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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 original article in *PLOS Medicine* in the ongoing call for *Machine Learning in Health and Biomedicine*.

Many advances of evidence-based medicine in diagnosis and treatment are established by showing 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 burgeoning machine-learning approaches that estimate expected predictability in future individuals is quantified in >100,000 simulated analysis scenarios and several medical datasets. We report that even small cross-validated predictions typically coincided with finding underlying significant statistical relationships across all cases. 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. Such synthetic evidence for the interplay between gold-standard hypothesis testing and brute-force algorithmic modeling will be a critical for reproducible research findings for personalizing clinical care.

Given that our results and conclusions have far-reaching implications for health policy, we anticipate our manuscript to attract wide attention in medicine, genetics, biology, big-data statistics, computer science, and beyond. We also provide the full programming code for our analyses and figures, executable Jupyter notebooks with extended findings, and an interactive Web-App to illustrate the presented findings. All used data are openly available to everybody. 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