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EDITORIAL COMMENT

# Is it Time to Rethink Screening for Familial Hypercholesterolemia?*

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The pivotal role of low-density lipoprotein cholesterol (LDL-C) in the pathogenesis of atherosclerotic cardiovascular disease is well established by preclinical, cohort, and genetic studies.[1] The consistent finding of cardiovascular benefit in studies of LDL-C lowering therapies further illustrates the importance of targeting dyslipidemia in primary prevention.[2] These observations have influenced treatment guidelines that strongly advocate for lipid lowering as a major component of cardiovascular prevention algorithms.

Increasing interest has focused on familial hypercholesterolemia (FH) as an important target for therapeutic modification in the community. With evidence that FH is common, with a prevalence of approximately 1 in 250 in all countries, and the role of lifetime exposure to LDL-C in premature atherosclerotic disease, there is a major need to introduce lipid lowering interventions early in life. For these therapies to have their greatest clinical impact, there is clear need to identify individuals with FH and their relatives as early as possible, via a range of cascade screening initiatives. However, the detection rate of FH in most countries remains poor, with more than 90% of FH cases failing to be identified, representing a substantial missed opportunity to impact cardiovascular morbidity and mortality. In an era of innovative and highly effective therapeutic approaches, this would suggest that we are failing to make the population impact in patients with FH. The need for better approaches to screening and diagnosis of FH cases and subsequent follow up of their relatives is clear.[3]

In this issue of the *JACC: Advances*, Gratton et al[4] investigated the utility of a machine learning model to aid detection of FH. In this analysis of more than 139,000 participants of the UK Biobank, which found the presence of a FH variant in 488 individuals. Using a machine learning algorithm, interrogation of concentrations of triglycerides, LDL-C and apolipoprotein A-I, use of statins, and a polygenic risk score for LDL-C, in addition to a number of other clinical factors, performed better than simply measuring LDL-C levels to predict the likelihood of carrying a FH variant. Similar findings were observed for the model when the polygenic risk score was removed. These findings suggest that the ability to look at patients on the basis of a number of factors, as opposed to simply examining LDL-C levels, may be useful to identify individuals with FH.[4]

What are the implications of this finding? Traditional approaches to FH screening are largely based on examination of LDL-C levels, by themselves or in combination with a number of clinical factors associated with FH. Identifying individuals who would appear to be at a greater likelihood of having FH would then lead to genetic testing and subsequent cascade screening within families. While a number of models have been developed and implemented in clinical practice, the reality is that we still struggle to identify most individuals with FH, since these approaches, in part related to the limited access to clinical experts who suspect the condition. Given that the relationship between elevated cholesterol levels and cardiovascular risk reflects lifetime exposure and is magnified in those with genetic dyslipidemia, the failure to start lipid lowering therapy early thwarts our efforts to reduce the burden of premature

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cardiovascular disease associated with FH. We clearly need better approaches to detection the community.

The promise of big data approaches to health care lies in their ability to see what cannot be seen via a traditional lens. Application of machine learning provides the opportunity to more accurately characterize both disease risk and phenotype, not only in a more rapid semiautomated manner, but also augments access to expert-level clinical diagnosis and decision-making. Given that the sequential, cascade approach to identifying individuals with FH is inefficient, the ability to look at whole populations and find those at a higher risk of FH can then focus resources to those more likely to have the genotype of interest. This efficiency permits the application of screening resources in a more strategic, whole of community, fashion and has the potential to identify a greater number of patients who may benefit from treatment at an early stage.

The performance of the algorithm after exclusion of polygenic risk scores highlights the ability to apply this approach to a broad sector of the primary care community, in which the other factors will be recorded. This has the potential to not only eliminate the cost for polygenic risk score determination in the first instance, but ultimately to focus the cost of genomic sequencing to those more likely to carry a variant. While the cost of genomic sequencing has substantially declined over the last decade, considerable barriers remain to its widespread use. It is also of note that the current analysis excluded variants of unknown significance, some of which may contribute to the clinical phenotype of FH and confer a greater cardiovascular risk. Additional work should look at these variants further.

While observations such as this are important, the ultimate determinant of its translation to clinical use will require further study. Implementation studies will be critical to determine how best to apply these algorithms at a community level. It will be important to understand how they perform in other populations, and potentially who they evolve over time. As acknowledged by the authors, the UK Biobank is an older cohort than ideal for the initiation of lipid lowering therapy in FH. Additional study of this approach will be required in younger individuals, where the totality of clinical data present may not be optimal. It will also be useful to directly compare their use against conventional approaches to validate their use and to ultimately determine their cost effectiveness.

FH remains a highly preventable cause of atherosclerotic cardiovascular disease. The ability to identify more individuals in the community with FH and to commence lipid lowering therapy at an early stage have the potential to impact cardiovascular rates considerably across the world. We need approaches that are easy to implement in clinical practice, and the use of big data analysis may provide that opportunity.

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