Reviewer's report

Title: Targeted next generation sequencing as a tool for precision medicine

Version: 1 Date: 28 Mar 2019

Reviewer: Matthew Ducar

Reviewer's report:

Overall an interesting article highlighting the potential utility of genomic screening in a clinical setting. Comments are relatively minor:

When listing concordance values, please include the confidence interval as well.

Switching between different sets of reference SNPs seems odd. When performing analysis of sequencing data for 146 pharmacogenes they used ESP and 1K genomes as reference. Later they used ExAC and dbSNP for population frequencies. Why not use gnomAD at both steps? It is a much larger data set.

The authors mention the need for "careful probe design" to sequence "genes with high sequence homology, nearby pseudogenes and complex structure". The methods presented only indicate using the Illumina Design Studio but don't detail any special steps taken for capturing these regions.

Algorithms such as SIFT, PolyPhen-2, and CADD are much better at predicting loss of function events than gain of function events. The authors did not discuss the expected higher false negative rate for correctly characterizing rare/novel gain of function variants of clinical interest.
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?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I recommend additional statistical review

Quality of written English
Please indicate the quality of language in the manuscript:

Needs some language corrections before being published

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