Reviewer’s report

Title: Value-based genomic screening: Exploring genomic screening for chronic diseases using triple value principles

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Reviewer: Wylie G. Burke

Reviewer's report:

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The authors propose the use of "triple value" principles to guide the use of genomic screening - that is, consideration of allocative, technical and personal value. They argue that this approach will assist clinicians and policy makers to make reasoned decisions about difficult trade-offs in the use of genomic screening. This approach seems sensible and is justified in the paper. However, the paper fails to address three challenges that are crucial in the current discourse about genomic screening. As a result, the discussion offers only a limited contribution to the discourse. These challenges are:

1- How should allocative and technical values be applied to the use of screening based on exome or genome sequencing? The difficulty here is that the evidence base for clinical utility is highly variable for different genes. What genes should be included if screening is accomplished in this fashion? How should this be decided? Perhaps the authors see the values principles as providing answers to these questions. If so, it would be helpful to discuss these issues explicitly. For example - how would a values-based approach evaluate the ACMG recommendation for opportunistic screening of 59 genes when exomes are done? Would the technical evaluation be done separately for each gene, or should policy makers ask for outcome evidence on the use of the 59-gene panel? How does this choice affect allocative judgements? Without this kind of specificity, it is difficult to see how the values would guide decision-making.
2- As a corollary to the first point, it would seem that a major question for genomic screening is whether it is acceptable to censor some genomic information when massive parallel sequencing is used. Is it OK to screen for the ACMG list of 59 genes and deliberately choose not to report on non-actionable genes, such as early-onset Alzheimer Disease? If such censoring is appropriate, who decides what information is reported and what information is not reported? How would the three values assist in such decision-making?

3- Finally, the authors omit discussion of the potential for a major conflict between the allocative and technical values on the one hand and personal values on the other hand. The current literature suggests that many people appreciate the opportunity to have exome- or genome-based screening - with reporting not only of the ACMG list of 59 genes but also other genomic risk information, including polygenic risk profiles. Yet the evidence for all these forms of genomic screening is very limited. How should clinicians and policy makers respond if allocative and technical analyses argue against the use of exome-based screening (or any other form of genomic screening), while patient surveys demonstrate a strong preference for such screening?

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