Unclear diagnosis or history suggestive of a non-genetic cause
- Any LQTS mutation positive (if clearly pathogenic)

**Prior genetic testing guidance (22556.14)**
- Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition.
- Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the ‘Genetic investigations’ section of the data capture tool to allow comparison of WGS with current standard testing.

PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.

**Long QT syndrome prior genetic testing genes (22557.14)**
Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice:
- KCNQ1, KCNH2 and SCN5A

**Closing statement (22558.14)**
These requirements will be kept under continual review during the main programme and may be subject to change.
Unexplained sudden death in the young (40116.1)

Unexplained sudden death in the young eligibility (40117.1)

| Level 3 Title | Cardiac arrhythmia (22549.14) |
| Level 4 Title | Unexplained sudden death in the young (40116.1) |

**Unexplained sudden death in the young inclusion criteria (40118.1)**
- Sudden death at age less than or equal to 40 (including Sudden Infant Death Syndrome), AND
- No diagnosis established on post mortem examination, AND
- Absence of a pre-existing condition to explain the death.
- Parents should be recruited under this category in paediatric cases if available
- In adult cases the deceased individual should be recruited as a singleton; if surviving relatives have a phenotype which points to a particular condition, they should be the focus of further investigation or recruitment to the programme.
- Surviving relatives must be available to provide appropriate consent.

**Unexplained sudden death in the young exclusion criteria (40119.1)**
- Death in the context of a known diagnosed disease or accident
- Cause of death determined by post mortem examination
- No post mortem examination carried out
- No DNA or frozen tissue stored at post mortem.

**Prior genetic testing guidance (22556.14)**
- Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition.
- Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the ‘Genetic investigations’ section of the data capture tool to allow comparison of WGS with current standard testing.

PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.

**Unexplained sudden death in the young prior genetic testing genes (40120.1)**
Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice:
- No genes listed

**Closing statement (22558.14)**
These requirements will be kept under continual review during the main programme and may be subject to change.
Cardiomyopathy (22562.14)

Arrhythmogenic Right Ventricular Cardiomyopathy (22563.14)

**Arrhythmogenic Right Ventricular Cardiomyopathy eligibility (22564.14)**

<table>
<thead>
<tr>
<th>Level 3 Title</th>
<th>Cardiomyopathy (22562.14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 4 Title</td>
<td>Arrhythmogenic Right Ventricular Cardiomyopathy (22563.14)</td>
</tr>
</tbody>
</table>

**Relevant diseases:**

- Arrhythmogenic right ventricular cardiomyopathy (ARVC)
- Dilated cardiomyopathy
- Dilated cardiomyopathy and conduction defects

**Cardiomyopathies inclusion criteria (Plural) (22565.14)**

- Patients with a clear diagnosis and at least one affected relative, OR
- Patients with no family history who have a clear diagnosis of primary hypertrophic cardiomyopathy under 40 years of age

Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease.

In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs.

**Cardiomyopathies exclusion criteria (22566.14)**

- Unclear diagnosis or history suggestive of a non-genetic cause

**Prior genetic testing guidance (22556.14)**

- Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition.
- Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the ‘Genetic investigations’ section of the data capture tool to allow comparison of WGS with current standard testing.

PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established.
It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.

**Arrhythmogenic Right Ventricular Cardiomyopathy prior genetic testing genes (22567.14)**
Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice:
- ARVC
- PKP2
- DSP
- DSG2
- DSC2

**Closing statement (22558.14)**
These requirements will be kept under continual review during the main programme and may be subject to change.
### Dilated Cardiomyopathy (27973.6)

#### Dilated Cardiomyopathy eligibility (27974.6)

<table>
<thead>
<tr>
<th>Level 3 Title</th>
<th>Cardiomyopathy (22562.14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 4 Title</td>
<td>Dilated Cardiomyopathy (27973.6)</td>
</tr>
</tbody>
</table>
| Eligibility Statement | **Cardiomyopathies inclusion criteria (Plural) (22565.14)**
- Patients with a clear diagnosis and at least one affected relative, OR
- Patients with no family history who have a clear diagnosis of primary hypertrophic cardiomyopathy under 40 years of age

Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios.
Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease.

In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs.

**Cardiomyopathies exclusion criteria (22566.14)**
- Unclear diagnosis or history suggestive of a non-genetic cause

**Prior genetic testing guidance (22556.14)**
- Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition.
- Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the ‘Genetic investigations’ section of the data capture tool to allow comparison of WGS with current standard testing.

PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.

**Dilated Cardiomyopathy prior genetic testing genes (27975.6)**
Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice:
- ABCC9, ACTC1, CSRP3, LMNA, MYH7, PLN, TNNI3, TNNT2, TPM1, TTN, RBM20

**Closing statement (22558.14)**
These requirements will be kept under continual review during the main programme and may be subject to change.
**Dilated Cardiomyopathy and conduction defects** (22575.14)

**Dilated Cardiomyopathy and conduction defects eligibility** (22576.14)

<table>
<thead>
<tr>
<th>Level 3 Title</th>
<th>Cardiomyopathy (22562.14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 4 Title</td>
<td>Dilated Cardiomyopathy and conduction defects (22575.14)</td>
</tr>
</tbody>
</table>

**Eligibility Statement**

**Relevant diseases:**
- Dilated cardiomyopathy
- Dilated cardiomyopathy and conduction defects

**Cardiomyopathies inclusion criteria (Plural) (22565.14)**
- Patients with a clear diagnosis and at least one affected relative, OR
- Patients with no family history who have a clear diagnosis of primary hypertrophic cardiomyopathy under 40 years of age

Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease.

In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs.

**Cardiomyopathies exclusion criteria (22566.14)**
- Unclear diagnosis or history suggestive of a non-genetic cause

**Prior genetic testing guidance (22556.14)**
- Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition.
- Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the ‘Genetic investigations’ section of the data capture tool to allow comparison of WGS with current standard testing.

PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.
Dilated Cardiomyopathy and conduction defects prior genetic testing genes (27978.6)
Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice:
LMNA

Closing statement (22558.14)
These requirements will be kept under continual review during the main programme and may be subject to change.
Hypertrophic Cardiomyopathy (22577.14)

Cardiomyopathies eligibility (Left Ventricular Noncompaction Cardiomyopathy and Hypertrophic Cardiomyopathy) (22570.14)

<table>
<thead>
<tr>
<th>Level 3 Title</th>
<th>Cardiomyopathy (22562.14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 4 Title</td>
<td>Hypertrophic Cardiomyopathy (22577.14)</td>
</tr>
</tbody>
</table>

Relevant diseases:
- Left ventricular non-compaction cardiomyopathy
- Dilated cardiomyopathy
- Hypertrophic cardiomyopathy

Cardiomyopathies inclusion criteria (Plural) (22565.14)
- Patients with a clear diagnosis and at least one affected relative, OR
- Patients with no family history who have a clear diagnosis of primary hypertrophic cardiomyopathy under 40 years of age

Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease.

In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs.

Cardiomyopathies exclusion criteria (22566.14)
- Unclear diagnosis or history suggestive of a non-genetic cause

Prior genetic testing guidance (22556.14)
- Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition.
- Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the ‘Genetic investigations’ section of the data capture tool to allow comparison of WGS with current standard testing.

PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.
<table>
<thead>
<tr>
<th>Left Ventricular Noncompaction  and Hypertrophic Cardiomyopathy prior genetic testing genes (22571.14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice:</td>
</tr>
<tr>
<td>- MYBPC3, MYH7, TNNT2 and TNNI3</td>
</tr>
</tbody>
</table>

**Closing statement (22558.14)**

These requirements will be kept under continual review during the main programme and may be subject to change.
Left Ventricular Noncompaction Cardiomyopathy (22569.14)

Cardiomyopathies eligibility (Left Ventricular Noncompaction Cardiomyopathy and Hypertrophic Cardiomyopathy) (22570.14)

<table>
<thead>
<tr>
<th>Level 3 Title</th>
<th>Cardiomyopathy (22562.14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 4 Title</td>
<td>Left Ventricular Noncompaction Cardiomyopathy (22569.14)</td>
</tr>
</tbody>
</table>

Relevant diseases:
- Left ventricular non-compaction cardiomyopathy
- Dilated cardiomyopathy
- Hypertrophic cardiomyopathy

Cardiomyopathies inclusion criteria (Plural) (22565.14)
- Patients with a clear diagnosis and at least one affected relative, OR
- Patients with no family history who have a clear diagnosis of primary hypertrophic cardiomyopathy under 40 years of age

Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios. Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease.

In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs.

Cardiomyopathies exclusion criteria (22566.14)
- Unclear diagnosis or history suggestive of a non-genetic cause

Prior genetic testing guidance (22556.14)
- Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition.
- Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the ‘Genetic investigations’ section of the data capture tool to allow comparison of WGS with current standard testing.

PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.
<table>
<thead>
<tr>
<th>Left Ventricular Noncompaction  and Hypertrophic Cardiomyopathy prior genetic testing genes (22571.14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice:</td>
</tr>
<tr>
<td>- MYBPC3, MYH7, TNNT2 and TNNI3</td>
</tr>
</tbody>
</table>

**Closing statement (22558.14)**

These requirements will be kept under continual review during the main programme and may be subject to change.
Congenital heart disease (22578.14)

Fallots tetralogy (22579.14)

Fallots tetralogy eligibility (27982.6)

<table>
<thead>
<tr>
<th>Level 3 Title</th>
<th>Congenital heart disease (22578.14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 4 Title</td>
<td>Fallots tetralogy (22579.14)</td>
</tr>
</tbody>
</table>

**Fallots Tetralogy inclusion criteria (27983.6)**

- Patients with Fallot’s tetralogy, including pulmonary atresia with ventricular septal defect and double outlet right ventricle (Fallot type), AND one of the following:
  - A consanguineous family history OR
  - At least one first degree relative with a structural cardiac abnormality OR
  - At least one additional extra-cardiac abnormality

**Congenital Heart Disease exclusion criteria (22582.14)**

- Antenatal history suggestive of non-genetic cause
- Chromosome analysis abnormal and clearly pathogenic
- Clinical diagnosis of a recognised syndrome with known genetic cause

**Prior genetic testing guidance (22556.14)**

- Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition.
- Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the ‘Genetic investigations’ section of the data capture tool to allow comparison of WGS with current standard testing.

PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.

**Congenital Heart Disease prior genetic testing genes (22583.14)**

Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice:
| Genome-wide copy number variation testing (e.g. aCGH, SNP array or other genomic microarray) |
| Where the phenotype is recognisable and is caused by 1-2 principle genes, these should have been tested prior to recruitment |

**Closing statement (22558.14)**

These requirements will be kept under continual review during the main programme and may be subject to change.
**Hypoplastic Left Heart Syndrome (22585.14)**

**Hypoplastic Left Heart Syndrome eligibility (27988.6)**

<table>
<thead>
<tr>
<th>Level 3 Title</th>
<th>Congenital heart disease (22578.14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 4 Title</td>
<td>Hypoplastic Left Heart Syndrome (22585.14)</td>
</tr>
</tbody>
</table>

**Hypoplastic Left Heart Syndrome inclusion criteria (27989.6)**
- Patients with Hypoplastic Left Heart Syndrome, AND one of the following:
  - A consanguineous family history OR
  - At least one first degree relative with a structural cardiac abnormality OR
  - At least one additional extra-cardiac abnormality

**Hypoplastic Left Heart Syndrome exclusion criteria (27990.6)**
- Antenatal history suggestive of non-genetic cause
- Chromosome analysis abnormal and clearly pathogenic
- Clinical diagnosis of a recognised syndrome with known genetic cause

**Prior genetic testing guidance (22556.14)**
- Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition.
- Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the ‘Genetic investigations’ section of the data capture tool to allow comparison of WGS with current standard testing.

PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.

**Congenital Heart Disease prior genetic testing genes (22583.14)**
Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice:
- Genome-wide copy number variation testing (e.g. aCGH, SNP array or other genomic microarray)
- Where the phenotype is recognisable and is caused by 1-2 principle genes, these should have been tested prior to recruitment

**Closing statement (22558.14)**
These requirements will be kept under continual review during the main programme and may be subject to change.
### Isomerism and laterality disorders (22589.14)

#### Isomerism and laterality disorders eligibility (28004.6)

<table>
<thead>
<tr>
<th>Level 3 Title</th>
<th>Congenital heart disease (22578.14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 4 Title</td>
<td>Isomerism and laterality disorders (22589.14)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Isomerism and laterality disorders inclusion criteria (28005.6)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Patients with Isomerism and laterality disorders</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Isomerism and laterality disorders exclusion criteria (28006.6)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Antenatal history suggestive of non-genetic cause</td>
</tr>
<tr>
<td>- Chromosome analysis abnormal and clearly pathogenic</td>
</tr>
</tbody>
</table>

**Prior genetic testing guidance (22556.14)**

- Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition.
- Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the ‘Genetic investigations’ section of the data capture tool to allow comparison of WGS with current standard testing.

PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.

**Congenital Heart Disease prior genetic testing genes (22583.14)**

Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice:

- Genome-wide copy number variation testing(e.g. aCGH, SNP array or other genomic microarray)
- Where the phenotype is recognisable and is caused by 1-2 principle genes, these should have been tested prior to recruitment

**Closing statement (22558.14)**

These requirements will be kept under continual review during the main programme and may be subject to change.
**Left Ventricular Outflow Tract obstruction disorders (22588.14)**

**Left ventricular outflow tract obstruction disorders eligibility (28000.6)**

<table>
<thead>
<tr>
<th>Level 3 Title</th>
<th>Congenital heart disease (22578.14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 4 Title</td>
<td>Left Ventricular Outflow Tract obstruction disorders (22588.14)</td>
</tr>
</tbody>
</table>

### Eligibility Statement

**Left ventricular outflow tract obstruction disorders inclusion criteria (28001.6)**
- Patients with Left Ventricular Outflow Tract obstruction disorders, AND one of the following:
  - A consanguineous family history OR
  - At least one first degree relative with a structural cardiac abnormality OR
  - At least one additional extra-cardiac abnormality

**Left ventricular outflow tract obstruction disorders exclusion criteria (28002.6)**
- Antenatal history suggestive of non-genetic cause
- Chromosome analysis abnormal and clearly pathogenic
- Isolated congenital heart disease with no family history

**Prior genetic testing guidance (22556.14)**
- Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition.
- Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the ‘Genetic investigations’ section of the data capture tool to allow comparison of WGS with current standard testing.

**PLEASE NOTE:** The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.

**Congenital Heart Disease prior genetic testing genes (22583.14)**
Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice:

- Genome-wide copy number variation testing(e.g. aCGH, SNP array or other genomic microarray)
- Where the phenotype is recognisable and is caused by 1-2 principle genes, these should have been tested prior to recruitment

**Closing statement (22558.14)**
These requirements will be kept under continual review during the main programme and may be subject to change.
### Pulmonary atresia eligibility (27992.6)

<table>
<thead>
<tr>
<th>Eligibility Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary atresia inclusion criteria (27993.6)</td>
</tr>
<tr>
<td>- Patients with pulmonary atresia with intact ventricular septum, AND one of the following:</td>
</tr>
<tr>
<td>- A consanguineous family history OR</td>
</tr>
<tr>
<td>- At least one first degree relative with a structural cardiac abnormality OR</td>
</tr>
<tr>
<td>- At least one additional extra-cardiac abnormality</td>
</tr>
<tr>
<td>Pulmonary atresia exclusion criteria (27994.6)</td>
</tr>
<tr>
<td>- Antenatal history suggestive of non-genetic cause</td>
</tr>
<tr>
<td>- Chromosome analysis abnormal and clearly pathogenic</td>
</tr>
<tr>
<td>Prior genetic testing guidance (22556.14)</td>
</tr>
<tr>
<td>- Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition.</td>
</tr>
<tr>
<td>- Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the ‘Genetic investigations’ section of the data capture tool to allow comparison of WGS with current standard testing.</td>
</tr>
</tbody>
</table>

**PLEASE NOTE:** The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.

### Congenital Heart Disease prior genetic testing genes (22583.14)

- Genome-wide copy number variation testing (e.g. aCGH, SNP array or other genomic microarray)
- Where the phenotype is recognisable and is caused by 1-2 principle genes, these should have been tested prior to recruitment

### Closing statement (22558.14)

These requirements will be kept under continual review during the main programme and may be subject to change.
## Transposition of the great vessels (22587.14)

### Transposition of the great vessels eligibility (27996.6)

<table>
<thead>
<tr>
<th>Level 3 Title</th>
<th>Congenital heart disease (22578.14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 4 Title</td>
<td>Transposition of the great vessels (22587.14)</td>
</tr>
</tbody>
</table>

### Transposition of the great vessels inclusion criteria (27997.6)
- Patients with Transposition of the great vessels, AND one of the following:
  - A consanguineous family history OR
  - At least one first degree relative with a structural cardiac abnormality OR
  - At least one additional extra-cardiac abnormality

### Transposition of the great vessels exclusion criteria (27998.6)
- Antenatal history suggestive of non-genetic cause
- Chromosome analysis abnormal and clearly pathogenic

### Prior genetic testing guidance (22556.14)
- Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition.
- Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the ‘Genetic investigations’ section of the data capture tool to allow comparison of WGS with current standard testing.

PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.

### Congenital Heart Disease prior genetic testing genes (22583.14)
Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice:

- Genome-wide copy number variation testing(e.g. aCGH, SNP array or other genomic microarray)
- Where the phenotype is recognisable and is caused by 1-2 principle genes, these should have been tested prior to recruitment

### Closing statement (22558.14)
These requirements will be kept under continual review during the main programme and may be subject to change.
## Connective Tissues Disorders and Aortopathies (22538.14)

### Familial Thoracic Aortic Aneurysm Disease (22539.14)

#### Familial Thoracic Aortic Aneurysm Disease eligibility (27257.7)

<table>
<thead>
<tr>
<th>Level 3 Title</th>
<th>Connective Tissues Disorders and Aortopathies (22538.14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 4 Title</td>
<td>Familial Thoracic Aortic Aneurysm Disease (22539.14)</td>
</tr>
</tbody>
</table>

**Relevant Diseases:**
- Familial Thoracic Aortic Aneurysm and dissection
- Thoracic aortopathy < 50 years with no other established risk factors
- Clinically diagnosed Marfan syndrome with no FBN1 mutation
- Loeys-Dietz syndrome and Loeys-Dietz syndrome like conditions
- Mutation negative Congenital Contractural Arachnodactyly (Beals syndrome)

**Familial Thoracic Aortic Aneurysm Disease inclusion criteria**
- Patients suspected to have the above conditions
- Individuals with severe or syndromic disease should be recruited according to standard guidance, typically as trios.
- Disease status of apparently unaffected participants should be determined according to standard clinical practice to detect cryptic disease. In other cases, unaffected individuals should not be recruited. Recruitment in such families should favour multiplex families over single isolated cases. These singleton recruits will not contribute to the overall singleton monitoring metrics applied to GMCs.

**Familial Thoracic Aortic Aneurysm Disease exclusion criteria:**
- Sporadic thoracic aortopathies with risk factors
- Family history with no affected proband to test

**Prior genetic testing guidance (22556.14):**
- Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition.
- Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the ‘Genetic investigations’ section of the data capture tool to allow comparison of WGS with current standard testing.

**PLEASE NOTE:** The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.

**Familial Thoracic Aortic Aneurysm Disease prior genetic testing genes:**
- Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local
<table>
<thead>
<tr>
<th>practice:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Loeys-Dietz syndrome TGFBR1 and TGFBR2</td>
</tr>
<tr>
<td>- Marfan Syndrome FBN1</td>
</tr>
<tr>
<td>- Congenital Contractural Arachnodactyly FBN2</td>
</tr>
<tr>
<td>- Isolated familial thoracic aortic aneurysms and dissection - ACTA2</td>
</tr>
</tbody>
</table>

**Closing statement (22558.14)**

These requirements will be kept under continual review during the main programme and may be subject to change.
Lymphoedema distichiasis (40130.1)

**Lymphoedema distichiasis eligibility (40131.1)**

<table>
<thead>
<tr>
<th>Level 3 Title</th>
<th>Lymphatic disorders (28800.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 4 Title</td>
<td>Lymphoedema distichiasis (40130.1)</td>
</tr>
</tbody>
</table>

**Eligibility Statement**

**Lymphoedema distichiasis inclusion criteria (40132.1)**
- Non-congenital lower limb lymphoedema, AND
- Distichiasis (extra eyelashes arising from the inner eyelid), AND
- Family history (if present) consistent with autosomal dominant inheritance, AND
- Lymphoscintigram (where available) suggestive of reflux or rerouting

**Lymphoedema distichiasis exclusion criteria (40133.1)**
- Congenital lymphoedema
- Lymphoedema of any other segment (e.g. arms/face)

**Prior genetic testing guidance (22556.14)**
- Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition.
- Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the ‘Genetic investigations’ section of the data capture tool to allow comparison of WGS with current standard testing.

PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.

**Lymphoedema distichiasis prior genetic testing genes (40134.1)**
Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice:
- **FOXC2**

**Closing statement (22558.14)**
These requirements will be kept under continual review during the main programme and may be subject to change.
Lymphatic disorders (28800.5)

Meige disease (28801.5)

Meige disease eligibility (28802.5)

<table>
<thead>
<tr>
<th>Level 3 Title</th>
<th>Lymphatic disorders (28800.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 4 Title</td>
<td>Meige disease (28801.5)</td>
</tr>
</tbody>
</table>

Meige disease inclusion criteria (28803.5)
- Non-congenital lower limb lymphoedema
- Multiple affected individuals in the pedigree with family history consistent with autosomal dominant inheritance
- Lymphoscintigram (where available) suggestive of deep rerouting with the presence of popliteal nodes

Meige disease exclusion criteria (28804.5)
- Congenital lymphoedema
- Lymphoedema of any other segment (e.g. hands/arms/face/genitalia)
- Systemic lymphoedema (e.g. intestinal or pulmonary lymphangiectasia, pleural or pericardial effusions)
- No family history of lymphoedema
- Syndromic lymphoedema including any major structural malformations
- Distichiasis (aberrant eyelashes arising from the meibomian glands)

Prior genetic testing guidance (22556.14)
- Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition.
- Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the ‘Genetic investigations’ section of the data capture tool to allow comparison of WGS with current standard testing.

PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.

Meige disease prior genetic testing genes (28805.5)
Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice:
- No genes listed
Closing statement (22558.14)
These requirements will be kept under continual review during the main programme and may be subject to change.
Milroy disease (40123.1)

Milroy disease eligibility (40124.1)

<table>
<thead>
<tr>
<th>Level 3 Title</th>
<th>Lymphatic disorders (28800.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 4 Title</td>
<td>Milroy disease (40123.1)</td>
</tr>
<tr>
<td>Milroy disease inclusion criteria (40125.1)</td>
<td>• Congenital lower limb lymphoedema, AND</td>
</tr>
<tr>
<td></td>
<td>• Lymphoscintigram (where available) suggestive of functional aplasia</td>
</tr>
<tr>
<td>Milroy disease exclusion criteria (40126.1)</td>
<td>• Non-congenital lymphoedema</td>
</tr>
<tr>
<td></td>
<td>• Lymphoedema of any other segment (e.g. arms/face)</td>
</tr>
<tr>
<td></td>
<td>• Syndromic lymphoedema or microcephaly or major structural malformation.</td>
</tr>
<tr>
<td>Prior genetic testing guidance (22556.14)</td>
<td>- Results should have been reviewed for all genetic tests undertaken, including disease-relevant genes in exome sequencing data. The patient is not eligible if they have a molecular diagnosis for their condition.</td>
</tr>
<tr>
<td></td>
<td>- Genetic testing should continue according to routine local practice for this phenotype regardless of recruitment to the project; results of these tests must be submitted via the ‘Genetic investigations’ section of the data capture tool to allow comparison of WGS with current standard testing.</td>
</tr>
<tr>
<td></td>
<td>PLEASE NOTE: The sensitivity of WGS compared to current diagnostic genetic testing has not yet been established. It is therefore important that tests which are clinically indicated under local standard practice continue to be carried out.</td>
</tr>
<tr>
<td>Milroy disease prior genetic testing genes (40127.1)</td>
<td>Testing of the following genes should be carried out PRIOR TO RECRUITMENT where this is in line with current local practice:</td>
</tr>
<tr>
<td></td>
<td>• FLT4</td>
</tr>
<tr>
<td>Closing statement (22558.14)</td>
<td>These requirements will be kept under continual review during the main programme and may be subject to change.</td>
</tr>
</tbody>
</table>