1.0 Protocol Title. Personalized Nutrition Program Algorithm Validation Study s1601059
Validation of Machine Learning Based Personalized Nutrition Algorithm to Reduce Postprandial Glycemic Excursions Among North American Individuals With Newly Diagnosed Type 2 Diabetes

2.0 IRB Review History. Approved by the IRB on 2/23/2018

3.0 Background information and specific aims
Type 2 diabetes (T2D) is an epidemic in the United States, affecting 29.1 million people. Poor glycemic control contributes to vascular complications of T2D (retinopathy, heart and kidney disease, stroke, and amputation) but recent clinical trials (ACCORD, ADVANCE, VADT) testing the potential benefits of aggressive medication management have been mostly neutral or negative. These trials targeted hemoglobin A1c (HbA1c) concentrations. However, there is growing evidence that glycemic variability (GV; from hyperglycemic peaks to hypoglycemic nadirs) may be a better treatment target than HbA1c. Although GV in early T2D is driven primarily by postprandial glycemic excursions, the results of dietary interventions to limit postprandial excursions have been mixed, perhaps because they used one-size-fits-all strategies such as low glycemic load (GL) diets that ignored the fact that individuals vary greatly in their glycemic response to food.

Several recent studies show that the composition and functional potential of the intestinal microbiota are critical factors in glucose homeostasis. With the Personal Nutrition Project (PNP); http://newsite.personalnutrition.org/WebSite/Home.aspx, Segal et al. devised the first personalized algorithm for predicting glycemic response to food. Using a machine learning approach, they developed a multi-dimensional profile that predicted food-specific glycemic excursions from gut microbiome data, various blood tests, questionnaires, and one week of mobile monitoring of food intake, glycemia, sleep, medication, physical activity, stress, and hunger. Subsequently, in a randomized trial among Israeli prediabetic individuals, the investigators successfully shown that tailored dietary recommendations from PNP algorithm were successful in reducing postprandial glycemic excursions.

Dr. Sevick's team at New York University School of Medicine will conduct an initial validation study of the PNP algorithm in a North American population with recently diagnosed T2D or pre-diabetes. This will be accomplished in a 2-stage, single-group feeding study in 20 individuals, including 10 participants managed with lifestyle alone, and 10 managed with lifestyle plus metformin.

4.0 Background
According to the Centers for Disease Control and Prevention, 29.1 million people in the US (9.3% of the population) have diabetes [1]. Diabetes is the most costly chronic disease in the US; with expenditures reaching $245 billion in 2012[2]. Between 2005 and 2050, the prevalence of diabetes is expected to double[3]. Patients with T2D are at increased risk of a variety of vascular complications, including heart and kidney disease, stroke, retinopathy, and amputation. Numerous epidemiologic studies show a continuous relationship between HbA1c and microvascular and cardiovascular complications. However the results of intensive glycemia medication management trials (including ADVANCE, ACCORD and VADT) have been largely neutral or negative [4-7] with several possible explanations:

- ✓ ***Interventions were too late in the disease trajectory*:** These studies were conducted in patients with established T2D who had already developed complications of the disease, limiting the ability of investigators to modify the disease trajectory.
- ✓ ***Reliance on medications:*** The trials managed glycemia aggressively with medications that increased the frequency of hypoglycemic episodes that, in-turn, increased the risks of cardiovascular disease, all-cause hospitalizations, and mortality.
- ✓ ***Poor initial management had long-term effects on subsequent vascular risks*:** From the point of diagnosis, management of T2D typically involves an incremental regimen that begins with lifestyle

behavior change. The regimen is managed reactively by adding medications when lifestyle efforts fail to achieve an HbA1c of either <6.5% or <7% (depending on the clinical practice guideline embraced by the clinician) [8, 9]. However, escalation of the medication regimen often is delayed [10] and vascular risks resulting from early poor glycemic control appear to be only partially remedied by subsequent better glycemic control. This phenomenon, termed "metabolic memory", appears to involve the accumulation of advanced glycation end-products (AGEs) that result in oxidative stress and inflammation. Accumulation of AGEs and activation of their receptors (RAGE) in-turn, mediate the tissue damage that results in diabetic complications. Activation of the AGE-RAGE pathway also has been shown in animal models to induce injury to pancreatic β-cells[11-13]. Studies show lower β-cell function to be associated with higher rates of treatment failure, poorer glycemic control, and greater GV in those with T2D, and experimental studies have shown clear metabolic benefits from even minimally preserved β-cell function [14]. Consequently, it is important to preserve β-cell function for as long as possible after the diagnosis of T2D is made [15] and early management of GV with diet is a potential solution.

- ✓ ***The wrong treatment target:*** ADVANCE, ACCORD and VADT targeted HbA1c, which reflects mean glycemia rather than glucose instability. Titrating medications to HbA1c without addressing postprandial glycemic excursions [which account for about 70% of overall glycemic exposure in patients with early T2D and remaining β-cell function [16]] increases the risk of hypoglycemia [17]. Compared to a constant high glucose, blood glucose fluctuations are more damaging [18] and appear to result in more pronounced metabolic memory effects[19]. Recent epidemiologic studies have shown postprandial hyperglycemic peaks to be a powerful predictor of cardiovascular risk, and suggest that GV may be a better treatment target than HbA1c[17-22]. Several pharmacologic agents are available that limit postprandial hyperglycemia (e.g. insulin, sulfonylureas, acarbose, glinides, DPP-4 inhibitors, and GLP-1 agonists). However, several problems are associated with these medications and they are occasionally prescribed for those with recently diagnosed T2D.

In early T2D GV is driven, primarily, by diet. While there is universal recognition that dietary management is key to successful T2D treatment, there is limited evidence regarding the best dietary approach(es) to take and the results of intervention studies have been mixed. Twelve recent (since 2008) randomized clinical trials of dietary interventions in those with T2D were found in the literature[23-33]. All used a 1-size-fits-all dietary prescription. However, the impact of diet on glycemia is influenced by many factors, including energy content, and the type and amount of carbohydrates, protein and fat in the meal; as well as how the foods were prepared and cooked. Also, each individual possesses their own unique physiologic response to food, based on their insulin resistance, β-cell function, gastrointestinal factors, and hepatic and peripheral glucose metabolism, which may be influenced by non-dietary factors including sleep, physical activity, medication/supplement regimen, and perhaps others [34, 35]. None of the dietary studies that we reviewed tailored counseling to minimize postprandial glycemic excursions. Nearly all evaluated the intervention on the basis of HbA1c but, as discussed above, GV (evaluated in only 1 of the dietary intervention studies) may be a better predictor of downstream complications of the disease [32].

Of particular relevance to managing postprandial glycemia is the innovative work of the Personalized Nutrition Project (or PNP; http://newsite.personalnutrition.org/WebSite/Home.aspx). Segal et al. developed personally tailored double-blinded dietary counseling that lowered postprandial responses in a sample of Israeli individuals with prediabetes [36-38]. With our pilot, we intend to validate this tailored approach in a US sample having recently diagnosed T2D. In a future trial, we will combine this tailored approach with our existing behavioral intervention and evaluate its efficacy for reducing GV, and minimizing metabolic memory effects.

5.0. Summary.

T2D poses a significant public health problem. Hyperglycemia is associated with a variety of vascular complications, but clinical trials of medication regimens designed to achieve near-normal HbA1c have been mostly neutral or negative. The lack of benefit observed in these trials may be due to the fact that they targeted HbA1c rather than GV, and were conducted in patients with established T2D that had already

experienced complications of the disease. In early T2D, management of postprandial glycemia may be particular important for minimization of metabolic memory effects and preservation of β-cell function. Postprandial glycemia in early T2D is largely driven by dietary intake, but research that guides clinicians regarding the best dietary approaches to prescribe are mixed. Studies done, to-date, in T2D has used one-size-fits-all dietary regimens that do not take into consideration the person's unique glycemic response to food. The PNP algorithm, which uses a machine learning algorithm to predict postprandial glycemic, may be efficacious for generating tailored dietary advice to moderate the participant's glycemic response to food. However, the PNP algorithm has not been validated in a diverse North American population having T2D.

6.0. Inclusion and Exclusion Criteria

6.1. Inclusion criteria.

The study will be conducted in a diverse sample of 20 patients with early T2D or pre-diabetes who were managed by lifestyle modification or on metformin. The study inclusion criteria include:

a. Age >21 years to <70 years
b. Diagnosed with T2DM within 2 years or pre-diabetes with an HbA1c<8%
c. Diabetes management by metformin or lifestyle intervention
d. Willing to use their own or a study loaner smart phone to monitor multiple factors influencing glycemic response to glycemia (e.g., sleep, physical activity, diet, stress, medication, and hunger)

6.2. Exclusion criteria.

We will exclude from participation those who:

a. are unable or unwilling to provide informed consent;
b. are unable to participate meaningfully in an intervention that involves self-monitoring using software available in English (e.g., due to uncorrected sight impairment, illiterate, non-English-speaking, dementia);
c. are pregnant, are currently trying to become pregnant, or who become pregnant during the study
d. are institutionalized (e.g., in a nursing home or personal care facility, or those who are incarcerated and have limited control over self-management)
e. have had or are planning to have bariatric surgery during the study
f. have a history of heart disease, kidney disease, or retinopathy (to rule-out those with long-standing, undiagnosed T2D)
g. those with an active infection requiring antibiotics in the last 3 months or who develop an active infection requiring antibiotics during the study;
h. those who use acetaminophen and are unwilling or unable to discontinue its use during the study (acetaminophen affects FGM accuracy)[39]
i. immunosuppressive drugs within three months prior to participation and
j. Chronically active inflammatory or neoplastic disease in the three years prior to enrollment.
k. Patients with known food allergy.

6 . 3 . Inclusion of women and minorities.

According to the most recent Behavioral Risk Factor Surveillance System data for adult diabetics in New York City 52.5% are female, 15.6% are Hispanic, 55.3% are non-Hispanic whites, 19.8% are non-Hispanic blacks, 3.4% are non-Hispanic Asians, 5.8% are non- Hispanic other with no data provided on American Indian/Alaskan Natives, or Native Hawaiians or Pacific Islanders. Our targeted/Planned enrollment table combines BRFSS data with local census data, showing that approximately 3.0% of participants will be American Indian/Alaskan Natives and 1.0% will be Native Hawaiians or Pacific Islanders.

Special effort will be made to recruit a sample with a race and gender distribution consistent with New York City's Department of Health rates provided above, with 20-25% of individuals of Latino ethnicity. We have a history of successfully recruiting minorities to our studies. No individual will be excluded from the study on the

basis of race or gender alone. It is possible that the study will have sufficient power to detect differences in intervention effect by gender and race. To our knowledge no research has been published showing a differential effect of interventions such as ours by race or gender.

7.0. Study-Wide Number of Subjects.

We will recruit a total of 20 individuals to the study. Preliminary data indicate that we will have access to 200 potentially eligible patients from which we must recruit only 10.0% to enroll 20.

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	2	8	10
Not Hispanic or Latino	6	4	10
Ethnic Category: Total of All Subjects *	8	12	20
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	2	4	4
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	4	6	10
White	2	4	6
Racial Categories: Total of All Subjects *	8	12	20

8.0 Study-Wide Recruitment Methods.

Potential participants will be recruited from NYUMLC Endocrinology and print and electronic advertisement. Signed informed consent will be obtained from participants who meet the study eligibility criteria. The following methods will be adopted for the recruitment of eligible participants.

8.1. Self-referral from advertisements placed in NYULMC Endocrinology Faculty Group Practices offices.

IRB-approved fliers and brochures containing an overview of the study will be created and displayed in the clinical practice setting for those who may be interested. Interested patients will be provided with the phone number of the investigators that they may call to obtain additional information about the study. Those participants contacting the study office will be provided a brief description of the goals of the study and what their participation would entail. Those who remain interested will be screened to assure that they meet eligibility criteria using EPIC to verify that their HbA1c levels are <8.0%. We will contact the patients' healthcare provider/agent to determine if their patient is fit to participate in the study. If eligible, a measurement visit is scheduled with the study participant.

8.2. Physician referral

During the provision of routine ambulatory care, physicians will identify potentially eligible participants and ask about their interest in a study that proposes to examine dietary patterns that predispose them to postprandial

hyperglycemia. Interested patients will be asked permission (yes/no) for study staff to contact them directly by telephone. Study staff will call patients who agree to be contacted, describe the study, and if the patient expresses an interest, conduct preliminary screening by telephone. Verbal consent is obtained by study staff prior to eligibility screening. Written informed consent will be obtained with a subsequent face to face measurement visit to the CTSI for eligible participants. Alternatively, patients can contact the study staff directly by telephone to discuss possible enrollment.
Interested patients will be provided with the phone number of the investigators that they may call to obtain additional information about the study. Those participants contacting the study office will be provided a brief description of the goals of the study and what their participation would entail. Those who remain interested will be screened to assure that they meet eligibility criteria and schedule a measurement visit.

8.3 Self-referral from print and electronic media advertisement

IRB-approved advertisement containing an overview of the study will be created and displayed in newspapers and electronic media. Our contact information will be provided for potential participants to call for information and pre-screening. All self-referring subjects that are not NYLMC patients will be asked to sign a release of information form authorizing the study team to contact their treating physician. The study PI will send the PA a patient participation approval form for the PA to sign whether they PA agree that the patient can enroll a weight loss and brisk walking intervention. Self-referred patients from media outlets will undergo an eligibility visit test (refer section 11.1) to confirm eligibility prior to the baseline measurement visit.

8.4. Consent.

Regardless of recruitment approach used, signed informed consent will be obtained at the measurement visit, prior to obtaining measurements. Participants will be provided ample time to review the consent form. An investigator or study staff person will view each section with the participant, ask the participant if they understand each section, and clarify any questions they may have. The participant and the person obtaining consent will sign and date the consent form. A copy of the consent will be placed in the participant's medical record. Informed consent will be considered an ongoing process throughout the study, and participants' questions regarding their rights and responsibilities will be addressed whenever they occur. Participants will be paid $50.00 for each of the 2 measurement visits as compensation for their time. Participants will be reimbursed $5.50 for roundtrip travel should they need to return for FGM replacement.

9.0. Study Timelines

We will recruit approximately 5 cohorts of 4 participants each for the sample size of 20 participants. A new cohort will be randomized approximately every 4 weeks. The maximum number of study participants at any point in the study will be 10.

10.0. Study Endpoints

We will validate the PNP algorithm for North American T2D and pre-diabetes patients in a 2-stage, repeated measures quasi-experimental trial in which participants serve as their own control. In stage 1, PNP methods will be used to conduct metabolic profiling and develop a patient-specific algorithm that predicts glycemic responses to food ($iAUC_{pred}$). In stage 2, participants will consume, for 6 days, isocaloric diets (breakfast, lunch, dinner, and 2 snacks), which will be prepared and delivered daily, including 2 days each of low, moderate, and high glycemic load (GL) foods.

10.1. Specific aim 1. We will characterize $iAUC_{pred}$ and $iAUC_{obs}$ and describe differences between the two. Prior studies suggest that any difference between two AUCs less than δ = 30% of $iAUC_{obs}$ is not important and will be considered equivalent. Thus we will describe the equivalence of $iAUC_{pred}$ and $iAUC_{obs}$ by testing the null hypothesis of non-equivalence: H0: $|iAUC_{pred} - iAUC_{obs}| \geq \delta$ and the alternative hypothesis of equivalence is H1: H0: $|iAUC_{pred} - iAUC_{obs}| < \delta$ overall and within each race/ethnicity.

10.2. Specific aim 2. We will describe the extent to which the equivalence of $iAUC_{pred}$ and $iAUC_{obs}$ differs by whether or not the participant is prescribed metformin.

10.3. Specific aim 3. In preparation for future grant applications, we will establish the feasibility and acceptable of the research protocol.

11.0. Procedures involved

11.1. Stage-1 Metabolic Profiling

The study flow chart is given in the **figure-1** (appendix). The total duration of the study is approximately 4 weeks and includes 2 visits and 7 scheduled telephone calls. Two days prior to the eligibility visit, we will call the patients and remind them about the study (Telephone- **prescreen**). During the eligibility visit, participants will attend a measurement visit at the NIH-CTSI-funded Clinical Research Center (CTSI-CRC) (**visit-1**). During visit-1, prior to the blood draw, the study procedures will be reviewed with the participants and signed informed consent will be obtained. During the eligibility visit, we will draw 5 ml of fasting blood (~ 1 teaspoon) for the assessment their HbA1c. We will measure patients' resting energy metabolism in fasting state using indirect calorimetry (Quark RMR, COSMED USA Inc, Chicago Il) with an activity modifier of 1.3, rounded up to one of the following daily energy expenditure levels (1600 kcal, 2000 kcal, 2400 kcal, 2800 kcal, 3200 kcal). The QUARK RMR is an open-circuit calorimeter for measurement of mechanically assisted patients and spontaneously breathing patients. We will use the conventional Mifflin equation for participants that are apprehensive of wearing a mask to undergo this procedure.

If the participants meets the inclusion criteria (HbA1c value of less than 8.0% then we will contact them include them for the study (Telephone-**1**). In advance of their appointment, participants will be mailed questionnaires and stool sample kit with directions for collection. They will bring their stool sample with them to the CTSI-CRC, at which time we will collect various measures required by the PNP algorithm. Participants will be contacted 2 days prior to their appointment (Telephone-**2**) to remind them of their profiling visit (visit-2). Researchers will review the questionnaires and clarify the questions related to the study. We will draw 15 ml of blood (~ 3 teaspoons) samples for the following blood tests:

- ✓ blood laboratory measures (complete blood count (CBC), biochemistry panel, serum albumin, C-reactive protein , ferritin, lipid panel, HbA1c, fasting insulin and glucose, alanine transaminase (ALT), aspartate transaminase (AST), thyroid stimulating hormone (TSH), serum creatinine)
- ✓ glycated albumin
- ✓ collect the anthropometric measurements (height, weight, waist circumference and body fat %)

Laboratory tests will be collected, spun, refrigerated, batched and sent for processing in the Clinical Laboratory Improvement Amendments (CLIA) certified NYU CTSI Translational Research Laboratories by personnel blinded to group assignment. A baseline questionnaire will be administered to collect various covariates, described below.

De-identified stool samples will be express-shipped to the Weizmann Institute, where microbiome features (16S rRNA and metagenomic relative abundance, KEGG pathway and module relative abundances and bacterial growth dynamics - PTRs) are extracted. The Weizmann Institute will combine these data with gut microbiome profiles and PNP app derived self-monitoring data to develop an individualized predictive model of glycemic response from which we will derive $iAUC_{pred}$.

A professional, blinded, flash glucose monitoring (FGM) device will be inserted on the backside of each of your arms to measure interstitial glucose every 15 min (Abbott Sensor Based Glucose Monitoring System, Freestyle Libre Pro; Whitney, UK) for 14 days (**Day-1**). The sensor is calibrated in the factory and needs no calibration during the 14 day wear. We will load the PNP app on the participant's smart phone or study loaner smart phone and train them in its use. The PNP app records time-stamped entries pertaining to meals, physical activity, sleep, medications, hunger, and stress. Participants will be instructed to enter meals, medications, and stress into the PNP app in real time. Participants also will be provided with a Fitbit to capture continuous sleep and physical activity data over the next 7 days.

Subsequently, for the next 6 days, participants will be instructed to follow their normal daily routine and dietary habits, except for the first meal of every day (hereafter referred to as the "test meal".) Test meals consist of one of three different types of standardized meals – each consisting of 50 g of available carbohydrates, given twice to each participant (110 g white bread, 110 g white bread and 30 g of butter, 50 g glucose. Participants will be instructed to enter foods (test and other meals), and amounts consumed into the PNP app (**Day:2-Day:7**). Participants also will be instructed to wear a Fitbit device that streams data on physical activity and sleep to the participant's smart phone (by FitBit app). A follow-up phone call (Telephone-**3**) to the subject will be made by the study personnel to check that the subject has been able to use the Abbott FGM, PNP app without any issues and let the subject know that the test meals for the next 3 days (**Day:5-Day:7**) will be home delivered. Any adverse events or device incidents will be recorded.

11.2. Stage 2 Feeding Validation*

10.2.1. Selection of foods for feeding study:

Using the nutrient composition data from derived from the Nutrient Data System for Research, we have established a database of 200 meals that vary in glycemic load (GL). From this database, we will select 60 meals, consisting of 4 breakfast, 4 lunch and 4 dinner meals, and 8 snacks from each of the following categories: low GL, moderate GL, and high GL. Participants will be directed to select 2 meals and 4 snacks from each GL category, or a total of 30 meals and snacks (5/day) that they would be willing to consume during Stage-2. Meals and snacks will be prepared off-site by PortableChef, a foodservice operation in New York City that specializes in tailoring meals and delivering them to clients. Food will be prepared from scratch, portioned to match their estimated energy requirements based on REE or Mifflin St. Jeor equations with a physical activity modifier of 1.3, using a commercial scale (TE10FT, Taylor Precision Products, Inc.; Oak Brook, IL), and delivered to the CTSI-CRC for participants to pick up or to the participant's home (Day-1 and Day-4).

11.2.2. Feeding study:

Stage-2 feeding will take place on the 8th day Beginning the following day, for 6 days, participants will consume prepackaged meals and snacks. In order to limit the effects of meal order on glycemic response, each meal day will contain a random breakfast, lunch, dinner and 2 snacks from among those selected. The study personnel will call the subject on the 7th day to let the patient know about the feeding phase in detail (Telephone-**4**). Also, they will discuss about the feasibility and the barrier of using Abbott FGM, PNP app and FitBit. Also, the study personnel will ask the subject to charge the FitBit device. During stage-2 feeding phase, participants will continue to monitor meals, physical activity, sleep, medications, hunger, and stress with the PNP app. We also will obtain FitBit data on physical activity and sleep. A follow-up phone call (Telephone-**5**) to the subject will be made on to check that the subject is consuming the foods provided by the study and has been able to use the Abbott FGM without any issues. Any AEs or device incidents (DIs) will be recorded. To ensure that the glycemic response to meals and snack can be detected, participants will be directed to leave at least two hours between eating occasions. Although they will be asked to consume all foods and beverages provided, and nothing else (other than water for hydration), participants will be directed to record and report any deviation from the prescribed diet. On the day following the final meal, upon awakening (Day **14**), we will

call the participants' (Telephone-**6**) and directed to remove the FGM, FitBit devices and return it to the investigators in a postage-paid sharps box provided to them. If the participants did not send the devices within 5 days after the study completion then we will call them 2 additional times (Telephone-**7** and Telephone-**8**).

11.3. Measurements

Data are collected with visits to NYU Clinical and Translational Resource Center. Participants are contacted 2 days prior to their appointment to remind them of their measurement visit. Laboratory tests are collected, spun, refrigerated, batched and sent for processing in the CLIA-certified NYU CTSI Translational Research Laboratories by personnel blinded to group assignment. Clinically significant out of range laboratory and/or blood pressure values, as pre-defined by the safety steering committee, will be reviewed by a study clinician and faxed to the treating physician of record for expedited notification. The timing of profiling, measurement, and feeding components are summarized in **Table-2** below.

Table-2	**Eligibility**		**Profiling phase**							**Feeding Phase**						
Procedures	**Day: -10**	**Day: -5**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**D12**	**D13**	**D14**
Visit	**1**		**2**													
ELIGIBILITY VISIT																
Informed consent	✓															
HbA1c	✓															
Demographics	✓															
Indirect calorimetry (REE)	✓															
Mailing kit: Questionnaires (Background, Physical activity, habits, 3 day food frequency, sleep, medication, general health information) Stool sample collection kit		✓														
METABOLIC PROFILING																
Blood chemistry: labs measurements			✓													
Gut microbiota			✓													
Anthropometrics			✓													
FitBit: Sleep and Physical activity			✓ ----------												✓	
PNP app: Lifestyle habits			✓ ----------												✓	
Abbott Libre Pro: Continuous glucose monitoring			✓ ----------												✓	
Test meals (Breakfast only)				✓----------					✓							
CONTROLLED FEEDING																
Controlled feeding*										✓ ----------					✓	
DEVICE REMOVAL																✓

*Definition: Participants would be directed to consume only those foods and beverages that are prepared for them in a commercial kitchen, and to avoid eating any non-study food and beverages.

11.4. Analysis plan.

11.4.1. Outcome: Observed incremental area under the curve ($iAUC_{obs}$) at 2 hours following each meal and snack will be evaluated via FGM using the Abbott Libre Pro, which captures interstitial glucose every 15 minutes. A sensor is inserted into the participant's arms. Participants will be blinded to glycemia tracings.

11.4.2. Covariates: Baseline characteristics. We will measure glycated albumin, a measure of glycemic control over a 2-3 week period. A questionnaire also will be administered to collect the following information:

- ✓ health characteristics of the participant and family members
- ✓ medication regimen
- ✓ general habits [dietary, sleep, physical activity, smoking, and bowel)]
- ✓ recent treatment with antibiotics
- ✓ birth history
- ✓ stress
- ✓ apnea risk

11.5. Data analysis:

A descriptive analysis of all data collected will be performed using appropriate graphical and numerical exploratory data techniques. Data transformations will be performed to account for non-normal distributions. We also will conduct sensitivity analyses pertaining to the effects of baseline medication regimen (use of metformin or not). To address privacy concerns around microbiome sequencing, we implement metagenomic analyses using secure computation using secureseq platform (https://github.com/HCBravoLab/MicrobiomeSC). The median PPGR to standardized meals for each participant with 16S rRNA relative abundance at the species to phylum levels, MetaPhlAn tag-level relative abundance and relative abundance of KEGG genes will be examined using the Pearson correlation. We will cap relative abundance at a minimum of 1e-4 (16S rRNA), 1e-5 (MetaPhlAn) and 2e-7 (KEGG gene). For 16S rRNA analysis, the taxa with <20% of the features will be removed. The information obtained from this preliminary investigation of the data will be used as follows.

(i). Specific Aims 1 and 2. We will compare $iAUC_{pred}$ and $iAUC_{obs}$ overall, and within racial/ethnic groups using the equivalence test for paired data (TOST option in the PROC TTEST in R).

(ii). Specific Aim 3. We will develop a recruitment funnel to estimate the number of patients that must be approached to enroll and retain one participant. We will describe adherence to PNP app use, and adherence to the feeding component of the study.

11.6. Data sharing plan.

Within the confines of human subject regulations, any data produced will be made available to the scientific community, in writing upon request. All transcriptomic profiling data, including the raw data (CEL files) and probe IDs and intensities) will be deposited in GEO Gene Expression Omnibus (81). Thus, the array data will be freely available to the scientific community upon publication of the work. Proteomics data will be deposited into publicly available databases.

12.0. Data and Specimen Banking.

For this study we will be storing fecal and serum samples (two aliquots of 500µl / vial). We will not perform any genetic testing for this study. The participation for storing the samples will be optional and it is not mandatory requirement to be in research study. The samples will be used mainly to examine the relationships between microbiome, diet, blood glucose response, and the risk of future complications of type 2 diabetes. We are also

interested to study the association of post meal glucose and oxidative stress. The long-term goals of the research are to learn how to better understand and manage post-meal blood glucose excursions in people with type 2 diabetes. We will store the sample for the maximum period of 3 years.
The samples will be stored at Human Specimen Resource Center (HSRC) research tissue bank is located within NYU Langone Medical Center's Office of Collaborative Science at 540 1st Avenue New York, NY 10016. The research coordinator will de-identify the name assign a unique identification number and store it in a -80°C freezer. They will use the code number to connect subject sample to their health information that is stored in a computer database. The computer database is protected with a password.

Within the confines of human subject regulations, any data produced will be made available to the scientific community, in writing upon request. All transcriptomic profiling data, including the raw data (CEL files) and probe IDs and intensities) will be deposited in GEO Gene Expression Omnibus [54]. Thus, the array data will be freely available to the scientific community upon publication of the work. Proteomics data will be deposited into publicly available databases.

13.0 Data Management
Information to be obtained from participants includes glucose measurements from FGMs, physical activity and sleep from FitBit, height and weight, blood tests, blood pressure, investigator-administered questionnaires (sociodemographics, comorbid conditions, and psychometric instruments), physical activity, and dietary data. None of the data to be collected is considered sensitive in nature. Some of the participant data such as laboratory results will be linked to the participant's name. Other data (e.g., height, weight, and surveys) will be linked to the participant through an ID number. We will maintain separate files for identified and de-identified data in locked file cabinets in a locked office. Access to these data will be restricted to the PI (Sevick), the medical co-Is (Dr. Bergman), the project manager, study interventionists, study staff responsible for gathering data and maintaining research files, Dr. Eran Segal, co-Principal Investigator at the Weizmann Institute of Science, and his data analyst Anastasia Godneva, also at Weizmann Institute of Science. Data will be entered into a centralized database maintained on a secure server. Data in these files will be linked to participants only through their ID number. All data collected will be used expressly for the purpose of the proposed study. Weizmann Institute of Science investigators and personnel will only have access to de-identified datasets shared through NYU's Box cloud drive.

14.0. Provisions to Monitor the Data to Ensure the Safety of Subjects.

- **Controlled feeding:** Every effort will be made to protect the patients from ensuing food allergies. We will ask the patients about their food preferences / food allergies before preparing the foods.
- **Risk to privacy and confidentiality:** A variety of measures will be used to prevent breaches of confidentiality. First, all study staff will be trained in the NYULMC Research Practice Fundamentals, which include training in issues of confidentiality. As private information is collected as part of this study, there is a risk to participants' privacy and confidentiality. The research staff will take every precaution to protect participants' identity and the confidentiality of the information collected.
- **Personalized Nutrition Project (the online dietary self-monitoring program)** will be programmed by study staff with participants' age, gender, height, weight, dietary recommendations, a study ID number and a password. Participants will be asked to enter their meals and physical activities into Personalized Nutrition Project. The app was specifically designed for this study and it is based on a machine-learning algorithm that integrates blood parameters, dietary habits, anthropometrics, physical activity, and gut microbiota.. The Personalized Nutrition Project app is secured and data encrypted. The Personalized Nutrition Project app does not collect to transfer: a) patient-related health information or personal identifiers; b) mobile phone numbers, serial numbers or any other information that can be used to identify the user; c) GPS tracking or locality information. Participants will be directed to enter their lifestyle logs into PNP app for the next 2 weeks.

15.0. Risk to subjects.

- Risks of blood testing. Blood testing will be performed for screening and baseline. Bruising, bleeding, and minor tenderness at the puncture site sometimes accompany blood tests. Occasionally, but rarely, infection and fainting may occur. In very rare cases, nerve damage may occur as the result of a blood test.
- The risk of fasting. Fasting for 8-12 hours could cause dizziness, headache, stomach discomfort, or fainting.
- FGM: Subjects may experience some mild or moderate symptoms associated with the Sensor application or the adhesive used to keep the Sensor in place. These include erythema, oedema, rash, itching, bruising, pain, bleeding, and induration. We will use numbing cream before inserting the sensor to minimize the discomfort. Infection, inflammation, or bleeding at the sensor insertion site is possible risks of inserting sensor to the skin. It is rare that subjects will require treatment other than over-the-counter treatment. Most cases are caused by a reaction to the device adhesive. A microscopic piece of the sensor membrane may occasionally leave underneath the skin after the sensor is removed. This poses no health or safety risk and will dissolve on its own.
- Adhesive: We will use Tegaderm and Skin tac to adhere FGM sensors to the participant's skin for the 1-week measurement period. We will first wipe the skin with Skin tac, and adhesive wipe. Tegaderm is a transparent, breathable, waterproof film that is commonly used to secure intravenous lines. Tegaderm is occlusive to liquids, bacteria, and viruses; yet water vapour, oxygen, and carbon dioxide can easily be exchanged. The film is made with a hypoallergenic, latex-free adhesive that is gentle to the skin. Even for dressings left in place for extended periods, the risk of patient discomfort and skin trauma is minimal. The film conforms to body contours, stretches easily and prevents stress on the skin when the patient moves. Although rare, it is possible that participants will experience a sensitivity to the film. Participants experiencing sensitivity or discomfort will be directed to return to the CTSI where the sensor and dressing will be visualized and removed if necessary. The participant may experience discomfort when the film is removed. To avoid discomfort, participants will be shown (with a video) to remove the dressing in the direction of hair growth, and to peel the dressing over itself rather than pulling it up from the skin. If necessary, they will be directed to use warm water on the adhesive edge while peeling the dressing from the skin.
- The risk of hypoglycemia (low blood sugar): Symptoms of hypoglycemia include sweating, jitteriness, and not feeling well. Occasionally, there is the possibility of fainting or seizures (convulsions). Because participants are not taking diabetes medications or are taking only metformin, it is highly unlikely that participants will experience hypoglycemia.
- The risk of hyperglycemia (high blood sugar): Hyperglycemia usually does not cause many obvious symptoms, but participants may become thirsty, or have higher levels of sugar in their urine. In severe cases of hyperglycemia, diabetic ketoacidosis (DKA) or coma may occur. Because the participants we have recruited early-stage diabetes and the body continues to produce enough insulin to maintain glucose homeostasis, it is highly unlikely that participants will experience hyperglycemia.
- Controlled feeding: Participants may experience a brief change in digestion during the first few days on the study as the study diet may differ from their normal eating patterns. Depending on the diet that participants' are on, they may experience bloating, abdominal distress or constipation as the study diet may differ in the amount of fiber compared to their normal eating patterns. Participants are encouraged to communicate with study staff if you experience inconvenience or digestive discomfort, as they can offer assistance.

  The risk to privacy and confidentiality**:** A variety of measures are used which will reduce information security risk. First, all study staff will be trained in the NYULMC Research Practice Fundamentals, which include training in issues of confidentiality. All study staff will be required to sign a confidentiality agreement. Data will be maintained in separate files for identified and de-identified data in locked file

cabinets in a locked office. Access to these data will be restricted to the PI (Sevick), the medical co-Is (Dr. Michael Bergman), the project manager, and study staff responsible for gathering data and maintaining research files. Data will be entered into a centralized database maintained on a secure server. Data in these files will be linked to participants only through their ID number. All data collected will be used expressly for the purpose of the proposed study

16.0. Withdrawal of subjects.

In the event that involuntary withdrawal is required, participants will be referred back to their treating physician of record for evaluation and management. Data collection will cease at the time of withdrawal. Data up until the point of withdrawal will be used in the analysis.

17.0. Potential Benefits of the Proposed Research to the Subjects and Others.

At the conclusion of the study, we will share with participants those foods that resulted in the largest postprandial hyperglycemic excursions. Participants may benefit from the knowledge they gain regarding their personal glycemic response to foods. However, there are no guarantees that participants will benefit from participation in the study.

18.0 Vulnerable populations.

No vulnerable populations are included in this study.

19.0. Multi-site research.

Not applicable.

20.0. Community-based participatory research.

Not applicable.

21.0. Sharing results with subjects.

At the conclusion of the study, we make available to participants descriptive information regarding their glycemic response to foods they consumed during Stage 2.

22.0. Setting.

All research activities will occur at the Translation Research Building located at 227 East 30th Street, NY, 10016. No community advisory board is involved with this study. Ethical review will be limited to the IRB of NYULMC.

23.0. Resources available.

Mary Ann Sevick, ScD (Principal Investigator) is a Professor in the Department of Population Health in the School of Medicine at New York University, and Director of the Unit for Behavioral Health Informatics (UBHI). Over the past 20 years, Dr. Sevick has had experience with a variety of large clinical trials involving behavior change strategies including ENHANCE, the Women's Health Initiative, the Activity Counseling Trial; the Arthritis, Diet & Activity Promotion Trial; the Reconditioning & Exercise for COPD Trial; and Applications for Lifestyle Exercise study. Her primary interest is in the area of chronic illness and she has recently been

involved, as principal investigator, in several studies to examine adherence to disease management regimens. Dr. Sevick was a member of two recent National Kidney Foundation working groups to develop: (1) the K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease, and (2) the K/DOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease. Particularly relevant to this application, Dr. Sevick was PI on the ENHANCE Study (NIH-R01-NR008792), a clinical trial to evaluate a lifestyle intervention paired with technology-based self-monitoring in those with type 2 diabetes. With funding from a K24 (K24 NR012226), Dr. Sevick recently migrated the ENHANCE intervention approach (which used PDAs) to one that employs mobile technology. She was PI on the recently completed BalanceWise-HD Study (NIH-R01-NR010135), an intervention that employed technology-based self-monitoring to reduce dietary sodium intake in hemodialysis patients. She was PI of the VA-STRIDE Study (HSR&D- IIR07154), a clinical trial to evaluate an expert system-based physical activity intervention in overweight or obese and sedentary veterans recruited from VA primary care services. These four studies, in combination her work as Co-I on the SMART [Burke (NIH-R01- DK071817)] uniquely prepare her to engage obese patients with type 2 diabetes with concurrent chronic kidney disease in the proposed study. Dr. Sevick has extensive experience implementing clinical interventions that employ technology in clinical populations. She will head the Steering Committee, and Measurement, Recruitment, and Intervention Subcommittees, and will directly supervise the project manager and staff.

Eran Segal, PhD (Co-Principal Investigator). Dr. Segal is a Professor of Computer Science and Applied Mathematics at the Weizmann Institute of Science, and heads a lab with a multi-disciplinary team of computational biologists and experimental scientists in the area of Computational and Systems Biology. His group has extensive experience in machine learning, computational biology, probabilistic models, and analysis of heterogeneous high-throughput genomic data. His research focuses on Nutrition, Genetics, Microbiome, and Gene Regulation and their effects on health and disease. His aim is to develop personalized nutrition and personalized medicine. Dr. Segal has over 100 publications, and received several awards and honors for his work, including the Overton prize, awarded annually by the International Society for Bioinformatics (ICSB) to one scientist for outstanding accomplishments in the field of computational biology, and the Michael Bruno award. He was recently elected as an EMBO member and as a member of the young Israeli academy of science. With the Personal Nutrition Project, using genetic, microbiome, food intake and continuous blood glucose data, Dr. Segal developed a machine learning algorithm that predicted post-meal glycemia. He also showed that using the algorithm to develop tailored dietary recommendations, significantly lowered postprandial responses and resulted in favorable alterations to gut microbiota composition. Dr. Segal will provide scientific direction to the implementation of this algorithm with study participants, and assist with the analysis and interpretation of data and the preparation of progress reports and publications.

Dr. Bergman, MD, (Co-Investigator) is a Professor in the School of Medicine at the New York University. He is an Endocrinologist with extensive clinical and research experience with individuals with T2D. He has held leadership positions at New York University, the NYU Langone Medical Center, and the New York Harbor VA. Dr. Bergman will provide medical oversight to the study and assist with interpretation of data from a medical perspective and generation of publications.

Huilin Li, PhD (Co-Investigator) is an Assistant Professor of Biostatistics, in the Division of Biostatistics in the Department of Population Health at New York University School of Medicine. She has extensive experience in the design, conduct, and analysis of both observational and intervention studies. Dr. Li will chair the Data Management and Analysis Subcommittee, and direct the work of the Data Coordinator and Data Analyst. She will oversee generation of preliminary reports for data quality, safety, and recruitment. She will perform all analyses specified in the proposal and collaborate in the development of abstracts and manuscripts.

OTHER PERSONNEL

Lu Hu, PhD, RN is a fellow at the Center for Healthful Behavior Change and was involved in the development of this intramural application and in the design of the 3 program projects. She is a nurse by training, with

expertise pertaining to the use of mobile technology in the clinical management of patients with chronic disease. She will assist the investigators with implementation of recruitment, measurement, and intervention protocols. She also will assist the PI in the development of the larger P01 application. She will be fully covered by internal resources and no salary support is required.

David St. Jules, PhD is an Assistant Professor at the Center for Healthful Behavior. He has expertise in clinical nutrition and nutritional epidemiology. He was involved in the development of the dietary measurement and validation components of this application. He will guide the feeding study component of the study, including generation of standardized menus, oversight of the metabolic kitchen meal preparation, and quantifying adherence to feedings.

Lisa Ganguzza, MS RD CDN is a licensed Registered Dietitian with a BA in Communication, and a MS in Clinical Nutrition. She is currently working with Dr. Sevick on the Diabetes Healthy Hearts and Kidneys Study. Lisa calculates participants' individual nutrient needs, updates their MyNetDiary profiles, monitors their food records, and sends feedback messages. She is also working with the Cardiology Clinical Research Center on Effects of a Whole-food Plant-based Vegan Diet on Markers of Inflammation and Glucometabolic Profile in Patients With Coronary Artery Disease where she counsels patients to adhere to their randomly assigned diet. Lisa is responsible for training and overseeing study staff; implementing quality control regarding data collection activities; and assisting with development of the Institutional Review Board protocols and submissions. She will assist in recruitment and measurement activities as needed.

Paige Illiano, RD CDN Paige will be responsible for screening, recruitment, and consent. She will attend CTSI-CRC baseline measurement visits during which she will collect stool samples for shipment, administer questionnaires, obtain height and weight, coordinate collection of blood, perform indirect calorimetry, collect meal preferences, and instruct participants in wearing the FitBit and use of the PNP app to record meals, stress, sleep, diet, and medications. Paige will monitor the PNP app to identify foods not found by the participant, and contact participants to learn the brand names, portion sizes, and time consumed. If the food is truly missing, details regarding nutritional content will be investigated using the USDA dataset, Nutrition Data System for Research, and/or internet searches. Under the supervision of Dr. St-Jules, foods most closely matching the missing food will be entered into the app on behalf of the participant and new food entries (if needed) will be created in the food database. Paige will deliver menus to the metabolic kitchen and coordinate meal deliveries. Because of the time consuming nature of these activities which involve daily contact with participants, for the effort requested, we anticipate that she will be able to manage 3-4 patients at a time.

Josh Li, MPH (Senior Research Data Associate) has a BS in Engineering, an MS in Oriental Medicine, and an MPH in Epidemiology with extensive training and experience in data management and statistics. He is currently working with Dr. Sevick on Diabetes Healthy Hearts and Kidneys Study. He will be responsible for screening, recruitment, consent. He will attend CTSI-CRC baseline measurement visits during which he will collect and process stool samples for shipment, administer questionnaires, obtain height and weight, coordinate collection of blood, perform indirect calorimetry, insert the continuous glucose monitoring device, collect meal preferences, and instruct participants in wearing the FitBit and use of the PNP app to record meals, stress, sleep, diet, and medications. Josh will be responsible for uploading FGM, Fitbit, and other metabolic profiling data collected at NYULMC into a cloud database.

Ram Jagannathan, PhD is a fellow at the Center for Healthful Behavior Change. Dr. Jagannathan was involved in the development of this application. He is a biochemist by training with substantial expertise in epidemiologic methods and biomarkers relevant to the development and progression of T2D.

Anastasia Godneva, MA (Data Analyst/Programmer) is a mathematician at the Weizmann Institute of Science with training and experience in Computer Science and Big Data. Ms Godneva will be responsible for receiving, managing, and analyzing de-identified datasets of FGM, Fitbit, and other metabolic profiling data collected into the NYLMC cloud database (phase I data collection) to create participant profiles for the PNP application by extracting self-recorded participant information in the PNP application, including timing and dosing of metformin when applicable, timing of meals, nutrient composition of meals, hunger levels before meals, and duration of meals. She will integrate this data with Weizmann's data on gut microbiome from collected stool samples to validate the PNP application for North American populations (phase II data collection).

24.0. Institutional setting

24.1. Department of Population Health, NYULMC: The Department of Population Health, within NYU School of Medicine, aims to integrate, support, and advance NYULMC's contributions to population health research and related disciplines, providing a vibrant departmental home for the "bedside-to-population" as well as the "population-to-discovery" domains of translational research. It provides an academic base for efforts to integrate research into NYU's expanding health care delivery system that transcends any particular school, department, or division. The Department is a research and training hub that brings together researchers in nursing, medicine, psychology, epidemiology, biostatistics, health services and policy, behavior change, comparative effectiveness, medical ethics, prevention, and related disciplines, affording a unique and collaborative environment focused on improving the health of populations. The Department was initiated in January 2012. A core focus of the Department is improving health outcomes through innovative interventions as well as in enhancing the impact of interventions already known to be effective through their more effective implementation and dissemination. Collaboration with key public sector stakeholders and with community partners is central to the Department's mission. As researchers, faculty are engaged in dual roles: building cutting-edge science in their areas of inquiry, and providing collaborative consultation to other investigators throughout the NYULMC academic community as well as across the University. Resources within the Department for this proposal include the use of over 5,000 square feet of dedicated office space located on the newly renovated 6th floor of the NYULMC Translational Research Building, telecom (phone, fax and LAN connections), administrative assistants, and grant, regulatory (IRB) and finance administrators.

24.2. Center for Healthful Behavior Change, NYULMC: The Center for Healthful Behavior Change (CHBC) is located within the Department of Population Health. The mission of CHBC is to become a national leader in translational behavioral medicine, research, training, and education. The CHBC works toward this mission through the development, implementation, and dissemination of innovative evidence-based behavioral interventions in routine clinical practice and community-based settings with the long-term goal of disseminating effective strategies nationally and internationally. The Center is comprised of core research faculty members with expertise in various fields relevant to translational behavioral research. Faculty engage in research pertaining to heart disease, hypertension, chronic kidney disease, diabetes, cancer, health disparities research, community-based participatory research, health psychology, behavioral informatics, and health education and counseling.

24.3. Unit for Behavioral Informatics, NYULMC: The Unit for Behavioral Informatics (UBI) Research is a new unit within the CHBC, initiated in August 2013 under the direction of Dr. Sevick. UBI is the NYULMC academic home for applied researchers who integrate behavioral sciences, health sciences, health service delivery, and health information technology for the purpose of understanding, preventing, diagnosing or addressing behavioral risk factors for and consequences of chronic disease. Initiated in August of 2013, the overarching goal of the Unit is to provide training opportunities and infrastructure support for programs of research involving the use of technology in health behavior research, and translation of behavioral intervention research into clinical practice as well as community-based settings. UBI consists of 3 program areas: Behavioral Management, Measurement, and Education. The Behavioral Management Program aims to develop and evaluate tailored, eHealth applications to address behavioral risk factors for disease including diet, physical

activity, addiction, violence prevention, and adherence to chronic disease self-management regimens. The Measurement Program aims to develop technological applications for and programs of research pertaining to collection of ecologically valid data (e.g. measurement of behaviors, behavioral risk factors, and related psychometric [e.g. pain] and biophysiologic [e.g. blood pressure] outcomes. The Education Program aims to develop, test, and implement of technology-based instructional programs (e.g. virtual worlds), and videos (e.g. childbearing & childrearing, prevention of vector-borne diseases, water sanitation) for populations with limited access to health care or disparate health outcomes.

24.4. NYU Langone Medical Center Endocrinology Faculty Group Practice (NYULMC Endocrinology FGP):
The Department of Medicine of NYU Langone Medical Center is Among the longest established in the U.S. and is the largest academic department in the NYU School of Medicine. It supports and oversees 10 subspecialty division inclusion the Division of Endocrinology, Diabetes and Metabolism

22.5. Smilow Research Building And Laboratory Space: This space contains multiple bay areas set up by Principal Investigator individual team, along with 8 individual walled-off rooms designated for equipment and animal surgery on site. Core equipment within Smilow includes services such as confocal microscopy, Nikon inverted microscope, bacterial shakers, dark room and X-omat for film development, facilities for ChIP and Affymetrix arrays, Biacore for surface Plasmon resonance studies, and beta/gamma counters. All of the needed equipment and expertise for the outlined studies is available at NYU. The laboratory has >10 Dell / Macintosh computers with scanner, printer, CD ROM, as well as connection to the Internet; additional computers are attached to specific equipment. Dr. Schmidt has personal laptops for use in preparation of grants, manuscripts, and correspondence. Equipment includes HPLC (Agilent), FPLC, PCR machines, Vmax ELISA reader, phosphoimager, Speed Vac, UV-VIS spectrophotometers, spectrofluorimeter (PTI), centrifuges, cold room, tissue culture facility, freezers/refrigerators, Beckmann Coulter DTX 880 fluorimetric plate reader, luminometer, centrifuges, electrophoresis systems, gel drier, facilities for the use of radioactivity, Amaxa electroporator. Microscopes include Zeiss AXIOSKOP microscope with video attachment and image analysis software, 2 Leica microscopes with attached video camera and image analysis software. An hypoxia environmental chamber is available (Biospherix). A dedicated room has been set up for onsite animal terminal sacrifice work or survival surgery as indicated; this includes Leica surgical microscope, Isoflurane machine, and the equipment needed for animal warming. Two isolated heart perfusion systems with ADI systems for cardiac function monitoring are available. There is a separate room for tissue processing equipped with facilities for fixing, embedding and cutting sections (Tissue Tek system) for light and electron microscopy, as well as a cryomicrotome).

24.6. Division of Biostatistics NYULMC: Dr. Li's office is in the Division of Biostatistics, Department of Population Health, NYU School of Medicine at 650 First Avenue, a short walk from Dr. Sevick's office. Dr. Li has access to state-of-the-art computing facilities that include a central server (Dell PowerEdge 2500) and a Sun Server. Statistical software available either on the network or the desktop includes SAS, SPSS, S-Plus (including Spatial Stats and Environmental Statistics Modules), R, PASS and Matlab.

25.0 Prior approvals. We plan to approach the NYU-CTSI for approval to use the phlebotomy services available through their ambulatory Clinical Research Center.

26.0 Recruitment methods. See item 8.4 above. Participants will be paid $50 for the completion of each measurement visit.

27.0 Local number of subjects. We will recruit a total of 20 individuals to the study.

28.0 Confidentiality. Some of the participant data such as laboratory results will be linked to the participant's name in Epic. Other data (e.g., height, weight, and surveys) will be linked to the participant through an ID number. We will maintain separate files for identified and de-identified data in locked file cabinets in a locked

office. Access to these data will be restricted to the PI (Sevick) and her staff - all of whom will be trained in ethical research practices. Data will be entered into a centralized database maintained on a secure, password- protected server. Data in these files will be linked to participants only through their ID number. All data collected will be used expressly for the purpose of the proposed study. The specimens and/or associated data will be banked (section **12** and **13**). Serum samples will be hand-delivered by study staff who travel by foot to NYULMC laboratories. Serum samples will be analyzed and then stored in the bio-repository center under the direction of Dr. Rachel Brody. Results of lab testing will be available on Epic. No one other than study staff, NYULMC laboratory personnel, and providers of record will have access to the specimens or their results.

29.0. Provisions to Protect the Privacy Interests of Subjects. Measures to be used to protect subjects' privacy interests are described in section above (need to describe). Data collection will occur in a private setting where there is no opportunity for the participants' responses to be overheard. Participants will be told that they can refuse to respond to any questions that make them uncomfortable, and that they can withdraw from the study at any time.

30.0. Compensation for research-related injury. NA. The study is not more than minimal risk.

31.0. Economic burden to subjects. Neither the patient nor the patient's health insurance will be billed for any study activities, tests, or procedures. The cost of all procedures and tests will be covered by funds received from the NYU intramural grants.

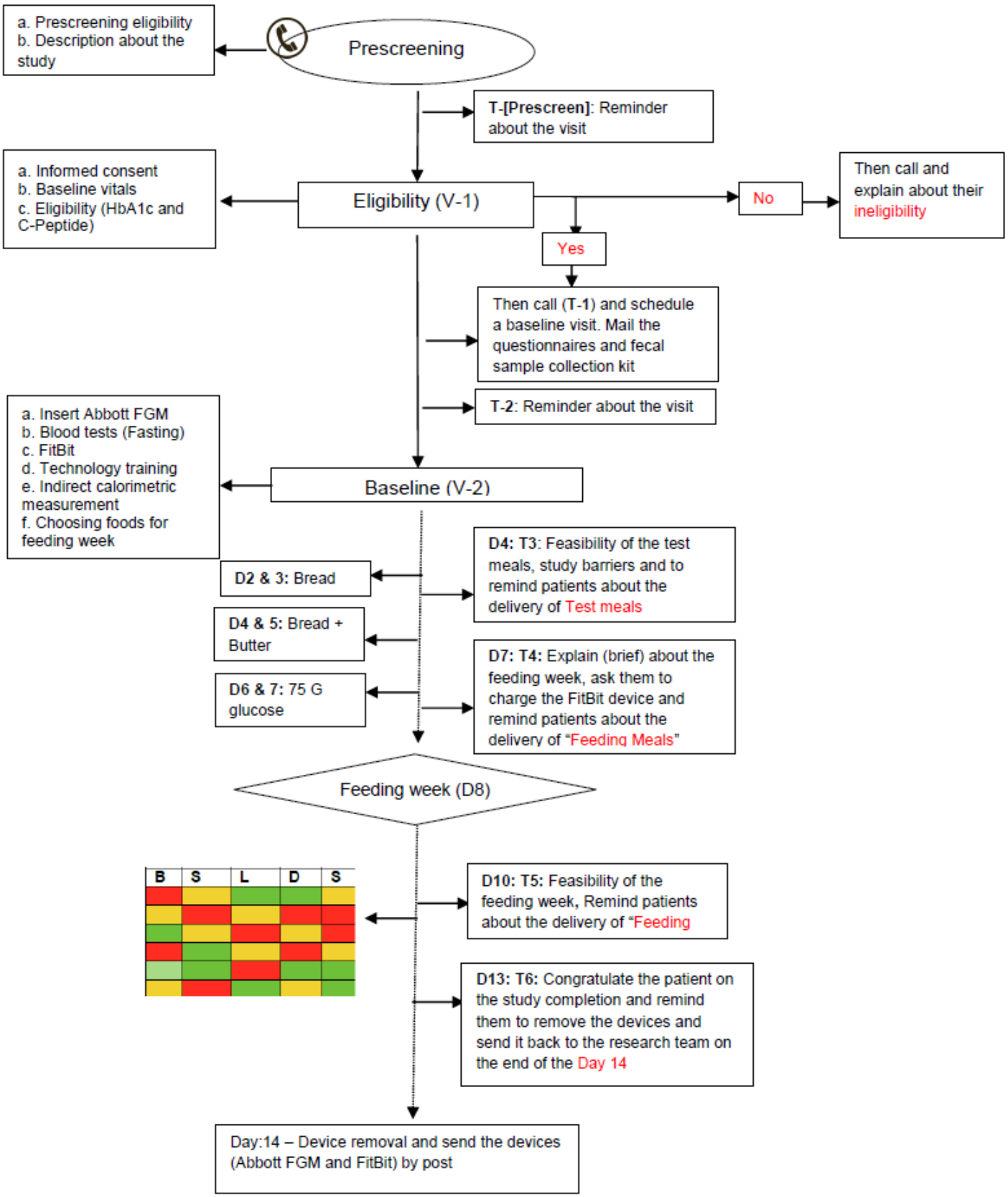
32.0. Consent process. A brief description of the study will be provided via telephone at the time of screening for the study. In order to minimize participant burden, a waiver of signed informed consent is requested for screening. We will verify eligibility. Signed informed consent will be obtained from remaining eligible participants. All questions will be answered. A copy of the consent form will be given to the participant and they will be encouraged to contact the PI with any and all questions that occur at any time during the conduct of the study. We will follow SOP: Informed Consent Process for Research (HRP-090). At this time, we will enroll only English-speaking participants, because the proposed software is currently only available in English.

33.0. Process to document consent in writing. Because the study does not pose more than minimal risk, consent will not be documented in the participant's medical record.

34.0. Drugs or devices. For this study we are using Abbott Flash Glucose Monitoring Pro (Libre Pro, FDA approved - enclosed annexure) to measure glucose levels and FitBit Alta to measure physical activity and sleep pattern (FDA exempted) .

Appendix-1:

Study flow


a. Prescreening eligibility
b. Description about the study
Prescreening
T-[Prescreen]: Reminder about the visit
a. Informed consent
b. Baseline vitals
c. Eligibility (HbA1c and C-Peptide)
Eligibility (V-1)
No
Then call and explain about their ineligibility
Yes
Then call (T-1) and schedule a baseline visit. Mail the questionnaires and fecal sample collection kit
T-2: Reminder about the visit
a. Insert Abbott FGM
b. Blood tests (Fasting)
c. FitBit
d. Technology training
e. Indirect calorimetric measurement
f. Choosing foods for feeding week
Baseline (V-2)
D2 & 3: Bread
D4 & 5: Bread + Butter
D6 & 7: 75 G glucose
D4: T3: Feasibility of the test meals, study barriers and to remind patients about the delivery of Test meals
D7: T4: Explain (brief) about the feeding week, ask them to charge the FitBit device and remind patients about the delivery of "Feeding Meals"
Feeding week (D8)
B S L D S
D10: T5: Feasibility of the feeding week, Remind patients about the delivery of "Feeding
D13: T6: Congratulate the patient on the study completion and remind them to remove the devices and send it back to the research team on the end of the Day 14
Day:14 – Device removal and send the devices (Abbott FGM and FitBit) by post

T 1 –T7: Telephone visits; V1&V2: visits; D: Days; Low glycemic load; Medium glycemic load; High glycemic load;