

Point-by-Point Response  
ESPS manuscript NO: 19472  
World Journal of Gastroenterology

*Reviewer 1. A comprehensive well written paper. Very useful for clinicians, no other comments than please add core tips and adjust reference style.*

Response. We thank this reviewer for his/her comments. We have added the core tips and adjusted the references.

*Reviewer 2. The paper by Carethers and Stoffel is a comprehensive narrative review on the complex topic of Lynch syndrome and its genetic determinants, taking into account recent achievements of molecular biology research. The distinction between Lynch syndrome with and without MMR deficiency is suggestive and may be useful for the clinical management of kindreds with clinical features of HNPCC.*

*The molecular defect underlying HNPCC kindreds is still often unknown, thus we have to recommend strict follow-up surveillance even in the absence of genetic diagnosis.*

Response. We thank this Reviewer for his/her perspective and comments, and we agree with the perspective of this reviewer.

*Major point.*

*I have some concern about the inclusion of a polyposis syndrome into the classification proposed by the authors (i.e., polymerase proofreading associated polyposis, PPAP), though the clinical manifestations of that syndrome are sometimes similar to that of a HNPCC syndrome.*

Response. We agree that there is overlap of clinical manifestations of the HNPCC syndromes and polymerase proofreading associated polyposis. This is exactly why we included this condition in the manuscript to raise awareness of the overlap so that the clinician would consider it when other HNPCC syndromes are being ruled out. We highlight in the article that PPAP can present with very few polyps. The key would be to show that the colorectal cancer is microsatellite stable (MSS), assuring that it is not Lynch, Lynch-like, nor sporadic MSI colorectal cancer. The awareness is to consider PPAP when other conditions are being ruled out.

*Minor points.*

*Correct some typing errors throughout the text (i.e., pg 3, introduction, paragraph 2, line 5, colorectal) Pg 3, paragraph 2, line 4, the "red flags" has been defined by several authors (for example Cancer 71:3493-501, 1993)*

*Pg 3, line 10: delete "with" after "without".*

*Pg 7, line 1: please explain the acronym "VUSs"*

*Pg 9, para 4, line 3: delete "of" after "several"*

Response. We have made all of the indicated corrections. The "red flags" are mentioned in several of our referenced manuscripts, and thus we did not further add the suggested reference. VUSs stand for variants of uncertain significance, and we added this to the abbreviations as well as in the text. We thank the Reviewer for catching these mistakes in the original version.