CARDIGEN

Cardiac Genetics in the North of England

Cardiac Family History Service
and
Northern Genetics Service

Guidelines

North of England Cardiovascular Network

The North of England
Cardiac Family History Service

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

Referral addresses:

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Abbreviations + definitions

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

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

[1] Van Driest et al. Sarcomeric genotyping in hypertrophic cardiomyopathy. Mayo Clinic Proceedings. 2005;80:463-9
[2] Charron et al. Accuracy of European diagnostic criteria for familial hypertrophic cardiomyopathy in a genotyped population. Int J Cardiol 2003;90:33-40

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 / LVNCC

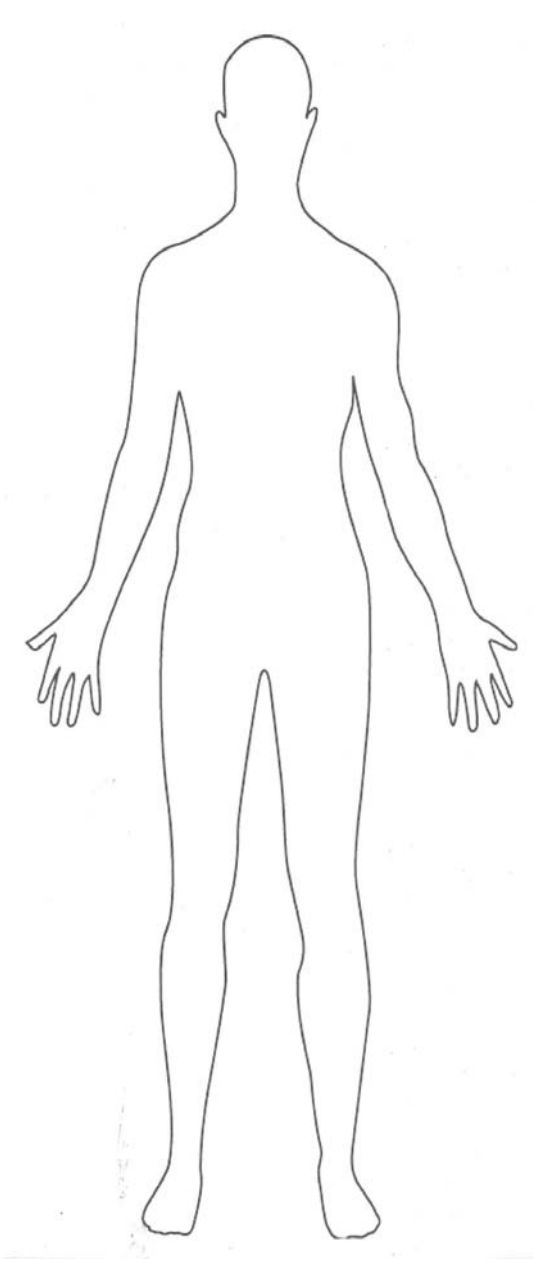
1. Obtain 3-generation family history

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	Danon disease
	Noonan syndrome
Ataxia	Friedreich ataxia
Eye	
Retinitis pigmentosa	mitochondrial cytopathy
Ear	
Deafness	mitochonrial cytopathy
	Fabry disease
Heart	
Congenital heart disease	Noonan syndrome
WPW	PRKAG2 gene
	Danon disease
Kidney	
Chronic renal failure	Fabry disease
Hydronephrosis	Noonan syndrome
Skin	
Red spotty rash	Fabry disease
Multiple pigmented naevi	NF/Noonan
Muscle	
Proximal myopathy	Danon
↑ CK	non-specific
contractures	laminopathy
fatigue	mitochondrial cytopathy
Nerve	
Acroparaesthesia	Fabry disease
Metabolic	
Diabetes	mitochondrial cytopathy
Diabetes + lipoatrophy	laminopathy
↑ lactate	mitochondrial cytopathy
Inheritance	
Maternal	mitochondrial cytopathy
X-linked	Fabry disease
	Danon disease

Traffic light guideline summary (hypertrophic cardiomyopathy)

Low probability *	Intermediate probability**	High probability***
– Cases with non-diagnostic family history – Cases not fulfilling conventional diagnostic criteria	Isolated case†	– 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
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. HRUK position statement[3]

- Genetic testing is not recommended for diagnosis of hypertrophic cardiomyopathy outside the setting of expert clinical and detailed family assessment.
- Genetic testing should be considered for patients with a firm clinical diagnosis of hypertrophic cardiomyopathy as a means of cascade screening of relatives, in the setting of expert clinical and detailed family assessment.

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. 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.

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.

[3] Heart Rhythm UK Familial Sudden Death Syndromes Statement Development Group. Clinical indications for genetic testing in familial sudden cardiac death syndromes: an HRUK position statement. Heart 2008;94:502-507

Level 3 guideline: cardiology

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

- at 50% risk (from Maron et al 2004[4]):

<12 years	Optional unless: family history of SCD competitive athlete in intense training programme symptoms or clinical suspicion of LVH present
12 – 21 years	12-18 monthly echo & ECG
>21 years	5 yearly echo & ECG to 50 • continue for longer if there is a family history of late-onset HCM • more frequent if there is a family history of a more malignant phenotype

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[5].

- HCM mutation carrier (normal heart on last exam)

<12 years *	Optional unless: family history of SCD family history of troponin T mutation competitive athlete in intensive training programme symptoms or clinical suspicion of LVH present
12 – 30 years	12 monthly echo & ECG
>30 years	5 yearly echo & ECG for life more frequent if family history of malignant phenotype

** 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[6]*

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

[4] Maron BJ et al. Proposal for contemporary screening strategies in families with hypertrophic cardiomyopathy. J Am Coll Cardiol 2004;44(11):2125-32.
[5] McKenna WJ et al. Experience from clinical genetics in hypertrophic cardiomyopathy: proposal for new diagnostic criteria in adult members of affected families. Heart 1997;77:130-132.
[6] McKenna WJ, Spirito P, Desnos M et al. Experience from clinical genetics in hypertrophic cardiomyopathy: proposal for new diagnostic criteria in adult members of affected families. Heart 1997;77:130-132

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

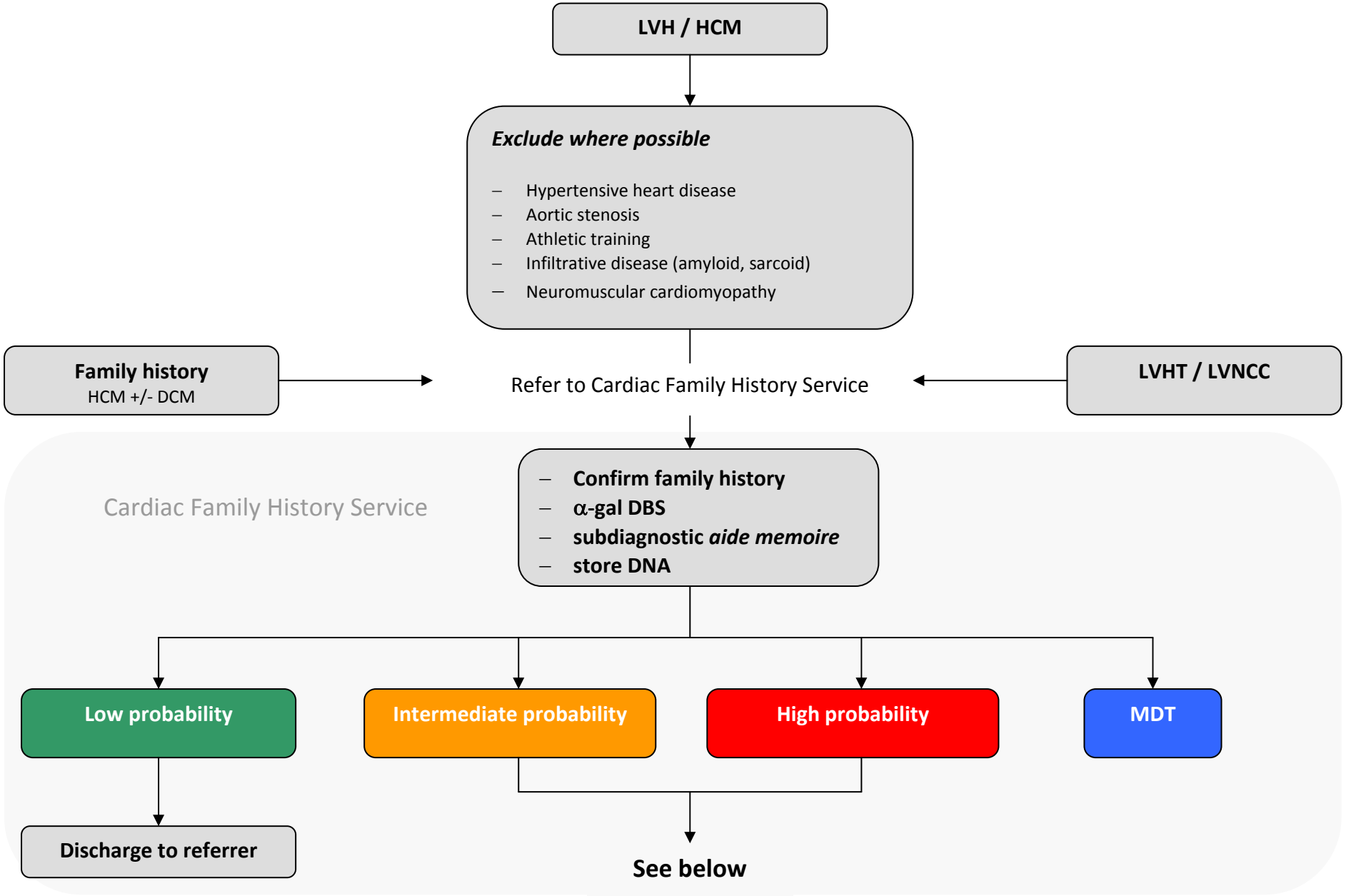
3. Sudden death prophylaxis in HCM [includes the use of ICD and/or amiodarone.]

Patients with ≥ 2 recognised risk factors warrant prophylaxis:

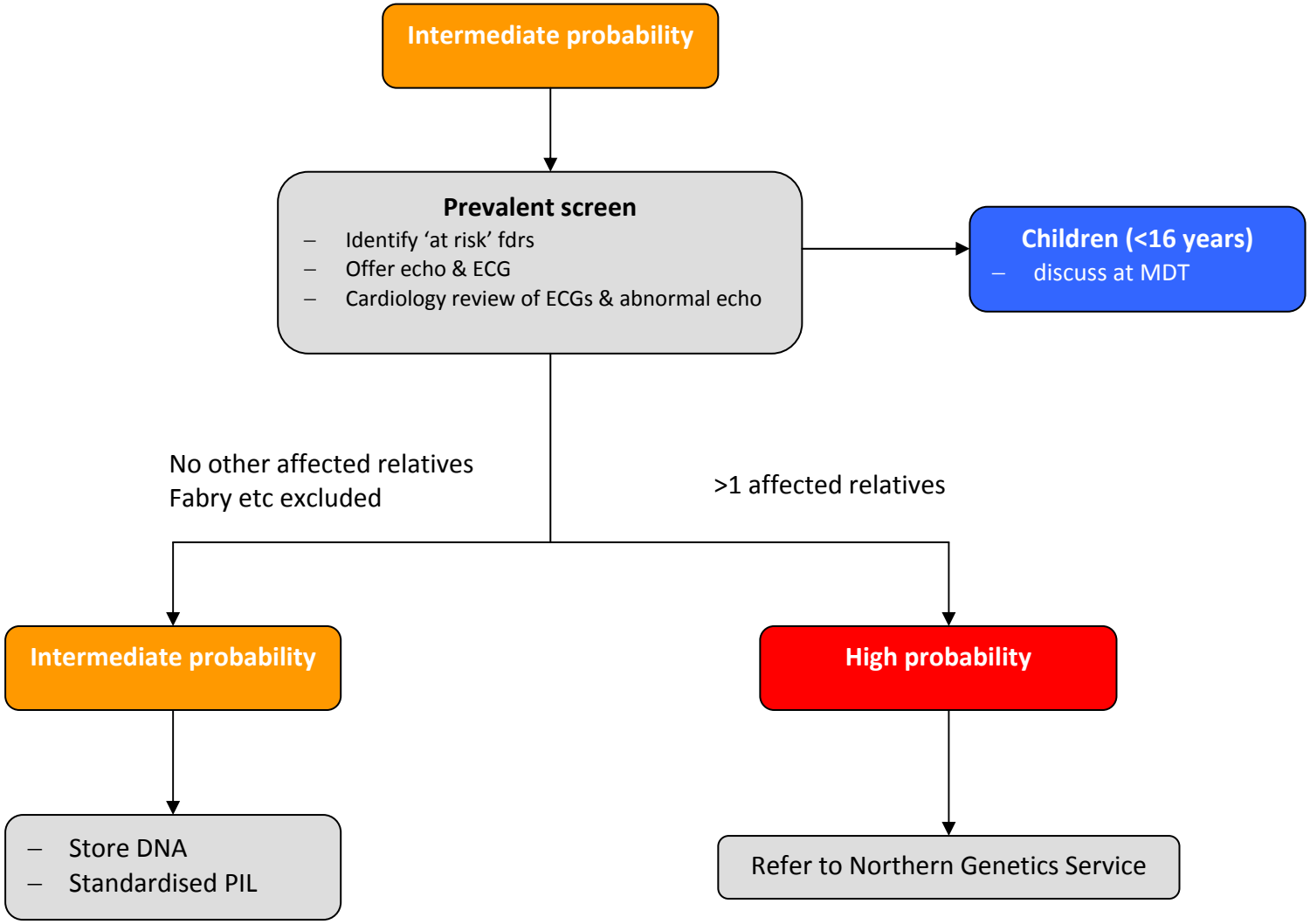
- Previous cardiac arrest
- Non-sustained VT on Holter or exercise
- Abnormal BP response on exercise
- Unexplained syncope
- Family history of premature sudden death
- Severe left ventricular hypertrophy >3 cm

Patients with 1 risk factor require an individualised decision in relation to the strength of the risk factor.

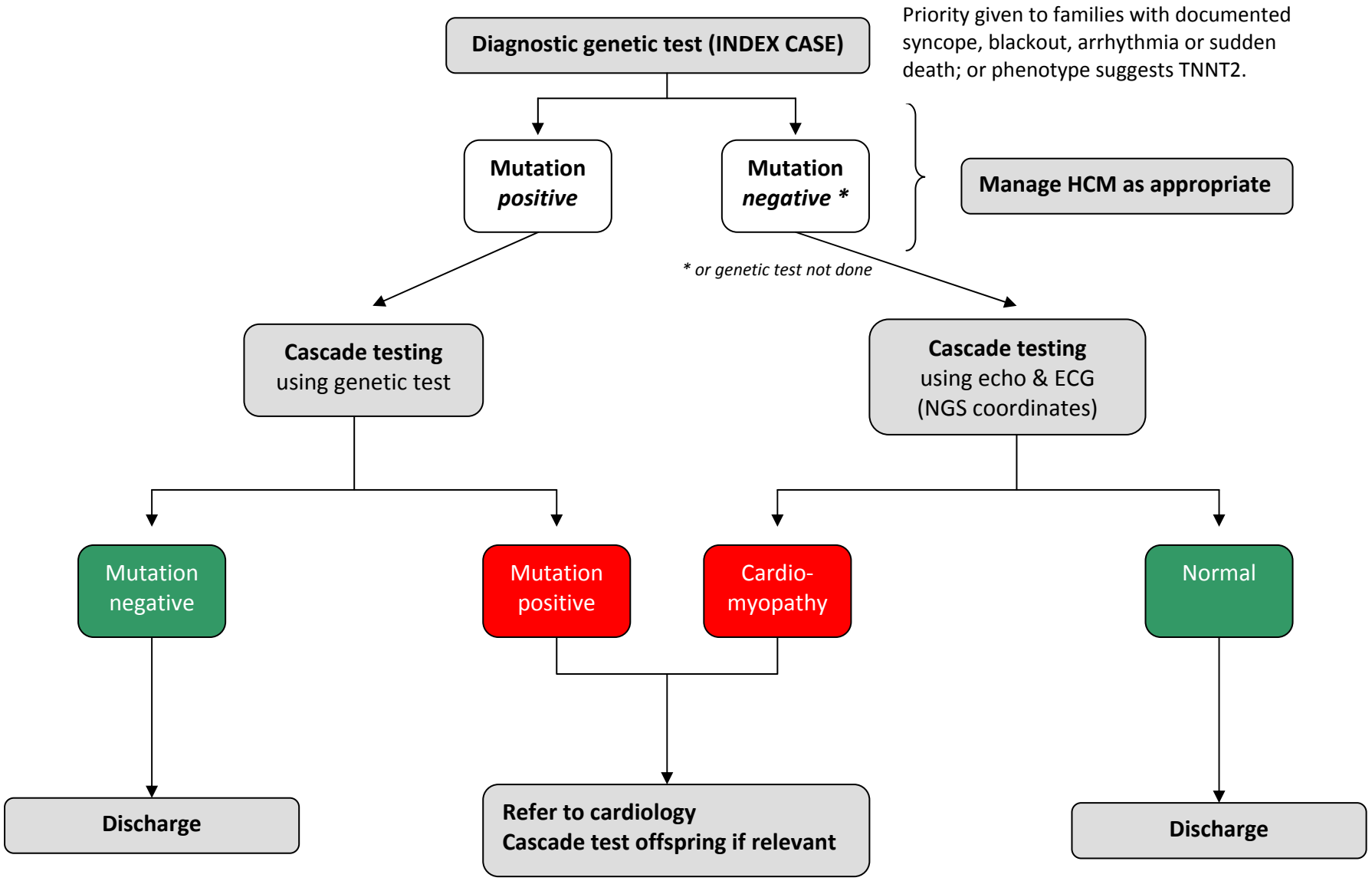
Initial HCM pathway summary (adults)



Cardiac Family History Service pathway summary (adults)



High probability of familial hypertrophic cardiomyopathy (Northern Genetics Service pathway)



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 1999[7])

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

[7] Mestroni L, Maisch B, McKenna WJ et al. Guidelines for the study of familial dilated cardiomyopathies. Eur Heart J 1999;20:93-102

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

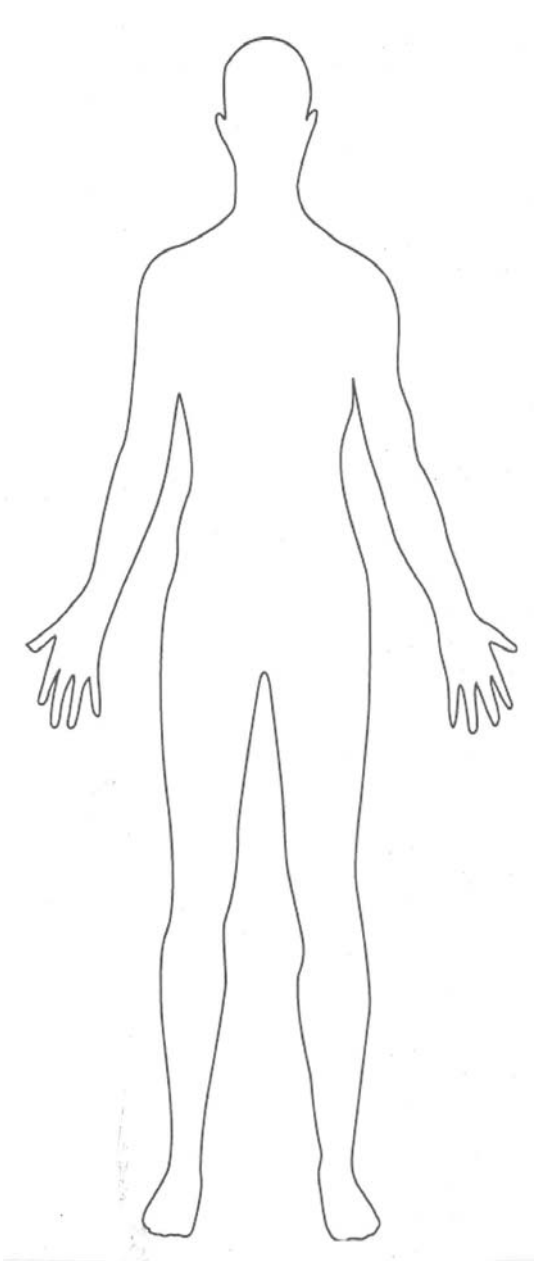
Refer to Northern Genetics Service

– families with 2 of 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	Danon disease
Ataxia	Friedreich ataxia
Eye	
Cataract	myotonic dystrophy
Ear	
Deafness	mitochondrial cytopathy
Heart	
Conduction disease	laminopathy desminopathy
Muscle	
Proximal myopathy	Becker MD
… with contractures	Emery Dreifuss MD (AD)
Fatigue	myotonic dystrophy
Metabolic	
↑ lactate	mitochondrial cytopathy
Inheritance	
X-linked	Becker MD Barth syndrome Danon disease
Pregnancies	
Recurrent hydrops	Barth syndrome

Traffic light guideline summary (dilated cardiomyopathy)

Low risk	Intermediate risk	High risk
– Cases with non-diagnostic family history – Cases not fulfilling conventional diagnostic criteria	Isolated case <50	– families with 2 of 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
Discharge to referrer	Family surveillance	Refer to Genetics

Level 3 guideline: Northern Genetics Service

1. HRUK position statement[8]

- Genetic testing is recommended for patients with a combination of AV block and DCM or where the family history shows evidence of AV block in different relatives[9].
- Genetic testing is not recommended for patients with unexplained DCM alone or unexplained AV block alone.

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 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.

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[8] Heart Rhythm UK Familial Sudden Death Syndromes Statement Development Group. Clinical indications for genetic testing in familial sudden cardiac death syndromes: an HRUK position statement. Heart 2008;94:502-507

[9] over 30% of patients with AV block and DCM have a mutation in LMNA

Level 3 guideline: cardiology

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

- at 50% risk :

20 – 50 years	2 yearly echo & ECG

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[10].

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

20 – 50 years	yearly echo & ECG
>50 years	5 yearly echo & ECG (depending on family history)

N.B. Most familial DCM is autosomal dominant. *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.

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*[11]

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

[10] 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
[11] Mestroni et al. Guidelines for the study of familial dilated cardiomyopathies. European Heart Journ**al 1999** 20(2):93-102

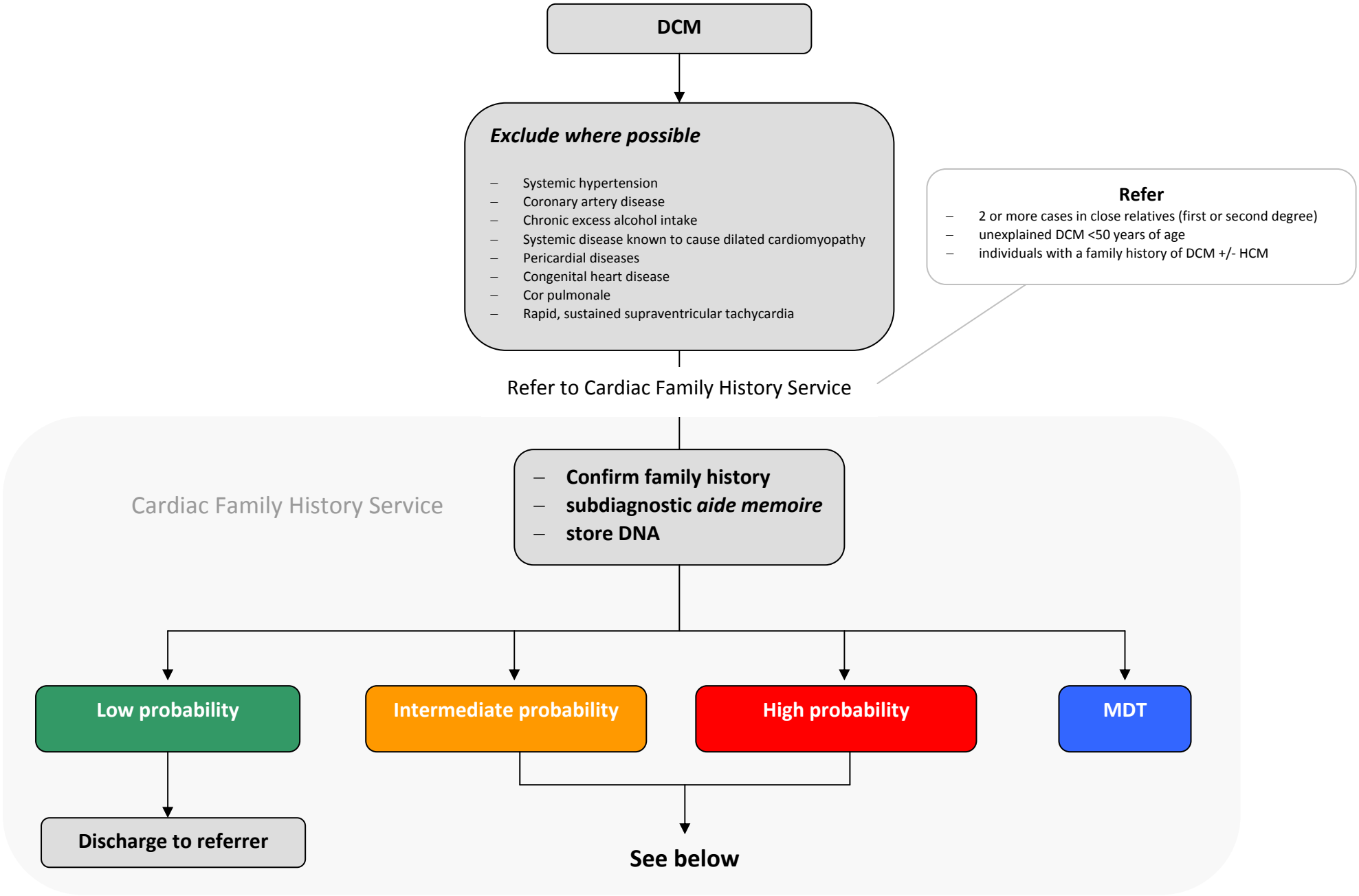
- Unexplained death or stroke before 50
- Segmental wall motion abnormality (>1 segment, or 1 if not previously present) in the absence of intraventricular conduction defect or ischaemic heart disease.

Note: it may be necessary to index LV chamber measurements against Body Surface Area in borderline cases (use Dubois BSA calculator[12] and BSE normal ranges[13])

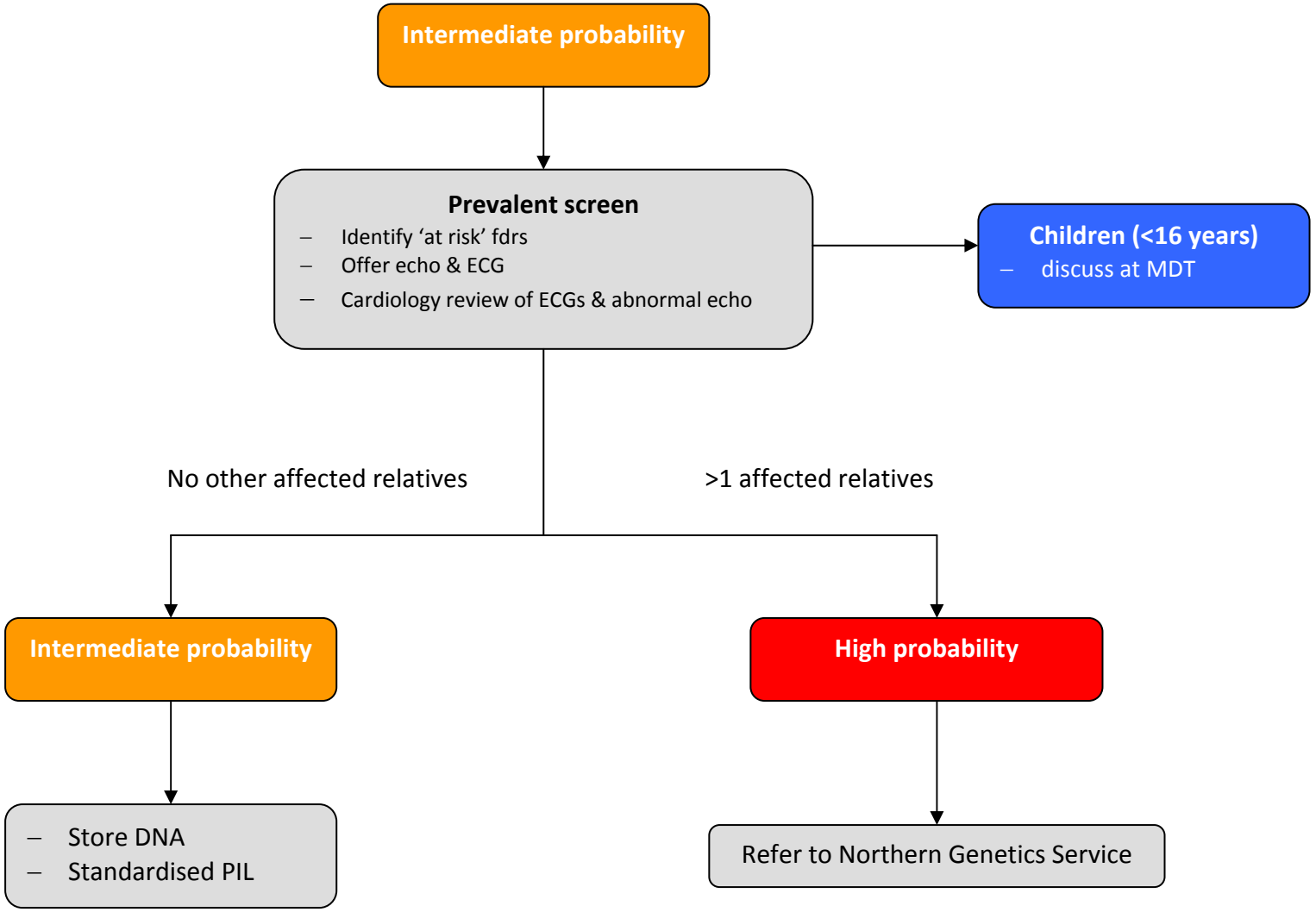
[12] Body Surface area (m) = 0.007184 × (patient height in cm)$^{0.725}$ × (patient weight in kg)$^{0.425}$; See http://bnf.org/bnf/extra/current/450018.htm

[13] British Society of Echocardiography Education Committee. Echocardiography: Guidelines for Chamber Quantification http://www.bsecho.org/Guidelines%20for%20Chamber%20Quantification.pdf

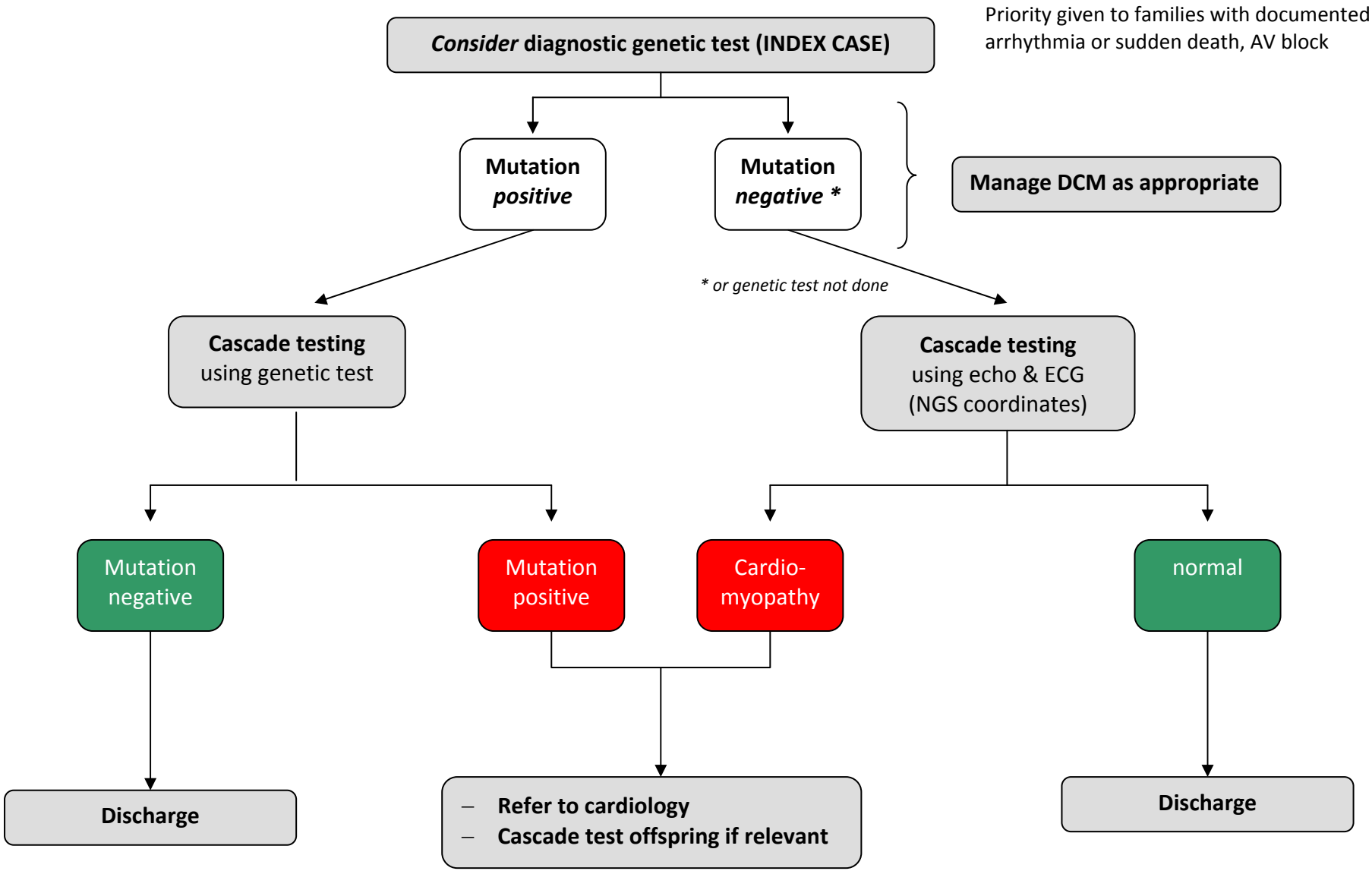
Initial DCM pathway summary (adults)



Cardiac Family History Service pathway summary (adults)

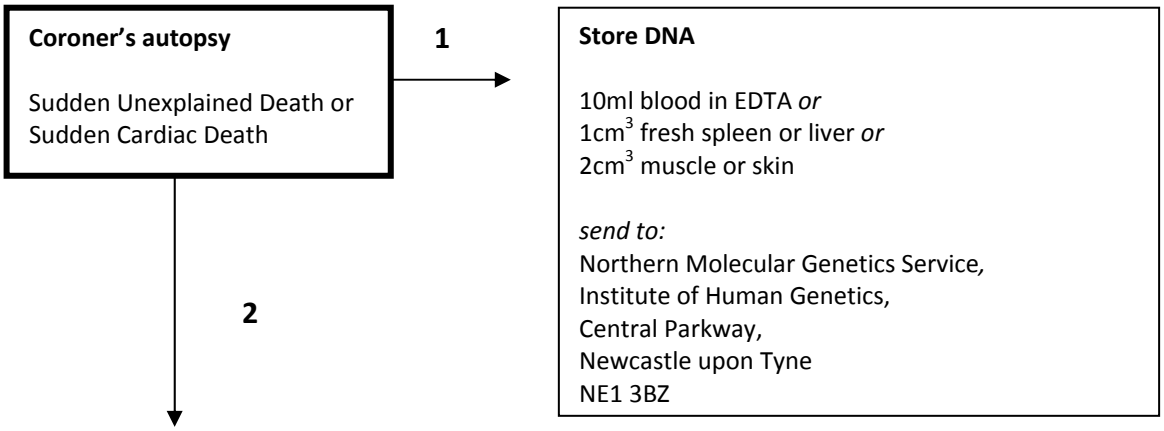


High probability of familial dilated cardiomyopathy (Northern Genetics Service pathway)



3. Premature sudden unexplained death (<40 years of age)

Level 1 guidelines: pathology pathway



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*or*
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 families where the circumstances of death suggest a particular diagnosis[14] but no surviving affected relative can be identified on prevalent screening.

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.

[14] e.g. death following exposure to loud noise (type 2 LQTS); familial drowning (type 1 LQTS; CPVT)

4. Heritable lipid abnormalities [Familial hypercholesterolaemia[15]]

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

[15] see NICE 2008 Familial hypercholesterolaemia: identification and management.

5. Arrhythmogenic Right Ventricular Cardiomyopathy

Level 1 guidelines: referral for genetic assessment

Refer to Northern Genetics Service

– all cases of ARVC meeting conventional diagnostic criteria

Conventional diagnostic criteria for ARVC (McKenna et al 1994[16])

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	Severe dilatation and reduction of RV ejection fraction with no (or only mild) LV impairment
	Localised RV aneurysms (akinetic or dyskinetic areas with diastolic bulging)
	Severe segmental dilatation of the RV
MINOR	Mild global RV dilatation or ejection fraction reduction with normal LV
	Mild segmental dilatation of the RV
	Regional RV hypokinesia

II. Characterisation of walls

MAJOR	Fibrofatty replacement of myocardium on endomyocardial biopsy

III. Repolarisation abnormalities

MINOR	Inverted T waves in right precordial leads (V2 and V3) in people >12 years and in the absence of RBBB

IV. Depolarisation / conduction abnormalities

MAJOR	Epsilon waves or localised prolongation (>110ms) or the QRS complex in right precordial leads (V1 to V3)
MINOR	Late potentials: signal averaged ECG

V. Arrhythmia

MINOR	LBBB-type VT (sustained or non-sustained): ECG, Holter or exercise ECG
	Frequent ventricular extrasystoles (>1000/24hr): Holter

VI. Family History

MAJOR	Familial disease confirmed at autopsy or surgery
MINOR	FHx of young sudden death due to suspected ARVC
	FHx based on clinical diagnostic criteria in relatives

[16] McKenna WJ et al. Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Br Heart J 1994;71:215-218

Level 3 guideline: Northern Genetics Service

1. HRUK position statement[17]

- Genetic testing is not recommended for diagnosis of ARVC outside the setting of expert clinical and detailed family history assessment.
- Genetic testing should be considered for patients with a firm clinical diagnosis of ARVC as a means of cascade screening of relatives, in the setting of expert and detailed family assessment.

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.

[17] Heart Rhythm UK Familial Sudden Death Syndromes Statement Development Group. Clinical indications for genetic testing in familial sudden cardiac death syndromes: an HRUK position statement. Heart 2008;94:502-507

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[18]

– ARVC in a first-degree relative plus one of the following:

- T wave inversion in right precordial leads (V_2 and V_3),
- 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.

3. Sudden death prophylaxis in ARVC: unfavourable prognostic factors[19]

- Previous cardiac arrest *
- Syncope or sustained VT with LOC *
- LV involvement *
- Increased QRS dispersion ($QRS_{max} - QRS_{min} \geq 40ms$)
- Early onset of symptoms
- Severe RV involvement

* merit consideration for ICD implantation

[18] 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
[19] Sen-Chowdhry et al. Arrhythmogenic right ventricular cardiomyopathy: clinical presentation, diagnosis, and management. Am J Med 2004;117:685-95

6. 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. HRUK position statement[20]

- Genetic testing should be considered for patients with a firm clinical diagnosis of the 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 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 is not recommended as routine in known or suspected cases of Brugada syndrome, but may be considered in the setting of expert clinical and detailed family assessment[21].

2. Diagnostic genetic testing (Consultant led)

Diagnostic genetic testing according to standard departmental protocol should be considered in patients who fulfil the conventional diagnostic criteria. These are not diagnostic tests in its own right, but enable more accurate cascade screening of relatives.

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.

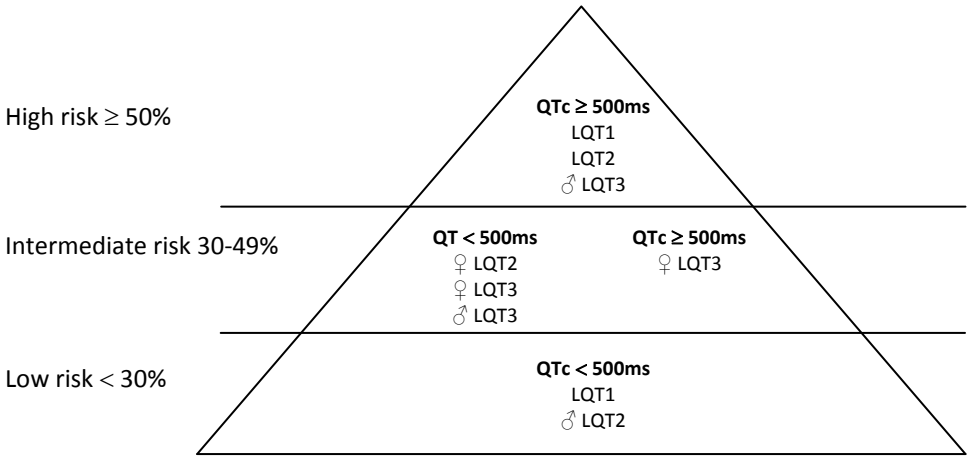
It is very difficult to give anything more than general prediction about the likely phenotype in a family.

[20] Heart Rhythm UK Familial Sudden Death Syndromes Statement Development Group. Clinical indications for genetic testing in familial sudden cardiac death syndromes: an HRUK position statement. Heart 2008;94:502-507

[21] Diagnostic SCN5A mutation analysis should be *considered* in all cases of Brugada syndrome. Priority will be given to those with at-risk relatives. This includes those with classical spontaneous type 1 ECGs, and those with sodium channel blockade-induced type 1 ECGs. Testing in patients with spontaneous type 2 ECGs should be avoided unless they convert to type 1 ECGs under sodium channel blockade. Patients should be informed that the mutation detection rate may be as low as 20%.

Level 3 guidelines: cardiology

1. Sudden death prophylaxis in LQTS : risk stratification[22]



Risk: the probability of a first cardiac event (syncope, cardiac arrest, or sudden death) before the age of 40 years and before therapy.

2. Sudden death prophylaxis in Brugada syndrome[23]

— see appendix 2.

[22] Priori et al. NEJM 2003;348:1866
[23] Antzelevitch C et al. Brugada syndrome. Report of the second consensus conference. Circulation 2005;111:659

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
  - Loeys Dietz syndrome

1. *Where there is no family history*, **a** clinical diagnosis of Marfan syndrome should be confirmed in patients who:

– fulfil major Ghent diagnostic criteria[24] in *two* systems with 'involvement' of a *third* system, OR

– fulfil major Ghent diagnostic criteria in one system with 'involvement' of one system and in the context of a FBN1 mutation known to have caused Marfan syndrome in other family members

2. *Where there is a positive family history* (clinical or genetic), a clinical diagnosis of Marfan syndrome should be confirmed in patients who:

– fulfil major Ghent diagnostic criteria in one system with 'involvement' of a second system

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

– TBFBR2 and TGFBR1 sequencing and MLPA
  - In individuals in whom a diagnosis of Loeys-Dietz syndrome is being considered

– Diagnostic testing in familial thoracic aortic aneurysm families should not be undertaken routinely in view of the multiallelic nature of this condition unless there are diagnostic clinical clues that suggest FBN1 or TGFBR2.

[24] De Paepe et al. Revised diagnostic criteria for the Marfan syndrome. Am J Med Genet 1996;62:417-26

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.

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[25] [26]
- For adults, aortic root measurements plotted on graphs published by Roman[27]
- For children and adolescents, aortic root measurements plotted on graphs published by Daubeney[28]

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)

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

2. Abdominal aorta (abdominal U/S)

scenario	**surveillance guideline**	**Site**
Marfan syndrome affected and FBN1 mutation carriers (normal heart on last exam)	5 yearly for life from 50	Cardiology clinic
Marfan syndrome affected (dilated aortic root)	5 yearly for life from 50	Cardiology clinic

[25] Mosteller RD Simplified calculation of body-surface area. ***NEJM*** 1987;317:1098
BSA (m^2) = ([Height(cm) x Weight(kg)]/ 3600)^{½}

[26] Body Surface area (m) = 0.007184 × (patient height in cm)$^{0.725}$ × (patient weight in kg)$^{0.425}$; See http://bnf.org/bnf/extra/current/450018.htm

[27] Roman MJ et al Am J Cardiol 1989;64:507-512

[28] 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

3. Rare variant and related phenotypes

Familial thoracic aortic aneurysm* (normal heart on last exam)	5 yearly echo from 20 for life	Cardiology clinic
Loeys Dietz syndrome**	Whole body MRA and cerebral MRA at diagnosis Annual echo	CCTD clinic

* 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 nosology (1998)[29] and the Oxford Desk Reference guidelines[30]

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.[31][32] Most deaths in vascular EDS are caused by arterial rupture / dissection in normal calibre arteries.[33]

- 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.

[29] Beighton P et al. Ehlers-Danlos syndromes: revised nosology, Villefranche 1997. Am J Med Genet 1998;77:31-37
[30] Firth HV & Hurst JA. Oxford desk reference: Clinical Genetics. Oxford: OUP 2005
[31] McDonnell NB et al. Echocardiographic findings in classical and hypermobile Ehlers-Danlos syndromes. Am J Med Genet 2006;140A:129-136
[32] Wenstrup RJ et al. Prevalence of aortic root dilatation in the Ehlers-Danlos syndrome. Genet Med 2002;4:112-117
[33] 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[34]
- Aortic root measurements plotted on graphs published by Roman[35]

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.

Hypermobile Ehlers Danlos syndrome (type III)	echo at age 20 or at time of diagnosis (whichever is later) Follow-up only if baseline abnormalities found	Cardiology clinic
Vascular Ehlers Danlos syndrome (type IV)***	Whole body MRA and cerebral MRA at diagnosis Annual clinical review	CCTD clinic

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

[34] Mosteller RD Simplified calculation of body-surface area. ***NEJM*** 1987;317:1098
BSA (m^2) = ([Height(cm) x Weight(kg)]/ 3600)^{½}
[35] 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.[36]

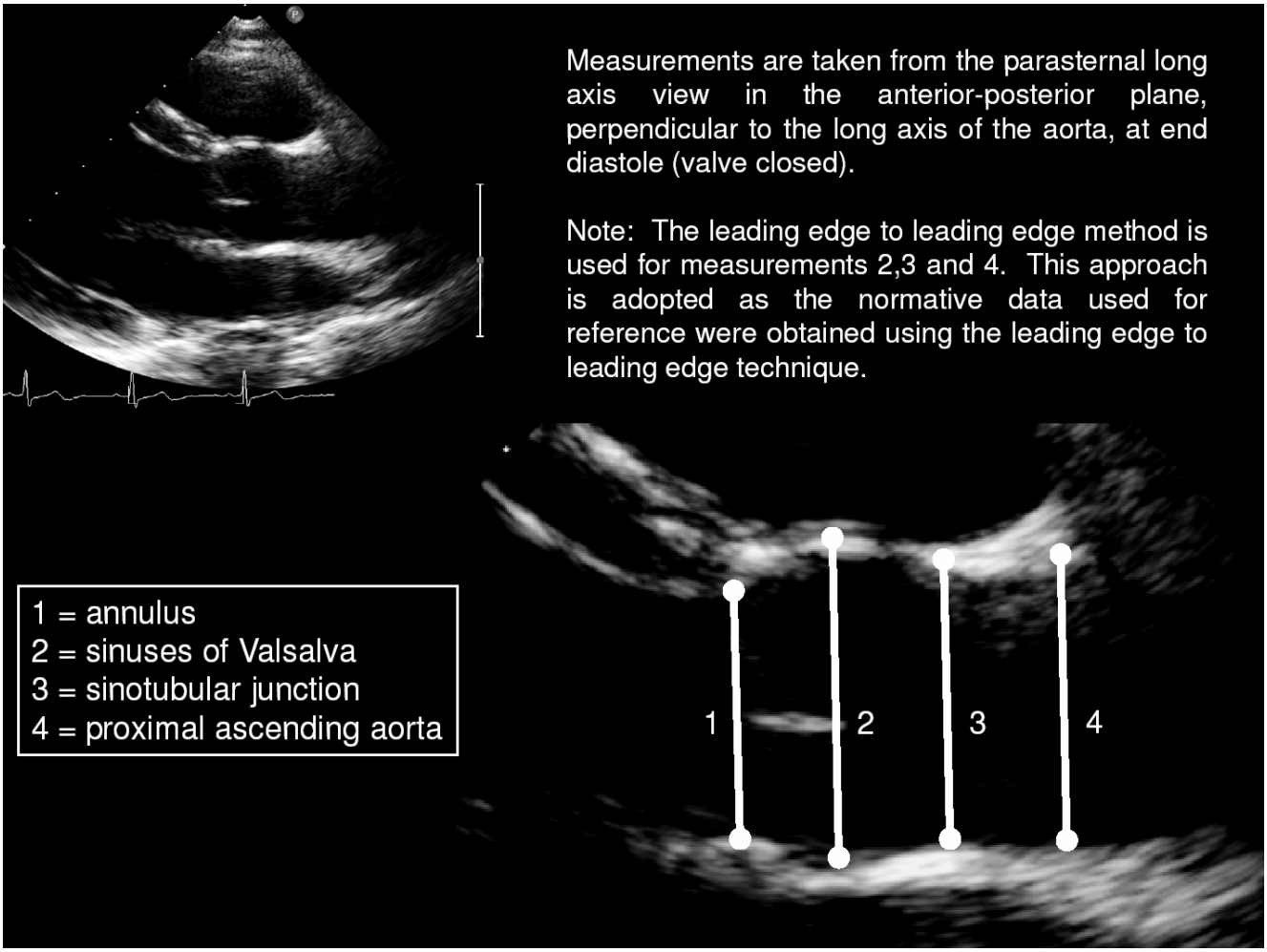
This is an area for further research, although it would seem sensible to offer the close relatives of such patients an echo to screen for BAV, and ongoing surveillance of the aortic root in those found to have a BAV.

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

[36] Garg V et al. Mutations in NOTCH1 cause aortic valve disease. *Nature* 2005; 437: 270–4.

Appendix 1: normal aortic root dimensions[1,2]

1. Standardised measurements

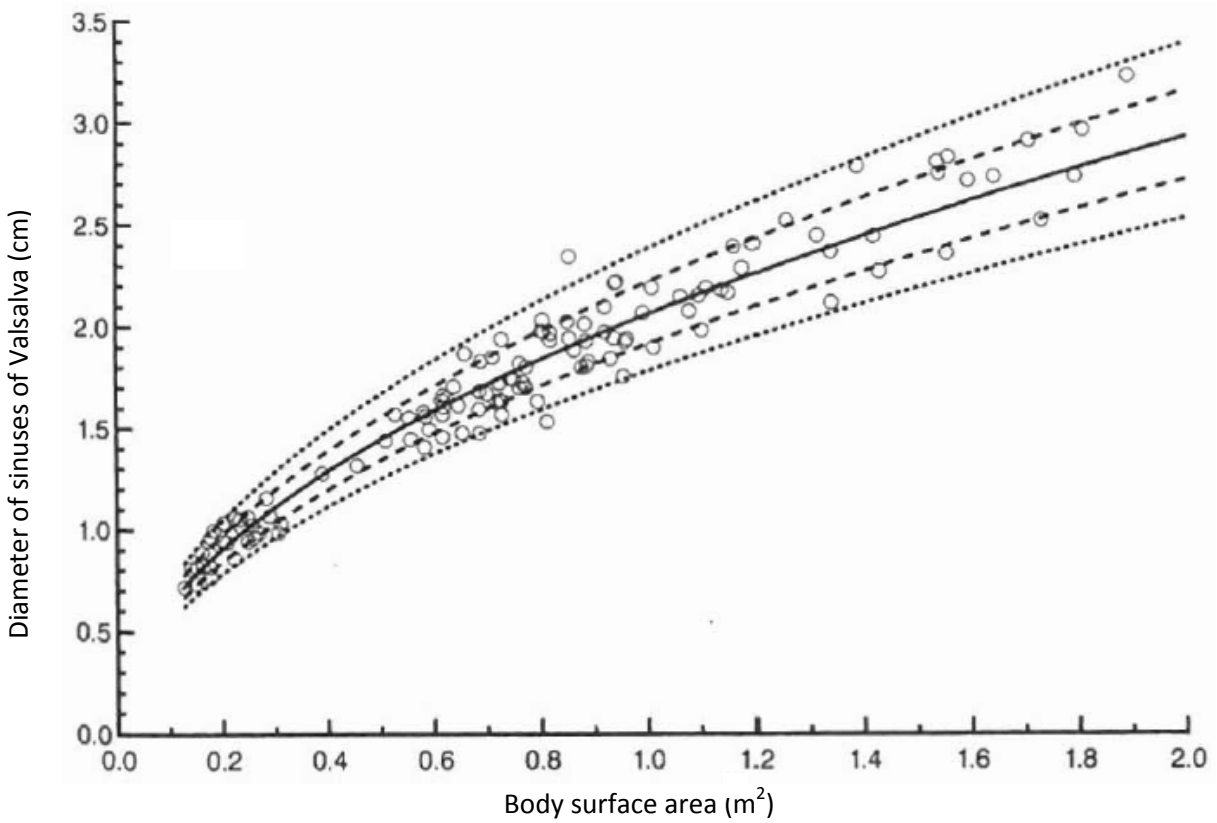


[1] Roman MJ et al. Two-Dimensional Echocardiographic Aortic Root Dimensions in Normal Children and Adults Am J Cardiol 1989;64:507-512

[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)

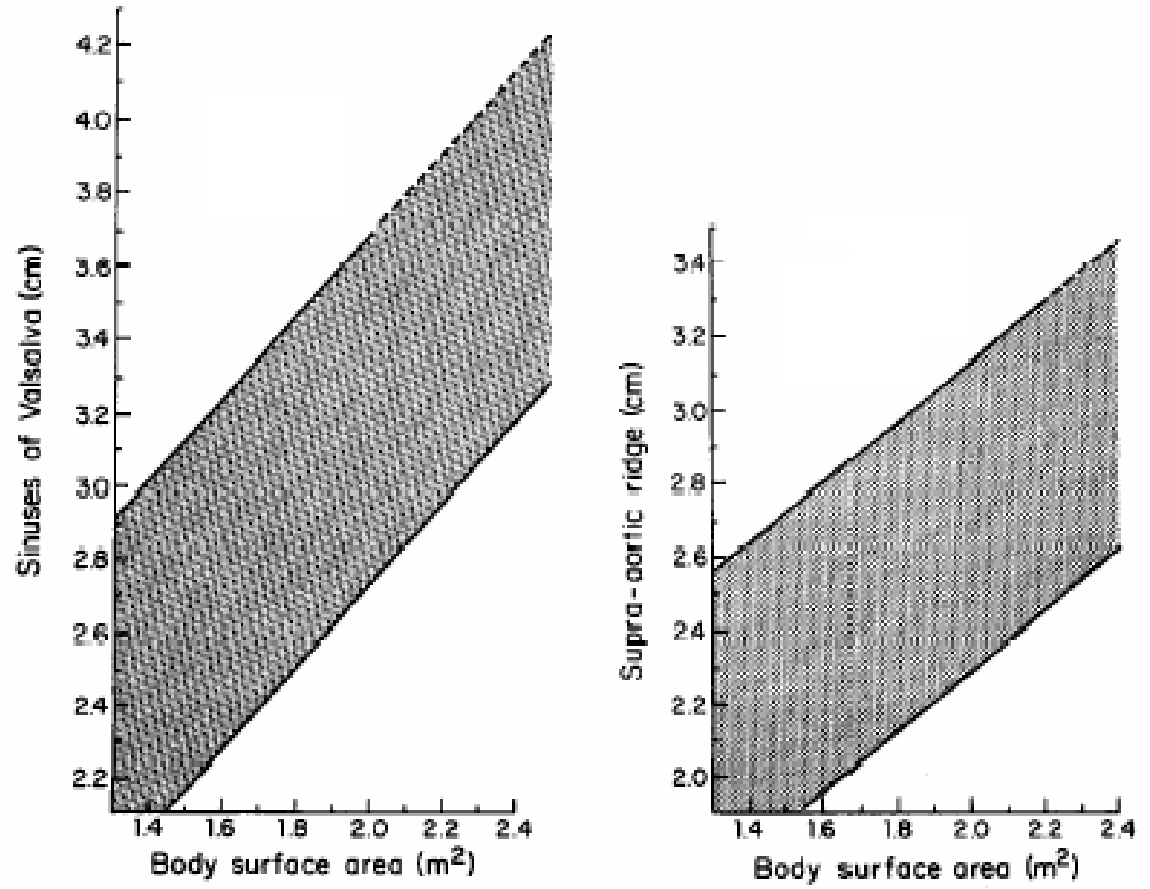


These data were derived from normal children. Note that the reference ranges in children with confirmed Marfan syndrome may be different[37]

[37] Rozendaal et al Marfan syndrome in children and adolescents: an adjusted nomogram for screening aortic root dilatation. Heart 1998;79:69–72

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

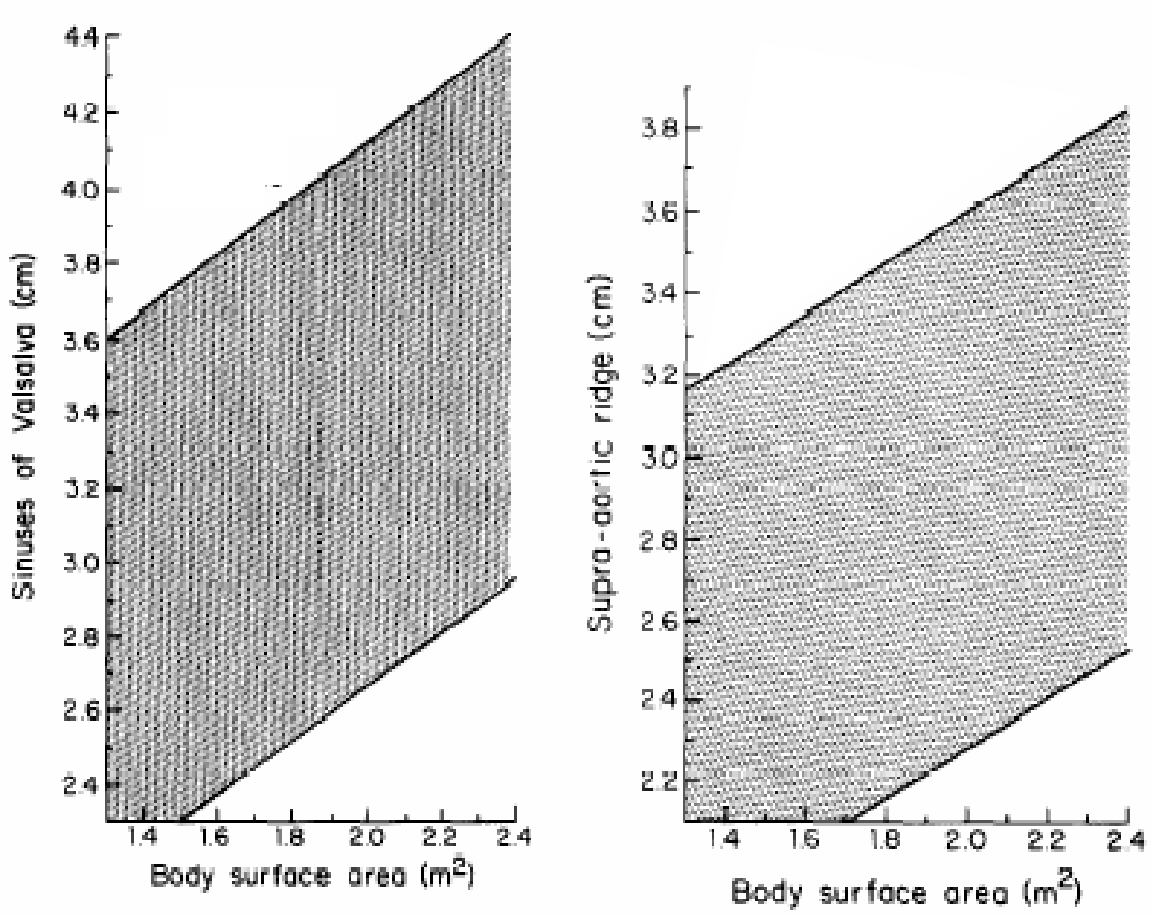
95% confidence limits



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)

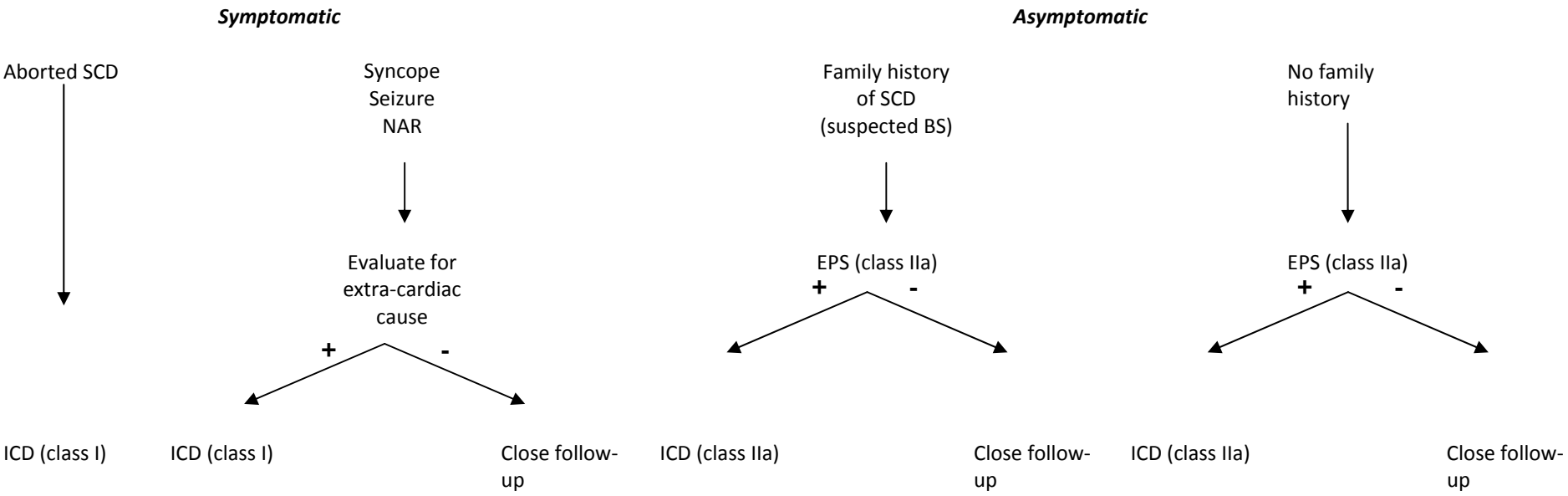
95% confidence limits



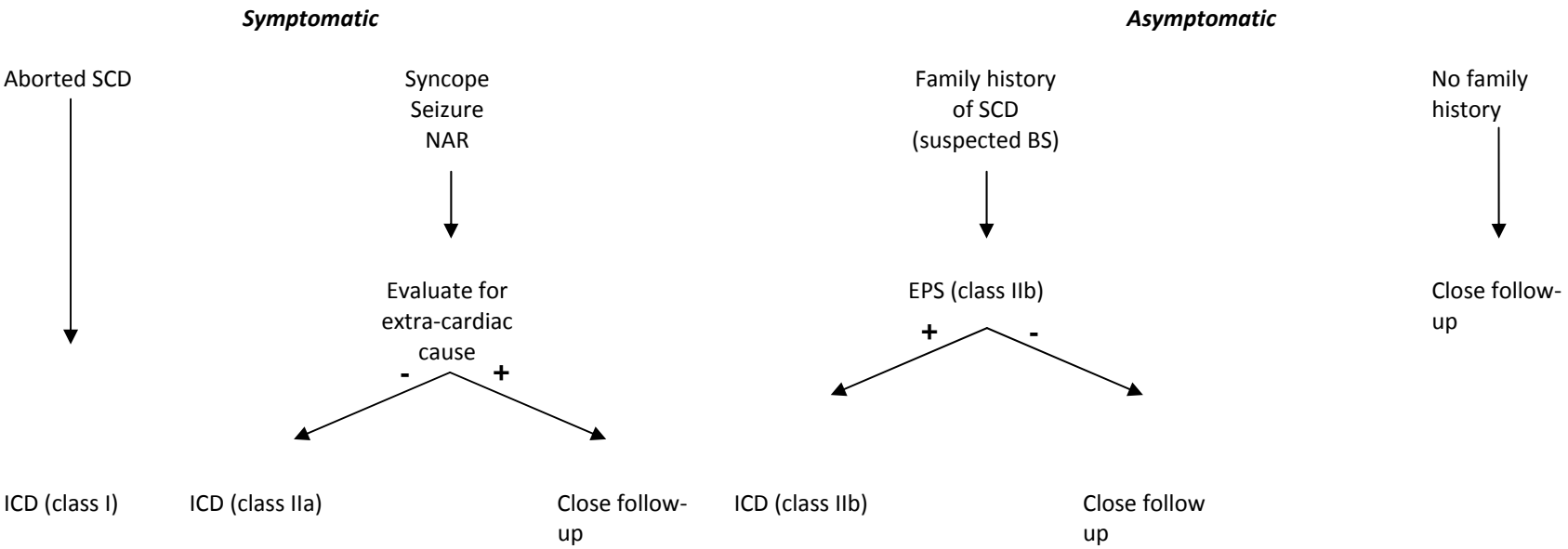
See also : British Society of Echocardiography Education Committee. Echocardiography: Guidelines for Valve Quantification (http://www.bsecho.org/Guidelines%20for%20Valve%20Quantification.pdf)

Appendix 2: sudden death prophylaxis in Brugada syndrome

1. Spontaneous type 1 ECG



2. Sodium channel block-induced type 1 ECG



Adapted from Figure 8 Antzelevitch C et al. Brugada syndrome: Report of the second consensus conference. Circulation 2005;111:659

NAR: nocturnal agonal respiration; SCD: sudden cardiac death.

Appendix 3: common clinical codes, Northern Genetics Service

Sudden unexplained death	59210		
Familial hypertrophic cardiomyopathy	192600	MYH7	160760
		MYBPC3	600958
		TNNT2	191045
Left ventricular hypertrophy, unexplained	55910		
Familial dilated cardiomyopathy	115200		
Familial restrictive cardiomyopathy	115210		
ARVC	107970	PKP2	602861
		DSP	125647
		DSG2	125671
		DSC2	125645
		JUP	173325
Long QT syndrome	192500	KCNQ1	192500
		KCNH2	152427
		SCN5A	600163
		KCNE1	176261
		KCNE2	603796
Brugada syndrome	601144		
CPVT	604772	RYR2	180902
		CASQ1	
Familial AF	607554	KCNQ1	192500
		KCNH2	152427
		SCN5A	600163
		KCNE1	176261
		KCNE2	603796
Marfan syndrome	154700		
Familial hypercholesterolaemia	143890		
Fabry disease	301500		