Dear Editors of *Science Translational Medicine*,

We are pleased to submit our manuscript entitled, *"Why Interpretable Causal Inference is Important for High-Stakes Decision Making for Critically Ill Patients and How To Do It"* to *Science Translational Medicine* as an article for your consideration.

Our paper focuses on introducing an interpretable causal inference framework based on a mechanistic model and highly-flexible nonparametric machine-learning-driven matching methods. This methodology is relevant for high-stakes decision-making scenarios in intensive care units. We apply this framework to an extremely important problem affecting critically ill patients, namely *the effect of seizures* and other potentially harmful electrical events in the brain (called epileptiform activity -- EA) on *outcomes*. EA is a key indicator of whether the patient will suffer long-term severe neurological disability or death. It is important to recognize that this is a question of causal inference and not a simple correlation: previous papers considered this as a prediction-only problem (but interpreted the results as causal, which is problematic). *The results provide actionable guidelines for enhancing the outcomes of patients in ICU.*

Potential reviewers with expertise in interpretable causal inference include Sam Pimentel, PhD (UC Berkeley, spi@berkeley.edu), and Luke Keele, PhD (U of Pennsylvania, luke.keele@gmail.com).

Potential reviewers with expertise in epilepsy include Jong Woo Lee, MD, PhD (BWH, jlee38@bwh.harvard.edu), Jan Claassen, MD (U Columbia, jc1439@cumc.columbia.edu), Larry Hirsch, MD (Yale, lawrence.hirsch@yale.edu), and Michel van Putten, MD, PhD (U Twente, m.j.a.m.vanputten@tnw.utwente.nl).

Drs. Westover, Rudin, and Volfovsky are the joint principal investigators and take full responsibility for the data and conduct of the research. We have full access to all the data and have the right to publish any data. The methods section includes a statement that this study was carried out with the approval of IRBs. There is no individually identifiable patient information in this manuscript. There is no related manuscript under consideration or in press elsewhere. All authors have read and have abided by the statement of ethical standards for manuscripts submitted to *Science Translational Medicine*.

Thank you for your consideration.

*Sincerely,*

*M. Brandon Westover, MD, PhD*

*Cynthia Rudin, PhD*

*Alexander Volfovsky, PhD*