Defining the challenges of FH Screening for familial hypercholesterolemia

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Abstract: The purpose of this article is to briefly review but also to highlight the rationale, motivation, and methods in the process of identifying patients of all ages with familial hypercholesterolemia (FH), an often hidden but very important genetic disorder. Since the initiation of population screening for FH in 1994 in the Netherlands, a vast amount of experience has been gathered, addressing almost all issues that are encountered in population screening.

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The first question that evolves is “why should we screen for FH in the first place?” The reasons to screen for FH are simple and evident: it is such an extremely common metabolic disorder, affected patients die from this disease if untreated, and highly effective treatment is available. The incidence in most countries lies between 1 in 300 and 1 in 500, which makes FH the most common genetic metabolic disorder of consequence.1 FH is associated with a significant risk for cardiovascular disease and cardiovascular death. When untreated, most patients with FH will die of myocardial infarction or other major vascular events.2

In the United States, the frequency has been estimated to be 1 affected person of 500 in the general population. That means that there are more than 600,000 Americans affected with FH, more frequent than cystic fibrosis, type I diabetes, or neonatal hypothyroidism.1 When a patient is identified, and the family screened, one often identifies several additional affected members because this genetic abnormality is an autosomal trait with complete penetrance. It is clinically evident from birth. This condition identified in children can lead to discovery of its association with vascular disease in relatively young family members as demonstrated in a study conducted by Stein et al.3 This study was the first trial with lovastatin in children. In 132 boys who were 10 to 16 years of age, a family history of cardiovascular disease was evident in most of them. FH was present in part of the fathers and part of the mothers, as can be expected, and cardiovascular disease was already present in 37% of the parents. Almost 60% of the fathers and 20% of the mothers were affected with clinical arterial disease. The mean age of onset of cardiovascular disease in the parents was 37 years. It was astonishing to find that almost 20% of the fathers of these young boys had already died as a consequence of FH.

Although the etiology of FH is well known and effective drugs are available for treatment, the disorder is still commonly undiagnosed and untreated. This is true even though diagnosis is in fact quite easy: determine the plasma cholesterol concentration and assess family history of hypercholesterolemia or early cardiovascular events. These simple steps usually identify the disorder with a high degree of specificity. Upon physical examination, tendon xanthomata will be virtual proof of the diagnosis. Finally, a genetic test, yielding a functional mutation in the low-density lipoprotein (LDL) receptor gene, will confirm the diagnosis of FH definitively.
The most important aspect of identifying FH as early as possible is that it is very treatable. Recent data from a long-term follow-up study of patients identified in the Dutch genetic cascade screening program for FH clearly demonstrated the benefit of statin treatment. Patients that were placed on statin treatment after screening had a reduction in their expected cardiovascular risk. After 10 years of therapy the vascular event rate had become identical to a normal, healthy control population. Therefore, it is very much worthwhile to find these patients and to begin treatment early. The late professor Roger Williams from Salt Lake City recognized this opportunity and compelling need for action more than 20 years ago. While traveling all over the world, he convinced cardiologists, internists, and researchers to commit themselves to become active in finding and treating persons with FH. Over the years, almost 40 countries have shown some form of commitment in supporting and/or funding programs to achieve these goals and joined the MEDPED program (Make Early Diagnosis to Prevent Early Death) he created. Different approaches to finding the FH patients have been tried in different countries. In the United States, the major approach appears to be identification of FH patients in practice and then, on the basis of family history, to contact relatives of this index case by phone or by letter, attempting to explain the concern. These candidates are then urged to visit with a specialist or a general practitioner to have their cholesterol measured and to develop a treatment plan if affected.

In Germany, it seems that index cases are usually urged to contact their relatives and to encourage them to seek medical evaluation. Of course, the most convenient way to manage this effort is to invite the relatives to come to your lipid clinic. However, the effect of this will be limited and local. A very special approach has been used in Iceland. There, ongoing genealogical investigations have been underway for years with extensive genetic testing. Relatives of any citizen are already defined in state records and affected families are offered DNA testing. In some countries like the Netherlands, Spain, and Wales, there is an active community approach, with follow-up with family members by health workers who make home visits and offer routine lipoprotein and genetic testing. Naturally, any combination of these methods is possible.

In the Netherlands, an index case is identified by standard clinical measures and the diagnosis is further confirmed by a DNA test seeking to demonstrate a mutation in the LDL receptor gene. After the patient has given informed consent, relatives of this index case are contacted by telephone to arrange a home visit. There, blood samples are collected and a DNA test for the mutation that is characteristic of the family is performed. This can be performed very quickly in the appropriate laboratory. In this way new patients are identified and from these new patients more family members are contacted, often creating a detailed description of an extensive familial occurrence of a very specific diagnosis.

At this moment, there are three screening programs ongoing that actually cover the whole nation. These are found in the Netherlands, in Spain, and in Wales. All are determined by genetic cascade screening. There are advanced regional programs ongoing in Australia, Brazil, the Czech Republic, Ireland, New Zealand, Norway, the Slovak Republic, and Slovenia. In addition, there are some recent successful local initiatives in Austria, Germany, Ireland, Italy, Malaysia, Poland, Portugal, Switzerland, Taiwan, and the United Kingdom outside Wales.

What are the requirements and the challenges in setting up a successful program to screen for FH? First, it is very important to have an organization or an association of health care professionals in place that will take up the charge and dedicate resources to disseminate information about the importance of FH screening through their networks. A very supportive network of lipid clinics is also an important element. If these groups can induce fiscal and workforce support from governmental agencies, that will also be very helpful. When there are governmental supported healthcare systems with electronic data files that can be made available, these can be very useful in case finding.

A patient organization of FH families or a patient support group is of crucial importance because patients are evidently the real stakeholders in FH screening. DNA diagnostic laboratories can add a new dimension, providing the final definitive genetic diagnosis. Having health insurance companies that adopt helpful support mechanisms, chiefly by covering costs, is most desirable, but that is, of course can be a difficult proposition. These requirements and challenges are summarized in Table 1.

Specifically addressing the program in the Netherlands, from the Lipid Clinic network approximately 1800 clinically diagnosed patients have been referred to the DNA diagnostic laboratory annually. Genetic analysis of these patients, by sequencing the LDL-receptor gene and specific parts of the apolipoprotein B gene, results in the identification of approximately 400 individuals per year, in which the diagnosis of FH is confirmed by the presence of an FH-causing mutation. Such patients are referred to as index cases. Index cases are actually the starting point for family investigation.

The experience has shown that it is possible to contact between 4500 and 6000 relatives yearly, which results in the identification of 1500 to 2000 new cases of FH per year.

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FH, familial hypercholesterolemia.
To date, there have been almost 44,000 contacts, resulting in the identification of more than 16,000 new documented cases of FH (Fig. 1B). This approach has been proven to be extremely effective. From one index case, an average of approximately 20 living family members have been contacted. Of these, 8 were documented to be FH patients by genetic testing. In addition, by simultaneously measuring cholesterol levels, individuals are identified that have high cholesterol levels but do not have a defective LDL receptor gene. Although they do not meet the criteria for the diagnosis of FH, these individuals with high LDL cholesterol values are still at increased risk, and it also is important to bring these individuals under treatment as well.

A follow-up study showed that 1 year after identifying FH patients, 93% were on LDL-lowering medication, and after 2 years, 80% were still adherent to drug therapy. The mean age of patients that entered treatment through this program has been 37 years, well younger than one might expect the first major vascular event. The high participation rate of 98% in the screening program is probably a reflection of the need and importance of such a program among affected families.

It was also noted from this follow-up study that patients that were already on cholesterol-lowering medication were in fact undertreated and that after identification through the program case finding more patients reached treatment goals. This finding indicates that the public and physicians need to be better educated about the disorder. As we learn more details about individual cases and relate these findings to outcomes, the observation may provide more compelling guidance to the health care system. Finally, an extensive cost effectiveness study has demonstrated that this approach is highly cost effective.

Within the 39 countries that have participated in these screening and management programs, there is an estimated 4.4 million FH patients and to date, roughly 50,000 have been identified. This finding indicates that the end is certainly not in sight and screening programs need to be intensified. However, during the last 20 years, a lot of experience has been gained, and the means to resolve most issues encountered in screening programs have been published. The pragmatic approach taken in the Netherlands, aiming for what is possible, feasible, and achievable, has probably provided a near-maximally effective approach from a clinical setting.

The effects of the program are now measurable in a statistical sense, and on a personal level, it has made a difference in the lives of thousands of our citizens. FH is a very significant but underestimated problem in the United States, and it is evident that the National Lipid Association (NLA) wishes to address this with effective programs. The NLA can contribute by promoting, supporting, and facilitating FH screening. An NLA subcommittee forming a supportive alliance with the MEDPED program can be a good starting point. Developing a plan that will secure some initial funding is the most logical way to start.
Initial goals should be modest with small and regional pilot studies, rather than an ambitious program to cover the whole country. This will give an opportunity to test those policies and procedures that work and this learning process will increase the chances of success. Small successes will be rewarded immediately; people will follow; and lives will be saved. Screening models and extensive experience derived from their implementation are readily available.

Looking to the future, new pathogenic genes, new technology, new tests, and new treatments can be expected. This continued learning should make us more capable and efficient in the long-term goal of reducing the personal damage to affected individuals and the cost of this disease to the population as a whole.

References