Dear Editors of Lancet Neurology,

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

Lancet Neurology 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

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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 Lancet Neurology.

Thank you for your consideration.

Sincerely,

M. Brandon Westover, MD, PhD

Cynthia Rudin, PhD

Alexander Volfovsky, PhD