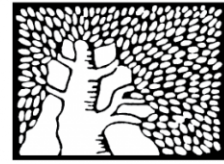


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## The rationale and design of the personal diet study, a randomized clinical trial evaluating a personalized approach to weight loss in individuals with pre-diabetes and early-stage type 2 diabetes

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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  
22 to evaluate two dietary interventions targeting weight loss in people with prediabetes and T2D: (1) a  
23 low-fat diet, and (2) a personalized diet using a machine-learning algorithm that predicts glycemic  
24 response to meals. Changes in body weight, body composition, and resting energy expenditure will  
25 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  
27 technology using the Social Cognitive Theory. Here, we describe the design, interventions, and  
28 methods used.

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30 Association.

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## 33 Introduction and Background

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

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.<sup>5-8</sup> Furthermore, minimizing PPGR may attenuate the decline in resting energy  
47 expenditure (REE) observed with weight loss.<sup>9</sup>

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

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

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

67 microbiota from lean humans to those with metabolic syndrome increased insulin sensitivity.<sup>27</sup> In  
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  
70 machine-learning algorithm that predicts individuals' PPGR to pre-consumed or unseen meals.<sup>28</sup> In  
71 a subsequent validation study, Segal et al demonstrated that a personally tailored intervention  
72 based on the predicted response significantly improved PPGR to meals<sup>28</sup>. Until now, no study has  
73 attempted to apply personalized nutrition in the context of a behavioral weight loss intervention in  
74 pre-diabetics and T2D.

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

88

## 89 **Objectives**

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

### 95 **2.1.1 Design**

96 The study is a two-arm, parallel-group, randomized clinical trial in overweight and obese adults  
97 with pre-diabetes and early-stage T2D. The trial involves two 6-month phases: an active  
98 intervention phase (phase 1) followed by a maintenance/observation phase (phase 2) (**Figure 1**).

99 Participants are randomized with equal allocation to either LFD or PD. Measurements occur at  
100 baseline and at 3, 6, and 12 months. All measurement visits and data are collected at NYU  
101 Langone Health (NYULH) in New York City. Microbiome analysis and data processing for the  
102 purpose of the PNP prediction algorithm are completed at the Weizmann Institute of Science in  
103 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  
106 mass index (BMI) between 27 and 50 kg/m<sup>2</sup>, and have a hemoglobin A1c (HbA1c) between 6.5 and  
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/1.73m<sup>2</sup>) using the  
109 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, are excluded to avoid  
110 recruiting patients with advanced T2D.<sup>34</sup> Furthermore, patients with conditions or treatments that  
111 affect glycemia (e.g., corticosteroids), or impact weight loss efforts are excluded. Because the PNP  
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  
114 are postponed 3 months prior to randomization because of the impact on the gut microbiota .  
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**

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

125 Screening for eligibility is completed by telephone. Individuals who meet screening criteria are  
126 scheduled for an in-person screening visit at the Clinical Research Center of NYULH's Clinical and  
127 Translational Science Institute (CRC-CTSI). At this visit, signed informed consent is obtained,  
128 height and weight are measured (see section 2.4.1). A non-fasting plasma and serum blood sample  
129 is collected by a certified phlebotomist to assess HbA1c and serum creatinine (i.e., eGFR). In  
130 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  
134 integrated with the USDA Food Composition Database (Release 28.1), allowing participants to  
135 select from thousands of food and beverage items. Participants are trained on how to enter meals,  
136 snacks, and physical activity, and on how to search for foods and beverages, enter serving sizes,  
137 create a “favorite” food-item, and create a “saved meal” into the PNP app. Participants with a BMI  
138 under 27 or greater than 50 kg/m<sup>2</sup>, HbA1c ≥8.0%, or an estimated glomerular filtration rate based  
139 on serum creatinine (<60 mL/min/1.73m<sup>2</sup>) are excused from further participation. **Table 2** provides  
140 a timeline of measurement visits.

## 141 **Measurements**

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

145

### 146 **3.1.1 Primary and Secondary Outcomes**

147 **Anthropometrics.** BMI is calculated from height and weight. Height is measured to the nearest  
148 1 cm using a portable stadiometer (SECA 213, Seca GmbH & Co. KG, Hamburg, Germany), and  
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  
151 measured in duplicate using a Gulick tape (McKesson Medical-Surgical, Fairfield, NJ, USA) to the  
152 nearest 1 cm using techniques detailed elsewhere.<sup>35</sup> Body fat percentage and fat-free mass (FFM,  
153 in kg) are measured using bioelectrical impedance analysis (BIA; InBody 270, InBody, Inc. Cerritos,  
154 CA, USA).

155 **Resting Energy Expenditure (REE).** REE is assessed via open-circuit indirect calorimetry  
156 (Quark RMR, COSMED USA Inc., Chicago, IL, USA) using a ventilated hood system after a 12-  
157 hour overnight fast. Participants are directed to lay supine for 10-minutes during which the  
158 metabolic cart is calibrated per the manufacturer’s instructions. Oxygen and carbon dioxide  
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.<sup>36</sup>

163 **Blood samples, resting heart rate and blood pressure.** Resting heart rate (RHR) and systolic  
164 and diastolic blood pressure (BP) are measured following a 5-minute, seated resting period using  
165 an automated blood pressure machine (Welch Allyn PROPAQcs, Welch Allyn, Inc., Skaneateles  
166 Falls, NY, USA). In both the PD and LFD groups, fasting **plasma and serum**(BOTH plasma and  
167 serum?-usually plasma) samples are collected by a certified phlebotomist to measure glucose and  
168 insulin at baseline, 3 and 6 months. A complete blood count (CBC) is collected at baseline only in  
169 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  
172 Efficacy Lifestyle Questionnaire.<sup>37</sup> Participants are asked to rate their self-efficacy for each item on  
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,  
175 availability, social pressure, physical discomfort, and positive activities.<sup>37</sup> An overall score and  
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  
178 randomization group.

179 **Glycemic Variability.** HbA1c is obtained using high-pressure liquid chromatography (HPLC;  
180 Variant II) Turbo analyzer, Bio-Rad Laboratories, Inc., Hercules, CA, USA). In addition, GV is  
181 examined for up to 7 days with a continuous glucose monitor (CGM; Abbott Freestyle Libre Pro,  
182 Abbott Park, IL, USA), which measures interstitial glucose concentrations every 15 minutes. The  
183 skin surface is prepared with Skin Tac (TORBOT Group, Inc., Cranston, RI, USA) to help prevent  
184 detachment of the CGM devices and, once inserted, covered with a Simpatch adhesive patch.  
185 Participants are blinded to glucose tracings.<sup>38</sup> CGM data will be used to calculate, standard  
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,  
188 ignoring excursions of less than 1 standard deviation (SD).<sup>39</sup> CGM data will be used to generate  
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  
191 (<70 and >180mg/dl), and extremely out of range (<50 and >300mg/dl).<sup>40</sup> All GV indices will be  
192 calculated using EasyGV 8.6 software.<sup>41</sup> Fasting **serum insulin and plasma** (again, serum or  
193 plasma?) glucose concentrations are measured and used to calculate insulin resistance (HOMA-IR)  
194 and  $\beta$ -cell function (HOMA- $\beta$ ). The HOMA2 model will be used for this purpose.<sup>42</sup>

195 **Advanced Glycation End products (AGEs) and inflammation.** The first 36 participants  
196 randomized to the study (18 in each group) having BMI  $\geq 35$  kg/m<sup>2</sup> are assessed for the  
197 RAGE/AGE/S100A8/A9 pathway with additional serum and plasma measurements. AGEs are  
198 detected using Fluorescence Microplate reader (BioTek Synergy HI microplate reader). RAGE,  
199 sRAGE and S100A8/A9 are determined using enzyme-linked immunosorbent assay (ELISA) kits  
200 (R&D Systems Quantikine Immunoassay, Minneapolis, MN, USA). In addition, inflammatory  
201 markers (e.g., TNF-alpha, IL1-beta, IL4, IL10, and IL-17) are also assessed.

### 202 **3.1.3 Covariates**

203 **Sociodemographic and clinical variables.** At baseline, the following sociodemographic  
204 variables are collected using self-administered questionnaires: age, race, gender, living arrangement,  
205 education, employment status, income, family countries of origin, comorbidities, weight history,  
206 hunger, sleep quality, smoking status, bowel habits and function, antibiotic use, birth and  
207 breastfeeding history, and menstrual cycle (females only). At each assessment time point, we will  
208 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 participant. Those in the PD group wear the device  
214 again during the profiling week. Participants in the PD group are instructed to carry out their  
215 habitual exercise routine during the profiling, and are not provided with any additional feedback  
216 regarding physical activity levels.

## 217 **Pre-intervention**

### 218 **4.1.1 Pre-intervention training (both groups)**

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



225 PNP app, which includes troubleshooting and PNP app clarification. Participants randomized to PD  
226 undergo additional procedures described below.

#### 227 **4.1.2 Pre-intervention glycemic profiling (PD group only).**

228 Participants in the PD group undergo 1 week of glycemic profiling immediately after the pre-  
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  
240 food with a minimum of 2 hours in-between meals and snacks in order to link meals and snacks to  
241 glycemic tracings. During the profiling week, study staff monitor participants’ PNP dashboards daily,  
242 and contact participants as necessary to ensure that meals are logged and reported as accurately as  
243 possible. At the conclusion of the profiling week, participants remove the CGM sensor, place it into  
244 a sharps-proof container, and return it to the investigators by mail. Time-stamped CGM and PNP data  
245 are uploaded to a HIPPA-compliant NYULH server, with baseline laboratory and physical assessment  
246 data.

#### 247 **4.1.3 Development of PNP algorithms**

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

254 A meal database was created consisting of Western-style meals (n= 135) and snacks (n=68)  
255 varying in GL to generate feedback on the PPGR to pre-consumed meals. Using the participants’  
256 PNP algorithm, personalized PPGRs are calculated for every meal and snack in the database based

257 on their nutrient composition, and calorie-adjusted quintile cutoffs of PPGR are used to create meal  
258 ratings of “excellent,” “good,” “medium,” “bad,” and “very bad.”

## 259 **Interventions**

### 260 **5.1.1 Phase 1 - Both groups**

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

267 Behavioral counseling is based on the SCT<sup>44,45</sup>. Group sessions are conducted via WebEx  
268 (Cisco Systems Inc., San Jose, CA, USA) using a smartphone to minimize participant burden of  
269 attending face-to-face group sessions. The duration of each group session is approximately one  
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  
276 questions designed to elicit discussion. At the conclusion of the session, the videos are posted on  
277 the study website for participants to review as desired, and all participants are e-mailed a link to the  
278 videos presented. All videos posted on the study website are integrated into BrainShark  
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  
284 delivery based on the proposed behavioral theories supporting the intervention. These recorded  
285 sessions are not posted or shared with participants.

286 For the duration of the intervention, participants are directed to self-report into the PNP app  
287 everything that they eat or drink, their physical activity, and their body weight (weekly). The PNP  
288 app is pre-programmed with a: (1) weight loss target (-7% body weight); (2) hypocaloric energy  
289 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  
297 they keep their daily intake below the 25% total fat and 7% saturated fat targets.

#### 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  
303 "excellent" PPGR), yellow ("medium" PPGR), and red (a "bad" or "very bad" PPGR). Participants  
304 are advised to maintain PPGR in the "good" or "excellent" range and, when they receive yellow or  
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.

#### 309 **5.1.4 Phase 2**

310 Phase 2 is a 6-month observation period. During this time, participants are encouraged to  
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

320 associations between variables. We will identify features of the data that may necessitate special  
321 methods (e.g., excess zeros, missing data, and departures from distributional assumptions). During  
322 preliminary analysis, we will examine: (1) comparability of treatment arms at baseline (based on  
323 Chi-squared statistics or t-tests, as appropriate), (2) relationships between the response variables  
324 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  
327 the participant will be the random effect. The intervention effect of interest is the treatment\*time  
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  
332 adjusted analyses. Model assessment will be conducted using appropriate regression diagnostics.  
333 The primary and secondary analyses will be done using SAS (SAS 9.4, Cary, NC, USA).

#### 334 **6.1.1 Sample Size**

335 The required sample of 164 (82 per group) is based on the assumption that a clinically significant  
336 minimum of 5% weight loss will be achieved by the LFD group, which is consistent with a pilot study  
337 (5.94%;  $SD_{\text{weight loss}} = 4.54\%$ ) to the Healthy Hearts and Kidneys study<sup>46</sup> (unpublished data) sentence  
338 needs clarification. The goal for both groups is 7% weight loss at 6 months, similar to the Diabetes  
339 Prevention Program and Look AHEAD trials.<sup>47,48</sup> We can detect a difference between weight loss of  
340 the LFD and the PD as small as 2% with a type I error  $\alpha=0.05$  and a power of 80%. To account for  
341 an expected loss of about 20% of participants to drop-out, we will recruit 200 participants.

#### 342 **6.1.2 Analysis of Primary Outcomes**

343 For hypotheses pertaining to weight loss, the primary outcome of interest is the percent of  
344 baseline body weight lost at 6 months and whether or not these losses will be sustained at 12  
345 months. A random effects linear regression model will be used to test time-specific differences  
346 attributable to the intervention. We also will use the “lincom” command to estimate differences in  
347 time-specific changes from baseline. In additional analyses, we will adjust for other covariates  
348 (e.g., insulin secretion, insulin sensitivity, glycemic control, habits and history that could influence  
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

351 compare changing trends in different periods: early intervention (0-3 months) and late intervention  
352 (3-6 months). In this analysis, adjustments will be made for the covariates noted above.

### 353 **6.1.3 Analysis of Secondary Outcomes**

354 For hypotheses related to body fat distribution and metabolic adaptation at 6 and 12 months, and  
355 weight regain at 12 months, the random effects linear regression model will be used to test time-  
356 specific differences attributable to the intervention using a similar approach to that of analyses for  
357 the primary aim of weight loss. Mediation analysis will be performed to assess whether, and by how  
358 much, self-efficacy mediates and the intervention effect on weight loss. Covariates (such as age,  
359 gender, race, and baseline T2D status) will be included in the model and explore the possibility of  
360 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  
385 intervention, the participants and dietitians providing counseling are unblinded to the treatment  
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  
390 potential behavioral determinants of intervention efficacy.

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  
395 food diary applications, PNP was developed using the USDA Nutrient Database for Standard  
396 Reference (Rel 28.1). While this ensures that the nutrient composition data is of high quality, many  
397 foods, in particular processed foods, are not included in the database. As a result, certain  
398 participants may have difficulty finding foods, or appropriate substitutions, which could impact  
399 adherence to self-monitoring.

400 **Discussion**

401 Body weight differences in response to weight-loss diets are substantial.<sup>49</sup> Standard dietary  
402 interventions targeting weight loss follow a "one-size-fits-all" approach in which uniform dietary  
403 recommendations are provided. However, evidence regarding the efficacy of these interventions for  
404 long-term weight loss is mixed. This paper describes the rationale for and methods being used in  
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  
407 machine-learning algorithm targeting PPGR to meals in order to facilitate weight loss attempts. The  
408 interventions are implemented using mobile health technologies that permit remote delivery of  
409 counseling and self-monitoring in a manner that is convenient for patients and has great potential  
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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