



PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 116028

Title: Emerging Role of DNA Polymerase Epsilon Non-Exonuclease Domain Mutations in Colorectal Cancer: From Sequence Variants to Clinical Implications

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer’s code: 08039404

Position: Peer Reviewer

Academic degree and professional title: PhD

Reviewer’s Country/Territory: China

Author’s Country/Territory: China

Manuscript submission date: 2025-10-31

Reviewer chosen by: Jia-Qi Xuan

Reviewer accepted review: 2025-11-05 11:02

Reviewer performed review: 2025-11-19 02:42

Review time: 13 Days and 15 Hours

Content to be reviewed	<p>Does the manuscript’s content fall within the scope of the journal? Yes</p> <p>Is there any Key Word that is not included in the manuscript title? Yes</p> <p>Do authors’ affiliations correspond to the content of the manuscript? Yes</p> <p>Does the Abstract contain the contents of each part of the manuscript (IMRaD)? Yes</p> <p>Are the Key Words complete? Yes</p>
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Is the content of the Introduction adequate? **Yes**
Is the content of the Materials and Methods complete?
Yes
Is the description of the experiments clear and
complete? **Yes**
Are the experimental data presented in the
manuscript's biostatistics content reliable? **Yes**
Are the experimental data of the Results true and
reliable? **Yes**
Are the quality and resolution of the images up to
standard? **Yes**
Do the selection and design of the figures and tables
follow the principles of necessity and clarity? **Yes**
Is there any duplication between various parts of the
manuscript and between the main text and the content
presented in the figures and tables? **Yes**
Are the figures and tables numbered consecutively in
the order in which they appear in the manuscript? **Yes**
Is the content of the Discussion reasonable? **Yes**
Is the Conclusion reasonable? **Yes**
Are all references necessary and reasonable? **Yes**
Do authors omit important references? **No**
Are all references related to the topic of the
manuscript? **Yes**
Do authors only cite their own earlier publications? **No**
Is the manuscript's text correct, concise, and clear? **Yes**
Will the manuscript's content be of interest to readers?
Yes
Are additional experiments needed for the study? **No**
Does the research scope comply with ethics? **Yes**



Scientific quality	Grade B (Very good)
Novelty of this manuscript	Grade B (Very Good)
Creativity or innovation of this manuscript	Grade C (Good)
Scientific significance of the conclusion in this manuscript	Grade C (Good)
Language quality	Grade C (Good)
Does this manuscript describe a study of the existing knowledge system?	Yes
Does this manuscript report a revolutionary innovation?	No
Does this manuscript report an unconventional innovation?	No
Conclusion	Major revision
Re-review	No
Peer-reviewer statements	Peer-Review: Anonymous
	Conflicts-of-Interest: No
Are your review comments generated by AI tools?	No

SPECIFIC COMMENTS TO AUTHORS

This manuscript by Jia-Ju Xu et al. provides a comprehensive editorial on the significance of non-exonuclease domain mutations (non-EDMs) in DNA polymerase epsilon (POLE) in colorectal cancer (CRC), building on the recent study by Taskiran et al. The authors highlight the potential clinical implications of these mutations, emphasizing the need for functional validation and integration into molecular subtyping frameworks. While the manuscript offers valuable insights and a forward-looking perspective, several critical issues need to be addressed to strengthen its scientific rigor and clarity.



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1. The manuscript emphasizes the high frequency of the p.V1446fs*3 variant in the Turkish cohort but lacks detailed functional validation. Given the potential population-specific effects, the authors should provide in vitro or in vivo evidence to elucidate the functional consequences of this variant on POLE activity and tumor biology.
2. The high prevalence of non-EDMs observed in the Turkish cohort may not be representative of other populations. The authors should discuss the limitations of extrapolating these findings to diverse ethnic groups and propose strategies for multi-center validation studies to assess the generalizability of their conclusions.
3. The manuscript mentions that most POLE-mutant tumors are MSI-Low or MSS but speculates on their potential hypermutator phenotype. This inconsistency needs clarification. The authors should provide data on tumor mutational burden (TMB) or reference studies that directly link non-EDMs to TMB levels to support their claims regarding immunotherapy responsiveness.
4. The manuscript advocates for comprehensive POLE sequencing but does not address the challenges of standardized detection. The authors should outline specific recommendations for high-quality next-generation sequencing (NGS) protocols and bioinformatics pipelines to ensure accurate identification of POLE mutations in clinical settings.
5. The manuscript suggests that POLE non-EDMs could guide personalized treatment strategies, including immunotherapy. However, the clinical evidence supporting this assertion is limited. The authors should temper their conclusions and emphasize the need for prospective clinical trials to validate the predictive value of non-EDMs for treatment outcomes.
6. The discussion of co-mutations with MLH3, MSH3, KRAS, PIK3CA, and BRAF is complex and lacks clarity. The authors should provide a more structured analysis of



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how these co-mutations interact with POLE non-EDMs, and their combined impact on tumor behavior and treatment response. Additionally, the manuscript should include a summary table of key co-mutations and their clinical relevance.



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Peer-review model: Single blind

Reviewer’s code: 08357049

Position: Peer Reviewer

Academic degree and professional title: Professor

Reviewer’s Country/Territory: China

Author’s Country/Territory: China

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Reviewer chosen by: Jia-Lin Zhang

Reviewer accepted review: 2025-12-05 09:32

Reviewer performed review: 2025-12-12 09:38

Review time: 7 Days

Content to be reviewed	<p>Does the manuscript’s content fall within the scope of the journal? Yes</p> <p>Is there any Key Word that is not included in the manuscript title? No</p> <p>Do authors’ affiliations correspond to the content of the manuscript? Yes</p> <p>Does the Abstract contain the contents of each part of the manuscript (IMRaD)? Yes</p> <p>Are the Key Words complete? Yes</p>
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Is the content of the Introduction adequate? **Yes**

Is the content of the Materials and Methods complete?

Not Applicable

Is the description of the experiments clear and complete? **Not Applicable**

Are the experimental data presented in the manuscript's biostatistics content reliable? **Not Applicable**

Are the experimental data of the Results true and reliable? **Not Applicable**

Are the quality and resolution of the images up to standard? **Not Applicable**

Do the selection and design of the figures and tables follow the principles of necessity and clarity? **Not Applicable**

Is there any duplication between various parts of the manuscript and between the main text and the content presented in the figures and tables? **No**

Are the figures and tables numbered consecutively in the order in which they appear in the manuscript? **Not Applicable**

Is the content of the Discussion reasonable? **Yes**

Is the Conclusion reasonable? **Yes**

Are all references necessary and reasonable? **Yes**

Do authors omit important references? **No**

Are all references related to the topic of the manuscript? **Yes**

Do authors only cite their own earlier publications? **No**

Is the manuscript's text correct, concise, and clear? **Yes**

Will the manuscript's content be of interest to readers?



	Yes Are additional experiments needed for the study? No Does the research scope comply with ethics? Not Applicable
Scientific quality	Grade A (Excellent)
Novelty of this manuscript	Grade B (Very Good)
Creativity or innovation of this manuscript	Grade B (Very Good)
Scientific significance of the conclusion in this manuscript	Grade B (Very Good)
Language quality	Grade A (Excellent)
Does this manuscript describe a study of the existing knowledge system?	Yes
Does this manuscript report a revolutionary innovation?	No
Does this manuscript report an unconventional innovation?	Yes
Conclusion	Minor revision
Re-review	No
Peer-reviewer statements	Peer-Review: Anonymous
	Conflicts-of-Interest: No
Are your review comments generated by AI tools?	No

SPECIFIC COMMENTS TO AUTHORS

This editorial emphasizes the potential significance of non-EDMs (non-enzymatic exon-deletion domains) mutations in DNA polymerase ϵ (POLE) of colorectal cancer (CRC), based on a study reported by Takkirian et al. in the World Journal of



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Gastroenterology. The study found a higher frequency of POLE mutations in the Turkish CRC population, mainly driven by the frameshift mutation p.V1446fs*3, whose pathogenicity remains to be clarified. It is notable that non-EDMs co-occur significantly with key gene mutations such as MLH3, MSH3, KRAS, PIK3CA, and BRAF, suggesting that DNA repair defects may synergize with the activation of oncogenic pathways. Although POLE mutation tumors are mostly of non-MSI-H phenotype, their high mutation load may still confer their immunotherapy sensitivity. Therefore, the authors call for functional experiments and multicenter studies to verify the biological and clinical significance of non-EDMs, and recommend including comprehensive POLE sequencing covering non-EDM regions in the molecular classification of CRC to optimize individualized treatment strategies. The overall language of this article is fluent, the structure is complete, and the logic is clear. It has certain reference value and enlightenment significance for the related research field. I believe that after making appropriate modifications and improvements to some details, this article can be accepted. Here are some minor issues that need further clarification or improvement:

- (1) The first occurrence of abbreviations should have their full definitions, for example, dMMR, although the full name is written when it appears for the second time;
- (2) Adding line numbers/page numbers would make it more convenient for reference;
- (3) The references can be supplemented with some from 2025 to enhance the timeliness and completeness of the literature review section.
- (4) The key words are quite numerous. They can be appropriately reduced to 5.
- (5) As an editorial, I think the manuscript is somewhat lengthy, and a moderate reduction in length is recommended.