Author’s response to reviews

Title: Single-center study of Lynch syndrome screening in colorectal polyps

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Author’s response to reviews:

Reply to Reviewer 1 reports (Steffen Pistorius, MD):

1) Before analyses of the germline (sequencing), genetic counselling of all patients is mandatory.
Reply: Materials and methods Patients: DNA extraction and sequencing part add a sentence “Patients exhibiting polyps with deficient mismatch repair (dMMR) were referral to genetic counselling and signed informed consent to receive genetic testing”.

2) The conclusion ("The efficiency of performed…is low…") is correct and supports the recommendation for inclusion of patients only meeting the revised Bethesda guidelines in MMR analyses. In this study, all patients in whom a pathogenic MMR mutation could be detected were younger than 50 years.
Reply: Detection of LS only performing MMR IHC and/or MSI testing of adenomas in young patients may not be the best strategy. In patients < 40 years-old with colorectal adenoma, MMR IHC and MSI testing found no abnormal results. It may be reasonable to evaluate for LS when a young adenoma patient has a family history of LS-associated cancers, or when a young adenoma patient has high-risk characteristics, such as large size, high-grade dysplasia, and malignant components.

3) The number of the references cited (eleven) appears too low in such a central field of interest.
Reply: It has been increased to 25 references.
4) The complete manuscript should be revised by an academic native speaker because of the poor quality of English and numerous mistakes.

Reply: Manuscript has been revised by American journal experts.

Reply to Reviewer 2 reports (Florentia Fostira):

The manuscript is very difficult to read through. It has multiple grammatical errors, while many sentences do not make sense, since the verb is missing. Please check the manuscript for spaces between words or sentences. Please refer to a native speaker for corrections.

Reply: It's has been revised (manuscript has been revised by American journal experts).

Moreover, some terms used along the manuscript are not correct, i.e. dMMR patients (use instead: patients showing polyp dMMR).

Reply: It's has been revised

Other comments:

Introduction:

- All gene names should be in Italics.

Reply: It's has been revised

- The last sentence of the paragraph should be changed to: "subsequent genetic testing based on the MMR IHC results will ultimately confirm LS diagnosis".

Reply: It's has been revised

- Please rephrase the second paragraph and check for errors (e.g. studys).

Reply: It's has been revised

Materials and Methods:

- Please rephrase the patient selection paragraph.

Reply: It's has been revised

- It is not clear what you are trying to say in your last sentence of IHC for MMR proteins.

Reply: It's has been revised

- Multiple grammatical and terminology errors in DNA extraction and sequencing section. What does German Qiagen means? What are the amplified objects? What does mutation style means? Please try to rephrase the paragraph.
Results:

- Please rephrase the sentence: "the mean age..." years should be added and this is the mean age of what?

Reply: It's has been revised

- Please avoid starting sentences with numbers.

Reply: It's has been revised

- State in the text what you are presenting in Table 1.

Reply: It's has been revised

- In tables 1 and 2, please review the legend (pathological information is not an accepted term).

Reply: It's has been revised

- In table 1, what does canceration means?

Reply: It's has been revised

- The paragraph following Table 1 is unclear, please rephrase.

Reply: It's has been revised

- The paragraph following Table 2 is unclear, please rephrase ("one case was not analysis")?

Reply: It's has been revised

- Merge information in Tables 3 and 4. When you do that, reconsider your legend.

Reply: It's has been revised

- When reporting mutations, HGVS nomenclature should be used (reporting in protein and cDNA level), while the RefSeqs used for each gene should be listed (Table 3).

Reply: It's has been revised

- Please review Table 3; Gene names in italics and phrases such as: not detection vs not detected, sanger sequence vs sequencing, not yet seen vs not detected.

Reply: It's has been revised

Discussion:
- Please get a native speaker to scan it through.

Manuscript has been revised by American journal experts.

Reply to Reviewer reports (Author Decision Letter)

1) This study is potentially extremely interesting coming at a time of significant discussion about Lynch syndrome (LS). The authors state that adenomas are the precursors to malignancy in LS - this may be true, it could also be wrong. The low percentage of LS cases identified using the strategy of the authors may be wrong and they may indeed have missed quite a few. It is important that all cases really should be screened for causative variants in the germline before you can categorically state that LS is present in a low proportion of CRC patients. The authors should include a sentence or two in the discussion raising this issue.

Thanks for reviewer comments, The reviewer's rigorous research attitude is worthy of our admiration and learning.

Reply: MMR-deficient adenoma and MMR-deficient nonpolypous are major precursors to cancer in LS, so we screening for LS from adenomatous polyps indeed have missed quite a few cases. We added a paragraph “Our study has limitations. First, MMR-deficient nonpolypous is another important precursor in LS, so we screening for LS from adenomatous polyps indeed have missed quite a few cases. Second, immunohistochemical screening strategy may also miss a few cases, genetic testing of all adenomatous polyps is the most accurate strategy.” in the discussion section of article.

2) Furthermore, they should tone down the statement that adenomas are precursors to malignancy in LS, it would be better to state that they are "likely precursors to cancer in LS"

Reply: MMR-deficient adenomas are well known as precancerous lesions to cancer in Lynch syndrome, but not the only one. And screening for LS from MMR-deficient nonpolypous is extremely difficult. So we think it would be better to state that “Adenoma is one of the important premalignant lesions to colorectal cancer in Lynch syndrome”