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 up to 3.5 times more likely to have a recurrent event upon 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*.

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 is thought to be owing to the lifelong exposure to high LDL C levels.

It is also clear that even after diagnosis, FH is often undertreated (AQ1: Clear from what? Evidence/reference?). 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 (AQ2: Reference?). This may in part explain the increased risk for subsequent events in FH (Hovingh and Kastelein, 2016; Nanchen et al, 2016). However, while identification after the first ACS event is far from ideal, it does at least present an important opportunity to prevent this pattern from reoccurring in the wider family through referral to FH services or lipid clinics for FH testing.

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 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

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Familial hypercholesterolaemia is an inherited condition characterised by severely high cholesterol levels from birth (AQ3: pic ok?)

age 10 in families with FH, which is where genetic screening can make the most difference to morbidity and mortality resulting from 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 also being effectively treated to optimal 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. This may be most effective in preventing the premature ACS otherwise associated with FH (Gidding, 2016). BJCN

References

Brice P, Burton H, Edwards CW, Humphries SE, Aitman TJ (2013) Familial hypercholesterolaemia: a pressing issue for European health care. *Atherosclerosis* **231**(2): 223–6. doi: 1016/j. atherosclerosis.2013.09.019

Department of Health (2013) *Cardiovascular Disease Outcomes Strategy.*
Improving outcomes for people with or at risk of cardiovascular disease. DH, London. http://tinyurl.com/nk5c5lu (accessed 23 January 2017)

Gidding SS (2016) Familial Hypercholesterolemia: Now Part of Cardiovascular Disease Genetic Epidemiology Research. *J Am Coll Cardiol* **67**(22): 2590–2. doi: 10.1016/j.jacc.2016.03.567

Hills A, Honeychurch J, Davies J et al (2016) 4 years' cascade genetic testing for familial hypercholesterolaemia in England – Increased referrals and ascertainment. *Atherosclerosis* **255**: e3. doi: e3. 10.1016/j.atherosclerosis.2016.09.051

Hovingh GK, Kastelein JJ (2016) Diagnosis and Management of Individuals With Heterozygous Familial Hypercholesterolemia: Too Late and Too Little. *Circulation* **134**(10): 710–2. doi: 10.1161/ CIRCULATIONAHA.116.023942

Khera AV, Won HH, Peloso GM et al (2016) Diagnostic Yield and Clinical Utility of Sequencing Familial Hypercholesterolemia Genes in Patients With Severe Hypercholesterolemia. *J Am Coll Cardiol* 67(22): 2578–89. doi: 10.1016/j.jacc.2016.03.520

Nanchen D, Gencer B, Muller O et al (2016) Prognosis of Patients With Familial Hypercholesterolemia After Acute Coronary Syndromes. *Circulation* **134**(10): 698–709. doi: 10.1161/ CIRCULATIONAHA.116.023007

National Institute for Health and Care Excellence (2008) *Identification and management of familial hypercholesterolaemia* [CG71]. NICE, London

National Institute for Health and Care Excellence (2013) *Familial hypercholesterolaemia* [QS41]. NICE, London

Nordestgaard BG, Chapman MJ, Humphries SE et al (2013) Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur Heart J* **34**(45): 3478–90a. doi: 10.1093/eurheartj/eht273

Wald DS, Bestwick JP, Morris JK, Whyte K, Jenkins L, Wald NJ (2016) Child-Parent Familial Hypercholesterolemia Screening in Primary Care. *N Engl J Med* **375**(17): 1628–37