Genetic diagnostics and genetic counselling in Hypertrophic Cardiomyopathy (HCM)

ICIN working group on Hereditary Heart Diseases

Dutch professional groups involved in drawing up this guideline: cardiologists, paediatric cardiologists, clinical geneticists, clinical molecular geneticists, genetic counsellors, psychosocial workers, associated with or cooperating with the university hospitals' outpatient clinics for cardiogenetics.

Approved by the NVVC, VKGN and NVK (paediatric cardiology section).

NVVC - Nederlandse Vereniging voor Cardiologie – Dutch Society for Cardiology; VKGN - Vereniging Klinische Genetica Nederland – the Netherlands Society for Clinical Genetics; NVK - Nederlandse Vereniging Kindergeneeskunde – Dutch Society for Paediatrics.

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Aim of this guideline: To describe the application of genetic diagnostics and genetic counselling in hypertrophic cardiomyopathy that is currently desired in the Netherlands: what it covers, how it should be done and by whom.

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Sources used (see also references):

- Existing guidelines:
 - NVVC guideline in pocket format: Hypertrophic cardiomyopathy
 - VKGN guideline: Predictive DNA-diagnostics
- Genetics Handbook: chapter on hypertrophic cardiomyopathy, Oxford Desk Reference Clinical Genetics, by J.A. Hurst, H.V. Firth, J.G. Hall, Oxford University Press, USA, 2005: pages 360-2.
- Literature pertaining to 'Diagnostic, predictive or prenatal genetic testing in HCM'
- Minutes of meetings of the Interuniversity Cardiology Institute of the Netherlands (ICIN) working group on Hereditary Heart Diseases
- Websites (in Dutch): www.dnadiagnostiek.nl, www.nvvc.nl, www.vkgn.org, www.cardiogenetica.nl

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Please refer to the journal's website at <http://www.cardiologie.nl> for the references and appendices to this guideline.

1. Introduction

Epidemiology

Hypertrophic cardiomyopathy (HCM) is a hereditary disease that occurs relatively frequently (prevalence for phenotypic 1:500, genotypic is higher). It is defined as the presence of a thickening of the heart muscle in the absence of stress conditions (hypertension, vascular disease) that could otherwise explain the thickening. The abnormality is found in all races, and occurs equally often in men and women.^{1,2}

Clinical presentation

HCM can occur at any age. Many patients are asymptomatic and are identified only by accident. Sudden cardiac death can also be the first expression of HCM. The most frequent symptoms are dyspnoea, thoracic pain, presyncope, syncope and palpitations.¹ A cerebral infarct resulting from emboli formed during atrial fibrillation can also be a complication of HCM.

Indications for HCM can be seen on an ECG, although the diagnosis is based on an echocardiogram and/or MRI.¹

Follow-up and therapy

HCM patients must be monitored lifelong by a cardiologist. The treatment (medication, surgical or percutaneous septum reduction, and/or internal cardioversion defibrillation (ICD) implantation) is determined based on the symptoms and the risk stratification for sudden cardiac death.¹

Lifestyle rules

Patients with HCM must not participate in competitive sports. Intensive physical exertion with peak activity or isometric exertion should be avoided, as described in the Dutch Society for Cardiology's (NVVC) guideline on HCM.¹

Differential diagnosis

HCM is usually caused by mutations in the sarcomere genes. There are also metabolic or neurological diseases and syndromes, such as Fabry's disease, Pompe's disease, amyloidosis, carnitine deficiency, mitochondrial diseases, Friedreich's ataxia, Noonan syndrome, and Leopard syndrome which can cause HCM.³ The chance of discovering such a disorder is greater in childhood than in adults. HCM can be distinguished from these disorders by dysmorphological examination, neuromuscular examination, metabolic screening, family information, and DNA diagnostics.

Genetic diagnostics

The term 'genetic diagnostics' covers all the diagnostic tests that could lead to establishing a diagnosis of a hereditary condition. In HCM, a cardiol-

ical examination therefore also falls under genetic diagnostics. A distinction is made between genetic diagnostics in symptomatic individuals and 'predictive' diagnostics in asymptomatic individuals who are tested on the basis of a family risk.

Performing an echo or ECG in an asymptomatic relative of an HCM patient is therefore a form of predictive diagnostics. In doing so, the same meticulous requirements for informed consent and counselling must be met as for performing presymptomatic DNA diagnostic (see chapters 8 and 9), also if the family examination is being performed by a cardiologist. A clinical geneticist should preferably be involved prior to a presymptomatic cardiological family examination. In time, all HCM index patients will be genotyped through the cardiogenetic outpatient clinics, so that a multidisciplinary approach to the patient and his/her family is ensured.

Family testing using the cascade method ('cascade testing')

In the Netherlands a pathogenic mutation can now be discovered in 65% of HCM patients. This means that systematic presymptomatic diagnostics by means of DNA testing, so-called cascade testing, is technically possible in these patients' families. It is not yet clear whether cascade testing in HCM families is cost effective. As long as it is impossible to indicate in advance which individuals or families will have the greatest advantage from early diagnosis, all index patients who carry an identified mutation should be offered family cascade testing (see chapters 8 and 9).

Psychosocial aspects of (predictive) genetic diagnostics and counselling in HCM

Little is known about the psychosocial effects of genetic counselling and DNA diagnostics in HCM. In France, a protocol similar to that for testing in Huntington's disease is being followed for predictive testing (see chapter 3).⁴ The same problems are reported in the psychosocial area as in neurogenetics and oncogenetics. In the Netherlands, a primary ethical study into the predictive testing of children for hereditary cardiological conditions (HCM, LQTS, FH) is being financed by the Netherlands Science Research Organisation (NWO). It was preceded by a qualitative psychological study. It appears that the concept of being a 'carrier' is difficult for children to understand, particularly in HCM, where there is uncertainty about the activities allowed, such as sports. This could lead to undesirable discrimination or self-discrimination. The quality of life of these children does not, however, appear to be less than that of contemporaries.⁵

In adults, the coping style appears to be a predictor for the level of distress experienced during the predictive testing for cardiogenetic disorders.⁶

Psychosocial studies have also reported on families with the long-QT syndrome.⁷ It appears that the psychosocial effects in the long term were better than initially anticipated, but that there are vulnerable groups that can be recognised in advance (sudden death in the family, less well educated, little social support, psychological problems, passive coping style). In the first consultation, being given an 'uncertain' result after the cardiological exam is also an additional risk factor for persistent distress in carriers, in addition to being identified as a carrier. The testing of children (see chapter 9) leads to great psychosocial stress in the parents (the children have not been studied in this respect).^{8,9} Individuals who have been identified as belonging to a vulnerable group should be given more intensive psychosocial support.

2. Genetic aspects of hypertrophic cardiomyopathy

Mode of inheritance

HCM is usually inherited as an autosomal dominant disorder, where penetrance is age-dependent and the expression changes within and between families. The chance that a child will inherit the predisposition for HCM is therefore 50%, while the chance that such a child will develop HCM is lower. Of index patients, 10% are reported to have a de novo mutation in the international literature, but far fewer than 10% are found among Dutch index patients in our experience. In all the other cases, the patient's parents, brothers and sisters also have a 50% chance of having a predisposition for HCM.

Congenital and juvenile HCM is rare and can arise from double or compound heterozygote or homozygote mutations in one or more of the HCM genes.^{10,11} If this is confirmed by DNA testing, it is usually found that each parent carries one of the mutations, and that these mutations are transmitted in an autosomal dominant manner.

Genes

HCM is usually caused by mutations in genes that encode for parts of the sarcomere of the heart muscle.¹²⁻¹⁴ There were 14 genes known when these guidelines were written (June 2009), (table 1). By far the most mutations are found in the cardiac myosin binding protein C gene (MYBPC3) and the beta-myosin heavy chain gene (MYH7). MYH7 mutations generally lead to an early appearing phenotype compared with MYBPC3 mutations, although the mortality is no different. Mutations in the cardiac troponin T gene (TNNT2) usually lead to notably little hypertrophy in combination with an increased chance of sudden cardiac death.

Hundreds of mutations have been reported in the involved genes, although most of the muta-

tions occur in only one or a few families. In the Netherlands there is a special situation; apparently there are some regional MYBPC3 mutations that occur in remarkably high frequencies. This is due to founder effects: patients with such a mutation have a common ancestor in whom the particular mutation originated. Thus the c.2373dupG mutation occurs in 19% of the Dutch HCM population, the p.Arg943X mutation in 9% and the c.2864_2865delCT mutation in 7%.¹⁵ The pathogenicity of some mutations in the sarcomere genes has not yet been proven; these are called 'unclassified variant' (UVs).

Mutations in HCM genes, such as described above, lead to isolated thickening of the heart muscle, and in rare cases this is accompanied by a clinically recognisable weakness of the skeletal muscles.

Mutations in non-sarcomere genes usually lead to non-isolated (syndromal, metabolic, neuromuscular) forms of HCM. These include the occurrence of HCM in the framework of a syndrome (for example, Noonan or Costello syndrome); HCM as the result of glycogen metabolic disease (in lysosomal Pompe's disease, Fabry's disease, Danon's disease and in hypertrophic cardiomyopathy/Wolff-Parkinson-White (HCM/WPW); other storage and metabolic diseases (such as carnitine deficiency); defects in the mitochondrial respiratory chains, and neuromuscular and neurodegenerative diseases, such as Duchenne/Becker disease and Friedreich's ataxia that are inherited in different ways (table 2).

3. Genetic (DNA) diagnostics and genetic counselling in the Netherlands

Genetic diagnostics

As stated in the introduction, genetic diagnostics covers all the tests that can lead to establishing a diagnosis of 'hereditary disorder'. This chapter covers the DNA diagnostic tests currently available.

DNA diagnostics

DNA diagnostics based on germ line mutations may only be performed in the Netherlands in DNA laboratories connected with the Departments of Clinical Genetics in the university hospitals, or in cooperation with them (Article 2: Execution of the Special Medical Procedures Act (*Wet Bijzondere Medische Verrichtingen*, WBMV)). These DNA diagnostic tests are covered by Dutch healthcare insurers. DNA tests for HCM can only be requested by, or in close consultation with, a clinical geneticist. The clinical geneticist always discusses the results with the patient*. Thus, genetic counselling

* Where 'clinical geneticist' is used, this may also mean a 'genetic consultant under the supervision of a clinical geneticist'.

Table 1. Genes involved in autosomally dominant inherited HCM.

Gene	Abbreviation	Locus	Frequency In the Netherlands	Elsewhere	Phenotype
Beta-myosin heavy chain	MYH7	14q12	~15%	15%	Early hypertrophy (<30 yrs)
Cardiac myosin binding protein C	MYBPC3	11q11.2	~40%	20%	Great variation in seriousness, incomplete degree of penetrance
Cardiac troponin T	TNNT2	1q32	~2%	2.6%	Mild hypertrophy, sudden death
Cardiac troponin I	TNNI3	19q13.4	1-2%	2%	
Alpha tropomyosin	TPM1	15q22	1-2	0.2%	
Alpha-myosin heavy chain	MYH6	14q12	?	Rare	
Cardiac troponin C	TNNC1	3p21.1	0%	Rare	
Myosin essential light chain 3	MYL3	3p21.3	0%	0.1%	Myopathy
Myosin regulatory light chain 2	MYL2	12q24.1	2%	1.6%	Myopathy
Alpha-cardiac actin	ACTC	15q14	0%	Rare	
Titin	TTN	2q31.2	?	Rare	
Myozenin 2	CSRP3	11p15.1	2%	Rare	
Myogenin 2	MYOZ2	4q26	?	Rare	
Telethonin	TCAP	17q12	1%	Rare	

Compiled from references 13 and 14 and combined with data from the Dutch cardio-genetic DNA laboratories.

Table 2. Other genes involved in HCM.

Gene	Abbreviation	Locus	Inheritance	Phenotype
Gamma sub unit AMP kinase	PRKAG2	7q36.1	Aut. Dom.	LVH/pre-excitation (WPW)/ conduction disturbance
Lysozyme associated membrane protein 2	LAMP2	Xq24	X-linked	Danon's disease: LVH/pre-excitation/ myopathy/mental retardation
Non-receptor protein tyrosin phosphatase SHP2	PTPN11	12q24	Aut. Dom.	Noonan, Leopard, CFC syndrome
V-KI-RAS2 Kirsten rat sarcoma viral oncogenic homolog	KRAS2	12p12.1	Aut. Dom.	Noonan, Costello, CFC syndrome
Son of sevenless, Drosophila, homologue 1	SOS1	2p22-p21	Aut. Dom.	Noonan syndrome
V-RAF murine sarcoma viral oncogene homolog	BRAF1	7q34	Aut. Dom.	CFC syndrome
Mitogen-activated protein kinase kinase 1	MAP2K1	15q21	Aut. Dom.	CFC syndrome
Mitogen-activated protein kinase kinase 2	MAP2K2	7q32	Aut. Dom.	CFC syndrome
V-HA-RAS Harvey rat sarcoma viral oncogene	HRAS	11p15.5	Aut. Dom.	Costello syndrome
Alpha-glucosidase	GAA	17q25	Aut. Rec.	Pompe's disease
Glycogen debranching enzyme	GDE	1p21	Aut. Rec.	Glycogen storage disease IIIa; Cori's/Forbes' disease
Alpha-galactosidase	GLA	Xq22	X-linked	Fabry's disease
Frataxin	FRDA	9q	Aut. Rec.	Friedreich's ataxia
Transthyretin	TTR	18q11	Aut. Dom.	Amyloidosis I
Mitochondrial DNA	OXPHOS	mtDNA/ nuclear	Maternal/ Aut. Dom., Aut. Rec.	LVH 'plus'

Aut. Dom. = autosomal-dominant, Aut. Rec.=autosomal-recessive, WPW=Wolff-Parkinson-White, CFC=cardio-facial-cutaneous, LVH=left ventricular hypertrophy.

surrounding DNA diagnostics is guaranteed in the Netherlands. The tests are performed in centres designated for that purpose by the Dutch National Consultation on DNA diagnostics (*Landelijk Overleg DNA-diagnostiek*, LOD; www.dnadiagnostiek.nl). At the moment these centres are located in the university hospitals in Amsterdam (AMC), Maastricht and Rotterdam. The diagnostic screening of one gene takes 3 to 6 months on average. If the family mutation is known, testing in relatives** (predictive DNA diagnostics) takes a maximum of 6 weeks. Successive DNA tests for a number of HCM genes can take 6 to 12 months. If no mutation is found, the DNA is stored for more diagnostic work in the future.

Genetic counselling

Complex genetic counselling is also covered by Article 2, *WBMV*, and may only be offered by the Departments of Clinical Genetics in university centres. As such, genetic counselling is also reimbursed by Dutch healthcare insurers. The definition of genetic counselling is 'a communication process concerning the human problems that are created by the occurrence or possible occurrence of a hereditary disorder in the family'. The purpose of genetic counselling is to provide individuals, parents or couples who face the possibility of an inherited or congenital disorder with the opportunity to make a conscious, well-considered choice regarding their own life and in planning a family. Genetic counselling is provided by clinical geneticists and genetic consultants. The Departments of Clinical Genetics also have specialised staff members available to provide psychosocial support; they may be social workers or psychologists.

Genetic counselling around predictive diagnostics is a special form of genetic counselling that is defined by protocols in many areas (neurology, oncogenetics) and that is associated with a higher risk than the counselling of symptomatic patients. The international protocol for predictive diagnostics in Huntington's disease, which has been in use for more than 20 years, is seen as a paradigm. Recently, a general guideline on predictive DNA testing was agreed upon by the *VKGN* for the Dutch situation.¹⁶ It describes 'cascade testing', which is a special form of family testing offering predictive diagnostics to as many at-risk relatives as possible. In cascade testing, entire families are systematically tested for the mutation that has led to the disease in their family. This is done in cooperation with the individual requesting advice (usually the index patient). Screening according to the cascade method is only offered for those disorders for which preventive treatment or alleviation of the symptoms is possible, such as with HCM.

Genetic counselling and DNA diagnostics, including cascade testing for HCM, are offered at the cardiogenetic outpatient clinics in the university hospitals. These clinics also provide outpatient services in outlying centres. In these centres, the clinical geneticists and genetic counsellors, in cooperation with the psychosocial workers, are primarily responsible for the genetic counselling process, including the DNA diagnostics.¹⁶ The cardiologists are responsible for the cardiac phenotyping and for the counselling provided to the patient or individual requesting advice on the clinical picture of HCM they have compiled.

Scientific research: GENCOR database

The clinical and genetic data of all cardiogenetic patients known from the outpatient clinics and of other patients with hereditary heart diseases, and any known carriers, are made anonymous and then registered in the Dutch GENCOR database, primarily for the purpose of scientific research. Access to this database is limited to registered users (clinical geneticists and cardiologists). They can review and use their own data, while access to other data is only possible after they have submitted a research proposal to the GENCOR steering committee and it has been approved (www.gencor.nl).¹⁷

4. Genetic diagnostics and genetic counselling in HCM patients over 10 years old

- a. Referral
- b. Information sent before counselling appointment
- c. First consultation
- d. DNA diagnostics
- e. Results
- f. Information to referrer/family physician
- g. Follow-up
- h. Initiating family testing using the cascade method

a. Referral

Referral for genetic counselling and DNA diagnostics can be made by a family physician or specialist. The patient or individual is registered in writing or by telephone to the secretariat of a Department of Clinical Genetics or Cardiogenetics (telephone numbers can be found at www.vkgn.org). A referral letter with the relevant clinical information is sent by the referrer, preferably prior to the appointment. The patient, with his/her partner or relatives if desired, is invited for a cardiogenetic consultation. The delay before an appointment can be made should not be more than 8 weeks for HCM patients.

b. Information sent before counselling appointment

The patient can learn about the hereditary aspects of HCM and the daily routine in a cardiogenetic

** Relative refers only to blood relatives in this guideline.

outpatient clinic by starting at the website www.cardiogenetica.nl. The Department of Clinical Genetics will also send this information to the patient in writing, together with an explanation about the procedure for the consultation and how it will be covered by healthcare insurance in the Netherlands.

c. First consultation

Sufficient time (30 to 45 minutes) should be taken for this appointment. Before the consultation, the clinical geneticist will discuss what is known about the patient and/or family with the cardiologist from the cardiogenetic outpatient clinic. The clinical geneticist should also check the patient's expectations of the consultation (and those of others present), what they already know about HCM and its heredity pattern, and what questions they have.

Then the cardiological information is evaluated (in principle, the case history according to the ESCAPE HCM form, see appendix, chapter 12, on our website at www.cardiologie.nl).

Next, a family tree is drawn up (for at least three generations), with particular attention paid to any relatives with HCM, metabolic or neuromuscular disorders (or any related symptoms) and to any sudden deaths that have occurred in the family. For deceased relatives, whether they had an autopsy or not should be checked. The relatives who have a bearing on the family's disease history should be identified (also noting with whom the patient has contact and who is aware of the heredity examination), in connection with possible cascade testing in the future. The patient should be informed about the hereditary aspects of HCM and the consequences for his or her relatives. If desired, the clinical aspects of HCM can be discussed, including the consequences for daily life.

The DNA diagnostic procedure should be discussed, including the duration, financial aspects and the consequences of whether or not a mutation is found. For the result here are three possibilities:

- I. If a *pathogenic mutation* is found, cascade testing will be offered to the family. However, this usually has no consequences for the management of the index patient or his/her prognosis.
- II. If a *mutation with unclear pathogenicity* is found (an unclassified variant, UV), the follow-up will be determined by supplementary DNA diagnostic testing, cardiological family testing, or a combination of these.
- III. If *no mutation* is found, the heredity mode is probably still autosomal dominant, but genetic cascade testing is not possible. Cardiological examination of relatives must be offered to these families.

Performing DNA diagnostic work in an already identified HCM patient has no consequences for their taking out insurance or life insurance policies.

Informed consent is recorded in the patient's case report, or a consent form is signed.

If it transpires that a serious case is under discussion, in either the patient and/or the family, and if no cardiological family testing has been performed so far, this can be offered without waiting for the results of the DNA tests. Any relatives with complaints or symptoms should be offered immediate cardiological examination.

The patient will be given an information letter about HCM to read later, which will describe the management of the disease as well as those people involved in the genetic counselling. See also www.cardiogenetica.nl.

If, during the consultation, it appears that the disease or the heredity examination is likely to lead to psychosocial problems (or has already done so), or that this patient falls into a vulnerable group based on personal or group characteristics (see Introduction), he/she should be referred to a psychosocial worker. One is normally available in the department during consultation hours.

If it appears that certain relatives are likely to become significant in helping to determine the family case, the clinical geneticist should ask them for their written permission to obtain their medical records.

d. DNA diagnostics

Blood samples (2 x 10 cc EDTA blood) will be taken from the patient and sent to one of the DNA diagnostic laboratories, together with a completed request form (can be downloaded from www.dnadiagnostiek.nl). The test result will be sent to the clinical geneticist and to the cardiologist in the outpatient clinic. The family physician or referring cardiologist will be informed by the cardiogenetic outpatient clinic.

The order of the genes to be screened is:

1. MYBPC3, MYH7
2. TNNT2, TPM1, TNNI3, MYL2, MYL3, ACTC, CSRP3, TCAP: simultaneously using high throughput techniques (such as array/chip technology)
3. LAMP2, PRKAG2, GLA (depending on phenotype and/or family history).

If no mutations are discovered, or if no other genes are to be considered, tests will be halted to await further scientific developments. The DNA will be stored and the patient will be informed about any possible diagnostic tests in the future.

If the case involves a serious phenotype, testing will be continued after detection of the first pathogenic mutation to see whether there is a mutation in any other genes, because it could involve a compound heterozygote, or a double heterozygote. The referrer and/or family physician will be in-

formed about the course being taken. During and after the process of genetic counselling and testing the patient remains under his/her own cardiologist for cardiological care.

e. Result of the DNA diagnostics

If a mutation is discovered, whether it is known to be pathogenic or not, the patient will be invited to the cardiogenetic outpatient clinic to discuss the implications for him- or herself and the family. The clinical geneticist will discuss the result with the patient, if necessary after consultation with the cardiologist. If the mutation is very likely pathogenic, cascade testing will be offered. If the pathogenicity is uncertain or unknown, additional cardiological and genetic testing of the patient or relatives should be performed if possible.

Even if no mutation is found, it is recommended to invite the patient for a closing discussion so that there is an opportunity to discuss any remaining questions. It will be made clear to the patient, or those who requested the counselling, that the patient's DNA will be stored and that supplementary DNA diagnostic tests will be performed as they become available.

f. Information to referrer/family physician

The family physician and referrer will be informed of the findings in writing and will also be sent a report on the counselling sessions. This report is also sent to the patient.

g. Follow-up

The cardiological follow-up of patients, and asymptomatic and at-risk relatives will be provided by their own cardiologist. If necessary, psychosocial follow-up will be provided by the Department of Clinical Genetics; such support may involve starting the cascade testing or informing the children of the patient. If required, follow-up sessions can be offered at the cardiogenetic outpatient clinic, for example, to those wishing to start a family.

If there were any indications during the first consultation that a metabolic, syndromal or neurological disorder is causing the thickening of the heart muscle, follow-up examinations will focus on this. The patient will be invited for a follow-up consultation, for further discussions, physical examination and/or for referral for additional examinations.

h. Initiating family testing using the cascade method

The index patient plays an important role in informing relatives and in passing on the offer for predictive DNA diagnostics. It is understandable that this sometimes poses a problem for the patient, both in a psychological sense as well as from an intellectual point of view. This may mean relatives are not informed or only incompletely. Since,

from a preventive point of view, the testing of as many relatives as possible makes good sense, the Department of Clinical Genetics will actively support the patient in stimulating the family to come for the cascade testing by providing information in the form of 'family letters'. Where necessary, and only with the express permission of the index patient, the clinical geneticist may directly approach relatives as indicated by the patient (this may also be done at a later stage in the process).

5. Genetic diagnostics and genetic counselling in paediatric HCM patients under 10 years old

The prevalence of HCM in patients younger than 10 years is much lower than at older ages.

The aetiology of juvenile HCM is genetically heterogenic and the presentation usually differs too. So far, a hereditary cause can be determined in 30-50% of the children with HCM through specific biochemical, dysmorphological, neuromuscular and molecular testing.^{18,19} Genetic diagnostics of juvenile HCM therefore demands a multidisciplinary cooperation between paediatric cardiology, genetics, neurology and metabolic specialists.

HCM in children due to a mutation in one of the sarcomere genes

Familial HCM is the most frequent diagnosis in thickening of the heart muscle at a juvenile age. The occurrence of juvenile HCM can be based on a compound or double heterozygote or homozygote, but also occurs in 'normal' heterozygotes with mutations in the sarcomere genes.^{20,21}

Syndromes with HCM (table 3)

In about 20% of the children with HCM, an initial syndrome diagnosis can be made based on a combination of congenital abnormalities and/or dysmorphological characteristics, and a growing number of these diagnoses can later be confirmed by DNA diagnostic testing.

The most frequent dysmorphological diagnoses in HCM are:

1. Noonan syndrome (hypertelorism, down slant of the palpebral fissures, epicanthic folds, low-standing and backwards tilted ears, growth delay, pulmonary stenosis, and developmental delay).
2. Costello syndrome (growth delay, skin folds in neck, fingers, hand palms and foot soles, papillomata around mouth and nose, curly hair and developmental delay).
3. Leopard syndrome (multiple lentigines, conduction disturbances, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, growth retardation, sensorineural deafness).

These three syndromes are based on defects in the RAS pathway.

Summary of daily routine in genetic diagnostics in HCM patients over 10 years old in the Netherlands.

a.	Referral	By family physician (GP) or specialist in cardiogenetic outpatient clinic (telephone numbers can be found at www.vkgn.org)
Maximum waiting time is 2 months
b.	Information prior to appointment	About HCM and heredity (www.cardiogenetica.nl), procedures, financial issues and DNA diagnostic tests
c.	First consultation (30-45 mins)	Discussion of expectations of patient, partner, family
Inventory of cardiological information
Drawing up of family tree, inventory of family relationships
Discussion of HCM and heredity
Discussion of DNA diagnostics
If necessary, mention the possibility of performing cardiological examinations in relatives
If necessary, request further family information
If necessary, refer patient to psychosocial worker
Provide written information about the above to take home
d.	DNA diagnostics	Take blood samples (2 x 10 cc EDTA)
Fill in a request form at www.dnadiagnostiek.nl
Ask for the result be sent to the clinical geneticist and to the cardiologist
Screen genes in the sequence of prevalence (6 months per gene), if necessary perform multiple screenings simultaneously
Note that a patient may have multiple mutations
e.	Results	Given to patient by clinical geneticist at the cardiogenetic outpatient clinic
If a pathogenic mutation is found, give explanation, initiate cascade testing
If an unclassified variant (UV) is found, give explanation and request supplementary tests if possible
If no mutation is found, store DNA for future diagnostic work and request cardiological examinations for relatives
f.	Information to referrer and family physician	The results are summarised in a letter to patient and copies are sent to referrer and family physician
g.	Follow-up	Cardiological examinations: by own cardiologist
Psychosocial: as indicated by psychosocial worker in Department of Clinical Genetics
Follow-up discussions planned when it is necessary to test children, those wishing to have children, etc.
If necessary, provide supplementary testing aimed at identifying a metabolic or syndromal cause
h.	Initiating cascade testing	In cooperation with or by index patient
Provide family letters to index patient to distribute, or
Send family letters to selected relatives
If necessary, clinical geneticist can contact relatives

4. Beckwith-Wiedemann syndrome (overgrowth, hemihypertrophy, omphalocele and macroglossia).

5. Chromosomal abnormalities.

Metabolic causes of HCM

About 25% of the genetic diagnoses in children with a cardiomyopathy (including HCM) involve metabolic diseases, where a distinction can be made between storage diseases and those based on a defect in the energy exchange. Some metabolic diseases are recognisable post-natally because of dysmorphological characteristics (coarse facial features, developmental and/or growth delay, skeletal abnormalities) or because of reduced vision or hearing, muscle weakness, or epilepsy.

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Neuromuscular causes of HCM

About 16-18% of the children with HCM have ataxia or muscle weakness. Cellular and molecular defects, including those of the dystrophin-sarcoglycan complex, the nuclear envelope, the mitochondria, and defects of the filaments of the sarcomere are also involved in juvenile HCM. Neuromuscular symptoms can also occur in the metabolic diseases described above. Because HCM may be the first symptom of these diseases, a paediatric neurological examination is always necessary for

age-dependent symptoms of hypotonia/localised muscle weakness, ataxia, myotonia and encephalopathy. Supplementary blood and urinary examinations (see appendix, at www.cardiologie.nl) and a muscle biopsy for histological, immunohistochemical and electron microscopy (EM) examination are recommended. The mitochondrial respiratory chain should be checked for any defects.

An autosomal recessive, X-chromosomal, or maternal inheritance occurs more often in these forms of HCM than in isolated, familial forms of HCM.

Overview of diagnostics in children with HCM

- Investigations for infection, intoxication
- Blood tests (haemogram, electrolytes, CPK, liver functions, carnitine, acylcarnitine, glucose, lactate, pyruvate, ammonia, uric acid, metabolic and chromosome examinations)
- Urine tests (pH, glucose, protein, reduction, sulphites, ketones, metabolic)
- Consultation with clinical geneticist: dysmorphology and family history, DNA diagnostics, sarcomere genes
- Echo and ECG of the parents
- Metabolic testing, including fibroblasts, in consultation with a metabolic team and neuromuscular neurologist/paediatric neurologist
- Consultation with neurologist/paediatric neurologist
- Muscle biopsy for histology, immunohistochemistry and mitochondrial diagnostics
- If necessary: endomyocardial biopsy (histology, EM and mitochondrial diagnostics).

6. Genetic diagnostics in the deceased HCM patient

When the family of a deceased HCM patient is referred for genetic counselling and DNA diagnostics, it is very important to obtain the medical records and DNA of the deceased patient (including the autopsy report) if the familial mutation is not known.

Requesting medical records and DNA

The medical records and DNA or tissue from the deceased patient can be requested by the clinical geneticist treating the referred relative(s). (The tissue will usually be in the form of paraffin blocks stored after autopsy or it may sometimes be frozen.) The doctor who has the records and possibly the DNA will determine whether this should be provided. This will normally be provided as long as the interests of the deceased are not damaged posthumously, as assessed by the doctor. Legally, permission from the blood relatives is not required although in practice, in the Netherlands, written permission is always requested and included with the request for the material. Because there are

no regulations to cover this situation, the genetic counsellor will determine who is best qualified to grant the permission.

DNA diagnostics

Paraffin blocks used for DNA diagnostics should preferably *not* originate from the heart due to the possible presence of somatic mutations. For technical reasons, blocks of liver tissue are also not preferred. In the DNA laboratory, an attempt is made to obtain DNA from these paraffin blocks. The quantity of DNA is usually limited and of average quality, so it must be handled carefully. Often, in practice, only known mutations (familial or founder) can be screened for.

If the DNA of a deceased individual was stored before their death, the entire DNA diagnostics can be performed as for a living index patient. If the individual died suddenly, tissue samples will often have been frozen for toxicological examination. It is often better to use these for isolating DNA than paraffin block tissue. Frozen tissue is usually stored for up to 6 months after death in the Netherlands.

Financing DNA diagnostics for a deceased person

Some Dutch healthcare insurance companies will reimburse DNA diagnostics for up to 1 year after the death of an insured person, so that it makes sense to screen all the genes simultaneously. Other insurance companies do not reimburse testing of deceased persons. In this case, reimbursement must be requested from the health insurance company of the relative requesting the genetic counselling. If the insurance company refuses, either the relatives must pay for the diagnostics, or they can discuss the matter with the laboratory to see whether the diagnostic tests can be performed but not billed. The DNA of the deceased person must *not* be registered in the name of a relative for financial reasons!

The result

The DNA result is discussed with the relative(s) who requested genetic counselling, as outlined in chapter 8.

DNA diagnostics in families where no DNA of HCM patient(s) is available

If there is no DNA of a patient available, and no other patients are discovered in the family during cardiological examinations, it is still possible to test the relatives who would have a 50% risk of carrying an HCM mutations. If a mutation is discovered, the familial mutation is then known and the status of the deceased patient can be recorded. However, if no mutation is discovered, the relative theoretically has a lower chance of being an HCM carrier without any cardiological characteristics of HCM,

Table 3. Dysmorphology and syndromes of HCM in children (according to Schwartz 1996).²¹

Organ System	Reference	Syndrome
Growth	Small	Noonan syndrome Multiple lentigines Mucopolysaccharidoses
	Macrosomia/overgrowth	Beckwith-Wiedemann syndrome Costello syndrome
Skeletal	Pectus Kyphoscoliosis	Noonan syndrome Mucopolysaccharidosis
Skin/Hair	Wiry hair Palmar keratosis	Cardio-facio-cutaneous syndrome Cardio-facio-cutaneous syndrome
	Lentigines Cafe au lait spots	Multiple lentigines Neurofibromatosis, type 1 Noonan syndrome
	Neurofibromas Cutis laxa/loose skin Deep plantar grooves Linear skin defects Lipodystrophy	Neurofibromatosis, type 1 Costello syndrome Costello syndrome Microphthalmia with linear skin defects Lipodystrophy, insulin resistance, leprechaunism
Facial	Characteristic	Noonan syndrome Cardio-facio-cutaneous syndrome
	Coarse	Mucopolysaccharidoses Pompe's disease
	Non-specific hypotonia	Metabolic disorder
Other craniofacial	Telecanthus Cataract	Telecanthus, MCA syndrome Sengers syndrome Leber congenital amaurosis
	Nystagmus Macroglossia	Leber congenital amaurosis Beckwith-Wiedemann syndrome Pompe's disease
	Ear grooves Neck webbing	Beckwith-Wiedemann syndrome Noonan syndrome
CNS	Microcephalia Contractures	Microcephalia, MR syndrome Marden-Walker syndrome
External genitalia	Hypogonadism	Hypogonadism, MCA, MR syndrome Hypogonadism, collagenoma syndrome Alstrom-like syndrome with hypogonadism
	Cryptorchism	Noonan syndrome

MCA=multiple congenital abnormalities, MR=mental retardation

but no definite statement can be made. If several relatives with a high a priori risk can be tested, the chance is great that the mutation will still be discovered.

In this way, genetic counselling can be provided

to relatives in the manner described in chapter 8, because there may be a matter of predictive DNA diagnostics in asymptomatic relatives.

Summary of genetic diagnostics for HCM in a deceased index patient.

a. Request medical records and DNA material of deceased patient	Treating physician is responsible, permission from family not legally required
b. DNA isolation from paraffin blocks	Usually of poor quality, screening only for known (founder) mutations
c. DNA isolation from post mortem frozen tissue	DNA diagnostics usually feasible
d. DNA from stored tissue samples (taken before death)	DNA diagnostics usually feasible
e. Financing the DNA diagnostics for the deceased	Sometimes covered by own health insurance company
Otherwise claimed via individual requesting advice
f. Result	DNA result is discussed with the relative who requested counselling
g. If no DNA of the deceased is available	Consider: DNA diagnostics in 50% risk carriers – presymptomatic diagnostics

7. Recommended laboratory procedure when a DNA diagnostics request for HCM is received from a cardiologist not associated with a cardiogenetic outpatient clinic*Request for DNA diagnostics by cardiologist of an HCM index patient*

Cardiologists who are not associated with a cardiogenetic outpatient clinic regularly request DNA diagnostic work for HCM patients. As described in chapter 3, these specialists are not formally allowed to request such tests. From research and experience, it is apparent that most cardiologists in the Netherlands are still not able to handle an informed consent in a responsible manner prior to the diagnostics. Nor can they fully interpret or discuss a DNA result or ensure proper follow-up in the form of cascade testing.²² Thus, for the time being, there are good reasons to maintain the existing regulations.

It is likely that, in due course, cardiologists will be able to handle DNA diagnostic work in an index patient. In the long term, the aim is that the standard molecular diagnostics for HCM should be requested by the patient's cardiologist, after which the patient will be referred to a cardiogenetic out-

patient clinic for discussion of the result and for recording the family history, counselling and any further family testing.

Managing the request for DNA diagnostics

As soon as the request for diagnostic testing is received, the requesting cardiologist is contacted by the laboratory. They will check whether a clinical geneticist is already involved. If so, his or her name is entered as the requesting specialist, and the cardiologist is recorded as the copyholder. After this the diagnostic work can be started.

If no clinical geneticist is involved yet, the guideline recommends that one be chosen. A copy of the request is then forwarded to the selected clinical geneticist and/or cardiogenetic outpatient clinic, asking that the patient be called in for genetic counselling. The DNA is stored until the clinical geneticist indicates the tests should be started.

Request by cardiologist for predictive DNA diagnostics for HCM

It is the intention that clinical geneticists will remain responsible for predictive DNA diagnostics and cascade testing in the future.

Summary of recommended procedure for laboratories when a cardiologist not associated with a cardiogenetic outpatient clinic requests DNA diagnostics.

a. Request for DNA diagnostics from HCM index patient	Lab contacts cardiologist
b. Clinical geneticist appears to be involved in request	Clinical geneticist becomes requesting specialist; cardiologist becomes copyholder. DNA tests started
c. There is no clinical geneticist involved as yet	Cardiologist is requested to approach clinical geneticist
Clinical geneticist calls index patient in for counselling
When the clinical geneticist indicates, the DNA tests are started
d. Request for predictive DNA diagnostics by cardiologist for relative of index patient (not permitted under Dutch guidelines)	Cardiologist is asked to approach a clinical geneticist
Clinical geneticist calls relative in for presymptomatic counselling
When the clinical geneticist indicates, the DNA tests are started

8. Family testing in HCM (predictive DNA tests and cardiological diagnostics)

I. Cardiological family testing

Because no mutation can be found in about 35% of HCM patients/families, cardiological family testing is sometimes the best way to identify risk carriers in the family. Although predictive diagnostics in HCM is also possible by means of cardiological examination(s), this will only provide clarity about the genetic status of a relative if cardiological abnormalities are discovered. For this type of family testing, specific ECG and echo criteria are used to make the HCM diagnosis.²³ If the relative has no clinical features of HCM, it is still impossible to exclude them from being predisposed for HCM. Regular monitoring will be necessary.

On the basis of the known clinical characteristics in HCM families, cardiological examination of at-risk children is needed from the age of 10 years. This recommendation can be adapted after counselling and discussion with the parents, in the case of symptoms, if it is a family with a young age of onset, or on psychosocial grounds. Some relatives may be against predictive DNA diagnostics, whether temporarily or not, but they may be more positive about cardiological examinations and monitoring. In which case, this should be offered.

II. Family testing using the cascade method for predictive DNA diagnostics

As soon as a pathogenic mutation is discovered in an index patient, cascade testing becomes possible. In principle, it is only offered to those older than 10 years of age. Initially, first-degree relatives of the index patient are invited for this testing. If mutation carriers are identified, their first-degree relatives are subsequently invited for testing, etc. If necessary, second-degree relatives are also tested. In this manner, an entire family can be systematically tested. On average, ultimately half of them will be identified as mutation carriers and the other half will be reassured because they do not carry the genetic predisposition for HCM.

The mutation carriers will be referred for extensive cardiological examination and regular monitoring (at the moment this means every 1 to 2 years).²⁴ It is hoped that the Dutch national ESCAPE-HCM study will provide more insight into the risk stratification of mutation carriers in a few years' time.

- a. Referral
- b. Information distributed before counselling appointment
- c. First consultation
- d. DNA diagnostics
- e. Result of the predictive DNA diagnostics
- f. Information to referrer/family physician

- g. Follow-up
- h. Initiating further family testing using the cascade method

a. Referral

Relatives can be referred for genetic counselling and predictive DNA diagnostics by the family physician or specialist. They are registered in writing or by telephone with the secretariat of a Department of Clinical Genetics (telephone numbers can be found at www.vkgn.nl or through www.cardiogenetica.nl). The patient is invited to a cardiogenetics appointment. When testing children, all the children in a family can be invited at the same time. Adult brothers and sisters also often want to attend together. This must be made possible, although attention must be paid to an individual's need for privacy.

The maximum waiting time for predictive diagnostics in HCM patients should not be longer than 2 months. If, on registration, relatives spontaneously indicate they already have symptoms, the family physician may be contacted to check whether an emergency consultation is necessary. The family physician is medically responsible for his/her patient until the patient is seen for the first consultation by a clinical geneticist.

b. Information distributed before counselling appointment

Relatives are usually informed by a family letter distributed by the index patient or by another relative. The referrer and relative can find out about the hereditary aspects of HCM and the daily routine in the cardiogenetic outpatient clinic through the web site www.cardiogenetica.nl. The Department of Clinical Genetics will also send the patient specific information about the counselling procedure and financial matters.

c. First consultation

Sufficient time (30 to 45 minutes) should be taken for this appointment. The clinical geneticist should check the counsellor's expectations of the consultation (and those of others present), what they already know about HCM and its heredity pattern, and what questions they have.

Then the cardiological information is evaluated (in principle, the case history according to the ESCAPE-HCM form, see appendix, chapter 12, at www.cardiologie.nl).

Next, a family tree is drawn up (for at least three generations), with particular attention paid to any relatives with HCM, metabolic or neuromuscular disorders (or any related symptoms) and to any sudden deaths that have occurred in the family. If the counsellor thinks that certain relatives may be significant in determining the family case, written permission should be obtained from them so that their medical records can be requested.

The counsellor should be informed about the hereditary aspects of HCM, of his/her risk for being a mutation carrier and the potential consequences for his/her closest relatives. If desired, the clinical aspects of HCM can be discussed, including the consequences for daily life and practising one's profession.

The predictive DNA and cardiological diagnostics are discussed, including the duration, financial issues and the consequences of finding a mutation in a relative. If the person is not a carrier then he/she has no increased risk for HCM, nor will his/her children be affected. If the person is a carrier then he/she has an increased risk for HCM and will be referred for cardiological examination and regular follow-up. This also means his/her children will have a 50% chance of being a carrier. The relative can indicate how he/she wants to learn of the test results. In principle this takes place at the outpatient clinic, but can be done by telephone or in writing if desired. There is always an opportunity for follow-up sessions.

Being a proven carrier of HCM can lead to an increase in the premiums for life insurance and for private work disability insurance. These consequences must be discussed with the individual before the cardiological examination and/or before a blood sample is taken for the DNA tests. A proven carrier may also be excluded from certain occupations and competitive sports. According to the guidelines, mutation carriers who show no symptoms of HCM during cardiological examination may perform competitive sports, as long as they have at least an annual cardiological check-up. The patient will receive an information letter about HCM to take home which should describe the management of the disease as well as stating the names of those involved in their genetic counselling.

If, during the consultation, it appears that the disease or the DNA testing is likely to lead to psychosocial problems (or has already done so), and/or that this patient falls into a vulnerable group based on personal or group characteristics (see Introduction), he/she should be referred to a psychosocial worker. One should normally be available in the department during consultation hours.

At the end of the intake phase, the clinical geneticist must be convinced that the counsellor is making a well-considered request for predictive DNA diagnostics and that the counsellor is able to undergo the testing. This phase is concluded with the counsellor giving his/her formal, informed consent for performing the DNA testing. A note of this must be made in the case history. There may be a local condition that the counsellor must sign for this. A waiting time for contemplation, between the first consultation and taking a blood sample, is not mandatory, but it can be discussed as an option.

d. DNA diagnostics

A blood sample is taken (2 x 10 cc EDTA blood) and sent to one of the DNA diagnostic laboratories, together with a completed request form (this can be downloaded from www.dnadiagnostiek.nl). The relevant information about the relative with a mutation must always be provided too. The result will be sent to the clinical geneticist making the request for the test, and a copy will be sent to the cardiologist involved. The family physician and referring cardiologist will be informed of the result by the cardiogenetic outpatient clinic. The result should be available within 6 weeks at the most.

For children up to 12 years of age, the parents or guardian must decide on whether predictive DNA diagnostics should be done. Between 12 and 16 years of age, the parents and child should together make the decision, and when the child is older than 16 he/she can decide. This is all done according to the Dutch Medical Treatment Contracts Act (*Wet geneeskundige behandelingsovereenkomst, WGBO*); for more information, see chapter 9.

Those who are unable to give informed consent can only be tested if this is in their medical interest.

e. Result of the predictive DNA diagnostics

The result should preferably be given to the individual at the cardiogenetic outpatient clinic. If desired, this can be done by telephone or in writing. Each counsellor will be sent a summary letter in any case. For the mutation carriers, this letter will also contain advice on the follow-up and expansion of the cascade testing.

f. Information to referrer/family physician

The family physician and referrer will be informed in writing about the results and will receive a report about the counselling. This is usually a copy of the letter to the counsellor. If the counsellor has explicitly indicated that he/she does not want the family physician and/or referrer to be informed about their being a possible carrier, this must be respected (on the basis of the *VKGN* guideline for predictive DNA examination). The professional groups involved consider that it is seldom in the interests of the counsellor not to inform the family physician. In such a case, the matter would be discussed with the counsellor.

g. Follow-up

Cardiological examination and follow-up are organised for identified carriers. It is important that the waiting time to the first examination is short, particularly for psychological reasons. As long as no symptoms of HCM are discovered, the cardiological examination should be repeated every one to two years. In some centres, an MRI examination is also performed (with gadolinium enhancement),

because fibrosis is related to an increased chance of ventricular tachycardias (VTs).²⁵ The exact value of this has not yet been elucidated.

If necessary, psychosocial follow-up should be offered. This can also mean that the process of cascade testing should be started or that the patient's (under-age) children need to be informed.

If desired, follow-up sessions can be offered at the cardiogenetic outpatient clinic, for example if the patient wishes to start a family.

h. Initiating further family testing using the cascade method

The mutation carrier is offered support to encourage further cascade testing in his/her family. 'Family letters' (giving information on the disease and need for wider testing in the family) can be provided and, if necessary, the counsellor can offer to approach relatives who are designated by the mutation carrier (possibly in a second stage). The genetic status of other relatives must, of course, never be disclosed in these discussions without their prior permission.

Summary of family testing in HCM.

I. Cardiological family testing	For unknown mutation in index patient with HCM, or in relatives who do not want predictive DNA diagnostics Only provides certainty if HCM present From age 10 years
II. Cascade testing by predictive DNA diagnostics	In families with known, pathogenic, HCM mutation in the index patient From age 10 years Maximum waiting time 2 months
a. Referral	On request of relative, after family letter By family physician or specialist, at Clinical Genetics outpatient clinic (telephone numbers at www.vkgn.org)
b. Information prior to appointment	Family letter about HCM and heredity, procedure, financial aspects of consultation and presymptomatic DNA diagnostics See also www.cardiogenetica.nl
c. First consultation	Duration 30-45 minutes Discussion of expectations of patient, partner, family Inventory of cardiac and other complaints in relative Expand family tree, make inventory of family relationships Discussion of HCM and heredity Discussion of presymptomatic DNA diagnostics If necessary, discuss cardiological examination of relatives If necessary, request medical records If necessary, refer to psychosocial worker Provide written information on above to take home
d. DNA diagnostics	Reflection time allowed, not required Take blood samples (2 x 10 cc EDTA), screen for familial mutation Fill in request form from www.dnadiagnostiek.nl
e. Result	Result sent to clinical geneticist, with copy to cardiologist Given to patient at cardiogenetic outpatient clinic, by clinical geneticist. If desired, can be done by telephone or in writing. Summary letter sent to patient
f. Information to referrer and family physician	Copy of letter to patient, if necessary supplemented by advice for treatment and follow-up.
g. Follow-up	Cardiological: for a carrier, if desired at a regional cardiologist Psychosocial: per indication by psychosocial worker Clinical Genetics Follow-up discussions planned when it is necessary to test children, couples wish to start a family, etc.
h. Initiating further cascade testing	If necessary, supplementary examination aimed at metabolic or syndromal cause In cooperation with or by relative Provide family letters for the tested relative to distribute or send family letters to selected relatives

If the mutation carrier has children, a psychosocial worker will offer support to the parents to discuss having predictive diagnostics for them. Only after this step, will the children be invited for further counselling and testing.

The family tree should be stored centrally, so that the various counsellors involved can check the state of affairs in the family testing. The counsellor should enter the results of all the family tests performed into the family tree.

A difficult situation: 50% risk carrier refuses testing, but his/her children want to be tested

When considering whether or not to perform predictive DNA diagnostics in a family, there is international consensus that the wish of the requesting individual should prevail, even if their test result could lead to information that another relative finds undesirable. This means that someone with a 25% risk of disease is eligible for DNA diagnostics even if their parent with a 50% risk does not want to be tested. Of course, the family dynamics will be a topic of discussion and the psychosocial worker should normally be involved in helping them to deal with this issue. From a practical point of view, for larger sibships, some pressure should be exerted on their parents who have a 50% risk, because DNA diagnostics might not be necessary in the children. Since the parent may also have a medical problem, this is ethically defensible.

9. Predictive DNA diagnostics in children

Introduction

Internationally, as a rule, no predictive DNA diagnostics are performed in children unless the potential disease has direct medical and/or social consequences. This can be the case in HCM in children under age 10 if they have symptoms, or for choosing a sport/school/occupation, or because of the family history or the family composition (see also chapter 8). An alternative to doing predictive DNA diagnostics in children older than 10 years is to offer cardiological examination and follow-up until age 18. This, too, can take on a predictive character and is not, by definition, any less drastic than doing DNA diagnostics.

In testing children, the child's age will determine to what degree he/she can be involved in the decision to test and the choice of the type of test (Dutch Medical Treatment Contracts Act, *WGBO*, see section 8.II.d). In all cases, it is important that the child be informed in a way that corresponds with his or her age. For this reason, it is recommended that children of varying ages should not be informed together about predictive testing or about the condition and its impact. Informed consent is given by the parents and/or the child, depending on his/her age, according to the *WGBO* rules.

Puberty and adolescence are significant developmental phases with respect to a young person's emotional life. These years can sometimes be stormy and, as a result, the impact of a possible hereditary predisposition may be seen as a burden or be rejected. For this reason children should, to some degree, be made aware of HCM and the heredity issues in the family before they begin puberty.

If parents are considering predictive diagnostics in their children in the situations described above, or if these diagnostics are deemed medically relevant, the parents must inform their children in a timely and suitable manner. Given the abstract level of the themes of heredity and predictive diagnostics, this can be a difficult task for parents. The tendency to avoid the topic is often present, and is sometimes even enhanced if the psychological impact of HCM is large for the parents. To help children and young people who prove to be carriers, it is advisable to promote open communication from the beginning. As they grow up, they can be encouraged to give the consequences of being a carrier a place in their lives in as responsible and relaxed a way as possible. When starting predictive diagnostics on behalf of children and young people, it is necessary to be aware how much the parents have told their children. The time during the counselling sessions with their children can then be used to inform the children as fittingly as possible.

In any case, psychosocial support by an expert in this area should be offered during the preparatory phase of predictive diagnostics. The information brochures written by psychosocial workers in Amsterdam, Utrecht and Nijmegen can be given to the parents (these are in Dutch).

Information about HCM and testing written for children is available at www.ikhebdad.nl (in Dutch). Further information about heredity in general is available at www.bogi.nl; this has been written for elementary school children (6-12 years).

Procedure for presymptomatic testing of children for a known HCM mutation

1. Upon registration, the parents and/or the children are informed about the involvement of a psychosocial worker, as prescribed by the protocol.
2. In the period after registration and before presymptomatic testing begins, the psychosocial worker will check the family's particulars with the parents (by telephone or in the outpatient clinic).
3. The counsellor and psychosocial worker compare the information they have obtained to determine what further counselling is needed.
4. The parents and children are invited for a consultation with the genetic counsellor and cardiologist. The attention here is primarily paid to the children and information is provided at their

level. The procedures for the case history/examination/DNA diagnostics/result are otherwise the same as for adults (chapter 8). At least 30 minutes should be reserved for the first consultation if one child is being tested and at least 45 minutes if more children are being tested.

5. The psychosocial worker can attend this consultation or should arrange to meet the family immediately afterwards.
6. Unless there are contraindications (medical or psychosocial), blood samples should be taken the same day for DNA diagnostics.
7. If the ages of the children in a family are rather widespread, the older children can be offered the opportunity to ask their own questions at the end of the family consultation, while the parents are with the younger children having blood samples taken.
8. If a young person of 16 years or older makes an appointment for him- or herself, he/she should first be invited to attend an exploratory consultation with a counsellor and psychosocial worker, who can work towards involving his/her parents in the process.
9. In principle, the DNA results are given to the counsellee at the outpatient clinic. This can also be done by telephone or in writing, if desired. The procedure for conveying the result should be discussed ahead of time (together with the children or not, on a date set in advance, or as soon as possible after the result is known).
10. If one or more of the children is a carrier, the psychosocial worker will follow up with the parents (by telephone or otherwise) and, if desired, with the children; this contact usually occurs within two weeks and/or after the result from the follow-up testing.
11. Up to the age of 16, children who are mutation carriers will be referred to a paediatric cardiologist. Over the age of 16, they will be referred to a cardiologist.

Deceased parent

Children are sometimes referred to as the 'index' patient, when the parent with HCM has died without the mutation being identified (see also chapter 6). In such cases the children have a 50% chance of being a carrier. If there are no other living relatives with HCM in whom DNA diagnostics can be performed, pursuing DNA diagnostics in the children can be considered. The chance of finding a mutation increases with the number of children that can be tested. Because this is also a form of presymptomatic diagnostics, the protocol described above must be applied.

On www.achterderegenboog.nl there is information (in Dutch) about death and coping with grief for medical and social workers and other professionals involved with children aged 0-18 years.

10. Pregnancy and prenatal diagnostics in HCM

Most women with HCM can manage a pregnancy well, unless they already have serious symptoms or a high-risk profile.¹ If, prior to a pregnancy, they request information about the HCM symptoms to be anticipated in a foetus or young child, the family history of the partner must always be considered too. If HCM also occurs in the partner's family, there is a chance that the child may have a double, compound heterozygote or homozygote mutation. These children can develop HCM at a young age. As stated in chapter 5, the chance of HCM symptoms appearing in heterozygote children is very small.

Prenatal testing for HCM is technically only reliable by means of DNA diagnostics. For this the familial, pathogenic, mutation must be known. The diagnostic test will then preferably be performed on tissue obtained from a chorionic villous sampling at 11 weeks pregnancy. The result will be known after 2 to 3 weeks and if it is abnormal, the pregnancy can be terminated. However, this is not a precondition for performing this test.

During the genetic counselling for HCM given to couples who would like to plan a family and to young people, the counsellor will inform them of the technical possibility of prenatal diagnosis for HCM by means of DNA diagnostics. The prenatal diagnostics are not, however, actively offered, conforming with the situation in oncogenetics.²⁶ In practice, so far prenatal diagnostics is almost never requested as soon as it is made clear that there are no preventive options other than performing an abortion. In the Netherlands, prenatal diagnostics for HCM is sporadically performed in families with a very serious form of HCM. This is also the case in other countries, as far as we know.²⁷

Because HCM does not, normally speaking, manifest itself before age 10, it is not useful to offer HCM parents a screening echo during the pregnancy. In the Netherlands, every pregnant woman is eligible for a general screening echo at 20 weeks. If a thickening of the heart muscle is observed during such a screening echo, it may be an isolated case of HCM, but usually such an HCM is seen as part of a genetic syndrome or metabolic condition, or it is due to pregnancy complications such as maternal diabetes, infection, autoimmune diseases or placental abnormalities. ■

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