**Author’s response to reviews**

**Title:** Colorectal cancer incidence in path_MLH1 carriers subjected to different follow-up protocols: a Prospective Lynch Syndrome Database report

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Author’s response to reviews:

Point-to-point response to reviewers:

Reviewer #2: This is an interesting study design for analyzing the effectiveness of colonoscopy screening intervals in LS. Your analysis found no difference in cancer incidence between those
screened every 3 years and every 1 to 2 years. You advocate that continued adherence to current protocols is recommended, but suggest that CRC in path_MLH1 carriers may not develop from polyps that cannot be detected with screening.

While you did not find a differences based on screening interval, Table 2 notes several studies which demonstrated a reduction in cancer incidence or improvement in survival in screened versus unscreened patients. In order to avoid your findings being misconstrued to mean that screening is not helpful, please expand upon your description of the data in table 2 in the background.

Response to reviewer:

All patients in our current study were under regular, continuous, endoscopy surveillance because it has been shown to be beneficial compared to no screening. In the manuscript, we are concentrating on a fact that there are no high quality evidence of better efficacy of shorter interval screening strategies compared to longer interval. We have added a sentence to emphasize the known benefits of surveillance colonoscopy on page 5, as requested, to avoid confusion.

The data in table 5 indicates that approximately half of the cancers that developed were detected within 2 years of a screening colonoscopy. Whereas the other half of the cancers were occurred outside of routine screening intervals. You indicate that you did not include stage in this analysis; however, that information would be valuable in order to better understand the cancers that are developing during screening. It seems that data would be available from your comprehensive dataset and it would strength the paper to at least report what was seen. If it is not going to be included because of plans to address this in future manuscripts, it would be helpful to more specifically outline plans for further analyses.

Response to reviewer:

As stated on page 6, the following observations were used: age at first colonoscopy, gender, age at last observation, months from last completed colonoscopy to diagnosis of CRC, age at any cancer together with the ICD diagnosis of the cancer, and age at death.

We did not have stage at diagnosis available for this study, as stated on page 8. It is true that some of the contributors may have had clinical information collected but it was not required for the PLSD minimum dataset that this manuscript was based on. We are in the process of expanding our dataset to include stage for future studies. We have added two sentences on this at the end of page 12.

The conclusion of the manuscript strongly states that despite the lack of resolution about the optimal screening interval, colonoscopy screening is still recommended. However, the abstract does not include that recommendation. Because some readers may not get past the abstract,
please modify the abstract conclusions to indicate that screening is still indicated as this topic continues to be investigated.

Response to reviewer:

We have modified the abstract accordingly.