Reviewer's report

Title: Incorporating Medical Interventions into Carrier Probability Estimation for Genetic Counseling

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Reviewer: David Euhus

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General
Risk prediction plays an integral role in medical decision making. Because BRCA gene mutation testing is very expensive it is reasonable to perform it only in individuals with a reasonable likelihood of carrying a mutation who would act on the information to reduce their risk of dying of the associated cancers. There are more than a dozen mathematical models for predicting BRCA gene mutation status based on personal and family history of breast and/or ovarian cancer. Because there is considerable overlap in the age-specific breast and ovarian cancer incidence curves for mutation carriers as compared to non-carriers none of these models is highly accurate (ROC AUC’s < 0.8). Adding additional information to the models, such as the phenotype of the breast cancers that have developed in the family, improves the discrimination considerably. Katki and colleagues seek to improve mutation prediction for the BRCAPRO model by incorporating information on oophorectomy which directly impacts the penetrance of BRCA gene mutations. This manuscript is an incremental advance that appropriately increases the sophistication of a risk prediction model to better match the complexity of the real world. It is only an opening foray, however, as it appears that the effects of oophorectomy are more complex than can be accounted for by a single hazard ratio. Though most clinicians are resistant to use models that require a great deal of up front data collection and entry, this is likely unavoidable in the complex field of cancer genetics. Increasing the number of factors considered by these models makes them more difficult to use in the clinic, but this must be accepted if the accuracy of risk prediction increases as well. As these models increase in complexity, it will be important to objectively determine which variables impact clinical decision making in a tangible way.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
1. Page 3: “...women can reduce ovarian cancer risk with frequent CA-125 tests or transvaginal ultrasounds”. These tests do not reduce the risk of developing ovarian cancer and have not been shown to reduce ovarian cancer-specific mortality.

2. Page 4: “In particular, we estimate that while carriers have a reduction of 88% in the risk of ovarian or peritoneal cancer after oophorectomy (see Methods), non-carriers enjoy a 95% risk reduction[19].” Reference 19 lumped primary ovarian and primary peritoneal carcinoma together so, though the statement is accurate in that respect, I am not aware of any evidence to suggest that the risk of primary ovarian cancer after oophorectomy is different in carriers as compared to non-carriers, nor am I aware of any evidence to suggest that oophorectomy reduces the risk of primary peritoneal carcinoma. This requires clarification.

3. Page 8: “For example, an oophorectomy at age 40 is more likely to be too late for carriers than non-carriers because the path to cancer is accelerated in carriers and thus carriers may progress more rapidly to an advanced stage where oophorectomy cannot stop the process.” I am not sure I follow the reasoning here. Molecular studies suggest that primary peritoneal carcinomatosis is multi-focal and multiclonal arising directly from the peritoneal lining. Oophorectomy does not stop progression at any age. It may occasionally result in the removal of an occult, localized ovarian cancer, but in this case, the relative would be classified as having had ovarian cancer. If the author is aware of data suggesting that ovarian function increases the risk of primary peritoneal carcinoma it should be cited here.

4. Page 14: “Also, the hazard ratio for breast cancer for mutation carriers does not appear to depend on pre-oophorectomy disease history, age at oophorectomy, time since oophorectomy, or by BRCA1 vs. BRCA2.” This statement does not seem consistent with the information reported in reference 15 and the situation seems too complex to be adequately handled by a single hazard ratio. For instance, the reduction in breast cancer risk was only significant for BRCA1 mutation carriers (OR = 0.43, p = 0.00006) and not BRCA2 mutation carriers (OR = 0.57, p = 0.11), oophorectomy <= 40 years of age was associated with an OR of 0.36 as compared to 0.50 for procedures performed between 40 and 50, and oophorectomy only reduced the breast cancer risk for 15 years following the procedure but not at all after 15 years (OR = 1.32).
Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
5. Page 5: “...but is an increase of 40%. Percent change is useful because...” I am not sure what is meant by “useful.” Percent change may be used as a metric to measure the impact of intervention information on carrier probabilities and may highlight the multiplicativity of the effect, but in the clinic 1.4% is the same as 1%.

6. Page 5: “...then the act of a relative choosing oophorectomy (or not) does not have extra information about carrier status.” Does not significantly impact carrier probabilities?

7. Page 5: “These scenarios show that interventions have more impact on the carrier probability as the benefits of intervention differ more between carriers and non-carriers.” Have more impact on carrier probability than on what?

Discretionary Revisions (which the author can choose to ignore)
8. Page 4: “...but she got oophorectomy at a young age.” ...underwent oophorectomy...

9. Page 4: “...the mother got cancer...” ...developed cancer...

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes

Declaration of competing interests:
I declare that I have no competing interests.