Reviewer's report

Title: MSH6 and PMS2 Mutation Positive Australian Lynch Syndrome Families: Novel Mutations, Cancer Incidence and Age of Diagnosis of Colorectal Cancer

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Reviewer: Noralane M Lindor

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The paper is a description of 35 families from Division of Genetics, Hunter Pathology Service in New Castle, South Wales, Australia, that have deleterious mutations in either MSH6 (n=29) or PMS2 (n= 6). As families with mutations in these genes are quite rare, all new information is a welcome addition in the medical literature.

Major: This paper would be more useful if there was additional information provided about how these families were ascertained. It appears that the minority of families fulfilled the clinical Amsterdam II criteria. Is there universal tumor IHC testing going on in South Wales? If so, this should be stated. If not, it is still vital to know how these families were picked up. The method of ascertainment can greatly influence the results of even descriptive studies, such as ages at diagnosis. If selection on clinical features was used, then those features become a self-fulfilling prophesy regarding what is observed.

Major: Would include the ethnic background/race of study participants.

Minor: Would include the colonic subsite wherever available.

Major: The authors have not attempted to assess penetrance or cumulative risks which is entirely appropriate. The descriptive tables of the cancers that occurred in families are really not helpful. These would be much more meaningful if there was some indication of how many relatives in each family existed, and how may were first degree/second degree etc to the gene mutation carriers. A numerator is of very little value without a denominator.

Minor: The mutations that are included in this study appear to all be unequivocally deleterious. In the tables, would suggest modifying use of the terms “aunty” and “mum” to more standard words.

Minor: Did not see the largest series on MSH6 mutation carriers referenced or compared. Please see Risks of Lynch syndrome cancers for MSH6 mutation carriers.

Baglietto L. et al. Journal of the National Cancer Institute. 102(3):193-201, 2010 Feb 3. Authors conclusions should be compared with this study to be current.

Minor: Last paragraph: Disagree that half of Lynch Syndrome families have no identified gene mutation. If one defines Lynch Syndrome in the usual current
manner as the syndrome with a DNA MMR defect (either proven germline mutation or evidence of MMR defect on tumor testing), then the number is not nearly so low. I think the author is referring to the Type X families in which the Amsterdam I criteria is met but no DNA mismatch repair defect is detectable in tumor. Half of Amsterdam I families do not have DNA MMR defect.

Also would disagree that GWAS studies hold any promise to find rare highly penetrant gene mutations. The new exome sequencing likely will succeed in this area, but the GWAS are looking for common, low penetrance genes by definition.

Appreciate that the authors are sending their mutation data to the databases for MMR gene mutations, which is a good reminder for readers to do the same.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.