



The rationale and design of the personal diet study, a randomized clinical trial evaluating a personalized approach to weight loss in individuals with pre-diabetes and early-stage type 2 diabetes

Document Version:

Accepted author manuscript (peer-reviewed)

Citation for published version: Popp, CJ, St-Jules, DE, Hu, L, Ganguzza, L, Illiano, P, Curran, M, Li, H, Schoenthaler, A, Bergman, M, Schmidt, AM, Segal, E, Godneva, A & Sevick, MA 2019, 'The rationale and design of the personal diet study, a randomized clinical trial evaluating a personalized approach to weight loss in individuals with prediabetes and early-stage type 2 diabetes', Contemporary Clinical Trials, vol. 79, pp. 80-88. https://doi.org/10.1016/j.cct.2019.03.001

Total number of authors: 13

Digital Object Identifier (DOI): 10.1016/j.cct.2019.03.001

Published In: **Contemporary Clinical Trials**

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- 1 The rationale and design of the Personal Diet Study, a randomized clinical trial evaluating a
- 2 personalized approach to weight loss in individuals with pre-diabetes and early-stage type 2
- 3 diabetes
- 4

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- 17
- 18 Abstract
- 19 Weight loss reduces the risk of type 2 diabetes mellitus (T2D) in overweight and obese individuals.
- 20 Although the physiological response to food varies among individuals, standard dietary
- 21 interventions use a "one-size-fits-all" approach. The Personal Diet Study, currently underway, aims
- to evaluate two dietary interventions targeting weight loss in people with prediabetes and T2D: (1) a
- low-fat diet, and (2) a personalized diet using a machine-learning algorithm that predicts glycemic
- response to meals. Changes in body weight, body composition, and resting energy expenditure will
- be compared over a 6-month intervention period and a subsequent 6-month observation period
- 26 intended to assess maintenance effects. The behavioral intervention is delivered via mobile health
- technology using the Social Cognitive Theory. Here, we describe the design, interventions, and
- 28 methods used.
- 29 Funding: This work was supported by Grant 17SFRN33590133 from the American Heart
- 30 Association.
- 31 ClinicalTrials.gov Identifier: NCT03336411
- 32

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33 Introduction and Background

The cause of obesity is under considerable debate.^{1,2} The conventional theory suggests obesity 34 is the result of energy imbalance where energy intake exceeds energy expenditure. In contrast, the 35 Carbohydrate-Insulin Model of obesity proposes diets with high postprandial glycemic responses 36 (PPGR) promote weight gain, stimulating hyperinsulinemia, suppressing fat mobilization (trapping 37 fat) and resulting in delayed hypoglycemia.³ This cascade of events leads to subsequent stimulating 38 of hunger, overconsumption of calorie-dense foods and a reduction in energy expenditure.⁴ 39 40 Proponents of this model assert that a diet designed to minimize PPGR is a valuable adjuvant to 41 weight loss interventions.¹

42 Carbohydrates primarily drive PPGR, but it also varies considerably with the type of 43 carbohydrate consumed. Glycemic Index (GI) and, glycemic load (GL), are often used to help 44 describe PPGR in response to specific foods. Several reports suggest that a reduction in the 45 consumption of high-GI and high-GL foods enhances weight loss due to the reduction in PPGR and 46 insulin secretion.^{5–8} Furthermore, minimizing PPGR may attenuate the decline in resting energy 47 expenditure (REE) observed with weight loss.⁹

The results of human intervention studies manipulating carbohydrates, GI, and/or GL for weight 48 loss are often no more efficacious than other diets.^{10–12} Indeed, recent obesity management 49 guidelines developed by the American Heart Association and American College of Cardiologists, 50 and affirmed by the Academy of Nutrition and Dietetics concluded that, in comparison to higher 51 carbohydrate/lower protein or lower fat diets, carbohydrate-restricted diets do not result in greater 52 weight losses.¹³ Furthermore, there was insufficient evidence to comment on weight loss 53 54 interventions involving complex versus simple carbohydrates, GL dietary approaches, or other dietary pattern approaches.¹³ 55

Standard dietary interventions based on GI/GL may fail to consistently produce weight loss because individuals vary in their glycemic response to the same foods.¹⁴ Consequently, patients may experience postprandial hyperglycemia despite consuming low-GI/GL meals. The disconnection between lifestyle efforts (e.g., following a low-GI/GL diet) and outcome (e.g., weight loss or blood glucose control), may be a disincentive for self-management efforts. Moreover, dietary interventions may fail to produce weight loss because they do not consider dietary habits and preference, or barriers to dietary choice.^{15–20}

A potential factor that may explain the between-subject variability to diets differing in GI/GL is the gut microbiota. Animal studies demonstrate that obese microbiome has an increased capacity to harvest energy from the diet.^{21,22} There is a strong association between the gut microbiota and glucose intolerance, insulin resistance, and T2D.^{23–26} In humans, the transfer of intestinal

microbiota from lean humans to those with metabolic syndrome increased insulin sensitivity.²⁷ In 67 68 2015, Segal et al. demonstrated that subjects have a high between-subject variability PPGR to the 69 same foods. Using this data, they developed the Personalized Nutrition Project (PNP), a novel machine-learning algorithm that predicts individuals' PPGR to pre-consumed or unseen meals.²⁸ In 70 71 a subsequent validation study, Segal et al demonstrated that a personally tailored intervention based on the predicted response significantly improved PPGR to meals²⁸. Until now, no study has 72 attempted to apply personalized nutrition in the context of a behavioral weight loss intervention in 73 74 pre-diabetics and T2D.

75 A potential mediator of weight loss and weight regain may stem from production of advanced glycation end products (AGEs), as they accumulate at an accelerated rate in the presence of 76 hyperglycemia, including acute glycemic variability (GV).²⁹ AGEs appear to be partly mediated 77 through their binding to the receptor for advanced glycation end products (RAGE), which generates 78 oxidative stress and inflammation.^{30,31} The AGE-RAGE axis is associated with diabetes and 79 obesity, and RAGE may serve as a "brake" to weight loss and predispose participants to weight 80 regain via metabolic adaptation.³² The presence of hyperglycemia also triggers neutrophil and 81 monocyte release of a protein complex, S100A8/A9, a ligand of RAGE.³³ Furthermore, soluble 82 83 RAGEs (sRAGE) serve as endogenous RAGE ligand-sequestering molecules, interfering with the 84 ability of the RAGE ligands to activate the cell surface receptor - blocking the ability of RAGE to brake energy expenditure, thereby facilitating weight loss. Little is known regarding the relationship 85 86 between GV and AGEs, sRAGE, RAGE activation (i.e., increased levels of proinflammatory RAGE ligands), and circulating mediators of inflammation as they relate to weight loss. 87

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Objectives

The purpose of the Personal Diet Study is to compare two weight loss interventions: (1) a lowfat diet (LFD) versus (2) a diet that is personalized (PD) using the PNP algorithm to predict PPGR. Interventions will be compared regarding their effects on body weight, body composition, and energy expenditure (e.g., metabolic adaptation). In addition, we will examine the mediating effects of self-efficacy, glycemic variability and the AGE/RAGE/S100A8/A9 pathway on these outcomes.

95 **2.1.1 Design**

The study is a two-arm, parallel-group, randomized clinical trial in overweight and obese adults with pre-diabetes and early-stage T2D. The trial involves two 6-month phases: an active intervention phase (phase 1) followed by a maintenance/observation phase (phase 2) (**Figure 1**). Participants are randomized with equal allocation to either LFD or PD. Measurements occur at
baseline and at 3, 6, and 12 months. All measurement visits and data are collected at NYU
Langone Health (NYULH) in New York City. Microbiome analysis and data processing for the
purpose of the PNP prediction algorithm are completed at the Weizmann Institute of Science in
Rehovot, Israel.

104 **2.1.2 Eligibility and sample requirements**

105 To be eligible for this study, patients must be between 18 and 80 years of age, have a body mass index (BMI) between 27 and 50 kg/m², and have a hemoglobin A1c (HbA1c) between 6.5 and 106 107 8.0% (Table 1). Patients treated with medications other than metformin or who have evidence of 108 kidney disease, assessed with estimated glomerular filtration rate (<60 mL/min/1.73m²) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, are excluded to avoid 109 110 recruiting patients with advanced T2D.³⁴ Furthermore, patients with conditions or treatments that affect glycemia (e.g., corticosteroids), or impact weight loss efforts are excluded. Because the PNP 111 112 application is currently only available in English and Hebrew, non-English literate participants are 113 also be excluded. Eligible participants with the recent use of antibiotics or antifungal medications are postponed 3 months prior to randomization because of the impact on the gut microbiota. 114 115 Those who fail to log an average of 2 meals per day during the run-in period are excluded (see 116 section 3.3).

117 **2.1.3** Recruitment, screening, and enrollment procedures

The first study cohort was recruited in January 2018 and recruitment is expected to conclude in
December 2019. The primary recruitment method involves an electronic medical record (EMR)
system to identify potentially eligible patients who receive care at NYULH-affiliated practices.
Patients meeting the search criteria are sent a message describing the study in their patient portal,
or via email. Patients self-refer by clicking on a link that notifies study staff of their interest in
participating. Secondary recruitment includes self-referrals from ClinicalTrials.gov and
CenterWatch.com.

Screening for eligibility is completed by telephone. Individuals who meet screening criteria are scheduled for an in-person screening visit at the Clinical Research Center of NYULH's Clinical and Translational Science Institute (CRC-CTSI). At this visit, signed informed consent is obtained, height and weight are measured (see section 2.4.1). A non-fasting plasma and serum blood sample is collected by a certified phlebotomist to assess HbA1c and serum creatinine (i.e., eGFR). In addition, participants are provided with a self-administered questionnaire to complete and bring to 131 their baseline visit. Participants without their own smartphones are provided loaner phones and no-132 cost service plans to use for the duration of the study. Each participant is provided the PNP 133 smartphone app to use to self-monitor their diet, physical activity, and body weight. This app is integrated with the USDA Food Composition Database (Release 28.1), allowing participants to 134 select from thousands of food and beverage items. Participants are trained on how to enter meals, 135 snacks, and physical activity, and on how to search for foods and beverages, enter serving sizes, 136 create a "favorite" food-item, and create a "saved meal" into the PNP app. Participants with a BMI 137 under 27 or greater than 50 kg/m², HbA1c \geq 8.0%, or an estimated glomerular filtration rate based 138 139 on serum creatinine (<60 mL/min/1.73m²) are excused from further participation. Table 2 provides 140 a timeline of measurement visits.

141 Measurements

Study visits are conducted at the CRC-CTSI at baseline and at 3, 6, and 12 months. Table 3
outlines the study variables obtained at each assessment time point and are described in more
detail below.

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146 **3.1.1 Primary and Secondary Outcomes**

Anthropometrics. BMI is calculated from height and weight. Height is measured to the nearest 147 1 cm using a portable stadiometer (SECA 213, Seca GmBH & Co. KG, Hamburg, Germany), and 148 149 body weight is measured in light clothing without shoes to the nearest 0.1 kg using a Stow-A-Weigh 150 scale (Scale-Tronix, Welch Allyn, Skaneateles, NY, USA). Waist, hip, and neck circumferences are measured in duplicate using a Gulick tape (McKesson Medical-Surgical, Fairfield, NJ, USA) to the 151 nearest 1 cm using techniques detailed elsewhere.³⁵ Body fat percentage and fat-free mass (FFM, 152 153 in kg) are measured using bioelectrical impedance analysis (BIA; InBody 270, InBody, Inc. Cerritos, 154 CA, USA).

Resting Energy Expenditure (REE). REE is assessed via open-circuit indirect calorimetry 155 (Quark RMR, COSMED USA Inc., Chicago, IL, USA) using a ventilated hood system after a 12-156 hour overnight fast. Participants are directed to lay supine for 10-minutes during which the 157 metabolic cart is calibrated per the manufacturer's instructions. Oxygen and carbon dioxide 158 159 production are measured for 20-25 minutes following a 5-minute run-in period, with participants in a 160 relaxed, awake state. Room temperature and humidity are maintained at a constant level, and 161 ambient noise and lighting are minimized as best as possible. REE is calculated from the Weir 162 equation.³⁶

Blood samples, resting heart rate and blood pressure. Resting heart rate (RHR) and systolic and diastolic blood pressure (BP) are measured following a 5-minute, seated resting period using an automated blood pressure machine (Welch Allyn PROPAQcs, Welch Allyn, Inc., Skaneateles Falls, NY, USA). In both the PD and LFD groups, fasting plasma and serum(BOTH plasma and serum?-usually plasma) samples are collected by a certified phlebotomist to measure glucose and insulin at baseline, 3 and 6 months. A complete blood count (CBC) is collected at baseline only in the PD group for the purposes of the predictive algorithm.

170 **3.1.2 Mediators**

171 Self-efficacy. Self-efficacy for weight loss is assessed using the validated, 20-item Weight Efficacy Lifestyle Questionnaire.³⁷ Participants are asked to rate their self-efficacy for each item on 172 173 a 10-point Visual Numeric Scale ranging from 0 (not confident) to 9 (very confident). Items assess 174 self-efficacy for resisting eating under various circumstances such as negative emotions, availability, social pressure, physical discomfort, and positive activities.³⁷ An overall score and 175 176 subscale scores will be computed by summing relevant questionnaire items. These scores will be 177 used to evaluate the mediating effect of self-efficacy on the relationship between weight loss and randomization group. 178

179 **Glycemic Variability**. HbA1c is obtained using high-pressure liquid chromatography (HPLC; Variant II) Turbo analyzer, Bio-Rad Laboratories, Inc., Hercules, CA, USA). In addition, GV is 180 examined for up to 7 days with a continuous glucose monitor (CGM: Abbott Freestyle Libre Pro. 181 182 Abbott Park, IL, USA), which measures interstitial glucose concentrations every 15 minutes. The skin surface is prepared with Skin Tac (TORBOT Group, Inc., Cranston, RI, USA) to help prevent 183 184 detachment of the CGM devices and, once inserted, covered with a Simpatch adhesive patch. Participants are blinded to glucose tracings.³⁸ CGM data will be used to calculate, standard 185 186 measures of GV, including mean amplitude of glycemic excursion (MAGE), which is a value of 187 variation about the mean by summing the absolute rises or falls of glucose levels encountered daily, ignoring excursions of less than 1 standard deviation (SD).³⁹ CGM data will be used to generate 188 189 other indices of GV including (1) SD, (2) continuous overall net glycemic action, (3) mean 190 postprandial area under the curve. (4) incidence and time spent outside the normal glycemic range (<70 and >180mg/dl), and extremely out of range (<50 and >300mg/dl).⁴⁰ All GV indices will be 191 calculated using EasyGV 8.6 software.⁴¹ Fasting serum insulin and plasma (again, serum or 192 plasma?) glucose concentrations are measured and used to calculate insulin resistance (HOMA-IR) 193 and β -cell function (HOMA- β). The HOMA2 model will be used for this purpose. ⁴² 194

Advanced Glycation End products (AGEs) and inflammation. The first 36 participants
 randomized to the study (18 in each group) having BMI ≥35 kg/m² are assessed for the
 RAGE/AGE/S100A8/A9 pathway with additional serum and plasma measurements. AGEs are
 detected using Fluorescence Microplate reader (BioTek Synergy HI microplate reader). RAGE,
 sRAGE and S100A8/A9 are determined using enzyme-linked immunosorbent assay (ELISA) kits
 (R&D Systems Quantikine Immunoassay, Minneapolis, MN, USA). In addition, inflammatory
 markers (e.g., TNF-alpha, IL1-beta, IL4, IL10, and IL-17) are also assessed.

202 **3.1.3 Covariates**

Sociodemographic and clinical variables. At baseline, the following sociodemographic variables are collected using self-administered questionnaires: age, race, gender, living arrangement, education, employment status, income, family countries of origin, comorbidities, weight history, hunger, sleep quality, smoking status, bowel habits and function, antibiotic use, birth and breastfeeding history, and menstrual cycle (females only). At each assessment time point, we will inquire about new health events and changes in medications and treatments during the prior interval.

209 Physical activity. Physical activity is measured using the Fitbit Alta HR (Fitbit, Inc., San 210 Francisco, CA, USA). Participants are instructed to wear the device for up to 7 days. Participants in 211 the LFD and PD group wear the device at baseline, 3 and 6 months. The screen on the device 212 provides the participant with daily feedback on heart rate, caloric expenditure and steps per day, but 213 weekly accumulated data is not shared with the participate. Those in the PD group wear the device again during the profiling week. Participants in the PD group are instructed to carry out their 214 215 habitual exercise routine during the profiling, and are not provided with any additional feedback 216 regarding physical activity levels.

217 **Pre-intervention**

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4.1.1 Pre-intervention training (both groups)

Participants in both the LFD and PD group attend a pre-intervention training visit one to two
weeks before the start of the intervention. Here the WebEx application is downloaded on their
phones or the study loaner phones, and participants are trained in its use and how to join
intervention meetings. WebEx is a communications application on the NYULH Cisco Server, which
is a HIPAA-compliant conferencing program. WebEx allows users to sign-in securely and join
meetings from mobile devices. During this time, the interventionist provides further training on the

PNP app, which includes troubleshooting and PNP app clarification. Participants randomized to PDundergo additional procedures described below.

4.1.2 Pre-intervention glycemic profiling (PD group only).

Participants in the PD group undergo 1 week of glycemic profiling immediately after the pre-228 229 intervention visit to generate personalized feedback regarding the predicted PPGR for the PNP 230 algorithm. At the baseline visit, participants are provided with an Omnigene stool collection kit (DNA 231 Genotek, Inc., Ottawa, ON, Canada) used for microbiota profiling. Stool samples are collected during 232 the pre-intervention visit and shipped to the Weizmann Institute for microbiome analysis. A new CGM 233 is then inserted and worn for 7 days. Participants are instructed to follow their normal daily routine 234 and dietary habits, except for the first meal of every day (hereafter "test meal") and to refrain from 235 eating for 2 hours after the test meal is consumed. Six test meals are provided to the participants, 236 including two of each of the following: (1) 110 g white bread, (2) 110 g white bread and 30 g of butter, 237 and (3) 50 g glucose. Test meals are labeled with the day that they are to be consumed. Participants 238 enter meals (test and other meals) and snacks, the timing of meals and snacks, physical activity, 239 sleep, and hunger over the next 7 days into the PNP app. Participants are instructed to consume food with a minimum of 2 hours in-between meals and snacks in order to link meals and snacks to 240 241 glycemic tracings. During the profiling week, study staff monitor participants' PNP dashboards daily, and contact participants as necessary to ensure that meals are logged and reported as accurately as 242 possible. At the conclusion of the profiling week, participants remove the CGM sensor, place it into 243 244 a sharps-proof container, and return it to the investigators by mail. Time-stamped CGM and PNP data are uploaded to a HIPPA-compliant NYULH server, with baseline laboratory and physical assessment 245 246 data.

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4.1.3 Development of PNP algorithms

Data collected during the screening and baseline visits are shared, using the NYULH server, with the Weizmann Institute where data processing occurs. Anthropometrics, a blood chemistry panel, microbiota profiling (metagenome sequencing), up to one full week of interstitial glucose measurements using a CGM, and a one-week log of date- and time-stamped meals and snacks from participants are integrated with the PNP database at the Weizmann Institute using gradient boosting regression to develop personalized PNP algorithms for predicting PPGR.

A meal database was created consisting of Western-style meals (n= 135) and snacks (n=68) varying in GL to generate feedback on the PPGR to pre-consumed meals. Using the participants' PNP algorithm, personalized PPGRs are calculated for every meal and snack in the database based on their nutrient composition, and calorie-adjusted quintile cutoffs of PPGR are used to create meal
ratings of "excellent," "good," "medium," "bad," and "very bad."

259 Interventions

260 **5.1.1 Phase 1 - Both groups**

The 6-month active intervention phase targets a weight loss of 7% through caloric restriction in both groups. Participants are also instructed to participate in 150 min/wk of moderate-to-vigorous physical activity (MVPA) and engage in resistance training 2-3 times per week.⁴³ Participants in both arms attend group behavioral counseling sessions that are guided by study dietitian. Group sessions (n=14) are limited to 10 participants, and are held weekly during the first month, and then every other week in months 2–6.

Behavioral counseling is based on the SCT^{44,45}. Group sessions are conducted via WebEx 267 (Cisco Systems Inc., San Jose, CA, USA) using a smartphone to minimize participant burden of 268 attending face-to-face group sessions. The duration of each group session is approximately one 269 270 hour. Each session is anchored by two brief videos (~5-7 minutes each) to enhance intervention 271 fidelity; one that provides educational content, and one focuses on behavior change. The 272 behavioral component is identical between the LFD and PD groups. The only between-group 273 differences for the educational content occurs at sessions 5 and 14. The content for all other 274 educational sessions is identical between groups. The content of these sessions is outlined in 275 **Table 4.** Periodically, the interventionist pauses the videos and introduces scripted open-ended questions designed to elicit discussion. At the conclusion of the session, the videos are posted on 276 277 the study website for participants to review as desired, and all participants are e-mailed a link to the videos presented. All videos posted on the study website are integrated into BrainShark 278 279 (Brainshark Inc., Waltham, MA, USA), a software program that allows the investigators to document 280 exposure to content independent of intervention sessions. The full sessions, including participant 281 discussions, are recorded, retained, and 20% are reviewed by a trained rater to assess fidelity of 282 the interventionist to the behavioral counseling techniques used in the session (i.e., motivational 283 interviewing). The rater provides feedback to the interventionist to ensure consistent counseling delivery based on the proposed behavioral theories supporting the intervention. These recorded 284 285 sessions are not posted or shared with participants.

For the duration of the intervention, participants are directed to self-report into the PNP app everything that they eat or drink, their physical activity, and their body weight (weekly). The PNP app is pre-programmed with a: (1) weight loss target (-7% body weight); (2) hypocaloric energy target (-500 kcal/day, based on REE measurements from indirect calorimetry and a physical activity 290 factor of 1.4 (lightly active); and (3) physical activity target of 30-minutes per day. Participants are 291 counseled to use the PNP app to monitor, in real-time, their behaviors concerning the study targets. 292 Example screenshots of nutritional details, meal totals, and physical activities are shown in Figures 293 2 and 3.

294

5.1.2 Phase 1 - Low-fat diet arm only

295 The LFD arm is counseled to follow a low-fat (<25% dietary fat) diet containing <7% energy 296 intake from saturated fat. They are instructed to review the PNP meal entries, in real time, to ensure they keep their daily intake below the 25% total fat and 7% saturated fat targets. 297

298 5.1.3 Phase 1 - Personal diet arm only

299 The PD arm is instructed to review their PNP meal entries daily in the smartphone app 300 concerning targets for total calories. PD participants receive personalized feedback regarding the 301 nature of their personalized predicted PPGR for foods entered into the PNP app prior to 302 consumption (See Figure 2). The feedback is color-coded in green (foods with a "good" or "excellent" PPGR), yellow ("medium" PPGR), and red (a "bad" or "very bad" PPGR). Participants 303 are advised to maintain PPGR in the "good" or "excellent" range and, when they receive yellow or 304 305 red scores, to make different choices/food substitutions. Initial guidance is provided regarding low-306 and high-GL foods, as well as the addition of healthy fats to the meal. However, participants are 307 informed that because their glycemic response is specific to them, experimentation will be required 308 to determine which meals and snacks are most suitable for them.

5.1.4 Phase 2 309

Phase 2 is a 6-month observation period. During this time, participants are encouraged to 310 311 continue monitoring diet, physical activity, and body weight, and enter the data into the PNP app, 312 however, no further contact is made by the interventionist or study dietitian. Three newsletters are 313 mailed to all study participants discussing topics outlined during the active phase of the intervention 314 to maintain communication and engagement.

315 General Approach

316 A descriptive analysis of all data collected will be performed using appropriate graphical and 317 numerical exploratory data techniques. The information obtained from this preliminary investigation 318 of the data will be used to: (1) assess data quality and completeness; (2) describe univariate and 319 bivariate distributions at baseline and at, 3, 6 and 12 months; and (3) identify univariate

associations between variables. We will identify features of the data that may necessitate special
 methods (e.g., excess zeros, missing data, and departures from distributional assumptions). During
 preliminary analysis, we will examine: (1) comparability of treatment arms at baseline (based on
 Chi-squared statistics or t-tests, as appropriate), (2) relationships between the response variables
 and potential covariates, and (3) predictors of missing data/drop-out.

325 A linear mixed model will be used to model the baseline, 3, 6 and 12 months outcome variables. 326 In the model, presence/absence of T2D, time, and intervention will be included as fixed effects, and the participant will be the random effect. The intervention effect of interest is the treatment*time 327 328 interaction in this model. Identified predictors of missing data will be included as covariates in this 329 random effect framework, to provide unbiased estimates of the intervention effect under an 330 assumption of missing at random (i.e., missingness depends on observed covariates but not on 331 unobserved covariates). Other demographic and clinical covariates will be included as necessary in adjusted analyses. Model assessment will be conducted using appropriate regression diagnostics. 332 333 The primary and secondary analyses will be done using SAS (SAS 9.4, Cary, NC, USA).

334 6.1.1 Sample Size

The required sample of 164 (82 per group) is based on the assumption that a clinically significant minimum of 5% weight loss will achieved by the LFD group, which is consistent with a pilot study (5.94%; SD_{weight loss} =4.54%) to the Healthy Hearts and Kidneys study⁴⁶ (unpublished data) sentence needs clarification. The goal for both groups is 7% weight loss at 6 months, similar to the Diabetes Prevention Program and Look AHEAD trials.^{47,48} We can detect a difference between weight loss of the LFD and the PD as small as 2% with a type I error α =0.05 and a power of 80%. To account for an expected loss of about 20% of participants to drop-out, we will recruit 200 participants.

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6.1.2 Analysis of Primary Outcomes

343 For hypotheses pertaining to weight loss, the primary outcome of interest is the percent of baseline body weight lost at 6 months and whether or not these losses will be sustained at 12 344 345 months. A random effects linear regression model will be used to test time-specific differences attributable to the intervention. We also will use the "lincom" command to estimate differences in 346 time-specific changes from baseline. In additional analyses, we will adjust for other covariates 347 (e.g., insulin secretion, insulin sensitivity, glycemic control, habits and history that could influence 348 349 weight loss, and sociodemographic, and medication regimen) unbalanced between the treatment 350 arms at baseline at p=0.10. A splined linear mixed model with repeated measures will be used to

compare changing trends in different periods: early intervention (0-3 months) and late intervention
 (3-6 months). In this analysis, adjustments will be made for the covariates noted above.

353

6.1.3 Analysis of Secondary Outcomes

For hypotheses related to body fat distribution and metabolic adaptation at 6 and 12 months, and weight regain at 12 months, the random effects linear regression model will be used to test timespecific differences attributable to the intervention using a similar approach to that of analyses for the primary aim of weight loss. Mediation analysis will be performed to assess whether, and by how much, self-efficacy mediates and the intervention effect on weight loss. Covariates (such as age, gender, race, and baseline T2D status) will be included in the model and explore the possibility of multiple mediators.

361 Similar mediation analyses including self-efficacy and glycemic exposure will be performed to 362 examine the underlying biologic mechanisms that influence weight loss/regain metabolic adaptation 363 and fat distribution at 6 and 12 months.

364 **6.1.4 Adherence**

365 Adherence to the study intervention will be assessed based on attendance to measurement 366 visits and WebEx intervention meetings and on viewing of the Brainshark videos. In addition, 367 adherence to self-monitoring will be evaluated based on the frequency of using the PNP app to 368 record diet, physical activity, and body weight, and the proportion of days meeting >50% of calorie 369 target. Adherence to the dietary interventions will be analyzed based on the proportion of meals and 370 days in which dietary fat is <25% calories (LFD arm), and the proportion of meals logged as "good" 371 or "excellent" (PD arm). Adherence to physical activity recommendations will be examined using the 372 proportion of weeks in which participants record >150 min/wk of MVPA.

373 6.1.5 Safety

374 During the study, participants' weights and HbA1c are monitored. Each participant's percent 375 weight change is assessed at each measurement visit. Participants are counseled by study 376 dietitians to slow their rate of weight loss if their percent weight change is severe defined as >7.5% 377 in 3 months, >10% in 6 months, and >20% in one year. Participants are reminded to continue to 378 see their primary care physician and that study procedures are not provided in lieu of standard 379 medical care. Participants are instructed to focus on a slow progressive increase in physical activity 380 until reaching a goal of 150 min/wk. These guidelines are in line with the 2008 American College of 381 Sports Medicine recommendations for sedentary individuals.

382 **6.1.6 Limitations**

383 Although this study will provide valuable data on personalized nutrition, and the Carbohydrate-384 Insulin Model of obesity, there are several limitations to consider. Due to the nature of the PD intervention, the participants and dietitians providing counseling are unblinded to the treatment 385 386 allocation. In addition, the PD arm undergoes additional metabolic profiling at baseline required for 387 the PNP algorithm. However, given the intensity of the behavioral interventions, it is unlikely 388 that metabolic profiling alone would cause added weight loss. We will examine differences in 389 participant adherence to self-monitoring, attendance at counseling sessions, and drop out rates, as potential behavioral determinants of intervention efficacy. 390

391 The PNP application also has inherent limitations. The application is currently available in 392 English and Hebrew, which restricted our target population. Importantly, English is common among 393 people from diverse racial/ethnic backgrounds in New York City, and if efficacious, the PD 394 intervention can be adapted, and tested in non-English speaking individuals. In addition, as in many food diary applications, PNP was developed using the USDA Nutrient Database for Standard 395 Reference (Rel 28.1). While this ensures that the nutrient composition data is of high quality, many 396 foods, in particular processed foods, are not included in the database. As a result, certain 397 398 participants may have difficulty finding foods, or appropriate substitutions, which could impact adherence to self-monitoring. 399

400 Discussion

Body weight differences in response to weight-loss diets are substantial.⁴⁹ Standard dietary 401 interventions targeting weight loss follow a "one-size-fits-all" approach in which uniform dietary 402 403 recommendations are provided. However, evidence regarding the efficacy of these interventions for long-term weight loss is mixed. This paper describes the rationale for and methods being used in 404 405 our study, currently underway, comparing a personalized diet to standard LFD recommendations in 406 a novel technology-supported behavioral intervention that utilizes real-time feedback from a machine-learning algorithm targeting PPGR to meals in order to facilitate weight loss attempts. The 407 408 interventions are implemented using mobile health technologies that permit remote delivery of counseling and self-monitoring in a manner that is convenient for patients and has great potential 409 410 for dissemination. Arming participants with food-specific recommendations tailored to their unique 411 physiological response to meals may increase their adherence to lifestyle changes and enhance 412 their weight loss success.

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