**Reviewer’s report**

**Title:** BRCA1 and BRCA2 mutation spectrum - an update on mutation distribution in a large cancer genetics clinic in Norway

**Version:** 0 **Date:** 15 Nov 2017

**Reviewer:** Jan Oosterwijk

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The paper describes an update of the BRCA1 and BRCA2 mutation spectrum in half of the Norwegian population. It concerns retrospective laboratory data over a 15 year period. Since no correlation is made to any phenotypic information, it is mainly population genetic. Therefore a direct link to clinical practice is weak.

I have some questions:

Given the fact that de novo mutations in BRCA1 and BRCA2 are supposedly very rare, I don't quite understand the relevance of the distinction between founder mutation and (high, moderate, less) frequent mutation. It's just a continuum.

The study population consists of 981 families of which 68% had a BRCA1 and 32% had a BRCA2 mutation. But nowhere I can find how 'family' has been defined. We know that separate nuclear families eventually show to be branches of large pedigrees, i.e. families.

What is the scientific message behind the given number of mutation carriers per family in the results section?. When we don't know family size nor phenotype, nor referral/testing criteria, this doesn't contribute much I think.

Given the fact that founder mutations are present in Norway, it would be interesting what their contribution is to the carrier frequency. This may affect clinical choices as to whether in presymptomatic setting, DNA testing should be more comprehensive than just for the familial mutation (as in Ashkenazi Jewish populations). This is hardly touched upon in the paper. (top of page 8 '.......when more than one mutation is suspected…)

P10 line 56: 2 out of 5 is too small a number to say it's 40%

P11 line 56: what is ment by 'quite extreme in both ends'? I see only one end.

The discussion part could be way much shorter.
In general, the clinical relevance of this paper is rather restricted: not only are we shifting towards NGS, but also towards breast cancer gene panel testing. Moreover, initial founder mutations, based on historic population structures and geographic/ethnic or religious boundaries are quickly deluting due to migration. Ethnicity and/or genetic background are rapidly becoming more diverse, which means that also in Norway, the relevance of this data is becoming less pronounced.

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