Familial hypercholesterolemia screening in the Netherlands: psychological and social consequences
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Chapter 1

Introduction
**Genetic screening**

Testing for the presence of risk factors like high blood pressure or high cholesterol has been common practice for years now, the context varying from screening in an apparently healthy population to screening patients who suffered from an acute myocardial infarction or cerebrovascular accident. Tests for genetically mediated risk factors have emerged recently and their range of applications widens. Predictive testing in healthy people is likely to become more broadly available for an increasing number of genetically mediated risk factors [1]. The prerequisites for the success of a screening programme using genetic testing are a) the possibility to diagnose the disease early, b) the possibility to treat the disease and c) a high prevalence of the disease within a certain population [2]. However, empirical evidence of direct beneficial health effects of the screening does usually not suffice to achieve broad acceptance and successful implementation [3]. This acceptance of a screening programme by both screenees and government depends not only on the acceptability of the screening process itself, but also on the psychological and social consequences of being tested and of the follow-up [2,3]. Furthermore, the implementation of a screening programme depends on the prevailing organisational setting for genetic test services [2,3]. In the Netherlands, genetic test services are largely supplied by genetic centres related to teaching hospitals. These centres are put in charge of genetic testing and counselling [4]. Given their bounded size, the rising demand for genetic testing can no longer be met by geneticist-driven centres alone. It is expected that part of the testing will shift to genetic services supplied by non-geneticists; consequently new procedures have to be developed, in particular when a new programme is launched [5,6].

Experience and variety of considerations suggest that a genetic screening programme requires careful, guided implementation, which starts with a broad assessment with its pros and cons.

As a guideline to assess a genetic screening programme the criteria by Wilson and Jungner as adapted by the Crossroads 99 Group could be used (see table 1) [2,3].
Table 1 Criteria for assessment of screening adapted from the Crossroads 99 Group, based on the Wilson and Jungner criteria [2,3]

1. Knowledge of population and disease
   a. Important burden of the disease
   b. Target population identifiable
   c. Considerable level of risk
   d. Preclinical phase of the disease existent
   e. Natural course (from susceptibility to precursor, early disease, and advanced disease) understood

2. Feasibility of screening procedures
   a. Suitable test or examination available
   b. Entire screening procedure acceptable to population
   c. Screening is a continuing process and encompasses all elements of screening procedures

3. Interventions and follow up
   a. Physical net benefit of the intervention likely
   b. Psychological net benefit of the intervention likely
   c. Social net benefit of the intervention likely
   d. Facilities for adequate follow-up available
   e. Consensus on accepted management for those with a positive test result

4. Societal and health system issues
   a. Balanced economic and medical costs
   b. Balanced psychological costs
   c. Balanced societal costs
   d. Appropriate screening services accessible to entire population without adverse consequences for non-participants
   e. Appropriate confidentiality procedures and anti-discrimination provisions for participants and non-participants

Familial hypercholesterolemia (FH)
FH is an autosomal dominant disorder of lipoprotein metabolism with an estimated frequency of 1 in 500 persons (in Western countries). In the past, the diagnosis FH was only based on clinical signs and family history [7,8]. A definite clinical diagnosis (in adults) requires 1) a total cholesterol level above 7.5 mmol/l or low-density lipoprotein (LDL) cholesterol levels above 4.9 mmol/l, plus 2) tendon xanthomas in patient or in first- or second-degree relatives. A possible diagnosis of FH requires hypercholesterolemia (see 1 above) plus one of the following: 3) a family history of myocardial infarction (MI) before the age of 50 in second-degree relatives or before the age of 60 in first-degree relatives, and 4) a family history of raised cholesterol above 7.5 mmol/l in first- or second-degree relatives [8]. Patients with a clinical diagnosis experience an excess mortality from cardiovascular disease (CVD), in particular at a young age [7-10]. Clinical experience shows that most FH patients are still diagnosed after having their first cardiovascular event; at this stage damage to the vessels is already prevalent and at best only partially reversible.

After characterising the genetic defect in FH in the seventies, the aetiology and pathophysiology
of the disease became gradually understood. It was shown that FH is characterised by a mutation in the low-density lipoprotein (LDL) receptor gene, resulting in LDL cholesterol accumulation and excess mortality from CVD [4]. Once the genetic defect could be diagnosed and effective lipid-lowering therapy (LLT) with HMG-CoA reductase inhibitors (statins) was available [11-16], early diagnosis and effective treatment was possible and genetic screening on FH in high-risk groups seemed feasible.

**Screening for FH**

With FH screening possible in high-risk groups, the 'Foundation for tracing hereditary hypercholesterolemia' (Dutch acronym: StOEH, 'Stichting Opsporing Erfelijke Hypercholesterolemie') was founded in 1994 to perform the FH screening in the Netherlands. Up to the beginning of 2002, 11613 persons were screened by the StOEH, of whom 4152 (36%) proved to be FH positive [17]. In this screening programme, first- and second-degree relatives of index patients (i.e. clinically diagnosed FH-patients with a known mutation) are actively approached by the StOEH using a pedigree investigation ('cascade screening') [18-20]. Relatives are tested for the mutation found in the index-patient only. Mutational analyses were performed on genomic DNA isolated from peripheral blood leucocytes using polymerase chain reaction (PCR) and restriction enzyme analysis as described by Jensen et al. [21]. By intent, cholesterol is not measured within this screening programme so far. If relatives test positive, their first- and second-degree relatives are approached and offered testing, etc. All test results are communicated to the screenee by mail only. Screen-positives get two additional letters: one directed to him/herself with the advice to consult the general practitioner (GP), and one to the GP, inviting the GP to refer the patient to a lipid clinic. This procedure requires the screen-positives to take the initiative to seek medical follow-up after receiving the letter. The StOEH is neither involved in the treatment phase of detected cases or the monitoring of the follow-up process.

**Evaluation of the screening for FH**

The main goal of the screening programme is to achieve health benefit for the screened persons. However, for some screenees the effects will not be exclusively positive, negative effects could occur. Henceforth, before implementing the screening programme, a broader evaluation is needed, as stated above. The evaluation of the FH-screening programme is based on the Dutch Health Council’s advice of what genetic screening programmes have to comply with in the Netherlands [22]. Their requirements are derived from Wilson and Junger’s criteria [2] while it is made clear that not only the achieved health benefit for the screenee should be evaluated, but the broader (psychological and societal) consequences including non-participants as well (see table 1).

In this thesis, we evaluate the provisional implementation of the Dutch FH-screening programme, focussing on the acceptability and feasibility of the implementation of the programme, in this thesis this is made operational as psychological and social consequences. Other components of the comprehensive evaluation, including the estimation of health benefits and financial burden, were published elsewhere [23]. In this evaluation the health benefits of early treatment of FH were estimated by using the Framingham function; by doing this it was assumed that the extra CAD risk in FH patients is caused completely by the raised serum cholesterol level and not by the mutation itself through another pathway [24].

As the combined results aimed to support decision-making on the future of the screening programme, the evaluation of the programme was organised separately from the actual
screening programme; this ‘third party’ approach is confirm the set-up of major studies to evaluate screening programmes in the Netherlands [25,26].

The adapted Wilson and Jungner criteria (see earlier) provide a format to assess available knowledge on FH screening (see table 2) [2,3].

Table 2 Known and unknown factors for the assessment of FH screening

<table>
<thead>
<tr>
<th>1. Knowledge of population and FH</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Disease burden: In Western countries 1 in 500 persons has FH [7]</td>
</tr>
<tr>
<td>b. Target population: Family members of clinically diagnosed and genetically confirmed patients</td>
</tr>
<tr>
<td>c. Level of risk: Patients with a clinical diagnosis have an excess mortality from CVD, in particular at a young age [7-10]</td>
</tr>
<tr>
<td>d. Pre-clinical phase: Present [7]</td>
</tr>
<tr>
<td>e. Natural course of FH: Known [7], however in clinically diagnosed patients only, not in genetically identified patients without clinical signs of FH</td>
</tr>
</tbody>
</table>

The natural course of FH in genetically diagnosed patients was estimated in the evaluation study of the Dutch FH-screening programme using the Framingham function [24], assuming that the extra CAD risk in FH patients is caused completely by the raised serum cholesterol level [23]

<table>
<thead>
<tr>
<th>2. Feasibility of screening procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Test: Feasibility of the mutation analyses within the Dutch screening programme is evaluated within the evaluation study of the Dutch FH-screening programme [23]</td>
</tr>
<tr>
<td>b. Acceptability of screening procedure to screened population: So far unknown, covered by Chapter 1 of this thesis</td>
</tr>
<tr>
<td>c. Screening process: In part covered by Chapter 6 of this thesis, the remainder is described in Chapter 2 &amp; 3</td>
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<tr>
<th>3. Interventions and follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Physical effects: health effects of the FH-screening programme are estimated within the evaluation study [23]</td>
</tr>
<tr>
<td>b. Psychological effects: So far unknown, covered by Chapter 2 to 5 of this thesis</td>
</tr>
<tr>
<td>c. Social effects: Described in Chapter 2 &amp; 3</td>
</tr>
<tr>
<td>d. Follow-up: Chapter 6</td>
</tr>
<tr>
<td>e. Consensus on management for those with FH: Present (cholesterol consensus) [27,28]</td>
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</tbody>
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<th>4. Societal and health system issues</th>
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<tbody>
<tr>
<td>a. Economic and medical costs: estimated within the evaluation study [23]</td>
</tr>
<tr>
<td>b. Psychological costs: Chapters 2 to 5</td>
</tr>
<tr>
<td>c. Societal costs: Chapters 2 to 5 and chapter 7</td>
</tr>
<tr>
<td>d. Appropriate screening services accessible to entire population: Chapter 6 for FH-positive screenees. FH-negative screenees and non-participants stay in regular clinical setting.</td>
</tr>
<tr>
<td>e. Confidentiality procedures and anti-discrimination provisions: Chapter 7</td>
</tr>
</tbody>
</table>
Contents of the thesis

Chapter 2
This chapter focuses on the critical first stage of the screening. It describes the screenees' view on and the short-term psychological and social impact of the approach of, until then, healthy persons for the FH-screening programme and evaluates non-participation to the screening programme.

Chapter 3
In principle, long-term and substantial transient quality of life (QoL) effects of a screening programme are not acceptable. Thus, the principal objectives of this chapter are to establish whether transient and long-term QoL effects of the screening are present, with a focus on psychological effects. If significant adverse effects are present, we intend to describe here the change over time and its dependence on personal characteristics, perceived and observed risk status, and on perceived social pressure to participate. Given these effects, we may further optimise the FH-screening programme.

Chapter 4
In this chapter we describe the possibility of inadequate or even paradoxical preventive behaviour in both FH-positive and FH-negative screenees. FH-positive screenees may think that hypercholesterolemia is inevitable, and resist treatment ('fatalism'), while FH-negative screenees may think that they are 'safe' or protected against hypercholesterolemia ('false reassurance'), and even show compensatory risk behaviour, e.g. smoking or eating less healthy.

Chapter 5
The evaluation in this chapter focuses on the essential role of the individual's risk perception and representation of information, the change of risk perception over time, as influenced by test result and other information/experience, and the consequential influence of risk perception on actual risk reduction (cholesterol-lowering medication use, stated attitude towards gene therapy, smoking cessation and losing weight).

Chapter 6
Chapter 6 focuses on the compliance with preventive care in screenees who tested positive for FH, which ultimately determines the programme efficiency. Not all screenees were unaware of a cholesterol problem and since some screenees were already aware of clinical hypercholesterolemia and were already treated, we distinguished in this chapter between newly identified and confirmed screenees. For both groups we evaluated what screening actually offers. To determine the impact of screening, we assessed the quality of care before screening, and at two points in time after screening. Guideline-based procedural quality and clinical outcome quality were established, taking the key recommendations of the Dutch hypercholesterolemia guidelines as reference.

Chapter 7
The participating in a genetic screening could have negative social consequences, such as problems with regard to the access to insurance. In this chapter we describe whether legislation protects participants of a genetic screening programme from experiencing problems in the access to insurance and make suggestions how to avoid problems.

With the information from this thesis the table based on the criteria of Wilson and Jungner (see above) can be filled out and makes a balanced assessment possible of the acceptability and feasibility of FH screening in the Netherlands. A quick balance will be given in the section 'Summary and Discussion' of this thesis.
Reference list


