Author’s response to reviews

Title: Recommended care and care adherence following a diagnosis of Lynch syndrome: A mixed-methods study

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Author’s response to reviews:

Dear Editor and Reviewers,
We appreciate your consideration of our manuscript for publication and are grateful for the reviewer comments, which we believe have helped us craft a stronger manuscript. We hope that you will consider our responses in your decision about publication. In summary, we have included specific language revisions as requested by Reviewer #1, including several revisions to the methods section for conciseness. Additionally, we have added content per both reviewers. We have included additional details requested by Reviewer #1 as relates to initiation of UTS within the KP care system, included a summary of large rearrangements as an addendum to Table 2 as requested by Reviewer #2, and added more detail regarding the qualitative analysis and its relationship to previous qualitative work by Schneider et al. as mentioned by Reviewer #1. We have also responded to comments in a point-by-point manner below and provided revisions in a track changes version of the document. Line and page notes are given as though the manuscript is viewed in track changes format. Thank you in advance for considering the revised version of the manuscript and these responses to reviews.

Reviewer reports:

Reviewer #1: It may seem like I made a ton of comments below, but I really love that you're publishing this great work! My questions and comments are mainly with regard to where the content can be expanded upon and a few places where reorganization and/or clarification is warranted. I do hope that you can address most of these comments. Thanks for your work! This is a thorough study that does fill a gap in the literature regarding adherence to provider recommendations to patients with Lynch syndrome and patient and provider ideas of how to remedy this problem, at least within one specific large medical system. It is a useful analysis that points to areas where providers can improve hospital systems to optimize adherence and therefore health outcomes for these high risk patients.

• We thank Reviewer 1 for the overall positive review of our manuscript, and their attention to detail. We appreciate the depth to which the reviewer considered our work and how their comments have improved the quality of the manuscript. We hope the reviewer finds that our responses are able to address the points made below.

Overall Comments:

* Since KPNW previously published in HCCP in 2018 on some of the same 22 Lynch syndrome patients that were identified through an EMR query, it would be interesting to compare the responses of patients to the actual EMR data.

• We are pleased that the reviewer is aware of other work from our group in this arena. We believe that the paper the reviewer references is by Schneider et al. We would lead with a minor clarification to the reviewer’s comments. This paper contained qualitative interview data from 12 patients and 10 providers – the same 12 patients and 10 providers who are included in this report. Different sections and focuses of the interviews were included in this separate report. That said, we appreciate the reviewer’s insight about linking the interview responses to the adherence data of individual patients. We have
added further details to the results that we believe will be of interest to the reader and add value to the manuscript (pg 13-14, lines 317-342; Table 5). We have also clarified that this is the same cohort of patients in the methods (pg 7, lines 170-172).

* Aim 1 seeks to assess the change of time to LS diagnosis after cancer diagnosis over time, but the paper doesn't mention in the methods the exclusion of LS patients who were diagnosed prior to having cancer. However in results, the authors are more specific and describe that 36% underwent testing due to family history. Please discuss this process in methods.

• Thank you for noticing this oversight. We have added details of this process to the methods as the introductory statement in Quantitative data and statistical analysis, reading, “For all patients…LS diagnosis,” on page 8, lines 185-186.

* Methods section needs to be refined/focused and more concise.

• Thank you for this comment. In addition to your specific comments below, we have made a few other revisions in track changes to the methods with this in mind, and we hope that these are helpful to the readership.

* Since using the initiation of UTS as a data point in patient cohorts, KPNW's start date of UTS for CRC and EC needs to be included in background.

• This is a valuable point that we feel merits clarification. We have included information about UTS in the background, methods, and discussion. Please see our responses to later reviewer comments about UTS for additional details. In brief, we have further clarified our hypothesis in the background that the increased awareness of LS generated by the EGAPP recommendation may improve time-to-diagnosis in spite of our healthcare organization not implementing a universal tumor screening program until after the conclusion of this study period (pg 4, lines 95-102), added additional information to the results (pg 10, lines 242-246; pg 11, lines 254-259), and provided additional discussion surrounding this point (pg 15, lines 347-349, 351-352).

* Results from Aim 4 are quite brief. Did anything else come out of these interviews of interest regarding improving adherence?

• We have provided additional details in the results (pg 13-14, lines 317-321, 323-342; Table 5), as discussed in the first bullet addressing the HCCP publication from 2018 from our group. Table 5 links specific adherence data on colonoscopy and endoscopy, which were focuses of the interviews, to specific patient qualitative responses.

Specific Comments on Content:

* Pg4 Lines 107-110: Focus methods section as it is not the place to state aims. "The aim…gaps in this population" should be replaced with statements about the actual design used
(e.g. EMR queries and chart reviews) used for obtaining data for aims 1-3 stated in the previous section.

- We appreciate the detail of this request and have revised this paragraph (including the bullet point below) to be more focused on an overview of design, rather than design as relates to aims (pg 5, lines 115-121).

  * Pg4 Lines 110: Delete "In order… care gaps" for same reason as above.

- We have revised this paragraph (including the bullet point above) to be more focused on an overview of design, rather than design as relates to aims (pg 5, lines 115-121).

  * Pg5 Line 124-126: Delete "Because these… diagnosis of LS" and perhaps just add to next sentence "Under guidance of a genetics professional"

- This edit is on pg 5, lines 133-138 of the revised manuscript.

  * Pg5 Line 131: Were only patients with genetic test results in the EMR stating likely pathogenic and pathogenic MMR variants included as "confirmed LS diagnosis" or were these clinically-described diagnoses as well? Later I see how this is presented in the results section, but seems appropriate for methods as it defined the cohort.

- Thank you for noticing this oversight. We have moved this to the methods section on pg 6 lines 143-146.

  * Pg 5 Line 131: "Adherence data… 2016" does not fit under the sub-heading "Study Population"

- Thank you for noticing this oversight. This detail is already present in a more appropriate section under the heading “Quantitative data and statistical analysis”, in the sentence, “Intervals were…through 2016” on pg 8 lines 198-199. As such, we have removed it from this subsection (pg 6, lines 146-147).

  * Pg6 Line 140: Was information on partial colectomies also collected? Was treatment information collected?

- Specific information on partial colectomies was not collected, as patients with partial colectomy are still eligible for surveillance in most cases, and where providers recorded surveillance should cease or pause, this was accounted for in surveilled intervals. We had at least one patient with a partial colectomy who was still undergoing regular surveillance at provider recommendation, and another patient with partial colectomy who were not adherent but still recommended to receive surveillance (Table 5). Information on treatment was also not collected and the study relied on documentation of recommendations. This would be captured where providers recommended a cessation of surveillance. This would be captured where providers recommended a cessation of
surveillance. In response to reviewer’s comment, we have re-examined our data to verify that appropriate RR procedures were otherwise adjusted for (where whole organ removal took place as a risk reducing surgery) and found that adjustments were not made in the initial analysis for CA-125 and TVUS, but were made for endometrial biopsy. This has been corrected in the text (pg 12, lines 276-281), table 3, and Figure 1. We clarified information about whole organ removal (risk reducing, rather than cancer, as some patients continued to have CA-125 following cancer diagnosis and ovary removal) in the methods (pg 8, lines 202, 204-206). We finally added a note about the limitations of using recommendations as documented in the EMR (pg 18-19, lines 433-436).

* Table 1: Delete "(Endometrial surveillance)"
  • Thank you; we have made this edit.
* Table 1: Delete "(TVUS)"
  • Thank you; we have made this edit.
* Table 1: Did you try to look at dermatology screening codes too?
  • We only reviewed codes related to procedures or screening that were abstracted by genetics professionals from the chart. As such, we did not review dermatological screening, as no such recommendations were abstracted.

* Pg6 Line 151: Delete "To gain… care delivery", focus on methods.
  • We have made this edit and have clarified that the recruitment methodology was the same as that used in Schneider et al. and was the same cohort of patients and providers, but with different interview focus. These edits are on pgs 7; lines 167-168 and pg 7, lines 170-172; pg 7, lines 178-181.

* Pg6 Line 152: This sentence makes it sound like patients that were already enrolled in something else were recruited. Is that the case?
  • We apologize for the confusion and thank you for pointing out this issue, which related to jargon within our care system. Because KPNW is both insurer and provider, only patients enrolled in the health system were eligible for recruitment. We have edited this sentence for clarity for general readership, on pg 7, lines 168-169.

* Pg7 Line 163-164: Delete "To determine… over time"
  • Thank you; we have made this edit, which is now located on pg 8, lines 185-186.
* Pg7, Line 166: Delete "after discovery of LS genes"
  • We have made this edit, which is now located on pg 8, lines 188-189.
These dates… and Prevent" can be moved into background. Also, a comment on whether KPNW initiated a UTS across their entire system the year that EGAPP came out is important. If adopted later, the date ranges chosen for analysis would be inappropriate. Also, it should be noted whether KPNW initiated screening of both endometrial and colorectal tumors or just CRC tumors as was the recommendation of EGAPP in 2009. If just CRC tumors, when did KPNW start to include endometrial tumor screening into their UTS?

KPNW did not institutionally implement UTS in full for CRCs until January 2016, though we hypothesized that the general awareness of LS would increase after the EGAPP recommendation, and would thus prompt an increase in testing. We have also clarified that awareness was the driving hypothesis in our introduction section (pg 4, lines 95-102), the date range selection reason in methods (pg 8, lines 191-194), as well as the discussion (pg 15, lines 347-349). Because some patients (n = 8, 25%) were identified by UTS through a clinical trial, we appreciate the reviewer’s concern and have decided it is appropriate to consider our hypothesis in their absence. We have addressed this issue by performing the test of significance following removal of the patients receiving UTS through the clinical trial with first LS cancer diagnosed in the date range 1995-2015 and thus present in our cohort (n = 7), and have shown that it is still significant (pg 11, lines 254-259).

Were patients who received a diagnosis of CRC who did not receive a total colectomy put were receiving chemotherapy during what would have been the screening interval also excluded from this?

No; the study relied on information provided to patients by their genetics providers and any updated recommendations given by their genetics providers, oncologists, primary care providers, or other providers and documented in the EMR; information on treatment was not collected. Where providers recorded surveillance should cease or pause, this was accounted for in surveilled intervals. As stated below in response to another reviewer question, we also did not collect partial colectomy as patients with partial colectomies are still eligible for colonoscopy surveillance in most cases. We have made a note about the limitations of this approach (pg 18-19, lines 433-436).

Were the qualitative themes from interviews used to abstract advice for care coordination specifically, or only for data reported elsewhere? Reference to findings from data reported elsewhere can be in background or discussion, not methods. However, this paper can be references for this methods section instead of describing it a second time since it's the exact same cohort. After referencing, specific note on which specific subset of this data from the interviews can be briefly mentioned.

Yes, qualitative themes from interviews were used to abstract the advice for care coordination specifically reported in Table 4; this data was not reported elsewhere. While certain themes were reported first elsewhere on an aggregate basis, in response to your point above about correlating patient responses to adherence data, we have added Table 5, which reviews these themes on a per-patient basis, in comparison to their colonoscopy
and endoscopy adherence, which were a focus of the interview. We have added clarifications to the methods (pg 7, lines 170-172, 178-181; pg 9-10, lines 229-232).

* Pg9 Lines 215-217: What were the mean and ranges for age of diagnoses for these cohorts being compared?

- These have been added and are located on pg 10-11, lines 251-253 in the revised version of the manuscript.

* Pgs9-10 Lines 228-31: Variability of these recommendations makes sense due to how the guidelines are laid out for non-CRC screening in LS. If you're going to draw conclusions from this variability, perhaps the variability in the guidelines themselves (and recommendation to tailor management based on family history and ethnicity) should be incorporated into the background section better. Adherence to what was recommended seems like the better item to be analyzing given the wording of LS guidelines. Conversely, this could also be mentioned in the discussion when the authors discuss that variability could be due to modifications of NCCN guidelines over time, when in fact the nature of the extracolonic guidelines not being strict recommendations seems like a more likely correlation.

- We agree with the reviewer’s note that it is better to analyze adherence to what was recommended, which is what we have done in this manuscript. However, the reviewer is also correct that it is possible that certain recommendations may have been conveyed in a less stringent manner or as less important, because the guidelines may have been less strong in these instances (using language such as “consider” or “may be considered at the provider’s discretion”). We have restructured the discussion to highlight this fact, and the fact that some extracolonic guidelines are less strict (pg 15-16, lines 364-366; pg 16-17, lines 377-389; pg 17, ines 395-398).

* Pg10 Lines 235-236, Table3: This statement is difficult to understand. How could patients that are 100% adherent be 0% adherent to certain recommendations? Please make more clear.

- We apologize for the confusion. We intended to highlight the proportion of patients who were perfectly (100%) adherent to a particular recommendation. No patients were perfectly adherent to endometrial biopsy, but 70% of patients receiving a recommendation for colonoscopy were perfectly adherent to that recommendation. We have added phrasing to the sentence to clarify (pg 12, lines 277-281).

* Pg 10 Lines 257-259: Were any of these women getting RR surgeries diagnosed with EC or OC when pathology looked at the resected tissue?

- There were 5 women who received a diagnosis of EC concurrent with a hysterectomy; however, all of these women received this hysterectomy prior to their LS diagnosis, and thus were not classified as having a RR surgery in this analysis. There were an additional 5 women who received a diagnosis of OC concurrent with an oophorectomy; again, these
surgeries were prior to the diagnosis of LS and thus were not considered RR for the purposes of this analysis. No women who had RR surgery classification (surgery following LS diagnosis) received a diagnosis of EC or OC concurrent or following the surgery. Two women had EC after LS diagnosis, and had a hysterectomy, but this hysterectomy was not classified as RR in the analysis because the EC diagnosis occurred first. We have added methodological detail regarding this classification to the section of the methods titled “Electronic data collection”, p 7, lines 163-164. We clarified these details in the results on p 13, lines 301-303, 306-307. In providing this response to reviews, we also identified and corrected one data error in the manuscript, on p 13, line 305 (a mistyped percentage) and two data errors in Table 2 (2 cancers that occurred in patients after their LS diagnosis were erroneously included).

* Pg12 Lines 277-278, 283-285: Since a chart review was performed, are the authors able to comment on how many of the cases in the pre-2008 and post-2008 LS cohorts were diagnosed through their UTS? This would help show the relationship between UTS and decreased time and ability to diagnosis LS in patients with CRC and EC.

- As KP did not institute universal screening pre 2008 and post-2008 until 2016 (January 2016 for CRC and November 2016 for EC), none of our tumors experienced “UTS” through KPNW usual care, though 8 patients experienced UTS through a clinical trial. We have provided a minor addition to the results section on p 10, lines 242-246, addressing the eight patients who received UTS through the clinical trial, as well as performed the statistical test after removing the seven patients who received UTS who were also in the cohort of individuals with first LS cancer between 1995-2008 (p 11, lines 254-259). One of these eight patients in the trial had a first LS cancer prior to 1995 and was thus not a part of the original analysis. Please also refer to our response to reviewer’s comment that begins with “Pg7, Line 167-169” for additional detail regarding CRC UTS. Below are the details of IHC testing for patients not in the UTS trial in our cohort, to address any further reviewer concern.

If the reviewer means IHC rather than UTS, it is true that most CRC tumors in our cohort received IHC testing. Because most of this IHC testing was ordered by the genetics department following referral for genetic evaluation, we did not include this detail in the manuscript, as we feel it is extraneous. However we provide it here to address any lingering questions the reviewer may have:

IHC details: While KPNW did not institutionally implement UTS for all cases of CRC until January 2016, most cases of CRC (n = 32, 86%) in our cohort were screened by immunohistochemistry (IHC). Of these 32 patients, IHC was initiated by the referring provider (n = 4, 13%), by the genetics department following receipt of the referral (n = 18, 56%) for LS evaluation, through a clinical trial of UTS (n = 8, 25%; NCT01582841), or outside of KPNW (n = 2, 6%). There were 5 patients in our cohort who did not have IHC on CRC tissue. One patient had been diagnosed with LS prior to CRC diagnosis following another LS cancer (initial CRC diagnosis in 2009). Two patients (initial CRC diagnoses in 2013 and 2014) were provided near-immediate genetic testing and diagnosed with LS within two months of their initial CRC diagnosis, one of whom had a known familial pathogenic variant. Two were diagnosed with LS
more than two years after their CRC diagnosis (CRC diagnoses in 2003 and 2007), one of whom had a known familial pathogenic variant. Of the patients receiving tumor IHC, all but two had at least one abnormal result. Of the two with normal IHC results, one had an abnormal MSI test.

* Pg12 Lines 301-204: Might this adherence also be due to the particular mutation that a women carried? Suggest including this.

- Thank you for this note – we agree this is likely a contributing factor. Because KP genetics department has maintained internal guidelines that closely mirror but may differ from NCCN guidelines, and also change over time, we elected to abstract the recommendations as they were documented in the patient charts, as we believe that is the closest way to mirror what the patient was actually told, and what the primary care provider would have access to. However, it is possible that certain recommendations were conveyed with more emphasis than others, or with more emphasis for patients with certain variants, which may have impacted adherence. This is an important point, so in addressing the point immediately above, we included in our discussion changes that better highlight these uncertainties and limitations of our approach (pg 16-17, lines 377-389).

Grammatical/Word choice (WC)/abbreviation corrections/comments:

* Pg2 Line 50, 52, 53: "an" should be either "a" or "any" when referring to "an LS-related cancer" in multiple sentences.

- Thank you for noticing. These have all been corrected to “a”. They have also been corrected in a few other instances throughout the manuscript, such as in the discussion.

* Pg3 Line 85: May consider alternate WC for "affected individuals" - perhaps "carriers of pathogenic variants", "LS individuals", or "at-risk individuals"?

- Thank you for appreciating this nuance – you are correct that what we mean to say is individuals at risk of LS cancers due to carrying a pathogenic variant. We have altered the language to clarify (pg 3, line 85).

* Pg3 Line 89 and Pg4 Line 94: The abbreviation "EMR" is used on page 3 but defined on page 4.

- We have moved the definition up to be after first use in the body of the manuscript, on pg 3, line 90.

* Pg4 Line 97": delete "and" prior to item 3 as this is not the last item in the list, move prior to last list item in live 98

- Thank you, we have made this correction, located on pg 4, line 105-106.
Reviewer #2: This is a descriptive study about different aspects of Lynch syndrome diagnosis and the utilization of the screening recommendation for cancer surveillance for a specific community. Although the number of patients with LS was very small in this study, the results might be of interest to the readers of this journal.

- We thank the reviewer for their review and appreciate that our sample size is small. We hope that the readership of Hereditary Cancer in Clinical Practice will remain interested in our work, which we believe adds to the limited knowledge in the field in this space.

It would be of interest if the authors can provide more details on the genetic mutations of the patients, in particular the large rearrangements if there is any among their patients.

- Thank you for the suggestion. We have added this detail to Table 2.