Reviewer’s report

Title: Adherence to National Comprehensive Cancer Network Guidelines for BRCA Testing among High Risk Breast Cancer Patients: a Retrospective Chart Review Study

Version: 0 Date: 28 Jun 2019

Reviewer: Cathryn Koptiuch

Reviewer's report:

The authors have chosen to assess an important area within the field of hereditary cancer genetics: analyzing the genetic testing rate of at-risk patients seen by community clinic providers and assessing how this practice can be improved, some key decisions made in how the data was analyzed and presented necessitates that the authors repeat this analysis slightly differently as noted in the comments below. Thank you for your effort on this publication!

Overall statements
The authors do not mention whether or not multigene panel testing was ordered for any of these patients as well? This is actually just as important as BRCA testing as billing codes only exist for BRCA, but there are NCCN management recommendations for other high-risk genes. Providers ordering only BRCA testing can actually hurt a patients ability to get more informative, comprehensive testing in the future if they maintain the same insurance between BRCA testing and pursuit of more comprehensive testing. As NGS with multigene panel testing is now the standard (including actionable genes on panels at a minimum) within the genetics community, it would be useful for the authors to include this data if available, or at least comment on it in the discussion if not available.

While the authors include in the discussion that published literature has assessed how testing rates have changed over time (Pg10 Lines 193-202), the authors themselves have not assessed their own data this way despite collecting data on hundreds of women over a four year time period. It would be great if the authors could include this assessment from their dataset to compared to the studies referenced in the discussion.

Entire analysis has to be re-worked with patients from HBOC families separated from the rest of the dataset in order to draw any proper conclusions.

Content comments
Pg1 Line 25: Suggest modifying "for their relatives" to "for both the patient and their relatives" (or something similar) for accuracy.
Pg2 Line 3: Instead of "2013 or later", include end date (2017)
Pg4 Line 98: Was the availability of Her2 receptor status a criteria or just ER and PR? Requiring Her2 would most often exclude patients with diagnoses o f DCIS who also qualify for testing, hence the clarification request.
Pg5 Line 101: Please clarify if the same NCCN guidelines used for the entire study or was the applicable version of NCCN guidelines used based on the year the patient was diagnosed (ideal).
A huge challenge to performing this type of analysis is the methods required to assess whether or not a patient has received genetic testing as there is no place in most electronic medical records for this type of information to be documented. Readers would benefit from knowing exactly how this information was mined from the EMR into the eCRF, especially for individuals that had negative genetic testing as documentation of LPV and PV status is a capability of many EMR but this is not the case for negative results.

The authors have inflated the difference between metastatic TNBC and metastatic Her2- patients by presenting the percents with a history of ovarian cancer as 2% and 5%, respectively, when the supplemental table reports these numbers as 2.9% and 4.9%. It is inappropriate to round one number down by 0.9% and the other up by 0.1%.

Redo table to separate women with one close relative with BRCA pathogenic variant from the rest of the data and reanalyze data for yield in other categories accordingly. Being a member of a HBOC family is seemingly confounding the data in the rest of the table as it cannot be separated out by readers.

Including the 68 women who had at least one close blood relative with a known BRCA1/2 pathogenic variant in the overall findings of positive yield seems misleading as it's such a greater likelihood that they'll test positive. It makes more sense to present those outcomes separately as 62 of 316 (19.6%) were positive without known family variant a 52 of 68 (78%) were positive with a known pathogenic family variant in a close relative. This is an important distinction.

Including any reference to an overall 30% positive yield is completely inappropriate analysis of this data especially with an inaccurate statement that this high yield is driven by TNBC and metastatic diagnoses. It is not. IT is driven by known family variants.

We encourage the authors to strongly consider the WC "mutations". While this was a long-accepted term historically, the genetics field has been encouraging all providers to use the term "variant" instead of "mutation". We suggest the authors consider switching to the terms (and corresponding abbreviations) "pathogenic variant (PV)", "likely pathogenic variant (LPV)", and "variant of uncertain significance (VUS)".

We encourage the authors to use italics when referring to the names of genes, e.g. BRCA1 and BRCA2.

WC makes it seem that this was the referral rate among women with hereditary cancer conditions. Please modify so it's clear these are women at increased risk for hereditary cancer instead.

The definition "proportion was calculated out of number of patients screened in each risk group" still leaves me wondering what this is referring to. Is this the proportion of individuals who received genetic testing? If so, genetic testing is not considered "screening". Revision of WC requested.
Can in this information be stratified by the year the patient was diagnosed? I imagine that these numbers improved over time for those with a family history of male breast cancer or aggressive prostate cancer?

The authors have left out the abbreviation they use most-often, BRCA, as it pertains to BRCA1 and BRCA2.

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