All Wales Medical Genomics Laboratory
Institute of Medical Genetics
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Polygenic risk score-score – information for clinicians

From 1st February 2022, the polygenic risk score will be reported on all samples sent for genetic analysis from patients with suspected Familial Hypercholesterolaemia. This will be performed as part of the expanded next generation sequencing panel.

The SNP score is a numeric score calculated by analysing 12 loci in a variety of genes and determining which genotype the patient has. From this a weighted score is calculated, with a higher score suggesting the patient has inherited a higher number of LDL-C raising alleles. The decile which this score would fall in a 'normal' population (please see below for details) will be given alongside the likelihood of there being a polygenic component to the patients hypercholesterolaemia.

Which SNPs are included in calculating the score?

This is the list of SNPs that will be tested and is the same as those commonly seen in the literature referred to as the 12 SNP-score:

Gene	SNP
PCSK9	rs2479409
CELSR2	rs629301
APOB	rs1367117
ABCG8	rs4299376
SLC22A1	rs1564348
HFE	rs1800562
MYLIP	rs3757354
ST3GAL4	rs11220462
NYNRIN	rs8017377
LDL-R	rs6511720
APOE	rs429358
APOE	rs7412

How are the polymorphisms identified?

The genotype the patient has inherited at these sites are identified by NGS sequencing and bioinformatics processing.

How is the 12 SNP-score calculated?

The presence of the different alleles at these sites are given a weighted score, based on the size of its effect.

For example, at the PCSK9 rs2479409 the LDL-C raising allele is guanine (G). The common allele is adenine (A) and the Global Lipid Genetic Consortium (GLGC) weight for the score calculation is 0.052.

This table illustrates the score the patient would be given for different genotypes:

Genotype	Number of LDL-C raising alleles	GLGC weight	Score (number of LDL-C raising alleles x GLGC weight)
GG	2	0.052	0.104
AG	1	0.052	0.052
AA	0	0.052	0

Such calculations are performed for each of the SNP loci and then summed to give a total score.

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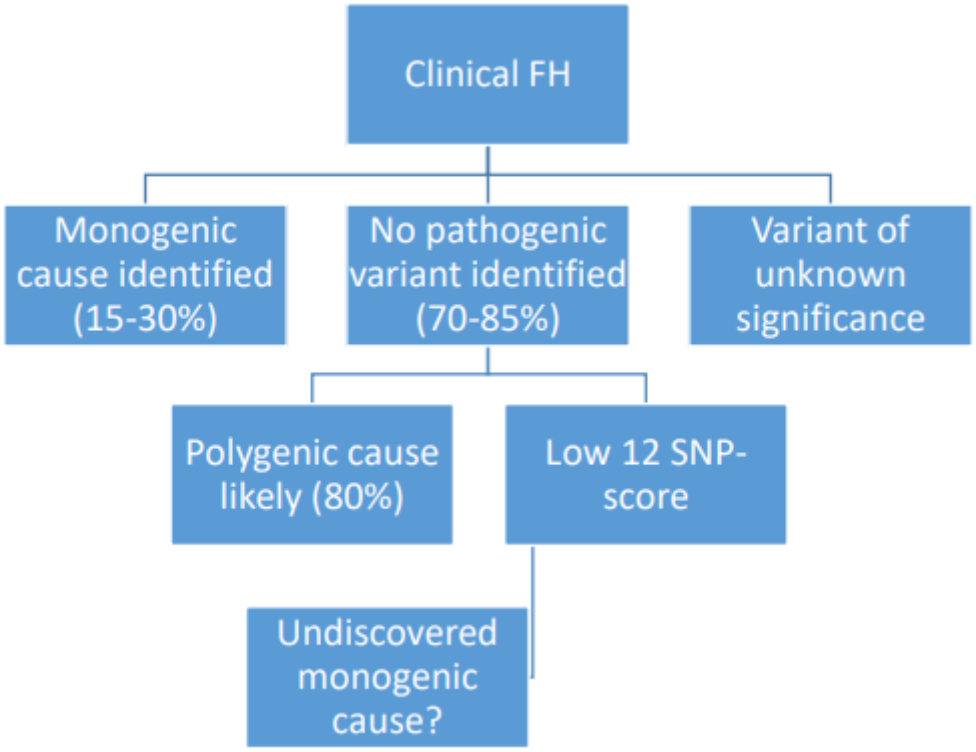
What does the 'Xth decile of the distribution' mean?

The distribution of weighted LDL-C gene scores from a group of 3020 healthy men and women from the Whitehall II study (https://www.ucl.ac.uk/epidemiology-health-care/research/epidemiology-andpublic-health/research/whitehall-ii) was divided into deciles and the range of SNP-score represented by each decile determined. When patient SNP-scores are reported, the decile of this 'normal' population within which the score would fall is given.

For patients who fall within the 1st -3rd decile, this means they have a low SNP-score (below 0.81) and hence a low likelihood of having a polygenic cause to their hypercholesterolaemia. Patients in the 4th and 5th deciles have a borderline likelihood of polygenic disease and those in the 6th decile and above, a high likelihood of a polygenic cause.

How might the score influence my management of patients?



This diagram illustrates the current proportions of patients who are expected to have a monogenic or polygenic form of hypercholesterolaemia. Within Wales our overall rate for identifying a pathogenic variant in index diagnostic testing is 21% (+4% VUS).

In those whom a polygenic cause is likely, evidence suggests that the extent of atherosclerosis is likely to be less (in comparison to monogenic FH). Risk algorithms can be used to calculate these patients coronary heart disease risk and they are likely to be able to be managed in a primary care setting.

In patients in whom there is a high clinical suspicion of FH, no pathogenic variant has been identified using the expanded NGS panel and who fall within the bottom 2 deciles of the SNP-score, it suggests there is potentially an undiscovered monogenic cause.

The information may also help to contribute towards classifying variants of unknown significance. If a VUS is identified but the patient is found to have a high SNP-score, this may suggest the variant is less

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likely to be pathogenic. However, if the SNP-score is low, that may mean the VUS could be pathogenic. The extent to which this might affect which families are recruited for further segregation analysis remains to be determined.

Will the score be reported on all patients or only those in whom no pathogenic variant is identified?

The SNP-score decile will be reported on all samples referred to the All Wales Medical Genetics Laboratory from 01/02/2022 onwards, regardless as to whether a pathogenic variant is detected in that patient or not. Data suggests that patients with a monogenic cause may also have inherited other LDL-C raising SNPs which may be contributing in addition to their phenotype.

How will the score be reported?

As part of the report issued from the laboratory the decile of the 'normal population' within which the score falls will be given alongside information to help interpret how likely it is that there is a polygenic component to the patient's hypercholesterolaemia.

What about patients of non-Caucasian ethnic background?

The data upon which the SNP-score has been calculated is based on samples from Caucasians. Due to the difference in allele frequencies in patients from other ethnic backgrounds it is not known how useful the score would be and whether different weightings maybe required. Currently the score will be reported regardless of ethnic background but caution in interpreting the information is required.

Further questions?

If you have any further questions regarding the reporting or interpretation of the SNP-score please contact Michelle Wood, Principal clinical scientist at the All Wales Medical Genomics Service (AWMGS) (michelle.wood@wales.nhs.uk) or Dr Dev Datta, Consultant in Biochemistry and Metabolic Medicine (Dev.Datta@wales.nhs.uk)

References:

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Talmud PJ, Shah S, Whittall R, Futema M, Howard P, Cooper JA, et al. Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolaemia: a case-control study. The Lancet. 2013;381(9874):1293-301