Application number/Title: 28967 - Predicting drug efficacy, potential adverse outcomes, and causal biology through phenome-wide association studies (PheWAS) and Mendelian randomization

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Keywords provided by the Applicant PI to describe the research project:

PheWAS, Mendelian randomization, drug efficacy

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Application Lay Summary:

1a: This project's goal is to use human genetics to investigate biological processes of disease and to predict efficacy and potential side effects of drugs targeting genes of therapeutic interest to Merck. We will use genetic and phenotypic data from the UK Biobank to 1) investigate other effects of disease-associated or functional variants in genes of interest via PhenomeWide Association Studies (PheWAS), and 2) test causal relationships between biological processes and clinical outcomes using Mendelian Randomization. Health conditions of interest include cardiometabolic, autoimmune, inflammatory, neurodegenerative, and eye diseases. Investigation of side effects will not be limited to this list.

1b: Merck is committed to developing medications that save and improve lives while avoiding side effects. Analysis of the UK Biobank data will contribute to our understanding of the biology of drug targets of interest and help to predict efficacy and potential adverse outcomes at a very early stage of the drug development process. Thus, our project is well aligned with the UK Biobank's aim of "improving the prevention, diagnosis, and treatment of a wide range of serious and life-threatening illnesses".

1c: Genes of therapeutic interest to Merck will be selected and functional

variants (related to diseases of interest) in those genes will be identified. A statistical test will be conducted to determine whether each variant is associated with any other diseases or traits in the UK Biobank data (i.e., a phenome-wide association study, or PheWAS). Mendelian randomization will also be performed. This involves identifying variants with known effects on molecular traits (e.g., serum protein levels) related to drug targets. Statistical tests will be performed to determine whether perturbation of specific proteins or pathways is related to disease.

1d: To maximize power, the full cohort is requested.