Reviewer’s report

Title: Genetic variants of prospectively demonstrated phenocopies in BRCA1/2 kindreds

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Reviewer: Katherine Agre

Reviewer's report:

I applaud the authors for a very well written paper. I think this brings interesting data to an area that continues to be understudied. However, I do have comments and questions after reading through this paper.

1) While the patient population is very specific, the n in this study is small. And I felt like information was missing regarding were there other women who were not included in this analysis. More information regarding selection of participants would be helpful. On my first read-through of the paper, it was difficult to figure out who the patient population was. It was written, at multiple points, that the women were those who had tested negative for a familial BRCA1 or BRCA2 mutation, and then had developed breast and/or ovarian cancer. But then in the abstract it says "We identified 10% (5/48) of the cases to carry pathogenic variants in ATM, BRCA2, MSH6 and MUTYH genes, of whom two were from families with a known path_BRCA1 (15% of 13 cases) and three from a demonstrated path_BRCA2 (9% of 35 cases)" which does not seem to echo the same patient population. I would encourage consistency in writing across the paper in terms of who the patient population is.

2) I question whether the recommendation to test all individuals with family history of a known pathogenic BRCA1 or BRCA2 mutation is necessary. In the cases of the patients who were found to have Lynch Syndrome through this study (not including the MSH6 mutation), it sounds as if the participants met criteria and should have been offered this testing prior to their diagnosis. If an individual is having a comprehensive family history obtained when they are being tested, this could reduce the need for further testing in many scenarios. I wonder if this was performed for the participants in this study? I think including the family histories of the other participants who tested positive would be helpful in assessing this.

3) Additionally, many of the genes included on the panel do not have concrete associations with breast/ovarian cancer (MAP3K1, RAD50B, CDK2, POLE) so while there is no recommendation to test these genes, I wonder why they were included in the analysis?

I appreciated that the authors highlighted the challenges of offering full panels to individuals seeking solely single site testing including risk for uncertainty and unexpected findings.

Overall, I think this is a well-written paper with an interesting concept that fills a gap in the knowledge regarding increased cancer risks in mutation-negative family members.
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An article of importance in its field

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