CARDIGEN
Cardiac Genetics in the North of England

Cardiac Family History Service
and
Northern Genetics Service

Guidelines version 2
CARDIGEN guidelines

This document offers guidance on three levels:

Level 1: referral guidelines for primary and secondary care teams within the North of England Cardiovascular Network.

Level 2: assessment and triage guidelines for the Cardiac Family History Service

Level 3: management guidelines for the Northern Genetics Service and Cardiology teams

Contents

<table>
<thead>
<tr>
<th>Abbreviations and definitions</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Unexplained left ventricular hypertrophy</td>
<td>4</td>
</tr>
<tr>
<td>2. Unexplained dilated cardiomyopathy</td>
<td>16</td>
</tr>
<tr>
<td>3. Arrhythmogenic Right Ventricular Cardiomyopathy</td>
<td>26</td>
</tr>
<tr>
<td>4. Arrhythmia syndromes</td>
<td>29</td>
</tr>
<tr>
<td>5. Premature sudden unexplained death (&lt;40 years of age)</td>
<td>31</td>
</tr>
<tr>
<td>6. Heritable lipid abnormalities [Familial hypercholesterolaemia</td>
<td>35</td>
</tr>
<tr>
<td>7. Cardiovascular connective tissue disorders</td>
<td>36</td>
</tr>
<tr>
<td>8. Appendix 1. Normal aortic root dimensions</td>
<td>44</td>
</tr>
<tr>
<td>9. Appendix 2. Sudden death prophylaxis in Brugada syndrome</td>
<td>48</td>
</tr>
<tr>
<td>10. Appendix 3. Common clinical codes, Northern Genetics Service</td>
<td>50</td>
</tr>
</tbody>
</table>

Referral addresses:

Cardiac Family History Service
Department of Cardiology
Sunderland Royal Hospital
Kayll Road
Sunderland
SR4 7TP

0191 5410118 or 0191 5656256 ext 42675

Dr Paul Brennan
Clinical Lead in Cardiovascular Genetics
Teesside Genetics Unit
James Cook University Hospital
Marton Road
Middlesbrough
TS4 3BW

01642 282673

Version 2
April 2012
Author: Dr Paul Brennan
### Abbreviations + definitions

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARVC</td>
<td>Arrhythmogenic right ventricular cardiomyopathy (dysplasia)</td>
</tr>
<tr>
<td>CAD</td>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>CCTD</td>
<td>Cardiovascular connective tissue disease</td>
</tr>
<tr>
<td>CK</td>
<td>Creatine kinase</td>
</tr>
<tr>
<td>CPVT</td>
<td>Catecholaminergic polymorphic ventricular tachycardia</td>
</tr>
<tr>
<td>DBS</td>
<td>Dried blood spot assay</td>
</tr>
<tr>
<td>DCM</td>
<td>Dilated cardiomyopathy</td>
</tr>
<tr>
<td>EDS</td>
<td>Ehlers-Danlos syndrome</td>
</tr>
<tr>
<td>fdr</td>
<td>First degree relative</td>
</tr>
<tr>
<td>FH</td>
<td>Familial hypercholesterolaemia</td>
</tr>
<tr>
<td>FHx</td>
<td>Family history</td>
</tr>
<tr>
<td>HCM</td>
<td>Hypertrophic cardiomyopathy</td>
</tr>
<tr>
<td>Incident screen</td>
<td>Ongoing screen in relatives of an index case. Captures incident disease.</td>
</tr>
<tr>
<td>LDLR</td>
<td>Low density lipoprotein receptor</td>
</tr>
<tr>
<td>LDS</td>
<td>Loeys-Dietz syndrome</td>
</tr>
<tr>
<td>LQTS</td>
<td>Long QT syndrome</td>
</tr>
<tr>
<td>LVHT</td>
<td>Left ventricular hypertrabeculation</td>
</tr>
<tr>
<td>LVNCC</td>
<td>Left ventricular non-compaction cardiomyopathy</td>
</tr>
<tr>
<td>MFS</td>
<td>Marfan syndrome</td>
</tr>
<tr>
<td>MWT</td>
<td>Mean wall thickness</td>
</tr>
<tr>
<td>MYBPC3</td>
<td>Myosin-binding protein C3</td>
</tr>
<tr>
<td>MYH7</td>
<td>Myosin heavy chain 7 (β myosin heavy chain)</td>
</tr>
<tr>
<td>NF</td>
<td>Neurofibromatosis</td>
</tr>
<tr>
<td>Prevalent screen</td>
<td>Initial screen in relatives of an index case. Captures prevalent disease.</td>
</tr>
<tr>
<td>RCM</td>
<td>Restrictive cardiomyopathy</td>
</tr>
<tr>
<td>sdr</td>
<td>Second degree relative</td>
</tr>
<tr>
<td>TNNT2</td>
<td>Troponin T2</td>
</tr>
<tr>
<td>WPW</td>
<td>Wolff Parkinson White syndrome</td>
</tr>
</tbody>
</table>
1. Unexplained left ventricular hypertrophy

Includes left ventricular hypertrabeculation / non-compaction cardiomyopathy (LVHT / LVNCC).

Level 1 guideline: referral for genetic assessment

If a common cause for a patient’s left ventricular hypertrophy cannot be identified, consider the possibility of an inherited disorder. Familial hypertrophic cardiomyopathy (HCM) is an heterogeneous entity that usually presents with asymmetric left ventricular hypertrophy but may present with a variety of other phenotypes (apical, mid-cavity, concentric). Patients with isolated, unexplained LVH may have familial HCM but only 29% have identifiable mutations in sarcomeric protein genes (c.f. 62% in familial cases)\(^1\), and careful family assessment is required. All patients (male and female) should also be screened for Fabry disease, which may mimic HCM.

**Conventional diagnostic criteria (Charron et al 2003\(^2\))**

Diagnosis requires

- Major echo and/or major ECG or
- Minor echo + 1 major ECG or
- 2 minor ECG

**Echo**

- Major  MWT>13mm
- Minor  MWT = 13mm

**ECG**

- Major  Abnormal Q waves in at least 2 leads (>40ms or >1/3 R wave)
  - T wave inversion in at least 2 leads (≥3mm)
  - LV hypertrophy (Romhilt-Estes score ≥4)
- Minor  left atrial enlargement (P wave in V1)
  - PR interval <120ms
  - Microvoltage (<5mV)
  - Minor Q waves in at least 2 leads
  - Bundle branch block or hemiblock

[MWT = maximum wall thickness]

Exclude where possible

- Hypertensive heart disease
- Aortic stenosis
- Athletic training
- Infiltrative disease (amyloid, sarcoid)
- Obvious neuromuscular cardiomyopathy

---


Refer to Cardiac Family History Service

- all cases meeting *conventional* diagnostic criteria, the above having been excluded
- individuals with a first- or second-degree family history of hypertrophic cardiomyopathy +/- dilated cardiomyopathy
- all cases with LVHT / LVNCC
Level 2 guideline: Cardiac Family History Service

Level 2 protocol: cardiac hypertrophy

1. Obtain 3-generation family history

2. Confirm diagnoses if possible

3. All cases: - sub-diagnostic aide memoire
   - prevalent echo + ECG in first degree relatives

4. All cases where male-to-male transmission not identified (including all sporadic cases):
   - dried blood spot test for α-galactosidase

5. Females with isolated HCM and normal α-galactosidase :
   - request slit lamp examination of cornea
   - urine dipstick for protein

Discharge to referring clinician

– individuals not fulfilling conventional diagnostic criteria;
– individuals in whom a reported family history of cardiomyopathy is not confirmed

Offer DNA storage

– to all isolated cases fulfilling conventional diagnostic criteria

Refer to local Cardiology service

– individuals found to have cardiac abnormality on surveillance investigations

Refer to Northern Genetics Service

– families characterised by 2 or more cases of HCM (first or second degree relatives of each other)
– or HCM + FHx SCD
– or HCM with a FHx of DCM (fulfilling conventional diagnostic criteria)
– confirmed α-galactosidase deficiency on DBS

Discuss at clinical supervision / MDT

– fdrs <16 who need cascade surveillance
– isolated case with early onset HCM (<30)
– HCM + subdiagnostic feature (see sub-diagnostic aide memoire)
Level 2 protocol: LVHT / LVCNCC

1. Obtain 3-generation family history

2. Ask specifically about neuromuscular problems (muscle weakness, joint contractures, ‘muscular dystrophy’)

3. Confirm diagnoses if possible

3. All cases: discuss at clinical supervision / MDT
LVH / HCM subdiagnostic aide memoire

**Brain**
- Learning disability
- Ataxia

**Eye**
- Retinitis pigmentosa

**Ear**
- Deafness

**Heart**
- Congenital heart disease
- WPW

**Kidney**
- Chronic renal failure
- Hydronephrosis

**Skin**
- Red spotty rash
- Multiple pigmented naevi

**Muscle**
- Proximal myopathy
- ↑ CK
- contractures
- fatigue

**Nerve**
- Acroparaesthesia

**Metabolic**
- Diabetes
- Diabetes + lipoatrophy
- ↑ lactate

**Inheritance**
- Maternal
- X-linked

Danon disease
Noonan syndrome
Friedreich ataxia

mitochondrial cytopathy

mitochondrial cytopathy

Fabry disease

Noonan syndrome
PRKAG2 gene
Danon disease

Fabry disease
Noonan syndrome

Fabry disease
NF/Noonan

Danon
non-specific
laminopathy
mitochondrial cytopathy

Fabry disease

mitochondrial cytopathy

Fabry disease
Danon disease
# Traffic light guideline summary (hypertrophic cardiomyopathy)

<table>
<thead>
<tr>
<th>Low probability *</th>
<th>Intermediate probability**</th>
<th>High probability***</th>
</tr>
</thead>
<tbody>
<tr>
<td>− Cases with non-diagnostic family history</td>
<td>Isolated case†</td>
<td>− families characterised by 2 or more cases of HCM (first or second degree relatives of each other)</td>
</tr>
<tr>
<td>− Cases not fulfilling conventional diagnostic criteria</td>
<td></td>
<td>− or HCM + FHx SCD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>− or HCM with a FHx of DCM (fulfilling conventional diagnostic criteria)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>− confirmed α-galactosidase deficiency on DBS</td>
</tr>
</tbody>
</table>

| Discharge to referrer | Family surveillance | Refer to Genetics |

* low probability of familial disease
** familial disease remains possible, but more investigation required
*** familial disease likely
† discuss cases <30 years of age at MDT/supervision meeting
Level 3 guideline: Northern Genetics Service

1. National & international position statements


- HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. Europace 2011;13:1077-1109


2. Diagnostic genetic testing (Consultant led)

- Diagnostic genetic testing according to standard departmental protocol should be considered in all families where there are 2 or more cases of confirmed HCM. At present (2012) testing should start with a first-line analysis of MYN7, MYBPC3, TNNT2 and TNNI3; further testing may be considered in selected cases.

- Priority will be given to those families in which syncope, blackout, documented arrhythmia or sudden death have occurred, or in which the combination of clinical history, family history and histology suggests TNNT2.

- Genetic testing in isolated cases should not be undertaken routinely at present, although testing may be considered on a case-by-case basis (it is recommended in the HRS/EHRA consensus statement).

- Phenotypic variation in HCM families may manifest as DCM or non-compaction cardiomyopathy (NCCM). Children with particularly severe HCM may have compound heterozygous mutations.

3. Predictive genetic testing (Counsellor led)

- Predictive genetic testing according to standard departmental protocol should be offered to all families where a pathogenic mutation has been identified. Testing in children below the age of 12 would not usually be considered unless there is an adverse family history, or for reasons of parental anxiety.

- The early literature suggests a relationship between the gene involved and the phenotype. For example, myosin heavy chain gene mutations are generally believed to cause ‘classical’ HCM with teenage onset; myosin binding protein-C mutations a milder, late-onset form of HCM; and TNNT2 mutations a severe form of HCM with little clinical hypertrophy but profound myocyte disarray and a high arrhythmia risk. In clinical practice it is common for these relationships not to exist; such a relationship must not be quoted in clinic. It is very difficult to give anything more than general prediction about the likely phenotype in a family.
Level 3 guideline: cardiology

1. Surveillance in cardiology clinics (echo & ECG)

- at 50% risk (from Maron et al 2004\(^4\)):

<table>
<thead>
<tr>
<th>Age</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12 years</td>
<td>Optional unless: family history of SCD</td>
</tr>
<tr>
<td></td>
<td>family history of LVH present</td>
</tr>
<tr>
<td></td>
<td>competitive athlete in intense training programme</td>
</tr>
<tr>
<td></td>
<td>symptoms or clinical suspicion of LVH present</td>
</tr>
<tr>
<td>12 – 21 years</td>
<td>12-18 monthly echo &amp; ECG</td>
</tr>
<tr>
<td>&gt;21 years</td>
<td>5 yearly echo &amp; ECG to 50</td>
</tr>
<tr>
<td></td>
<td>• continue for longer if there is a family history of late-onset HCM</td>
</tr>
<tr>
<td></td>
<td>• more frequent if there is a family history of a more malignant phenotype</td>
</tr>
</tbody>
</table>

Criteria for diagnosis of HCM in this screening context are probably different to those used in a diagnostic context. Since a positive family history increases the prior risk of disease, subtle changes otherwise considered non-diagnostic may indicate early disease\(^4\).

- HCM mutation carrier (normal heart on last exam)

<table>
<thead>
<tr>
<th>Age</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12 years *</td>
<td>Optional unless: family history of SCD</td>
</tr>
<tr>
<td></td>
<td>family history of troponin T mutation</td>
</tr>
<tr>
<td></td>
<td>competitive athlete in intensive training programme</td>
</tr>
<tr>
<td></td>
<td>symptoms or clinical suspicion of LVH present</td>
</tr>
<tr>
<td>12 – 30 years</td>
<td>12 monthly echo &amp; ECG</td>
</tr>
<tr>
<td>&gt;30 years</td>
<td>5 yearly echo &amp; ECG for life</td>
</tr>
<tr>
<td></td>
<td>more frequent if family history of malignant phenotype</td>
</tr>
</tbody>
</table>

* predictive genetic testing would not be considered routinely before the age of 12 unless there is an adverse family history, or where knowledge of the child’s genetic status is important for life planning (e.g. sport).

All echo reports should contain absolute or indexed LV wall measurements. A statement that the LV dimensions are ‘normal’ or ‘within normal limits’ is unacceptable.

2. Definition of ‘affected status’ in fdr of index case\(^5\)

Diagnosis requires
- One major criterion or
- Two minor echo criteria or
- One minor echo criterion plus two minor ECG criteria

---


Echo  Major  LV wall thickness >13mm in anterior septum or posterior wall or LV wall thickness ≥15mm in posterior septum or free wall  Severe SAM (septal-leaflet contact)

Minor  LV wall thickness of 12mm in anterior septum or posterior wall or LV wall thickness of 14mm in posterior septum or free wall  Moderate SAM (no septal-leaflet contact)  Redundant MV leaflets

ECG  Major  LVH + repolarisation abnormality (Romhilt-Estes)  T wave inversion in leads aVL (≥3mm), V3-V6 (≥3mm) or II, III and aVF (≥5mm)  Abnormal Q waves (>40ms or >1/4 R wave) in at least 2 leads from II, III, aVF (in absence of left anterior hemiblock), V1-V4 or I, aVL, V5-V6

Minor  complete BBB or intraventricular conduction defect  minor repolarisation changes in LV leads  deep S in V2 (>25mm)  unexplained chest pain, dyspnoea or syncope

3. Sudden death prophylaxis in HCM [includes the use of ICD and/or amiodarone.]

Patients with ≥ 2 recognised risk factors warrant prophylaxis:

- Previous cardiac arrest
- Non-sustained VT on Holter or exercise
- Abnormal BP response on exercise
- Unexplained syncope
- Family history of premature sudden death
- Severe left ventricular hypertrophy >3 cm

Patients with 1 risk factor require an individualised decision in relation to the strength of the risk factor.
Initial HCM pathway summary (adults)

LVH / HCM

Exclude where possible
- Hypertensive heart disease
- Aortic stenosis
- Athletic training
- Infiltrative disease (amyloid, sarcoid)
- Neuromuscular cardiomyopathy

Family history
HCM +/- DCM

Refer to Cardiac Family History Service

LVHT / LVNCC

Cardiac Family History Service
- Confirm family history
- α-gal DBS
- subdiagnostic aide memoire
- store DNA

Low probability
Discharge to referrer

Intermediate probability

High probability

MDT

See below
Cardiac Family History Service pathway summary (adults)

**Intermediate probability**
- Prevalent screen
  - Identify 'at risk' fdrs
  - Offer echo & ECG
  - Cardiology review of ECGs & abnormal echo

**Children (<16 years)**
- discuss at MDT

**No other affected relatives**
- Fabry etc excluded

**Intermediate probability**
- Store DNA
- Standardised PIL

**High probability**
- >1 affected relatives
- Refer to Northern Genetics Service
High probability of familial hypertrophic cardiomyopathy (Northern Genetics Service pathway)

- **Diagnostic genetic test (INDEX CASE)**
  - Mutation *positive*:
    - Cascade testing using genetic test
    - Mutation *negative* (*or genetic test not done*):
      - Manage HCM as appropriate
      - Normal
  - Mutation *negative*:
    - Cascade testing using echo & ECG (NGS coordinates)
    - Mutation *positive*:
      - Cardio-myopathy
      - Refer to cardiology
      - Cascade test offspring if relevant
    - Normal

Priority given to families with documented syncope, blackout, arrhythmia or sudden death; or phenotype suggests TNNT2.
2. Unexplained Dilated Cardiomyopathy

Level 1 guideline: referral for genetic assessment

If a common cause for a patient’s dilated cardiomyopathy cannot be identified, consider the possibility of an inherited disorder, especially in young people. Familial dilated cardiomyopathy (DCM) is a heterogeneous disorder that shows a marked degree of variability within families. A significant proportion of the first degree relatives of an individual with unexplained DCM will have LV dimensions at – or just outside – the normal range but it is not clear whether this represents familial DCM. Many genes are implicated in familial DCM, and service diagnostic testing is extremely limited.

Conventional diagnostic criteria for idiopathic dilated cardiomyopathy (Mestroni et al 1999⁶)

Inclusion criteria

- Ejection fraction of the left ventricle < 45% and/or fractional shortening < 25% (> 2 SD below the mean), as ascertained by echocardiography, radionuclide scanning, or angiography
- Left-ventricular end-diastolic diameter > 117% of the predicted value corrected for age and body surface area, which corresponds to 2 SD above the predicted normal limit +5%

Exclude where possible

- Systemic hypertension
- Coronary artery disease
- Chronic excess alcohol intake
- Systemic disease known to cause dilated cardiomyopathy
- Pericardial diseases
- Congenital heart disease
- Cor pulmonale
- Rapid, sustained supraventricular tachycardia

Refer to Cardiac Family History Service

- 2 or more cases in close relatives (first or second degree)
- unexplained DCM <50 years of age
- individuals with a family history of dilated cardiomyopathy +/- hypertrophic cardiomyopathy

---

Level 2 guideline: Cardiac Family History Service

Level 2 protocol: dilated cardiomyopathy

1. Obtain 3-generation family history

2. Confirm diagnoses if possible

3. All cases:  - sub-diagnostic *aide memoire*
   - cascade echo + ECG in first degree relatives according to CARDIGEN guideline

4. Males: plasma CK if not already done

**Discharge to referring clinician**

– individuals not fulfilling conventional diagnostic criteria;
– individuals in whom a reported family history of cardiomyopathy is not confirmed

**Offer DNA storage**

– to all isolated cases fulfilling conventional diagnostic criteria

**Refer to local Cardiology service**

– individuals found to have cardiac abnormality on surveillance investigations

**Refer to Northern Genetics Service**

– families with 2 or more cases fulfilling conventional diagnostic criteria
– or DCM with FHx of:
  ▪ HCM (fulfilling conventional diagnostic criteria)
  ▪ sudden unexplained death
  ▪ conduction block / pacemaker
  ▪ fetal hydrops or neonatal cardiomyopathy

**Discuss at clinical supervision / MDT**

– fdrs <16 who need cascade surveillance
– isolated case with unexplained very early onset (<20)
– DCM + subdiagnostic feature (see diagnostic aide memoire)
DCM subdiagnostic *aide memoire*

**Brain**
- Learning disability
- Ataxia

**Eye**
- Cataract

**Ear**
- Deafness

**Heart**
- Conduction disease

**Muscle**
- Proximal myopathy
- ... with contractures
- Fatigue

**Metabolic**
- ↑ lactate

**Inheritance**
- X-linked

**Pregnancies**
- Recurrent hydrops

---

Danon disease
Friedreich ataxia
myotonic dystrophy
mitochondrial cytopathy
laminopathy
desminopathy
Becker MD
Emery Dreifuss MD (AD)
myotonic dystrophy
mitochondrial cytopathy
Becker MD
Barth syndrome
Danon disease
Barth syndrome
## Traffic light guideline summary (dilated cardiomyopathy)

<table>
<thead>
<tr>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>− Cases with non-diagnostic family history</td>
<td>Isolated case &lt;50</td>
<td>− families with 2 of more cases fulfilling conventional diagnostic criteria</td>
</tr>
<tr>
<td>− Cases not fulfilling conventional diagnostic criteria</td>
<td></td>
<td>− or DCM with FHx of:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ HCM (fulfilling conventional diagnostic criteria)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ sudden unexplained death</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ conduction block / pacemaker</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ fetal hydrops or neonatal cardiomyopathy</td>
</tr>
<tr>
<td>Discharge to referrer</td>
<td>Family surveillance</td>
<td>Refer to Genetics</td>
</tr>
</tbody>
</table>
Level 3 guideline: Northern Genetics Service

1. **National and international position statement**


   - HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. Europace 2011;13:1077-1109

2. **Diagnostic genetic testing (Consultant led)**

   - Diagnostic genetic testing of LMNA and SCN5A should be undertaken according to standard departmental protocol in all patients with DCM and significant conduction disease (first, second or third degree heart block) +/- family history of sudden cardiac death.

   - Diagnostic genetic testing of other genes may be considered in families where there are 2 or more cases of confirmed DCM, but should not be undertaken routinely at present in view of the extreme genetic heterogeneity of this disorder. Genetic testing in isolated cases should not be undertaken routinely.

     - Autosomal dominant DCM may be caused by mutations in the same genes that cause familial HCM.
     - Autosomal dominant DCM may be caused by mutations in LMNA; this may be suggested by the presence of AV block, joint contractures, proximal limb weakness or partial lipodystrophy.
     - Male-only cardiomyopathy should prompt exon dosage analysis of dystrophin.
     - Male-only cardiomyopathy with a family history of fetal hydops should prompt mutation analysis of tafazzin.

     - Phenotypic variation in DCM families may manifest as HCM or LVNCC.

3. **Predictive genetic testing (Counsellor led)**

   - Predictive genetic testing according to standard departmental protocol should be offered to all families where a pathogenic mutation has been identified. Testing in children below the age of 12 would not usually be considered unless there is an adverse family history, or for reasons of parental anxiety.

   - It is very difficult to give anything more than general prediction about the likely phenotype in a family.
Level 3 guideline: cardiology

1. **Surveillance in cardiology clinics (echo & ECG)**

   - at 50% risk:

<table>
<thead>
<tr>
<th>20 – 50 years</th>
<th>2 yearly echo &amp; ECG</th>
</tr>
</thead>
</table>

   Criteria for diagnosis of DCM in this screening context are probably different to those used in a diagnostic context. Since a positive family history increases the prior risk of disease, subtle changes otherwise considered non-diagnostic may indicate early disease.\(^8\)

   - DCM mutation carrier (normal heart on last exam):

<table>
<thead>
<tr>
<th>20 – 50 years</th>
<th>yearly echo &amp; ECG</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;50 years</td>
<td>5 yearly echo &amp; ECG (depending on family history)</td>
</tr>
</tbody>
</table>

   N.B. Most familial DCM is autosomal dominant. \textit{X-linked} adult DCM is very rare, usually linked to dystrophin and often associated with a Becker muscular dystrophy phenotype. Surveillance probably needs to be annual but this is rare enough for a bespoke ‘best practice’ decision to be made. At present it is unusual for us to know the genetic cause of DCM in a family.

   \textit{All echo reports should contain absolute or indexed LV chamber measurements. A statement that the LV dimensions are ‘normal’ or ‘within normal limits’ is unacceptable.}

2. **Definition of ‘affected status’ in fdr of index case\(^9\)**

   Diagnosis requires:
   
   – Presence of major diagnostic criteria (LV dilatation and systolic dysfunction) or
   – Dilated LV (>117%) and one or more minor criteria or
   – Three minor criteria

   Major criteria
   
   – Fulfils conventional diagnostic criteria

   Minor criteria
   
   – Unexplained supraventricular arrhythmia (AF or sustained arrhythmia) or ventricular arrhythmia (frequent (>1000 beats in 24hours) or repetitive [3 or more beats >120bpm] before the age of 50
   – LV dilatation >112% of predicted
   – LV dysfunction: EF<50% or FS<28%
   – Unexplained conduction disease: II or III AV conduction defects, complete LBBB, sinus node dysfunction

---

\(^8\) Baig MK et al. Familial dilated cardiomyopathy: cardiac abnormalities are common in asymptomatic relatives and may represent early disease. J Am Coll Cardiol 1998;31(1):195-201

Unexplained death or stroke before 50
Segmental wall motion abnormality (>1 segment, or 1 if not previously present) in the absence of intraventricular conduction defect or ischaemic heart disease.

Note: it may be necessary to index LV chamber measurements against Body Surface Area in borderline cases (use Dubois BSA calculator\textsuperscript{10} and BSE normal ranges\textsuperscript{11})

\textsuperscript{10} Body Surface area (m) = 0.007184 \times (\text{patient height in cm})^{0.725} \times (\text{patient weight in kg})^{0.425} ; \text{See http://bnf.org/bnf/extra/current/450018.htm}

\textsuperscript{11} British Society of Echocardiography Education Committee. Echocardiography: Guidelines for Chamber Quantification http://www.bsecho.org/Guidelines%20for%20Chamber%20Quantification.pdf
Initial DCM pathway summary (adults)

DCM

Exclude where possible
- Systemic hypertension
- Coronary artery disease
- Chronic excess alcohol intake
- Systemic disease known to cause dilated cardiomyopathy
- Pericardial diseases
- Congenital heart disease
- Cor pulmonale
- Rapid, sustained supraventricular tachycardia

Refer to Cardiac Family History Service

Refer
- 2 or more cases in close relatives (first or second degree)
- unexplained DCM <50 years of age
- individuals with a family history of DCM +/- HCM

Cardiac Family History Service
- Confirm family history
- subdiagnostic aide memoire
- store DNA

Low probability
- Discharge to referrer

Intermediate probability

High probability

MDT

See below
Cardiac Family History Service pathway summary (adults)

Intermediate probability

Prevalent screen
- Identify ‘at risk’ fdrs
- Offer echo & ECG
- Cardiology review of ECGs & abnormal echo

Children (<16 years)
- discuss at MDT

No other affected relatives

Intermediate probability
- Store DNA
- Standardised PIL

>1 affected relatives

High probability
- Refer to Northern Genetics Service
High probability of familial dilated cardiomyopathy (Northern Genetics Service pathway)

Consider diagnostic genetic test (INDEX CASE)

Mutation positive

Cascade testing using genetic test

Mutation negative *

Cascade testing using echo & ECG (NGS coordinates)

Manage DCM as appropriate

* or genetic test not done

Mutation negative

Discharge

Mutation positive

Cardiomyopathy

- Refer to cardiology
- Cascade test offspring if relevant

normal

Discharge

Priority given to families with documented arrhythmia or sudden death, AV block
3. Arrhythmogenic Right Ventricular Cardiomyopathy

Level 1 guidelines: referral for genetic assessment

Refer to Northern Genetics Service

— all cases of ARVC meeting revised 2010 diagnostic criteria

2010 diagnostic criteria for ARVC ¹²

Diagnosis requires 2 major criteria or
  1 major criterion + I minor criterion or
  4 minor criteria

I. Global or regional dysfunction and structural alterations

MAJOR

By 2D echo:
• Regional RV akinesia, dyskinesia, or aneurysm, and 1 of the following (end diastole):
  — PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥19 mm/m²)
  — PSAX RVOT ≥36 mm (corrected for body size [PSAX/BSA] ≥21 mm/m²)
  — or fractional area change ≤33%

By MRI:
• Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following:
  — Ratio of RV end-diastolic volume to BSA ≥110 mL/m² (male) or ≥100 mL/m² (female)
  — or RV ejection fraction ≤40%

By RV angiography:
• Regional RV akinesia, dyskinesia, or aneurysm

MINOR

By 2D echo:
• Regional RV akinesia or dyskinesia and 1 of the following (end diastole):
  — PLAX RVOT ≥29 to <32 mm (corrected for body size [PLAX/BSA] ≥16 to <19 mm/m²)
  — PSAX RVOT ≥32 to <36 mm (corrected for body size [PSAX/BSA] ≥18 to <21 mm/m²)
  — or fractional area change >33% to <40%

By MRI:
• Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and 1 of the following:
  — Ratio of RV end-diastolic volume to BSA ≥100 to <110 mL/m² (male) or ≥90 to <100 mL/m² (female)
  — or RV ejection fraction >40% to <45%

II. Characterisation of walls

MAJOR

• Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in >1 sample, with or without fatty replacement of tissue on endomyocardial biopsy

MINOR

• Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in >1 sample, with or without fatty replacement of tissue on endomyocardial biopsy

III. Repolarisation abnormalities

MAJOR

• Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals >14 years of age (in the absence of complete right bundle-branch block QRS ≥120 ms)

MINOR

• Inverted T waves in leads V1 and V2 in individuals >14 years of age (in the absence of complete right bundle-branch block) or in V4, V5, or V6
• Inverted T waves in leads V1, V2, V3, and V4 in individuals >14 years of age in the presence of complete right bundle-branch block

IV. Depolarisation / conduction abnormalities

MAJOR

• Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3)

MINOR

• Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS duration of ≥110 ms on the standard ECG
• Filtered QRS duration (fQRS) ≥114 ms
• Duration of terminal QRS <40 μV (low-amplitude signal duration) ≥38 ms
• Root-mean-square voltage of terminal 40 ms ≤20 μV
• Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R0, in V1, V2, or V3, in the absence of complete right bundle-branch block

V. Arrhythmia

MAJOR

• Nonsustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)

MINOR

• Nonsustained or sustained ventricular tachycardia of RV outflow configuration, left bundle-branch block morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis
• >500 ventricular extrasystoles per 24 hours (Holter)
VI. Family History

MAJOR

• ARVC/D confirmed in a first-degree relative who meets current Task Force criteria
• ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative
• Identification of a pathogenic mutation categorized as associated or probably associated with ARVC/D in the patient under evaluation

MINOR

• History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria
• Premature sudden death (≤35 years of age) due to suspected ARVC/D in a first-degree relative
• ARVC/D confirmed pathologically or by current Task Force Criteria in second-degree relative
Level 3 guideline: Northern Genetics Service

1. National & international position statements


- HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. Europace 2011;13:1077-1109

2. Diagnostic genetic testing (Consultant led)

- Diagnostic genetic testing according to standard departmental protocol should only be considered in patients who fulfil the conventional diagnostic criteria for ARVC. It is not a diagnostic test in its own right, but enables more accurate cascade screening of relatives.

- Testing in patients who do not fulfil the diagnostic criteria should be undertaken with caution.

3. Predictive genetic testing (Counsellor led)

- Predictive genetic testing according to standard departmental protocol should be offered to all families where a pathogenic mutation has been identified. Testing in children below the age of 12 would not usually be considered unless there is an adverse family history, or for reasons of parental anxiety.

- It is very difficult to give anything more than general prediction about the likely phenotype in a family.
Level 3 guideline: cardiology

1. Surveillance of at-risk individuals

- 2-5 yearly echo and ECG from 20

The roles of cardiac MRI and Holter monitoring in a screening context have not been established.

Familial disease may be present in 28% of cases. Criteria for diagnosis of ARVC in this screening context are probably different to those used in a diagnostic context. Since a positive family history increases the prior risk of disease, subtle changes otherwise considered non-diagnostic may indicate early disease.\(^{11}\)

2. Definition of ‘affected status’ in fdr of index case\(^{13}\)

- ARVC in a first-degree relative plus one of the following:
  - T wave inversion in right precordial leads (V₂ and V₃),
  - Late potentials on signal-averaged ECG,
  - LBBB-type VT on ECG, Holter monitoring or during exercise testing; >200 extrasystoles over a 24 hour period,
  - Mild global RV dilatation or reduction in ejection fraction with normal LV; mild segmental RV dilatation; regional RV hypokinesia.

---

\(^{13}\) Hamid MS et al. Prospective evaluation of relatives for familial arrhythmogenic right ventricular cardiomyopathy/dysplasia reveals a need to broaden diagnostic criteria. J Am Coll Cardiol 2002;40(8):1445-50
4. Arrhythmia syndromes

Level 1 guidelines: referral for genetic assessment

Refer to Northern Genetics Service
— all cases of defined arrhythmia syndrome (long QT syndrome, Brugada syndrome, CPVT etc.)

Level 3 guidelines: clinical genetics

1. National and international position statement¹⁴

- HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. Europace 2011;13:1077-1109

2. Diagnostic genetic testing (Consultant led)

- Diagnostic genetic testing according to standard departmental protocol should be considered in patients who fulfil conventional diagnostic criteria. These are not diagnostic tests in its own right, but enable more accurate cascade screening of relatives.
- Genetic testing should be considered for patients with a firm clinical diagnosis of congenital LQTS irrespective of the presence of symptoms or the existence of other family members.
- Genetic testing is not recommended for diagnosis of uncertain or ‘borderline’ congenital LQTS [including suspected drug-induced QT prolongation / TdP] outside the setting of expert and detailed family assessment.
- Genetic testing is recommended for patients with a clinical diagnosis of Jervell Lange-Nielsen, Timothy or Andersen syndromes.
- Genetic testing is recommended in individuals with clinical features typical of CPVT following expert clinical assessment.
- Genetic testing may be helpful in individuals with confirmed Brugada syndrome, although its role in individuals with asymptomatic incidental type 1 and type 2 Brugada ECGs is not clear and should only be undertaken in the context of expert clinical and detailed family assessment.

3. Predictive genetic testing (Counsellor led)

- Predictive genetic testing according to standard departmental protocol should be offered to all families where a pathogenic mutation has been identified. Testing in children below the age of 12 would not usually be considered unless there is an adverse family history, or for reasons of parental anxiety. It is very difficult to give anything more than general prediction about the likely phenotype in a family.

4. *Cascade clinical testing (Consultant led)*

- In families in which a gene mutation has not been identified in the index case, first degree relatives (and beyond, according to clinical assessment and family wishes) should be offered clinical screening using 12 lead ECG. This may be repeated periodically if there is a concern that they are at risk of a detectable arrhythmia syndrome, although the recommended interval between ECGs is a matter for individual consideration.
5. Premature sudden unexplained death (<40 years of age)

1. International position statement

   - HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. Europace 2011;13:1077-1109

   “For all SUDS and SIDS cases, collection of a tissue sample is recommended (5–10 mL whole blood in EDTA tube, blood spot card, or a frozen sample of heart, liver, or spleen) for subsequent DNA analysis/genetic testing.”

2. Level 1 guidelines: pathology pathway

   **Coroner’s autopsy**

   Sudden Unexplained Death or Sudden Cardiac Death

   **1 Store DNA**

   10ml blood in EDTA or 1cm² fresh spleen or liver or 2cm³ muscle or skin

   send to:
   Northern Molecular Genetics Service, Institute of Human Genetics, Central Parkway, Newcastle upon Tyne, NE1 3BZ

   **2 Notify deceased person’s GP & HM Coroner about possible hereditary nature of findings**

   Add statement to PM report (the following are examples):

   **SUD:**

   “Unexplained death may be caused by inherited cardiac disease. The deceased individual’s relatives may therefore be at risk. Please refer the deceased individual’s next of kin to the Cardiac Family History Service, Sunderland Royal Hospital, Kayll Road, Sunderland, SR4 7TP or equivalent local service (for those whose families reside outside the Northern region).”

   **SCD:**

   “Death has been caused by a cardiac disease which may have a genetic basis. The deceased individual’s relatives may therefore also be at risk. Please refer the deceased individual’s next of kin to the Cardiac Family History Service, Sunderland Royal Hospital, Kayll Road, Sunderland, SR4 7TP or equivalent local service (for those whose families reside outside the Northern region).”
Level 1 guidelines: referral for genetic assessment

Include either
1. Sudden unexplained death: no cause identified, age <40
2. Sudden unexplained death: no cause identified, age <40, past history of ‘epilepsy’
3. Sudden cardiac death: possible genetic cause identified (e.g. unexplained aortic root dissection in young person, cardiomyopathy)

Exclude where possible
− Cases where an alternative cause of death has been established

Refer to Cardiac Family History Service
− all first degree relative or spouse/partner of deceased individual
Level 2 guidelines: Cardiac Family History Service

Level 2 protocol: sudden unexplained death

1. Obtain 3-generation family history

2. Confirm reported diagnoses if possible (cardiac, epilepsy, sensorineural hearing loss, drowning, coroner’s autopsies)

3. Obtain copy of deceased individual’s coroner’s autopsy. Confirm whether a DNA sample has been stored.

3. All first degree relatives of the deceased individual:
   - standard 12 lead ECG
   - transthoracic echocardiogram

   In addition, if there is a history of faints, dizzy spells, unexplained LOC:
   - Holter ECG
   - exercise ECG

Discharge to referring clinician

– individuals with normal cardiac investigations

Refer to local Cardiology service

– individuals found to have cardiac abnormality on screening investigations

Refer to Northern Genetics Service

– families in which a diagnosis of an inherited cardiovascular condition is made

Discuss at clinical supervision / MDT

– fdrs <16 who need screening investigations
Level 3 guideline: Northern Genetics Service

1. Molecular autopsy

There is currently no role for *routine* molecular autopsy using DNA from a deceased individual. This technique should be considered in autopsy negative SADS where the circumstances of death suggest a particular diagnosis (such as emotional stress, acoustic trigger, drowning as the trigger of death)\(^{15}\) but no surviving affected relative can be identified on prevalent screening. This requires a stored DNA sample from the deceased individual.

2. Diagnostic and cascade testing

- Genetic testing should be considered in all families where an inherited cardiac condition is identified in at least one surviving first-degree relative of an individual who has died suddenly and prematurely. The mutation should be confirmed in the deceased where DNA has been stored at autopsy.

- Genetic testing should be undertaken in keeping with the relevant section of this document.

Level 3 guideline: cardiology

Clinical management is dependent on the disease identified.

\(^{15}\) e.g. death following exposure to loud noise (type 2 LQTS); familial drowning (type 1 LQTS; CPVT)
6. Heritable lipid abnormalities [Familial hypercholesterolaemia\textsuperscript{16}]

New diagnostic DNA analysis and DNA-based cascade testing has yet to be commissioned. This component of the guideline has been temporarily suspended.

\textsuperscript{16} see NICE 2008 Familial hypercholesterolaemia: identification and management.
7. Cardiovascular connective tissue disorders (CCTD)

Includes Marfan syndrome, Ehlers Danlos syndrome and bicuspid aortic valve + dilated aortic root

Level 1 guidelines: referral for genetic assessment

Refer to Northern Genetics Service

Marfan syndrome:
- People with a known family history of Marfan syndrome or related disorders
- People thought to have Marfan syndrome on the basis of their skeletal morphology (most of these are adolescents). Include a recent echocardiogram report detailing aortic root dimensions if possible.*
- Young people (<50) with dilated aortic roots in the absence of an obvious risk factor.
- People with a young first degree relative (<50) who has died from aortic root dissection / rupture. Sometimes the deceased relative was thought to have Marfan syndrome by a pathologist; sometimes there appears to be a family history of familial aortic root dissection / aneurysm.

Ehlers Danlos syndrome:
- Young people presenting with unusual vascular disease, such as unexplained iliac, mesenteric or subclavian artery aneurysms or rupture (i.e. possible vascular Ehlers-Danlos syndrome)
- People with a young first degree relative with a similar presentation
- Suspected Ehlers-Danlos syndrome with mitral valve prolapse / aortic root dilatation

'Bicuspid aortic valve plus':
- Individuals with bicuspid aortic valve plus proximal aortic dilatation and/or aortic coarctation or patent ductus arteriosus

* All echo reports should contain absolute or indexed aortic root measurements. A statement that the aortic root dimensions are ‘normal’ or ‘within normal limits’ is unacceptable.
A. Marfan syndrome

Level 3 guideline: Northern Genetics Service

1. Clinical diagnosis

- Record all examination findings on a Marfan syndrome diagnostic chart and take a 3-generation family history.
- Children below 6 require ophthalmologic assessment; those above 6 are unlikely to have dislocated lenses unless they have a significant refractory error.
- Differential diagnosis includes:
  - familial thoracic aortic aneurysm/dissection (FTAAD)
  - osteoarthritic-aneurysm syndrome
  - Loeys Dietz syndrome
  - Beal syndrome
  - vascular Ehlers Danlos syndrome

Diagnosis should be undertaken using the revised Ghent diagnostic criteria17 (Appendix 2)

2. Diagnostic genetic testing (Consultant led)

- Diagnostic genetic testing according to standard departmental protocol should be considered on a case-by-case basis in the following groups:
  - FBN1 sequencing and MLPA
    - In individuals where the presence of a mutation would confirm a diagnosis using Ghent criteria
    - In individuals requesting prenatal or pre-implantation genetic diagnosis
    - In large families where the identification of a mutation would allow exclusion of individuals from surveillance
    - In selected individuals with FTAAD
  - TBFBR2 and TGFBR1 sequencing and MLPA
    - In individuals in whom a diagnosis of Loeys-Dietz syndrome is being considered
    - In individuals with FTAAD
  - ACTA2, MYH11, SMAD3
    - In individuals with FTAAD.
    - SMAD3 only in individuals with suspected osteoarthritic-aneurysm syndrome.
  - COL3A1
    - In individuals with suspected vascular EDS or selected individuals with FTAAD.

---

3. Predictive genetic testing (Counsellor led)

- Predictive genetic testing according to standard departmental protocol should be offered to all families where a pathogenic mutation has been identified. Testing in children should be considered routine. It is difficult to give anything more than general prediction about the likely phenotype in an individual, although aortic root pathology and lens dislocation tend to breed true in Marfan syndrome.
Level 3 guideline: cardiological surveillance (see also Appendix 1)

Standardisation

- Aortic root measurement at annulus, sinuses of Valsalva and sinotubular junction (see Appendix 1)
- Body surface area calculation using the Mosteller or Dubois formulae\textsuperscript{18,19}
- For adults, aortic root measurements plotted on graphs published by Roman\textsuperscript{20}
- For children and adolescents, aortic root measurements plotted on graphs published by Daubeney\textsuperscript{21}
- Z scores are increasingly being used: online calculators\textsuperscript{22} may be used with caution

All echo reports should contain absolute or indexed aortic root measurements. A statement that the aortic root dimensions are ‘normal’ or ‘within normal limits’ is unacceptable.

1. Thoracic aorta (transthoracic echocardiography)

<table>
<thead>
<tr>
<th>scenario</th>
<th>surveillance guideline</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>‘at risk’ (insufficient Ghent diagnostic criteria)</td>
<td>Echo at referral, 5,10,15,20 and 25 discharge if echo normal at 25</td>
<td>CCTD clinic</td>
</tr>
<tr>
<td>‘at risk’ (50% familial risk)</td>
<td>As above, continue until 5 years after last pregnancy in females</td>
<td>CCTD clinic</td>
</tr>
<tr>
<td>Marfan syndrome affected and FBN1 mutation carriers (normal heart on last exam)</td>
<td>5, 10, 2 yearly 10-20, then 5 yearly for life</td>
<td>Cardiology clinic</td>
</tr>
<tr>
<td>Marfan syndrome affected (dilated aortic root)</td>
<td>Minimum annual, depending on rate of dilatation</td>
<td>Cardiology clinic</td>
</tr>
</tbody>
</table>

2. Abdominal aorta (abdominal U/S)

<table>
<thead>
<tr>
<th>scenario</th>
<th>surveillance guideline</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marfan syndrome affected and FBN1 mutation carriers (normal heart on last exam)</td>
<td>5 yearly for life from 50</td>
<td>Cardiology clinic</td>
</tr>
<tr>
<td>Marfan syndrome affected (dilated aortic root)</td>
<td>5 yearly for life from 50</td>
<td>Cardiology clinic</td>
</tr>
</tbody>
</table>

\textsuperscript{18} Mosteller RD Simplified calculation of body-surface area. \textit{NEJM} 1987;317:1098

\textsuperscript{19} Body surface area (m\textsuperscript{2}) = \left(\frac{\text{Height(cm) \times Weight(kg)}}{3600}\right)^{0.75}

\textsuperscript{19} Body surface area (m) = 0.007184 \times (\text{patient height in cm})^{0.725} \times (\text{patient weight in kg})^{0.425} ; \text{See http://bnf.org/bnf/extra/current/450018.htm}

\textsuperscript{20} Roman MJ et al Am J Cardiol 1989;64:507-512

\textsuperscript{21} Daubeney PEF et al Relationship of the dimension of cardiac structures to body size: an echocardiographic study in normal infants and children. Cardiol Young 1999;9:402

\textsuperscript{22} e.g. http://aoroot.parameterz.com/
3. Rare variant and related phenotypes

<table>
<thead>
<tr>
<th>Familial thoracic aortic aneurysm* (normal heart on last exam)</th>
<th>Whole body and cerebral MRA at diagnosis, depending on family phenotype and / or genotype</th>
<th>CCTD clinic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 yearly echo from 20 for life</td>
<td>Cardiology clinic</td>
</tr>
<tr>
<td>Loeys Dietz syndrome**</td>
<td>Whole body MRA and cerebral MRA at diagnosis</td>
<td>CCTD clinic</td>
</tr>
<tr>
<td></td>
<td>Annual echo</td>
<td>Cardiology clinic</td>
</tr>
</tbody>
</table>

* this usually presents in adulthood; those with dilated aortic roots should be managed as for Marfan syndrome.

** aortic dissection may occur at relatively normal aortic root diameters; aortic root surgery should be considered when the SVS diameter reaches 40mm; distal arterial ectasia, aneurysm and dissection occur; intracranial haemorrhage is well described.
B. Ehlers-Danlos syndromes

Level 3 guideline: Northern Genetics Service

1. Clinical diagnosis

- Clinical diagnosis should be in keeping with the revised diagnostic criteria\(^{23}\) and the Oxford Desk Reference guidelines\(^{24}\).

2. Diagnostic genetic testing (Consultant led)

- Diagnostic genetic – or ultrastructural / biochemical – testing is not recommended routinely for classical or hypermobile EDS.
- Patients with possible vascular EDS should be offered skin biopsy for studies of collagen III biochemistry and ultrastructural study using TEM. COL3A1 mutation analysis may also be considered.

3. Role of echocardiography in diagnostic assessment

Mild aortic root dilatation or mitral valve abnormalities have been reported in limited cross-sectional series of classical or hypermobile EDS patients.\(^{25,26}\) Most deaths in vascular EDS are caused by arterial rupture / dissection in normal calibre arteries.\(^{27}\)

- Transthoracic echocardiography may be considered as part of the diagnostic assessment for classical and hypermobile EDS but is of little value in suspected vascular EDS.

4. Predictive genetic testing (Counsellor led)

Predictive genetic testing according to standard departmental protocol should be offered to all families where a pathogenic mutation has been identified. Testing in children should be considered routine.

*It is difficult to give anything more than general prediction about the likely phenotype in an individual.*

---


\(^{27}\) Pepin M et al. Clinical and genetic features of Ehlers-Danlos syndrome type IV, the vascular type. NEJM 2000;342:730-732
Level 3 guideline: cardiological surveillance

**Standardisation**
- Aortic root measurement at annulus, sinuses of Valsalva *and* sinotubular junction
- Body surface area calculation using the Mosteller formula\(^2^8\)
- Aortic root measurements plotted on graphs published by Roman\(^2^9\)

The cardiac natural history of classical and hypermobile Ehlers Danlos syndrome is poorly understood and currently extrapolated from small cross-sectional series. Although mild abnormalities are prevalent in published series, the risk of aortic root dissection and clinically significant mitral valve disease appears to be lower than in Marfan syndrome, with only occasional case reports.

- There is currently no longitudinal evidence base to support on-going cardiac imaging surveillance in patients with either classical or hypermobile EDS.
- There is currently no evidence base to support on-going cardiovascular imaging surveillance in patients with vascular EDS.

<table>
<thead>
<tr>
<th>Hypermobile Ehlers Danlos syndrome (type III)</th>
<th>Echo at age 20 or at time of diagnosis (whichever is later) Follow-up only if baseline abnormalities found</th>
<th>Cardiology clinic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular Ehlers Danlos syndrome (type IV)***</td>
<td>Whole body MRA and cerebral MRA at diagnosis Annual clinical review</td>
<td>CCTD clinic</td>
</tr>
</tbody>
</table>

*** predisposes to extreme vascular fragility, rupture and dissection; the role of surveillance has not been established

---

\(^{2^8}\) Mosteller RD. Simplified calculation of body-surface area. *NEJM* 1987;317:1098  
\(^{2^9}\) BSA (m\(^2\)) = ( [Height(cm) x Weight(kg)] / 3600)\(^{1/2}\)  
\(^{2^0}\) Roman MJ et al. Am J Cardiol 1989;64:507-512
C. ‘Bicuspid aortic valve plus’

There is some evidence that the triad of bicuspid aortic valve (BAV), dilated aortic root and aortic coarctation / patent ductus arteriosus is a discrete phenotype caused by abnormalities in the NOTCH signalling pathway.\textsuperscript{30}

This is an area for further research, although it would seem sensible to offer the close relatives of such patients an echo to screen for BAV, and ongoing surveillance of the aortic root in those found to have a BAV.

This is probably a rare phenotype and at present there is no indication for a standardised protocol.

Appendix 1: normal aortic root dimensions\textsuperscript{1,2}

1. Standardised measurements

Measurements are taken from the parasternal long axis view in the anterior-posterior plane, perpendicular to the long axis of the aorta, at end diastole (valve closed).

Note: The leading edge to leading edge method is used for measurements 2,3 and 4. This approach is adopted as the normative data used for reference were obtained using the leading edge to leading edge technique.

1 = annulus  
2 = sinuses of Valsalva  
3 = sinotubular junction  
4 = proximal ascending aorta

\textsuperscript{1} Roman MJ et al. Two-Dimensional Echocardiographic Aortic Root Dimensions in Normal Children and Adults  
Am J Cardiol 1989;64:507-512

\textsuperscript{2} Daubeney PEF et al Relationship of the dimension of cardiac structures to body size: an echocardiographic study in normal infants and children. Cardiol Young 1999;9:402
2. Standardised reference ranges

2.1 Infants & children (Daubeney et al Cardiol Young 1999;9:402)

These data were derived from normal children. Note that the reference ranges in children with confirmed Marfan syndrome may be different.\(^{31}\)

2.2 Adults < 40 (Roman et al Am J Cardiol 1989;64:507-512)

95% confidence limits

See also: British Society of Echocardiography Education Committee. Echocardiography: Guidelines for Valve Quantification (http://www.bsecho.org/Guidelines%20for%20Valve%20Quantification.pdf)
2.3 Adults > 40 (Roman et al Am J Cardiol 1989;64:507-512)

95% confidence limits

See also: British Society of Echocardiography Education Committee. Echocardiography: Guidelines for Valve Quantification (http://www.bsecho.org/Guidelines%20for%20Valve%20Quantification.pdf)
Appendix 2: 2010 Ghent diagnostic criteria for Marfan syndrome

In the absence of family history:

1. Dilated aortic root (Z ≥ 2) AND ectopia lentis
2. Dilated aortic root (Z ≥ 2) AND FBN1 mutation
3. Dilated aortic root (Z ≥ 2) AND Systemic score of ≥ 7 points *
4. Ectopia lentis AND FBN1 mutation with known dilated aorta

In the presence of family history:

5. Ectopia lentis AND FHx of MFS (as defined above)
6. Systemic score of ≥ 7 points AND FHx of MFS (as defined above) *
7. Dilated aorta (Z ≥ 2 above 20 yrs old, ≥ 3 below 20 yrs) + FHx of MFS (as defined above) *

* Without discriminating features of Shprintzen-Goldberg syndrome, Loeys-Dietz syndrome or vascular EDS AND after TGFBR1/2, collagen biochemistry, COL3A1 testing if indicated

Systemic score calculator:

<table>
<thead>
<tr>
<th>Feature</th>
<th>Value</th>
<th>Enter Value if Present</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrist AND thumb sign</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Wrist OR thumb sign</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pectus carinatum deformity</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Pectus excavatum or chest asymmetry</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hindfoot deformity</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Plain flat foot (pes planus)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Dural ectasia</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Protrusio acetabulae</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Reduced upper segment / lower segment and increased armspan/height</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Scoliosis or thoracolumbar kyphosis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Reduced elbow extension</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>3 of 5 facial features</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Skin striae</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Myopia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Appendix 3: common clinical codes, Northern Genetics Service

<table>
<thead>
<tr>
<th>Condition</th>
<th>Code 1</th>
<th>Code 2</th>
<th>Code 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden unexplained death</td>
<td>59210</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial hypertrophic cardiomyopathy</td>
<td>192600</td>
<td>MYH7</td>
<td>160760</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MYBPC3</td>
<td>600958</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TNNT2</td>
<td>191045</td>
</tr>
<tr>
<td>Left ventricular hypertrophy, unexplained</td>
<td>55910</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial dilated cardiomyopathy</td>
<td>115200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial restrictive cardiomyopathy</td>
<td>115210</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARVC</td>
<td>107970</td>
<td>PKP2</td>
<td>602861</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DSP</td>
<td>125647</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DSG2</td>
<td>125671</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DSC2</td>
<td>125645</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JUP</td>
<td>173325</td>
</tr>
<tr>
<td>Long QT syndrome</td>
<td>192500</td>
<td>KCNQ1</td>
<td>192500</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KCNH2</td>
<td>152427</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SCN5A</td>
<td>600163</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KCNE1</td>
<td>176261</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KCNE2</td>
<td>603796</td>
</tr>
<tr>
<td>Brugada syndrome</td>
<td>601144</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPVT</td>
<td>604772</td>
<td>RYR2</td>
<td>180902</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CASQ1</td>
<td></td>
</tr>
<tr>
<td>Familial AF</td>
<td>607554</td>
<td>KCNQ1</td>
<td>192500</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KCNH2</td>
<td>152427</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SCN5A</td>
<td>600163</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KCNE1</td>
<td>176261</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KCNE2</td>
<td>603796</td>
</tr>
<tr>
<td>Marfan syndrome</td>
<td>154700</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Familial thoracic aortic aneurysm / dissection</td>
<td>607086</td>
<td>MYH11</td>
<td>160745</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ACTA2</td>
<td>102620</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SMAD3</td>
<td>613795</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MYLK</td>
<td>600922</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TGFBR1</td>
<td>190181</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TGFBR2</td>
<td>190182</td>
</tr>
<tr>
<td>Familial hypercholesterolaemia</td>
<td>143890</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fabry disease</td>
<td>301500</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>