Reviewer's report

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

Version: 0 Date: 13 Feb 2019

Reviewer: Randall W. Burt

Reviewer's report:

This is a very interesting report that suggests BRIP-1 may be a colon cancer susceptibility gene.

The two cases of CRC that have germline mutations of BRIP-1 make a good argument for further investigation of this gene as a CRC susceptibility gene. Multiple CRC cases in a single family would be more convincing. That said, this is an important observation that should be further investigated.

I would not agree that it is now time to put this gene on multi-gene panels. It should first be examined in a research, not a clinical setting.

Thus I would suggest:

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."

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.

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.

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."
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
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