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The Editors

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**PLOS call: Machine Learning in Health and Biomedicine**

Dear Professor Butte, Dear Professor Saria, Dear Professor Sheikh,

Please find enclosed our manuscript entitled **"**Prediction and inference diverge in biomedicine: Simulations and real-world data**”** for consideration as an article in *PLOS Medicine* in the ongoing call for *Machine Learning in Health and Biomedicine*.

Many advances of evidence-based medicine in medical diagnosis and treatment are established based on statistically significant group differences. In the beginning of the 21st century, however, biomedicine has growing ambitions to achieve detailed predictions at the single-patient level. In our work, this discrepancy between null-hypothesis testing to obtain p-values and machine-learning approaches that estimate expected prediction in future individuals is quantitatively characterized in >100,000 simulated analysis scenarios and several widespread medical datasets. Across all cases, even small predictive performances typically coincided with finding underlying significant statistical relationships. Yet, even statistically strong findings with very low p-values shed only modest light on its value for goal of prediction based on the same data. Elaborating such interplay between statistical hypothesis testing and brute-force algorithmic modeling will be a prerequisite for reproducible research findings that can be exploitable for personalizing clinical care.

Given the fundamental nature of our results and conclusions, we anticipate that the manuscript should attract wide attention in medicine, genetics, biology, big-data statistics, computer science, and beyond. We also provide executable iPython notebook, the full programming code, and an interactive Web-App to illustrate the presented findings. We hope that our work will be considered for publication in *PLOS Medicine* and thank you for your time and consideration.

Yours sincerely,

Danilo Bzdok, Denis Engemann, Olivier Grisel, Gaël Varoquaux, Bertrand Thirion