One test, a lifetime of precision familial hypercholesterolemia reports

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Introduction
Familial hypercholesterolemia (FH) affects approximately 1 in 250 people in the UK, of which less than 10% are diagnosed[1]. Here, we evaluate the utility of the StoreGene whole genome sequencing (WGS) approach to comprehensively characterise individuals with FH.

Methods
Saliva samples from 16 participants who met the Simon-Broome FH diagnostic criteria were sent for DNA extraction and sequencing. Four StoreGene reports were generated: 1) FH 4-gene variant assessment, 2) LDL-C polygenic risk score (PRS), 3) *SLCO1B1* variant linked to Simvastatin-induced myopathy, and 4) Lp(a) concentration gene scores. Results were compared to previous biochemical and panel tests by NHS-accredited laboratories.

Results
One sample per participant was used to carry out WGS, and StoreGene reports were generated in 22 days, vs. 2 samples and 42 days for comparator testing[2]. One sample was discarded due to low mapping quality. 15 WGS samples were analysed yielding 100% concordant results with comparators. Identical pathogenic variants were identified in 9 (60%) of cases, with 11 (73%) cases likely to have a polygenic aetiology (LDL-C PRS > 5th decile). The c-index for Lp(a) concentration between the two methods was 0.79. A pharmacogenomic risk variant in *SLCO1B1* was identified in one participant.

Conclusions
StoreGene WGS showed significant benefits where multiple testing is required, including concordant outcomes with available panel tests, faster turnaround time, a wider range of available tests, and minimised sample collection with environmental savings on laboratory consumables. Further research should measure its cost-effectiveness and clinical utility.

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[1] Familial Hypercholesterolemia Section (NHS England 2020) (accessed 21/08/2023)
[2] SouthWest Genomic Laboratory Hub Target Turnaround Times (accessed 21/08/2023)