**ESPS PEER-REVIEW REPORT**

**Name of journal:** World Journal of Gastroenterology

**ESPS manuscript NO:** 30970

**Title:** BRAF inhibitor treatment of melanoma causing colonic polyps: an alternative hypothesis

**Reviewer’s code:** 03475830

**Reviewer’s country:** Australia

**Science editor:** Yuan Qi

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| **CLASSIFICATION** | **LANGUAGE EVALUATION** | **SCIENTIFIC MISCONDUCT** | **CONCLUSION** |
| [ ] Grade A: Excellent[ Y] Grade B: Very good[ ] Grade C: Good[ ] Grade D: Fair[ ] Grade E: Poor  | [ Y] Grade A: Priority publishing[ ] Grade B: Minor language  polishing[ ] Grade C: A great deal of language polishing[ ] Grade D: Rejected | Google Search: [ ] The same title[ ] Duplicate publication[ ] Plagiarism[ ] NoBPG Search:[ ] The same title[ ] Duplicate publication[ ] Plagiarism[ ] No | [ Y] Accept[ ] High priority for  publication[ ] Rejection[ ] Minor revision[ ] Major revision |

**COMMENTS TO AUTHORS**

The authors have postulated a hypothesis, that BRAF inhibitor induced colonic polyps may arise due to activation of the serrated pathway. The writing is excellent and the paper is worthy of publication as a hypothesis generating work. I have two comments: 1. While the idea is interesting, the evidence supporting this presently limited. The paper would benefit from suggestions for future scientific investigation to confirm this hypothesis, rather than skipping this step to suggest molecular treatment. 2. The paper is very "gene heavy" and probably would be difficult for the general readership of the journal to read and understand. Nevertheless I think this paper should be published if the editor feels it is suitable.

ANSWERING REVIEWERS:

1. **Future scientific investigation to confirm the hypothesis**

A comprehensive compilation of a series of patients on BRAF inhibitor treatment of melanoma in whom colonic polyps arise is mandated. This will permit histological characterization as to whether these polyps are serrated or adenomatous. Bi-sulfite sequencing analysis of genes that are proposed to be epigentically silenced by CpG island promoter methylation should inform on the relative merits of the epigentic component of the iatrogenic disease model. DNA and RNA of the selected genes of interest is suggested. Lastly RNAi screening to asses the level of MAFG in these polyps, itself a silencer of p16INK4A should provide evidence supporting the senescent tenet of the hypothesis