DANNY LENNON: David thank you so much for taking the time to join me on the podcast today.

DAVID ZEEVI: Thank you for your interest.

DANNY LENNON: Yes, I've read a couple of your papers, one that I remember reading back in 2015 when it first came out and that was one that made quite a splash because there's so much in it and we're hopefully going to cover some of that today; and then there's also another paper published that you were lead author on from this year which I also hope to get into. But before we discuss any specifics of those papers, maybe give people some context, can you give them rundown on your background in terms of research, also maybe what you're currently working on, what areas of research excite you, and kind of an overview picture of where you are as an academic right now?

DAVID ZEEVI: Yeah, definitely. I'll just start by saying that both of these works were performed in the lab of Professor Eran Segal, even though the second one that you mentioned from this year, I continued working on after I left the lab, both of them were done with Eran and also with Tal Korem who's now at Columbia University. As far as my background goes, I studied computer science and biology at Tel Aviv University. I

then did my Master's with Professor Tal Pupko at the Tel Aviv University working on molecular evolution. And eventually, I decided that I'd like to see something done that's a little more on the applicable side and I moved to the Weizmann Institute, also in Israel, and worked with Professor Eran Segal. When we started working on this project we were we were looking at rates of obesity in the US population, and this is really interesting, because in 1990, the average rate of obesity per state was about 10%; and obesity is defined – the US government defines it is a BMI of over 30, so there were about 10% on average obese people per state in the United States in 1990. In 2000, it was around 20%, 15 to 20%; and in 2010, it was around 25 to 30%. So when you see it like this, when you see it all on one timeline, it seems like an epidemic, except it's not a communicable disease, it's a noncommunicable issue.

So when I started my PhD with Eran, we wanted to address this growing problem of obesity. It's not just obesity, by the way, it's also diabetes and other noncommunicable diseases that have been on the rise. So diabetes, for example, was 5% of the population in 1980 and now it's about prevalent as much as in 10% of the US population. This costs a lot to governments and healthcare systems. I think that I only have that data from about five years ago when it was about $250 billion per year indirect costs of diabetes to the United States government. So this was motivation for us to start researching these topics.

DANNY LENNON: So maybe a good place to actually start the conversation is to get into that 2015 paper that was published in Cell, and for listeners, I will link to this in the show notes so you can go and check out that paper in its entirety which I thoroughly recommend that you do. And really, where is the best place to start with this because this was one of the most comprehensive studies with so many different elements that I think I ever remember reading

and there's so much to piece through here, we have these kind of three different phases that we can maybe look at separately, but just from an overview, how would you introduce people to the methodology behind that particular paper?

DAVID ZEEVI: The methodology we took was to look at nutrition personally, and I think that what motivated us to do that is that when we looked at things universally, trying to see what happened between 1990 and 2010, for example, we saw that there are changes to nutrition, I mean, to global nutrition that are common to almost the entire western world, fat consumption decreased because fat was considered not healthy to the heart, sugar consumption increased to make up for the lost calories and to make up for the taste of the products from which fat was taken out, and we started changing our mealtimes and so on. And we thought, okay, if nutritional changes did drive this metabolic disease epidemic, could it be treated with healthy nutrition? Except there was no good handle on what healthy nutrition is. And maybe I'll send you, I have this this slide I sometimes show at conferences, showing Time magazine covers from 1972 and on. So some of them say that cholesterol is bad for you, some of them say that cholesterol is good for you, some say that you should be a vegetarian, some say that you should eat butter, and it's all – so when you look at it all on one slide, it seems to have a huge disagreeing on what is healthy nutrition, except this is not the question of trend or fashion or opinion, it's a scientific question, healthy nutrition and what it is.

So we wanted to address it with scientific tools, and in order to really address it, we wanted to find a good marker of healthy nutrition. So we wanted something that would be objective, that we could measure on a large scale, that would be clinically relevant both to obesity and diabetes, and that would be actionable, meaning that we could measure it, take some

action, and see how it changes. And we chose to look at postprandial glucose responses because they are directly associated with fat storage weight gain and with hunger with a mechanism behind it; they're also associated with other chronic metabolic disorders, cardiovascular disease, obesity, and diabetes, and we can easily measure them and get a response variable not only for each week of intervention but for each and every meal. So we have a lot of data, so this is our side of this data revolution. We don't only measure, for example, weight of people every week. And in the case of weight, if an intervention worked, you would probably see it on the weight; but if it didn't work or if the weight didn't change as much as you thought it would, it's really hard to go back to the exact meals in which something went wrong. But with postprandial, post-meal glucose responses, you have a response variable to each and every meal that our participants ate; and given all the association with disease, it's not surprising and neither did we come up with it that maintaining normal blood glucose levels is key to fighting the rise in metabolic disease. So it would seem that we had a solution that we just have to control how people respond to meals, find some global meals that would be good for everyone and not spike blood glucose, except that was not as easy – because we saw that even in the same foods, there were many small-scale studies, maybe, I don't know, 20 people in each study that showed that even the same meal can cause very different glucose responses to different people.

So to address this we asked what could drive a personalized response, and we came up with three main factors on the personalized response, except for different people having different responses to the same meal. And these were genetics, which can really affect your response to food but you were born with it and you likely will die with the same genetics unless gene editing will come into play. So there's not much you can do about that. Also, there's lifestyle, but we all agree that it's better

to be active and sedentary. And also, last but not least, there was, at the time, when we started working on it in 2012, there was this factor that was flying under the radar of the human microbiome and it showed promise because we saw a few studies from Stanley Hazen's lab and Jeff Gordon's lab, I can send you the links afterwards, that showed that the microbiome is not only related to the states of metabolic health of the host – meaning, it's not just related to whether the host is obese or not obese; it also causally effects sometimes with a mechanism the response of the host to nutrition. So the microbiome was indeed important in people's response to food.

So in order to take all of these factors together, genetics, lifestyle, and nutrition, we came up with what we called the personalized nutrition project in which we recruited 800 people, we measured their blood glucose levels using continuous glucose monitor for a week, and we also supplied them with a smartphone in it in which they recorded what and when they ate, slept, exercised, and so on. Overall, we collected data on more than close to 50,000 meals, we had more than 5000 days of logging and about 1.5 million separate glucose measurements. We also measured the major determinants of variability in response to food, blood tests, the gut microbiome, we let them fill in food frequency, lifestyle, and medical questionnaires, and we measure the people anthropometrically, and using all this data we started doing our research. Now, there were countless people working on this project and most of this data collection was managed by Adina Weinberger from Eran [Segal]'s lab. So this is the motivation and how we got to ask these questions.

DANNY LENNON: We can jump in anywhere you think is relevant, but maybe one of the real interesting findings that I think immediately catches people when they read that paper is looking at not only the overall trends with postprandial glucose response, but the interesting stuff that comes

out when we look at differences between individual participants in how they responded to not only certain types of foods but the same food between different people or the same individual different foods that we would think are fairly comparable at least in their carbohydrate count. So can you maybe just give people an idea of how that initial testing was done of those different test foods, what ones were used, and then maybe some of the things that caught your eye and showing that inter-individual response to different foods that may not be obvious?

DAVID ZEEVI: Definitely, but first and foremost, I think that one of the main results of this paper, one of the three main results is that there is a huge variability even in response to the same meals. So we only saw this before in very small groups, statistics were not very strong, and we want to show it in a huge cohort and we did that. So as the most controlled way to study variability, we replaced the breakfasts of all our subjects in our cohort with standardized meals, each of these meals contain 50 grams of available carbs and was provided by us, and we asked the subjects to eat one of these meals first thing each morning and gave them various instructions on how to minimize variance, for example, to avoid eating and exercising for two hours after eating. And I think the hardest thing for participants was to avoid drinking coffee in the morning because they had to consume these standardized meals without any other food, and these meals were either bread, bread and butter, glucose or fructose each with 50 grams of available carbs. And a good validation of our scientific method was that the same person would have a very similar post meal responses to the same standardized meals across different days. But across participants, we saw a huge variability in the paper. There is a histogram showing the range of responses to each and every standardized meals, and we can see that people have replicable and similar responses to the same loaf of bread or to the same drink, sugary glucose drink, but two

different people are very different from one another. And you could say that, okay, maybe responses are different but at least the order is preserved, so there could be still some foods that are categorically better than others, meaning that, well, you would expect perhaps that glucose is always worse in terms of blood glucose than bread, but even this is not the case. We saw that some people had a higher response to glucose than to bread, other people had a higher response to bread, and a minority of people had a higher response to bread and butter, but this was usually very well replicated within the same person. So one person would have a higher response to glucose, they would consistently have a high response to glucose; and we saw that not only for standardized meals but also for real-life meals, for example, for some people, bananas were better than cookies, and for others, cookies induced a low response.

DANNY LENNON: And those graphs, some of them are fascinating; if you look at individual participant numbers, I think, there's a comparison of the white bread versus glucose in an individual and then there's also a comparison of the banana and the cookie like you mentioned there; and between two different participants you see that the patterns of their postprandial glucose response, the lines look the same, but they're actually just opposite way around for those foods, like it's a completely flipped comparison from person to person, it's just crazy when you first see it.

DAVID ZEEVI: That's exactly right, and I think that this is a major take-home message for our entire discussion because what it means as a whole is that general dietary recommendations given to the public without personalization are wrong at least for some of the people. So you would construct these recommendations based on a cohort, you would take the average for the cohort, you would not look at personalization, and then for some people these recommendations would be wrong, they would

be probably okay for most people. But if you don't personalize, there will always be at least a subgroup of people for which it's not optimal, probably more than just a subgroup.

DANNY LENNON: And especially things that are taken to be logical or just taken to be true of that as someone has more carbohydrate in a meal, the expectation that people would have is that that glucose response will just get higher and higher and higher based on a linear increase in carbohydrate. But as, again, some of the data in your paper showed, for some people, that's true, you get this kind of linear relationship between carbohydrate amount in that meal and their postprandial glucose response; but for others, with increasing carbohydrate, it almost looked like a flatline for various fold increases of carbohydrate amount.

DAVID ZEEVI: That's true, yeah exactly.

DANNY LENNON: With that, that kind of first phase had these really interesting findings, and I think that individual response to not only certain foods but also to carbohydrate in general, and that difference between people was really profound. From there, things get even more interesting, which is why this paper has so much in it that you were able to use all that data that was collected and were able to start creating this meal response predictor. Can you give an overview of what that was and how it was actually built using that original data collection?

DAVID ZEEVI: We said, okay, there's a huge variability in response to food, but can we account for this variability using the things that we measured, for example, I said that we measured the microbiome, we measured blood tests, we ran some – we measured anthropometrics and so on. So the first thing we did was to look at univariate correlations, just look at correlations between people's responses to test foods and these measurements, and we found hundreds of significant correlations between blood tests

such as not surprisingly glycated hemoglobin and response to meals, anthropometrics – there was a positive correlation, for example, between BMI or hip circumference and the response to standardized meals. But also, hundreds of correlations between microbiome factors and these responses, and some of them were previously reported in the literature, for example, there's a group of genes in the microbiome that determines some functional capacity of the microbiome. These genes are called ABC transporters and they were found to be positively associated in our study with the response to all of the standardized meals, and they were previously found to be associated with type 2 diabetes. So we got some reinforcement, some corroboration of these correlations. But what we really wanted to do is to use all of this data and account for it completely by trying to predict people's responses to any given meal. We asked, in essence, can we use the information that we can find in all of these correlations between meal response and all of the variables we collected to construct a predictor which is a computational method and algorithm that would predict for any given meal people response to it.

So we trained our predictor on the cohort of 800 participants. In the predictor we used data in computational lingo, I'll try not to use a lot of it, you call that features, and we used information on the microbiome, it was about 70 something features on the microbiome, about 15 blood test features, around 10 questionnaire based features, lifestyle features such as mealtimes, stress, hunger, exercise, medication, and meal features, for example, macro and micronutrients in the meal. And combining all this information, we reached quite a good predictor for our 800 person cohort. But that was not enough, we want to – if we really want to prove that we have an algorithm that can predict people's responses, any person's responses to any given meal, what we really had to do is to collect new

participants and use this same predictor that we constructed using the 800 participants to predict their responses to meals. And we did exactly that, we collected a 100 new participants that weren't involved in the creation of the algorithm or this computational method, and we tested the predictor on them and got the exact same results. And what this as a whole means is that this predictor would be applicable to any given person, pretty applicable to any given person, meaning: it's generalizable at least as far as the Israeli population is considered. A recent study done at the Mayo Clinic used the same algorithm on the US population and got the same results.

DANNY LENNON: So, just to kind of recap for people to make sure we're all keeping up that initial 800-people cohort, you collect this ton of data that you kind of work through; using that, you're able to create this algorithm, this meal response predictor which I encourage people to go read the paper about it, because it's so incredibly cool to see of all these different features that could potentially impact that and layered into essentially all these decision trees, but this meal response predictor is created and then you took a new group of people, tested out the predictor with them to kind of validate that it works and now you've just said that it's been same, it's been validated in the US population as well. So with that, if we're all correct to that point, then this kind of sets the stage for – one of the coolest parts of this whole thing is, now, going and having this validated algorithm, you actually were able to go and do an intervention trial, were able to test out some of these ideas around personalized nutrition. Can you again talk through some of the overview of the intervention trial?

DAVID ZEEVI: Yes. So we wanted to do a short proof-of-concept trial that would show that we can use this predictor in order to design meals that would at least normalize blood glucose and you can't see much longer term effects than normalizing blood glucose on a week, but we

want to see at least that; that our predictor blindly predicting people's meals, people's responses to meals, can do well enough in this task, in reducing people's responses to food. So we collected additional participants, mostly prediabetics, it was 26 participants. We profiled them for a week, and this is the first time such a trial has been performed, so we needed to have a gold standard. And as a gold standard we used two people, a dietician Ollie and a computer scientist Stefna who were very good at looking at people's glucose responses to meals, to just look at people's data on the meals that they had using the profiling week and decide what are good meals and what are bad meals. On the other arm of the predictor, not the gold standard, we just let the predictor choose meals from, even from meals that people had not eaten during the trial. So we had one arm that was a gold standard that people looked at the responses and found which foods were better for people, and this can only be based on stuff that people ate before; and the other arm was the predictor in which it could predict from whatever set of inputs that you give it what the response of the person would be.

So we then took all of these good meals and bad meals and for each person we designed a good diet week, it's a "good diet week", we don't know... Scientifically, I'm not feeling comfortable saying good, but it was a diet that was designed to reduce blood glucose responses; and a bad diet week that was designed to increase blood glucose responses. These diets were assigned double blindedly, meaning that neither the dietitians that spoke with the subjects knew what they were giving nor did the subjects know what they were getting. And I sometimes show that it's not really easy to guess – do you want to do this exercise, I'll give you two diets and you try to guess what's the good diet and what's the bad diet?

DANNY LENNON: Sure, let's go for it.

DAVID ZEEVI: Okay, so the first diet is measly, sushi, marzipan corn and nuts and Toblerone and coffee. This was consumed throughout the entire day. The other diet is egg with bread and coffee for breakfast, hummus and pita for lunch, a snack of edamame, vegetable noodles with tofu and an ice cream.

DANNY LENNON: There's not too much in that, right?

DAVID ZEEVI: No.

DANNY LENNON: Either one of those you could make probably a case for.

DAVID ZEEVI: Yeah, so the last one was the good diet, the one with the ice cream, and it's not straightforward because ice cream is now considered good in anyway, and sushi is usually not considered bad. But in fact for this participant specifically the bad diet contained sushi and the good diet contained ice cream. And interestingly, for some foods, they were on the bad diet of some people and on the good diet of others. For example, pizza was on the bad diet of four people but on the good diet of two. So statistically speaking, with a very small, 33% chance of having pizza as a good food, and these diets worked beautifully. If you look at the paper, you can see graphs of people's glucose responses throughout the diet week, throughout the bad and good day weeks; and when you look at the bad diet week, people's responses are very high and very wide, meaning that they look almost as bad as a prediabetic response to food. But in the good diet week, it's almost normal. So just by using an algorithm, we've almost normalized people responses to food, and this is I think one of the nicest results of the trial. And just as an anecdote, one person who saw these results on themselves continued following our recommendations and even lost some weight afterwards.

DANNY LENNON: Again, I'll do a quick recap because I think it's worth going because there's so much in there. Using the algorithm, you wanted to compare that to what we can classify as this gold standard, where you would have the two experts that were there in the lab would map out what based on data you had for those participants from responses to meals that they had been prescribed, which meals had a low blood glucose response, which had a high and they would be then classified to make a good diet week or a bad diet week based on the magnitude of those responses and put those up against the prediction algorithm essentially to see if it would give just as good of a result of those differences seeing that you had the "bad diet" had significantly higher postprandial glucose response and then you had less of those glucose responses and fluctuations as well as a smaller area under the curve of those responses as well for the good diet. So after that was done, what was the kind of thinking of the plans for that algorithm of how that could be used either in further research or is there any plan for that to be able to be accessed by people more broadly, what are some of the applications that may come from that?

DAVID ZEEVI: So there's a company using this algorithm to do exactly that, to predict good and bad meals for people. The company is called Day2. I'm not involved with them, I mean, I know of them and happy that they succeeded, but I'm not really involved, so I don't really know what their algorithms are doing, but you can go to their website day2.com and see all the information. Regarding follow-up studies, I think that Eran Segal's group at the Weizmann Institute are now working on longer-term proof of concept, so not just proof of concept, longer term studies using this algorithm to show that it can maybe even reverse diabetes. I'm not sure, so I'm not going to say stuff that I'm not sure of.

DANNY LENNON: I would love to just touch on the paper that came out earlier this year, and again, with time

constraints, and just the nature and depth of the paper, will probably be only to give some very surface level discussion, so I apologize. But I just want to get to it because it was again another paper I think a lot of people will have an interest in. It was published in Nature and it looked at structural variation and they've got microbiome. So there's a lot of in-depth stuff here. So if we were to kind of, from, again an overview level, discuss what the paper is looking at and some of the key things maybe that people should know off the bat, where would we start with that?

DAVID ZEEVI: Yeah, definitely. So the motivation for this was we wanted to understand better how the microbiome exert its effects on the host in terms of metabolism. And interestingly, you and I can have the exact same microbiome in terms of who's there, but when you peer into the microbiome, when you look into the genomes of microbes, you would see tiny differences in the DNA that, for example, some regions of the DNA that exist in your microbiome we do not exist in mine. And these regions are called structural variations and they were shown to be very important because having one of these regions in your microbiome can make a microbe pathogenic, for example, a benign microbe can become pathogenic just by harboring one of these regions, it can be antibiotic resistance. It can even – so there was a study published in 2017 that showed that changing only a few genes in the microbes of a worm can extend the life span of the worm. So this looked like a good direction to look into. So could there be regions in the microbiome that are associated with metabolism, with host metabolism? So we developed an algorithm again, we're computer science people, we studied the different variable regions of the microbiome; and we tried to correlate them with host disease risk factors, for example, BMI, body weights glucose throughout the entire test week, age, total cholesterol, HDL cholesterol, and we found a bunch of

correlations between a lot of these regions and a lot of risk factors.

I'm skipping through a lot of the papers, so if people are interested, they can, of course, read it and drop me a line on Twitter, I will be happy to answer questions. But I'll just give you an example of one region that we found that was associated with disease risk. So this region is deleted in about 40% of the people, it exists in the microgram of about 60%. It's not very long, but it's very strongly associated with disease risk factors. People who have this region are on average 13 pounds thinner than people who don't have this region. They have almost a two-inch slimmer waist, they have lower BMI, they have a higher HDL cholesterol, so they are overall more metabolically healthy. And when you look into that region to look at what genes on this region are doing, so they're taking up sugar from the gut and they're turning it into butyrate, and butyrate is what we call a short chain fatty acid and its strongly associated with decreasing inflammation and better metabolism of the host. So this is of course not proof that this is what this region does and how it exerts its effect on the host. It could be circumstantial. It could be a lot of things. But we have suggested a mechanism just by looking at variable regions in the microbiome, and this could help us, in the future, design microbes that really act to improve host metabolism. This is where we think this is going.

DANNY LENNON: So if there was kind of a couple of takeaways from that you think are the most interesting, and again it could be just repeating some of the things you just mentioned, what would be the few things you'd point out to people that are of most importance or relevance from that paper do you think?

DAVID ZEEVI: Well, that one that there is widespread variability in response to food. We are all individuals, as Monty Python said. Two is that, using machine learning, we are able to account for this variability and predict personal

responses to food. And three, that using these personalized predictions, we can maybe design diets that would lower people's responses to food, and also, maybe in the long run, assist with weight management and disease management. The last thing is that if we want to examine the microbiome regions that maybe responsible for these effects, we can peer into variable regions and expose purity of mechanisms that may affect these responses to food through the microbiome.

DANNY LENNON: And David, for people who are looking to find you online on Twitter, any of your work on the Internet, where would you direct their attention to?

DAVID ZEEVI: Yeah, sure. So you can follow me on Twitter, it's DaveZeevi on Twitter, one word. My website is zeevi.science, and you're welcome to DM me on Twitter if you have questions, I love questions.

DANNY LENNON: Great, and for everyone listening, I will link up to all those places that David has just mentioned as well as linking to both of the papers that we brought up in today's discussion. And so, David, with that, that brings us to the final question that I always end the podcast on, and this can be completely divorced from anything we've discussed today and can be to do with any topic in general, and it's simply: if you were to advise people to do one thing each day that would have a positive impact on any area of their life, what would that one thing be?

DAVID ZEEVI: Use less plastic.

DANNY LENNON: I like it man, and a great way to finish off this conversation, you've been incredibly kind with your time. I've really enjoyed talking through some of this, especially, after having read the work that you've put out, and I just want to say thank you for coming on the podcast, and thank you for doing all the work you've done and the contributions you've made.

DAVID ZEEVI: Thanks so much for having me.