PROTOCOL TITLE: Pragmatic Impact of Proteomic Risk Stratification in Diabetes Mellitus (PORTRAIT-DM)

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OTHER DEPARTMENTS INVOLVED IN THIS STUDY (IF APPLICABLE):
☐ N/A

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Objectives

Primary Aim: To determine whether risk stratification from SomaLogic's Cardiovascular Risk in Type 2 Diabetes (CVD-T2D) test leads to risk-concordant changes in prescriptions and/or medical management in patients with diabetes.

Key outcome measures: The relation of prescription rates of cardioprotective medications (SGLT2i or GLP1 RA) to CVD-T2D test risk assessment in the Informed group vs. Uninformed group (primary outcome of the study).

Secondary Aims:
Secondary Aim 1: To evaluate the perspectives of healthcare providers on the impact of SomaLogic's Cardiovascular Risk in Type 2 Diabetes (CVD-T2D) test risk calculator in clinical practice.

Key outcome measure: Survey of healthcare providers on the impact of SomaLogic's CVD-T2D calculator on patient care, medication prescription, and risk perception.

Secondary Aim 2: To enable future health economic analyses of the impact of precision risk-stratified treatment.

Key outcome measure: Cost effectiveness of additional therapies using actual uptake and event rate reductions estimated from protein predicted risks

Secondary Aim 3: In an open-label extension, to determine the impact of additional Metabolic Factor test results (beyond the SomaSignal Cardiovascular Risk in Type 2 Diabetes (CVD-T2D)) on medical management of the previously uninformed group at the end of the study.

Key outcome measure: Proposed change in medical management in the uninformed group after revealing the result at the end of the study

Background

Despite the development of novel lipid lowering (1,2,3), anti-inflammatory (4,5), antithrombotic (6), dual antiplatelet (7) and anti-diabetic (8,9) treatments, cardiovascular disease remains the leading cause of death and disability worldwide (10).

In clinical practice, it has also been observed that the use of novel glycemia lowering therapies with cardioprotective features remains profoundly low (less than 10% of eligible patients) despite proven efficacy, professional society guideline endorsement, and regulatory labels for cardiovascular benefit (11). The overall prescribing deficiency seems particularly acute in individuals with type 2 diabetes, where it has been described in 2021 as a “Call for action to the cardiology community” (11).

As current clinical trials and guidelines tend to “bundle” patients together, there is an absence of individualized assessment of residual cardiovascular risk. This leads to physicians, patients, and payors being uninformed as to the need for and/or benefits of such therapies in an individual. Simply giving every eligible patient a drug regardless of residual risk would be unaffordable and would create adverse effects and costs for people at low residual risk who might not actually benefit from the drugs.

This problem arises because traditional cardiovascular risk factors report unresolved risk inadequately in vulnerable patients with high observed event rates (13-15) and because benefits occur independently of traditional risk factors (4, 5, 16, 8, 16, 17) as do adverse drug effects (18). Additionally, physicians’ traditional empirical use of some therapies, which is effective for lipids, blood pressure and glycemic control is militated against by the insensitivity to improvements of many traditional cardiovascular risk factors (age, sex, race, diabetes status and hypertension history) and imaging measures (calcium score, carotid, and coronary imaging). This is important because novel agents, such as sodium-glucose co-transporter 2 inhibitors (SGLT2i), glucagon-like peptide 1 receptor agonists (GLP-1 RA) or anti-inflammatory drugs like canakinumab, reduce cardiovascular risk independently of changes in these factors.

Precision risk assessment tools can be helpful in identifying individuals at highest cardiovascular risk, who can be targeted with intensive preventive therapies. Proteomic analysis has shown promise in risk stratification owing to simultaneous evaluation of multiple pathophysiologic mechanisms implicated in the development of cardiovascular

disease. SomaLogic has performed the largest ever proteomic program to date with over 36,000 samples from 26,000 participants in eleven clinical studies, for a total of over 180,000,000 protein measurements, to develop and validate a proteomic surrogate endpoint for cardiovascular outcomes. The SomaSignal Cardiovascular Risk in Type 2 Diabetes (CVD-T2D) test, a 27-protein model encompassing ten biologic systems was validated to predict the four-year likelihood of myocardial infarction, stroke, hospitalization for heart failure or death. Outcomes prediction in six validation datasets was consistent across morbidities, demographics, and geographic regions and superior to a clinical model using typical risk-factors and laboratory measurements: the Net Reclassification Index was +0.43, AUCs were 0.73 vs. 0.63. Event rates in four defined risk categories were 5.6%, 11.2%, 20.0% and 43.4% (the latter commonly viewed by our practitioners as catastrophically high). There are no risk calculators currently available specifically for a higher risk population. SomaLogic developed a clinical model derived from the ASCVD risk score (Pooled cohort equation or PCE), scaled to a 4-year prediction and calibrated to the higher event prevalence in a higher risk population (Manuscript submitted). The validation datasets were divided into quintiles based on event rates and compared the ratio of event rates from the highest risk quintile to the lowest risk quintile. The ratio of observed event rates from quintile 5 to quintile 1 was 7.8 for the 27-protein model and 2.9 for the derived clinical model.

The table shows the key results and comparisons with the PCE-derived clinical model using demographic, medical and laboratory measures, and how the SomaSignal CVD-T2D test responds more consistently to changes in risk than any one of the common biomarkers of risk:

Table 1: Discrimination capabilities of Somalogic's CVD-T2D assessment tool in high risk populations

Predictor of 4-year likelihood of: MI, stroke, heart failure or death in higher risk populations *(HUNT3 secondary, ARIC secondary, ARIC primary >age 65, BASEL VIII, EXSCEL placebo, ACCORD standard therapy group)*	**Quintile 5 to Quintile 1 observed event ratio**	**Net reclassification index (continuous)**	**4-year AUC**	**C-statistic**
27 Protein model (validation meta-cohort, n=11,608)	7.8	Event NRI: +42% Total NRI: 0.43	0.73	0.71
Optimal clinical/laboratory Model (validation meta-cohort n=5,593)	2.9	Reference	0.63	0.62

Responsiveness to change: Inter-group change in protein predictions and common biomarkers in paired samples *Bold/colored symbols are p<0.01 corrected for multiple comparisons*		**27 Proteins, absolute change in risk**		**CRP**	**Cystatin-C**	**GDF-15**	**Myelo-peroxidase**	**NTproBNP**	**Troponin**
Expected Adverse Change	Approaching an event, 1-year change vs. no event (EXSCEL)	+2.9%	↑	↑	NS	NS	NS	↑	↑
	Approaching an event, 2-year change vs. no event (ACCORD)	+6.0%	↑	NS	NS	NS	NS	NS	NS
	Anthracycline chemotherapy, 3 month within-subject change (PRADA)	+6.2%	↑	NS	↑	↑	↑	NS	NS
Expected Neutral Change	Intensive diabetic control, vs. standard control (ACCORD)	NS	NS	↑	↑	NS	↑	NS	NS
	Angiotensin receptor blocker in chemotherapy vs. placebo (PRADA)	NS	NS	NS	NS	NS	NS	NS	NS
	Beta blocker in chemotherapy vs. placebo (PRADA)	NS	NS	NS	↓	↓	NS	NS	NS
Expected Beneficial Change	Exenatide, within-subject change vs. placebo (EXSCEL)	-1.5%	↓	↓	NS	↓	NS	↓	NS
	Dietary weight loss in diabetics in one year vs. standard diet (DiRECT)	-6.7%	↓	↓	NS	↓	NS	↑	NS

In summary, compared to the PCE-derived clinical risk factor model, the SomaSignal Cardiovascular Risk in Type 2 Diabetes (CVD-T2D) test has a superior dynamic range of stratification, a greater ability to find patients whose risks are under assessed by traditional risk factors, and an improved discrimination between patients with different risks. Compared to typical biomarkers that might be used to capture some of the benefits of these novel mechanistic drugs, it is more sensitive and more consistently responsive to changes in risk. Elevated cardiovascular risks were also correctly detected in non-cardiovascular conditions with known higher cardiovascular event rates: diabetes, cancer, rheumatoid arthritis and smoking.

Additionally, an in-silico assessment of protein-based risk stratification as a tool to identify patients who would most benefit from enhanced cardio-protection was performed in the archived samples and data from the EXSCEL study (19) of approximately 5000 participants with type 2 diabetes. During the study, the random "drop-in" rate of additional novel cardioprotective-antidiabetic drugs (SGLT2i) was approximately 15%. When stratifying this population with the SomaSignal Cardiovascular Risk in Type 2 Diabetes (CVD-T2D) test, the rate of predicted vs. observed events were found to be accurate (Table 2). Equally important, SGLT2i utilization reduced the cardiovascular event rates in the sub-group at "high" risk defined by protein-based risk stratification when compared with those "high" risk sub-group who did not receive additional cardioprotective medications. Of note, the allocation of additional medications during the study showed no relation to protein risk prediction (i.e. physicians making these therapeutic decisions were unaware of actual residual risks).

Table 2. SomaSignal CVD-T2D Test stratification and 4-year observed event rate in the presence/absence of drop- in medications in the EXSCEL trial

Risk Bin	Drop in CP Medication (%)*	4-year Event Rate (Events)	Hazard Ratio	Log-estimated Hazard Ratio (HR)	p-value (logHR)
Low Risk (N = 115)	Yes = 17 (14.8%)	0% (N = 0)	N/A	-18.274	0.998
	No = 98 (85.2%)	7.14% (N = 7)			
Medium-Low Risk (N = 1,759)	Yes = 222 (12.6%)	9.01% (N = 20)	0.940	-0.062	0.782
	No = 1,537 (87.4%)	9.63% (N = 148)			
Medium-High Risk (N = 1,944)	Yes = 238 (12.2%)	14.7% (N = 35)	0.957	-0.044	0.790
	No = 1,706 (87.8%)	15.0% (N = 256)			

High Risk (N = 1,387)	Yes = 162 (11.7%)	25.9% (N = 42)	0.7 12	-0.340	0.030
	No = 1,225 (88.3%)	32.8% (N = 402)			

The SomaSignal CVD-T2D test has also been tested and found to be robust for consistency over time, insensitivity to interfering substances and to differences in sample quality. It is currently commercially available as a laboratory developed test under CAP accreditation /CLIA certification from SomaLogic's central laboratory in Boulder, CO. It is also in-use by several pharmaceutical companies in their clinical trials programs.

Our overarching hypothesis is that the provision of precise, individualized protein-based cardiovascular risk assessment to the clinician and the patient results in risk-concordant prescription of novel cardioprotective therapies in individuals with type 2 diabetes, such that the patients with the highest residual risk are more likely to receive additional therapy than the patients at low risk. Furthermore, we will explore the impact of the Metabolic Factors panel of tests include testing for Liver Fat, Glucose Tolerance, Alcohol Impact, Cardiorespiratory Fitness (VO2 max), Resting Energy Rate, Body Fat Percentage, Visceral Fat, and Lean Body Mass.

Inclusion and Exclusion Criteria for Patients (Participants)
Participants' eligibility will be determined by study staff.

Inclusion Criteria

- Patients receiving care at a University Hospitals location
- Patients 40-89 year of age
- Diagnosis of Type 2 Diabetes Mellitus
- Eligible for but not currently prescribed a SGLT2i or GLP1RA per drug label. This includes a diagnosis of type 2 diabetes plus established atherosclerotic cardiovascular disease or high risk for atherosclerotic cardiovascular disease (including age ≥55 years with coronary, carotid, or lower-extremity atherosclerotic disease) or heart failure or chronic kidney disease with or without albuminuria.
- Patients that are able to provide consent

Exclusion Criteria

- Intolerance or contraindication for use of both GLP1RA and SGLT2i
- Use of SGLT2i or GLP1RA within the 3 months prior to enrollment
- History of, an active, or untreated malignancy, in remission from a clinically significant malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) for less

than 5 years prior to, or are receiving or planning to receive therapy for cancer, at screening
- Patients that have Systemic Lupus Erythematous (SLE)
- End-stage renal disease
- Pregnancy (as determined by self-report)
- Inability to understand English (since must be able to understand risk report which is not translated by the manufacturer)

Inclusion and Exclusion Criteria for Providers
Providers' eligibility will be determined study staff based on the eligibility of their patients.

Inclusion Criteria
- Provider of care for patients eligible for inclusion in the study

Exclusion Criteria
- Unwilling to participate in the study
- Not a provider of an eligible patient for the study

Number of Research Participants
Up to 600 participants at UHCMC.

Number of Providers of Research Participants
Up to 600 providers at UHCMC (possible 1:1 participant to provider ratio).

Recruitment Methods
We will apply for waiver of HIPAA for identification of eligible patients. We will review medical records to ascertain inclusion/exclusion criteria for eligible patients. Eligible providers will be identified based on whether they have a treating relationship with eligible patient participants. Providers of eligible patients will then be contacted via email with a REDCap link that will direct them to the information sheet and survey to determine if they elect to participate. If the provider agrees to participate, the corresponding patient will then be approached at their clinical encounter (clinic visit, imaging testing, etc) in a private area for study overview and informed consent.

A participant-screening log will be maintained throughout the study. The log will record all participants considered for enrollment in the trial and indicate whether they were enrolled or not enrolled. In the case of non-enrollment, an explanation will be provided on the log as to the reason for their exclusion.

Setting
Study procedures will be performed at a UH facility (hospital or health center) based on the patient's treatment location. We will screen all patients who have an appointment for coronary artery calcium scoring, primary care physicians, endocrinologists and cardiologists at UH who meet inclusion and exclusion criteria. Study personnel will

identify potential research participants through screening the eligibility criteria. Study personnel will provide study information to the eligible providers (see recruitment method above) and eligible patient participants at the UH location and obtain informed consent. Demographic and clinical information will be obtained and phlebotomy will be performed for SomaSignal Cardiovascular Risk in Type 2 Diabetes (CVD-T2D) and Metabolic Factors testing. Study personnel will then send the blood specimen for processing and shipping. Based on the protocol allocation, the SomaSignal Cardiovascular Risk in Type 2 Diabetes (CVD-T2D) and Metabolic Factors test information will then be provided to the patient's treating physicians/providers.

Consent Process

Providers of patient participants consenting to participation in the study will be contacted (as described above in Recruitment) and asked to complete a survey. Since the completion of the survey implies consent but we will not collect a signature, we are requesting a waiver of signature for providers.

Physical (face-to-face) electronic informed consent with an electronic signature will be obtained for all patients prior to participation through REDCap.

Consent will take place in a private location where a study staff member will spend approximately 15 minutes reviewing the goals of the study, inclusion/exclusion criteria, risks and benefits of participation, and procedures involved in participation. Sufficient time will be given to read, comprehend, and understand the goals and procedures of the study. Participants will provide a summary of their role in this research study to the study personnel to ensure complete understanding of the study prior to signing the consent form. After the electronic signature is obtained from both the participant and the study team member reviewing the consent, the patient will have the option of having a copy of the consent emailed or printed for their records.

Tablets will be protected with a case that also allows for disinfecting in between volunteers.

If in some rare occurrence the tablets do not allow for proper informed consent and electronic signatures, patients will be given a written paper copy to review and sign. The consent will then be uploaded to REDCap for secure storage and privacy. The patient will be given a paper copy for their records.

Sharing of Results with Research Participants

For Arm 1 (Informed arm), the results for the SomaSignal Cardiovascular Risk in Type 2 Diabetes (CVD-T2D) test will be provided to the care team (physician participants) approximately 4 weeks after the blood draw. Sharing of this information with patients will be left to the discretion of the clinical care providers. The additional Metabolic Factors test will be provided to the care team (physician participants) approximately 12 weeks after the blood draw in the second phase (open label extension) of the study.

For Arm 2 (Uninformed arm), the clinicians will provide standard of care without the SomaSignal Cardiovascular Risk in Type 2 Diabetes (CVD-T2D) test result in the first phase of the study. The results for the SomaSignal Cardiovascular Risk in Type 2 Diabetes (CVD-T2D) and the additional Metabolic Factors test will be provided to the care team (physician participants) approximately 12 weeks after the blood draw in the second phase of the study.

Study Design
Single-center, prospective, 2:1 randomized controlled parallel-group study, with an open label extension to evaluate SomaSignal Informed Medical Management (informed) versus Standard of Care (uninformed).

Study Procedures
Randomized Clinical Study: 2:1 Randomized Controlled Parallel-Group
Arm 1: SomaSignal Cardiovascular Risk in Type 2 Diabetes (CVD-T2D) Test Informed Medical Management (Informed). The SomaSignal Metabolic Factors test results will be provided in the Open Label Extension; results will not be provided to provider and participant until study conclusion.
Arm 2: Standard of Care (Uninformed). The SomaSignal Cardiovascular Risk in Type 2 Diabetes (CVD-T2D) and Metabolic Factors test results will be provided in the Open Label Extension; results will not be provided to provider and participant until study conclusion.

Participants' eligibility will be determined by study staff.
Once deemed eligible based on the inclusion/exclusion criteria, participants will be enrolled after informed consent. Eligible patient identification and consent may be carried out prior to the clinic/test visit, as allowed by local regulatory policies.

Participants will be randomized using permuted mixed block randomization, in a 2:1 ratio, i.e., 2 participants to Group 1 (informed of their test results) and 1 participant to Group 2 (uninformed of their test results)

Procedures

Patient Intake Questionnaire
Participants will be asked to complete an intake questionnaire about their past medical history, diet and lifestyle. Survey completion will take approximately 15 minutes. All surveys will use the REDCap database platform for collection and storage.

Biological Sample Collection
During the research visit consent will be obtained. After consent occurs, medical history will be collected from the subject and/or his/her medical records. A blood sample (approximately 5ml) will be collected using an EDTA tube. The blood sample will be processed following the *SomaSignal Collection, Processing, and Shipment Instructions*. The samples will be sent to SomaLogic, Inc. at a frequency agreed by the Principal Investigator and SomaLogic, Inc. for analysis. The individual results will be delivered

to UHCMC using secure electronic means. Participants will be compensated 20$ for their time for participating in the study.

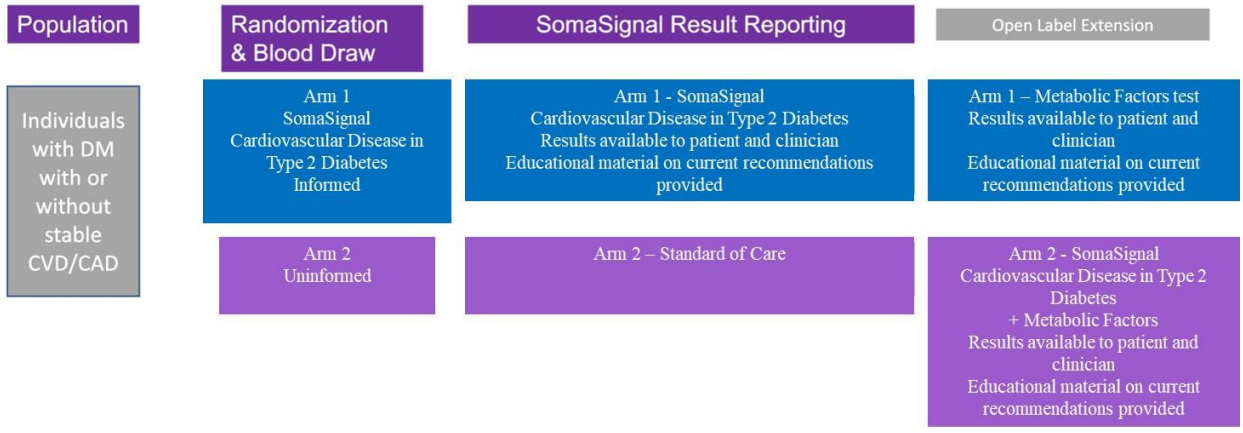
Medical Record Review
Clinical Data Abstraction will occur during the study (baseline, 8 weeks, and 16 weeks). Participants will be provided a SomaLogic patient information booklet at the time of recruitment

Communication of Risk
In the informed groups (arm 1, and open-label extension of arm 2), a risk report will be provided to providers (primary care, cardiologists, endocrinologists) involved in the patient care. Providers will receive a report by email approximately 2-4 weeks after blood draw. A copy of the report will also be scanned into the AEMR for permanent storage and view by other providers.

Open Label Extension
Aims: The open label extension phase will be conducted in participants randomized to both arms. This phase is designed to gather additional data on the impact of providing CV and metabolic risk information to care team of participants on prescription rates of cardiovascular preventive therapies. The clinicians will discuss results of the SomaSignal Tests with the participant and make any adjustments to the care plan as needed. Medical treatment decisions and recommendations will be confirmed by established clinical methods, including blood pressure monitoring, BMI, lipids, and clinical judgement. This information will be documented in a case report form.

Provider Survey:
A simple survey will be emailed to providers of participants approximately 8 weeks after providing risk report in arm 1 (informed) and 8 weeks after unblinding/open-label extension of participants in arms 1 and 2. The survey includes information on provider's perspectives on the risk communication and its impact on patient care.

Study Design



Study Timeline
The overall study participation will be 20 weeks (primary study plus open label extension).

2 Parallel Group Study

Treatment Arm	Intervention
Arm 1: SomaSignal Informed Medical Management (CVD-T2D Test Informed)	Blood draw for SomaSignal Cardiovascular Risk in Type 2 Diabetes (CVD-T2D) and Metabolic Factors tests at baseline SomaSignal Cardiovascular Risk in Type 2 Diabetes (CVD-T2D) test results will be sent to the clinicians and participants. Medical record will be reviewed by the study team to evaluate changes in treatment strategy.
Arm 2: Standard of Care (CVD-T2D Test Uninformed)	Blood draw for SomaSignal Cardiovascular Risk in Type 2 Diabetes (CVD-T2D) and Metabolic Factors Tests at baseline However, results the test will not be provided to clinicians in this phase of the study. Medical record will be reviewed by the study team to evaluate changes in treatment strategy
Open Label Extension: Both Arm 1 and 2	Arm 1 - Metabolic Factors test results will be sent to the clinicians and participants in the open label extension at the conclusion of the primary study phase. Arm 2 - SomaSignal Cardiovascular Risk in Type 2 Diabetes (CVD-T2D) test results will be sent to the clinicians and participants in the open label extension at the conclusion of the primary study phase.

Event	Baseline	4 weeks	12 weeks	20 weeks
Informed Consent	X			
Inclusion/Exclusion Criteria	X			
Randomization	X			
AEMR Medical Record Review	X	X	X	X

Concomitant Medications	X	X	X	X
SomaSignal Test -Blood draw -Sample Prep & Shipping	X			
SomaSignal Cardiovascular Risk in Type 2 Diabetes (CVD-T2D) test results of Arm 1 (informed)		X		
Assess Treatment changes and reasons in Arm 1			X	
Provider Survey in Arm 1			X	
Cardiovascular Risk in Type 2 Diabetes (CVD-T2D) (Arm 2) and Metabolic Factors test results (Arms 1 and 2) in Open Label Extension			X	
Assess Treatment changes and reasons in both Arms				X
Provider Survey in both Arms				X

Data to be Collected for your study
(AFTER consent and HIPAA Authorization have been obtained)
Upon enrollment in the study, the information listed below will be obtained for each participant from the existing AEMR medical record from clinical interactions that are part of their standard of care visits. Data will be captured on the study-specific case report forms, to be developed by the study team in paper and/or electronic format. All data

- Participant's Date of Birth (DOB)
- Participants ID number (MRN)
- General demographic information
  - Participant's contact information
  - Age, gender, height, weight, body mass index (BMI)
  - Race and ethnicity
- Medical history
- Documentation of presence or absence of typical CV risk factors
- Vital signs and physical examination (i.e., blood pressure, heart rate, oxygen saturation) as available
- Concomitant Medications
- Changes to any treatment regimen, including any medical management

Outcome Measurements:
The following measurements will be made:
1. Changes in cardioprotective prescription medications and lifestyle interventions

2. Comparison of SomaSignal Cardiovascular Risk in Type 2 Diabetes (CVD-T2D) and Metabolic Factors test results with standard of care risk assessments (laboratory results, CAC, BMI)
3. Provider surveys

Record Retention
The Principal Investigator and/or designated study team member are responsible for maintaining accurate, complete, and current records relating to the conduct of the investigation, in accordance with ICH GCP E6 (R2) guidelines and CFR. Refer to ICH GCP E6(R2) 8.1 to 8.4 for a list of essential documents for retention.

In addition, the Principal Investigator and and/or authorized study team member are responsible for retaining any additional documents as required by UHCMC, in accordance with departmental and/or institutional records retention policy.

If there is inadequate records storage space at any Intermountain facility, all or part of the clinical study records can be sent to an Intermountain-approved archival storage facility that has a current executed service contract with Intermountain. As appropriate, the study sponsor and other stakeholders will be notified.

If the Principal Investigator transfers custody of all or part of the clinical study records to another person or entity, the IRB must be notified within 10 working days after the transfer occurs. In addition, and as appropriate, the study sponsor and other stakeholders will be notified.

Data Analysis Plan
Sample Size Calculation

In this study, there are 2 arms – 1) the Informed group and 2) the Uniformed group so we will collect samples for 600 patients total with 400 patients in the Informed group and 200 patients in the uniformed group (with 2:1 randomization)

In the Informed group, out of the 400 patients, we anticipate at least 160 individuals (40%) to be prescribed medication. Under this circumstance, we will be able to detect a 17% or greater difference between the high-risk individuals in the informed group and the control/uninformed group with 80% power and a 5% Type I error rate. In other words, if we assume that the Uninformed/control group has even prescribing rates across all risk levels (which is 25% across all levels), then we will be able to detect a prescribing rate of 42% or higher in the high-risk group or a prescribing rate of 8% or lower in the low-risk group.

Statistical Analysis and Methods
We will summarize the prescribing rates in each bin using frequency tables and histograms. Our primary analysis will be in the informed group, where we will perform a multivariate goodness-of-fit test using the multinomial test under the null hypothesis that

the prescribing rates in each risk set are equal to each other (and thus are all equal to 25%).

Following this analysis, we will examine the data from the informed arm. If the numbers are large enough, we will use Poisson models to determine if the total number of individuals prescribed medication are statistically significantly different between the control and informed arm, allowing for a different slope or bin effect for the different treatment arms. If sample sizes allow, we will include random intercepts as needed (e.g., for clinician). If sample sizes are small, particularly in the control group, we will again employ multinomial tests, chi-square goodness-of-fit tests, tests for equal proportions, and/or Fisher's Exact Test and adjust p-values for multiple testing.

Risks to Research Participants

-Questionnaire: Participants will be asked about sensitive topics such as their health status which may create discomfort. Participants will be made aware that they are always free to skip a question that makes them feel uncomfortable.

-Blood draw- risks associated with phlebotomy include pain as the needle enters the participant's vein and the risk of bruising at the site of blood draw have been minimized by using existing trained staff. In the event that a participant has a reaction to the blood draw, staff will follow standard clinical procedures.

- -Breach in confidentiality- risk of inadvertent disclosure of PHI. Study Information sent from UHCMC to SomaLogic will be sent such that the participant cannot be identified: site, age, and gender are not enough to identify these individuals. SomaLogic will not have access to the link between number and participant name as that will be maintained within UHCMC. In the event of a breach, HIPAA reporting requirements will be followed.

Provisions to Protect the Privacy Interests of Research Participants

Information sent from UHCMC to SomaLogic will be sent such that the participant cannot be identified: site, age, and gender are not enough to identify these individuals. SomaLogic will not have access to the link between number and participant name as that will be maintained within UHCMC. In the event of a breach, HIPAA reporting requirements will be followed.

Potential Benefit to Research Participants

-Potential benefits:

-There may be no direct benefit to participation. If the study hypotheses are confirmed, there is potential for direct benefit but this cannot be guaranteed. These potential benefits if study hypotheses are confirmed include:

-Increased patient engagement and satisfaction from increased personalized medical knowledge

-Potential for increased patient recruitment and retention from offering cutting-edge innovation and technology

-There is potential benefit to society including:
-More efficient resource allocation and improved cost-effectiveness of pharmaceutical interventions through enhanced patient risk stratification
-Improved patient outcomes through personalized risk stratification, more precise clinical care, and improvements in triage of medical interventions and education

Withdrawal of Research Participants
Voluntary Withdrawal of Consent
Participants shall have the ability to withdraw consent for study participation, and/or withdraw the use of their clinical information and/or biological samples at any time, without penalty or loss of benefit to which the participant is otherwise entitled, by contacting the Principal Investigator or a designated member of his research team. This must be done in writing and addressed to the Principal Investigator at the address indicated on the cover page of the Informed consent form.

If a participant enrolled in this study decides to withdraw from the research, or an Investigator decides to terminate his/her participation, study investigators must follow accepted standard practices regarding the management of collected data about these participants, as follows:

- Investigators must document in the research record each instance of a participant's withdrawal, including the reasons for the withdrawal, if known.
- Previously collected blood samples, information that has been gathered, and all material from the participant's identifiable blood samples that they have at the time of the participant's withdrawal from the study will remain in the study to maintain the integrity of the research, in accordance with current FDA regulations.
- The investigator(s) may ask the participant whether he/she will agree to continued follow-up and further collection of clinical information following his/her withdrawal.
- If the participant withdraws and does not agree to the continued follow-up and collection of clinical information, the investigator(s) will discontinue access to the participant's medical record or other confidential records, for purposes related to the study.
- Following the participant's withdrawal from the study, the study team will no longer contact the participant nor have access to his/her medical records for research purposes (unless specific informed consent has been obtained as described above).

Lost to Follow-Up Participants
Because this study will have periods of time between research-related interactions, retention of participating participants until study completion may have challenges. To facilitate participant retention, specific information will be obtained during the first research encounter and updated at all subsequent encounters. Although critically important to the successful completion of the study, if a participant expresses concern and/or refuses to provide this information, they will not be excluded from the research.

The following specific information will be collected and used for this purpose:

- Contact information of the participant (i.e. address, phone number, email)
- Contact information of one or more contact persons (close friend or family member) not living with the participant

This contact information will be stored in a secure database and will not be shared outside of the study-specific research staff.

If a research participant becomes lost to follow-up, the research team will contact the participant or designated individuals named by the participant. A maximum of 3 telephone calls and/or email will be attempted. If there is no response, an IRB-approved certified letter signed by the Principal Investigator requesting for a response may be sent. If contact is reestablished, interest in continued participation will be verbally confirmed and documented, and the participant will return to active study participation as appropriate, based on their status/time point in the research. With failure to re-establish contact after three direct attempts and a certified letter in the mail, and failure to find new contact information, the participant will be considered lost to follow up. Participant's that are lost to follow-up will be followed by electronic medical records.

End of Study Considerations

A participant will be considered as having completed the study if he/she has met the following:

- Completed the SomaSignal Tests described in this protocol
- Has reasonably responded to the follow-up visits (in-person, telephone, video chat, or FaceTime)
- Has voluntarily provided the blood samples required by this study
- Has continued to allow the Principal Investigator and/or his duly designated study staff to access his/her medical records

Costs to Research Participants

This study is funded by SomaLogic, Inc.
The tests and procedures listed below are considered non-standard of care and will be paid for by the study budget. All other tests, procedures, and study visits are either conducted by study personnel (e.g. questionnaire administration, etc.) or charged to the patient as routine, standard of care activities.

The budget, contract, and financial agreements will be available in a separate document.

Non-standard of care tests and procedures covered by the study budget are as follows:

- SomaSignal Test

- Blood collection for the SomaSignal Test

Disclosure of Conflicts of Interest

The Principal Investigator, Co-Principal Investigator, Sub-Investigators and protocol authors declare that they have no conflicts of interest relevant to this study.

Research Participant Compensation

Participants will be reimbursed $20 via check for their participation. They will be given the check after completion of the blood draw. To receive payment the participant must agree to complete a W-9 form which requires an address and social security number to the University Hospitals accounting department. This payment may be considered taxable income by the IRS. The participant will be issued a 1099-Misc form only if payment exceeds $600 from all studies in which they are participating, in a fiscal year.

Providers will be compensated $20 for their time completing Physician Surveys.

The investigators and their research team will not receive any monetary or other forms of direct compensation for conducting this research study. Payment is made directly to UHCMC to cover the costs of study conduct.

Provisions to Monitor the Data to Ensure the Safety of Research Participants

Monitoring

A safety officer will be appointment for the trial. The safety officer will be a qualified individual who does not have any affiliation with the study. A formal safety officer charter will be developed. The safety officer will review recruitment, adverse events, and stopping criteria at a minimum of every 6 months. The Safety Officer charter will be kept on file at UHCMC. Monitoring plans will be provided to SomaLogic, Inc. upon request as required by current applicable regulations.

Safety Reporting

In the event of a safety issue, safety-related data for this study will be collected on standardized reporting forms (paper and/or electronic). Safety-related events will be defined in accordance with ICH GCP E6(R2), the CFR, UHCMC research policy, and all current applicable regulations. All events that meet the definition of an Unanticipated Problem will be reported to IRB) within the required time period as defined by IRB's unanticipated problem policy.

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