Clinical genetic care in diseases predisposing to sudden cardiac death
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Chapter 5

How to trade off the medical benefits from genetic tools and the complex societal side effects in rare catastrophic disease:
A case study in familial sudden death

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Appendix 1: Questionnaire
Summary

Background: Sudden death in the young has an unprecedented emotional impact on all involved. When its cause is suspected or established to be genetic, the latter happening more and more, relatives not only experience the grief of losing their loved one, but also face the psychological, social and medical problems that arise from this knowledge for themselves and their family, including their (future) children. Prevention of sudden death in those identified to be at risk is possible, by change of life style, medication or invasive measures like implantation of pacemakers or internal defibrillators. Although the benefits of such preventive measures seem to outweigh the burden of medical side-effects at this stage, the precise risks of premature death in asymptomatic relatives of a given age and a given genetic status are largely unknown, evoking a dilemma due to the considerable societal side effects.

In the last few years, of several genes predisposing to sudden death in apparently healthy children and young adults were identified. Estimated prevalences are at least 1:500 and 1:5000 in the most common sudden death syndromes (hypertrophic cardiomyopathy and long QT syndrome). Consequently, identification of risk carriers by predictive DNA testing through cascade screening has been actively offered to hundreds of relatives of patients with a proven mutation in one of these genes. Due to limited availability of these tests, no general evidence exists on the ethical, legal, social, and psychological impact of predictive testing in sudden death syndromes, nor on the normative views of the public.

Methods: Based on a concise review of the literature on predictive testing, and our expertise with predictive DNA-diagnostics of and research in premature familiar sudden death, we developed a detailed questionnaire that was used in face to face interviews with both stakeholders (families involved in predictive DNA-testing, and consumer groups) and (medical) professionals. All 12 extensive interviews were conducted by two senior staff members, taped, transcribed and summarized and sent to the interviewees for approval. The summaries, highlighting common views as well as points of disagreement, are part of this essay. The interviews focused on the justification of offering family based predictive testing (cascade screening) and, if cascade screening was thought desirable, the questions were entailed on the organisation of the predictive testing procedure. Additionally, legal, psychosocial, ethical and societal topics associated with the identification of an increased risk for sudden death were dealt with.

Results and Conclusions: All interviewees unanimously justified cascade screening for (penetrant) mutations predisposing to sudden cardiac death. They also widely supported the multidisciplinary approach in academic centres. The interviewees differed in their opinions on population strategies dealing with these diseases and the preferred position of general practitioners. Regarding cascade screening, guidelines are needed. In spite of a lack of information on many aspects (medical as well as psychosocial and societal), design of guidelines is desirable, but revision should be guaranteed with accumulating evidence from further studies. A committee consisting of stakeholders and professionals could assist in designing and updating these guidelines. Future research needs to address medical aspects (risks of premature death in asymptomatic mutation carriers including children, compliance to
and burden of preventive measures), psychosocial aspects (family dynamics, psychosocial care on demand or imposed under specific circumstances), and ethical aspects (patient autonomy, family rights and responsibilities). Political issues involve the preferred population strategy concerning sudden cardiac death, as well as the still unresolved debate on unrestricted access to health insurances.

For (recently published) polymorphisms increasing the risk of premature sudden death in triggering circumstances (like the use of certain medications), we advise individually based, not family based, predictive DNA-testing in these particular occasions. These tests might be offered by the specialists treating these patients.

1. Introduction and hypothesis

The Human Genome Project, which has largely decoded the human DNA sequence, has a potentially far-reaching effect on the diagnostics and preventive treatment of hereditary diseases. To reduce hereditary diseases to their molecular origin is to create a basis for novel, complicated predictive medicine. Until several years ago only a small number of genetic tests were available. Due to the incentives of university laboratories and commercial research centers, availability of screening methods for a growing number of conditions is now increasing. In some cases, accurate predictions can be made using genetic tests. In several other cases only the genetic disposition of a particular disease is revealed, whereas the manifestation of the disease depends on involvement of other genes and environmental factors like lifestyle, diet, and societal status (monogenetic disorders with low penetrance and multifactorial disorders).

1.1 Novel diseases

With regards to the Human Genome Project, several genes were identified which are involved in hereditary cardiac diseases in the last couple of years. An example of such a hereditary disease is congenital long QT syndrome (LQTS), an autosomal dominant disease with reduced penetrance (risk of symptoms in a carrier of the mutation). In a majority of the cases LQTS is diagnosed by means of typical deviations on an electrocardiogram (the EKC or ECG). Patients suffering from this hereditary disease have a higher risk of short and usually self-limiting arrhythmias, which can cause conditions varying from short spell of dizziness to complete blackout. When the arrhythmia persists and resuscitation is unsuccessful, the patient dies within a few minutes of what is called 'Sudden Cardiac Death.' For several years now, the molecular disposition of LQTS can be detected and is used as a (predictive) molecular test in among others the AMC.

In these 'novel diseases' such as hereditary cardiac arrhythmias and for example hereditary forms of cancer, a distinction is made between genotypical and phenotypical illnesses. A person who is genotypically ill knows that he or she can become phenotypically ill because a mutation is detected but he or she is not sure this will actually happen. In this essay we define 'disease' as having an increased risk for cardiac arrhythmias as a result of a predisposing mutation. Preventive interventions in patients who are genetically predisposed of having a hereditary
cardiac arrhythmia correspond with the line of treatment provided for symptomatic patients. This treatment consists of medication with or without lifestyle restrictions and sometimes (solely) the implantation of a pacemaker or internal defibrillator (ICD). As a result, patients who are genotypically ill but phenotypically without symptoms can be confronted with the same psychosocial and societal consequences with respect to e.g. insurance and employment as a patient who also is phenotypically ill.

Another aspect of these novel diseases is that the diagnosis and treatment sometimes result in (and occasionally require) involvement of family and relatives. In some cases the family is already concerned with diagnostic screening, but they often get involved when a mutation in a family member is discovered and predictive diagnostics (cascade screening) are offered to relatives.

Another important issue concerning these novel diseases is the fact that acquired knowledge is enduring and has far-reaching implications for offspring. Particularly in case of treatable diseases such as hereditary cardiac arrhythmias the right not to know vs. the wish to be treated) may give rise to conflicting experiences for the younger generation. For example, tension may arise within a family e.g. when one of the parents is a carrier and one of the children wishes not to be tested. These situations can further influence the way people judge prenatal or preimplantation-genetic diagnostics, namely in the context of suitability of genetic diagnostics in children, school, career choices, and other societal consequences (e.g. insurance).

In general, the most important dilemmas are related to the protection of privacy. For example, should the next of kin of a patient who has just been diagnosed with a hereditary cardiac arrhythmia be informed about genetic screening by the index patient? In such scenarios the specific approach depends on the quality of family relations. One can conclude from these and other examples that there is an essential need for guidelines for predictive genetic diagnostics in hereditary cardiac arrhythmias.

1.2 Public Health

In the process of developing guidelines for predictive genetic diagnostics one generally has to take into account the rapid expansion of genetic research and the evolution of public opinion on prevention of diseases, as well as societal changes in prenatal screening. In general, patients are much better informed owing to the media and the rapid increase in the use of information over the Internet. In the case discussed here it is important that society becomes aware of the possible relation between premature sudden death and hereditary cardiac arrhythmias, and the possibility of cascade screening in family members. In the near future new mutations will be found which are related to sudden death. We expect low penetrance genes as well as polymorphisms (several different forms of one gene which in essence do not harm a carrier's health) to increase the chance of sudden cardiac death only to a limited extent. This presents new dilemmas for the medical profession and the general public. Ethical constraints need to be specified to determine justifiable indications for predictive diagnostics of hereditary cardiac arrhythmias. When is predictive screening of hereditary cardiac arrhythmias to be recommended? The less specific the definition of relevant constraints is, the more we will notice
a shift in the highly individualized availability of predictive diagnostics towards (accepted) population screening. The rapid developments in genetics implicate to the medical profession and the society in general that one has to adopt new points of view concerning the preferred novel strategies. These strategies involve public health and the appropriate way in which the medical profession and other representatives should act and regulate.

In The Netherlands there are a number of historical prevention programs, which are regulated by the government, varying from heel puncture to certain ‘obligatory’ vaccinations. These ‘historical’ pre-evidence based medical programs indeed raise the question whether the screening would be acceptable or not according to current standards if implementation would be proposed now. In societal and medical decision-making, especially concerning the constraints and the population perspective, the perceived aim of predictive genetic screening plays a crucial role. Is the emphasis on early detection of the predisposition for a condition in order to provide optimal treatment, or is the actual aim beyond optimal treatment with emphasis put on prevention and eradication of the disease? An example of this shift from individualized approach to a population approach is the proposal of the Gezondheidsraad (Dutch Health Council) to offer prenatal screening for Down’s syndrome and neural tube defect to all pregnant women. [7]. The former, more selective approach is based on the individual increased a priori risk due to high maternal age.

Currently 500 patients have been identified with LQTS in the Netherlands. Based on a prevalence of 1 in 5000, at least 2,700 unknown patients are unaware of their condition. If untreated, at least 10 % of them will die suddenly before the age of 40. [2]. The question arises to what extent one wants and has to go in identifying people who for that reason have an increased risk of sudden premature death due to being ‘genotypically’ ill.

1.3 Main questions

The following questions are essential in this essay. It should be taken into account that only preliminary answers shall be formulated.

1. Is cascade screening in hereditary arrhythmias desirable, from an individual as well as a societal point of view?
2. How should the initial contact with family members take place?
3. What should be the practical role and the moral responsibility of the index patient when the family is approached?
4. Should the first explanatory part of cascade screening take place in a collective (family education) or individual setting?
5. Which setting is most appropriate for the next sessions after the initial counselling?
6. How to communicate the test results?
7. What should be the range of screening of hereditary cardiac arrhythmias, taking the medical and societal consequences into account?
8. What is known about the risk perception in case of increased risk of premature sudden death and what is the impact on policy making and the appraisal of cascade screening?
9. Should cascade screening be offered to children under 18? If yes, what are the conditions?
10. What disadvantages are associated with participating in cascade screening with respect to employment and insurance, taking the negative consequences experienced in FH diagnostics into account?
11. What can be recommended with respect to offering cascade screening when it concerns a mutation which only slightly or in certain circumstances increases the risk of hereditary cardiac arrhythmias?

Based on the preliminary answers to these questions, recommendations will be made to complement for remaining answers. These concern the description of information minimally required to develop guidelines. This information is usually collected through scientific research.

2. Background information

The opportunities of screening a new population of patients suffering from hereditary cardiac arrhythmias (autosomal dominant with low penetrance) are rapidly increasing. In case a mutation is found in a patient, it is possible to perform family-based predictive screening (cascade screening) with full accuracy.

In the beginning of 1996, the Departments of Cardiology and of Clinical Genetics initiated the foundation of a Cardiogenetics outpatient clinic. Predictive DNA diagnostics has been done at this clinic in over 200 family members of index patients with hereditary arrhythmias up to this moment (2002). Nowadays, patients can also seek genetic advice and DNA diagnostics in Cardiogenetic clinics in other academic hospitals. If a mutation is found in a patient, these clinics also offer family screening. (Similar developments can be found for other genetic disorders and in other academic centers).

There are two forms of hereditary cardiac arrhythmias. First, in case of primary electrical diseases, the structure of the heart is completely normal, but the electrical characteristics are abnormal. Therefore, under certain circumstances (e.g. physical or mental stress), life-threatening arrhythmias can occur. In this type of hereditary arrhythmias the patient often dies suddenly before 40 years of age. Sudden death is even regularly seen in the young and adolescents. These diseases can be treated succesfully by means of medication (beta blockers) and by either implantation of a pacemaker or an Implantable Cardioverter Defibrillator (ICD). Lifestyle changes are advised as well to avoid provoking circumstances as much as possible. All these measures are deployed either to prevent or interrupt an arrythmia. A specific example of this form of hereditary disease is, as mentioned in section 1.1, the Long QT syndrome (LQTS). LQTS is characterized by an abnormally long QT interval on the ECG and by an increased risk of ventricular fibrillation. The first symptoms often occur during youth or adolescence and consist of syncope and epileptic-like seizures, as well as sudden death during precipitating circumstances such as physical activity and emotional stress. The diagnosis LQTS is based on clinical criteria. [1]. Currently, five LQTS genes are known and a mutation that differs among
families can be detected in these genes in approximately 80% of the affected families. All these genes are involved in the structure of ion channels. Due to various types of ion channels, the various types of LQTS differ in characteristics and therefore the disease can be classified according to the underlying defects. In practice, it has been shown feasible to distinguish the disorder in three common types of LQTS. In asymptomatic family members the diagnosis cannot always be made on the basis of cardiologic investigation (e.g. ECG). Furthermore, this type of screening may yield an incorrect diagnosis, based on a positive test result while the disease is actually absent (false-positive test result). DNA diagnostic testing is the only test which ensures a fully accurate test result of carriership. The treatment of symptomatic patients and the preventive interventions taken for asymptomatic mutation carriers is successful: the risk of premature or sudden death in the first group decreases drastically if given (adequate) therapy. With non-symptomatic genotypically positive patients preventive measures decrease the risk of sudden death to less than 1% in 5 years. The risk of sudden death in asymptomatic patients without preventive interventions is uncertain because it is ethically no longer appropriate to conduct experimental research in this stage. Other examples of primary electrical heart diseases are the Brugada syndrome and the familial polymorphic ventricular tachycardia.

The second group of hereditary arrhythmias are the cardiomyopathies (disorders of cardiac muscle tissue). Here mutations are most often detected in genes that regulate the structure of cardiac muscle tissue. With time, the muscle tissue will perform less well, which can present itself as cardiac failure. It is also possible that arrhythmias lead to sudden death. The decreasing cardiac function is not easy to treat. As it constitutes the risk of premature and sudden death, the treatment is focused on the prevention and control of arrhythmias (by means of medication or pacemaker/ICD placement). DNA-diagnostics is primarily appropriate for familial hypertrophic cardiomyopathy (HCM, prevalence 1 in 500), a disease characterized by thickening of the cardiac muscle (mainly the space in between the ventricles, the so-called interventricular septum). Nowadays, a mutation is found in at least 40-50% of index patients in the Netherlands. It usually concerns a type of HCM which is associated with a low risk of premature death before the age of 40. However, there is an apparent increase in risk later on due to complications e.g. lethal arrhythmias, chest pain caused by oxygen depletion and cerebrovascular accidents following cardiac embolism. At the moment (2002), cascade screening at the cardiogenetics outpatient clinic (AMC) is merely offered to a restricted number of families with a ‘malignant’ type of HCM. The ‘malignant’ type differs from the mild types of HCM, as this type is associated with a considerable increase in risk of sudden death due to cardiac arrhythmias and/or extreme hypertrophy. This risk is assessed on the basis of the type of mutation that was found and the clinical manifestation in the family.

3 Essay methods

The hereditary cardiac arrhythmias described here are relatively rare conditions and the genes involved have only been discovered during the last couple of years. Therefore, little information is currently available. This involves amongst others information about:
• Life-time mortality risk (per age-group) per disorder and especially per subgroup (genotype) of the specific conditions;
• The predictive value of clinical parameters (e.g. ECG characteristics, patient’s complaints, results of additional cardiologic tests);
• The effect of rules of living and currently used therapies (medication, pacemakers and ICDs);
• The effect of non-genetic factors which eventually may contribute to the risk of sudden death (e.g. diet, physical and mental stressors);
• The cost-effectiveness of predictive genetic-diagnostics in which quality of life is also taken into consideration when choosing between various preventive measures.

An additional problem is the lack of knowledge of family physicians and some cardiologists on the cardiogenetics of hereditary cardiac diseases. The lack of knowledge described above does not necessarily hamper the careful organization, structuring and standardization of predictive genetic diagnostics in these diseases. It does, however, demand revision when additional evidence becomes available and a flexible code of behavior is needed to make this revision possible. The researchers have therefore attempted, with the conducted interviews (see below), to inquire the interviewees on their views on the (un)desirabilities and conceptions, despite the imperfect knowledge of the issues mentioned above.

3.1 Preliminary analysis

In May/June 2002 a preliminary investigation was undertaken into the general requirements of predictive genetic screening (Chapter 4), the overall concepts that possibly are important for the development of the frame supporting predictive diagnostics, and particularly into the specific questions and dilemmas concerning (predictive) genetic screening of hereditary cardiac arrhythmias (Chapter 5).

3.2 Interviews

A list of explicit questions was developed from disease-specific characteristics and general hypotheses gathered from the preliminary analysis described in section 3.1. This final questionnaire was presented to experts during personal interviews. Precise composition and interpretation of these interviews is further discussed in Chapter 6.

3.3 Recommendations and conclusions

Recommendations for further development of research will be given in Chapter 7, in which the development of medical care, medical innovations and organizational and societal aspects of predictive screening are emphasized.
4. General principles of genetic screening

Characteristically, population screening is performed outside the boundaries of individual care, in that sense that it is not offered on individual demand, but is being offered unrequested. Furthermore, the persons whom are offered genetic screening typically do not have symptoms that are related to this disorder. Finally, it is important that population screening involves diseases as well as risk-indicators of disease. Genetic screening or genetic population screening involves the detection of genetic characteristics that may be related to (future) disease in the investigated persons or even in their offspring. Cascade screening of hereditary arrhythmias is most often actively offered to first degree relatives and is therefore part of WGBO legislation.

In 1968 Jüngner and Wilson formulated criteria for the evaluation of medical screening programs. 9 In a revised edition, specifically aimed at genetic screening, these criteria are the starting point for currently most important policy document on genetic screening in

Table 1. Stages in Assessment and Implementation of Population Genetic Screening

1. Assessment-Evaluation of evidence:
   a. Causal association between genetic trait and health conditions
   b. Prevalence of the genetic trait: attributable risk for the associated health condition
   c. Positive and negative predictive value of genetic test for the clinical condition
   d. Efficacy of intervention(s) to improve health outcome in persons with a positive test result
   e. Beneficial psychological or social consequences of testing or test results
   f. Risk of testing process
   Potential for stigmatization or discrimination based on test results
   Adverse psychological or social consequences of testing or test results
   Risks of interventions
   g. Resources and costs
      Tests and associated health care
      Interventions and associated health care
      Counselling and education (pre-testing and post-testing)
      Safeguards to ensure informed consent, avoidance of coercion or manipulation, and protection of privacy

2. Policy Development-Consensus process:
   a. Participation of all stakeholders
   b. Evaluation of evidence to determine likelihood of net benefit of screening and identify uncertainties
   c. Consider screening context, including feasibility of screening and community values and priorities

3. Program Evaluation-Ongoing assessment after program is implemented:
   a. Quality of testing and clinical services
   b. Provision of appropriate follow-up care
   c. Health outcome (morbidity, mortality, and quality of life) of target population
   d. Adverse events including breaches of confidentiality and genetic discrimination
   e. Acceptability of screening to target population
   f. Need for revision of screening protocol based on new evidence

Adapted from: Burke W. et al. 2001, Table 5
the Netherlands: the the Health Council report Genetic Screening [10]. Recently, Burke et al. have revised the same criteria into process criteria for genetic screening (see Table 1). The guidelines used by the American Medical Association (http://www.ama-assn.org/ama/pub/print/article/2036-4077.html) the Burke criteria, and our own research on screenings (e.g. in obstetrics and neurology) as well as our experience in the cardiogenetics department have been used to develop the questionnaire.

5. DNA-diagnostics and cascade screening

Until recently, (predictive) DNA-diagnostics were particularly used for monogenetic disorders with high penetrance. Thanks to the Human Genome Project there is an increasing demand for (predictive) DNA-diagnostics for disorders with low penetrance and multifactorial disorders like hereditary heart and vascular disease. Care providers are confronted with a number of specific problems that call for guideline development. When developing guidelines, one needs to distinguish between DNA-diagnostics for symptomatic patients and predictive genetic tests, e.g. predictive DNA-diagnostics. In the case of, amongst others, hereditary types of cancer, familial hypercholesterolaemia (FH) and cardiac arrhythmias a specific type of predictive DNA diagnostics is being offered which is called "cascade screening" because of the way the screening strategy is offered: testing is repeatedly offered to all the first degree (or second degree) family members of newly identified mutation carriers.

5.1 Existing protocols for predictive DNA diagnostics in Huntington's disease and Hereditary Breast/Ovarian cancer

The first protocol that was developed for the regulation of predictive screening on hereditary disorders was a protocol for the screening on Huntington's disease. Huntington's disease is an untreatable and progressive neurological disorder that presents at adult age and leads to a severe movement disorder, psychiatric symptoms and dementia. The inheritance is autosomal dominant with full penetrance. This protocol, eventually implemented and used globally, for predictive DNA diagnostics for Huntington's disease served as a model to other disorders for which this type of diagnostics became possible. The prototypical protocol consists of guidelines for the (multidisciplinary) provision of information and counselling in multidisciplinary contexts prior to the DNA diagnostics (pre-test counselling), guidelines for the waiting time between the first counselling session and blood taking, the informed consent procedure on blood taking, and guidelines for counselling and support after the test result has been disclosed (post test counselling and follow up). Moreover, description of societal, psychological and ethical problems concerning predictive DNA diagnostics are often formulated with the experiences with Huntington's disease as starting point. The active approach of a patient's family members as in cascade screening was and still is not the aim of predictive testing in Huntington's disease. Cascade screening however is indeed being actively offered in case of hereditary types of cancer, e.g. breast cancer. Three to five percent of all breast cancers, are caused by autosomal
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dominant disease with incomplete penetrance. The largest part of hereditary breast cancer is caused by mutations in one of the two tumor suppressor genes BRCA1 and BRCA2. Since 1995, DNA diagnostics for mutations in these two genes is performed in the Netherlands. The test result is important for women who have to decide on taking preventive interventions (check ups, breast amputation or surgical removal of the ovaries) that reduce the risk of disease and mortality considerably. [14].

Regarding preventive options, various forms of hereditary types of (breast) cancer and also hereditary cardiac arrhythmias differ from Huntington's disease. In the case of Huntington's disease, all carriers will develop symptoms over time for which no adequate therapy exists. In hereditary types of cancer and in cardiac arrhythmias definite development of symptoms is certainly not the case and individuals will have to weigh the advantages and disadvantages of the presently available preventive interventions versus the risk of disease and mortality with and without these inventions. One characteristic of population and cascade screening of hereditary types of cancer and cardiac arrhythmias is that individuals exchange a life without worries and concerns for the opportunity to enjoy longer life. People tend to risk everything for the prevention of serious diseases and premature death [15]. Guidelines for predictive diagnostics in Huntington's disease and hereditary types of cancer therefore cannot be used for hereditary cardiac arrhythmias without proper revision. The first essential difference is the burden of disease: the prognosis in hereditary cardiac arrhythmias is an unpredictable, acute and catastrophic event (i.e. premature sudden death at young age) for which effective, though severe and heavy, (preventive) treatment is available and effective but far-reaching. Huntington's disease is more predictable and the manifestation of hereditary types of cancer is rarely acute nor catastrophic.

The second essential difference is the age at which the disease may become manifest; in contrast to Huntington's disease and hereditary types of cancer, hereditary cardiac arrhythmias may even emerge in childhood, and even children in the age of 4-5., and sometimes even younger, are at increased risk to die suddenly. Another important difference in case of hereditary cardiac arrhythmias is that most patients and their families are (currently) unaware that a familial disorder is present, which "family knowledge" is often known in the other diseases.

While in case of hereditary breast and ovarian cancer there are some indications that affected women are referred for predictive genetic screening too quickly (Cancer Research Campaign and Imperial Cancer Research Fund), most inherited forms of cardiac arrhythmias are unknown to general practitioners, the general public and occasionally even amongst cardiologists [16]. That is why general practitioners, in our experience, often do not take family members seriously who request referral for (cascade) screening, and sometimes even tend to discourage further investigations. Not unusual, many family members eventually learn at the moment cascade screening is offered, that the risk of an inherited and potentially catastrophic heart disease is present. This may lead to emotional stress and put the death of family members in a different perspective. Previous grief therefore can be re-experienced which increases emotional stress even further when testing is offered [17]. Research in families with inherited arrhythmias shows that patients (and especially parents when children are being tested) report more stress and anxiety than the ones who undergo predictive DNA-diagnostics for Huntington's disease or
inherited forms of cancer [18]. All aforementioned arguments therefore suggest that careful adaptations of the model for predictive DNA-diagnostics to the specific characteristics of inherited arrhythmias are urgently required.

5.2 Relevance of DNA-diagnostics for patients with (possible) hereditary arrhythmias

**Differential diagnosis of several disorders**

Potentially public health can be significantly improved if genetic variants of sudden death are systematically considered in the differential diagnosis of, for instance, pharmaceutically induced QT-prolongation (acquired LQTS), syncope, epileptic like attacks, unexplained death by drowning and premature sudden death [19]. Premature familial sudden cardiac death can also be caused by coronary artery disease (premature arterosclerosis) as well as by cardiomyopathies or primary electric heart diseases and probably also by combinations of these disorders. There are several pharmaceuticals that affect the ion channels which can induce an increased risk of cardiac arrhythmias and sudden death (acquired LQTS) in certain individuals. In the future, genetic profiles (for instance on DNA-chips) may be used to determine which individuals have an increased risk of arrhythmia when using these type of pharmaceuticals. Some of these polymorphisms (common genetic alterations) have been identified by now [5]. DNA-diagnostics therefore can be an instrument to optimize the diagnostic process in symptomatic patients and, before a possible QT-prolongating drug is prescribed, to investigate whether someone is susceptible for such a side effect.

**Selecting treatment in arrhythmias**

The determination of the genetic basis of disease bears an important advantage: it provides the opportunity to optimize treatments. Previously, all patients with the long-QT syndrome received a beta-blocker, a drug that stabilizes the heart rhythm and therefore reduces the risk of arrhythmias significantly. (Besides, it is commonly used for the treatment of high blood pressure.) It is shown recently that beta-blockers in case of a particular type of LQTS are not effective at all, and possibly even harmful. The diagnosis of the underlying genetic disorder therefore is of direct importance for the selection of treatment [2]. The same applies to the treatment of cardiomyopathies.

5.3 Predictive DNA-diagnostics of hereditary arrhythmias

In the document "Artsen en genen" of the KNMG it is stated: The care provider should not advise undergoing predictive DNA diagnostics for the predisposition of diseases for which no prevention is available. [2, 4]. If, however, preventive options are available by which patients with a mutation either can lower (or eliminate) the risk of acquiring the disorder or improve prognosis, a more directive approach is acceptable. The basic principle should then be that advice on the basis of genetic makeup made in terms of lifestyle (or monitoring) is more appropriate the larger the potential health gains and the smaller the burden of the preventive measures to be
taken. Hence, actively offering predictive DNA-diagnostics in hereditary arrhythmias is justified when the health gain of preventive interventions outweighs the burden and strains these interventions impose. Although adequate information on the burden and strains of preventive interventions is currently lacking, these treatments yield considerable health gains because of the strongly reduced risk of premature and sudden death, so in principle offering predictive DNA diagnostics is defendable. The guideline should indicate at least when and how the screening of individuals with an increased risk of sudden death should take place; under which conditions one is eligible for (predictive) DNA diagnostics or other forms of (cardiologic) carrier screening; which treatment for preventive intervention is necessary and at which age treatment should start; when and how family members should be informed about the increased risk of sudden death; how communication with family members and healthcare professionals should take place; and how the information should be recorded and stored.

**When should screening take place? Who should be screened?**

Genetic screening can take place on two levels: family screening following the identification of an index patient (cascade screening of the first degree relatives of a mutation carrier) or population screening. The aim is the early and timely detection of the disorder in order to initiate optimal (preventive) treatment or action. The prevalence of hereditary arrhythmias varies between 1 per 5000 and 1 per 500 persons. Research in Japan and England showed that population screening of disorders that are associated with sudden death is currently not recommended [20, 21]. Moreover, population screening is currently ineffective because of the strong genetic heterogeneity in the majority of these disorders, as if nearly each family has its own genetic variant. Therefore cascade screening seems a more prudent approach. The age at which cascade screening can be offered at its earliest is determined in principle by the youngest expected age at which the genotype may lead phenotypical expression. Additionally, the age at which prophylactic treatment by means of medication or by pacemaker or ICD is technically safe plays a role. That is, in certain forms of hypertrophic cardiomyopathy (caused by a mutation in the troponine T gene) the rather small risk is probably already existent below the age of ten. But, in our opinion, prophylactic implantation of an ICD is only beneficial after the age of ten because after this age the mortality risk exceeds that of potential complications and risks associated with this therapy.

The question when and to whom predictive DNA diagnostics via cascade screening should be offered should not be addressed apart from the dilemmas that concern the right not-to know and the right on information. Originally, the emphasis in clinical genetics is on non-directivity and respect for client's autonomy in decision-making. However, other specialists counsel less non-directive. With the increasing demand for predictive DNA diagnostics of treatable disorders, new dilemmas arise. [22]. Client's (patient's) autonomy and the inherent freedom of choice can, as the result of increasing knowledge on human genes and their implications, may become jeopardized due to conflicting interests (e.g. the interests of third parties). [23]. Particularly in case of inherited disease, family ties imply certain duties that do not apply or apply less to strangers. Rhodes additionally states that the right not-to know is a philosophically hardly defendable principle, which mainly arises from the right of autonomy.
(mainly in the USA) and the ideal of non-directivity, which is based on the controversial history of the eugenetics [8]. Rights and obligations mirror each other: being a right for one individual often is an obligation for someone else. For example, if someone is entitled to genetic information, there must be someone else who has the obligation to provide that information. However the latter person also has the right to privacy of the information. That gap cannot be reconciled. In fact, someone has the right to be informed and that right is violated if he/she is not informed (even if someone wants to be uninformed from the beginning). This is no violation of autonomy because someone can only make an informed autonomous choice if he/she is well informed. According to Rhodes, autonomy and non-directivity are the most important moral principals but in most cases do not necessarily imply the right not-to know as logical outcome of this. This particularly applies to the above mentioned disorders in which not knowing may result in catastrophic outcome. From a legal perspective, the right not-to know in the sense of the WGBO-legislation does not apply to family members because the physician who treats the index patient has (as yet) no formal professional relationship in the sense of the WGBO with these relatives. If the index patient is willing to give up his right to privacy in the interest of his relatives, there are no obstacles to inform these relatives either directly or via the index patient.

**Therapy: when and how**

For those who turn out to be carriers, possible prophylactic treatment aimed at prevention of sudden death will differ between patient categories. In case of the long QT syndrome for example, prophylactic treatment usually exists of medication (beta blockers) and life style rules (for example, avoid practicing competitive sports or buy a 'friendly' sounding alarm clock or door bell because physical exercise, emotions, and loud sounds can provoke arrhythmias). Beta blockers have potential physical and psychological disadvantages: hypotension and dizziness, cold extremities, gastro intestinal complaints, impotence, decreased attention and reaction span, headache, depression, disturbed sleeping pattern (sometimes combined with vivid dreams or nightmares). [24]. Maximal compliance in the daily use of beta-blockers is necessary as the risk of sudden death after abrupt discontinuation of prophylaxis is higher compared to not starting prophylaxis at all. The compliance rates in asymptomatic carriers of different ages are yet unknown.

In case of the Brugada syndrome and sometimes in the other mentioned arrhythmias, preventive intervention consists of the implantation of an internal defibrillator (ICD) in order to end life-threatening arrhythmias as soon as possible. Research into the societal and psychosocial consequences of prophylactic ICD implantation on those involved (insurances, employment, family relationships) relative to the risk of sudden death is yet to be conducted. Only when the results of such a study are in favor of prophylaxis, a true health gain is created. In addition, the psychological burden for the relatives should be considered here. The previous loss of a family member as well as the fact that someone is at risk himself and the risk of having passed on a hereditary disease without being aware, may lead to stress, grief and sorrow. [17]. Psychosocial counselling performed by professionals can be of great importance.
Information and communication: When and how

Most patients wonder what it implies when the mutation that was found in their DNA is confirmed in an asymptomatic family member. As yet medical science is not as sufficiently advanced to assess these consequences, but several clinical parameters can provide a rough estimate. Obviously, close and more distant relatives are likely to carry the same mutation (i.e. genotypically ill). This does not, however, imply that they also have the (same) high risk of sudden death (i.e. phenotypically ill). To discuss with the patient the magnitude of the risk of sudden death is also not easy because, in our experience, every elevation above 'normal' (low) risk will be experienced as 'too high' for those involved. Thereby, any 'rational' weighing of the risk of sudden death and possible side effects of diagnostics and preventive treatment turns out to be virtually impossible. This is also why cascade screening is very often accepted. Again, the dilemma concerning patient autonomy and the way of counselling is an issue here.

Another issue is what the role of the primary caregivers should be and which other professions or professionals preferably should be involved. General practitioners may play a role by recognizing individuals who should be referred to secondary or tertiary care for genetic evaluation. For this type of disorders formal predictive testing in primary care is too complex. A study that investigated the perceptions of general practitioners on their possible anticipation in new genetic techniques concluded that general practitioners prefer to remain in their generalistic role. Moreover, general practitioners were reluctant to confront individuals with genetic risks, thereby causing temporary anxiety without the possibility of effective prevention [25]. On the other hand, it was also shown that general practitioners refer too many women for genetic testing of breast and ovarian cancer compared to the established guideline. Probably they are not familiar with risk assessment based on family history and therefore tend to refer too quickly for security reasons. This could possibly harm the patient, since it causes unnecessary stress and anxiety. [16].

It is strongly recommended to provide information to cardiologists on genetics and the implications of genetic diagnostics, testing and counselling in order to enable cardiologists to request simple DNA diagnostics in the future. It is estimated that one third of all physicians who request genetic tests is currently capable of interpreting the test results. In cardiology, this is estimated to be merely 5-10%. [26,27]. Perhaps a genetic counsellor (an official with a BSc degree who provides basic counselling in the Clinical Genetics Department) could function as liaison between primary care, secondary care and the departments of clinical genetics.

Documentation of information

At this moment (2002) there is no nationwide registry of families with hereditary arrhythmias. There are a few laboratories in the Netherlands that provide DNA diagnostics for these disorders. It is possible that the DNA of several members from one family is analyzed at different laboratories and that these labs search for the same mutation, causing a waste of money and energy. It is therefore recommended that family trees (consisting of all ancestors up to five generations back) of each index-patient are drawn-up and become partially accessible to each clinical geneticist researching families with inherited arrhythmias. However, without further procedures, this might prove problematic if patient’s privacy is violated. Such a system can only
be accomplished if there are conclusive guarantees regarding privacy. A specific possibility is for example the Canadian system which functions satisfactory. [28]. In the Canadian system of pedigree-drawing, patient and personal characteristics are separated from medical data and separately stored, and two different codes are required to gain access to these databases and retrieve the patient and personal characteristics and medical data. A similar registry already exists in the Netherlands for families in which persons carry a mutation for breast/ovarian cancer (GEO-study).

**Access and intake**

At the moment, index patients and families with a history of (prevented) sudden cardiac death have access to medical care (AMC) in three ways: the cardiogenetics outpatient clinic, the premature arteriosclerosis outpatient clinic (including familial hypercholesterolaemia) and the Department of Cardiology. This may not be the most efficient way to gain access: familial premature sudden cardiac death may be caused by coronary disease (premature arteriosclerosis) but cardiomyopathies, primary electrical disease or a combination of these factors are equally possible causes. One could consider creating a joint point of entrance for families in which sudden cardiac death has occurred, as well as offering cascade screening in a similar way in case of FH and hereditary arrhythmias, and possibly even for other disorders.

Another aspect relevant when guidelines are composed is how actively trace carriers of a mutation. Research into the costs, effects and societal consequences of nationwide screening of FH by the Department of Social Medicine (AMC) showed that the efficiency of FH screening according to current standards is less than expected for two reasons. The main reason is the duration of treatment. The second reason is the fact that some patients were already being treated for high cholesterol levels without having any knowledge on the presence or absence of a genetic mutation. [29]. In a British study, however, it was shown that cascade screening is indeed a cost-effective method for population screening for FH. [20]. This may constitute a dilemma if cardiologists and general practitioners become more aware of the fact that genotyping of patients with hypertrophic cardiomyopathy (HCM) currently results in the detection of a mutation in at least 40 to 50% of cases in the Netherlands. HCM has the same prevalence (1 in 500) as FH and is expected to have the same profile of sudden death in many cases if untreated (premature, but after the age of thirty). In what respect organizations like Stichting Opsporing Erfelijke Hypercholesterolemie (StOEH: The Foundation for the Tracing of Hereditary Hypercholesterolemia) and Stichting Bloedlink should or could play a role, needs to be investigated.

### 5.4 Disease-specific and general concepts in guideline development

Undoubtedly, the determination of a framework for guidelines on hereditary arrhythmias leads to a more general reflection of the current affairs in clinical genetics diagnostics. This does not only involve the aspects that need to be evaluated to judge if genetic screening is justified, or the phases that need to be passed before the the guideline can be introduced. The question of how far one wants to go in tracing carriers and the implications for the counselling approach
are just as important. Furthermore, the construction of a framework offers an opportunity to critically evaluate current practices, in light of the rapid developments in genetics and a society that is getting increasingly used to this knowledge and the associated problems. From the medical and legal point of view, disorders like hereditary arrhythmias are new diseases. As far as hereditary arrhythmias are concerned, there are several 'new' disease-specific characteristics that are important in determining a point of view on more general concepts, as addressed in the protocols for hereditary cancer and Huntington's disease. These specific characteristics are:

- The catastrophic nature of the disease;
- The (early) age at which the first symptoms present themselves (from four- five years of age);
- The absence of a severe sick-bed or long illness;
- Type of preventive interventions and associated burdens;
- The specific risk to the carrier to develop complaints and the extent to which preventive measures reduce that risk reduction.

These specific characteristics will influence the general principles that need to be addressed when a guideline is developed:

- Autonomy, the associated right not-to know, and the right to information;
- Privacy protection, including the question of how information and education when actively offering of cascade screening ought to be done;
- Criteria for the application of predictive DNA diagnostics for children under 18 years of age (first degree relatives);
- How far one wants to go in tracing carriers; a dilemma that is related to the sense of directivity in counselling and that is being influenced by the views one has on the degree of emotional stress and decrease in quality of life that preventive interventions may cause;
- Allowing or actively offering prenatal diagnostics;
- How to deal with societal ramifications associated with predictive DNA diagnostics, such as the consequences on employment and insurance, including the delivery of information;
- Managing risks and the perception of risk;
- The organization of the health care system, including genetic counselling, support in readjustment after testing, and psychosocial support.

6. Interviews

In July and August 2002 we interviewed several specialists having experience with cardiogenetic diseases using a questionnaire sent prior to the meeting. All meetings took place at the expert's location and were attended by two interviewers. The interviews were recorded and written down on paper with the expert's consent. The transcriptions of the interviews were returned to the interviewees for confirmation, consistent with the agreements.

We also interviewed several (index) patients and their family members who all were familiar with LQTS as disease and with the procedures of the cardiogenetics outpatient clinic (AMC).
Two index patients (i.e. the first patients in a family to be discovered to have the mutation) were selected from two different families in which LQTS was detected. Additionally, an asymptomatic relative who was identified as a mutation-carrier after DNA diagnostics (from the first family, diagnosis at the age of 20) and a relative not carrying the mutation after having received DNA diagnostics (from the second family) were included. The following experts-specialists were interviewed on behalf of their profession:

**Clinical genetics:** Prof. Dr. H.G. Brunner, Professor of Anthropogenetics, Nijmegen

**Cardiology:** Dr. M. Witsenburg, pediatric cardiologist, Rotterdam; Dr. M.A. Galjee, cardiologist, Enschede; and Dr. V. Manger Cats, president of the Netherlands Heart Foundation

**Philosophy:** Prof. Dr. H.J. Achterhuis, Enschede

**Patient support groups:** Dr. H. van Laarhoven, president of the ‘Bloedlink’ Foundation; Dr. C. Oosterwijk, president of the VSOP; Mr. F. Vogelzang, consultant of the Hartezorg Federation

The questionnaire was divided into six major topics. Questions were asked on:

1. The ‘initial’ information on the disease and the offering of predictive DNA diagnostics to the family (by whom and how should this information be given);
2. The ‘second’ counselling session by a medical expert (by which expert and how?);
3. The guidance and support during genetic screening (psychosocial care, time for reflection, cardiologic testing awaiting the genetic test results);
4. The test results (communicated by whom and how?)
5. Predictive diagnostics in children under 21 years of age;
6. General contemplative or reflective issues (autonomy, the role of patient support groups, prenatal diagnostics, coping with risks, premiums for life and health insurances);

The questions (without the possible response mode) mentioned above are enclosed in Appendix 1. The full questionnaire is available upon request. This study and its results must be seen as an explorative survey due to the limited time available. The **general principles** that are relevant when developing guidelines are summarized separately. If specific characteristics of the disease (i.e. catastrophic nature, the probability of sudden death) were to the matter discussed, it is clearly pointed out in the text.

### 6.1 Summary of the most important interview results

#### 6.1.1 Organization of the health care system

**Initial counselling**

Most interviewees agreed on the way the initial counselling should take place. Preferably, the patient has to be contacted in writing; by doing so he/she can choose to receive the information and when, while an unannounced phone call may be too intrusive or offensive. Another disadvantage of a phone call is the possibility that the situation may not be convenient to hold a private conversation. The interviewees who mentioned this particular problem also suggested a personal meeting after receipt if the information letter, preferably with a doctor from a team
specialized in genetic screening and counselling. A minority of the interviewees preferred to be contacted by their family physician orally first before receiving written information.

One of the index patients said that she had negative experiences with having to inform her family. She thought it was emotionally too painful because she was already struggling with all the emotions associated with having the disease herself. One of the cardiologists posited that a medical specialist should inform relatives (by writing) instead of the index patient. A frequently mentioned argument was that not every relative is a good messenger. This strongly depends on the mutual relationships within the family.

Several representatives of the patient support groups and Galjee and Achterhuis stated that communication skills during the first meeting are far more important than the exchange of medical and technical information, which preferably should take place in a follow-up consult. This is also the main reason why a specialized medical professional may not necessarily be involved in the first contact, whereas a (specialized) nurse or a general practitioner are considered proper alternatives.

**Written information**

The tone of the first letter (initial counselling) should be neutral according to some of the interviewees. Others thought that the written information should also mention the public interest. One of the relatives mentioned that not only the interest of the possible carrier is at issue but also his/her family that is constantly confronted with mourning and death. He emphasized that all relatives should cooperate to prevent another relative's sudden death. The opinion of the two index patients was remarkable; they thought the letter had to propagate an overall sense of optimism to prevent unnecessary worrying of the family about the possible danger of sudden death. Both patients emphasized that this risk should not be 'over-exaggerated'.

One interviewee compromised between these two conceptions. First, the letter could address the subjects concerning the individual patient; this part has to be phrased positively but also earnest (e.g. the risk of sudden death is diminished but not completely eliminated after treatment). Next, the patient should be informed on his possible elevated risk of premature sudden cardiac death and that he might possibly pass on (t)his elevated risk to die young and suddenly to his offspring. Finally, the interest of the family could be mentioned by stressing that prevention of (another) death avoids family burden, and referring to the importance of scientific research (increasing knowledge of hereditary cardiac arrhythmias).

**Secondary counselling**

The majority of the interviewees indicated that a secondary, more substantive counselling should preferably occur during a meeting with a multidisciplinary team where both a clinical genetic counselor and a cardiologist are present. Important considerations were the specific knowledge of the medical specialists and the availability of psychosocial support. Surprisingly, cardiologist Dr. Galjee questioned the value of a cardiologist in the process, because he believes a genetic counselor has enough knowledge concerning cardiology. In contrast, Achterhuis and one family member indicated that the cardiologist should be the expert and a genetic counselor.
may not necessarily be involved. Prerequisite for this are, however, good communication skills and knowledge of medical genetics.

If all relatives agree, family counselling can be a valuable tool in the process of genetic screening. Uniformity in the information given to the various relatives would be one of the advantages; this prevents the dissemination of inaccurate and presumptuous information within the family. A second advantage emphasized by one of the index patients was the opportunity of sharing the burden. After the session relatives can supplement and clarify the information received. Van Laarhoven mentioned a third advantage of family counselling; in this way the interest of the whole family would be emphasised. Achterhuis, on the other hand, emphasized the communal sense and the importance of eliminating feelings of guilt. Achterhuis also stated explicitly that emphasis on the public interest should be no means to create social pressures, forcing as many relatives as possible into participating in the screening process. The two relatives and Witsenburg and Manger Cats thought, in contrast to the family counselling mentioned above, that secondary counselling should be individual or only with one or two close family members.

**Psychosocial care**

All interviewees were unanimous in their opinion on the importance of psychosocial care. According to most of the interviewees the possibility of psychosocial care should be offered to every participant during the second meeting. Some others preferred psychosocial care to be offered on indication of the specialist or on specific request by the patient. Van Laarhoven rejected the idea of psychosocial care being an integral or obligatory part of an established protocol as is the case in Huntington's disease and hereditary breast cancer.

**Communicating test results**

Several interviewees indicated they would like to receive their test results over the telephone, but the majority preferred the information to be sent by letter. All agreed on a personal meeting after receiving bad news. Most of the interviewees agreed that both favorable and unfavorable test results should be communicated in the same way, even if this would mean that some of the patients (those with a favorable test result) have to visit the hospital just to be reassured they are healthy. It should be realized that even a favorable test result could give rise to further questions.

**Patient support groups**

Predominantly the medical experts are in favor of patient support groups, especially because these organizations offer the possibility of patient-to-patient contact. According to Van Laarhoven, the most important goal of patient support groups was their possible role in counselling and tracing persons with (possible) hereditary cardiac or cardiovascular disorders.

No consensus could be reached on the role of patient support groups in information and education of patients and their families between the first and second visits. Some rejected this opportunity but others were more sympathetic provided that quality of the information and education could be guaranteed.
Role of the general practitioner

Both the two index patients and Achterhuis disagreed with the other interviewees on the role of the general practitioner (GP) in the process of genetic screening. For the patients, the GP was very important both as a doctor and a medical confident. Achterhuis thought the 'gatekeeper function' of the GP still to be viable but he also admitted to possibly have a romantic vision on the GP's current position. Before the interview, Achterberg discussed the matter with a befriended GP and that doctor reacted quite restraint with respect to active participation in the process of genetic counselling. As Galjee already mentioned, GP's working models in daily practice change almost constantly. According to Witsenburg the GP only gets involved in case of unfavorable test results, as he is the one who has to 'deliver the bad news'. All the other interviewees thought it preferable to inform the GP from the beginning without any active participation considering his lack of time and specific knowledge.

6.1.2 Protection of privacy

Aspects of privacy frequently play a role in the process of genetic screening. From a legal perspective, only the index patient's rights are guaranteed; the family is not a patient yet and as such only has general citizen rights and duties, like the medical professional involved. First, privacy aspects are important in the procedure of the first contact with the patient's family. These aspects apply in particular when the patient himself is not willing or capable to inform the family and requests the doctor to do it for him, and providing him the addresses and other contact information needed. Furthermore, privacy issues are important in the dilemmas which arise when a relative, after receiving sufficient information, declines genetic testing but is still detected as mutation carrier (without his consent) as one of his/her children has tested positive for the mutation. According to both index patients and Vogelzang the general practitioner should be informed but only with the child's consent. In this way the GP is able to act adequately in case of manifestations of the cardiac disorder. The majority, however, stated that nothing should be done if previous information offered to the parent(s) appears to be sufficient. Van Laarhoven proposed to give the child an explanatory letter for the parents but not to put further pressure on the child.

6.1.3 Predictive genetic screening in children under 18

Three out of four family members believed that children have to be tested as young as possible whereas almost every professional stated this to be valuable only if children reach the age on which treatment can be and should be initiated. An exception can only be made when the parents cannot cope with the emotional stress of waiting. Van Laarhoven thought it to be efficient and beneficial to store blood extracted from the umbilical cord or a extract blood at a similar procedure because blood sampling can be very traumatic for children aged 10-12. He believed that a child, if possible, has to be able to decide if and when he/she wants to be tested. Galjee replied to this decision problem as being the parent's and not the doctor's, because it tends to disrupt the relationship with the care provider. Brunner was the only interviewee who
thought a doctor is never allowed to deviate from the ‘clinically correct’ age of testing, even if the parents request that.

Most interviewees stated that the child’s right (the right to know) is more important than the right of the parents (the right not-to know). Achterhuis, however, indicated that the parent’s right prevails when the child is under 16, but only if risks are small.

6.1.4 Societal consequences

Although no one accepted insurance companies to raise premiums for people who have been tested and who are treated for hereditary cardiac arrhythmias, there is no consensus concerning possible carriers who are unwilling to get tested and/or treated. Some believed premium increases in these cases to be partially defendable. Members from both families included in our investigation paid considerably higher premiums due to slightly increased risks or did not participate in genetic screening because of the anticipated societal consequences. (Family members were not selected on these aspects.) Both Galjee and Achterhuis remarked that insurance companies should return to the policy of covering overall risks and not individual risks.

6.1.5 Population strategies

Manger Cats, Oosterwijk and Van Laarhoven stated specifically that one should not just screen, detect and prophylactically treat people but one should also inform persons/patients on the possibility of pre-implantation or prenatal diagnostics even if this means pregnancies are terminated. They also believed no pressure should be put on people to get tested, whereas others indicate that one attempt of persuasion is allowed; this could be achieved by means of a letter or via the relatives. Achterhuis considered the possibility of offering diagnostic screening of hereditary cardiac disorders in the population to be an adverse development. Nevertheless, he realizes it is not entirely clear to him what the impact of preventive interventions is on the life of patients, especially regarding the daily use of beta-blockers.

6.1.6 Autonomy

All family members supported a large degree of autonomy. This influenced their answers concerning the moment on which a child should be tested, the right of the counselor to reject the request for cascade screening, and the decision to be informed on the possibilities of prenatal diagnostics, the latter remaining a subject of discussion for some interviewees. Autonomy was also a significant issue for the three patient support groups, Manger Cats, Achterhuis and Galjee. Most of the physicians were more paternalistic concerning decisions in which weighing risks is vital and suggested the use of protocols.
6.1.7 Management and perception of risk

According to the relatives questioned, a counselor is never allowed not to offer cascade screening whenever he believes the stress associated with preventive interventions would be greater than the risks of sudden death. Additionally, the representatives of the patient support groups stressed the importance of patient's autonomy in these matters. Only one patient accepted a situation in which the physician decides for the family. Galjee remarked that a physician needs to assess this kind of dilemmas everyday while for a patient decision-making concerning increased risk of premature sudden death is much more demanding. Several experts indicated the importance of implementing protocols for these particular situations. They believe it cannot be justified that different physicians take these decisions individually. Furthermore, the public interest cannot be ignored, according to Achterhuis, and in these cases even paternalism may be necessary.

6.1.8 Prenatal diagnostics

In general, two different views existed concerning the question if the possibilities of prenatal diagnostics had to be discussed in the genetic counselling sessions with the carriers. One part of the interviewees believed that this should not be standard procedure because these kinds of hereditary arrhythmias can be treated. The others believed that information giving implies that everything should be discussed in counselling in order to support patient decision making. Achterhuis considered individual benefits and the public interest important and considered it difficult to balance between those two aspects. He rejected prenatal screening of the entire population for hereditary cardiac arrhythmias but admitted that the burden of preventive interventions may be unbearable for the individual patient. Van Laarhoven and Manger Cats stated that prenatal screening is part of a strategy focusing on prevention and treatment and that it cannot be justified to terminate that process before it is completed. Additionally, Oosterwijk stated that the patients have the right to receive all information known about hereditary disorders and emphasized that termination of a pregnancy after unfavorable test result is not always the main reason for prenatal screening. The need for assurance or the wish to anticipate on the birth of an affected child, are amongst others reasons for prenatal screening.

6.2 ‘Consensus’

The results of the interviews showed that the interviewees essentially agreed on the following issues:
- The method of the first counselling: written information (instead of a phone call) given to the index patient or directly to the relatives. Formally, there are no legal consequences as long as the patient agrees with the violation of his privacy; ethical dilemmas may arise, however.
- The benefits of cardiologic testing preceding predictive diagnostics with the purpose to
bridge the waiting period before the results of DNA-testing become available.

- Obligatory reflection periods between the first counselling session and the genetic test should not be routinely included in guidelines.
- The advantage of a multidisciplinary setting in which also experts in psychosocial care participate;
- The value of good communication skills;
- The appreciation of patient support groups.

6.3 Dilemmas in policy making

Several subjects concerning genetic screening of hereditary cardiac arrhythmias are mainly politically determined:

- The first major question is how far one would go to trace carriers. Subsequently, a clear point of view should be formulated referring to the difficulties concerning prenatal and even pre-implantation diagnostics. An additional issue that deals with the population strategies in particular, but which can also be regarded separately from these strategies, is in what setting the intake should take place of people who have been resuscitated before the age of 40 or have relatives who have been resuscitated before the age of 40. At this moment, a central unit to which all (possible) patients can be referred is absent; possibly causing delayed referral of patients to professionals specialized in hereditary cardiac arrhythmias. To optimize care, everyone whose complaints or family history correspond to defined intake criteria of (suspected) hereditary cardiac arrhythmias or familial hypercholesterolaemia (FH) should be referred and treated alike, following an established collective protocol.

- A second problem that should definitely be solved are the societal consequences concerning insurance and employment. Once again this assessment points out that insurance companies are one step ahead of the societal discussion as they increase insurance premiums of affected persons even when they are treated and their risk of sudden cardiac death is diminished. This is also the case in (treated) people suffering from FH. [30].

- A final political (and legal) problem is the question how to identify and inform a carrier who refuses to be tested. It is legally possible to hand over the explanatory letter which was intended for the parent(s) to a child that proved to be a carrier. However, the question arises whether it is better to inform the general practitioner because it concerns medical information that might influence the physician’s treatment in life threatening situations.

7. Conclusions and recommendations

On the basis of the interviews and a limited review of the literature we are able to answer the questions presented in Chapter One. Additionally, we recommend different strategies and guidelines for future purposes. It has to be noted again that all the answers given in section 7.1 are preliminary.
7.1 Answers to previously formulated questions

1. Is cascade screening in hereditary arrhythmias desirable, from an individual as well as a societal point of view?
   This question can be answered with an unconditional 'yes'. In this respect hereditary cardiac arrhythmias should be compared to hereditary breast or ovarian cancer instead of Huntington's disease. Cascade screening is not offered in Huntington's disease actively and only takes place on a patient's request. Regarding the question whether or not to offer cascade screening, it is remarkable that for most relatives the balance between the patient and the professional (autonomy) turns in favor of the autonomy for the patient and his/her family.

2. How should the initial contact with family members take place?
   Most interviewees preferred sending a personal letter initially. The tone of the letter should be positively persuading, contain the correct information, and refer to the interest of the family. Nearly all interviewees therefore preferred the strategy used in hereditary breast and ovarian cancer which differs from the protocol used in the initial counselling in FH, which is provided by a genetic field worker.

3. What should be the practical role and the moral responsibility of the index patient when the family is approached?
   Opinions on this matter differ widely. One group considers the index patient to have an important function in the communication between the doctor and the relatives. The other group believes the patient should not play any role in the process of contacting relatives except for providing addresses. It is not known how often and why (there are family conflicts or it is emotionally too challenging) the role of the index patient is an obstacle in the counselling process. It is also not known what percentage of the relatives is currently uninformed and what the consequences are for these 'missed patients'.

4. Should the first explanatory part of cascade screening take place in a collective (family counselling) or individual setting?
   On this matter the opinions also differ widely. When family contacts allow family counselling, this brings about some important advantages. For example, the whole family receives the same information and the relatives can help and support each other in understanding and dealing with the information. Collective counselling and screening is more common in FH compared to hereditary breast and ovarian cancer. It is unclear whether one can expect the possible disruption of family relations beforehand.

5. Which setting is most appropriate for the next sessions after the initial counselling?
   Although most interviewees preferred a multidisciplinary setting, some preferred either a cardiologist or a clinical genetic counselor. Almost everyone prefers the counselling to be continued in a specialized setting. A general hospital is only sufficient if a cardiologist is available who has specialized in hereditary cardiac arrhythmias. The screening of hereditary breast and
ovarian cancer also takes place in a multidisciplinary setting. We highly recommend a closer examination of the role of a new type of care provider, namely the genetic counselor, in the communication and cooperation between secondary and tertiary care, especially for frequent and (in the Netherlands) less genetically heterogenic disorders like HCM.

The general opinion on psychosocial care provision is that it should be part of the multidisciplinary team but can only be provided 'on demand'. This differs clearly from current protocols in Huntington's disease and hereditary forms of breast and ovarian cancer where psychosocial support is an integral part of the protocol. Whether 'on demand' provision of psychosocial care is beneficial under all circumstances remains to be elucidated. Especially when it becomes apparent that the emotional stress and anxiety of parents whose children carry a mutation involved in cardiac arrhythmias appear to be more severe compared to hereditary breast or ovarian cancer. Additionally, one of the interviewees claimed to be emotionally incapable of informing her family at that particular moment.

Clearly, two opposing opinions are formed with respect to the role of the general practitioner in cascade screening: one group grants the general practitioner a central role as gatekeeper and medical confident. The other group believes that the general practitioner must be informed from the beginning but is not able to ascertain these functions in the subsequent phases of the process. A possible task for the GP might be the recognition of possible carriers of hereditary cardiac and vascular diseases. Unfortunately, the feasibility of this option is unclear.

6. How to communicate the test results?
As a rule, it is stated that an unfavorable test result should always be communicated in person. There is no consensus concerning the communication of favorable test results: this could be in person (to avoid indirect recognition of the results) or by letter. In the case of Huntington's disease or hereditary breast or ovarian cancer both unfavorable and favorable test results are communicated in a personal meeting.

7. What should be the range of screening of hereditary cardiac arrhythmias, taking the medical and societal consequences into account?
According to all persons involved, cascade screening should be offered to all relatives when a mutation has been found in the index patient (this accounts at least for all mutations identified so far). Moreover, relatives state that cascade screening is desired in possible future mutations which only slightly increase the risk of sudden death (low penetrance mutations or polymorphisms). In the end of August 2002 it was announced that such a polymorphism had been found with a high prevalence in African-Americans. In our opinion screening is justified when it concerns these polymorphisms in ethnical groups, provided that the polymorphism considerably increases the risk of hereditary cardiac arrhythmias and subsequently sudden death. This might be the case when for example certain drugs are prescribed. [31].

There is no unambiguous answer to the question whether prenatal diagnostics should always be mentioned during the post-test counselling session. Strictly speaking it concerns treatable disorders; however, the precise residual risk after preventive interventions remains unknown as well as the burden of these particular interventions. The Dutch Association of Clinical Genetics
(Vereniging Klinische Genetica Nederland) recently stated publicly that discussing the possibilities of prenatal screening in hereditary breast and ovarian cancer is ethically justifiable.

8. What is known about the risk perception in case of increased risk of premature sudden death and what is the impact on policy making and the appraisal of cascade screening? Every increase in the risk of premature sudden death, as little as it might be, is unacceptable for most patient's relatives. They feel they are autonomous in the decision to test or not. On the contrary, medical experts believe that this process of weighing the elevated risk of premature sudden death and the pressure of preventive interventions needs to be protocolized in stead of leaving the responsibility to the individual physician. The communication of (small) risks or probabilities are closely related to risk perception and risk communication. Concerning this issue, knowledge is lacking, which also applies to hereditary types of cancer and FH.

9. Should cascade screening be offered to children under 18? If yes, what are the conditions? The interviewees unanimously believed that testing of children under 18 is justified from the age on which the risk of sudden death significantly increases. In case of hereditary breast and ovarian cancer no children under 18 are tested because the risk of developing a tumor is not yet elevated and professionals choose the right of the child to 'not knowing' over the parent's right to know. The opinions differ on testing young children on request of the parents, before children's risk of sudden death is increased and in whom preventive measures are not yet effective. On the one hand some interviewees are in favor of the autonomy of the parents in this situation as well; on the other hand others claim it is not acceptable to test children as long as the risk is not increased. Still unraveled is the level of emotional distress that comes with living in uncertainty, as well as the reaction of both parents and outsiders on children carrying a mutation without having, at that moment, an increased risk of sudden death.

10. What disadvantages are associated with participating in cascade screening with respect to employment and insurance, taking the negative consequences experienced in FH diagnostics into account? These interviews suggest that employment and insurance are obstacles with respect to an increase in insurance premiums following an unfavorable test result as well as to the refusal of getting tested, because of fear of the consequences. This has been a societal problem for many years: in Huntington's disease carriers of the mutation are not able to get life insurance and disability insurance. This is also the case in other disorders like FH and hereditary types of cancer. Problems with insurance and employment are urgent political issues and not just a problem which can be solved by conducting more (medical) research. At this moment, it is important to inform counselees adequately about the difficulties they might encounter and about the correct way to fill out questionnaires and application forms.

11. What can be recommended with respect to offering cascade screening when it concerns a mutation which only slightly or in certain circumstances increases the risk of hereditary cardiac arrhythmias?
We believe that different guidelines for different types of hereditary arrhythmias should be designed for offering **cascade screening** to relatives of patients who carry a high-penetrance mutation. Predictive genetic testing (on request) for polymorphisms or low-penetrance mutations which increase the risk of sudden death only to a limited extent is justifiable, especially when the environment and circumstances (e.g. prescription of specific drugs) of the carrier enhance the effect of the mutation and increase the risk of sudden death. Cascade screening seems of limited use here because of the small importance of knowing for relatives and because of the fact that environmental and other genetic elements differ greatly within one family. This type of predictive diagnostics used in individual patients is the first and second line's prerogative but only when professionals are sufficiently trained to use the results.

### 7.2 Development of guidelines

Surprisingly, there appeared to be no overt differences between the patients and the professionals in their opinions on the organization of the health care system. Almost every interviewee believes a multidisciplinary setting to be the most important part in tracing persons with a familial increased risk of premature sudden death. In the development of guidelines for hereditary cardiac arrhythmias this means stakeholders with different backgrounds have to agree on a variety of issues. Especially for a group of disorders in which risk estimation is very important we recommend to cooperate with an epidemiologist experience in decision-analysis. Some subjects dealt with in this essay should be discussed again while further developing these guidelines. Additionally, the contents of a national registraty of hereditary cardiac arrhythmias should be managed carefully to enhance the efficiency of the health care system. Furthermore, after implementation, guidelines should constantly be evaluated and adjusted when supplementary evidence becomes available from scientific research. In addition to this, we would like to emphasize the importance of cost effectiveness analysis of predictive DNA diagnostics compared to other types of carrier identification.

In general, our research method in which the views of the families involved, specific experts, representatives of patient support groups, cardiologists, clinical genetic specialist and a philosopher on current practices in cardiogenetics are investigated, functioned satisfactory. We therefore recommend the formation of a committee to further develop guidelines related to (predictive) genetic diagnostics. This committee should consist of cardiologists (academic and non-academic), a clinical genetic specialist, an epidemiologist with experience in decision-making, a health law expert and a psychologist. A group consisting of a general practitioner, a philosopher, patient support groups (for patient-to-patient contact, possibilities of expanding scientific research, general information and expert-witnesses) and several informed laymen. This distinguishes our proposed committee from most other committees involved in guideline development. Our system, however, focuses on predictive medicine which clearly differs from conventional medicine. Additionally, the diseases discussed here were, until a couple of years ago, hardly recognized as being hereditary disorders. Novel diseases, which moreover cause major legal, societal and psychosocial difficulties, demand novel and creative solutions.
References


3. van Langen IM, Birnie E, Alders M, and et al. Molecular diagnostic services in the long QT syndrome: possible with high yields if phenotypic information is used. (submitted)


Appendix 1: Questionnaire

The initial counselling
A mutation is found in a patient, the index patient. This index patient agrees on the counselling of his/her family. The first contact with the family will be used to inform them about the nature of the disease, the hereditary aspects, cardiologic and genetic diagnostics and treatment. The family is also invited to attend an additional counselling session for further explanation of his/her personal situation and perhaps genetic diagnostics.

1. How should this first counselling take place? Would you state both your first and second choice?
2. Who is the right person to give the first information? Would you state both your first and second choice?
3. The information can be given in several different manners. You can choose your personal statement from the 4 options below. What option is, in your opinion, in general the best way to inform the family? Your choice may depend on what person you are going to inform. Can you point out how this has affected your choice?
4. Between the first and second meeting consists a waiting period. Imagine the family wants additional information during this period. What is the best way to give it to them? Would you state both your first and second choice?

The secondary counselling
The relatives are informed about the diagnosis of the index patient and the consequences for the rest of the family. They are subsequently invited to a second meeting with a specialized genetic counselor and a cardiologist (secondary counselling). More in-depth information is given and several options are discussed, for example genetic testing.

1. Who is the right person to give the secondary counselling? If you choose the general practitioner or a non-academic cardiologist, realize that if a mutation is found the patient will be referred to a hospital with a cardiogenetic outpatient clinic.
2. The choice for a capable health worker to give the secondary counselling can be influenced by different aspects. What was the decisive aspect concerning your choice?
3. The second meeting can be an individual session or a family session. Which of those two options do you prefer?

Psychosocial support during genetic screening
1. In most hereditary disorders in which genetic testing is performed on persons without manifestations of the disorder (predictive diagnostics), psychosocial care is offered to everyone who is considering to be tested. To whom should psychosocial care be offered in this case, according to you?
2. A different opportunity would be a short questionnaire or personal meeting to interview all persons that consider cardiologic and genetic diagnostics to assess their psychological vulnerability. Are you in favor of such a questionnaire or meeting?
3. In most hereditary disorders in which genetic screening is performed on persons without
manifestations of the disorder, a certain period of reflection is mandatory between the different steps in predictive testing. The advantage of such a reflection time is that one can weigh the advantages and disadvantages of genetic screening. Specifically, in these hereditary cardiac arrhythmias, however, one could suddenly die in this reflection period while effective treatment could have prevented sudden death. Are you in favor of such a reflection period?

4. For technical reasons there is a waiting period of 6 weeks from the day of blood extraction to the announcement of test results. Specifically in these hereditary cardiac arrhythmias one can die in this waiting period. This is the reason why some people prefer cardiologic diagnostics (ECG) to be performed in this period. Patients with ECG abnormalities can be treated immediately. Are you in favor of cardiologic diagnostics during the waiting period?

Test results
1. In case of good news; who should announce the test results and in what manner?
2. In case of bad news: who should announce the test results and in what manner?

Predictive diagnostics in children under 18
Adults with a known mutation can opt for additional cardiologic tests and when necessary treatment. Children with a mutation only have to be treated from a certain age (for example the age of 10) because the risk of sudden death below that age is significantly increased.

Below you find a separate section of questions concerning genetic diagnostics in children under 18:
1. At what moment do children have to be genetically tested?
2. What will, eventually, determine this moment?
3. It happens that a child wants to get tested but its parents do not want to know if they are a carrier. When the mutation is found in the child, the parents are automatically carriers as well. How should you balance the right to know (of the child) to the right to not-know (of the parents)?
4. Imagine the child is over 18, gets tested without the parent’s awareness and is a carrier of the mutation. It is now clear that at least one of the parents is also a carrier and subsequently has a higher risk of sudden death if not treated. What should be the policy in this case?

Finally, we ask you some questions about general contemplative or reflective issues on the advantages and disadvantages of cascade screening in hereditary cardiac arrhythmias.
1. It is possible that a family member or relative does not want to get tested. How far should one go to persuade a person into the screening process?
2. One can perform genetic testing on a fetus during pregnancy on hereditary cardiac disorders; the consequence can be termination of the pregnancy (prenatal diagnostics). The possibility can be discussed with a carrier of the mutation. In which situation(s) should the opportunity of prenatal screening be discussed?
3. Are patient support groups important to families with cardiac arrhythmias?
4. Different mutations cause different increases in risk of sudden death and as a result demand different types of treatment. The (emotional) pressure of these treatments is variable as well (ranging from life style changes, diet and daily medication, to a pacemaker or internal defibrillator). Is it acceptable that relatives of the index patient are not informed of the disease running in the family, because the physician believes the burden of treatment exceeds the risk of sudden cardiac death?

5. In the previous question we took the point of view that the physician decided on the desirability of treatment but this is obligatory. In your opinion, who has the right to decide if it is sensible to offer predictive testing to family members?

6. Is it acceptable that diagnostic testing is only available for people who want to be treated when they turn out to be carriers of the mutation?

7. Is it acceptable that insurance companies are increasing life and disablement insurance premiums of affected persons (carriers with a higher risk of sudden death) even when they are treated and their risk of sudden cardiac death is diminished?

8. Is it acceptable that insurance companies are increasing life and disablement insurance premiums of affected persons who have an increased risk of sudden death and who do not want to be treated?

9. Is it acceptable that insurance companies are increasing life and disablement insurance premiums of affected persons who do not want to get tested and subsequently are not treated?

10. The possibilities of genetic screening are expanding. Does the age on which the risk of sudden death significantly increases, influence the decision on testing?

11. The courses of illness of different types of hereditary disorders are variable. Some types are slowly progressive other are rapidly progressive. In the worst case a person can suddenly die of cardiac arrest. Do you consider the natural course of a disease important in the decision (not) to get tested?

12. Is the availability of an effective treatment decisive in your consideration (not) to get tested?