Familial hypercholesterolemia (FH) is perhaps the most common single-gene variant causing premature morbidity and mortality (1). Initially thought to affect about 1 in 500 people, recent estimates suggest a prevalence of approximately 1:200. Research on its natural history has been limited to demonstrations of the more rapid progression of coronary heart disease (CHD) among those affected or case-control comparisons. Often, the control population is poorly reflective of the general population because of recruitment constraints imposed by the need to collect data related to atherosclerosis or subclinical atherosclerosis markers.

Epidemiological population-based studies generally have insufficient sample sizes for separate analyses of those with FH, because they can only consider participants’ data from the time of study entry. Those with lifelong exposure to elevated low-density lipoprotein (LDL) cholesterol levels cannot be differentiated from those with similar LDL cholesterol levels that rose slowly over time. In countries that systematically identify those with FH, such as the Netherlands or the United Kingdom, comparisons of those with FH to the remaining population have provided powerful observational evidence of the effect of genetically elevated LDL cholesterol on CHD and the impact of treatment (2,3). Nonetheless, these studies can only provide observational evidence of the benefit of early recognition and treatment of FH.

Genetic epidemiology, particularly with the advent of whole-exome sequencing, could rectify some of these limitations. In this issue of the Journal, Khera et al. (4) have performed an ambitious whole-exome sequencing analysis directed toward identifying those with FH in a large cohort culled from: 1) case-control studies of those with early myocardial infarction compared with those without (Myocardial Infarction Genetics Consortium); and 2) longitudinal epidemiological studies with rigorous phenotyping (CHARGE [Cohorts for Heart and Aging Research in Genomic Epidemiology] consortium). These diverse cohorts included men and women with European, African-American, and Pakistani ancestry. By combining cohorts, a sufficient subsample of those with genetically confirmed FH could be identified. Limitations of prior investigations have been overcome by including populations of interest: those with early CHD; those with incident CHD in cohort studies; and a small number with sufficient longitudinal data to allow calculation of chronic exposure to elevated LDL cholesterol.

The most important finding is confirmation of the malignity of the presence of an FH gene, which increased the likelihood of CHD independent of LDL cholesterol level. The highest odds ratio, 22:1, compared those with an FH gene and LDL cholesterol >190 mg/dl to those with no mutation and LDL cholesterol <130 mg/dl (the odds ratio for LDL cholesterol >190 mg/dl without a mutation compared with the same control group was 6:1) (4). These results are extraordinary and provide further evidence of the importance of early recognition of FH so that statin therapy can be initiated before development of significant atherosclerosis. Studies of large cohorts with FH generally show that almost 10% of such
individuals have events very early in life, by 30 years of age (5). At the other end of the age spectrum, about 10% do not develop CHD; however, this analysis confirms the lifelong higher risk in those with FH.

In this study, the yield of FH identification was about 2% (4), similar to findings in a study conducted in the United Kingdom of patients presenting with myocardial infarction at an early age (6). At first look, this outcome may be disappointing. However, the population prevalence of FH in the cohorts studied by Khera et al. (4) was about the same as is now generally recognized, just above 1:200. Interestingly, raw prevalence was lower in the previously less well-studied African-American and Southeast Asian subjects, although statistical power was insufficient to comment on this finding (4).

A key limitation to this analysis relates to the longitudinal cohorts selected for whole-exome sequencing. The Cardiovascular Health Study began recruitment at 65 years of age, well beyond the age when many with FH will have died. The Rotterdam Study began at 55 years of age. Although analyses were adjusted for statin treatment, pre-treatment LDL cholesterol levels were ultimately unknown. The presence of undiscovered genes that cause FH could also lower prevalence estimates. These factors likely biased the sample toward a lower prevalence than has been seen in purely European cohorts or prior case-control comparisons. All current FH diagnostic schemata rely on family history; thus, the benefit of knowing family history of elevated cholesterol or premature CHD and its impact on genetic testing efficiency could not be assessed in this study (7).

Nonetheless, identification of 2% of a population with CHD who have a genetic variant that increases risk means that this 2% would be eligible for cascade screening of first-degree family members and subsequent identification of many asymptomatic carriers eligible for statin treatment and its subsequent benefit. Treatment of those with identified FH is highly cost-effective (8).

In this study, many of those with FH had LDL cholesterol <190 mg/dl and higher risk than those with equivalent LDL cholesterol (4). As genotyping of at-risk individuals with FH has evolved, the prior classification of FH, which linked heterozygous FH to LDL cholesterol levels of 160 to 190 mg/dl and 400 to 500 mg/dl and homozygous FH to higher LDL cholesterol levels, was shown to be incorrect (1). LDL cholesterol levels overlap between those with heterozygous and homozygous FH (9). The situation is further complicated by interactions with the many genes that have a small effect on LDL cholesterol, which in combination can substantially increase or decrease LDL cholesterol levels, depending on their presence in a given individual (10). The authors emphasized the difficulty in using explicit thresholds of LDL cholesterol for defining FH, a problem highlighted in recent scientific statements on FH (1,11). Both phenotypic and genotype-based definitions are needed. The FH phenotype is based on family history, LDL cholesterol levels, and presence of physical findings. This allows for risk assessment (driven by higher LDL cholesterol levels) and diagnosis when genetic testing is not available. Genetic testing is critical for cascade screening and genetic counseling. As time goes on, I suspect that the value of genotyping to confirm a diagnosis of FH will likely increase, particularly because whole-exome sequencing could help identify some of those with currently undiscovered genes and also provide information on both large- and small-effect genes.

There are 2 indirect implications of this study. First, middle age might not be the most efficient time to try to identify those with FH. Cholesterol increases with age, gradually in men, and with menopause in women (12). Yields of genetic testing based on LDL cholesterol levels alone vary by age, with better than 90% discrimination at 1 to 9 years of age, and falling decade by decade to below 50% in middle-aged subjects from families with an index case (13). In a cohort with a mean age of 53 years, Khera et al. (4) showed that about 2% of those with CHD were gene positive for FH. Given the high risk for CHD associated with FH and the availability of effective treatment, greater emphasis on early identification is imperative. In Slovenia, where universal screening for elevated cholesterol begins at 5 years of age, Klancar et al. (14) showed that 57% of children who met phenotypic criteria for FH had genetically confirmed FH; many of the rest had the APOE4 allele. Data from the Netherlands showed almost no CHD events at 30 years of age in patients with FH treated with statins beginning in adolescence, which was statistically lower than their parents, who experienced an event rate approaching 10% (15). It is now time to consider that those with FH and elevated LDL cholesterol are undertreated if treatment has not begun by 20 years of age (16).

The second implication relates to the 98% without the FH gene and with elevated LDL cholesterol. Diet plays an important role in the rise in cholesterol over time, and important inroads have been made in lowering population levels of LDL cholesterol. Nonetheless, and because of the obesity epidemic, saturated fat as a harmful component of the diet has received less attention than added
sugars and total calories. This emphasis may need to be revisited.

Finally, the work of Khera et al. (4) and others points to a new direction for FH research and perhaps for clinical care. An FH registry now exists in the United States (7). The FH Foundation is exploring ways to use existing information technology resources and databases to identify patients with a high likelihood of having FH. de Ferranti et al. (12), although recognizing its limitations, used the NHANES (National Health and Nutrition Examination Survey) database to examine the population prevalence of FH in the United States. The U.S. Centers for Disease Control and Prevention considers FH a tier 1 genetic condition, similar to those responsible for breast cancer and colon cancer; families with identified FH must be offered cascade screening of first-degree relatives (1). Linking genetic studies to resources that can identify the FH phenotype will bring us much closer to the goal of early recognition of all those in a given population with FH much sooner than might have been thought possible even 5 years ago.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Samuel S. Gidding, Nemours Cardiac Center, A.I. DuPont Hospital for Children, 1600 Rockland Road, Wilmington, Delaware 19803. E-mail: sgidding@nemours.org.

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