Research Proposal:
Behavioral Interventions Combining AI/ML and Personalized Medicine to Reduce Cardiovascular Risk

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Specific Aims: This project will assess the efficacy of a newly developed AI-based digital health intervention to reduce cardiovascular risk and will reoptimize the tool based on personalized medicine principles to account for heterogeneity in treatment effects. The specific aims are as follows:

Aim 1: Study the effects of the AI-enhanced digital health program on clinical health outcomes and health behaviors. This will be based on a pilot in which patients will be referred to the program via healthcare professionals to increase takeup and ensure ability to study intent-to-treat (ITT) in an event study design.

Aim 2: Design, conduct, and assess an RCT to study the efficacy of treatment intensity in terms of the extent of personalized information and behavioral advice provided by the tool. This will include a randomized component in the pilot from Aim 1 after patient recruitment.

Aim 3: Incorporate behavioral predictions of differential treatment effects into the personalized product design. Associations with patient characteristics from Aim 1 and heterogeneity in treatment effects from Aim 2 will be fed back into the AI tool to reoptimize the patient-personalized intervention.

Background/Significance: Digital innovations and the abundance of medical data are transforming the healthcare landscape in the U.S. and worldwide. Two related approaches that are among the key drivers of the paradigm shift in the delivery of care include the integration of AI/ML techniques into the provision of care and the design of personalized and precision medicine—both perceived to hold great promise for improvements in population health and reductions in healthcare costs.

Artificial intelligence machine learning (AI/ML) platforms involve computational techniques that learn from experience. Examples of AI/ML usages include predicting patients' likelihood to be readmitted to a hospital and using remote patient monitoring to predict whether a patient's condition may deteriorate (Shani et al. 2023). Personalized and precision medicine refers to the targeting of medical treatment and interventions based on an individual's biological, genetic, or clinical characteristics. Personalized and precision medicine can increase the gains from medical care by better matching patients to treatments, as well as by identifying individuals with elevated health risks who would benefit from timely preventive measures and targeting them for behavioral interventions (Berndt et al. 2019).

Economic and medical research are at their infancy of assessing the social value of new digital health technologies, specifically those that leverage AI/ML techniques for personalized medical care and interventions. Moreover, there is scarcity of work that provides evidence-based insights for the design of patient-tailored healthcare tools and products that can improve their efficiency.

Innovation: In this project, we will evaluate, and subsequently improve, a newly developed AI-driven lifestyle intervention service for patients with hypertension (Leitner et al. 2022).

The automated intervention platform consists of a remote monitoring system that ingests lifestyle and blood pressure data and builds a personalized machine learning (ML) model to generate tailored lifestyle recommendations most relevant to each patient's blood pressure. Lifestyle data is collected via a wearable device and a mobile-app questionnaire which includes activity, sleep, stress, and diet information. Blood pressure data is remotely collected using at-home digital monitoring devices. The system then uses these data to train random forest models that predict blood pressure from lifestyle features and uses Shapley Value analysis to estimate the impact of features on blood pressure. Precise lifestyle recommendations are generated based on the top lifestyle factors for each patient.

Overall, the project will advance the science on digital health solutions by assessing the efficacy of the new AI-based tool in improving patient health and by using the analytical findings to reoptimize the tool with evidence-based insights for product design.

Approach and Analytical Plan: The intervention focuses on cardiovascular risk due to its prominence as a leading cause of death in the U.S. (Ahmad and Anderson 2021) and since cardiovascular risk can be effectively modified through changes in healthy behaviors (including drug intake, exercise, and diet). Since hypertension and cardiovascular risk significantly increase over the course of life, the project has the potential to broadly improve population health as people age.

Our project involves a collaboration between UC San Diego's Departments of Economics, Family Medicine, and Electrical and Computer Engineering. The Population Health Services Organization (PHSO) of UC San Diego Health has been collaborating with faculty and trainees in Electrical and Computer Engineering to pilot test the AI-enhanced tool. Ming Tai-Seale in Family Medicine is the Director of Research and Learning at the Population Health Services Organization within UC San Diego Health. She coordinates and oversees the collaboration across the product developing team and the research evaluation team. Itzik Fadlon from Department of Economics is in charge of the statistical and economic analysis of the digital health program. The planned intervention will be employed by the Population Health Services Organization and will be offered to its diverse patient population.

So far, the developers began their efforts to test the system's ability to improve blood pressure levels with very small initial pilots that were designed for "proof of concept" purposes (Chiang et al. 2021, Leitner et al. 2022). Across two pilot studies, enrolled hypertensive patients were included in one of the following groups: (1) a control group (N=19) consisting of patients who did not receive any recommendation but were provided with a blood pressure cuff and a digital watch for data collection; (2) experimental group 1 (N=6) consisting of patients who received a one-time recommendation; (3) experimental group 2 (N=13), from a separate recruitment and pilot, consisting of patients who received weekly lifestyle recommendations based on their dynamically updated data and a personal model over a six-month period. The recommendations were sent via text message. Each message included a summary of the patient's blood pressure progression for the current week in addition to the lifestyle recommendation.

The limitations of these pilots are clear: (1) the very small number of participants does not enable econometric evaluations; (2) the analysis of only enrollees who self-selected into the program (following a mass recruitment email that was sent to UCSD Health hypertensive patients) does not facilitate causal analysis. These pilots were not designed to assess the product and its features. The goal of our proposed project is to rigorously assess the efficiency of the new tool in a scalable way.

To accomplish our specific aims, we plan to proceed as follows:

Aim 1: To assess the effects of the modified AI-enhanced intervention we will recruit more patients to the program. Until now, there have been approximately 150 patients who participated in the latest version of the intervention, where approximately 115 of them are currently still engaged with the program. There are two practical limitations in assessing the causal effects of the program. First, due to ethical considerations of a functioning academic health system, we cannot randomize hypertensive patients to a control group—this is because it will prevent these patients from being able to receive treatment that may improve their health with minimal risk. Second, one cannot simply study self-selected enrollees for a causal interpretation. Estimations of the intent-to-treat (ITT) are required to overcome selection. The current method of recruitment through a mass email has proven very undesirable, as it induced extremely low takeup rates (150 patients out of thousands of email recipients). This makes ITT assessments severely under-powered.

To deal with these two limitations, future rounds of recruitment will be done by primary care physician (PCP) referrals. This is based on lessons we have learned as part of a recent remote patient monitoring intervention for hypertension management at UCSD Health (Fadlon et al. 2023). An initial recruitment round offered the program to patients through a mass robocall which induced takeup of only 5 percent. The program then quickly shifted to recruiting patients through PCP referrals. PCP referrals induced around 50 percent takeup (presumably due to increased trust from the more personal nature of the referral), allowing for a sufficient pool of patients for an ITT analysis. For assessing the overall efficacy of the AI program, we will use an event study design around PCP referral (that will include all referred patients), which we will accompany with analysis of different potential control groups from the overall patient population for robustness (similar to our analysis in Fadlon et al. 2023). We are only now at the stage of learning insights from the behaviors and health outcomes of the 150 patients, so unfortunately we have not been able to conduct power calculations in time for the proposal submission.

Since the tool collects data on adherence (e.g., information on exercise following an exercise recommendation), we will also be in a position to assess potential mechanisms that could govern the program's effects. The embedded mobile-device survey tool will also allow us to make additional inquiries among participants.

Aim 2: While we cannot randomize patients into a control group at the PCP setting, we can randomize patients at the back end by the research team into different treatment arms. Moreover, at this stage we will also significantly increase potential power by focusing on patients who wish to enroll since we will randomize those who take up the program. While they are selected compared to all referred patients, their randomization into treatment arms will guarantee internal validity.

Our main target in Aim 2 is to assess aspects of the main innovation—personalized lifestyle recommendations—in a rigorous way, while simultaneously being attuned to insights from existing work in behavioral sciences. Richness of information can improve behaviors via directed personalized messages, but it can also lead to information overload and salience effects. For example, receiving more than one recommendation can divert a person's attention to the latest one (although a previous recommendation might be predictively more important) or even lead to inaction altogether. Hence, a key aspect we wish to manipulate will be the intensity of recommendations in terms of, e.g., frequency, number, and density of information provided.

Since we hypothesize a non-monotone relationship between behavioral improvements and recommendation intensity, we plan to create three arms: low, medium, and high intensity. While this will be designed to study a particular angle of the intervention, it can provide additional evidence of the overall efficacy of the program, since the personalized recommendations are the key innovation of AI/ML products for personalized precision medicine. This can be achieved by setting the low intensity arm to provide "very" low levels of interventions (e.g., one time recommendation as in the original pilot). The randomization of enrolled patients into treatment arms will be done jointly by the product developing team and the research evaluation team.

Aim 3: By design of AI/ML tools for personalized and precision medicine, the developed tool embeds dynamic learning and reoptimization based on new data within a patient. However, we can push this frontier further by going beyond predictive statistical associations to predictions of treatment effects. Specifically, we will study how the mean causal effects of intervention intensity from Aim 2 may vary by patient observables, including age, gender, education, and location of residence. We will then feed these predictions back into the model, so that the modified product will additionally offer recommendation intensity per patient that best matches the predicted response of the patient to the intervention itself.

Anticipated Budget Needs: The rollout of the intervention and the provision of equipment to patients is planned to be financed by UCSD Health. The requested budget in this application will pay for the research efforts involved in designing, implementing, and evaluating the intervention to assess the AI-based tool and its effects on patient health outcomes. Ideally, funding will include the following in direct costs:

- Investigators' salary:
    - Fadlon:
        - 3 summer months, rate: $20,325/month with 6.7% in fringe benefits, total: $65,060
        - 1 course buyout (if covered by this initiative), total: $62,805
    - Tai-Seale
        - 10% salary (at NIH cap) and benefits, total: $28,278
- Research support:
    - GSR: one year at 50%, rate: $37,210, tuition remission: $22,878, total: $60,088
- Total: $216,831

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