A window into the heart of familial hypercholesterolaemia in the community

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Familial hypercholesterolaemia is due to a major genetic defect in the LDL receptor pathway and is the most common cause of premature coronary artery disease in the community.[1] If it is overlooked and untreated, familial hypercholesterolaemia increases the relative risk of a coronary event at least 20-fold and curtails lifespan by 15 years. With a population frequency as high as 1 in 200,[2] familial hypercholesterolaemia is now an important public health issue that needs to be addressed in primary care.

Expert guidelines recommend specific clinical tools, such as the Simon Broome, Dutch Lipid Clinic Network (DLCN), and Make Early Diagnosis to Prevent Early Deaths (MEDPED) criteria, for making the diagnosis of familial hypercholesterolaemia.[1] These diagnostic tools are, however, dependent on detailed family histories of hypercholesterolaemia and premature coronary artery disease, and the detection of physical stigmata of familial hypercholesterolaemia, which make them impractical for use in primary care. Genetic testing is also at present not feasible in this setting.[1] As a consequence, clinical case ascertainment tools linked to electronic health records have been designed for detection of familial hypercholesterolaemia in general practice.[3,4]

A well developed tool is the familial hypercholesterolaemia case-ascertainment tool (FAMCAT) algorithm, initially derived and internally validated using data from 3 million patients in primary care in the UK.[3] FAMCAT is a regression equation that contains simpler elements of the aforementioned diagnostic tools, as well as other variables, including triglyceride concentration, diabetes, and chronic kidney disease, which increase the specificity of the search.[3] The initial algorithm was demonstrated to be highly predictive of familial hypercholesterolaemia,[3] but more widespread implementation of the tool required further validation.

In *The Lancet Public Health*, Stephen Weng and colleagues[5] undertook an external assessment of FAMCAT in 747 000 adult patients from 1500 primary care practices recruited into the UK QResearch database. The algorithm was compared with the Simon Broome, DLCN, and MEDPED tools, as well as screening for cholesterol concentrations higher than the 99th percentile of the general population in the UK, in predicting an encoded diagnosis of familial hypercholesterolaemia, made independently by specialists based on phenotypic or genetic criteria. Essentially, FAMCAT was demonstrated to be a better discriminator, as assessed by the area under the receiver operator characteristic curve, than the other clinical tools. This finding establishes the value of FAMCAT as a first-stage screening tool for familial hypercholesterolaemia and justifies its integration into computer systems in primary care in the UK. Extension to countries with different health-care systems to the UK has to be limited, but pilot studies merit consideration.

The investigation has certain limitations. Electronic screening algorithms are only as valid as the accuracy of the primary data extracted from the electronic health records.[6] The sample population was ethnically restricted and did not include children. The reference diagnosis of familial hypercholesterolaemia was in part based on phenotypic criteria alone, which are inherently prone to error. A cost-utility analysis was also not presented. Future investigations with reference to a genetic diagnosis of familial hypercholesterolaemia and a formal health economic evaluation will further consolidate the value of FAMCAT.[5] Elevated lipoprotein(a) is common and might reduce the specificity of the phenotypic diagnosis of familial hypercholesterolaemia;[7] its inclusion in future FAMCAT regression equations is recommended.

The rationale behind FAMCAT is to more efficiently identify patients with familial hypercholesterolaemia in the community and to streamline referrals to specialist centres for further evaluation.[3] Supplementary detection methods for familial hypercholesterolaemia include opportunistic screening during consultations, pathology report alerts to general practitioners, and inclusion of cholesterol testing in routine health checks in people aged 40–75 years old.[6] But primary care might also have a role in making a formal diagnosis of familial hypercholesterolaemia and managing cholesterol-lowering therapy, particularly in uncomplicated cases.[6] Testing close family members would also be possible, but appropriate resources and training are required, especially with genetic testing.[1] However, fundamental barriers still

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need to be overcome to ensure the success of models of care for familial hypercholesterolaemia in primary care. These barriers include a lack of general knowledge and skills in lipid management, poor documentation of family history data, and lack of knowledge and skills in cascade testing.[6] Improved public awareness about the value of cholesterol testing, inherited heart disease, and familial hypercholesterolaemia is also essential for successful implementation of detection strategies in the community.[8]

Population modelling has suggested that to detect the majority of familial hypercholesterolaemia cases in the community requires more than the systematic searching of electronic health records followed by cascade testing, indicating the worth of universal screening approaches.[9] Furthermore, acknowledging the natural history of familial hypercholesterolaemia, probably the greatest missed opportunity is the detection of the condition in children at a suitable age when effective lifestyle modifications and statin therapy can be instituted.[1] Universal screening of children and child–parent cascade testing has now been shown to be a highly effective method for identifying young people with familial hypercholesterolaemia, as well as a parent and their own siblings, before they develop a coronary event.[10] This approach appears to be an acceptable and potentially cost-effective method of screening but, as with FAMCAT, requires more implementation research.

In aggregate, FAMCAT is a precision medicine tool for use in a primary care system similar to that of the UK that is likely to play an important part in improving life expectancy and relieving suffering for families with familial hypercholesterolaemia in the community. However, its success will derive from its coordinated use with other screening and testing methods referred to previously and the development of compendious and context-specific models of care that are well integrated between primary and specialist medical services.[1,6]

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