Reviewer's report

Title: Cumulative BRCA mutation analysis in Greek population confirms that homogenous ethnic background facilitates genetic testing

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Reviewer: Amanda Toland

Reviewer's report:

The manuscript by Tsigginou et al. is a review of the literature of BRCA1/2 genetic testing in the Greek population with the goal of identifying mutations that are more frequent in that population. After a review of the literature they identified 14 studies that met criteria. From these they identified 6 mutations that are frequent in Greek individuals with a personal and/or family history of hereditary breast cancer. These 6 mutations make up approximately 60% of all the mutations described in these 14 studies. The authors suggest that this information might be used to streamline testing in individuals of Greek ancestry. Despite the potential clinical impact there are a number of issues that need clarifying. As important, the manuscript is very poorly written and needs substantial editing.

Major:

There is a range of breast cancer risks associated with BRCA1 and BRCA2 mutations depending on the publication. It is more accurate to include a range (i.e. 50-85%) than a single number which is at the higher end of reported risk.

Polymorphisms typically refer to gene variants that are present at 1% or higher in a population. Typically founder mutations, even though more common a particular population, are less than 1%. The authors should be more clear on their nomenclature. (Additional references on founder BRCA1/2 mutations might provide better rationale here. There are numerous examples ranging from Iceland, the Dutch population, Mexican populations and of course, Ashkenazi Jewish individuals.).

Mutations in BRCA1/2, although constituting a majority of known familial risk for breast cancer, actually occur in less than 50% of all hereditary breast cancers. The authors should check for the most recent proportion of hereditary breast cancer that is thought to be due to BRCA1 or 2.

The exact search terms for the PubMed Search should be included in the methods. The authors should also mention how the majority of mutational analyses were done for these studies (or this could be included in the supplemental materials—Sanger Sequencing? Were rearrangements looked for?).

The authors should define in this study what they mean by founder mutation.
How common does a mutation need to be within a population to be called a “founder”?

The authors should address how testing for founder mutations may change given the shift from Sanger sequencing to next-generation panel testing. Is there a cost-benefit to founder mutation testing over these other technologies? Should founder mutation testing be done first and then reflex to other modes of testing?

The paper needs editing for grammar/readability.

Minor:
Gene names should be italicized.

These numbers don’t make sense. This should be reworded, “60% of BRCA1 & 2 mutations and 70% of BRCA1 mutations identified in Greek populations are 6 mutations”

There are numerous awkward sentences beginning with the title (should have an “a” before Greek population).

The running title is a bit odd as it sounds as if there is a Greek form of BRCA analysis.

& should be spelled out as “and”

There is no space between BRCA and 1 or 2.

It is totally unclear what is meant by, “blaring that many carriers do not”

Unclear what this means, “Increasing the Greek experience in genetic syndromes, in a recent study”

Level of interest: An article of limited interest

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests