Author’s response to reviews

Title: BRIP-1 germline mutation and its role in colon cancer: Presentation of two case reports and review of literature

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Reviewer 1

1. The conclusion should be changed to state that the BRIP-1 gene "may" be associated with colon cancer predisposition and "should be further investigated."

Change

I agree with the reviewer suggestion and made following change.

(Conclusion section, Page 11, line 25-26) – “Our case reports suggest that germline BRIP1 mutation may be associated with colon cancer predisposition and should be further investigated”.

2. I would delete the statement that it is now time to put BRIP-1 on clinical gene panels. Even the NCCN reference that the authors quote list several candidate CRC genes, each of which have more indication than the BRIP-1, and state that their inclusion on clinical panel tests is questionable at this time. It would thus be more appropriate that it be said that BRIP-1 be put on research level panels. Having a clinical result at this point would be confusion to clinicians as to how to proceed.
I agree with the reviewer that we do not have sufficient evidence to routinely put BRIP1 on hereditary colon screening multigene panel. We tested this patient for BRIP1 germline mutation primarily based on next generation testing. I have made the following changes

(Discussion section, page 10, line 47-49)- I have deleted the following sentence- “and that colorectal cancer should be added to the list of tumor types (which includes breast and ovarian cancers) for which BRIP1 mutation carriers have an increased risk”.

(Discussion section, page 11, line 19-20)- I have rephrased the last lines in discussion section- “Larger studies will provide more evidence to ascertain if this association is strong. This information can be obtained with the addition of the BRIP1 gene to research level panels evaluating germline mutations and colon cancer predisposition”.

Reviewer 1- Minor comments:

1. In the first case where the statement is made that "no other germline mutations" were identified, it should be added "with the panel testing used, so as not to confuse that next gen sequencing found no other mutations.

Change- (Case presentation case report 1- Page5, line 5)- “No other germline mutations were identified with the panel testing used”.

2. In the discussion where it is stated that 3% of CRC samples have BRIP-1 mutations, it would be more complete and eliminate any confusion if it was stated "samples" be replaced with "colon cancer tissue samples."
Change- (Discussion section, page 10, line 30) – “BRIP1 mutations have been reported in 3% of the colon cancer tissue samples analyzed in the colorectal adenocarcinoma TCGA (The cancer genome atlas) dataset”.

REQUESTED REVISIONS: Typographical errors were corrected in the revised manuscript

There are several typographical errors in the present manuscript and are listed below:

1. Page 2, line 12: cancer-related
2. Page 2, line 21: 20%
3. Page 2, line 26: genes should be italicized throughout the manuscript
4. Page 2, line 52: has not been previously reported. We describe
5. Page 3, line 27: rectosigmoid
6. Page 3, line 30: A CT scan of the chest and abdomen…
7. Page 3, line 33: rectosigmoid
8. Page 3, line 36: Pathology showed an invasive, moderately-differentiated…
9. Page 3, line 38: subserosal
11. Page 4, line 5: She was staged as IIIB disease
12. Page 4, line 9: fluorouracil
13. Page 4, line 19: 5-fluorouracil
14. Page 6, line 18: She was assessed as stage IV given metastatic…
15. Figure 3 legend: Family pedigree…
16. Page 7, line 21: genetically-determined
17. Page 7, line 54: treatment planning, e.g., analyses of…
18. Page 8, line 8: can help predict the presence of germline mutations.
20. Page 9, line 35: A 31-gene…
22. Page 10, line 10: NCCN recognized the..
23. Page 10, line 38: fluorouracil
24. Page 10, line 39: 5-fluorouracil