

Familial hypercholesterolemia: a missed opportunity in preventive medicine

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Familial hypercholesterolemia (FH) is caused by a codominantly inherited defect in the synthesis or function of the LDL receptor (LDLR) that reduces the catabolism of LDL particles and markedly increases plasma cholesterol concentrations.¹ The population prevalence of heterozygous FH is at least 1 in 500, and could be as high as 1 in 50 in communities with a 'founder gene', such as the Christian Lebanese. More than 1,000 LDLR mutations have been identified to date. Patients with FH have an increased incidence of atherosclerotic cardiovascular disease (CVD), particularly coronary artery disease (CAD).² When left untreated, FH confers a 100-fold excess risk of CAD in young men. Women with FH are also at a substantial risk of CAD, but the risk is lower than that for men and, on average, women develop the disease 10 years later.² Lifestyle measures, including fat-modified diets, and pharmacotherapy, particularly with statins, can substantially decrease the risk of CAD.² Despite impressive advances in our understanding of the pathophysiology of FH, over 80% of patients with FH in Western countries go undetected,³ and this easily diagnosed disorder remains a major challenge for preventive medicine. We urge that this challenge be met by the transformation of existing nihilism into a rigorous and cost-efficient strategy for detecting and treating FH.

FH fulfils all the WHO criteria for disease screening.¹ Relatives of probands can and must be screened for FH before they develop clinical CVD, but this seldom occurs in current clinical practice.^{4,5} The most cost-effective approach is undoubtedly 'cascade screening' of first-degree relatives of index cases.⁶ Identifying index cases is fundamental to the success of such programs, but at present there are no internationally agreed criteria for the diagnosis of FH. We favor the Dutch Lipid Clinic Network Criteria, in which a score is derived from the LDL cholesterol level, the family and personal history of premature CVD, and the presence of tendon xanthomas or corneal arcus.³ All patients with a history of premature CVD should be screened for FH,

but regrettably this is not practiced regularly at present.^{4,5}

Screens for LDLR gene mutations indicate that up to 30% of FH cases might be misclassified when phenotypic detection alone is used.⁷ LDLR mutations can, however, only be detected in some 70% of patients with definite phenotypic FH and 20% of those with probable or possible FH. Hence, it is unethical to exclude families from phenotypically-based cascade screening if no mutation is found in an index patient with clinically evident FH.^{2,7} Genotypic screening alone is less efficient in heterogeneous populations, where FH can be caused by a large number of LDLR mutations. Once a family-specific mutation is identified, however, testing for that mutation in the kindred is highly cost-effective.⁷ Genetic screening should be avoided when the clinical diagnosis of FH is equivocal, at least until the capacity for extensive testing has been established. We favor a co-ordinated clinical and genotypic screening strategy,^{2,7} but the success of this approach is still to be evaluated. Furthermore, all screening programs should include genetic and psychological counseling services.

Countries vary in the organizational and legislative environments in which FH screening is performed. Often, as in the UK and Australia, privacy laws permit only indirect contact via index cases, greatly reducing the efficiency of cascade screening. Given the grave risk of CAD in individuals with FH,² we consider it ethical to contact relatives directly, but with due sensitivities. Moreover, we maintain that current privacy legislation is inappropriately cautious and needs to be balanced against the consequences of failing to detect and treat new cases of this lethal condition. Screening for FH could also be impeded by concerns about the psychological impact of the diagnosis, as well as the effect on health insurance premiums and employment opportunities.⁸ Several studies collectively demonstrate that the detection of FH within families does not have a major adverse impact on mental health or quality of life.^{7,9} Although health insurance premiums

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