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Peer Review

Review of: "A Claim-Governed Framework for Conservative Molecular Candidate Prioritization in Schizophrenia"

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The authors' goal of providing a conservative framework for interpreting lines of evidence relevant to candidate prioritization for schizophrenia is laudable, and the example they generate is instructive and makes sense. However, the case for applying such a framework may not be persuasive enough to generate any uptake of this kind of framework. Presently, within the industry, candidate prioritization involves live expert review by scientists from different backgrounds who make judgments with regard to the quality of data to support the case to pursue any novel candidate. Of course, prior to the evolution of analytic tools and forms of AI to access and summarize the very large literature that might mention a particular candidate, expert review was based on more narrow and selective readings of the literature, which may indeed be biased toward making a stronger case than would have occurred had a much broader range of literature been considered applying a claim-governed framework. But is this really such a problem, and have AI tools been that extensively embraced that something like the proposed framework is necessary to prevent too much weight from being given to a target just because it is mentioned in so many ways in the literature, even without scientifically meaningful support? It is true that certain targets are pursued way beyond any reasonable scientific basis, but these instances arise from clinical reports of efficacy rather than genetic and other data implicating some targetable pathophysiology.

From my perspective as someone who relies on team input with regard to candidate prioritization, I am not able to assess exactly how the framework is applied in the generated example and how the evidence layers are applied in the illustrative example. Put another way, is enough information provided in the

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paper that one could ask the informatics team accessible to a company to see if they could replicate the same audit results from the list of 406 candidates? Given the reliance on words, is it the case that the precise wording of evidence layers drives the findings and must be fixed? Are these evidence layer wordings meant to be illustrative, and what should be included in a framework, or are they fixed on some basis of an approach that leads to the conclusion that a certain number of evidence layers is optimum for the intended goal?

I believe the potential value of this proposal needs to be made clearer to readers outside of individuals involved in the task of trying to digest the strongest takeaways from existing sources of data potentially relevant to the question of candidate prioritization. My current bias is against giving weight to AI-generated assemblages of information about a particular target since, as the authors note, such information requires some sort of critical auditing process. I can appreciate that something like the proposed framework could serve that purpose, but the timeliness of the proposal would be helped by contextualizing the extent to which decisions are currently being influenced by AI-generated digestions of accessible data rather than exploring what it might yield in comparison to the current critical evaluations of lines of evidence that influence candidate prioritization in organizations with experienced drug discovery and development teams.

Declarations

Potential competing interests: No potential competing interests to declare.