POST-AI RISK ASSESSMENT

Expert-led checks for your AI-assisted manuscript

editage

Dear Author,

Thank you for choosing to work with Editage!

I have reviewed your AI-assisted manuscript draft with a focus on references, disclosures and ethics, and confidentiality, to identify potential risks in these areas prior to journal submission.

I have also assessed whether AI has introduced inaccuracies or technical inconsistencies across manuscript sections, unsupported claims, or misrepresentations of your research findings.

In addition, the following reports have been provided separately for your reference:

- Similarity report by iThenticate
- Image integrity report by Imagetwin
- AI detection report by Paperpal

Please review the assessment in this report along with the additional reports listed above and address any points of concern prior to journal submission.

Regards,
Your Editage Expert

OVERALL ASSESSMENT

Moderate issues identified

Executive summary

- **Requirements met**
  - The title accurately reflects the main focus of the manuscript and is consistent with the content in the abstract. Both focus on the use of a synthetic ecDNA model to investigate ecDNA maintenance and genomic instability.
  - The manuscript demonstrates good overall internal consistency, with the objectives, methods, results, and conclusions generally aligned, although some statements would benefit from more cautious wording.
  - The Methods section includes detailed descriptions of the experimental and computational approaches, including cell models, syn-ecDNA construction, sequencing analyses, and genomic assays.
  - The manuscript includes a well-developed background on ecDNA biology and integrates structural, functional, and clinical literature.
  - The reported results correspond well with the methods presented.

- **Items requiring attention**

- The current gap in knowledge regarding sequence determinants of ecDNA maintenance is somewhat overstated in the Introduction. Recent work in this area of research should be acknowledged.
- Recent engineered ecDNA models should be acknowledged when describing the novelty of the present syn-ecDNA system in the Introduction.
- Some statements in the Discussion and Conclusion extend beyond what the results directly demonstrate and should be qualified. In particular, the proposed mechanistic model and the suggested use of syn-ecDNA as a platform for future epigenetic editing should be distinguished from capabilities demonstrated in the current study.
- Several reporting elements recommended by STROBE guidelines are not fully addressed in the manuscript.
- Some wording is vague and could be replaced with more specific descriptions of what the model demonstrated.
- Two references could not be verified.
- Some citations in the Methods and related methodological discussion do not directly support the specific claims for which they are cited.
- Disclosure statements for generative AI use and data availability are absent.
- The DOI in one reference requires careful validation.

Detailed checks

FIDELITY CHECK

Title–Abstract alignment
Assessment: No issue

CONTENT VALIDATION

Objective–Methods correspondence
Assessment: Minor concern • Example: “Here we establish a controllable experimental model to dissect how defined sequence elements and DNA circles contribute to ecDNA maintenance and cellular responses.” (Page 3, line 56) Issue: The stated objective refers broadly to determining how defined sequence elements contribute to ecDNA maintenance; however, the Methods describe testing a single approximately 15-kb EGFR-associated fragment rather than systematically dissecting individual sequence elements. The objective may imply a broader investigation of sequence-specific determinants than was actually performed in the current study. Recommended action: Consider narrowing the objective to reflect the testing of the selected EGFR-associated sequence or clarify that the study provides a model for future investigation of individual sequence elements.

Methods–Results correspondence
Assessment: No issue

Results–Discussion–Conclusion correspondence
Assessment: Minor concern • Example 1: In the Discussion, the authors state that the findings “substantiate a mechanistic model” in which the combined effects of circular topology and transcriptional activity generate topological strain and recurring DNA lesions that recruit DNA-damage-response pathways to facilitate episome maintenance. (Page 8, line 204) Issue: The experimental findings support an association between syn-ecDNA, DNA damage signaling, and genomic instability, but the wording may imply a more fully established mechanistic relationship than is directly demonstrated by the experiments. Recommended action: Consider using more cautious wording to distinguish the findings shown in the study from the proposed mechanism. • Example 2: In the Conclusion, the authors state that syn-ecDNA “provides a ‘blank’ genetic template for precision epigenetic editing.” (Page 9, line 221) Issue: The manuscript demonstrates that the synthetic ecDNA system is programmable and labelable, but the proposed use as a platform for precision epigenetic editing extends beyond the specific applications demonstrated in the current study.

Recommended action: Qualify this statement as a potential future application of the model rather than as an established capability demonstrated by the current study.

Vague/unscientific language check

Assessment: Minor concern

- Example: "The syn-ecDNA platform offers a powerful and highly versatile system for unlocking the complex biology of ecDNA and providing unprecedented insights into its dynamic behavior." (Page 2, line 16)
  Issue: The syn-ecDNA system is described in broad, promotional terms, such as "a powerful and highly versatile system for unlocking the complex biology of ecDNA". Such wording is subjective and does not specify what the system has actually demonstrated. It may also make the contribution sound broader or more established than the study shows.
  Recommended action: Replace promotional wording with a specific description of the capabilities demonstrated in the study, such as its use for examining ecDNA maintenance, DNA damage, and genomic instability.

REFERENCE VALIDATION

Unverifiable references

- Reference 6: "Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal"
- Reference 13: "The selective activator protein-1 inhibitor T-5224 regulates the IRF4/MYC axis and exerts cooperative antimyeloma activity with bortezomib"

Inaccurate references

- Reference 19: Liao W, McNutt MA, Zhu W-G. The comet assay: a sensitive method for detecting DNA damage in individual cells. Methods. 48:46–53. DOI: 10.1016/j.ymeth.2009.02.999. The DOI provided is inaccurate and does not correspond to the cited article.

Retracted/flagged references

- No citations to retracted or flagged publications were identified during the validation performed.

Outdated (≥10-year-old) references

- 7 of 49 references are older than 10 years. These include Cox et al. (1965), Robinson et al. (2011), Liao et al. (2009), Karin et al. (1997), Bonner et al. (2008), Wang et al. (2011), and El-Khamisy & Caldecott (2006). Some of these cover the historical description of ecDNA; therefore, their age alone does not indicate a problem. In particular, Cox et al. (1965) provides the historical basis for the description of ecDNA and can be retained. Similarly, Robinson et al. (2011) may be retained as the original reference for Integrative Genomics Viewer, and Liao et al. (2009) as a methodological reference for the comet assay. However,

the references by Karin et al. (1997), Bonner et al. (2008), Wang et al. (2011), and El-Khamisy & Caldecott (2006) support general biological or methodological concepts related to ecDNA. Consider replacing these with more recent references.

Unrelated references

- Reference 34: Meng et al. (2018) showed that engineered circular DNA can be formed but did not show that current techniques are incapable of making stable circular DNA with a predetermined sequence. Therefore, the citation does not support the specific limitation claimed by the authors.
- Reference 52: Luan et al. (2021) examined the expression of circular RNAs in urinary exosomes from patients with IgA nephropathy and identified differentially expressed circular RNAs associated with the disease. This study does not investigate genome engineering, synthetic ecDNA, or the generation and maintenance of sequence-defined circular DNA. It therefore does not directly support the statement that current genome-engineering approaches have limitations in generating stable, sequence-defined ecDNA.
- Reference 59: Rao et al. (2019) investigated a multitargeted probe-based strategy for identifying signaling vulnerabilities in cancer, rather than generating or characterizing the GBM39EC whole-genome sequencing dataset. Its use as the source for the GBM39EC WGS data in this study should therefore be verified.

DISCLOSURE VALIDATION

PARAMETER	RATING	DESCRIPTION
Ethics statements	Present	No further action required.
EQUATOR reporting guidance compliance	Minor concern	Review the manuscript against the STROBE checklist (https://www.equator-network.org/reporting-guidelines/strobe/) and provide the following missing details: study setting and dates, participant selection and eligibility criteria, handling of potential sources of bias, and basis for determining the study size.
Data availability statement	Absent	Specify how the TCGA data were accessed and provide the accession number for the GBM39EC WGS data.
Funding statement	Present	No further action required.
Conflict of interest statement	Present	No further action required.
Author contribution statement	Present	No further action required.
Informed consent statement	Present	No further action required.
Generative AI use statement	Absent	In line with your target journal's policy, provide a Generative AI use statement, including confirmation that the authors remain responsible for the accuracy and integrity of the manuscript.

PARAMETER	RATING	DESCRIPTION
AI listed as author	No	No AI tool has been listed as an author.

CONFIDENTIALITY VALIDATION

Adequacy of patient image/dataset anonymization
• No patient-identifying information is apparent from the manuscript. Public datasets used in the study are identified, including the TCGA/cBioPortal data and the GBM39EC WGS dataset.

REPORTS ATTACHED

Similarity Report
***Summary*:** The Similarity Index (8%) is within acceptable limits per standard journal requirements (<15%). The Introduction and Methods sections show the largest text matches.

Image Integrity Report
***Summary*:** One potential similarity involving panels in Figures 2 and 6 was identified.

AI Detection Report (only for writing patterns)
***Summary*:** The overall level of AI-assisted writing detected is 71%. Sections with flagged text include the Introduction, Methods, and Discussion.

FINAL RECOMMENDATIONS

Please address the following major issues likely to be raised by the target journal upon submission:

1. Review and qualify statements in the Discussion and Conclusion that extend beyond the results, particularly the proposed mechanistic interpretation and potential future applications of the syn-ecDNA system.
2. Review the manuscript against the STROBE guidelines and address the incomplete reporting elements, particularly study setting and dates, participant selection, potential sources of bias, and study size.
3. Verify the two references flagged as unverifiable and correct them if necessary.
4. Review and correct any inaccurate bibliographic details, including incorrect DOIs identified during validation.
5. Review the citations in the Methods section, particularly those supporting the TMB calculation, genome-engineering methods, and the GBM39EC WGS data source, to ensure that each reference directly supports the claim being made.
6. Update the Introduction to acknowledge recent work on ecDNA retention elements and engineered ecDNA models when describing the current research gap.

You've received your *Post-AI Risk Assessment*. Now what?

Risk assessment gets you halfway.
Editing gets you closer to submission.

Nothing has changed in your manuscript yet.

Revise your manuscript to include the facts, judgment calls, and claims only you can supply, then let our editing services move it closer to submission-ready.

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