SomaSignal Tests on Medical Management and Change in Risk in Patients With Diabetes

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PROTOCOL TITLE: Precision SomaSignal DM: Evaluating the Impact of SomaSignal Tests on Medical Management and Change in Risk in Patients with Type 2 Diabetes at Higher Risk of Cardiovascular Disease

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REVISION HISTORY

Revision #	Version Date	Summary of Changes
1	12 Jan 2022	Changes for clarification.
2	12 May 2022	Updated transportation reimbursement and recruitment language
3	6 Sep 2022	Removing Kidney Function Test from Metabolic Factors Panel platform
4	29 Sep 2022	Addition of Vital Signs collection at 6 month time point
5	14 Nov 2022	Clarifying language regarding re-consenting participants

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1. Study Summary

Project Title	Precision SomaSignal DM: Evaluating the Impact of SomaSignal Tests on Medical Management and Change in Risk in Patients with Type 2 Diabetes at Higher Risk of Cardiovascular Disease
Project Design	Single-center, 2 parallel-group study, with an open-label extension to evaluate SomaSignal test Informed Medical Management (Informed) versus Standard of Care (Uninformed).
Primary Objective	**Primary Aim:** To determine whether informing clinicians of the SomaSignal Cardiovascular Disease in Type 2 Diabetes Test (SSCVD) leads to changes in prescriptions and/or medical management of participants with T2D in concordance with SSCVD results over a 6-month period (Informed arm) when compared to participants whose physicians are not informed of the test results (Uninformed arm).
Secondary Objective(s)	**Secondary Aims:** • To evaluate longitudinal changes in the (i) SSCVD test results and (ii) conventional risk factors over 6 months in participants whose clinicians were informed vs. those whose clinicians were uninformed of the SSCVD results. • To determine whether changes in the SSCVD results and conventional risk factors over 6 months relate to (i) baseline SSCVD risk category group and (ii) changes in treatment. • To evaluate the health economic impact of precision risk-stratified treatment. • To determine if the additional information provided by the SomaSignal Metabolic Factor tests to the Uninformed group at the end of 6 months provides useful information to the patient and the clinician.
Research Intervention	SomaSignal Testing
Study Population	Individuals with T2D with or without cardiovascular disease.
Sample Size	450 participants
Study Duration for individual participants	6 months
Study Specific Abbreviations/ Definitions	Cardiovascular (CV), Cardiovascular Disease (CVD), Type 2 Diabetes (T2D), SomaSignal Cardiovascular Disease in Type 2 Diabetes (SSCVD), Complete Blood Count (CBC), Comprehensive Metabolic Panel (CMP), Hemoglobin A1C (HBa1C), Cardioprotective (CP),

	Laboratory developed test (LDT), College of American Pathologists (CAP), Clinical Laboratory Improvement Amendments (CLIA)
Funding Source (if any)	SomaLogic, Inc

2. Objectives

Primary Aim:

1. To determine whether informing clinicians of the SSCVD test results leads to changes in prescriptions and/or medical management of participants with T2D in concordance with SSCVD results over a 6-month period (Informed arm) when compared to participants whose treatment is not informed by SSCVD test results (Uninformed arm).

Secondary Aims:

2. To evaluate longitudinal changes in the (i) SSCVD results and (ii) conventional risk factors over 6 months in participants whose clinicians were informed vs. those whose clinicians were uninformed of the SSCVD test results (Uninformed arm).
3. To determine whether changes in the SSCVD score and conventional risk factors over 6 months relate to (i) baseline SSCVD risk category group and (ii) changes in treatment.
4. To evaluate the health economic impact of precision risk-stratified treatment.
5. To determine if the additional information provided by the SomaSignal Metabolic Factor tests provide useful information to the patient and the clinician.

Open Label Extension

Aims: The open label extension phase will be conducted in participants randomized to Arm 2 only (Uninformed arm with participants and clinicians not receiving SomaSignal tests results until the end of the study). This phase is designed to gather additional information about the clinical utility of the SSCVD test along with the SomaLogic Metabolic Factors panel with 9 test results that reflect changes in: Liver Fat, Glucose Tolerance, Alcohol Impact, Cardiorespiratory Fitness/VO2 max, Resting Energy Rate, Body Fat Percentage, Visceral Fat, Lean Body Mass. After the 6-month trial period is completed, 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 documented in a case report form.

3. 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 (CVD) 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 CV benefit (11). It has been proposed that such low uptake is more related to insurance type and coverage than to risk assessment (12). The overall

prescribing deficiency seems particularly acute in individuals with T2D, where it has been described in 2021 as a "Call for action to the cardiology community" (11).

While it can be easy to blame prescribing deficiencies on complacent physicians and/or over-frugal payors, SomaLogic believes there is more likely to be a fundamental problem with the cost and risk-effective allocation of such therapies, which are neither low in cost nor free of adverse events. 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 relatively uninformed as to the need for and/or likely 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 assess unresolved risk inadequately in vulnerable patients with high observed event rates (13-15) and 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 are effective for lipids, blood pressure and glycemic control is undermined by the insensitivity to improvements of many traditional cardiovascular risk factors (age, sex, race, T2D 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.

To resolve this lack of precision in risk assessment, 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 surrogate proteomic endpoint for cardiovascular outcomes. The SomaSignal Cardiovascular Risk (SSCVD) test, a 27-protein model encompassing ten biologic systems. The SSCVD has been found to be robust for consistency over time, insensitive to interfering substances and to differences in sample quality. It is currently commercially available as a laboratory developed test (LDT) 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.

The SSCVD test was validated in patients with T2D to predict the four-year likelihood of a composite endpoint of myocardial infarction, stroke, hospitalization for heart failure or death. Outcome prediction was consistent across morbidities, demographics, and geographic regions and superior to a clinical model using typical risk-factors and laboratory measurements in six validation datasets; the Net Reclassification Index (NRI) was +0.43, AUCs were 0.73 vs. 0.63 and c-statistic 0.71 vs. 0.62. Event rates in four defined risk categories, based on the SSCVD were 5.6%, 11.2%, 20.0% and

43.4%. There are no risk calculators currently available specifically for a higher risk population, so 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. Table 1 shows the key results and comparisons with the PCE- derived clinical model using demographic, medical and laboratory measures, and how the SSCVD responds more consistently to changes in risk than any one of the common biomarkers of risk:

Table 1: Prediction of major adverse events using the SSCVD test compared to conventional clinical assessment

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 SSCVD 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 risk was also correctly detected in non-cardiovascular conditions with known higher cardiovascular event rates including T2D, cancer, rheumatoid arthritis, and smoking. (Manuscript submitted)

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 T2D. During the study, the random “drop-in” rate of additional novel cardioprotective-antidiabetic drugs (SGLT2i) was approximately 15%.

When stratifying this population with the SSCVD test, the rate of predicted vs. observed events were found to be accurate (Table 2) (Manuscript in preparation).

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.

Risk Bin	Drop in CP Medication (%)*	Observed Event Rate	Hazard Ratio	Log-estimated Hazard Ratio (HR)	p-value (logHR)
Bin 1 – Low Risk **(N = 115)**	Yes = 17 (14.8%)	0% (N = 0)	0.000	-18.274	0.998
	No = 98 (85.2%)	7.14% (N = 7)			
Bin 2 – 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)			
Bin 3 – 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)			
Bin 4 – High Risk **(N = 1,387)**	Yes = 162 (11.7%)	25.9% (N = 42)	0.712	-0.340	0.030*
	No = 1,225 (88.3%)	32.8% (N = 402)			

Table 2: SSCVD stratification and 4-year observed event rate in the presence/absence of drop-in medications in the EXSCEL trial.
Note that the participants in the EXSCEL trial match the intended population to be recruited for this study.
*The highest risk bin (Bin 4) had a statistically significant impact of therapy.

Median Follow-Up for the EXSCEL trial was 3.5 years, which is less time than the 4-year event prediction time horizon, so observed event rates are lower than predicted event rates.

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 guideline-based cardioprotective therapies in individuals with T2D, such that the patients with the highest residual risk are more likely to receive additional therapy than the patients at low risk.

4. Study Endpoints

PRIMARY ENDPOINTS

1. To determine whether informing clinicians of the SSCVD test results leads to changes in prescriptions and/or medical management of participants with T2D in concordance with SSCVD results over a 6-month period (Informed arm) when compared to participants whose physicians are not informed of the test results (Uninformed arm).

SECONDARY ENDPOINTS

1. To evaluate longitudinal changes in the (i) SSCVD results and (ii) conventional risk factors over 6 months in participants whose clinicians were informed vs. those whose clinicians were uninformed of the SSCVD results.
2. To determine whether changes in the SSCVD score and conventional risk factors over 6 months relate to (i) baseline SSCVD risk category group and (ii) changes in treatment.
3. To enable future health economic analyses of the impact of precision risk-stratified treatment.
4. To determine whether provision of the SSCVD test along with the SomaLogic Metabolic Factors panel with 8 test results that reflect changes in: Liver Fat, Glucose Tolerance, Alcohol Impact, Cardiorespiratory Fitness/VO2 max, Resting Energy Rate, Body Fat Percentage, Visceral Fat, Lean Body Mass to physicians whose participants are randomized to the Uninformed group after 6 months results in changes in participant management.

Outcome Measurements:

The following measurements will be made at baseline and after 6 (+/-1 months).

Primary Aim

Changes in prescription medications and lifestyle interventions

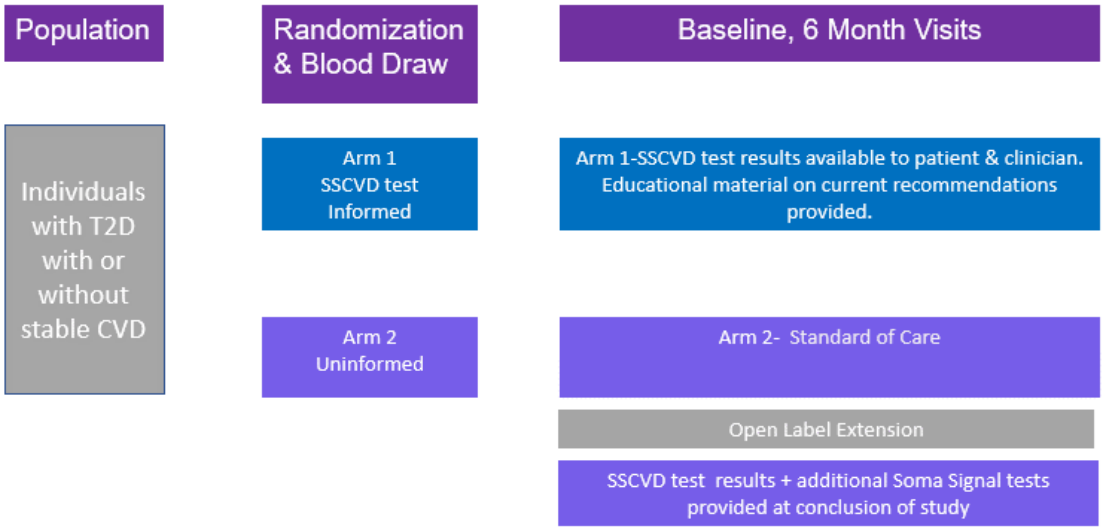
Secondary Aims:

(i) SSCVD test results at baseline and 6 months;
(ii) change in CVD risk factors measured using laboratory assessments (Complete Blood Count (CBC), Basic Metabolic Panel (BMP), Hemoglobin A1C, Lipid panel), anthropometric measurements (height, weight and BMI), lifestyle/behavioral changes (smoking, diet and exercise) measured using questionnaires.
(iii) Physician experience questionnaire
(iv) Participant adherence: to their medications will be quantified using the medication possession ratio (# of scripts filled/# of months participants are script eligible).

Blood will be frozen at -80 degrees C for future evaluation of biomarkers including metabolites and micro RNAs.

5. Study Intervention

Figure 1:



All participating providers will be provided education and training on SomaSignal testing including how to interpret and educate participants on the results. The documents used in this training are included in Appendix A.

Enrolment and Randomization:

Eligible participants based on the inclusion/exclusion criteria will provide written informed consent.

All participants in the Informed arm will be provided SSCVD test information. The Uninformed arm will receive both the SSCVD and SomaSignal Metabolic Factor test information at the end of 6 months.

Participants will be randomized to one of 2 arms of the study. Randomization will be stratified based upon the presence on CVD.

Treatment Arm	**Intervention**
Arm 1: (SSCVD Informed) SomaSignal Informed Medical Management SSCVD	Blood draw for SSCVD test at baseline and 6 months (±50 days). SSCVD results will be sent to the providers and participants approximately 2-4 weeks after testing. Participants visit or are contacted by their physician up to 50 days after baseline testing to discuss treatment strategy (no changes, add/remove medications, lifestyle intervention, etc.)

	Medical records will be reviewed by the study team to evaluate changes in treatment strategy. Participants will be called 2 weeks, 2 months, and 4 months (+/- 7 days) after the baseline visit to ask if they are following the treatment strategy.
Arm 2: (SSCVD Uninformed) Standard of Care where the provider is not informed of the SSCVD test results	Blood draw for SSCVD test at baseline and 6 months (±50 days). SSCVD results will not be provided to the provider or participant until the 6-month visit. Participants visit or are contacted by their physician up to 50 days after baseline testing to discuss treatment strategy (no changes, add/remove medications, lifestyle intervention, etc.) Medical records will be reviewed by the study team to evaluate changes in treatment strategy. Participants will be called 2 weeks, 2 months, and 4 months (+/- 7 days) after the baseline visit to ask if they are following the treatment strategy. After the 6-month period is completed, the providers will discuss results of the SSCVD and SomaSignal Metabolic Factor tests (obtained during the Baseline and 6-month blood draws) with the participant and make any adjustments to the care plan as needed. Medical records will be reviewed by the study team to evaluate changes in treatment strategy.

6. Procedures Involved

Blood Draws: Blood samples (45 ml) will be collected either at an Emory or Grady site from participants in both arms of the study at Baseline and after 6 months (+/- 50 days) for the SSCVD test and CVD risk factors measured using laboratory assessments (Complete Blood Count (CBC), Basic Metabolic Panel (BMP), Hemoglobin A1C, Lipid panel).

Blood samples for the SomaSignal tests will be shipped to SomaLogic for analysis and the results will be delivered to Emory using secure electronic means. Remaining blood will be frozen at -80 degrees C and stored at Emory for future evaluation of biomarkers including metabolites and micro RNAs.

Vital Signs
Participants in both arms of the study will have their vital signs taken and recorded at their Baseline and 6 month visits.

Questionnaires
Participants will be asked about their medications, family and medical history, and lifestyle. These questionnaires may be administered in person or online via REDCap.

Medical Record Review
Clinical Data Abstraction will occur from the baseline visit to the 6-month (+/- 50 days) study visit.

Phone Visit
Participants will be called 2 weeks, 2 months, and 4 months (+/- 7 days) after the baseline visit to ask if they are following the treatment strategy.

Clinician Intervention/s:
All participating clinicians will be educated through materials and webinars provided by SomaLogic.

Informed Arm:
For participants randomized to the Informed arm, the SSCVD test results will be provided to the participant's clinicians approximately 2-4 weeks after the baseline blood draw.

Clinicians will discuss results with the participant and make adjustments to the care plan as needed based on the SSCVD test results within 50 days of receiving results. Clinicians may advise participants to (i) either change the doses of existing medications within existing guidelines, (ii) prescribe additional guideline-based medications, (iii) advise additional lifestyle interventions, or (iv) advise no change. This information will be documented in the case report forms.

This test is neither intended to diagnose cardiovascular disease (CVD) nor replace standard of care protocols for this disease. The physician should not rely solely on this information to make a decision on the best course of action for this patient.

Uninformed Arm:
Clinicians will provide standard of care based on routine test results and without the SSCVD results.

SSCVD and SomaSignal Metabolic Factor Panel results from participants from both the baseline and 6-month period will be provided to the study team at the 6-month study visit.

The SomaSignal Metabolic Factor tests include evaluation of Liver Fat, Glucose Tolerance, Alcohol Impact, Cardiorespiratory Fitness/VO_2 max, Resting Energy Rate, Body Fat Percentage, Visceral Fat, and Lean Body Mass.

Any recommendations made to the participant by the physicians, based on obtaining the aforementioned test results will be collected.

7. Data Specimen Banking

Data obtained from this study will be shared with SomaLogic, Inc. as per the clinical research data sharing agreement that will be developed as a separate document, prior to the start of this study. If applicable, all shared data and/or biological samples will be de-identified as per the Privacy Rule of the NIH (National Institutes of Health, 2007) and in accordance with Emory policies.

In the event that SomaLogic, Inc. performs similar studies with other institutions, the data obtained during this study may be combined for internal future studies or a meta-analysis as appropriate. Data generated as part of this study will not be shared outside Emory and SomaLogic, Inc., unless expressly agreed to in writing and with the proper regulatory and contractual approvals.

Blood will be frozen at -80 degrees C and stored at in secure freezers in the Woodruff Memorial Research Building for future evaluation by Emory investigators of biomarkers including metabolites and micro RNAs.

All specimens and data will be identified with a study ID number. Direct identifiers will not be attached to any records or samples. Study data will be kept in a secure storage area or password-protected database. Access to this database will be restricted by a database manager. Only those members of the study staff listed on the delegation of authority log will have access to identifiers.

De-identified study data and specimens may be shared with Emory and non-Emory investigators to help them study cardiovascular diseases. Any future use of data and specimens for research must be authorized by the Principal Investigator and approved by an Institutional Review Board. The research investigators involved in this study and in future studies and any other individual who may have access to the blood sample and its derivatives are not authorized to and are forever prohibited from using this material for any attempt at cloning a human being.

Information that may be released to researchers may include, but is not limited to: medical information, age, gender, ethnic background, family history, imaging data, blood samples and blood sample products. Identifiers, like names, addresses, and social security numbers, will not be released, except if patients need to be contacted again for specific purposes in new studies. All efforts will be made to keep identifying information confidential.

8. Sharing of Results with Participants

Clinicians in both arms of the study will receive results of participants' routine lab tests and will share them with participants.

9. Study Timelines

Event	Screening and Blood Draw 1 (Baseline - 1month)	Baseline Visit	Phone Visit 2 weeks, 2 months, 4 months	Blood Draw 2 + 6 months after Baseline Visit	Final Study Visit
Informed Consent	X				
Inclusion/Exclusion Criteria	X				
Medical History	X				
Standard of Care Visit		X			X
Vital signs/exam	X				
Review of Medical Record/Concomitant Medications*	X	X		X	X
Questionnaires	X		X		X
Laboratory Tests-CBC, BMP, Hb A1C, Lipid panel	X			X	
SomaSignal Test (blood draw)	X			X	
Treatment changes and reasons		X			X
Open Label Extension					X[1]

[1]only for the Uninformed group

*Review of Medical Record including concomitant medications will occur during the course of the study

10. Inclusion and Exclusion Criteria

Patient Inclusion Criteria

- Male and female participants 40 years and older
- Diagnosis of T2D (according to ADA guidelines)
- Able to provide consent

Eligible for (per drug label/guidelines) at least one of the following drug classes: SGLT2i, PCSK9i, GLP-1 RA and not currently prescribed any of these classes of drugs, or only prescribed PCSK9i.

Patient Exclusion Criteria

- Systemic Lupus Erythematous (SLE)
- Pregnancy (as determined by self-report)
- Intolerance or contraindication for use of GLP1RA, SGLT2i, and PCSK9i

- 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
- Inability to understand English (Currently, SomaSignal testing information, guides, educational materials, and reports are only available in English.)

11. Vulnerable Populations

Vulnerable populations will not be enrolled in this study.

12. Local Number of Participants

Screening up to 600 participants with a goal of enrolling 450 participants.

13. Recruitment Methods

Participants will be recruited from Emory and Grady clinic providers treating individuals with T2D. Participants will be contacted via email (if available) and telephone calls to inquire about their interest in study participation. For prospective participants that are unable to be contacted by email or telephone, an IRB approved opt-out letter will be sent to the participants address that is on file by the coordinating staff through the United States Postal Service.

Eligible participants will sign an informed consent form prior to any research activities. Participants' eligibility will be determined by the Principal Investigator and/or authorized study team member.

Participants who have a treatment relationship with the participating providers and deemed to meet the eligibility criteria, will be screened for this study. The Principal Investigator and/or authorized study team member will review the participant's history and medical records. Data gathered will be used to evaluate the participant's eligibility according to the inclusion and exclusion criteria.

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.

14. Withdrawal of Participants

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).

15. Risk to Participants

- 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. If a participant has a reaction to the blood draw, staff will follow standard clinical procedures.
- SomaSignal test: All participants are to receive at least standard of care regardless of their SomaSignal insights.
    - A false positive risk prediction would lead to potential prescription of a drug that the participant might not need; given that participants across the risk spectrum were included in the pivotal clinical trials for registration of the drugs, this is unlikely to lead to novel consequences not already observed in those studies – the most likely outcome is that the increment of benefit is small and not cost effective
    - A false negative risk prediction would lead to the avoidance of a prescription of a drug that the participant actually does need. Given that the participants are already eligible for these drugs but not taking them, this is at least no worse than the current standard of care.

- Breach in confidentiality- risk of inadvertent disclosure of PHI. Study Information sent from Emory to SomaLogic will be sent using a unique study ID 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 study ID and participant name as that will be maintained within Emory. In the event of a breach, HIPAA reporting requirements will be followed.

16. Potential Benefits to Participants

- Likely benefits to the participant:
    - Improved health outcomes in the subset of participants who have residual risk based on the SSCVD test that they were previously unaware of, and who may receive treatment with a drug or additional lifestyle intervention they were previously eligible for but were not undertaking at the start of the study
        - While this is likely to be manifest earlier in the informed group than in the uninformed group, the latter will ultimately be informed at the end of the 6-month study period
        - Participants in the low-risk group, based on the SSCVD test who do not receive any change in management will receive knowledge of their low-risk status
- Potential benefits:
    - Increased participant engagement and satisfaction from increased personalized medical knowledge
    - Potential for increased participant recruitment and retention from offering cutting-edge innovation and technology
    - More efficient resource allocation and improved cost-effectiveness of pharmaceutical interventions through enhanced participant risk stratification
    - Improved patient outcomes through personalized risk stratification, more precise clinical care, and improvements in triage of medical interventions and education
- Expanded research opportunities through providing participant proteomic measurements to Emory researchers

17. Compensation to Participants

Participants will receive $50 for each blood draw visit to compensate them for travel and parking. If participants complete both blood draws they will receive $100 total.

For participants that meet inclusion criteria into the study and require travel accommodations to and from Emory University, Grady Memorial Hospital and participating sites, contracts with Uber and Lyft have been negotiated to help

participants get to and from their appointments. A study team member will help the participant set up and execute this task.

18. Data Management and Confidentiality

A duly assigned study team member will perform primary data collection, drawn from review of source- documents (hospital charts) and from on-going study procedures. Some specific data for this study will be collected on a simplified Case Report Form either hardcopy or electronic.

Participants will receive a unique study identification (ID) number such that the participants' identifiable information will be held separate from the main study database, using standard practices to protect participant confidentiality. This study ID number, with the participant gender and date of birth, will be included on the blood tube for the SomaSignal assay, as well as SomaSignal report.

Data will be stored in a secure, HIPAA-compliant electronic study database. Only SomaLogic, Inc. and study team from Emory will have access to this secure database. If data is shared with any other external collaborators, as described in the consent form, it will be de-identified and study ID numbers will not be included.

Data will be archived by SomaLogic, Inc. for 15 years and will be destroyed at the end of that time, in accordance with company policies. Destruction will include any paper documents as well as the electronic database.

Every precaution will be taken to protect the privacy of research participants and the confidentiality of their personal information. The Principal Investigator and his/her study team will maintain all participants' information in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and Emory's guidelines for compliance and privacy.

19. Provisions to Protect the Privacy Interest of Participants

The study team will only collect participants' personal information as described in the protocol. Study data will be kept in a secure storage area or password-protected database. Access to this database will be restricted by a database manager. Only those members of the study staff listed on the delegation of authority log will have access to identifiers.

To ensure privacy, participants' data and samples will be identified with a study ID number. The code linking participant identifiers to the study ID number will be kept in a separate password-protected file with access limited to the PI and a few members of the study staff.

Participants will be informed that their participation in the study is voluntary and they are free to withdraw from the study at any time. Participants can refuse to answer any questions or have any procedures that make them uncomfortable.

The study team will request a partial HIPAA waiver for identifying potential participants and determining eligibility.

20. Economic Burden to Participants

Participants will not have to pay for any of the research procedures in this study.

21. Informed Consent

The study team will obtain written informed consent from participants prior to performing any study procedures.

- Consent will be obtained in a private office, clinic or hospital room or via Zoom video conference or phone call using Docusign.
- Prior to the first study visit, a member of the study staff will fully explain the study to participants either in-person or via an Zoom video conference or phone call. Participants will be given a copy of the consent form or it may be mailed or emailed via encrypted email to the participant prior to the consent discussion. Participants will be given time to read the approved informed consent form (ICF) and ask questions about the study prior to signing the consent form.
- If there has been a substantial change to the research since the time of the original consent, such that research participation may no longer be consistent with the participant's preferences and interests and the participant may need to reconsider the decision. If this occurs the tchanges to the study will be explained to the participant prior to their next scheduled study visit and they will be asked to sign a new consent form.
- Members of the study team who may be involved in the consent process include the principal investigator, research coordinators, co-investigators, and research fellows.
- Before enrollment, each prospective patient will be given a full explanation of the study. The participant will be allowed to read the approved ICF and have any questions answered. Once the investigator is assured that the patient understands the implications of participating in the study, the participant will be asked to give consent to participate in the study by signing the ICF.
- To minimize the possibility of coercion or undue influence, the person conducting the informed consent discussion will not be the participant's usual healthcare provider. Participants will be given the opportunity to read the consent form and discuss the research with family and friends before signing.
- To determine capacity to consent, the participant will be asked a series of questions about the research to assess his/her understanding or the study procedures and potential risks.

22. Setting

Potential participants will be recruited from outpatient cardiology, diabetes, and primary care clinics at Emory University Hospital (EUH), Emory University Hospital Midtown (EUHM), Emory Saint Joseph's Hospital (ESJH), and Grady Memorial (GMH) hospitals and at Emory Clinic (EC) locations

Research procedures will be performed in private research/clinic rooms at EUH, EUHM, ESJH, GMH, EC and the Woodruff Memorial Research Building (WMB).

23. Resources Available

A Clinical Research Coordinator will be allocated to recruit participants and conduct study procedures. He/she will be assisted by Cardiology Research Fellows. Other study staff will assist with the identification of potential participants, chart review and data entry. The study team has approximately 800 square feet of dedicated research space in 5 rooms in the Woodruff Memorial Research Building (WMB) with 3 beds and 2 recliners available. In Emory University Hospital (EUH), there are 2 research exam rooms and 3 offices available to conduct study visits.

It is not anticipated that additional medical services will be needed as a result of the research. If necessary EUH is a state-of-the-art, acute-care hospital that includes cardiac care, surgery, and 24/7 emergency services. The WMB is directly adjacent to EUH and is equipped with defibrillators. Additionally, study staff are trained in Basic Life Support.

All study staff will be trained on the protocol prior to study initiation. Documentation of training and qualifications will be maintained in the study regulatory binders. The Research Manager will oversee the day-to-day activities of the coordinators/study nurses and other members of the study staff. The PI meets meet regularly with all personnel to review the progress of the study and communicate with them as needed to monitor adverse events and provide timely updates on changes to the protocol or procedures.

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Appendix A

Provider Education and Training Materials are attached as a separate file. See Emory University Provider Education Deck_15Sep2021.