Reviewer’s report

Title: Mutation analysis of PALB2 in BRCA1 and BRCA2-negative breast/ovarian cancer families from Eastern Ontario, Canada

Version: 2 Date: 3 March 2014

Reviewer: Melissa Southey

Reviewer’s report:

The report by Hartley et al is well written and well presented overall. It contributes to the growing literature related to genetic testing for PALB2 mutations in the context of breast cancer susceptibility and risk management.

I have some Minor Essential Revisions.

1) The use of the word “moderate” risk gene is unfortunate. Certainly much of the literature and lay reports refer to mutations in this gene as “moderate risk” but this is unfortunate, given the lack of evidence for such a designation. Could the authors be more balanced in this assessment of risk in the text - could PALB2 be simply a “breast cancer susceptibility gene” (eg first line of abstract, second para of the introduction)?

2) In the era of gene panel testing the second sentence of the abstract appears to be inaccurate. Testing of PALB2 could be done along side the testing for BRCA1 and BRCA2 and be very efficient? Also it is not the prevalence (frequency) of PALB2 mutations that are most challenging in genetic counseling - rather it is the uncertainly around the penetrance and treatment options.

3) Second para of the introduction: “2.3 to as high as 6.0 depending of the methods used”…do the authors mean statistical methods or molecular methods or study design of something else by “methods used”? 

4) The last para of the introduction would benefit from reference to the onset of panel testing in diagnostic services and what impact this is having on this subject.

5) Material and Methods: I think a subheading for the
   a. N1096S testing description and
   b. The LOH methods description

   would be helpful for clarity.

6) Results and discussion para 5: The cumulative risk of breast cancer is not supported/reported in all references cited (5,7,11,12,13,14,19) this text should be adjusted for accuracy.

7) Results and discussion para 7: The work has been conducted on research participants rather than “patients”, in my opinion.

8) Results and discussion para 7: It is interesting that the literature has a number of reports of ER-PR-/basal like breast cancers in PALB2 mutation carriers - but
how many of these are related to the one PALB2 mutation (ie the Finnish founder PALB2 c.1592delT)? Could this tumour phenotype be a feature of this specific mutation?

Level of interest: An article of importance in its field

Quality of written English: Acceptable

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