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Invited commentary

Familial hypercholesterolaemia: A pressing issue for European health care

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ABSTRACT

The recent European Atherosclerosis Society (EAS) guidelines for the management of familial hypercholesterolaemia (FH) succinctly reiterate the under-diagnosis and poor management of this common genetic disorder, which is associated with greatly increased mortality from coronary heart disease (CHD), especially in young people. The prevalence of FH is thought to be between 1/500 and 1/200, and thus in Europe 1.8–4.5 million individuals have FH. In most European countries including the UK, fewer than 15% of cases have been identified to date, amounting to over 100,000 undiagnosed cases in the UK alone. There are a number of issues that have impeded the implementation of FH diagnostic and management guidelines in Europe; here, we briefly review the current situation in the UK, and propose ways to start to break down implementation barriers that may be applicable across Europe. Despite guidelines by the UK National Institute of Health and Clinical Excellence (NICE) published in 2008 that recommend genetic testing of index cases and cascade screening of their family members, and the recent NICE Quality Standards for management of FH (QS41), there has been little action towards systematic diagnosis in England despite implementation of systematic screening programmes in Scotland, Wales, Northern Ireland and in other selected countries in Europe. This is surprising because early treatment with statins provides an effective and cheap treatment that reduces mortality to near that found in the normolipidaemic population. With increasing emphasis on preventive medicine and genetic diagnosis across the medical specialties, FH is a clear example of how new genome technologies can - and should - be deployed now for the benefit of patients.

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The recent EAS guidelines for the management of familial hypercholesterolaemia (FH), have documented the under-diagnosis and poor management of this common genetic disorder [1], which is associated with greatly increased mortality from coronary heart disease (CHD), especially in young people. While the generally accepted estimate for the prevalence of FH is 1/500 members of the general population, a recent study from Denmark suggested a frequency approaching 1/200 [2]. Using these estimates, between 14 and 34 million people are likely to have FH world-wide, including some 1.8–4.5 million individuals in Europe, and at least 120,000 individuals in the UK. The EAS guideline documents the current extent of FH under-diagnosis in Europe, with only Holland and Norway having already identified approaching half of the predicted number of their patients, and most other countries having identified under 10% [1].

FH is characterised by high serum cholesterol levels detectable from birth, caused by genetic defects that prevent the normal clearance of low-density lipoprotein cholesterol (LDL-C), leading to its accumulation in the circulation. This results in the development of accelerated atherosclerosis, as well as the characteristic cholesterol deposits (xanthomas) seen in tendons. The most severe homozygous form of FH is very rare, affecting only one in a million of the general population, and this is usually detected in childhood. It

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requires aggressive lipid lowering treatment, usually only being treatable by LDL-apheresis, which has been shown to prevent the onset of CHD that otherwise occurs in the first or second decade of life. [3] The much commoner heterozygous FH is typically asymptomatic, but in the absence of detection and appropriate treatment, CHD develops in 50% of men and 30% of women by the age of 55 [4].

The mutations that cause FH occur in one of three genes, LDL-receptor (*LDLR*), apolipoprotein B (*APOB*) and proprotein convertase subtilisin/kexin type 9 (*PCSK9*) [5]. Mutations in any of these genes can partially or wholly block normal uptake of LDL-C and clearance by the liver. A rarer autosomal recessive form of FH is caused by mutations in the LDL-receptor adaptor protein gene *LDLRAP1* (also called *ARH*) [6]. However, the overwhelming majority of cases of FH (>90%) are due to mutations in *LDLR*. While some of the patients where no mutation can be detected in any of these genes may have a defect in an as yet unidentified 'FH-gene', recent evidence shows that the majority of the mutation-negative FH patients have inherited a greater than average number of common lipid-raising variants of small effect [7]. This suggests that a polygenic cause is the most likely explanation for elevated cholesterol in the majority of clinical FH patients in whom monogenic mutations in the known causal genes cannot be found [7].

Effective treatment for FH is available in the form of healthy lifestyle modification including dietary fat restriction, an exercise programme and avoiding smoking, combined with HMG-CoA reductase inhibitors (statins), which lower LDL-C and reduce the risk (or progression) of CHD. Other options include alternative cholesterol-reducing medications, or in extreme cases lipoprotein apheresis, with various potential new therapies in development [8]; some, such as monoclonal antibodies to PCSK9, show promising results in trials [9], with 50–60% additional LDL-C lowering being achievable in patients already being maximally treated with statins. Prior to the introduction of statin therapy, CHD mortality in adult FH patients was almost 100-fold higher for 20–39 year olds and five-fold for 40–59 year olds, although the risk for older FH patients was not markedly different from that of the general population, suggesting a 'survivor effect' [10]. Comparison of CHD mortality in FH patient cohorts in the pre- and post-statin eras showed that statin therapy can reduce the risk of CHD in both men and women by around 80%, to almost that of the general population, especially in those who have not yet developed CHD [11]. For children with genetically diagnosed FH, there is evidence that atherosclerosis develops and progresses rapidly from the age of 10 years [12], and current recommendations are that treatment with statins should be considered from this age [13]. The early and definitive identification of FH is therefore crucial for prompt clinical intervention to prevent premature CHD, especially in younger people.

There are several clinical diagnostic criteria for FH, with the Dutch Lipid Clinic Score being widely used in Europe [14] while the UK uses the Simon Broome criteria [15]. The sensitivity and specificity of these two methods for identifying carriers of an FH-causing mutation is similar [16]. The "positive" genetic test result of identifying an FH-causing mutation in an individual provides a definitive diagnosis, whereas using cholesterol levels alone results in both false-positive and false-negative results and is therefore unreliable for family cascade testing [17]. However, DNA testing is complicated by the very large number of potentially causative mutations in the *LDLR* gene; over 1200 have been identified worldwide [5,18]. While FH index cases are usually identified opportunistically because of their very high LDL-C levels (often only after a myocardial infarction), testing their close relatives, who have a 50% chance of also having FH, is an effective way to identify new patients.

In the Netherlands, systematic screening and family cascade testing was established in 1994, leading to detection of more than 33,000 Dutch FH cases since that time [19]. In the UK, cascade screening initiatives have been established in Scotland, Wales and Northern Ireland but, despite the 2008 National Institute of Health and Clinical Excellence guidance recommending genetic testing of index cases and family members [15], there is no systematic programme in England and FH therefore remains a compelling public health issue. A recent UK audit by the Royal College of Physicians indicated that 85% of the estimated 120,000 or more affected individuals in the UK remain undiagnosed, leaving more than 100,000 individuals at high risk of early death [20], including some 75,000 in England.

Health economic studies argue strongly in favour of systematic screening for FH. Analysis of the clinical and cost-effectiveness of different approaches to such cascade screening showed that using diagnostic DNA testing for the relatives of patients with identified mutations combined with diagnostic cholesterol testing for relatives of those patients in whom mutations were not identified, was the most cost-effective method, with an incremental cost-effectiveness ratio (ICER) of £2700 per Quality-Adjusted Life Year (QALY) [21]. This compares very favourably with the typical NHS benchmark for cost-efficacy of £20–30,000/QALY. Later analysis confirmed that comprehensive genetic testing to diagnose FH in a patient was more cost effective than cholesterol measurement, and supported the previous recommendation for cascade screening using diagnostic DNA testing (targeted sequencing) for the relatives of patients with identified mutations [22]. Recently, economic modelling has estimated that treatment of every 1000 FH patients (between the ages of 30 and 85 years) with high intensity lipid-lowering statin therapy would lead to 101 fewer cardiovascular deaths when compared with no treatment. Overall, the UK could save almost £380 million from CHD events avoided if all relatives of index cases were identified and treated optimally over a 55 year period, equating to savings of £6.9 m per year [23].

We believe that in the UK there have been three major impediments to introduction of cascade screening for FH, and that these are also important in European countries. Firstly, FH is not considered a rare disease (the usual definition of rare disease is less frequent than 1 in 2000, whereas FH has an estimated prevalence of 1 in 500), and thus the funding for FH screening cannot come from this source. The second issue is that paradoxically FH is seen as too common to be affordable, with the cost of comprehensive genetic testing being around £400–£800 per index case, although much less for testing relatives for an identified family mutation. However, the introduction of next-generation sequencing technologies and use of simultaneous targeted sequencing of all three FH-causing genes will reduce the cost of testing an index case by as much as four-fold [24,25], paving the way for effective testing at lower costs than has previously been possible. Including known 'polygenic' variants in such a test would add negligibly to the cost and would allow a distinction between those with a likely polygenic aetiology and those with an unidentified monogenic cause [5]. While all individuals with elevated LDL-C will require statin treatment, whether due to a monogenic or a polygenic aetiology, to focus scarce resources on cascade testing in the 40% of clinical FH patients with a monogenic cause (where cascade testing has demonstrated clinical utility [26]) will also lead to greater cost efficiency. Besides offering improved diagnosis, advanced sequencing approaches may even facilitate improved management by incorporating pharmacogenetic markers that can predict risk of statin-associated toxicity [25].

Despite the major longer-term cost savings that an FH cascade screening programme would generate, we believe that the third major impediment to its introduction is a bias in health care

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