haematologica
Journal of the Ferrata Storti Foundation

Interpreting fusion-transcript stability as one layer of leukemogenic fitness. Comment on: "Chromosomal rearrangement-enhanced mRNA stability drives the oncogenic potential of fusion genes in pediatric leukemia"

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Received: July 15, 2026.
Accepted: July 16, 2026.

Citation: Yuan Liu, Tong Cui and Xuan Wang. Interpreting fusion-transcript stability as one layer of leukemogenic fitness. Comment on: "Chromosomal rearrangement-enhanced mRNA stability drives the oncogenic potential of fusion genes in pediatric leukemia".
Haematologica. 2026 July 23. doi: 10.3324/haematol.2026.301610 [Epub ahead of print]

Interpreting fusion-transcript stability as one layer of leukemogenic fitness. Comment on: "Chromosomal rearrangement-enhanced mRNA stability drives the oncogenic potential of fusion genes in pediatric leukemia"

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Authors' contributions

All authors contributed equally to the conception and drafting of the manuscript and approved the submitted version.

Disclosure

The authors declare no conflict of interest.

Shao X and colleagues address an important question in hematology: Chromosomal rearrangement-enhanced mRNA stability drives the oncogenic potential of fusion genes in pediatric leukemia. [1] The article is valuable because it tackles a clinically recognizable problem and provides a useful basis for discussion. The key issue, however, is whether increased mRNA stability is sufficient to explain fusion-gene oncogenicity across genetically diverse pediatric leukemia contexts. This distinction matters because readers may otherwise move too quickly from an interesting observation to a clinical or methodological conclusion that the present evidence does not fully establish. We therefore believe the article should be read not only for its main result, but also for the assumptions that determine how far that result can travel.

The first issue is that the mechanistic argument would be stronger if transcript stability were separated from promoter strength, chromatin context, fusion-partner expression, and clone-specific selective pressure. The second is that because pediatric leukemia contains multiple lineage states and treatment histories, the same rearrangement-associated stability signal may not carry the same functional meaning in all cellular backgrounds. [2], [3] These concerns do not diminish the contribution of the study, but they define the conditions under which the findings can be applied. A strong letter should make this boundary visible, because the most important risk for readers is not that the result is uninteresting, but that its practical meaning is broader than the data can support. In this sense, the central question is not whether the work is useful; it is what exact decision, hypothesis, or future study the work can legitimately support.

This distinction has practical consequences for interpretation. If the study is read as definitive, readers may focus on the headline conclusion and overlook design features that shape the estimate, such as patient selection, timing of measurement, endpoint definition, missing data, operator behavior, or treatment pathway after enrollment. If it is read as a carefully bounded contribution, however, the same findings become more useful because they identify where the evidence is strong and where replication or refinement is still required. That framing is especially important for studies likely to influence clinical language before they change clinical practice.

A third issue is that the most useful next step would be perturbation experiments that directly destabilize the fusion transcript while preserving coding sequence and expression context. [4] The next study should therefore be designed around a small number of prespecified questions: which subgroup is most likely to benefit from the proposed interpretation, which outcome should be considered decisive, and what level of follow-up, technical quality, or data completeness would make the conclusion reproducible. Answering these questions would help move the field from an interesting report to a usable clinical or methodological standard. Such a design would also make negative or neutral findings more informative, because it would show whether the original signal fails generally or only under specific biological, technical, or operational conditions.

The findings should also be discussed with attention to negative and neutral results. A focused letter is most useful when it protects readers from a one-directional interpretation of promising data. If the reported strategy performs well only under selected conditions, that limitation should be visible early. If the observed effect is clinically attractive but operationally

difficult, implementation barriers should be treated as part of the evidence rather than as a secondary concern. This is not a conservative posture for its own sake. It is a way to keep promising results actionable without turning them into recommendations before the necessary comparative or external evidence exists.

We would therefore encourage future work to report the elements that determine transportability. For clinical studies, these include baseline risk, co-interventions, follow-up intensity, competing events, safety, and patient-centered outcomes. For biomarker, registry, artificial-intelligence, or methodological studies, they include calibration, missingness, data provenance, annotation quality, temporal drift, and external validation. Making these elements explicit would allow readers to distinguish a robust finding from a finding that is promising but context-dependent.

In summary, Chromosomal rearrangement-enhanced mRNA stability drives the oncogenic potential of fusion genes in pediatric leukemia is a meaningful contribution to the literature. [1] A stability-centered model is attractive, but it should be framed as one layer of oncogenic fitness rather than a complete explanation of fusion-gene activity. Its greatest value lies in opening a practical discussion about how the reported evidence should be used, verified, and communicated. Clearer boundaries can strengthen, rather than weaken, the impact of a well-conducted study, because they show readers exactly what should change now and what still requires confirmation.

Reference

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