POLICY

Molecular screening for familial hypercholesterolaemia: consequences for life and disability insurance

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In The Netherlands, cascade screening to identify patients with familial hypercholesterolaemia (FH) has been introduced in 1994; a nationwide screening programme is currently ongoing to detect all – approximately 40 000 – carriers by molecular screening. Active identification by DNA testing has social implications such as difficulties in obtaining life and disability insurance. In The Netherlands, insurance companies are restricted in the use of genetic information of their clients by the Medical Examination Act (1998). Within the scope of this specific law, the Foundation for the Identification of Persons with Inherited Hypercholesterolaemia, the patient support association, representatives of the medical profession as well as insurers designed guidelines for risk assessment of mortality and morbidity of FH carriers. Risk assessment should be based on phenotype, that is, lipoprotein profile and the presence of classical cardiovascular risk, instead of the LDL receptor gene mutation. Applicants with FH should be accepted at normal rates if LDL-c levels are <4.0 mmol/l, in the absence of additional risk factors. After implementation of these guidelines, the number of complaints about insurance contracts has decreased markedly.

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Introduction

Patients with familial hypercholesterolaemia (FH) have markedly raised levels of LDL cholesterol as a result of mutations in the LDL receptor gene. The age- and sex-standardised cardiovascular mortality in these patients is 4–5 times higher than the general population.¹ The prevalence of the heterozygous form is high and in fact constitutes the most common hereditary metabolic disorder (1:400–1:500).^{2,3} In The Netherlands, a nationwide

molecular screening programme is currently ongoing and strives for the detection of all – approximately 40 000 – FH patients by 2010.⁴

This active identification of FH by DNA testing has started an intense debate that is primarily focused on themes such as cost–benefit ratio, privacy, efficiency, and ethical dilemmas like access to insurance.^{5–10} In this essay, we discuss the current approach in our country with regard to such insurance issues with emphasis on life and disability insurances.

Screening of FH carriers

Patients with FH are identified according to uniform diagnostic criteria at Lipid Clinics, for which in The Netherlands the Dutch Lipid Clinic Network criteria are

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used.¹¹ DNA samples of patients with the clinical diagnosis of FH are analysed for the presence of an LDL-receptor or Apolipoprotein B gene mutation. After a mutation is identified, this patient is referred to as an index case and approached by the Foundation for the Identification of Persons with Inherited Hypercholesterolaemia to start family investigation. Subsequently, the first-degree relatives are actively contacted by genetic fieldworkers and offered the possibility of testing. After obtaining informed consent from the family members, genetic testing is performed by DNA analysis for the presence of the specific FH gene mutation that was identified in the index case. A cascade screening is performed to screen more distant relatives using the inheritance patterns across the pedigree. Both FH carriers and their general practitioners are informed by letter. Patients are referred to a Lipid Clinic or advised to visit a specialist for further assessment of their cardiovascular risk.¹² Till now 13 500 FH carriers have been identified by the screening programme.

Insurance and access to genetic test results

In The Netherlands, like in most European countries, insurance companies adhere to a moratorium on the use of DNA tests. In 1998, the Medical Examination Act was implemented with the aim to provide protection to individuals undergoing a medical examination, who sought to obtain a civil employment contract, a pension or an insurance. By law medical checks are forbidden at commencement of employment; for life and disability contracts, insurance companies are restricted in the procurement of medical information. A crucial aspect of the law is whether a condition is treatable, since screening for untreatable conditions is considered an unjustified invasion of privacy. However, untreatable, as it is laid down in the Act, has a broad definition that comprises deficiency of possibilities to treat, to prevent, and to inhibit the progression of the disorder by medical intervention. Hence, if no opportunities exist to beneficially influence a serious disorder, the Medical Examination Act prohibits questions and tests to detect the presence of that condition, independent of the amount insured. The same restrictions apply to serious untreatable hereditary conditions, but in these specific cases restrictions of access are based on the amount that the patient seeks to insure. Applicants for an insurance below a predefined sum are not obliged to answer any question about the (outcome of) genetic research on their own person or relatives of the first- and second-degree (<€160 000 for life insurance policies; for disability insurance <€32 000 in the first year, <€22 000 in the second and subsequent years). If however, results of genetic tests are already available, the insurance company has to disregard this information in the risk assessment procedure. The applicant on the other hand is obliged to report any symptomatic disease.^{13,14}

Screening for FH and access to insurance

Before the approval was obtained to execute a nationwide screening programme, the Minister of Health asked the Dutch Health Council for advice regarding the treatability, life expectancy, and access to insurance for FH patients. This was deemed necessary since some insurance companies applied excess mortality ratings to FH carriers, independent of the LDL-c levels.^{15,16} The Council concluded that FH is a serious but treatable condition.¹⁷ The effectiveness of statins in reducing mortality and morbidity is well established with hard clinical end point trials.^{18,19} In FH, statins decrease LDL-c levels and intensive statin therapy resulted in regression of atherosclerosis of the carotid arteries compared to conventional statin therapy.^{20,21} Due to the Council's decision to label FH as a treatable condition, insurers are permitted to use information supplied by FH carriers to calculate mortality ratings, that frequently are in excess of the mean of the population. This could theoretically have a negative effect on the access to insurance, limiting the feasibility of this large-scale screening programme. On request of the Ministry of Health, the Foundation for the Identification of Persons with Inherited Hypercholesterolaemia, representatives of the medical profession, the patient support organization, and the Association of Insurers decided to seek an agreement on guidelines for risk assessment of mortality and disability of FH carriers prior to the implementation of an up-scaling of the screening programme in 2003.

FH exhibits a large diversity in the expression of its clinical phenotype, which is demonstrated for example by the percentage of FH carriers diagnosed by DNA diagnosis with LDL-c levels below the 95th percentile.^{22–24} In fact, a substantial proportion of untreated FH patients have a normal life expectancy and large variance of mortality was observed among carriers of identical LDL receptor mutations.²⁵ Therefore, accurate risk assessment in FH should be based on phenotypic information like extent of hypercholesterolaemia and the presence of additional cardiovascular risk factors such as smoking, hypertension, and diabetes mellitus.

In general, risk classifications are based on calculations of the mortality ratio relative to a reference population using age, duration of the contract, and the presence of risk factors. It is obvious that in FH the phenotype is clearly dominant in risk assessment over the molecular information. Neither specific LDLR mutations, nor mutations like APOB or PCSK9 or other genetic factors are determining factors. Individuals with an identified homozygous or compound heterozygous genotype at the LDL receptor are considered to have a treatable disorder.

Consequently, the present guidelines of the Association of Insurers states that (treated) individuals with FH that apply for a life or disability insurance should be accepted at standard rates if the LDL-c level is below 4.0 mmol/l and no additional cardiovascular risk factors are present. Before

adequate treatment was available, FH patients had eight times higher risk of cardiovascular disease compared to unaffected relatives.²⁶ Cardiovascular disease in the family history is, however, not considered as a risk factor, because a substantial reduction of cardiovascular risk is expected by the present-day treatment modalities.

If the target LDL-c level is not achieved by adequate lipid-lowering treatment, the application for insurance can still be accepted, but at a higher premium. In fact, the possibility for reassessment of the premium can be offered, when the desired lipid profile is achieved at later date. The consequences for the individual LDL-c >4.0 mmol/l and additional cardiovascular risk factors are not precisely described in the agreement, because it depends on the policy of an insurance company. The guidelines are explained in detail in a special information brochure that can be distributed to those wishing to participate in the screening programme.²⁷ Insurance companies, especially medical officers, were well informed by the Dutch Association of Insurers.

The patient organisation reported a decrease in the number of complaints about insurers: on average 10 complaints were received per annum before the implementation of the guidelines in 2003 and afterwards it dropped to two per year, whereas the number of FH carriers identified by the screening programme actually increased more than four times during the last 5 years, that is 507 FH carriers identified in 2001 vs 2271 in 2006. Furthermore, the Dutch Association of Insurers did not receive complaints of insurance companies.

Apart from the effect of the guidelines, other factors should also be considered that might explain the decrease in complaints. One reason could be the fact that family members with a specific type of mutation, known to give rise to a serious phenotype with high LDL-c levels, have already been traced before 2003. However, the number of identified persons increased more than four times and the total number of policies for life insurance did not change during that period, so this does not seem to be a likely explanation. We are currently planning an additional study to obtain more specific data from the insurance companies in terms of risk assessment, with reference to received medical information, the type insurances (life, disability) and the requested amount of insurance cover. These data will then be subsequently linked to the information given by FH carriers, to more formally address these issues.

Conclusion

The goal to identify all FH carriers in The Netherlands through a large-scale molecular screening programme does not seem to be limited by a restriction in terms of access to insurance. This might be partially a consequence of the

development of special guidelines for insurance companies on how to deal with risk assessment and genetic screening for FH.

The large-scale screening programme for FH offers the opportunity to serve as a model for screening for other hereditary diseases like haemochromatosis or hereditary nonpolyposis colorectal cancer. In The Netherlands, a small-scale screening programme is currently carried out for hereditary haemochromatosis. Excess mortality ratings by insurers were not noted for homozygous haemochromatosis patients, and therefore the necessity to come to an agreement for treatable diseases like this or comparable disorders was not urgent until now. Therefore, this strategy in which insurers reach an agreement with medical and lay organizations could have wider relevance for the screening of other prevalent genetic disorders.

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Conflicts of interest

The authors state no conflict of interest.

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