Reviewer’s report

Title: Mechanisms of change and participant outcomes in a Recovery Education Centre for individuals transitioning from homelessness: a qualitative evaluation.

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Reviewer: Weelic Chong

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Here, Carlson et al sheds light on an important topic that were previously less focused on. One of the rationales for this study is a previously published study which enrolled 44 healthy Jewish centenarians. Participants had underwent WGS, and there were pathologic variants in certain genes that were associated with heritable diseases. Yet, these participants did not have the disease, which suggests that some pathologic variants have incomplete penetrance.

The long life familial study (LLFS) is a cohort of participants who are old and relatively healthy, their siblings, and children. Having a record of family pedigree thus increases the usefulness of this data, but mostly to reinforce that there were no heritable disorders that were clinically significant going on. The larger sample size of broad European descent were meant to extend the generalizability of that study.

The key result was that pathogenic variants can be found in the LLFS cohort at a prevalence rate similar to public databases of the general population (i.e. gnomAD and some ClinVar). The study suggests that the penetrance of pathologic variants may be lower in the general population as compared to targeted patient populations with a strong family history of specific Mendelian disease.

The study data supports the ACMG clarification on the list of 59 genes. The ACMG had clarified that the incidental genetic findings after clinical WGS or WES to be made known to patients, but this guidance is not to be applied for general population screening. Thus, more research on genotype-phenotype associations is needed.

I think this study is pertinent, and is important, particularly when it comes to data that tells us that even "pathologic" variants identified from well-conducted studies of cohorts with diseases, these variants are not so pathologic for the general population.
Note that the LLFS study had 464 genes sequenced. Of these, 25 genes were associated with Mendelian defects, familial cardiovascular, familial cancer predispositions, familial neurodegenerative disorders. Of these, 7 were on the ACMG 59. (The other 18 were associated with autosomal recessive conditions.) Of course, if all 59 genes could be used for analysis, that would be much better, but I think overall this is still fine. The other interesting thought is that the public database of the general population that was used for comparison is gnomAD. Its not perfect because this is an aggregate of many cohorts, many different research topics, some of which have participants that have been diagnosed with diseases, for example there's a lot of TCGA, which would be fine for looking at diseases other than cancer...e.g. familial neurodegenerative disorders. but taken overall, I think it would be ok with saying gnomAD represents the general human population. (The prevalence result hinges upon this.)

Overall, the study is well-written, language is clear and needs no editing, the results are clear, the discussion is relevant to the results and the bigger picture, the conclusions are written conservatively, and the methods are well-described. I have no reservations regarding the publication of this article.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
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Yes

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