



EUROPEAN SCIENTIFIC JOURNAL
by European Scientific Institute



Paper: “Predicting Pathogenicity: Benchmarking SIFT, REVEL and AlphaMissense on ClinVar Missense Variants”

Submitted: 16 September 2026

Accepted: 13 October 2026

Published: 31 October 2026

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Doi: 10.19044/esj.2026.v22n30p52

Peer review:

Reviewer 1: Mamta Rathore
Mohanlal Sukhadia University, India

Reviewer 2: Hiqmet Kamberaj
International Balkan University, Macedonia

Reviewer 3: Blinded

Reviewer A:
Recommendation: Revisions Required

The TITLE is clear and it is adequate to the content of the article.

Yes

The ABSTRACT clearly presents objectives, methods, results, and conclusions.

Yes

There are a few grammatical errors and spelling mistakes in this article.

The English can be improved.

The study METHODS are explained clearly.

The validity of the dataset used is questionable and must be proven. The authors performed the analysis on the ClinVar GRCh38 VCF dated 5 September 2026, which was downloaded on 13 September 2026. They should explain how the validity of the dataset was proven in such a short time.

The results are clear and do not contain errors.

The authors must explain the use of different seeds for random numbers during the Statistical Analysis section (seed 20260913 and seed 20260915).

The authors must explain how the bootstrapping sampling improved the statistics.

How can the authors justify the sample size in their analysis from a statistical viewpoint?

The authors must provide the statistical errors of the AUC values.

The CONCLUSION or summary is accurate and supported by the content.

Partially. The authors must explain the implications of this study.

The list of REFERENCES is comprehensive and appropriate.

Yes

Please rate the TITLE of this paper.

[Poor] 1-5 [Excellent]

5

Please rate the ABSTRACT of this paper.

[Poor] 1-5 [Excellent]

4

Please rate the LANGUAGE of this paper.

[Poor] 1-5 [Excellent]

3

Please rate the METHODS of this paper.

[Poor] 1-5 [Excellent]

3

Please rate the RESULTS of this paper.

[Poor] 1-5 [Excellent]

3

Please rate the CONCLUSION of this paper.

[Poor] 1-5 [Excellent]

2

Please rate the REFERENCES of this paper.

[Poor] 1-5 [Excellent]

4

Overall Recommendation!!!

Accepted, minor revision needed

Comments and Suggestions to the Author(s):

Reviewer B:

Recommendation: Revisions Required

The TITLE is clear and it is adequate to the content of the article.

Yes, the title is clear and adequate, but you can emphasize the "circularity," or you can highlight coverage and real world transcript utility.

The ABSTRACT clearly presents objectives, methods, results, and conclusions.

Yes, it defines all four divisions.

There are a few grammatical errors and spelling mistakes in this article.

No there are no major mistakes in this article.

The study METHODS are explained clearly.

- 1) Add explicit justification for choosing the December 2023 ClinVar snapshot date.
- 2) Clarify statistical testing methods for AUC/F1 differences (e.g., percentile bootstrap vs. bias-corrected accelerated bootstrap; formula for p -value derivation).

3) Explicitly state denominator rules in threshold tables (Table 6) when comparing tools with abstentions against full-coverage tools.

The results are clear and do not contain errors.

- 1) Add a matched $n=710$ comparison row to Table 6 for direct apples-to-apples threshold evaluation.
- 2) Expand Figure 2 to show ROC curves for the additional ($n=3,018$) and snapshot-absent ($n=983$) cohorts alongside the original sample.
- 3) Clarify the impact of class imbalance (59.82% B/LB) in the snapshot-absent results text.

The CONCLUSION or summary is accurate and supported by the content.

The conclusion and summary elements are coherent, and supported by the empirical data. It is free from over statement. Incorporating a brief reference to predictor coverage trade-offs in the final paragraph will complete the paper's synthesis.

The list of REFERENCES is comprehensive and appropriate.

The reference list is appropriate, highly pertinent, and well-aligned with the paper's main themes. Addressing the few missing methodological citations (statistical bootstrap reference and alternative predictor context) will make it completely comprehensive.

Please rate the TITLE of this paper.

[Poor] 1-5 [Excellent]

4

Please rate the ABSTRACT of this paper.

[Poor] 1-5 [Excellent]

4

Please rate the LANGUAGE of this paper.

[Poor] 1-5 [Excellent]

5

Please rate the METHODS of this paper.

[Poor] 1-5 [Excellent]

4

Please rate the RESULTS of this paper.

[Poor] 1-5 [Excellent]

4

Please rate the CONCLUSION of this paper.

[Poor] 1-5 [Excellent]

4

Please rate the REFERENCES of this paper.

[Poor] 1-5 [Excellent]

4

Overall Recommendation!!!

Accepted, minor revision needed

Comments and Suggestions to the Author(s):
