

Nurse-led cascade screening for FH: filling in the gaps

*The most common genetic cause of premature coronary heart disease is familial hypercholesterolaemia. In this comment, **Lisa Gritzmacher** shares her experience of a nurse-led cascade screening service for this inherited condition, identifying the benefits of such services, as well as gaps that remain across the country and that need attention*

Familial hypercholesterolaemia (FH) is the most common genetic cause of premature coronary heart disease (CHD) (Nordestgaard et al, 2013). Recent evidence suggests that the prevalence of the heterozygous form of FH is much higher than previously estimated, and is now thought to affect 1 in 200–300 of the population (Khera et al, 2016; Wald et al, 2016). Heterozygotes inherit a single defective gene from one parent; there is a more severe form of FH called homozygous FH where an individual inherits a defective gene from both parents.

FH is an autosomal dominant condition—meaning that first-degree relatives (parents, siblings and children) of someone with FH will have a 50% risk of inheriting FH. For the purpose of this article, FH relates only to heterozygotes.

FH results in a raised blood low-density lipoprotein cholesterol (LDL C/bad cholesterol) level, which is present from birth and leads to premature development of atherosclerosis and CHD. Young adults with FH have a 100-fold increased risk of CHD (Brice et al, 2013). Patients identified and treated at a young age have a completely normal life expectancy. However, the average age for the first acute coronary syndrome (ACS) event in untreated FH is 44 years, with a mean age of death of 60 years. People with FH post ACS are less likely to reach treatment targets and are up to 3.5 times more likely to have a recurrent event on treatment, compared with people without FH (Nanchen et al, 2016).

Approximately 80–90% of FH patients in the UK remain undiagnosed (NICE, 2013). This represents an important opportunity to reduce premature mortality and morbidity from CHD in the UK by identifying and treating people with FH. The need for better identification of families and individuals at very high risk of cardiovascular disease is recognised in the Department of Health’s (DH) (2013) *Cardiovascular Disease Outcomes Strategy*.

Identification after the first ACS event does present an

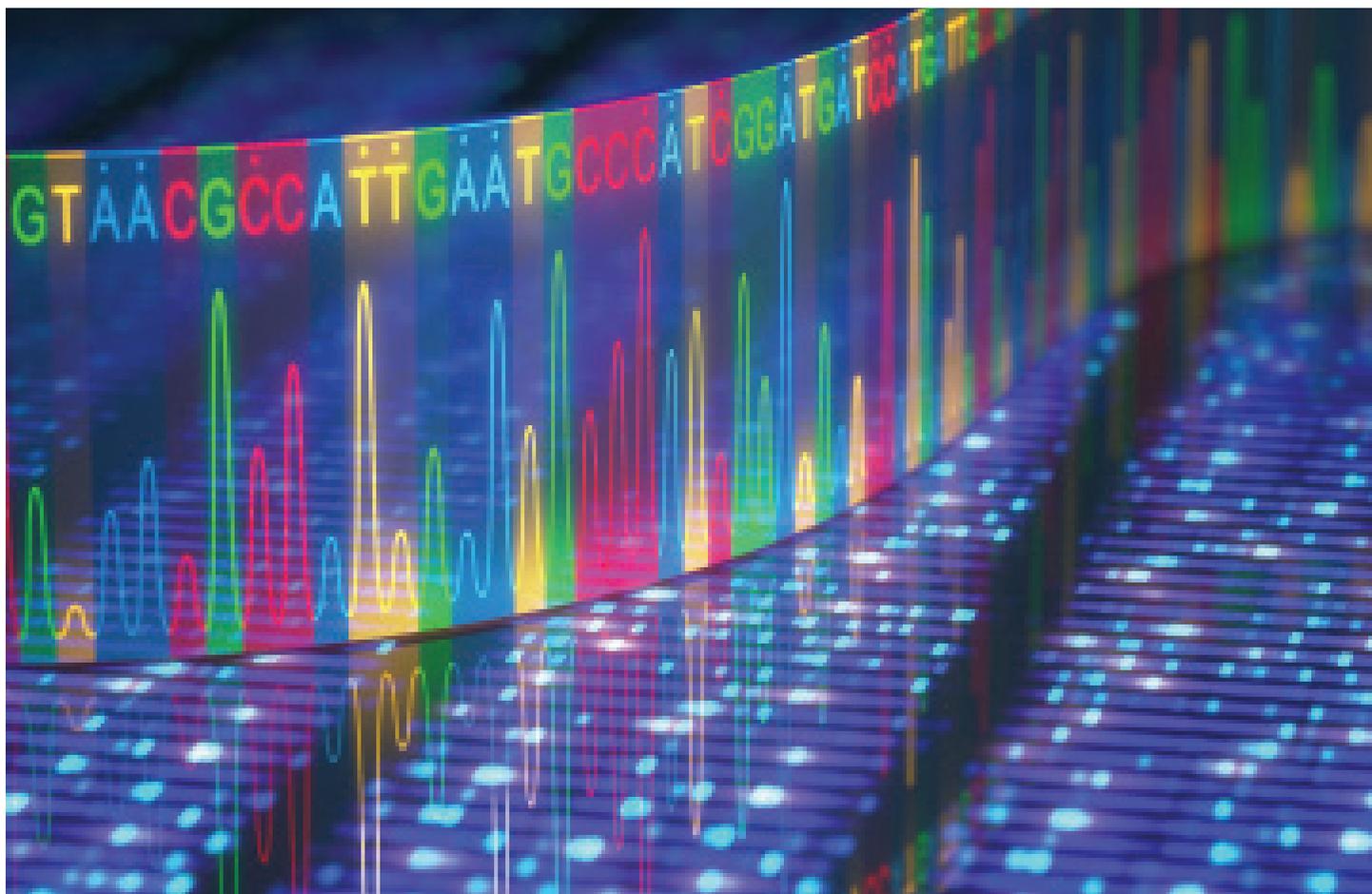
opportunity to prevent this pattern from occurring in the wider family through referral to FH services or lipid clinics for FH testing and family screening. However, when diagnosis is made after the first ACS event, secondary prevention is not sufficient this late in the game to prevent further ACS events and premature death. This may in part explain the increased risk for subsequent events seen in FH (Hovingh and Kastelein, 2016). The increased morbidity and mortality in FH resulting from patients not reaching treatment targets may be improved by more aggressive treatment with new agents such as proprotein convertase subtilisin kexin 9 inhibitors (PCSK9) (Nanchen et al, 2016).

Khera et al (2016) found that at any given level of LDL C, people with an FH mutation had a significantly higher risk of CHD than those without an FH mutation. Genetic screening for FH therefore identifies those at increased risk at the same LDL C level, which results from lifelong exposure to high LDL C levels in FH. Genetics therefore provide further information about an individual’s cardiovascular risk than cholesterol levels can alone.

The BHF provided funding in two waves (2014 and 2015) for development of nurse-led cascade screening services nationally. The National Institute for Health and Care Excellence (NICE) (2008; 2013) recommended a systematic nationwide family-based service to enable comprehensive cascade screening of geographically-spread families. England, Wales and Northern Ireland use a national registry (PASS), which is both a database and workflow-management tool that allows different services to link in to shared families and efficiently manage screening for geographically-spread relatives. This is working well in areas that have access to PASS, but will never be fully cost-effective or efficient until systematic cascade screening is available nationally, as you cannot comprehensively screen families when their relatives live in areas with no access to testing. Unfortunately, there remain many areas in England where cascade screening is still not available.

Since the FH nurse-led services came into being, cascade testing referrals at one genetic laboratory in England have increased by approximately 400%, and 70% of these referrals were via PASS (Hills et al, 2016). Integrated use of PASS by FH services and laboratories has also proven worthwhile in terms of reducing unnecessary duplication

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Familial hypercholesterolaemia is an inherited condition characterised by severely high cholesterol levels from birth

of index case tests (first individual tested in each family) across services. This provides significant savings for the NHS, as index tests cost approximately three times more than the targeted cascade relative's test (Hills et al, 2016). NICE (2008; 2013) recommends screening children by age 10 in families with FH, which is where genetic screening can make the most difference to morbidity and mortality related to this inherited condition.

Cascade screening of all at-risk relatives via genetics not only reliably identifies all relatives who have inherited FH, but also provides opportunities to ensure they are being effectively treated to optimal primary prevention targets. NICE (2008) recommends reduction of LDL C by 50% from that of baseline levels. Cholesterol-based screening of relatives can lead to underdiagnosis of FH. I have seen this several times in my clinical practice, where families were previously screened via cholesterol. Genetic screening, therefore, identifies a cohort of patients at high risk for CHD that could otherwise be missed (Khera et al, 2016).

Cascade screening also facilitates early identification of FH in childhood where highly cost-effective treatment can be commenced before significant atherosclerosis has developed. Early identification of FH and timely treatment is the most effective way to prevent premature ACS associated with FH (Gidding, 2016; Khera et al, 2016). **BJCN**

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