Author’s response to reviews

Title: Survival by colon cancer stage and screening interval in Lynch Syndrome: a Prospective Lynch Syndrome Database report

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Dear Editor,

Thank you for the positive and constructive review comments of the manuscript above. We have revised the manuscript in line with the reviewers’ suggestions, and we respond to the reviewers as follows:

Reviewer #1

-Comment: I think the limitation of the study is the relatively limited number of cases; although it is mentioned by the authors in the discussion, it should be more emphasized, even in the abstract to avoid confusion on drawing new guidelines.

Response: Yes, agreed. Which is why we will use the upcoming PLSD business meeting in Barcelona next month (https://ehtg.org/meeting/programme/) to design the obvious follow-up study: Inviting all contributors to the PLSD not having to contributed to this study, to repeat this study in an independent data set to validate the results in this paper. This is now also mentioned in the text (Abstract and Discussion Sections)

- Comment: Maybe include/clarify in the abstract that this observation mainly involves MLH1 and MSH2 carriers.

Response: Among the 186 cases with one prospectively detected colon cancer for survival analysis, 96 path_MMR carriers having had no prior or prevalent cancer in any organ were later prospectively diagnosed with colon cancer at age 65 years or younger. These 96 paths_MMR carriers were selected for survival analysis and included 77 path_MLH1, 17 path_MSH2 and 2 path_MSH6 carriers. It has been clarified in the Abstract section, as suggested. The referee points to a logical problem: The risk for CRC in path_MSH6 and especially path_PMS2 carriers under follow-up is so low that numbers are insufficient for calculating risk after prospectively detected CRC. With increasing numbers of path_MSH6 carriers this may be overcome, but the risk for CRC under follow-up in path_PMS2 carriers is so low that there may possibly never be such a study.
- Comment: What was the median time in years of follow-up?

Response: Median time from previous colonoscopy to colon cancer was 28 months (2.3 years), median follow-up time after diagnosed colon cancer was 14 years, both now included in the text (Results Section, Page 8-9).

- Comment: Were there any individuals included on a CaPP study? Was any information on aspirin uptake collected?

Response: Information on aspirin uptake was not included in the study. PI of the CAPP studies has so far not responded positively to our wish of merging the datasets, which – as we understand – may be a function of their informed consents allowing for to do so, and identifying who in these series got Aspirin, and who got placebo. Analyses would be complicated when remembering the time from treatment to observed effect in the CAPP studies (the difference between placebo and aspirin is seen after five years of treatment with ASS for 2 two years). We do agree that merging the two datasets is a goal, but we are not there yet.

Reviewer #2

- Comment: Very powerful article that may influence how we manage individuals who are pathogenic and likely pathogenic variants in the MMR genes. It would be interesting to capture a larger population to understand how this many affect individuals who carry MSH6 and PMS2 mutations.

Response: Yes, indeed. See response to similar comment from the Reviewer #1 above.

- Comment: I would like to see additional numbers for 3.5 to 4.5 and beyond.

Response: We agree as PLSD is on the process of recruiting new contributors (version 4) and, we may be able to increase the numbers and analysis, as the referee suggests. Such cases, however, will by definition be drop-outs from the follow-up programmes because – to our knowledge – no centre has intentionally scheduled longer intervals than 3 years. Such a study would be outside the current design of examining the effects of the different protocols suggesting 1, 2 or 3-yearly intervals. Exactly how to analyse such data should be considered in detail and with power calculation before deciding to launch such an extensive and laborious effort.
With these alterations, we hope that the manuscript may be acceptable for publication in Hereditary Cancer in Clinical Practice Journal.

On behalf of the authors

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