Sigma Nutrition Premium

EPISODE STUDY NOTES

EPISODE:

#522: Does Personalized Nutrition Outperform General Dietary Advice?

Table of Contents

Introduction to this Episode

"Personalized nutrition" has been promoted as an approach that will improve people's health by prescribing them specific dietary recommendations based on their own genetic and phenotypic data.

The premise is that given we each respond differently to foods, having general dietary recommendations may be doing many people a disservice. And by using an array of personal data, it is now possible to give unique diets that improve health.

The early and interesting findings of research in this area was met with much fanfare, and indeed, many companies are now offering commercial direct-to-consumer services based on genetic and physiological testing, followed by "personalized" dietary prescription. Such testing may include genetic tests, microbiome testing, glucose monitoring data, and more. This data is then fed into machine learning algorithms to prescribe dietary recommendations.

However, do the marketing claims match the current evidence? Does the "proof" it works that is often cited, actually back up the claims? Do personalized nutrition diets actually lead to improved health outcomes over generic, conventional dietary recommendations? Do personalized nutrition diets lead to better outcomes than standard dietetic/nutrition practice?

To answer these questions, we go through the main studies cited in favor of personalized nutrition being superior to typical dietary advice, and see if they indeed support the claims.

So is personalized nutrition superior to standard dietary advice? Let's find out…

Connection to Previous Episodes

#361: Sarah Berry, PhD – The PREDICT Study, Postprandial Metabolism & Personalized Nutrition

- Dr Sarah Berry is a researcher and senior lecturer in nutritional science at King's College London.
- She is one of the authors of the PREDICT-1 trial, published in Nature Medicine, that looked at a personalized nutrition approach for improving postprandial responses.
- You can find the episode page here.

#298: David Zeevi, PhD – Genes of Gut Microbes & Inter-Individual Variation in Glucose Response

- Dr. Zeevi was lead author on an important personalized nutrition study that came from Eran Segal's lab, published in Cell.
- In this episode, we discussed that study and the ideas behind it.
- This is one of the studies discussed in the current episode.
- You can find the episode page here.

#414: Will Machine Learning Overtake Traditional Nutrition Research Methods?

- In this episode, the Sigma team discusses the claim that machine learning and data science may overtake traditional research methods in nutrition.
- They discuss how machine learning could solve some current limitations of traditional methods, studies on its use so far, potential applications in future trials, and potential limitations or problems with the increased use of data science (including ethical and societal concerns).
- They also ponder on how tech is currently being used (and abused) in relation to personalized nutrition, tech products, continuous glucose monitoring use, among other things.
- You can find the episode page here.

Definition & Terminology

- Some degree of "personalization" has long been at the core of standard dietetic practice
    - In this case, "personalized" meaning that advice and recommendations are based on the individual's needs, history, preferences, goals, reporting, etc.
    - This is **not** what was being discussed in this episode.
- Rather, the term *"personalized nutrition"* has more recently come to refer to specific approach; using lots of data from testing on the microbiome, postprandial responses to meals, genetics, etc. .
    - From the website of one of the leading companies providing direct-to-consumer testing in this space, they state:
        - *"Personalized nutrition uses factors about you as an individual to develop targeted nutrition recommendations for you. This is different to tailored nutrition advice that dietitians or nutritionists can provide."*
- From Berry et al., 2020:
    - *"A person's unique postprandial glycemic and lipaemic responses are likely attributable their biological (e.g. microbiome and nuclear DNA variation) and lifestyle characteristics, as demonstrated previously for specific meals."*
    - *"... characterizing postprandial regulation of lipids and identifying the factors responsible for individual variations could help optimize diet recommendations targeting broader improvements in cardiometabolic health."*

Claims Made About Personalized Nutrition

The intention of this episode was to look at the evidence to date on personalized nutrition approaches and see if they match both the media hype and the marketing claims of the many companies now offering direct-to-consumer testing and "personalized" diets.

Specifically, we want to ask:

- ***Is personalized nutrition superior to general nutrition advice?***
- ***Is it superior to nutrition advice one would get from a dietitian or nutrition professional?***

In other words, do the algorithms, genetic tests, CGM data, fecal samples, etc. actually improve people's health outcomes, relative to just following the current dietary advice?

This does not detract from any interesting findings or potential uses for future technology. Rather, it simply reflects on whether the potential for the future and/or the interesting findings to date have been used in a misleading way by companies (and researchers) to sell people on an idea that is not backed by evidence and could have downsides.

As Bernadette Moore put it in a 2020 review:

- "While scientists have remained largely circumspect about clinical utility and the extent to which genetic or polygenic risk scores can explain overall risk for common, multifactorial diseases (e.g. obesity, diabetes, fatty liver) or micronutrient status; an astonishing number of direct-to-consumer (DTC) genetic testing companies have proliferated offering personalised nutrition advice to individuals based on nutrigenetic testing via the Internet"
- "There are multiple scientific concerns with the personalised nutrition promises offered by DTC nutrigenetic testing companies, given the marked absence of published studies assessing either analytical or clinical/predictive validity of these tests."

So to answer the above questions, we looked at the studies most commonly cited by DTC personalized nutrition companies as the best evidence to support their claims that using their service will lead to a personalized diet and better health.

Food4Me Study

- Food4Me is the largest RCT on personalized nutrition: n = 1,607
- In the episode we referred to two publications from it:
  - Livingstone et al., 2016
  - Celis-Morales et al., 2017
- You can see the full list of publications from the Food4Me group here.
- It was a 6-month, 4-arm study
- Across seven countries in Europe: Ireland, Holland, Germany, Poland, Spain, Greece, and the UK.
- The 4 groups had different levels of personalization. Namely:
  - **Level 0** = Conventional dietary advice
  - **Level 1** = PN advice based on current diet
  - **Level 2** = PN advice based on diet and phenotype
  - **Level 3** = PN advice based on diet, phenotype, and genotype
- In this instance:
  - Phenotype = anthropometry and blood biomarkers
  - Genotype = five diet-responsive genetic variants

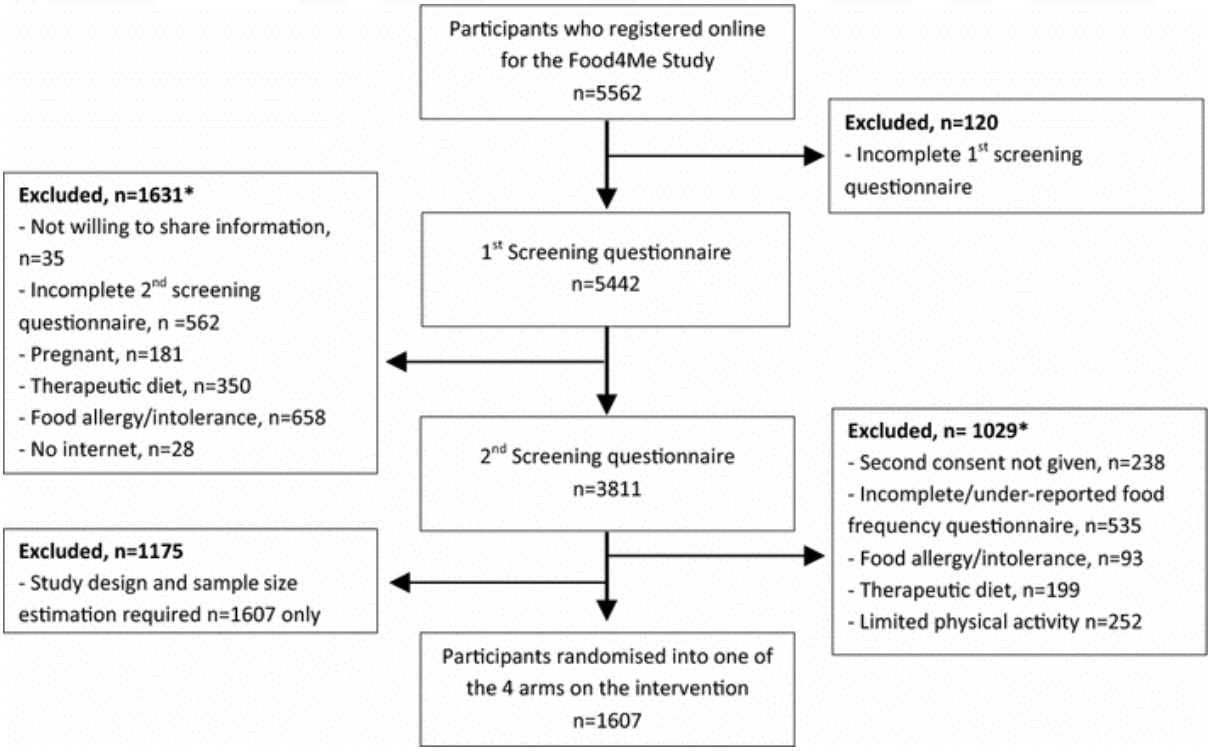


Figure from: Livingstone et al., Am J Clin Nutr. 2016 Aug;104(2):288-97.

MedDiet Score - Livingstone et al.

- The objective of the Livingstone et al paper was to evaluate the effect of the PN interventions on dietary changes associated with the Mediterranean Diet (using a MedDiet score).
- So the goal is to see if PN leads to improvements in dietary patterns.
    - The 14-point PREDIMED MedDiet score (see *Table 1* here) is used as a proxy measure of improved diet.
- While this paper (and other papers on other outcomes) report 'statistically significant' differences between general advice (L0) and PN approaches (PN1, 2, 3), we must ask whether the magnitude of difference is pragmatically or clinically meaningful.
    - Consider the MedDiet scores after 6 months in the conventional advice and PN diet groups:
        - L0 = 5.20
        - PN (average) = 5.48
    - Even looking at the change in MedDiet score across the intervention (which was the finding that was used as the main indicator of benefit), do we see anything meaningful?:
        - L0 = + 0.03
        - PN = + 0.38

TABLE 3. Effect of PN intervention on MedDiet score components at baseline and month 6[1]

			PN			*P*		
	Control mean (L0)	PN (mean L1, L2, L3)	L1	L2	L3	L0 vs (L1+L2+L3)	L1 vs (L2+L3)	L2 vs L3
Baseline, *n*	360	1120	373	376	371			
MedDiet score at baseline	5.17 ± 0.09	5.10 ± 0.05	5.16 ± 0.09	5.05 ± 0.09	5.09 ± 0.09	0.49	0.36	0.75
MedDiet score at month 6	5.20 ± 0.05	5.48 ± 0.07	5.43 ± 0.10	5.38 ± 0.10	5.63 ± 0.10	0.002	0.46	0.029

Figure from: Livingstone et al., Am J Clin Nutr. 2016 Aug;104(2):288-97.

- Furthermore, remember that the only intervention using genotype data (i.e., like the PN DTC companies) was L3. Does that offer any meaningful advantage of L1 or L2?

Celis-Morales et al., - Health-related behavior change

- This study is also held up as showing the superiority of PN as it demonstrated that "personalized nutrition" was more effective than standard population advice in relation to dietary behavior.
- The paper reported that after the 6-month intervention, participants randomized to PN (compared to control) consumed:
    - Less red meat [-5.48 g, (95% confidence interval:-10.8,-0.09)]
    - Less salt [-0.65 g, (−1.1,-0.25)]
    - Less saturated fat [-1.14 % of energy, (−1.6,-0.67)]
    - More folate [29.6 µg, (0.21,59.0)]
    - A diet with a higher Healthy Eating Index score [1.27, (0.30, 2.25)]
- But to put these findings in context we need to again consider:
    - The magnitude of difference (and how clinically meaningful this is)
    - What "personalized" means
- So consider those results:
    - Is the reduction of about 5.5g less red meat by using PN vs. general, conventional advice a difference that changes health outcomes?
    - For saturated fat, we see a difference of 1% of kcal.
    - No differences for vegetables, whole grains, dietary fiber, oily fish, etc.
- Now, let's think about what aspects of "personalization" out-performed the conventional advice…
    - "Personalization" here was based on weight, physical activity, and dietary intake.
    - And in this study, the inclusion of phenotypic/genotypic data to refine the recommendation **did not produce additional benefits**.
    - How does this relate to how companies are marketing their testing?

Zeevi et al., 2015 Study – Postprandial Glucose

- ***Study:*** Zeevi et al., 2015 - Personalized Nutrition by Prediction of Glycemic Responses
- You can find an interview with the lead author, David Zeevi, in episode 298 of the podcast.
- Continuously monitored week-long glucose levels in an 800-person cohort
- Found high variability in the response to identical meals
- Devised a machine-learning algorithm

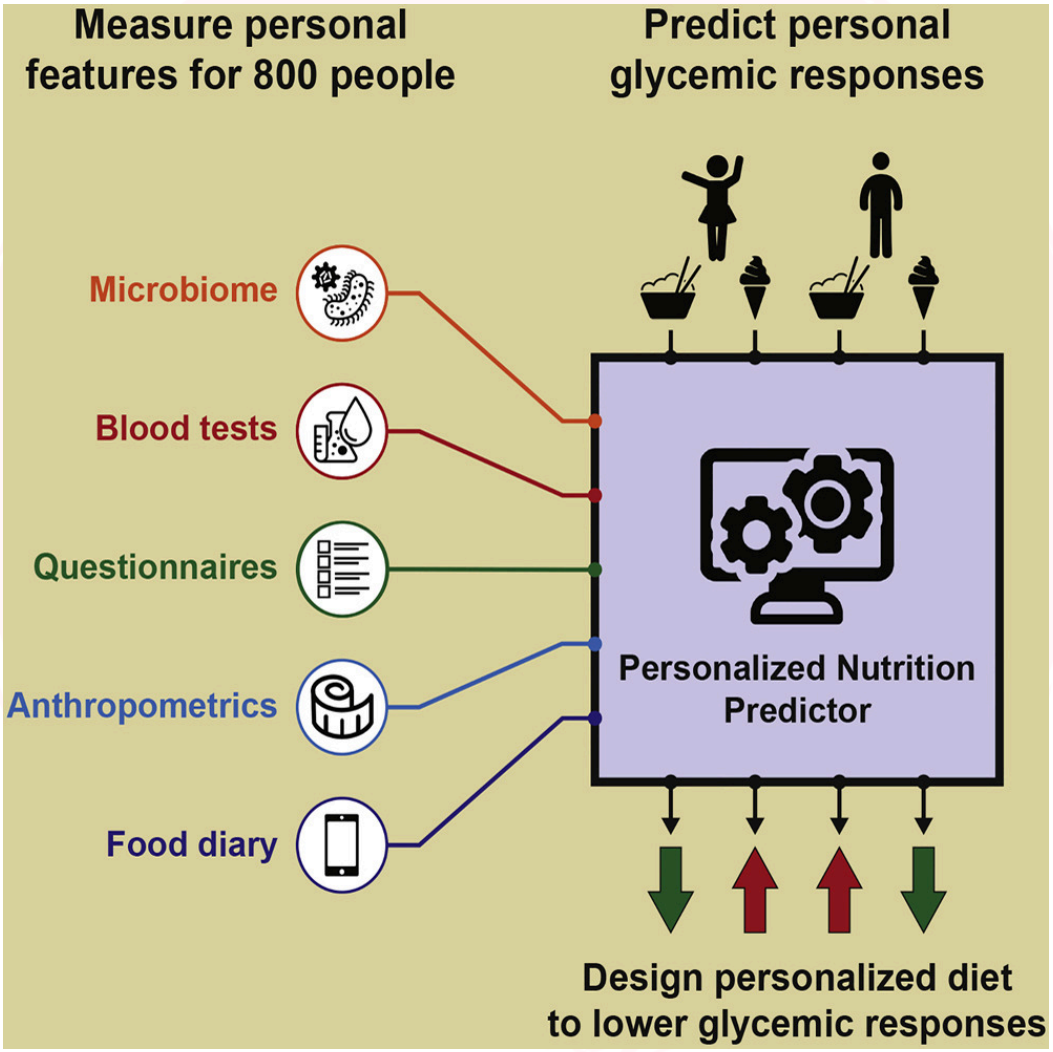
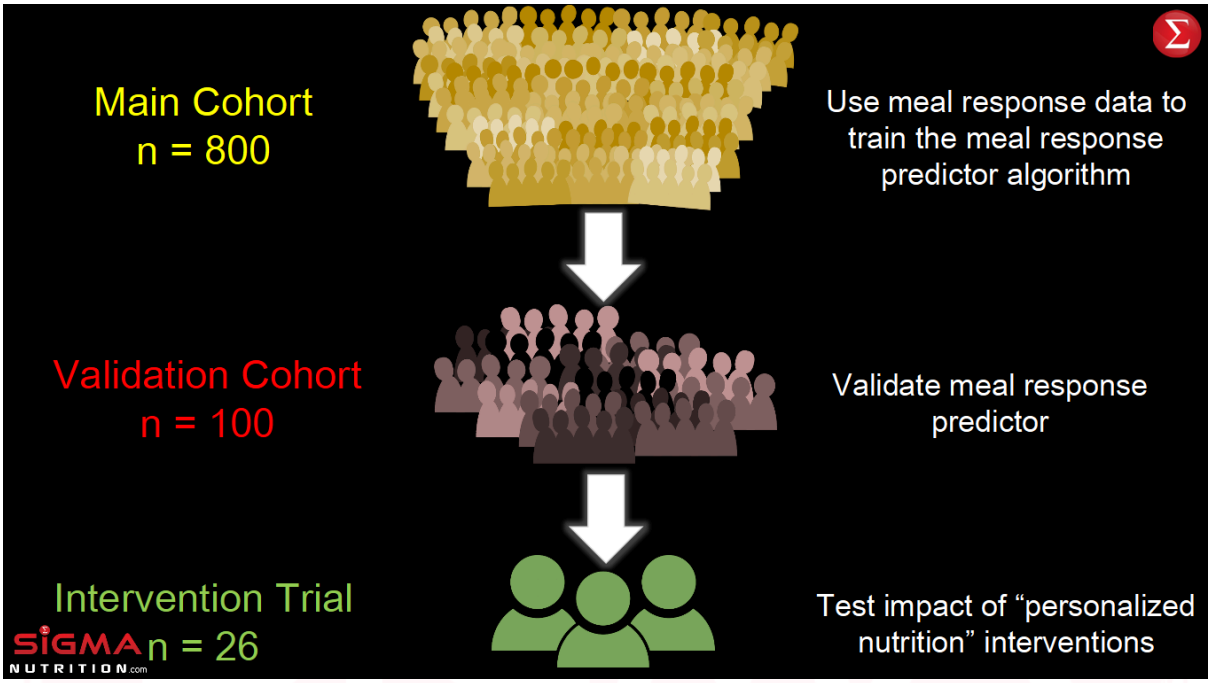
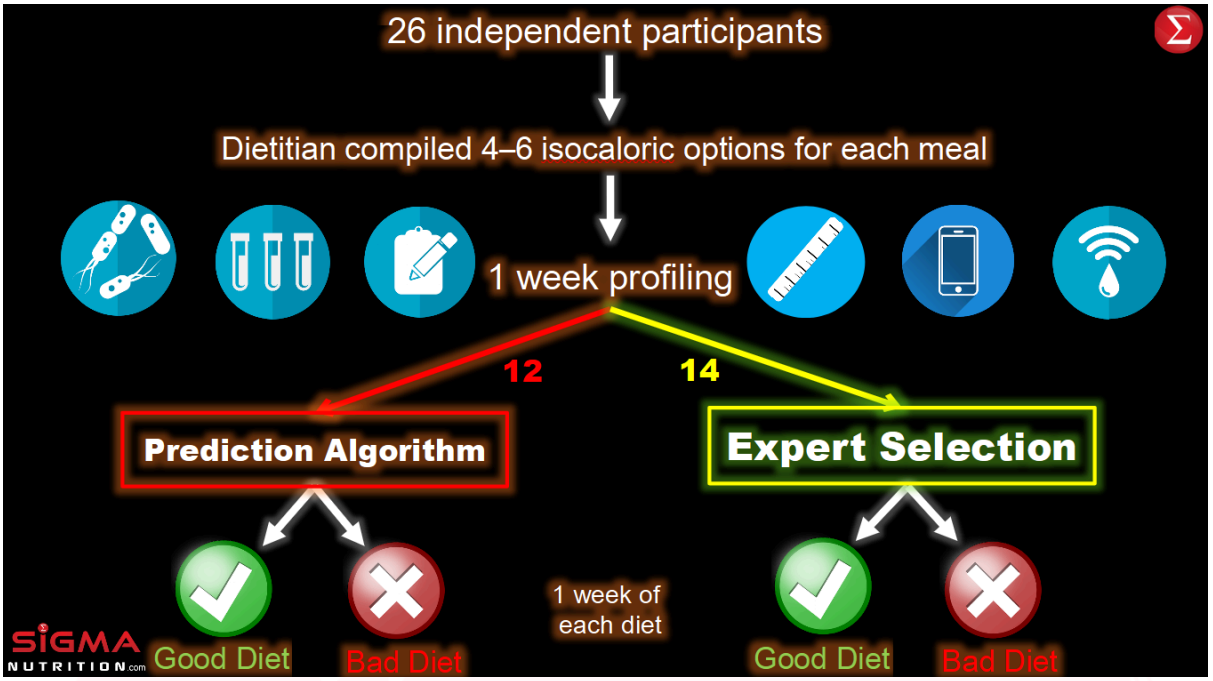


Figure from: Zeevi et al., Cell, Volume 163, Issue 5, 19 November 2015, Pages 1079-1094

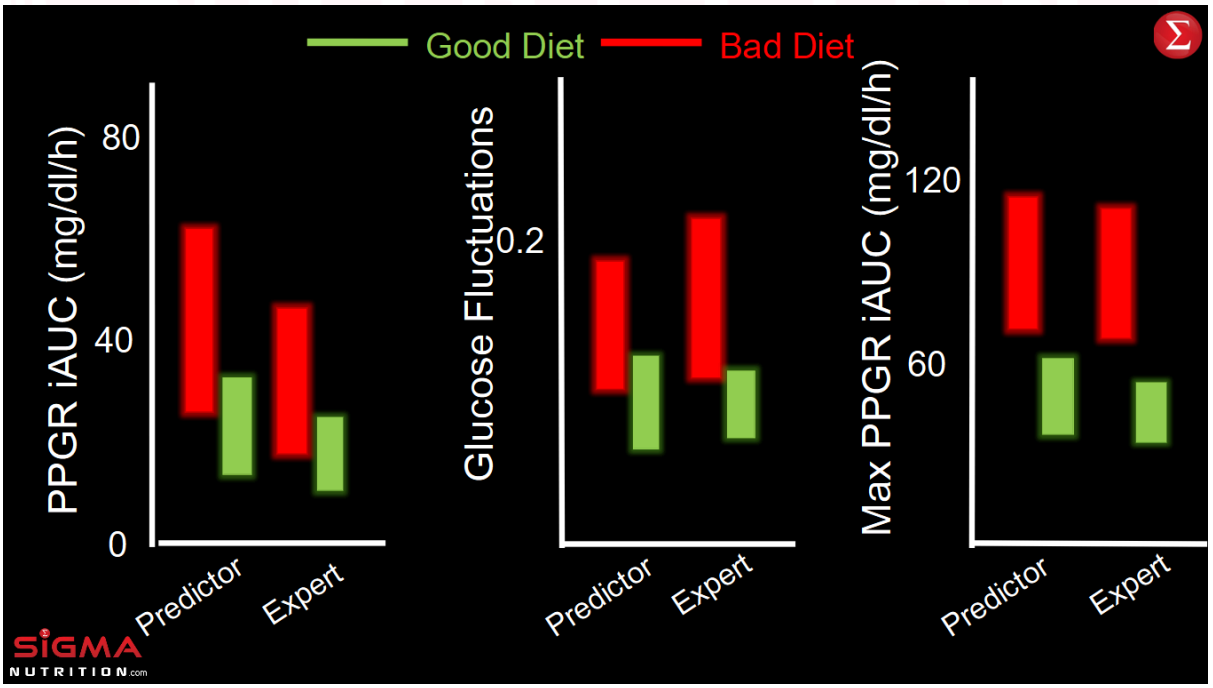
- Validated this in a 100-person cohort
- Predicts personalized postprandial glycemic response to real-life meals
- Then did a blinded randomized controlled dietary intervention based on this algorithm



- Intervention compared the algorithm to a dietitian-led group



- Resulted in significantly lower postprandial responses and consistent alterations to gut microbiota configuration
- In this study it was the gut microbiota that most strongly correlated with the inter-individual variability in glycemic response



Some points to consider:

- When the algorithm was used in a pilot clinical trial, it recommended that *all* individuals consume:
    - More high-protein foods and intact grains.
    - Less high-fat and high-glycaemic carbohydrates.
- As Nicola Guess wrote: *"This makes sense when you base a diet entirely on the glucose response because dietary protein lower glucose, and a high-protein, reduced-carbohydrate diet lowers glucose even in people with type 2 diabetes. What clinical utility the gut microbiome plays in all this is unclear."*

Ben Yacov et al: Personalized Postprandial Glucose Response–Targeting

- Study: Ben Yacov et al., Diabetes Care 2021;44(9):1980–1991
- Randomized controlled dietary intervention of six month duration (plus six month follow-up period)
- Compared two diets aimed at being diets that are good for glycemic control:
    - Mediterranean
        - between 45 to 65% energy carbohydrate
        - 15 to 20% protein
        - less than 35% energy from total fat
    - Algorithm-based diet (PPT)
        - Aimed at targeting postprandial glycemia
        - Same algorithm that was used in the Zeevi et al. study
- Main outcome = time spent in a hyperglycemic state
    - Defined here a > 140 mg/dl (7.8 mmol/L)

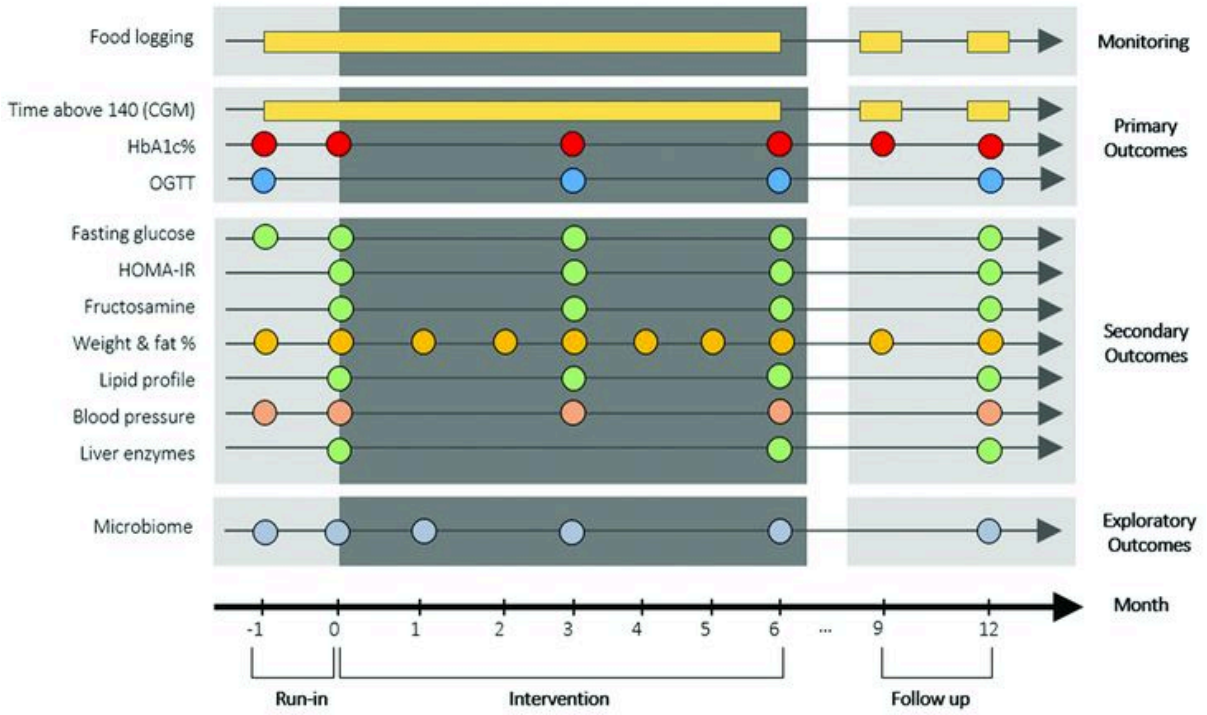


Figure from: Ben Yacov et al., Diabetes Care 2021;44(9):1980–1991
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- Main results:
    - Both interventions reduced the daily time with glucose levels >140 mg/dL (7.8 mmol/L) and HbA1c levels.
        - But reductions were significantly greater in PPT compared with MED.

- The mean 6-month change in “time above 140” was:
  - MED = −0.3 ± 0.8 h/day
  - PPT = −1.3 ± 1.5 h/day
- The mean 6-month change in HbA1c was:
  - MED = −0.08 ± 0.19% (−0.9 ± 2.1 mmol/mol)
  - PPT = −0.16 ± 0.24% (−1.7 ± 2.6 mmol/mol)

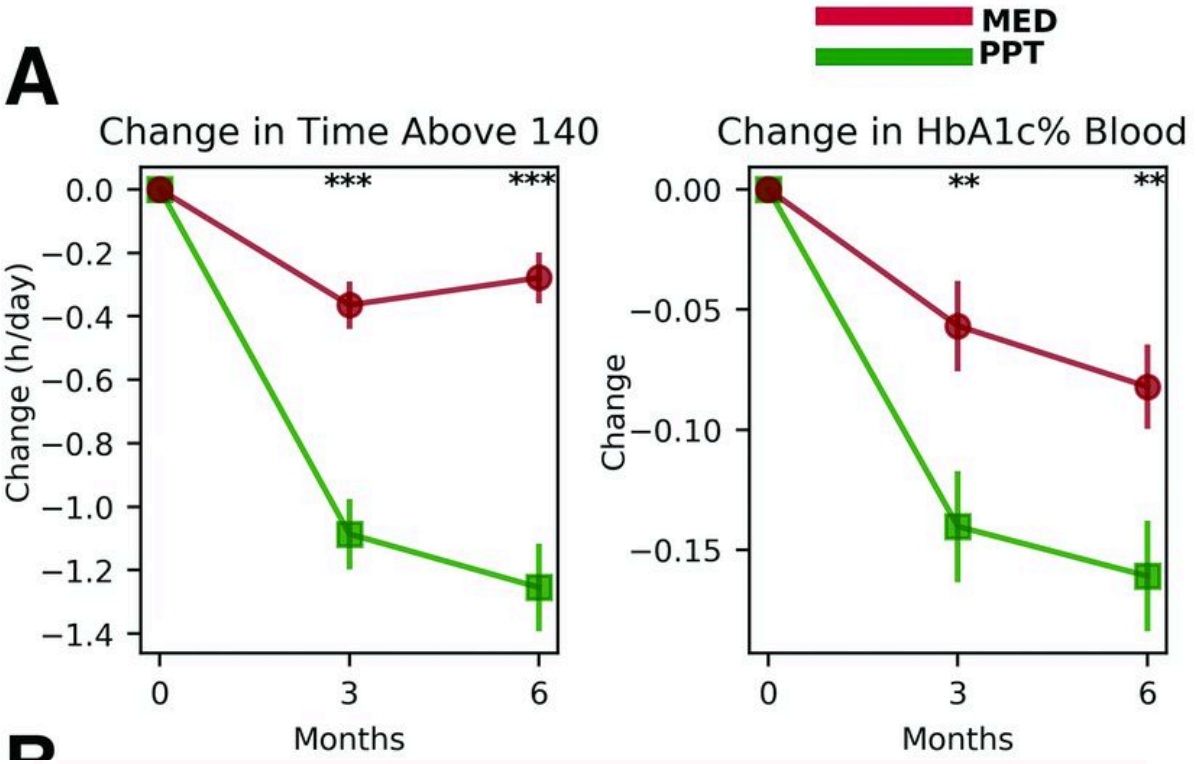

Figure from: [Ben Yacov et al., Diabetes Care 2021;44(9):1980–1991]
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Considerations for Interpretation:

- This is a study looking at glycemia specifically.
- In the algorithm/PN group you see at the 6-month point a carbohydrate intake of 20% of kcal, compared to the Med diet group's intake of 42% of kcal.
- If we have an algorithm largely set-up for glycemic responses, is it surprising it spits out recommendations that lead to lower CHO content?
  - Moreover, does this actually mean these diets are healthier?

PREDICT Study

- Study: Berry et al., 2020 – Human postprandial responses to food and potential for precision nutrition
- Find a full interview with lead author Dr. Sarah Berry in episode 361 of the podcast.
- 1,102 healthy individuals
    - 60% of the cohort was recruited from the TwinsUK registry, of which 230 were twin pairs
- PREDICT 1 was specifically designed to quantify and predict individual variations in postprandial triglyceride, glucose, and insulin to 8 standardized test meals.
- Person-specific factors, such as gut microbiome, had a greater influence (7.1% of variance) than did meal macronutrients (3.6%) for postprandial lipemia, but not for postprandial glycemia (6.0% and 15.4%, respectively)
- Genetic variants had a modest impact on predictions
    - (9.5% for glucose, 0.8% for triglyceride, 0.2% for C-peptide).
- On this basis of this, they then developed a machine-learning model that predicted both triglyceride (r=0.47) and glycemic (r=0.77) responses to food intake.

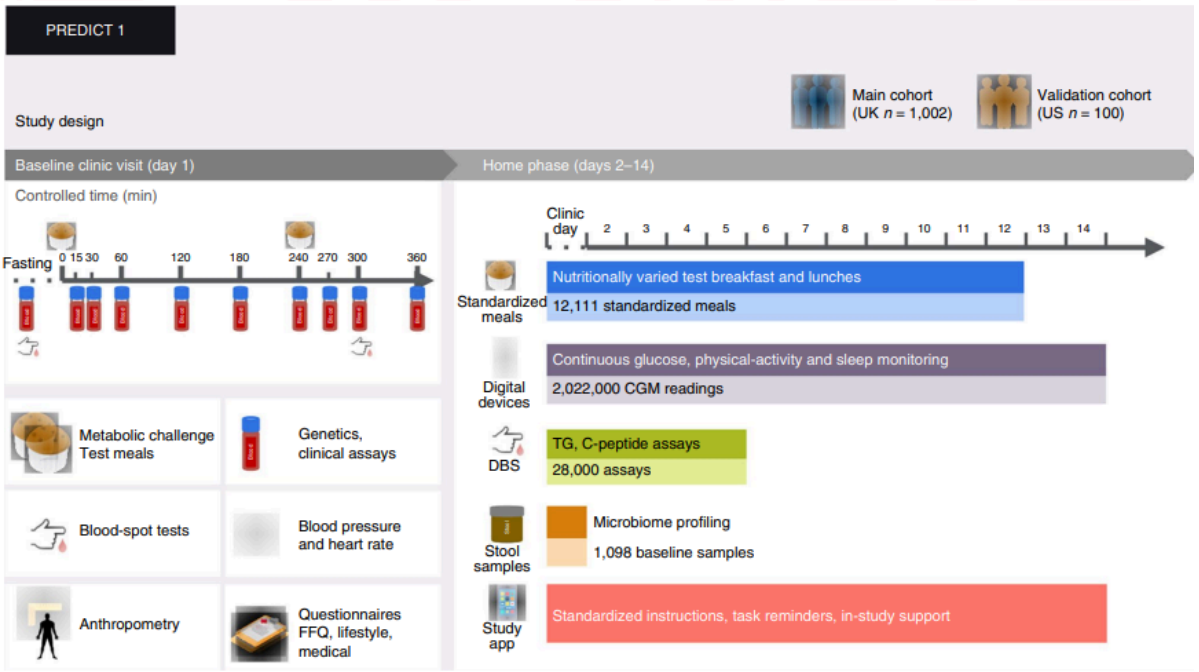
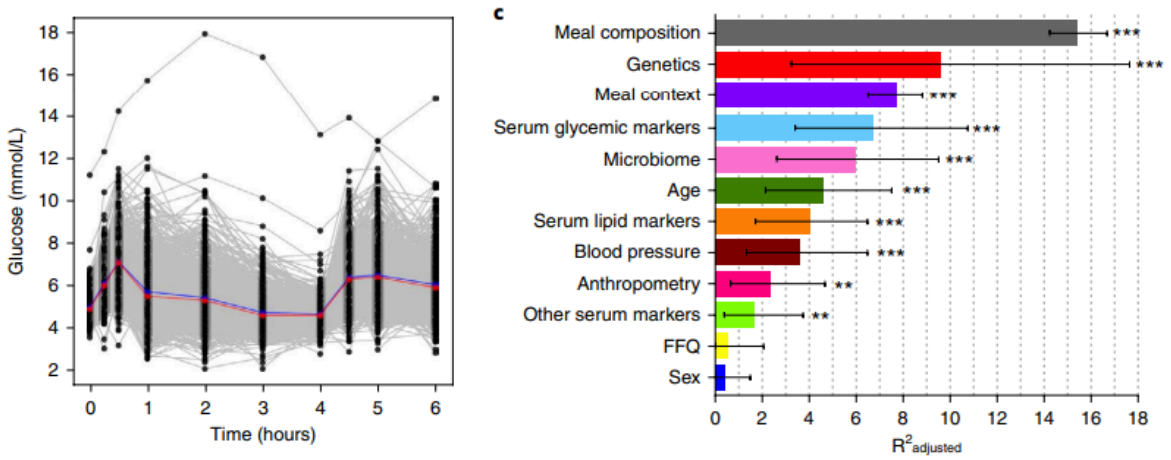


Fig. 1 | Experimental design. The PREDICT 1 study comprised a primary UK-based cohort (n_{max} = 1,002 participants) and an independent US-based validation cohort (n_{max} = 100 participants). TG, triglyceride.

Figure from: Berry et al., Nat Med 26, 964–973 (2020)

Variation in postprandial responses:



Determinants of glucose iAUC 0–2h measured by CGM (comparison of 7 test meals; 1, 2, 4, 5, 6, 7 and 8). Values represent adjusted proportion of variance explained (R2), and error bars show the 95% CIs

Figure from: Berry et al., Nat Med 26, 964–973 (2020)

Issues to Consider:

- **Meal specific responses don't explain much of the variation**
  - The prediction of whether an individual fell into a high or low postprandial responder explained only about 18% of the actual variants in glucose responses
    - means that there are other factors involved in what is explaining the difference from one person to another in their glucose response
  - actual individual meal specific responses only explains 7.6% of the variants in inter individual glucose response
- **Lack of replicability for microbiome-glycemia**
  - While Zeevi et al. found that the inter-individual glycemic variability was primarily explained by the gut microbiota, PREDICT found that the microbiota did not mediate glucose responsiveness.

Person-specific diversity in postprandial response. Effect size for factors explaining glycemic response:

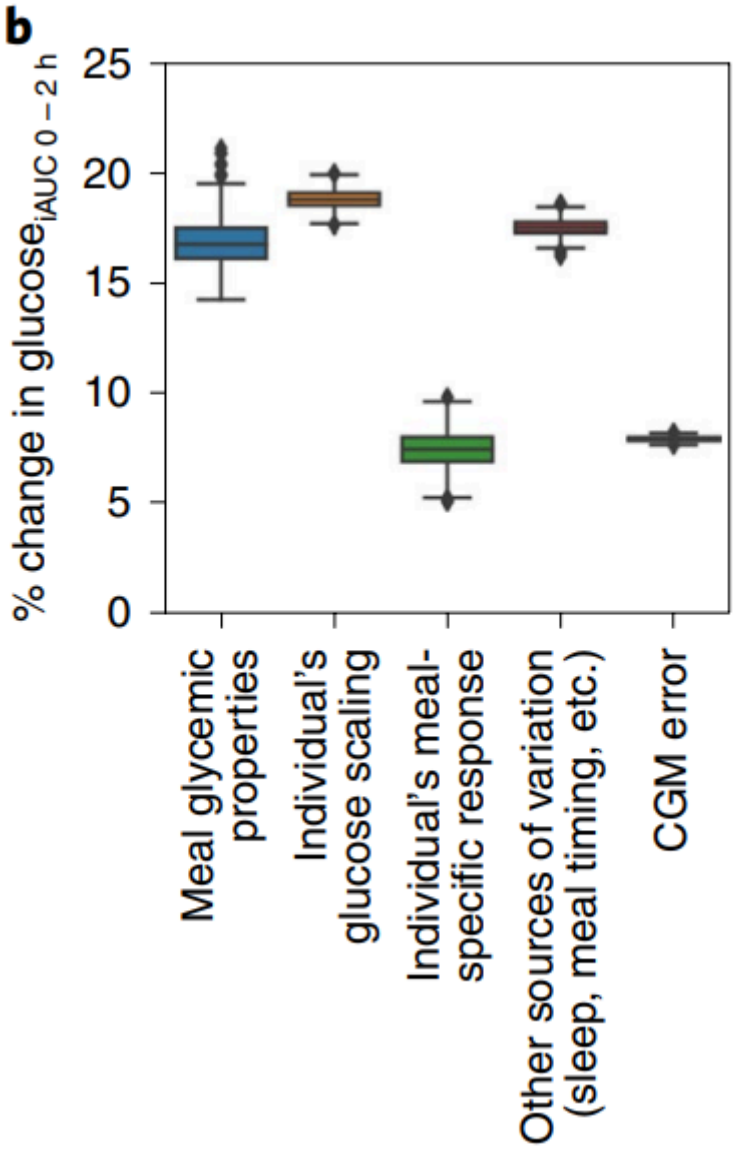


Figure from: Berry et al., Nat Med 26, 964–973 (2020)

How Marketing & Hype is Misusing Current Evidence

- While findings from PN research are interesting and there is much to have excitement about in relation to future research, the current hype and marketing seems to be disconnected from a fair appraisal of published evidence.
- As an example, on one PN company's website they state:
    - *"Experts also suggest that personalized nutrition is more effective than general advice for preventing or managing diabetes."*
- And there is a hyperlink to a reference, supposedly supporting that claim.
- When you go to that reference, it is a 2019 Consensus Report published in Diabetes Care by Evert and colleagues, titled: *'Nutrition Therapy for Adults With Diabetes or Prediabetes: A Consensus Report'*
    - If you read the paper, under the 'Personalized Nutrition' section, the authors' consensus recommendation is clearly stated as:
        - *"Studies using personalized nutrition approaches to examine genetic, metabolomic, and microbiome variations have not yet identified specific factors that consistently improve outcomes in type 1 diabetes, type 2 diabetes, or prediabetes."*
    - Then the paper goes on to add:
        - *"no clear conclusions can be drawn regarding their utility owing to wide variations in the markers used for predicting outcomes, in the populations and nutrients studied, and in the associations found."*
        - *"Further, overall findings tend to support evidence from existing clinical trials and observational studies showing that people with markers indicating higher risk for diabetes, prediabetes, or insulin resistance have lower risk when they reduce calorie, carbohydrate, or saturated fat intake and/or increase fiber or protein intake compared with their peers."*