Reviewer's report

Title: Targeted genetic testing for familial hypercholesterolaemia using next generation sequencing: a population-based study

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Reviewer: Zosia Miedzybrodzka

Reviewer's report:

It was a well written paper addressing an important question. I think it should be published with revisions.

1 Key thing is that the paper assesses the rate of FH associated mutation in a people with higher than average "cholesterol" within a general practice selected cohort study. Those being tested are unselected for family history as the current clinical practice guidelines recommend. It is interesting that 2% of this population had mutations. It is not clear if these patients would have been selected for testing using the standard clinical diagnostic criteria (Simon Broome or MedPed). AS family history information is available for the generation scotland cohort this should be added if possible. If not possible this limitation of the work should be discussed. The paper gives its main purpose as looking for FH in a general practice population. I feel the paper would benefit from refocusing to indicate the general practice population in whom mutations were found were selected for "high cholesterol" not only being in general practice.

2 There are frequent references in the manuscript to patients with "high cholesterol". This should be more accurately defined throughout- in FH the abnormality is of high LDL cholesterol. The criteria for a definition of high cholesterol used in the study should be clearly set out in the methods. If only total cholesterol was available then this should be explained, and the cut-off thresholds for each category should be defined. In discussion the relation of these to conventional diagnostic criteria should be discussed.

3 Regarding the performance of the next-generation sequencing assay, the coverage of each base / fragment would not meet the recently accepted criteria for clinical grade sequencing. That does not mean these data are not valuable, but I think it would be reasonable to ask the authors to indicate that the assay would require more development before being used in routine clinical practice.

Other specific recommendations:
Add numbers to the % in results.