Reviewer’s report

Title: Identification of genetic variants for clinical management of familial colorectal tumors

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Reviewer: Randall W. Burt

Reviewer's report:

Comments:

This study is well conceived, timely, well written, incredibly well carried out and well reported.

The weak point is that after all the detailed, expensive, highly technical, and incredibly well done genetic work, nothing was found of clinical significance. CHEK2 is well known to affect colon cancer susceptibility only very modestly. Finding a pathologic mutation in CHEK2 certainly does not affect risk or screening guidelines more than the family history that is already present. Thus does one really need to ever check for CHEK2 in the clinical setting?

But the strong point of this study is precisely the same as the weak point. All the genetic work that was done really doesn't help clinically. So should one bother?

This is relevant issue presently. Some commercial genetic testing companies are already adding CHEK2 and similarly modest risk genes to colon cancer genetic testing panels. And when mutations are found in such genes, it is difficult to know if screening should be changed at all. Thus, should one worry a family with telling them they have a mutation for colon cancer when it doesn't even make enough difference to do genetic testing in other family members, and it rarely would change screening guidelines.

The present investigation thus hits this issue head on. I would suggest it tells us that outside the well known high risk susceptibility genes, we don't really know what to do with the gene mutations that only modestly affect susceptibility. The same comments apply for the VUS problem. Many VUS's will be found with genetic testing and the more loci tested the more VUS's that will be found---what do we do with them. The authors have done an outstanding job looking at the VUS mutations they found. But most were found to be of no consequence and others were even in conflict with the various VUS testing approaches. Are commercial companies going to do all this for us clinically---very unlikely, so the clinician is left with little helpful information and often serious confusion as to what to make of the results they are given.

Thus, again, outside the highly penetrant, high risk susceptibility genes, there is little utility in adding a list of modest susceptibility genes to genetic testing panels. Such genes and loci remain in the realm of investigation where a group like the one of this investigation can deal with the issues properly.
I would only suggest the authors add some clinical comments if they wish, as it would strengthen the conclusions.

**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?**
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Consultant for Myriad Genetics 4 years ago, but not since.

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