Polygenic hypercholesterolaemia: why do we want to know?

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Mutations in any of four genes (*LDLR, APOB, PCSK9, APOE*) are known to cause autosomal dominant FH, but a mutation can be found in only ~40% of patients with a clinical diagnosis of FH. In the remainder a polygenic aetiology may be the cause of the phenotype, due to the co-inheritance of common LDL-C raising variants. In 2013 we reported the development of a 12-SNP LDL-C "SNP-Score" based on common variants identified as LDL-C raising from genome wide association studies, and have confirmed the validity of this score in samples of no-mutation FH adults and children from more than eight countries with European-Caucasian populations. In more than 80% of those with a clinical diagnosis of FH but with no detectable mutation in *LDLR/APOB/PCSK9/APOE*, the polygenic explanation is the most likely for their hypercholesterolaemia. In this group, cascade testing will be less cost effective, since only ~30% of relatives will have elevated LDL-C compared to the 50% that is seen in monogenic families. Those with a low score (in the bottom two deciles), may have a mutation in a novel gene, and research including whole exome or whole genome sequencing is warranted. The clinical utility of the polygenic explanation is that it supports a more conservative (less aggressive) treatment care pathway for those with no mutation. Several lines of evidence suggest that these patients with polygenic hypercholesterolemia have lower levels of atherosclerosis and CHD risk and, based on published evidence, NICE guidelines recommend that it is appropriate to base their care pathway in general practice. The ability to distinguish those with a clinical diagnosis of FH who have a monogenic or a polygenic cause of their hypercholesterolaemia is a paradigm example of the use of genomic information to inform Precision Medicine, using lipid lowering agents with different efficacy and costs.

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Steve Humphries is a world-renowned expert in cardiovascular genetics, a field in which he has worked for over 40 years. He worked at University College London from 1991, where he was the British Heart Foundation Professor of Cardiovascular Genetics, retiring in September 2015 and is the UCL Emeritus Professor of Cardiovascular Genetics. He directed a major research programme to develop and implement molecular strategies to study the causes and clinical and psychological consequences of Familial Hypercholesterolaemia (FH). He was the Lead Advisor to the UK NICE guidelines on FH published in 2008, and updated in 2017, and has published on the health economics of cascade testing and Universal Screening for FH. He is the chair of the Pan-London FH action group and the Director of the UK FH Pediatric Register and the Simon Broome FH Register. He is actively involved with teaching, ethics, and public awareness aspects of the implementation of genetic testing for FH.