Reviewer’s report

Title: Testing for BRCA1 mutations using a combination of homogeneous selection criteria and immunohistochemical characteristics of breast cancers

Version: 1 Date: 17 August 2009

Reviewer: Alison P Klein

Reviewer’s report:

The association of BRCA1 mutations and basel-medullary carcinomas of the breast, which are typically ER-/PR- and HER (weak) is an important factor to consider when recommending BRCA1 testing and we applaud the authors with exploring this in the context of Italian HBOC kindreds.

While the authors do demonstrate how BRCA1 IHC among those with a strong family history of breast and ovarian cancer predict those patients who are likely to be BRCA1 carriers and demonstrate this in modest cohort of FBC kindreds the clinical utility of this is not discussed. Several previous studies, most notably those by Lakhani, have show the predictive power of IHC in larger cohorts of FBC kindreds. Furthermore, the overall high prevalence of BRCA1/2 mutations (10.8% and 9.7%) in this population, suggest that these kindreds should be genetically tested for BRCA1/2 regardless of IHC status. In fact, the high sens/spec of IHC is only applicable to individuals with a strong family history of breast/ovarian cancer.

Major Revisions:

1) More detail needs to be provided on the ages cases who were ER+/PR+ and BRCA1/2-, ER-/PR- is far more common in young onset, premenopausal breast cancer.

2) A detailed description of the family history of the cases tested is needed. Number of breast cancer case and ages, number of ovarian cancer cases and ages. Numerous risk models, BRCAPRO, and others exist, reporting the pre-test carrier probabilities will be of interest.

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.