Episode Transcript

Danny Lennon: Hello and welcome to another episode of Sigma Nutrition Radio. My name is Danny Lennon, and with me is Dr. Alan Flanagan. Alan, how are you today?

Alan Flanagan: I'm very well, sir. I'm waiting for some sunshine to come out, but I'm otherwise as below average as ever.

Danny Lennon: Yeah hopefully some comes your way pretty soon so that we can raise your spirits with some lovely sun. Don't want you getting too gloomy!

Alan Flanagan: Or I'll end up coming your way down to Spain to chase it.

Danny Lennon: Speaking of potentially being of a gloomy disposition, today we're going to talk about a topic that is quite in vogue right now, and we have many things that hopefully will be useful for people listening. We're going to

be talking about personalized nutrition and its potential utility or not, and in relation to maybe some claims about it.

But before getting to the specific question that we're going to address, I think the first thing to make very clear is a clarification of terminology, because of course, some degree of personalization has been something that has been at the core of dietetic practice and nutritional practitioner practice for a long period of time, in the sense of "personalized" meaning: giving advice and recommendations to clients and patients on the basis of individual needs, their medical history, their preferences, goals, perhaps even some blood testing results, et cetera, that would typically be available to practitioner and giving advice that is individual or personalized to that person.

That is not what we are discussing in this episode. But rather we're focusing on personalized nutrition as it has been more recently used and is more commonly used now, certainly in relation to the literature we're going to discuss, and specifically it's in relation to a field that, if we can call it a field right now, that is typically taking some genetic and biological data and using that in combination with algorithms to essentially assess and tell people what foods they should or shouldn't consume or what diets would be best for them to consume.

So it might use things like blood glucose reporting, microbiome testing, a whole range of other variables that we'll mention as we discuss different types of studies and how maybe even different consumer companies have set up their testing. But regardless of that, we're looking at this combination of big data from genetics, biological data, putting that in through some algorithm and then spitting out some recommendations that are told to be personalized to that person. And even if you look at some of the sites for some of the consumer testing companies that do this, they'll say that this is something that is distinct from advice you might get from a dietician or a nutritionist and is targeted just for you. So that is the personalized nutrition that we're discussing today.

And really what we thought would be most useful to discuss as a question is this idea of is personalized nutrition superior to general nutrition advice? We

can maybe go an extension from that. We can then discuss: is personalized nutrition superior to even targeted nutrition advice from a professional or otherwise?

And then within that, essentially we're asking, okay, do these genetic tests blood glucose responses, these fecal samples all this other day that's being collected and used and put in through these algorithms, do they have any extra benefit for predicting health outcomes or for improving health outcomes within the population? What really is the crux of this issue to you?

Alan Flanagan: Yeah, I think there's a number of themes or issues that arise. As you've outlined, there's an explosion of popularity of various commercial, direct-to-consumer testing that is all using the quote unquote "science" of personalized nutrition to support that this is a superior way to go.

You can also see advocates of personalized nutrition position it as if this is something that will be more effective for public health than, for example, general advice we might find in our dietary guidelines. I think there are a number of potential issues that we can think about this potential of personalized nutrition relative to our basic dietary guidelines, the Eat Well Guide or otherwise, one is the concept of risk versus treatment.

So advocates of personalized nutrition will typically say this is preventative in concept; we're using genetics or biological data that we've gathered, for example, with continuous glucose monitors to actually use this information to then make predictive anticipatory changes to someone's diet.

And that's going to be inherently superior to something that is just focused on just treatment of disease. So this idea that it's predictive and that it really is focused on risk and that is a superior approach than just waiting till someone has, for example, high LDL or maybe they've already got cardiovascular disease or pre-diabetes and then saying, Hey, let's make these changes with your diet. So that's one potential way we can think about it.

The second then is this idea of individual risk versus the population or versus public health. And again, this is quite a common argument in this area. So

advocates of personalized nutrition will say look, our current approach is just we take this eat well guide, we recommend people to follow it.

And that's not really going to reflect everyone's special individuality and deserves their own particular specialized individualized advice. And it doesn't cover everyone. And this idea, personalized nutrition may be able to move us away from just generic or general nutrition advice to this really targeted, individualized, or personalized, in this case, nutrition.

And that would be more useful for addressing either disease risk or health in the population. And then I think the final one then is this concept of, and we've layered it on now we've touched on it tangentially with the concept of risk versus treatment, or individual versus population is precision versus general.

And this probably is at the core, I think right now, of the advocates for personalized nutrition who would say this is precision nutrition. This is where we can get people following specific targets for recommendations for macronutrients or even micronutrient intake and specific foods that's tailored to their genetic and physiological biological risk of a disease; this is going to be inherently superior, advocates would say, than just broadly recommending the same general principles of good diet to individuals, although obviously those broad recommendations of good nutrition best practices that form the basis of our guidelines are also obviously targeting the level of the whole population.

So I think those are the three themes: this idea you're getting in targeting risk predictively rather than just treatment, you are focused more on the individual and that's more targeted than a population-wide approach. And then within that obviously then is this concept that if we're targeting the individual, we have the capacity to use this information to be very specific and precise and that has inherent advantages over general advice. And I think with those three themes in mind, we can really frame them as hypotheses almost and really test these themes as we go through some of the literature and see whether the claims in favor of personalized nutrition really stand up to that scrutiny.

Danny Lennon: Yeah. So maybe to start walking through some of that literature, and as you say, this is something that has certainly been framed as built on science, and we have these different studies and different experts pointing to this as superior to maybe general advice, or at least there's something that will improve people's health.

And there are now a number of publications that tend to be most routinely cited or most widely cited, at least pointed to some of which regular sources of podcasts may have heard us mention on a couple of previous episodes specifically, so going back to episode 414 where we looked at machine learning versus other methods of nutrition research. We mentioned a couple of these in relation, more specifically on machine learning, but we did go through in some details, some of the studies. So we may not have to get through all the details here. For example, we mentioned the study from Zeevi and colleagues that we might get into, or the Food4Me.

So for people who want deeper dives on some of those, they can again listen to episode 414, but for now, it might be useful to touch on some of the core elements of some of those most widely cited papers. So I think as a general shortlist to put a pin in, we have a few papers from Eran Segal's lab in Israel, including the Zeevi study and a more recent one in 2021 that we might discuss. We have the Food4Me RCT, and then we also have the PREDICT-1 trial, which is where a lot of the focus gets to be. And there are a few others that we might mention along the way. But to maybe start us off walking through the literature in relation to those three core components you've already mentioned Alan, where might be a good place to start investigating to see what we have in these studies versus maybe some of those hypotheses that we've placed so far?

Alan Flanagan: I think possibly Food4Me if only because chronologically some of the publications from the Food4Me study were in 2016 and preceded some from the research group in Israel. And I also think that it really allows us to start to stack up some of the evidence against some of these teams that we highlighted at the start. So the Food4Me trial was a six month trial, 4-arm randomized control trial participants. Across seven countries in Europe: Ireland, Holland, Germany, Poland, Spain, Greece, and the UK.

And these four groups were characterized by different levels of personalization, in terms of dietary advice. So the control group, which they called Level Zero, was just non personalized dietary advice. So they got dietary body weight and physical activity advice that was just based on general European guidelines. And then there were three different levels of personalized nutrition. And the first was just personalized nutrition advice that was based on the individual dietary intake data. So in the context of, having information about the individual's diet and then personalizing that dietary advice. So it's personalized dietary advice in the absence of any additional phenotype data, genotype data.

And then the second two levels added those on. So the second level was the personalized, individualized, dietary advice based on intake, and then it also added phenotype data. And then the third level was both of the proceeding interventions with the addition of gene data on top of that. And the main outcome was dietary intake, but there's been a number of different publications looking at various factors like Med diet scores, which we'll get into.

I think, and we've discussed this before, ultimately the hypothesis was that providing personalized nutrition based targeted advice would result in greater changes in actual dietary intake. And the most common targets for personalized nutrition advice were salt, dietary fiber, saturated fat, polyunsaturated fats, and folate. And so we have these five food nutrient based recommendations that are fairly generic to most guidelines that we would have at either a national or even European level. For example, most of our guidance recommends the reduction of salt and saturated fat. And the increase of polyunsaturated fat, fiber and folate.

And what you saw in the Food4Me study was that yes, the various levels of personalized nutrition advice had “statistical significance”. And explained why I've put that in quotation marks, differences in, for example, red meat reduction in red meat reduction in salt improvements in the healthy eating index and reductions in, for example, say saturated fat as a percentage of energy.

But part of the problem, I think when we start to really try and stack some of these outcomes up against our question of whether, for example, a targeted individual is superior to population and whether precision is better than general, is that the magnitude of difference? Is fairly minuscule. So the mean difference, for example, in red meat grams per day from the personalized nutrition advice across all three of the personalized nutrition groups.

So just getting the personalized dietary advice, then getting it with genotype data and then getting it with phenotype and genotype data on top was about five, five and a half grams less of red meat. If we look at individual nutrients, saturated fat as a percentage of energy: 1.14% less in personalized nutrition compared to just following the general European population advice.

So when you really start to look at the actual dietary changes that occurred in Food4Me over six months, what we see is negligible differences in diet. These are statistically significant but those negligible differences have occurred in the context of changes in diet that anyone that actually just adhered to, for example, the Eat Guide, would still make, they would lower red meat, lower salt, lower saturated fat they would consume more fiber.

There wasn't a significant difference in dietary fiber, nor was there a significant difference in polyunsaturated fat. Although it was slightly higher in the personalized nutrition group. I think overall when you look at Food4Me, there was another publication, Livingstone and colleagues also 2006 that looked at did it increase if you looked at the dietary changes through the context of a Mediterranean diet score.

And again, there is a statistically significant difference, but the actual effect size, the actual magnitude of difference was negligible between groups. And this is pooling your various levels of personalized nutrition advice together and comparing them to control, and. I think the most important thing to come out of Food4Me, both the previous study that looked at the overall nutrient specific changes and the study that looked specifically at changes in med diet score is that there was no additional benefit observed in the study to improvements with the addition of either phenotype or genotype data. i.e., Taking someone's dietary intake and telling them a few recommendations on

top of that was sufficient to explain the improvement in their diet. And the addition of genotype and phenotype data on top of that didn't confer any additional benefit. And I think that's probably the most important finding to come out of Food4Me.

But I think then if we're talking about this idea of this is superior because it's individualized and precision rather than population general, then I think that this would have to fall concluding, that there doesn't seem to be, at least on the basis of Food4Me much evidence to support that our general population advice is somehow inferior in the context of both the magnitude of change and the variables, food based and nutrient based, that in fact changed in response to the personalized nutrition intervention.

Danny Lennon: And so to really make that clear, because there's two elements to what you've just said. First of all, if we look at one of those papers, for example, in the dietary behavior changes where there was these reported differences, first of all, as we can look at the magnitude of these changes comparing personalized to general advice and then being of what we can consider a small magnitude like this five gram difference in red meat I think you said.

But probably more importantly is that when people are holding this up as some sort of proof that personalized nutrition is better than general, they're thinking of that personalized nutrition in the context of how it's being marketed and hyped right now, which is through the suite of testing and this is going to give you something really precise and specific to you that is going to confer this benefit when the reporting that you see in this paper of personalized nutrition being more effective than standard population advice was small magnitude changes that you mentioned, but personalized in that sense was related to just taking into account body weight, physical activity, and dietary intake. That was the level of personalization.

Adding in all these bells and whistles of these phenotypic and genotypic data did nothing on top of that. So if anything, looking through this in an accurate lens, you would say, actually this is probably something that doesn't support, and in many ways pushes back against, some of the large claims that are

made for a suite of individualized testing to give some predictive power of diet.

Alan Flanagan: Absolutely. That this essentially is saying that if you just went to a dietician or nutritionist and explained your current eating pattern, they would be able to give you sufficient advice based on the information you're there providing without you having to hand over a tube sample of your poop.

In order to make changes that are a reflection of current nutrition, best practice guidelines across multiple nutrition recommendations, whether that's the UK EAT Guide, the Nordic Nutrition recommendations, European level recommendations or otherwise. So reducing red meat, salt, saturated fat, increasing fiber vegetable intake, for example, folate as a concomitant byproduct of eating more greens.

That's all just generic general population based advice that reflects current evidence. And anyone, and we know this now we've had this conversation multiple times in relation to dietary guidelines, not just in terms of epidemiology, but some of the interventions like the Cresta study, that if people just adhere to that, they will have a meaningful improvement in blood pressure, blood lipids and cardiometabolic disease risk factors.

So again I think that this is what Food4Me was saying was that, if you actually went to a nutrition professional, you'll probably get good nutrition advice. But the idea that there is some additional predictive power at play here that supports some of these angles that position nutrition positions itself as being inherently more individualized in and therefore inherently more precise and targeted and superior; certainly that was not supported in the data from Food4Me at all.

Danny Lennon: With some of those Food4Me publications that we mentioned, we've had outcomes like Mediterranean Diet score or the certain dietary behaviors and changes in nutrient intakes that we would like to see. When you look at much of the other publications that are held up in this area, a lot of them tend to, as an outcome, focus on postprandial responses.

Typically postprandial glucose in many of them. In some others they also take into account maybe postprandial lipemia. But we definitely have this focus on postprandial glucose which is interesting as we may get to a bit later on, given that it is both the outcome and also something that is tested going into the algorithm. But nevertheless it's, I just want to put a pin in that for people to think about.

What outcomes are actually being looked at in studies that people are showing you for these? So we have a number of these publications looking at postprandial glucose. You've already mentioned that we have this 2021 study from Israel, the Ben Yacov paper. We also have previous work from that lab from going back to 2015 that looked at some of these outcomes. We also have things like PREDICT and others. So with regards to these, if there's any particular place that's best to start we can do that. So there's one that you think is probably the most representative of a useful point that would tie in where we're at now, maybe let's jump to that.

Alan Flanagan: And I think maybe starting with the Zeevi and colleagues study and then jumping to the Ben Yacov and colleagues study because I think they'll dovetail nicely in terms of some of the points that we're going to make. The Zeevi and colleagues study was really interesting, and in many respects, a very rigorous study, which began with 800 individuals that were both otherwise healthy and would've been classified as having pre-diabetes.

And for an entire week, these participants, all 800, wore a continuous glucose monitor. They had measurements of anthropometrics, so bodies, weight and height, physical activity levels. They monitored diet intake using an app and they also had some standardized meals containing exactly 50 grams of available carbohydrates that they were instructed to eat.

And that, again, was used to like help to monitor the continuous glucose monitoring data. And basically, from all of this, they had data on the gut microbiota composition as well. All of this data went into a machine learning model to devise an algorithm that would predict postprandial glucose responses. They took the data from that machine learning algorithm, and then they validated that in an additional cohort of 100 individuals who were

not included in the original sample of 800 from whom the data was. And then from that they ran a randomized control trial, quite small in terms of sample size 26 participants.

And the idea behind this was that there was going to be one group receiving tailored dietary advice based on the predictive algorithms and one that was going to get general good advice from a dietician. And this is I think really where we can start to see some of these themes become relevant again is precision really present or do we end up coming back to more general?

So the 26 participants, like I said, one on the algorithm to predict their glycemic response to diet and then following a diet based on that predictive algorithm's output for the individual. And then the control was dietician led guidance. That was based on the participants' continuous glucose monitoring data. And these groups were compared to each other. And so they consumed what for them was recommended as a quote, good diet or quote, bad diet that was either predicted by the algorithm or was dietician-led. And that was based on that participant's blood glucose responses for one week to that baseline of continuous glucose monitoring recording.

So when we actually look at the numbers that were in each group, there were 12 in the algorithm driven group, and there were 14 dietician led group. So the algorithm correctly predicted 10 out of the 12 participants in the algorithm group, that the bad diet would result in higher postprandial glucose responses.

The dietician led control group still resulted in the dietician predicting what would be, better postprandial blood glucose responses. i.e., the good diet in 11 of 14 participants. It's hardly a slam dunk win for the predictive power of the algorithm over the dietician led control group.

So both approaches were similarly effective and I think what's really, has to be factored in here for listeners from a methodological perspective to really be thinking about the fact that this isn't like a traditional randomized control trial where we think that an intervention may have benefit, but we're specifically testing that hypothesis in by randomizing individuals to an

intervention, they haven't received the intervention before and other people to a control group. So although these trials come with the ported rigor of being labeled randomized control trials. These are very different types of studies to what we might usually expect because we're, you're already having a phase before your randomized study begins, where you're basically sussing out how an individual's going to respond.

You're finding out what's going to benefit for your intervention before your intervention, and then you're putting people on an intervention and saying, see, look what happened. This algorithm or this personalized nutrition has led to this outcome. And it's but you knew that this was going to be the outcome because you've already previously established who's going to respond to.

And so I think that's a really important point that we'll come back to. But certainly for this study, I think that the fact that the dietician led prediction because the dietician had the individual's participant glucose responses to their one week of CGM recording of their glucose data, was able to give just as good advice in terms of an individual lowering their postprandial glucose responses as the algorithm overall.

What the potential pushback in terms of coming back to where the main themes we identified as the start would be is someone could say think about risk versus treatment, this algorithm would have the capacity to take information that people would have at baseline and be predictive in capability. Whereas with a dietician led context that would require data from the individual before you'd be in a position to make recommendations. So we're back to treatment rather than risk intervention. I do think there is potentially some argument that lies there but again, in the overall context of the methodology and certainly in the context of whether it's superior.

Again I don't think that was necessarily shown in this study based on the performance of the dietician led control group in accurately predicting that individuals would have lower postprandial glucose responses if they modify their diet based on the dietician's recommendations.

Danny Lennon: When we think about the outcome being postprandial glucose, When we then have this terminology of good diet, bad diet, or the a good meal versus a bad meal that it's this algorithm is producing for you, that is with the sole index of the postprandial glucose response to that meal, right? So that's maybe a distinct step from maybe what some of the marketing claims out there might be of this is a diet that's going to necessarily make you healthier, reduce your disease risk, et cetera.

Whereas here we're focusing on this very specific thing and again for clarity for people. If we think about what's happening here in this Zeevi study where we take these glucose measurements across this cohort, we find this variability. We use this to make an algorithm, and then after that, then we set up this smaller RCT and then use that algorithm to essentially prescribe what we would if we are aiming to keep a low postprandial glucose response, then maybe some of this is less fascinating and and as I think it's important to say, okay, like this is a, was a really comprehensive trial. There was a lot that went into it. In fact, we had the lead author David Zeevii on the podcast back in episode 298 to talk through that. So a lot has gone into it.

But in terms of using this then, and how that gets interpreted and applied is where there's a difference. And one thing that Nicola Guess said at a recent event that we had was, in particular in relation to this study, we have a situation where what the algorithm ended up spitting out was for all those individuals consume more high protein foods, more intact grains, and that all those individuals reduce high fat and high glycemic carbohydrates.

And I think, as Nicola said, this makes complete sense when you are basing the diet from this algorithm entirely on glucose response because they're the things that we would already know are going to give this lower response and so from that, how much of this is going further than what we'd be able to get without such an algorithm.

Alan Flanagan: Yeah. I think the one thing about that study, because it's going to be relevant when we discuss the PREDICT trial, is that in the Zeevi and colleagues study, where they looked at what factors explained or had the strongest correlation with variability or variation in individual's glycemic

response between person, from person to person. Then it was in that study, the gut microbiota. So I think just for listeners to put a tab open that in the Zeevi and colleagues study, it was the gut microbiota that most strongly correlated with the inter-individual variability in glycemic response. But yeah, just to reiterate that point that I think we need to be really thinking about methodology here.

As it relates to outcomes and this again is going to be relevant when we discuss the next study because, we were talking off air beforehand and it's like we're having studies that are finding out what would be beneficial before they run their quote randomized trial. And then they're going, Hey, look, this was beneficial. Just to give people a slight point of reference imagine that you were doing a study of a lipid lowering drug. And before the study, before your study happens, you give people this lipid lowering drug to see whether it lowers their blood lipids. And it does. And then you get that information and you use it to, for example, titrate dose. And then you compare a high dose arm to a lower dose arm and you're like, Hey, look, this high dose arm lowered blood lipids more and it's but you knew that going into, you knew that going into the study.

So we need to, I think about how these trials and this is, obviously just something that would probably be for going forward in this research area. In terms of improving the rigor of some of these outcomes, the outcomes are basically often foretold just by virtue of the advanced level of personalization that's been done.

And I think you know, that we could highlight that by reference to the other study from this group, which was Ben Yacov and colleagues, which is 2021. And an interesting trial in some respects. It's a randomized controlled dietary intervention, a six month period that compares two diets. And both diets were aimed at being diets that are good for glycemic control. And then it was followed by a six month follow-up period. The two diets in this study were Mediterranean. And that was, a typical Mediterranean diet characteristics in terms of, between 45 to 65% energy carbohydrate, 15 to 20% protein, less than 35% energy from total fat.

People could possibly argue whether that's Mediterranean, but overall, including the foods that we would expect to see in low fat dairy. Legumes, yogurts, et cetera. And this was compared then to an algorithm-based diet that was deliberately aimed at targeting postprandial glycemia. And so this was again, using algorithm-based personalized, dietary recommendations based on the algorithm similar to the one that was used at the same algorithm that was used in the Zeevi and colleagues study.

You had 94 participants in the med diet group, 83 participants in the personalized nutrition diet group. And the main outcome was time spent in a hyperglycemic state, which was in this study over 140 mg/dl of blood glucose. So the amount of time individuals spent in that range.

And then they also looked at HbA1C and response to an oral glucose tolerance test. And in the personalized nutrition group compared to the med diet group, there was a significant reduction in time spent above 140 milligrams per deciliter of blood glucose a day. And the confidence interval ranged from one hour and a half less to just over an hour less.

And HbA1C similarly decreased. It was about 0.14% to 0.02%, and then there was no difference in the oral glucose tolerance test. And again, you're like, wow big advantage, certainly to time spent in a hyperglycemic state to this personalized nutrition algorithm-based, predictive diet that they were recommended to follow.

But then you look at, first, let's go to think about diet composition. So in the med diet group, the average intake at six months after the intervention, before the follow up of carbohydrate was about just over 42% of energy. And in the algorithm-based, predictive, personalized nutrition diet group it was 20%. Protein was pretty much the same. And then fat obviously was balanced to the amount of carbohydrate in the diet and made up the balance of macronutrients. So again, similar to that point you just raised that Nicola Guess mentioned at the Sigma conference, it's like, You're getting this algorithm already de facto because it's based on postprandial glycemia going to give you certain characteristics of diet to follow. And in this case, this is quite evident in the personalized nutrition group consuming, like 50% less

carbohydrate compared to the Mediterranean diet group. And then when you look at the most popular foods that were consumed in the Mediterranean diet, there were things like natural yogurt, salad, potato, hummus, bread, rice, whole wheat bread, chicken breast. When you look at the popular foods in the personalized nutrition group, it was salmon, beef, salad, chicken, breast, chicken, legs, almonds, cheese, walnuts, omelet, tahini. So at the level of foods, we're seeing fairly distinct differences, obviously in the types of dietary patterns that were followed with the group and the personalized nutrition group following a low carbohydrate, high fat diet.

And again, based on wider knowledge that we have evidence that have compared, for example, various iterations or percentage of low carbohydrate in the diet in terms of HbA1C or glycemic control. And what we typically see in that literature is that lower carbohydrate intake can be superior in the short term over a six month period, the exaggeration of the intervention of this particular study.

And then we typically see that washout over, over one year. And so again, we have to really ask a question, are we really seeing some sort of inherent personalized advantage here? Or are we seeing people who were individuals with pre-diabetes at baseline following a diet that we would simply expect to lower and improve their glycemic control in that short term timeframe, which dietary advice could be provided independent of having an algorithm predict what should be eaten because it's grounded those recommendations in wider evidence that already exists. So again, we have to come back to these themes.

We were asking, is this really inherently getting at risk or are we still really just looking at treatment dressed up as something more fancy? Is this really something that is very individualized versus, more just taking advice that we could have at a more population level specifically obviously individuals with pre-diabetes. And is it really that related to precision rather than just general advice when, again, much of this type of dietary pattern that people followed in this study could be available for individuals to follow. And indeed, there are multiple lower carbohydrate programs that exist for diabetes management that are used in the NHS, for example.

So I think we've got a big question over how precise is this over? Do we just end up back at general advice that we could already find in the literature? Is this really that individualized? Really are we still coming back to broadly speaking, that could be applicable at the population level. And again, is this really that predictive and enhancing addressing individual risk or are we still just really considering treatment in the context of risk factor management?

Danny Lennon: Yeah, there's something about looking at these outcomes and then these comparisons that, I don't know, just doesn't sit right with me that I can't exactly put my finger on. But it's something to the effect of, we have situations here where, In a number of these studies, we have this outcome of how we're assessing it is some measure of glycemic control, whether that's postprandial glucose or whether it's time in above a range. For example, in this study time above one 40 milligrams per deciliter.

And that's the outcome we're assessing to determine which of these diets we're comparing is best. But then we're taking a dietary pattern that is held up as general advice to the public because of its benefit to health across a wide range of outcomes generally for general health, general disease prevention as opposed to a very specific outcome.

So something like a Mediterranean diet or there are healthy dietary patterns where we're thinking more about the totality of health, across many different risk factors and outcomes in chronic diseases. And then we're comparing that to this precision nutrition diet that is specifically set up to care primarily about the outcome that we're then testing for. So this glycemic control.

And so that seems like a bit of a strange comparison in the sense of if I were to compare one of these precision nutrition diets to a salmon only diet, then what do we see there? We're not going to claim that a salmon only diet is better than general nutrition advice or better than a Mediterranean diet for the population. Although our outcome that we cared about was just the time above a certain level of blood glucose. Yeah, probably the salmon only diet would do better on that outcome than these dietary patterns that we typically advise. But it would seem strange then to say it's outperformed this diet there.

There's just something odd about thinking our outcome is going to be this specific measure of blood glucose elevations or postprandial responses. And then I'm going to specifically have a diet that's aimed at addressing that, using actual collected blood glucose measures from people and the responses to meals as part of the algorithm, and then compare that to a general advice and then use that as a way to say it is better or is better for that person's health. Seems just something strange about that.

Alan Flanagan: Yeah, because it doesn't add up at various levels. It's like we said before, it's like you're discovering in advance of your intervention what is going to work, and then you're telling people to do that thing that is going to work in relation specifically to postprandial glucose.

It's like we have more than sufficient, wider evidence to understand what dietary factors typically are going to aggravate or attenuate an individual's postprandial glucose and improve their overall glycemic control. And there's obviously potential differences in terms of duration of effect with this.

And so I think the uneasiness that you're expressing really is an accurate reflection of this feeling overall because they're predicting as they're finding out determining what is going to be beneficial for a specific outcome. They're then having that as the specific primary outcome of an intervention where diet is being tailored along just lines that we would expect to improve that specific outcome.

And then it's being labeled as being personalized and targeted. And typically what you can see in these studies is, you can see some graphs of, oh look, this was one participant's response to a banana versus a cookie. And I don't think that they're particularly useful because I think they're over exaggerating potential differences because what I think we typically end up seeing with these trials is a degree regression to the mean where we have this general benefit that would be expected to occur for the outcome of interest where, for example, someone lowers their carbohydrate intake and eats this good dietary composition, low carbohydrate, higher fat, moderate protein diet for six months. So I think there's a chain of reasoning here that the field is using to argue in favor of its benefit. And I actually think that's self-defeating.

When we look at a lot of the effects Food4Me, these negligible effects sizes, the Zeevi colleagues' paper, it's like your dietician did just as well as your predictive algorithm, I genuinely think that at this juncture and let's keep the healthy skepticism that some of these algorithms could be predictive at risk in individuals potentially that are higher risk but at this point I really do think that this field is a house of cards and is primarily existing to bolster commercial kind the commercialization of science rather than the rigor.

Danny Lennon: Yeah. Speaking of the commercialization of science, there are many of these companies now, but there's one commercial company that is probably, I would say the largest, at least in the UK right now, that is directly tied to, to, to one of the trials. So maybe we will mention that finally, before we actually get into this more overview level thoughts on this general area, because people will reference the PREDICT-1 study specifically because that is held up as directly tied to this.

And again, for regulars for the podcast, this is a trial that was discussed on the podcast before with one of the authors on that paper Sarah Berry. And so again, there are some interesting aspects to PREDICT. I think the disconnect comes from when we look through some of this and then see how that is maybe being interpreted or at the very least how it's being marketed.

So with PREDICT-1, and there's a series; PREDICT-1 is the one that's been published. We have this thousand person plus cohort from the Twins registry in the UK. And again, we're looking at some of these individual responses to meals. So postprandial, triglycerides, glucose, insulin, et cetera. Taking a bunch of these measures and then in very much the same way we've described, coming up with something that should predict these and then therefore show some superiority to precision nutrition. Now, of course, if you want the details of that, we not only have that episode on it, but we've also referenced this on some of the episodes that Alan and I have done previously, which I'll link to in the show notes.

But from an overview level, what is the main learning point we can maybe make people aware of in relation to PREDICT, certainly from what we see in

that trial, and then maybe some of the things that tend to flow from that from other areas outside of the actual paper?

Alan Flanagan: Yeah, so I think for me, there's two things that really stand out with PREDICT. The first is, again, much of the focus is we've been discussing the research papers in this area. And the purported benefit of this personalized, algorithm machine learning driven model approach is postprandial, glycemia or postprandial glucose responses. And again, this is offered then to support this contention that everyone will respond differently to the same food. And that means we need, to consider, meal specific recommendations for a given individual.

But you actually dig into PREDICT then, so PREDICT similarly used a widespread period of baseline data collection to then feed into a machine learning model, which produced a predictive algorithm for an individual's response to diet. And it looked at these inter-individual differences and basically showed that there were these quote statistically significant differences in response to identical meals for glucose, insulin, and trig. Again, discuss the relevance of the magnitude of difference, but in particular in relation to glucose and postprandial glucose responses.

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. So this means that there are other factors involved in what is explaining the difference from one person to another in their glucose response.

But as it relates to this idea that we're going to then tailor specific dietary advice, actual individual meal specific responses only explains 7.6% of the variants in inter individual glucose response. And again, I think that's a pretty damning finding for... that again, some of these findings have been commercialized as saying *“Hey, everyone will have amazing blood glucose response and maybe a banana is not for you”.*

But more importantly, and this is the second, so that's the first point, is the actual meal specific responses explained very little of the variation between

people in their blood glucose responses. And then from a more general scientific perspective of replication and the importance of replication, recall that I said to leave a tab open on the Zeevi and colleague's paper, which found that the inter-individual glycemic variability was primarily explained by the gut microbiota. PREDICT, in contrast, found that the microbiota did not mediate glucose responsiveness. So again, when you think about how this is blown up and all the buzz words that are attached to a lot of these commercial programs is very much contingent on the microbiome, the microbiota as this mediating factor is this crucial linchpin.

And yet you go into PREDICT and you're like, wow, okay so big finding in relation to glucose variation in the Zeevi colleagues study was the mediation mediating effect of the microbiota. And in PREDICT that is not replicated. And I think that speaks to, again, the fact that the microbiome as an overall research area is still a relatively nascent field.

I think we're still really scratching at the surface of our knowledge which we've discussed before, and I have this idea that obviously there's going to be variation. We're comparing in the Zeevi colleagues study, we've got a population in Israel, different genetic backgrounds, different diets, et cetera, and we know that are all factors that will influence. There's regional variation in the composition of the gut microbiota, and then we're comparing a population, for example, in the UK a few other places that are potentially different. But again, this idea that we're jumping all over, “oh it's the microbiome and that's what we're targeting here” to get personalized with things.

And it's your glucose response to meals that's different and that's why we have this need for personalization. And I don't really see any strong support for that from the data in PREDICT, particularly when we think about the meal specific responses explaining such a negligible amount of the variance in inter-individual glucose responses.

Danny Lennon: And that really is crucial. So we of course, are seeing this individual re response the difference in response between people to meals, right? That's totally unsurprising. But when we're looking at what is

accounting for that variance, if I'm reading the results from this correctly, they have listed as person specific factors, one of which is the gut microbiome. So not even the microbiome alone, but that lumped in with other person specific factors they report as having a greater influence than the macronutrients of the meal, specifically for postprandial lipemia. But that total person specific factors is 7.1% of variance compared to 3.5% for macronutrients. So about, yeah, three and a half percent difference there. But for postprandial glucose, we don't see these person specific factors having any greater influence. In fact, it looks like it's worked like 6% of variants for these person specific factors including the microbiome, whereas just the meal macronutrients are explaining 15 point a 5% of the variants there.

And again, like you said, completely against what we're seeing maybe from the Zeevi study and certainly nothing that would ascribe to much of the marketing and much of the reporting on podcasts about this huge role of gut bugs influencing all our response to meals and feeding them the goal if you want to improve your blood glucose and these other health markers?

Alan Flanagan: Exactly. Yeah. This relationship between the gut microbiome and glycemic responses and the idea that this is something to specifically target in terms of modulating for improved glycemic control. Again, I think this is a gross overreach from data that does not well support that contention. And again I think that alone is a microcosm for this entire research area at this point. It's some interesting findings that could more appropriately be treated as hypothesis generating. These are studies that are self confirmatory because they're finding out what's going to benefit before conducting an intervention, which I think has some methodological problems that need to be considered in and of itself.

And ultimately the actual contribution of the personalization element in these studies, whether it's related to the predictive of glycemic responses in the PREDICT study, or whether it's the actual food and nutrient based changes in Food4Me, or whether it's how well the dietician did against the algorithm and the Zeevi colleagues study. It's like these are really negligible effect sizes of questionable relevance that I think really don't match the

enthusiasm with which personalized nutrition, certainly in the general wider public conversation about nutrition is being discussed.

Danny Lennon: And that's in that wider conversation. It's mainly people thinking of this commercial testing where you can send off some of your samples and get back this very specific prescriptive advice on a diet that is going to be best for you. And I think as we've outlined, certainly any of the studies that typically are referenced in support of that don't really support that particular claim where you could perhaps make some use of some personalized nutrition, although I wouldn't even call that it's probably more targeted based on very specific things is for example, in, in the case of apoE4 genotype, and we have a RCT we might reference here, where you have a situation where knowing your apoE4 genotype could therefore let you know if you are at a heightened risk of cardiovascular disease due to the type of your fat and your saturated fat intake as an example.

And so knowing that might be useful for an individual, but that is not the same as doing a bunch of this testing an algorithm, then spitting out a diet that is then best for your health. This is actually just working out, okay, I have this certain genotype which puts me at higher risk. So maybe I might want to change how much fat and saturated fat is in my diet in order to mitigate some of this risk if I am at higher risk. And so that might be part of this interesting conversation, but that is separate to maybe how some of this publicized, commercialized precision nutrition is put forward.

Alan Flanagan: Yeah, I think that there is some potential here, and the apoE example would sit, I think with how we would consider other examples of monogenic conditions. So for example, individuals with a genetic deficiency. In MTHFR, and their requirements for supplemental folic acid. And there are other examples here as well, where that knowledge, that genetic knowledge is going to be very helpful for an individual in terms of their health and being able to manage diet accordingly.

So with apoE, obviously apoE4 in particular, the big worry would obviously be cardiovascular and neurological disease in relation to Alzheimer's and

dementia. And they may have a unifying mechanism in terms of disordered cholesterol metabolism.

But one of the big questions that then arises is, it's one thing to have the knowledge that you have a certain risk factor. The second part is human behavior in terms of acting on that knowledge. And I'm reminded of a paper, it's old at this point. It's Stuart Knox and colleagues back in 2009. And they basically did a European wide survey on attitudes to genetic testing. And then, who would follow a personalized nutrition plan based on that knowledge. And if I remember correctly, about two thirds of the respondents said that they would get a genetic test, but about 25-26% said that they would follow a personalized nutrition plan.

The idea that the testing itself or the knowledge would precipitate motivation to change doesn't actually have much support in the literature. And the reason I went back to some of that research was because of this other publication in relation to apoE that also came from the Food4Me trial.

So what they were looking at was, okay, in individuals that have apoE4 what is the effect of either having the apoE4 risk versus non-risk allele genetic predisposition, and how does that then relate to changes in, for example, total and saturated fat intake?

And what's quite interesting in this again is how the findings of the study are positioned. There was a significantly greater reduction in total and saturated fat as a percentage of energy in individuals that were positive for apoE4 that received gene-based personalized nutrition.

So remember we discussed the various levels of personalization in the Food4Me study. The last level was the personalized nutrition advice plus this genotype information. But when you look at when those differences lay, you're like, okay, cool. So someone that knew they had apoE4 risk, with their genetic information and their personalized nutrition was able to significantly reduce total and saturated fat.

But that was the comparison against the control group. When you actually looked at the differences in individuals with APOE risk apoE4 positive, for example, APOE risk across the various levels of personalization, those without the genotype information just getting their personalized nutrition advice had a greater reduction of saturated fat in terms of magnitude decreased by two point a half percent compared to those in the actual group receiving gene-based personalized nutrition where their saturated fat intake decreased by 1.9%.

So again, You look at, say for example, the difference in saturated fat as a percentage of energy in individuals where they looked at the effect of knowledge of your genotype. So those that had a non-risk, so apoE4 negative versus the risk apoE4 positive type, and the reduction in saturated fat in the precision nutrition group was pretty much around the same, there was no significant difference between these groups at all. And overall, we're coming back to this question of is knowledge sufficient motivation to change? And although I think that APOE, just as an example along with MTHFR is where there is some utility for the concept of say, nutrigenetics and Nutrigenomics because it's going to be helpful for someone to have that information in terms of managing or potentially being able to act on and manage risk associated with their genetic predisposition.

Again, the Food4Me study really doesn't offer up that much of a convincing case that even knowledge of a genetic risk genotype would be sufficient to drive. greater magnitudes of dietary change, compared to just advice based on your personal diet, weight and height, history, et cetera.

Danny Lennon: And this is useful to consider because this is actually a point that someone put to me before when I mentioned something about the enthusiasm for personalized nutrition maybe exceeds what we know about it and, or at least the point is made. Okay? This is maybe something that is not really going to move the needle for public health specifically.

When we look at the population diet and population health, how are we going to most effectively help the most number of people? The answer as of right now, probably isn't for them to go and get this personalized nutrition.

And I can see the logic in the thinking was like do you not think if more people did this, even if it wasn't doing anything, just doing the test would be enough motivation to change diet?

I was like, I don't know. I think, no, if you're going to go and do a test, you're probably motivated to change your diet. I don't think in of itself, getting this data is what's going to get people to follow certain dietary patterns consistently. Even if it was doing something positive.

Alan Flanagan: I think this is the question. There was another, there was a review by Soo and colleagues in 2013 on direct to consumer genetic testing. And again it's, it comes back to this question. I think people have this theory in their head because it sounds truthy that if you get a test, you know that and you find out this information, you'll be motivated to change.

There's no real consensus that's the case, certainly from other realms research, psychology or otherwise, that doesn't seem to be that well supported a proposition. The idea that knowledge alone is sufficient for change, is to ask any cardiologist, it's like someone who's been told, Hey, you're going to need a stent and you're, and all of this, and how much do they actually change behavior? That got them to that point. So I just don't think this theory, I think it sounds quaint and truthy that people will have this knowledge and that will lead to this widespread, explosion of individual health. I think we'll come back to that in a general summary because I think the other problem with this is it keeps the emphasis on personal responsibility and individual level behavior change, which is just a failed paradigm of public health nutrition at this point.

But yeah I don't know that we could say, with any degree of confidence that simply getting your genetic test done and finding out you have apoE4 positive, for example is sufficient for that individual to be motivated to reduce their saturated fat if they have a particular love for burger and butter like yeah.

Danny Lennon: Yeah. And I think on this idea, improving public health. Because sometimes it is positioned as this is such a breakthrough field that

this could change the future, right? And often probably in, in ways getting funding or presenting a message that is nice. It's positioned as this is the future because this is the thing that can tackle the obesity epidemic or the diabetes epidemic or all these other things that it's marketed and claimed to do.

And when really, when you look at it, at least in its current form, when we think about how this is available to people, right now it's through commercial testing that comes at a significant cost. And therefore what you have is really a situation akin to the worried well, or maybe not even worried.

The worried affluent versus actual, most of the population that needs to improve overall health through maybe dietary change if we can do that. And so thinking that this currently is offering some solution, I don't know where people would get that from. I believe one of the researchers involved in this, I heard him talk on a podcast, said of course it's going to be a tiny percentage of the population that can maybe currently afford and use these services, but at least gets people thinking and gets the conversation started about this type of thing, which will benefit everyone.

I don't know what that can possibly even mean. Yeah so again, it's a situation of yes, there's, when you think about who is going to be going for this testing, it's people who have been made aware of this messaging are worried because of that. Think that they need to do this, otherwise their blood glucose is going to be all over the place.

And if they have a banana they're destroying themselves. And then yeah. how that is tied to improving the overall health of the population. I still am unclear about how people are making that connection.

Alan Flanagan: Yeah, because it I mean almost classically neoliberal. The point you articulated from that particular person on the podcast is basically trickle down economics applied to commercialized science.

Don't worry, we'll, just this will benefit the few and the privileged, but it'll reach the masses and everyone will benefit. It's an absurd premise, I think, to

proceed from. And I think it just as an example of the fundamental limitations to this. The case for personalized nutrition, at its highest, this idea of risk versus treatment suggests that individually accurate risk can be predicted from genetics and these other factors, and then we can tailor it. But it's but that is already the paradigm that we operate in for the most part.

Since Framingham, the basis of public health has been the identification of factors associated with the subsequent appearance and progression of disease, which is the quote from Framingham, which we've come to term as risk factors. And so we identify risk factors at the population level. We see those risk factors at the individual level.

We address those risk factors with the appropriate intervention, which could involve diet or pharmacotherapy or whatever other treatments or interventions are available. And this idea that this is. Beneficial for public health is really just, I think, probably the most insidious positioning of personalized nutrition.

Because I think it's just putting this massive speculative cart before the public health horse. The idea that this, if we think about the foresight map of factors related, Obesity rates at the individual and population level. The idea that this helps unravel any of that is just totally divorced from reality.

And the evidence that we have, it does boil everything back on to the level of the individual. It's clearly at this point only accessible to people with means We know from wider research in terms of public health messaging that the people most likely to respond to this messaging are the people with the means to do which means that de facto this technology and its advances is going to miss out on the people in society who are most vulnerable to the food environment and other.

And so the idea that what those people need is to send their shit to Tim Spector to find out whether they can have a banana or not, is an absolutely insulting approach to public health. And the idea that, for example, getting individuals that are below recommended levels for dietary fruit and vegetable intake or other just basic general best practice nutrition advice that's been

established over decades of research and is fairly in uncontroversial at this point that where we to actually achieve that across the whole population level, we would see a much greater shift in the burden of disease.

So this really comes back to Jeffrey Rose's conception of sick individuals versus sick populations. This could benefit a tiny minority of individuals in the population, and that would have absolutely wouldn't even dent the magnitude of scale of these chronic conditions at the population level, and if we compare a hypothetical example where we get everyone in the population, particularly those from low income strata, to consume the dietary guidelines to adherence versus targeting a small number of individuals with precision nutrition.

Where do we think the greatest magnitude of effect in shifting the burden of chronic disease risk in the population would derive from? And I think everyone knows the answer to that question unless they're being incredibly dishonest.

Danny Lennon: Yeah. People are "Spoofing" to some level at least. Yeah and I think, the other part is that there's almost this assumption baked into some of these claims that this is positive across the board, or at very least there's no negatives.

But of course there are very real harms of using such services, whether that's just from the fact of testing a whole bunch of things, which we've talked about before, or even in relation to the significant cost that this has, the drain and resources for many people that report maybe excess worry then about the types of foods they're consuming, hyper-focusing on the response to meals, worrying if they have a meal that's been flagged as bad for them.

I think again, to reference Nicola Guess, she only put up a post I think yesterday on her Instagram talking about one of her clients that came to see her in clinic, who had bought one of these personalized nutrition services, got back this report telling her that she was intolerant to carbohydrate despite having a totally normal HbA1C.

And this person went from normally consuming a Mediterranean style diet because she was of Greek origin to then making all these dietary changes to try and limit glucose excursions to meals and ended up eating a diet that then worsened her already high blood cholesterol and then reported feeling that she was worried, anxious about the her diet all the time.

She stopped having social meals and making pizza with her family, and all these slew of changes that negatively affect quality of life. Of course, one example, but I'm sure there's many of these cases to realize that there are potential harms to this for a number of people, particularly when they're led to believe you need to be doing this to improve your health.

And otherwise these normal things you think are healthy for you, fruit or vegetables or oats, you could actually be really harming yourself unless you get this test that might not be the best message to, to send the people. Yeah.

Alan Flanagan: And I think it comes back to this idea of what are the barriers that are in the way to improving public health at the minute from a nutrition standpoint and a knowledge deficit about good diet is not one of them. And I think that the emphasis on personalized nutrition really puts us back to this level of personal responsibility, individual risk management, and individual level behavior change. This is what's going to shift the needle, and that's just a failed paradigm. So it's putting some sexy sounding technology on a failed paradigm and trying to dress it up as something else.

Danny Lennon: The government's not responsible for your gut microbiome. So yeah, take charge yourselves. With that maybe to finish, I'll leave the final word with you, Alan. What is the final concluding thought on anything we might have touched on today that currently is coming to mind for you that you would most like to leave with our dear listeners?

Alan Flanagan: We've been quite strongly critical of this field. I think that's not a bad thing, is the first caveat. I think the second is that it's still a nascent emerging field. There is some potentially interesting stuff here and I think it is a field that does deserve attention. But that said, the enthusiasm and

hyperbole for the evidence is way out over its skis in terms of what that evidence actually says and supports at this point.

And I think at this point the glycemic response data is interesting, but much of it just boils down to factors that we already know. And so I think that yeah, like we'll await more research to come out in this area, but I would currently say that the kind level and magnitude of claims being made is divorced from the reality of what we see in the evidence at this point.

Danny Lennon: Perfect. We will leave it there. Thank you everyone for listening to this episode. I hope you enjoyed it. Alan and I were back with another episode very soon, so I hope you tune in for that. And of course, if you enjoyed this episode, let us know. We'll be back soon with another episode. And until then, have a great week, stay safe and take care.