Clinical genetic care in diseases predisposing to sudden cardiac death
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Chapter

Family and population strategies for screening and counselling of inherited cardiac arrhythmias

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Abstract

Family screening in inherited cardiac arrhythmias has been performed in the Netherlands since 1996, when diagnostic DNA-testing in LQTS and HCM became technically possible. In multidisciplinary outpatient academic clinics, an adjusted protocol for genetic counselling, originally known from predictive testing in Huntington's disease, is being used. 1110 Individuals, including 842 relatives of index patients, were informed about their risks, and most were tested molecularly and/or clinically for carriership of the disease present in their family. Of 345 relatives who were referred for cardiologic follow-up, 189 are being treated, because of an increased risk of life-threatening arrhythmias.

Evaluation of the psychological and social consequences of family screening for inherited arrhythmias can be performed by using the adapted criteria of Wilson and Jüngner, i.e., from a point of view of Public Health. Preliminary results of psychological research show that parents of children at risk for LQTS show high levels of distress. Many other aspects have to be evaluated yet, making final conclusions about the feasibility of family screening difficult, particularly in HCM. Clinical guidelines are urgently needed. Population screening by molecular testing, for instance in athletic preparticipation screening, will become possible in the future and has its own prerequisites for success.

Key Messages:
- Family screening, based on DNA-testing, in inherited arrhythmias is technically possible in LQTS and HCM and leads to identification and treatment of many at risk relatives.
- Population screening by DNA-testing for life threatening arrhythmias is not yet feasible, while the usefulness of clinical screening has not been evaluated properly.
- Clinical guidelines for family and population, molecular and clinical, screening in inherited arrhythmias are needed and should be based on the outcomes of clinical and psychosocial evaluation studies.
**Introduction**

Inherited cardiac arrhythmias can be divided into two main categories: diseases in which alterations in the electrical properties of the heart cause arrhythmias (primary electrical diseases), and diseases in which structural alterations create an arrhythmogenic substrate (cardiomyopathies). Primary electrical diseases include Long QT syndrome (LQTS), Brugada and Andersen syndromes and familiar polymorphic ventricular tachycardia (FPVT). Cardiomyopathies include hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), and arrhythmogenic right ventricular dysplasia (ARVD). The most frequent mode of inheritance by far in both categories is autosomal dominant. Reduced penetrance (the percentage of mutation carriers who develop symptoms during their lives) and varying expressivity (the severity of symptoms) are common.

While the genetic predisposition can not be cured yet, prevention of symptoms and especially of sudden death, the most feared complication of these disorders, is possible to a large extent by the prophylactic use of medication, pacemakers or implantable cardioverter defibrillators (ICD's). Therefore, screening of yet unidentified people at risk seems useful.

**Screening**

**State of the art in family screening for cardiac arrhythmias**

Systematic cardiologic screening of first and second degree relatives, starting with the index patient (cascade screening) has been performed since the discovery of the genetic nature of these disorders, particularly in primary electrical diseases. Family screening in cardiomyopathies is advocated as well, but is performed less often in the Netherlands. A recent survey among Dutch cardiologists revealed that only 59% of cardiologists inform their HCM patients about the genetic nature of their disease and only 54% discuss the consequences for offspring [1]. Clinical screening cannot uncover all asymptomatic relatives at risk, because these diseases have a reduced penetrance.

True cascade screening only became possible after the genes that cause inherited cardiac arrhythmias were discovered in the nineties of the last century. DNA-testing allows identification and subsequent surveillance of all mutation carriers and reassurance of those in whom these mutations were excluded. DNA diagnostic services for these diseases are not yet widespread, but are available for the primary electrical diseases and some cardiomyopathies, particularly HCM. In The Netherlands, in LQTS a mutation is detected in 80% of index patients after screening all six genes. In HCM, a mutation is found in 60% after screening MYH7 and MYBPC3 routinely, and TNNT2 when considered appropriate [2,3].
State of the art of population screening in inherited cardiac arrhythmias

Population screening for a predisposition to cardiac arrhythmias is rarely offered. In Japanese schoolchildren, ECG examinations are regularly conducted in the 1st (age 6 or 7 years) and 7th (age 12 or 13 years) grades. The effect of screening on the prevention of sudden death is smaller than expected, predominantly due to poor compliance to the prophylactic use of beta-blockers [4,5].

In Italy, ECG-screening of neonates and follow-up in the first year of life has been performed in a research setting since 1976 [6]. The aim was to develop strategies to reduce the incidence of the sudden infant death syndrome (SIDS), e.g., by treating those with a long QT interval with beta-blockers. Prolongation of the QT interval beyond the 97.5th percentile in the first week of life was strongly associated with SIDS (OR 41.3, 95% CI 17.3-98.4). Due to the low incidence of SIDS (< 1:1000), 100 children would have to be treated to save 2 lives (assuming that beta-blockers save lives in this context, which is unlikely in those cases caused by SCN5A mutations, which may be the majority based on literature). However, many false-positives were also identified, causing undue anxiety in a substantial number of parents of healthy children. Consequently, a commission advising the Italian Superior Council of Health proposed the implementation of ECG-screening at 15-25 days to reduce the false-positive rates. No reports have been published since, so the (cost-) effectiveness of this approach and the societal and psychological side effects still await evaluation.

Preparticipation screening (PPS) in competitive and recreational physical activities in asymptomatic persons and patients known to have cardiovascular disease can be viewed as a form of population screening as well. Its aims are the identification of those prone to sudden cardiac death from arrhythmias during sports or fitness training. Identification may lead to disqualification or to adaptations in training programs believed to reduce sudden death in the population as a whole. Several guidelines approved by professional organisations such as the American Heart Association (AHA) have been published. These are aimed at prospective high school and collegiate competitive athletes, at those (of all ages) planning to engage in a health or fitness programs and at patients already diagnosed with HCM (or other myopericardial diseases, and mitral valve prolapse) [7-9]. The effectiveness of these measures still needs to be proven, because the accuracy of the screening cannot be demonstrated due to the lack of randomised control groups and data on subjects who were inappropriately cleared or restricted [10]. Conversely, no harmful effects have been reported either.

One of the few reports that meet the requirements for evaluation of effectiveness was published by Corrado et al. [11]. PPS in young prospective competitive high school and collegiate athletes has been performed in Italy for more than 30 years because legislation from 1971 requires a yearly clinical evaluation of this group. Corrado et al. prospectively assessed among athletes and non-athletes under the age of 36 whether this strategy results in the prevention of sudden cardiac death from HCM. In this study (from 1979 to 1996) 49 of 269 sudden deaths occurred in athletes. Only one death in athletes was caused by HCM (2%), compared to 16 (7.3%) in non-athletes, not including the 22 subjects who were disqualified for athletic activities based on the diagnosis of HCM during PPS. In the United States, HCM
is reported to have been the cause of sudden death in up to 30% of deceased competitive athletes. These results show that PPS may have prevented sudden death in those diagnosed with HCM. Most strikingly, ARVD caused 22% and coronary atherosclerosis 18% of deaths in the athletic population. Furthermore, 82% of those dying from arrhythmias caused by ARVD had clinical findings indicative of cardiovascular disease (but not leading to disqualification). In the last decade the awareness of ARVD increased, resulting in disqualification of significantly more patients than before [12].

The most cost-effective screening protocol, according to these authors, consists of history taking, physical examination and a 12-lead ECG, with approximate cost per year of life saved of 2,527 euro [13].

Mandatory cardiac investigations or DNA testing and the requirement to provide data on earlier performed DNA tests in people who apply for certain jobs or for life/job insurances may also be regarded as a form of cardiovascular screening aimed at excluding the ones that have an increased risk. It has been recommended that the AHA guidelines for PPS in young athletes be also used in those engaged in careers where public safety is involved (e.g., fire-fighters, police officers, airline pilots). In Italy, all males ≥ 17 years of age undergo comprehensive medical screening (personal and family history, physical examination, chest X-ray, blood pressure measurements and 12-lead ECG) to assess their suitability for mandatory military service. In a recent study of Nistri et al., the effectiveness in detecting conscripts with HCM was evaluated over a 4 year period in 34,910 participants [14]. After abnormal findings were obtained during the initial screening, 2,766 men were selected for 2-dimensional echocardiography. Nineteen of these were given a definitive diagnosis of HCM, including six who had been diagnosed before. Two of the HCM conscripts were symptomatic. Follow-up revealed that all those diagnosed with HCM stayed alive and well over a 6-year period. No data were given concerning the follow-up of those who passed the screening tests.

**State of the art in screening of other forms of genetic predisposition for sudden cardiac death**

Systematic family screening for another type of cardiovascular disease that also predisposes to sudden cardiac death is increasingly offered - familial hypercholesterolemia (FH). Similar to the inherited arrhythmias, FH is an autosomal dominantly inherited disorder with reduced penetrance and variable expressivity in which prophylactic measures reduce morbidity and mortality. The estimated frequency of FH is 1 in 500. Predictive DNA-testing has long been possible, but only achieved clinical relevance after effective lipid lowering therapies became available in the last decade. In the Netherlands, cascade screening in FH is performed by a organisation, the ‘Foundation for tracing hereditary hypercholesterolemia’ (Dutch acronym StOEH), which actively approaches and visits relatives of index patients at home, where information is given and blood samples may be taken. Mutation carriers receive the results by mail and are advised to visit their general practitioner with a letter stressing the need for treatment and follow-up through lipid clinics. Clinical genetic centres are therefore not involved in this form of screening. Systematic evaluation studies revealed that psychological consequences are relatively small.
but societal adverse effects do exist. Follow-up, prophylactic treatment, and adherence to life
style advice of those who are eligible appear disappointing [15-18].

DNA-testing in unselected populations is currently not feasible in genetically heterogeneous
and relatively rare diseases like primary electrical diseases and cardiomyopathies.

**Paradigms in genetic (family)screening**

*From a Clinical Genetic viewpoint*

Presymptomatic or predictive DNA-tests and counselling surrounding this, took off in the 1990s
when the gene for Huntington's disease was identified. Huntington's disease is an untreatable, very
disabling neurological disorder, leading to mental and physical deterioration and death between
30 and 50 years of age. Penetration is complete and expressivity is similar in patients who have
similar ages of onset. Since that time, presymptomatic counselling and diagnosis has frequently
been performed in clinical genetic centres all over the world. Guidelines for multidisciplinary
counselling were established after extensive psychological research and were implemented in
all centres offering this service [19]. These guidelines consist of at least six counselling sessions,
three with a clinical geneticist and three with a psychologist/social worker with intervals of 3-6
weeks each. A personal declaration of results is obtained and long term psychosocial follow-up
is offered. Consultation of psychiatrists or neurologists is optional. These guidelines are aimed at
supporting the patient’s autonomy and at self-selection of those with sufficient ego-strength to
handle possible negative results. With the use of these guidelines, no catastrophic events have
been reported in the last 10 years in those eventually opting for DNA-testing (about 50% of first
applicants). In total, only about 15% of those at high risk opt for testing.

From 1995 predictive DNA-testing for heritable cancer syndromes, particularly breast/ovary
and colon cancer, became increasingly possible. Guidelines for counselling are heavily based
on the 'Huntington paradigms,' which is remarkable because in these disorders preventive
strategies, following cascade screening and identification of high risk individuals, are of great
value. Still, reinforcement of autonomy and (self)selection of those capable of handling bad
outcomes remain important goals of counselling. In contrast to Huntington's disease, cascade
screening is often facilitated by the distribution of 'family-letters' (formulated by a clinical
geneticist) by the index-patient. These letters explain the risks, the possibility of DNA-testing
and the preventive options in a particular family. About 30-50% of consultations in clinical
genetic centres are aimed at heritable cancer syndromes nowadays. The psychosocial negative
effects of cascade screening are reported to be small, probably because, like in Huntington's
disease, only motivated and psychologically strong applicants start and proceed with testing.
Genetic counselling leads to significant decreases in generalized anxiety in women who opt
to be tested for breast cancer. Genetic counselling also leads to a better understanding of
the limitations of genetic testing in familial colon cancer syndromes. However, as in PPS, few
studies used a randomised trial design, and follow-up to date has been short [20-22].

A systematic review of the implications of predictive genetic testing in neurological disease
and cancer syndromes revealed that in these self-selected populations those eventually
undergoing testing do not experience severe adverse psychological consequences, although
follow-up time was no more than one year in most studies. Pre-test emotional state was predictive of subsequent distress in 14 of 27 analyses. Test-results (being a carrier or not) were rarely predictive. Therefore testing protocols should include a pre-assessment of emotional state, selecting the ones that need more psychosocial care (23).

**From a Public Health viewpoint**

Testing for the presence of risk factors for cardiovascular morbidity and mortality, like high blood pressure or high cholesterol, has been common practice for years. The context varies from screening in an apparently healthy population (primary prevention) to screening patients who suffered from an acute myocardial infarction or cerebrovascular accident (secondary prevention). The prerequisites for the success of a screening programme using genetic testing are: 1) the possibility to diagnose the disease early, 2) the possibility to treat the disease and 3) a high prevalence of the disease within a certain population [24]. In order to establish that screening programmes are truly beneficial for the health of a certain (high risk) population, the psychological and social consequences of being tested and of the follow-up should also be evaluated. Furthermore, the implementation of a screening programme depends on the prevailing organisational setting for genetic test services. Evaluation of genetic screening programs is possible by using well known criteria of Wilson and Jüngner, published by the WHO in 1968. Adaptation was made for the use in genetic screening for heritable cancer syndromes.

<table>
<thead>
<tr>
<th>Table 1. Criteria for assessment of screening adapted from the Crossroads 99 Group, based on the Wilson and Jüngner criteria [24,25].</th>
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<tbody>
<tr>
<td>1. <strong>Knowledge of population and disease</strong></td>
</tr>
<tr>
<td>a. Important burden of the disease</td>
</tr>
<tr>
<td>b. Target population identifiable</td>
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<tr>
<td>c. Considerable level of risk</td>
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<tr>
<td>d. Pre-clinical phase of the disease existent</td>
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<tr>
<td>e. Natural course (from susceptibility to precursor, early disease and advanced disease) understood</td>
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<td>2. <strong>Feasibility of screening procedure</strong></td>
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<tr>
<td>a. Suitable test or examination available</td>
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<tr>
<td>b. Entire screening procedure acceptable to screened population</td>
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<tr>
<td>c. Screening process continuing process and encompasses all elements of screening procedures</td>
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<td>3. <strong>Interventions and follow-up</strong></td>
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<tr>
<td>a. Physical net benefit of the intervention likely</td>
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<td>b. Psychological net benefit likely</td>
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<td>c. Social net benefit likely</td>
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<tr>
<td>d. Facilities for adequate follow-up available</td>
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<tr>
<td>e. Consensus on accepted management for those with a positive test result</td>
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<tr>
<td>4. <strong>Societal and health system issues</strong></td>
</tr>
<tr>
<td>a. Economic and medical costs balanced</td>
</tr>
<tr>
<td>b. Psychological costs balanced</td>
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<tr>
<td>c. Societal costs balanced</td>
</tr>
<tr>
<td>d. Appropriate screening services accessible to entire population without adverse consequences for non-participants</td>
</tr>
<tr>
<td>e. Appropriate confidentiality procedures and anti-discrimination provisions available for participants and non-participants</td>
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</table>
by the Crossroads 99 Group in 2001 (see Table 1) [25]. The use of these criteria recently proved to be valuable in the evaluation of the current screening for FH in the Netherlands [15-18].

The British National Screening Committee recently recommended a paradigm of individual informed choice for participants in screening programs. This may lead to a more ‘clinical genetic counselling’ way of informing those eligible, in which uncertainties and possible harms are equally emphasised as the benefits. Only those who are really motivated for screening are asked to participate. This probably leads to a decreased uptake but also to an increased compliance to changes in lifestyle and/or taking medications of those proven to be at risk [26].

Current predictive screening for inherited arrhythmias in the Netherlands

Multidisciplinary cardiogenetic outpatient clinics exist in five academic hospitals in The Netherlands since 1996. Here cardiologists, clinical geneticists, genetic nurses and psychosocial workers cooperate in the ‘genetic work up’ and predictive DNA-testing of families with (possible) genetic cardiac arrhythmias. Cardiogenetic counselling currently comprises 20% of all consultations at our department, which means that more than 200 families are handled each year. Since 1996, 1110 people were counselled about their predisposition to inherited cardiac arrhythmias (463 LQTS, 298 HCM and 349 other). Guidelines for predictive testing for these diseases do not exist. We use the Huntington guidelines, adapted by us to the needs of families with cardiologic diseases (Table 2). Compared to the Huntington guidelines, the time for reflection before predictive testing is reduced or omitted (especially in LQTS), because the risk of sudden death necessitates expeditious identification and institution of prophylactic treatment to mutation carriers. Moreover, in our clinical experience, anxiety is raised, particularly in LQTS-testing, when applicants are forced to postpone testing. Also, while psychosocial support is

Table 2. Proposed guidelines for genetic cascade screening in heritable arrhythmias (adapted from the Huntington guidelines and used by the authors since 1996)

1. Genetic counselling (including the drawing of a extended pedigree), extension of cardiologic evaluation (if necessary) and DNA testing of the index patient in a multidisciplinary outpatient cardiogenetics clinic
2. If a mutation is detected: education of the index patient and initiation of cascade screening
3. Information of first and second degree relatives by the index patient (if necessary by the medical specialists), using an information letter written by the medical team
4. Genetic counselling of relatives prior to testing, during a family meeting and/or individually
5. Clinical testing of relatives at first consultation (mainly in LQTS and in relatives complaining of symptoms, irrespective of the familial disease)
6. DNA testing of relatives at first consultation (or at a second appointment, if desired by an individual needing more time to consider testing)
7. Psychosocial care (psychologist, social worker) mandatory for all families in whom minors are tested. If this is not the case: actively offered psychosocial care, but not mandatory
8. Results given personally, by telephone or by letter, dependent on the preference of the individual
9. Actively offered follow-up appointments (including psychosocial care) for mutation carriers, especially those having children
10. Cardiologic testing and follow-up in mutation carriers, or referral for testing and follow-up to a cardiologist familiar with the disease in the neighbourhood of the residence of the mutation carrier
actively offered to each applicant, it is no prerequisite before testing, except in the testing of children. Counselling sessions combine the consultation of a cardiologist and a clinical geneticist (or genetic nurse), different from most predictive testing sessions in Huntington's disease and in cancer syndromes. The distribution of family-letters is encouraged. In some (large) families we start the predictive counselling process with a family session, in which up to 30 people can be informed at the same time. Test results are not necessarily revealed in a personal consultation, but may be given (based on the preferences of applicants) in writing or by telephone. Mutation carriers are always offered the opportunity of a follow-up consultations (including psychosocial care) immediately after receiving the results and are actively referred for follow-up cardiologic care.

Follow-up of the 842 relatives of 268 index patients who visited our outpatient clinic, shows that 345 (40.9%, 1.3 relatives/index patient) have been referred for cardiologic follow-up, based on DNA- and/or clinical testing. Of these 345, 189 (54.8%) are already being treated. LQTS-carriers are predominantly cared for in academic hospitals, while most HCM-carriers have been referred to general cardiologists. Of those relatives tested for LQTS, 41% proved not to carry the familial mutation and could therefore be reassured about their own and their descendants' risks. We are not aware of the exact number of first- and second-degree relatives who did not participate in testing. In LQTS the amount of non-participants seems to be lower than in HCM, which is undoubtedly partly related to the perceived risk of sudden death in those eligible for testing, being higher in LQTS than in most HCM families. Extension of cascade screening to more distant relatives sometimes is problematic, due to the lack of personal contacts. In each LQTS family with a known mutation, a mean of 3.5 mutation-carrying relatives have been identified, of whom the majority is taking prophylactic medication. As reported before, prophylaxis is not completely protective. In the follow-up period, three of these relatives have suddenly died: one is a 45 year old lady from a LQTS2 family who started prophylaxis with propanolol three months before. The other is a female 65 year old LQTS3 carrier, who also used propanolol and who died a few days after pacemaker implantation, most probably due to ventricular fibrillation. The last is a male LQTS2 carrier aged 61, who died of a heart-attack during a biking-tour in Spain. He was not using prophylaxis. Seventy-seven children from LQTS families have currently been tested in our hospital.

Until now, in The Netherlands, genetic test services (counselling, testing, follow-up) are largely supplied by departments of clinical genetics of teaching hospitals, as described above for Huntington's disease and heritable cancer syndromes. It has been recognised internationally that master's degree genetic counsellors are increasingly taking over the work of clinical geneticists (and psychosocial workers). This is due to the explosion of demands for predictive testing, the relatively low number of medical specialists in this field, and the good experiences with this new profession. In the future, though, it is expected that this will not be sufficient to meet the demands of the continuously growing number of people who opt for predictive testing. Therefore, regular medical specialists like cardiologists, who treat index patients with inherited arrhythmias, will be asked to perform part of this testing in the future, most preferably backed up by the professionals currently in charge of cascade screening for these and other genetic disorders.
Preliminary evaluation of predictive DNA-screening for inherited arrhythmias (LQTS and HCM) based on the Wilson and Jüngner criteria

Although the current cascade screening for primary electrical diseases (mostly LQTS) and cardiomyopathies (mostly HCM) is based on clinical genetic paradigms, as described above, evaluation of the acceptability and feasibility of screening can be performed using the 'Public Health' Wilson and Jüngner criteria, as has been shown in FH. This might help in guiding future research and adaptation of screening guidelines in these disorders that share a preventable risk of sudden cardiac death at young age in unidentified mutation carriers.

1 Knowledge of population and disease (see Table 1)
The prevalences of clinically detectable LQTS and HCM are estimated at 1:5000 and 1:500 respectively, which points at an important disease burden. Improved results of genetic testing might show that the numbers of asymptomatic mutation carriers are (much) higher, as has already been indicated for LQTS [27].

In both diseases the target population for screening is easily identifiable and consists of relatives of clinically diagnosed and genetically confirmed LQTS and HCM patients, including children.

In LQTS the level of risk is considerable, at least in symptomatic patients: untreated patients have a sudden death risk of 5%/year, dependent on age and sex [28]. In HCM the levels of risk vary: in academic populations under surveillance it is 3%-5%/year and in unselected populations 1%/year. The sudden death risks of unidentified mutation carriers are not yet known, but will be dependent on the genes involved, on several clinical parameters and on the occurrence of sudden death in a certain family. In both disorders a pre-clinical phase (defined as aberrations in clinical measurements, e.g. ECGs or two-dimensional echocardiography) is probably present in the majority of patients at risk for arrhythmias. The natural course of both diseases is understood in clinically diagnosed patients only, not yet in genetically identified carriers without clinical symptoms.

2 Feasibility of screening procedure
In both LQTS and HCM suitable diagnostic DNA-tests are available in families with a known mutation (80% and 60% respectively). In a pilot study, we found that cascade screening in LQTS families seems to be acceptable to both families and providers involved [29]. Acceptability of cascade screening in HCM has to be evaluated, especially in presumed 'low risk families'. The screening process in LQTS and HCM is not yet part of a formal screening program in the Netherlands as is FH. The continuation and completeness is not assured yet: extension of screening to more distant relatives depends on the enthusiasm and power of persuasion of the medical personnel and on the quality of family relationships and the perceived severity of the disease in a certain family.
3 Interventions and follow-up

In LQTS, physical net benefit of prophylaxis in asymptomatic mutation carriers is likely, provided that the subjects are compliant to medication and rules of living. Compliance studies are needed to evaluate this. In our experience, many children and adults are handicapped by the side effects of the prescribed beta-blockers and are confused by the rules we give them. In asymptomatic HCM mutation carriers, except for regular cardiologic screening and attentiveness to warning signs for arrhythmias, no prophylaxis can be offered yet. The results of trials with medications supposed to slow down the development of hypertrophy in asymptomatic HCM carriers, have to be awaited.

Little is known yet about the psychological net benefit of cascade screening for LQTS and HCM. Psychological research in Dutch LQTS families is pending. Preliminary results show that the impact of screening is high, especially in families with children. Psychological distress of 36 parents was assessed before and after delivery of predictive DNA test results of their children. Twenty-four individual parents were informed that at least one of their children was a mutation carrier, while twelve parents were told that none of their children were mutation carriers. Distress in parents was already high prior to mutation detection, due to abnormal or indecisive results of ECG-registrations at first consultation. Up to fifty percent of the parents of mutation carriers showed clinically relevant high levels of distress. Factors that predicted high levels of distress were familiarity with LQTS for a longer time, experiences with (aborted) sudden cardiac death in the family, and receiving unfavourable results for all of the children. Parents of non-carrier children showed significantly less test-related and general anxiety. It is concluded that psychosocial intervention right from the first consultation is necessary in LQTS, when abnormal or indecisive results (of ECG-registrations) have been given and LQTS-carriership in the children may be expected [30]. In HCM cascade screening, no results of psychological studies have been reported yet. The recently published experiences with a French population point at similar psychological susceptibilities in HCM testing [31].

Whether social net benefit of cascade screening is likely, is not known yet for both LQTS and HCM. Social pressure seems likely in families in which cascade screening is actively offered. It is a matter of debate whether this should be regarded as negative. Adequate follow-up is available in LQTS. In HCM this could become a problem in the near future: the prevalence of HCM is at least 10 times as large as of LQTS and with the increasing possibilities for mutation screening in HCM patients, many asymptomatic mutation carriers will be recognised. Regular follow-up in cardiologic outpatient clinics will be very time consuming for the cardiologists who are already too few in numbers to meet the demands of the growing group of symptomatic elderly patients with heart failure. Creative measures to enable cardiologic follow-up and perhaps prophylaxis, e.g. by physician assistants or cardiologic nurses, are probably needed. In LQTS, consensus on the management of those with positive test results exists and is refined continuously. Consensus on 'adequate follow-up' and the need for prophylaxis in HCM carriers is still lacking.
4 Societal and health system issues

It is unknown whether economic and medical costs are balanced in cascade screening for LQTS and HCM. Cost-effectiveness studies will have to be performed. Compliance studies are also important in this respect.

Psychological costs in LQTS are considerable (see above). Quality of life studies still have to be performed in both LQTS and HCM carriers.

Although guidelines and legislation on the use of genetic test information exist in the Netherlands, examples of discrimination for life-insurances and of non-participation in screening because of fear of discrimination have occurred in our patients. The prophylactic use of ICD's may lead to problems with (future) occupation and with driving allowance. It is therefore unknown yet whether societal costs are balanced.

Appropriate (DNA) screening services are currently accessible to the entire population in the Netherlands for LQTS and HCM, but the awareness of cardiologists to refer HCM patients has to increase. The same holds for referral by primary care givers of families in whom sudden unexpected death at a young age has occurred. The cardiogenetic outpatient clinics seem to satisfy the needs of the families that have already been referred. Whether a more formal form of cascade screening, like in FH, will be necessary in the future, depends on the results of medical, psychological and societal evaluation studies on the advantages of identification, follow-up and prophylaxis of asymptomatic mutation carriers of LQTS and HCM. If the follow-up of mutation carriers in HCM can not be guaranteed, cascade screening will only be of use for the relief of non-carriers.

Confidentiality procedures and anti-discrimination provisions are available for the tested LQTS and HCM relatives. This does not mean that unjustified discrimination does not exist. Unfamiliarity with (the results of prophylaxis in) LQTS and the use of outdated information on the risks in HCM by insurance companies may partly account for this. Also, tested individuals may give too much information without being prompted, as has been proven in FH, leading to discrimination [18]. Genetic counselling therefore has to stay a prerequisite for testing, to ensure that those eligible for testing are educated about the proper handling of test information in the communication with insurance companies and employers. Financial discrimination of those deliberately not participating in screening for LQTS or HCM or those who do not comply to proposed prophylactic measures is justified by some stakeholders and professionals [29].

Conclusions

Cascade screening technically became a possibility in cardiac arrhythmias during the last decade. Clinical guidelines for a multidisciplinary approach in predictive testing for these diseases are still lacking as are cost-effectiveness studies and international evaluation studies of psychological and societal consequences. Evaluation studies already performed in the Netherlands, show positive but also potentially negative consequences of cascade screening in cardiac arrhythmias. Genetic counselling is important for education and psychosocial care for those confronted with the risk of dying suddenly. Without any doubt, the still growing
opportunities to identify and subsequently treat those at genetic risk for sudden death have to be considered with enthusiasm. At the same time one has to reckon with the possible negative implications of family screening in psychological, social and financial aspects. Families deserve our watchfulness for these issues. The necessity of screening children at risk brings along its own delicacies. The development of guidelines therefore is urgently needed, with the participation of all stakeholders, including the families involved. Adjustment of these guidelines should be performed as soon as growing evidence in different fields of research makes this possible. The adapted criteria of Wilson and Jüngner can be used for continuous monitoring. Evidence and guidelines in LQTS are more developed than in HCM and the population involved in HCM is potentially much larger, urging the need for studies and guidelines in HCM especially.

Screening of unselected populations, like newborns or schoolchildren, by means of DNA-testing seems not to be advocated yet and is technically not feasible at present. In the near future, targeted DNA-testing might be considered to uncover people with silent mutations or polymorphisms in certain ion channels, when they require drugs that predispose to arrhythmias in the presence of these gene variants. Also, preparticipation DNA-testing for cardiomyopathies in young athletes might be considered. Guidelines for privacy protection, informed consent and consequences for relatives in these forms of screening (apart from those in family screening) need to be developed in the meantime.

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