**PRECISION MEDICINE FOR TREATMENT-RESISTANT DEPRESSION**

Clinicians throughout history have worked to tailor both prevention and treatment strategies to the individual patient’s needs; it is a fundamental credo to the practice of medicine. However, the vast majority of evidence-based clinical practice is based on research results acquired from measuring the common treatment effect on the “average person” in a restricted patient population with limited data, which we now know does not necessarily apply to the real-world setting. This clinical concern has stimulated the world-wide pursuit of Precision Medicine across disease areas. The audacious mission appears to be gaining momentum, given recent advancements in precision cancer treatment. Unfortunately, much less progress has been made in other areas of medicine; nowhere is this more evident than in mental health care. Treatment-resistant depression is of chief concern, since the primary method of antidepressant treatment generally provides little improvement in symptoms or functioning. Recent evidence suggests that second generation antipsychotic agents (SGAs) combined with antidepressants may be effective, but more evidence is needed to determine who would benefit from tailored augmentation.

The NIH’s *All of Us Research Program* (AoURP) offers the potential infrastructure to effectively realize the mission. The AoURP seeks to enroll 1 million individuals across the United States, who agree to complete longitudinal surveys on lifestyle and environment, a clinical visit with a physical evaluation and biospecimen collection, and to share their full electronic health record data. It is designed to support ‘open science’ for researchers to propose, and answer, important research questions. Overall, AoURP will provide the largest infrastructure of its kind to stimulate innovation in precision medicine, and is currently NIH’s top research program. Because any US resident is eligible, the major strength of the cohort will be its broad generalizability to understand the intersection of environment, genetics, and clinical history and subsequent risk or etiology of specific diseases (including mental health). But, there likely will not be a large enough sample to answer questions about therapeutics or personalized treatment, especially for rare conditions – such as treatment-resistant depression. The AoURP will have the capacity to expand its base infrastructure for affiliated studies, and there is a dedicated effort to involve disease-specific NIH-institutes and centers in that effort. This could include additional enrollment targeted to specific therapeutics, however, the design and protocol for implementing this process has not been developed. In addition, while all of the AoURP participants agree to share their EHR data, most of the participating health systems do not have longitudinal or comprehensive capture (including clinical capture of patient-reported outcomes on depression) necessary to support accurate measurement of outcomes related to treatment selection. Mental Health Research Network (MHRN) health systems (including several that are also part of AoURP) can provide the ideal setting and expertise.

This proposed project provides a unique opportunity to pilot test new methods of AoU enrollment of 1,000 participants with treatment-resistant depression into the AoURP, based specifically on their favorable-unfavorable response to SGA augmentation across two MHRN / AoURP affiliated health systems (Henry Ford in Michigan and HealthPartners in Minnesota). The project would generate important information on how, and for who, physicians should tailor antidepressant augmentation with SGAs for TRD. Also, this project would develop and test new innovative methods for specialized enrollment based on treatment response and provide the first real opportunity for “open science” for researchers to leverage the joint infrastructure of MHRN and AoURP. Successful enrollment could support other future opportunities for larger-scale targeted enrollment into AoU based on treatment-response. Both NIMH and AoU leadership have approved this project, given the bi-directional commitment of priorities and the likelihood of future funding opportunities for other projects. MHRN is well-positioned to provide the best data, and to test a solution in this area of opportunity for AoU enrollment.

**The specific aims are**:

1. Develop and test methods for targeted AoURP enrollment of 1,000 participants who initiate an SGA for treatment resistant depression and have longitudinal clinical measurement of patient-reported depression outcomes at two MHRN sites.
2. Characterize the enrolled sample using MHRN electronic health records data to provide baseline information for use in future studies.
3. Use detailed EHR data to characterize differences between participants and non-participants.

Lead Investigator – Brian Ahmedani; Sites Interested – Henry Ford, HealthPartners

**Anticipated total budget** (including F&A costs) will be ~$225,000 for Henry Ford (lead site) and ~$375,000 for HealthPartners – for a total of ~$600,000. This would be divided across two project budget years starting later in the grant period.