The Personalized Nutrition Study (POINTS): Evaluation of a genetically-informed weight loss approach

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Co-Investigators: Christoph Höchsmann, Ph.D.; John W. Apolzan, Ph.D., James L. Dorling, Ph.D.

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Protocol Version Date: October11, 2021

NCT04145466

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Overview and Objective

A person's genetic code is believed to affect how much weight he/she will lose during diets that vary in carbohydrate and dietary fat content. 'Carbohydrate responders' are hypothesized to lose more weight on diets that are high in carbohydrates, as compared to high in fats. 'Fat responders' are hypothesized to lose more weight on diets that are high in dietary fat, as compared to high in carbohydrates. The purpose of the proposed study is to test these hypotheses in a randomized controlled trial.

Background

Obesity and its comorbidities are major public health challenges[1]. To combat the obesity pandemic, many weight-loss strategies have been studied, often emphasizing either high carbohydrate (low fat) diets or high fat (low carbohydrate) diets[2,3]. Mean weight loss differences between high-carbohydrate and high-fat diets that induce equal caloric deficits have been reported to be small[4]; however, the individual weight loss response varies substantially within diet groups[3], suggesting that different individuals react differently to high-carbohydrate or high-fat diets. This assumption is supported by retrospective data showing that participants with carbohydrate-responsive polymorphisms lost 2-3 times more weight when assigned to a high-carbohydrate diet compared to a high-fat diet, and vice versa for those with dietary fat-responsive polymorphisms[5]. Conversely, a recent randomized clinical trial aimed to determine the effect of a healthy high-fat diet (high in unsaturated fats) vs. a healthy high-carbohydrate diet (high in whole-grain foods) on 12-month weight change but did not find significant differences between the two groups and failed to find the hypothesized association between genotype patterns and weight loss induced by diets that varied in fat and carbohydrate content[6]. However, an important caveat of their approach is that the single nucleotide polymorphisms selected by the investigators had not been previously associated with obesity or with dietary response, which may explain their lack of predictive value in identifying differences in inter-individual responses[7]. In addition, the fat composition of the diets was relatively high in both high- and low-fat groups[8]. The inconsistent findings in the literature indicate a need for further research to determine if genetic factors affect weight loss when exposed to diets that vary in carbohydrates and dietary fats.

The purpose of this randomized controlled parallel arm trial is to test the following hypotheses.

Hypothesis 1 will test if participants assigned to the diet that corresponds to their genotype lose more weight than those assigned to a diet inconsistent with their genotype.

Hypothesis 2 will analyze the fat responders and carbohydrate responders separately.

- ***Hypothesis 2a***: Fat responders will lose more weight on the high-fat diet vs. the high-carbohydrate diet.

- ***Hypothesis 2b:*** Carbohydrate responders will lose more weight on the high-carbohydrate diet vs. the high-fat diet.

Carbohydrate and dietary fat responders will be identified *a priori* based on their combined genotypes at pre-determined genetic variants using specific algorithms. Carbohydrate responders and fat responders will be randomized to one of the following two diets:

1. A high-quality high-carbohydrate diet that is rich in whole-grain foods, or
2. A high-quality high-fat diet that is rich in unsaturated fats and oils (Table 1).

Table 1. Overview of the study design and expected relative weight loss (double arrows reflect greater expected weight loss). The total number per group is an estimate. We will not close cells to enroll this exact number per group, and the total number of people enrolled will not exceed 154.

	High-Fat Diet	**High-Carb Diet**
Fat Responder	***Cell A*** n=52 ↓↓	***Cell B*** n=52 ↓
Carb Responder	***Cell C*** n=25 ↓	***Cell D*** n=25 ↓↓

Both diets will last 12 weeks and have the same levels of protein (15% of energy). The high-carbohydrate diet will consist of ~20% of energy from fat and ~65% from carbohydrates. The high-fat diet will consist of ~40% energy from fat and ~45% from carbohydrates. All participants will be assigned an energy intake target that will result in a daily deficit of ~750 kcal, though no energy intake targets below 1,100 kcal/d (women) and 1,300 kcal/day (men) will be prescribed. At the discretion of the PI or MI, modest diet modifications will be allowed if needed for participant safety. Baseline energy requirements will be calculated with the formulas of Mifflin St. Jeor[13]. The Remote Food Photography Method (RFPM)[14,15] and SmartIntake smartphone app will be used sporadically as needed to facilitate dietary adherence. These are process data and will not be immediately analyzed to quantify dietary intake, though the images can be fully analyzed later. Rather, the food images will be reviewed by the interventionists in near real-time to help the participant select and eat foods consistent with their meal plan.

The dietary program and intervention materials will be developed and delivered by employees of Pennington Biomedical Research Center (PBRC). Outcome assessors will be blind to diet assignment and genotype pattern. Interventionists will be blind to genotype pattern, but not diet type. To enhance internal validity, participants will not be told if they are carbohydrate or fat responders until after they complete the study. The **primary outcome** variables are weight change (kg and %) over 12 weeks. All other measures are secondary endpoints. The schedule of procedures is provided in **Table 2**.

Table 2. Schedule of visits and procedures.

	Orientation	Baseline (Week 0)	Week 6**	Week 12
Location	**IBL**	**Clinic**	**IBL**	**Clinic**
Consent, eligibility, demographics, medical history form	X			
Height	X			
Weight	X	X	X	X
Genealogy test kit	X			
Waist/hip circumference, bioelectrical impedance analysis, blood pressure, heart rate, Food Craving Inventory, Food Preference Questionnaire, Eating Inventory		X		X
Blood draw: fasting serum glucose, insulin		X		
Randomization		X		
Intervention Satisfaction Survey				X
Diet Personalization Survey (completed after randomization and at week 6 and 12)		X	X	X
** There is no clinic visit at week 6. The week 6 weight will be collected at the participants' intervention visit, where participants will also complete the Diet Personalization Survey.If participants miss this visit, they will complete the Diet Personalization Survey during the next intervention visit.* *** **Weight will be collected at each of the 12 intervention visits.***				

Pilot Participants

Before the start of the study, we will conduct a trial run of the process of determining the genetic risk score from the Ancestry.com, 23andMe, and GeneticDirection raw data. We will recruit up to 6 volunteers who either: 1) have the raw data from 23andMe or Ancestry.com and are willing to share these data with us, or 2) are willing to complete 23andMe or Ancestry.com, or GeneticDirection testing (paid for by the study/PBRC) and share the raw data with us to determine their genetic risk score. These pilot participants will receive their genetic risk score but will not receive weight-loss treatment, though they are eligible to screen for, and possibly enroll in, the main trial. These participants will meet the same inclusion and exclusion criteria as those for the main study.

Inclusion Criteria:

- Male or female age 18-75 years
- BMI ≥ 27.0 kg/m^2 to ≤ 47.5 kg/m^2
- Completed genealogy test by a company, such as Ancestry,23andMe or GeneticDirection that allows customers to download the raw data files. Willing to provide the research team with the raw genealogy data. Has a genetic profile indicating the predisposition to respond favorably to either a high-carbohydrate or high-fat weight loss diet. We estimated that approximately 1/3 of people are fat responders, 1/3 are carbohydrate responders, and 1/3 are neither or will respond to either diet. Only carbohydrate and fat responders are eligible.
    - It is unclear what percentage of the Baton Rouge population has genealogy data. Thus, the budget will include funds ($125/each) to pay for genealogy testing.

Exclusion Criteria:

- Current smoker or has smoked in the previous year

- For females, pregnant or planned pregnancy during the study duration, or breast-feeding, based on self-report
- Conditions, diseases, or medications that affect body weight or metabolism (e.g., certain antipsychotic medications; type 2 diabetes mellitus; heart failure; cancer, excluding certain melanomas; etc.)
- Has gained or lost more than 10 pounds in the last 3 months
- Currently diagnosed with an eating disorder, major depression, or other condition that, in the judgment of the investigators, could affect risk to the participant or study completion

Power analysis

This study will plan to obtain data on up to 154 participants in total. During a previous 12-week study that had a similar weight loss strategy, participants lost 5.1 kg with an SD of 3.3 kg. This SD is larger than the SD for between-group differences observed in other studies conducted by the PBRC group, which range from 2.1 to 2.8 kg;[16,17] therefore, an SD for between-group differences in weight change of 2.8 kg was utilized. The power analysis for the proposed study uses a T-test to determine differences and assumes an alpha level of 0.05 and power $\geq$ 0.80 as acceptable. Weight loss in cells A and D are both expected to be similar in the previous study while the weight loss in cells B and C would have similar but approximately half that effect of the previous study. To detect a 2.0 kg difference in weight change between either A vs. B or C vs. D, this study would have a power of 0.80. A 2.0 kg difference is approximately 2.2% of body weight assuming the mean body mass of participants is 90 kg. Based on the assumptions above, this study has power over 0.95 to test if the diet that corresponded to their genotype lost more weight than those assigned to a diet inconsistent with their genotype.

Data analytic plan

The biostatistics department will handle the randomization and use adaptive randomization to promote equal numbers of men and women in each cell and to promote similar BMI across the groups.

The primary outcome variable is body weight change, represented as kg and percent change. All other variables are secondary and will be analyzed using a similar statistical approach. Repeated mixed linear models will be used to determine if change in the outcome variables differs among the groups. Covariates will include the baseline value of the outcome, sex, and race. Additional variable selection in the models will be determined through model fit statistics such as AIC.

Two sources of body weight data are obtained – weights collected in the clinic at baseline and week 12, and weights collected at the 12 intervention sessions. Both sources of data will be analyzed, though the presence of only two clinic weights means that analysis of the clinic weights will be a completers' analysis. The weekly weight data, however, will be analyzed using an intent-to-treat approach, and all participants' data will be analyzed who have a weight from their first and at least one subsequent intervention visit. Sensitivity analysis will be conducted to determine how the two methods effects the results.

The primary models will be a mixed effect model that accounts for the correlation of the subject over time modeling. Least square means based on the estimates from the mixed effect model will be used to test for differences of weight change between groups. Normality of the responses will be checked based on the Shapiro–Wilk test. Heterogeneity of variance effects for genders for each of the treatments will be analyzed first as potential subgroups.

Hypothesis 1 will test if participants assigned to the diet that corresponded to their genotype lost more weight than those assigned to a diet inconsistent with their genotype.

- H1: Weight loss in Cells A and D (combined) in Table 1 was significantly larger than weight loss in Cells B and C (combined).

Hypothesis 2 will analyze the fat responders and carbohydrate responders separately.

- H2a: Fat responders lost more weight on the high-fat diet (Table 1, Cell A) vs. the high-carbohydrate diet (Cell B), and
- H2b: Carbohydrate responders lost more weight on the high-carbohydrate diet (Table 1, Cell D) vs. the high-fat diet (Cell C).

The *a priori* comparisons noted above will rely on an alpha level of 0.05 for both measures of body weight (kg and %). In addition, we will conduct tests with alpha equal to 0.05 to determine if baseline insulin levels and HOMA (homeostatic model assessment) are associated with weight loss and differential weight loss between the groups and diets. Alpha will be adjusted in the analyses of all other variables using the family-wise error rate employing the Holm–Bonferroni method, which is based on the number of p-values less than alpha.

The Report to the sponsor will include data tables for all outcome variables at all assessment visits, as well as tables depicting change on the outcome variables and the associated inferential statistics. Tables depicting participant demographics will also be provided.

Recruitment Methods

The marketing and the recruiting core will utilize traditional PBRC recruiting methods. The Advertising and Recruitment Cores are responsible for recruiting potential participants for clinical trials from a population that includes a wide range of people of various ages, ethnic backgrounds and with varying degrees of health. PBRC has a team of full-time employees dedicated to the recruitment and initial screening of clinical trials. Potential subjects will be identified via a large database of previous study participants along with the use of web, print, and media advertising. The Recruitment and Advertising Cores create and implement individualized, trial-specific advertising and awareness campaigns, including mass media, traditional advertising, and novel methods including social media, digital and email marketing. All advertising and awareness are approved by our on-site IRB to ensure ethical and disclosure standards are met. The PBRC database will also be utilized to find potential subjects for this study.

Study Procedures

The study consists of an orientation visit, and if participants are eligible and wish to participate, two clinic visits (one before and one after the intervention), and 12-weekly intervention visits.

<u>Orientation Visit: About 1 hour.</u>

The orientation visit will take place at Pennington Biomedical Research Center and it will include the following procedures:

- Informed consent
- Questionnaires assessing medical history, current medication and supplement use, and demographics
- Measurement of height and weight
- If participants have completed a genealogy test before the study, their data will be reviewed to verify eligibility to participate in the study
- If participants have NOT completed a genealogy test before the study, they will be provided with a genealogy test kit and the data will be reviewed as soon as they are available to us to determine eligibility to participate in the study

Baseline Clinic Visit: About 1.5 hours.
If participants are eligible and wish to participate in the study, the first clinic visit will be scheduled. The visit will take place in the Outpatient Clinic of Pennington Biomedical Research Center. *This is a fasting visit (nothing to eat or drink before the visit, following a 12-hour fast).*
The clinic visit will include the following procedures:

- Measurement of waist/hip circumference
- Bioelectrical impedance analysis (weight and body fat %)
- Measurement of blood pressure and heart rate
- Completion of the following self-report instruments: Food Craving Inventory, Food Preference Questionnaire, Eating Inventory
- Fasting serum glucose and insulin (no archiving)

- If participants will be using their own scale for at home weights during intervention, they will be asked to bring the scale in for calibration.

Weekly Intervention Visits (approximately 1.5 hours per visit)
The 12 weekly intervention visits will take place at Pennington Biomedical Research Center or virtually and they are designed to be specific to participants' random assignment, i.e., either the high-fat or the high-carbohydrate diet group. Body weight will be recorded by study staff at each of these 12 intervention visits. Additionally, participants will regularly weigh themselves at home (approximately once per day) and they will turn in a record of these self-measured weights at each weekly intervention visit. Participants will either be provided a loaner scale to use during the intervention or they will use their at home scale, calibrated by study staff at the Baseline visit.

The first intervention visit will be a one-on-one in person or virtual meeting with the interventionist following the baseline visit where participants will complete the Diet Personalization Survey. The next 11 intervention visits will be in person or virtual group meetings with other participants and a facilitator. The facilitator is a Pennington Biomedical Research Center staff member. Participants will receive personalized meal plans that are tailored to their calorie and (group-dependent) macronutrient target and they will include precise portion sizes of daily meals and snacks, a shopping list, and restaurant options. Two snacks per day (e.g., granola bar) will be provided by the sponsor, WW. The sponsor will further provide a food scale for each participant to facilitate adherence to the prescribed portion sizes. Discussions and content delivered during the sessions will focus on helping participants adhere to their assigned diet. At the week 6 intervention visit, the Diet Personalization Survey will be completed.

Week 12 Clinic Visit: About 1.5 hours.
The visit will take place in the Outpatient Clinic at Pennington Biomedical Research Center. *This is a non-fasting visit.*
The visit will include the following procedures:

- Measurement of weight and waist/hip circumference
- Bioelectrical impedance analysis (weight and body fat %)
- Measurement of blood pressure and heart rate
- Completion of the following self-report instruments: Food Craving Inventory, Food Preference Questionnaire, Eating Inventory, Intervention Satisfaction Survey, Diet Personalization Survey
- If participants were loaned a scale for intervention, they will be asked to return it at this visit.

Provisions to Monitor the Data to Ensure the Safety of Subjects
Adverse events will be monitored at each intervention visit. The PI and his co-investigators will review all data continuously to ensure the safety of each subject.

Withdrawal of Subjects
Subjects may be withdrawn from the study if he/she misses study visits and will be notified of their withdrawal via telephone or mail. If a subject voluntarily withdraws from the study, no additional data will be collected and they will be considered dropouts in the study.

Risks to Subjects
This study does not involve major risk to study participants.

- **Bioelectrical Impedance Analysis** (BIA): There is no known risk associated with the BIA measurement.
- **Blood Pressure Testing:** Temporary discomfort may be experienced during blood pressure recordings due to the pressure of the cuff inflating on their arm. No other known risks are associated with blood pressure testing.
- **Self-reported Questionnaires:** There are no anticipated risks from completing self-report questionnaires. Due to the sensitive nature of the questionnaires, participants may skip any questions that they do not wish to answer.
- **Blood collection:** The risks of taking blood include pain, a bruise at the point where the blood is taken, redness and swelling of the vein and infection, and a rare risk of fainting. Aseptic (sterile) technique and trained personnel minimize these risks.
- **Genetic Information:** As part of this study, Pennington Biomedical Research Center will analyze the results from the 23andMe, Ancestry.com or GeneticDirection genealogy test and work with participants' genetic information to determine if they are a carbohydrate or fat responder. All attempts will be made to maintain a subject's privacy. Safeguards such as password-protected computer and networks have been put in place in order to limit access to subject data.
- **Diet Risk:** There are no anticipated risks associated with the expected amount of weight loss during this study. The high carbohydrate diet is higher in carbohydrate and the high-fat diet is higher in fat than typical recommendations during weight maintenance. In the high-fat diet, expected dietary fat intake is about 11% percentage points higher than the typical American diet, but the proposed diet keeps saturated fat intake to less than 10%, which is consistent with guidelines. The high carbohydrate diet is about 22% higher than the typical American diet. There are limited anticipated risks of following such a high fat or high carbohydrate diet for 12 weeks, particularly when body weight is being reduced. The changes in dietary intake may lead to minor abdominal and bowel issues.
- **Information collected via 23andMe, Ancestry.com, and/or GeneticDirection:** Pennington Biomedical Research Center will create an online account for each participant, using a newly created email address (POINTS_01@gmail.com, POINTS_02@gmail.com, etc.) and the participant's date of birth. If a name and phone number are required for creating the online account, we will use POINTS_01, POINTS_02 etc. for the name and a Pennington phone number. Pennington Biomedical Research Center will have access to the login information during the study to retrieve the raw data once they are available. After completion of the study, the login information will be provided to each participant, which will give them access to their genealogy data.
    - Participants further have the option to provide additional information about themselves through surveys, forms, features, and applications. Unless they consent to sample storage ("Biobanking") and additional analyses, their saliva

sample and DNA are destroyed after the laboratory completes its work, subject to the laboratory's legal and regulatory requirements.

- 23andMe, Ancestry.com, and GeneticDirection give the ability to share information, including Personal Information, through their services related to health and ancestry. Participants have the option to share directly with individuals with via their accounts through (i) forums, (ii) relative finding features (e.g., "DNA Relatives"), and (iii) other sharing features and tools.
- Participants are advised to read the current version of the Privacy Statement for 23andMe, Ancestry.com or GeneticDirection provided as aa link within the consent form to understand how these companies will use their information
  - https://www.23andme.com/about/privacy/
  - https://www.ancestry.com/cs/legal/privacystatement
  - https://geneticdirection.com/privacy-policy/
- Participants are made aware that for the purpose of this study, the collaborating institutions, but no one else, needs to receive their genetic information. Should they choose to provide additional information to 23andMe, Ancestry.com or GeneticDirection, have their samples stored by these companies, or share their genetic information with others, they do so at their own risk.

Potential Benefits to Subjects
Participants will learn if they are a fat or carbohydrate responder and they are expected to lose weight, which conveys many health benefits. No further benefits can be promised.

Sharing of Results with Subjects
The participants may receive information such as body weight, anthropometrics, and other health-related outcomes assessed during the study. Those results will be provided to the participant at the end of the study if requested.

Setting
We will utilize the clinical facilities at PBRC to conduct this study. The dietary program and other intervention materials will be developed and administered by PBRC staff.

Compensation
Participants will receive $150 for successful completion of the study.

Provisions to Protect the Privacy Interests of Subjects
All attempts will be made to maintain a subject's privacy. Safeguards such as password-protected computer and networks have been put in place in order to limit access to subject data. Subjects will be given ample time to read over the consent, ask questions, and agree to participate in the research study. Subjects may decline to answer questions they are not comfortable with. Each procedure will be explained to the subject before it is performed. We will always ensure the privacy of the subjects. Participants will attend group session and will, therefore, be known to other participants in the study. If you are participating in a virtual (online) visit, we ask you to *not* share the participation link with anyone else.

Compensation for Research-Related Injury
No compensation will be provided for research-related injury.

Economic Burden to Subjects
All study-related tests and procedures will be at no cost to the subject. The subject will incur transportation costs in getting to PBRC.

Consent Process

The PI or one of the designated clinic staff will obtain informed consent in the PBRC clinic during the first visit. Ample opportunity will be given for the subject to review the consent and ask any questions prior to signing the consent form. If subjects wish, they can take the form home and return at a different visit. Also, as we are aware, consent is an ongoing process.

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