Reviewer’s report

Title: PALB2: research reaching to clinical outcomes for women with breast cancer

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Reviewer: Annemieke van der Hout

Reviewer's report:

This is a consise and well written review of the current knowledge of PALB2 germline mutations and their clinical consequences. As the focus of this review is on the relation between PALB2 en hereditary breast cancer, it zou goed zijn to have the words hereditary breast cancer in the title. As PALB2 is (at least) also involved in Fanconi anemia and pancreatic cancer

In this review the authors describe why it is now justifiable to include mutation scanning of PALB2 in the search for germline mutations in cases of familial breastcancer. As many laboratories are in the process of setting up (breast)cancer gene testing panels this is much needed information.

Some comments:

1. As the focus of this review is on the role of PALB2 in hereditary breast cancer and not or less on other diseases in which PALB2 is involved like pancreatic cancer or Fanconi anemia, breast cancer should be mentioned in the title of this review.

2. In the abstract it is stated that 'women who carry mutations in the PALB2 gene are at similarly elevated breast cancer risks to those who carry mutations in BRCA2'. This should be loss-of-function mutations as the authors discuss at the and of this abstract that 'classification of the vast array of non-loss-of-function genetic variants identified in PALB2 is in its infancy'.

3. In the introduction, the authors write that 20% of women who undergo testing are found to carry a mutation in BRCA1 or BRCA2, and that the remainder of the tests are
uninformative. This is an unclear statement. In half of the cases in which a mutation is found in BRCA1 or BRCA2 the outcome of the test is still uninformative because the mutation found is a 'variant of unknown clinical significance'. It is better to mention the percentage of pathogenic or causative mutations. How high this percentage is, is dependent on the inclusion criteria for women in the testing program, and is nowadays often much lower than 20%.

4. On page 6 the 'PALB2 interest group' is mentioned for the first time, reference to the list of references [36] is missing here.

5. There is no reference in the main body of the review to figure 1. The majority of the text of the legend can be incorporated in the body of the review.

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