Review of: "AI-Generated Hallmarks of Aging and Cancer: A Computational Approach Using Causal Emergence and Dependency Networks"

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Potential competing interests: No potential competing interests to declare.

This paper takes an ambitious and innovative approach to modeling aging and cancer using hallmark-level features. However, there are a few limitations that should be addressed to make the findings more reliable and robust.

First, the reliance on a single data source for each disease, often from the same GEO dataset, raises questions about how well the conclusions will generalize. Using independent datasets for validation would really help strengthen the findings and show how applicable the model is to broader populations. Additionally, the sample sizes for some diseases, like osteoporosis and atherosclerosis, are pretty small, which could affect the reliability of the predictive models and causal analyses. Larger and more diverse sample cohorts would help make the results more solid.

If I understand correctly, there are more than 30k models generated and evaluated on the same dataset, which raises the question of overfitting.

The paper mainly focuses on neurological and cancer-related conditions, leaving other important categories—like cardio-metabolic diseases—underexplored. Including these categories would give a more complete understanding of multimorbidity and its underlying mechanisms.

The methodology for hallmark generation, particularly the selection criteria for Traditional Chinese Medicine (TCM) hallmarks, could use more detail. The subjective nature of keyword selection may introduce bias, and being more transparent about this process would help support the study's findings.

The dependency analysis, while detailed, might overestimate the importance of some hallmarks due to inherent correlation structures in DNA methylation data. This could introduce biases in the network modeling, making some hallmarks seem more important than they actually are. Addressing these correlations through de-correlation methods or permutation-based analyses would make the conclusions more robust.

It's also worth noting that the figures seem to be missing data for two diseases: COVID severity and atherosclerosis. Including these would provide a more complete picture and help support the conclusions.

I am guessing that the model used is a logistic model with LASSO; however, it's not entirely clear what type of model was used in this study, and clarifying this would help in evaluating the results. Additionally, the model for osteoporosis shows

suspiciously high performance, but this is not discussed in the paper. Addressing why this performance might be unusually high would provide more transparency and trust in the findings.

Overall, the study presents a compelling framework for hallmark engineering, but addressing these concerns would strengthen its contributions to aging and multimorbidity research.