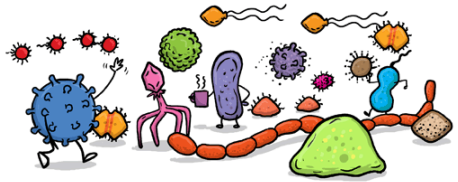
Towards Personalized Medicine Based on the Gut Microbiota

Eran Segal
Weizmann Institute of Science

: **@segal_eran**
Lab site: **http://genie.weizmann.ac.il**


Diabetes
Obesity
Asthma
Mental illness
Neurodegeneration
Cancer
Hypertension
Depression
Cardiovascular disease
Autoimmune disease
Allergies
Drug metabolism

MICROBIOME ORIGIN



Rothschild et al., **Nature** 2018

PERSONALIZED NUTRITION

Zeevi et al., **Cell** 2015
Korem et al., **Cell Metab.** 2017

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MULTIPLE SCLEROSIS

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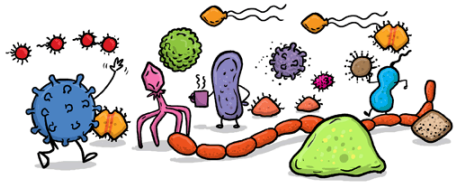

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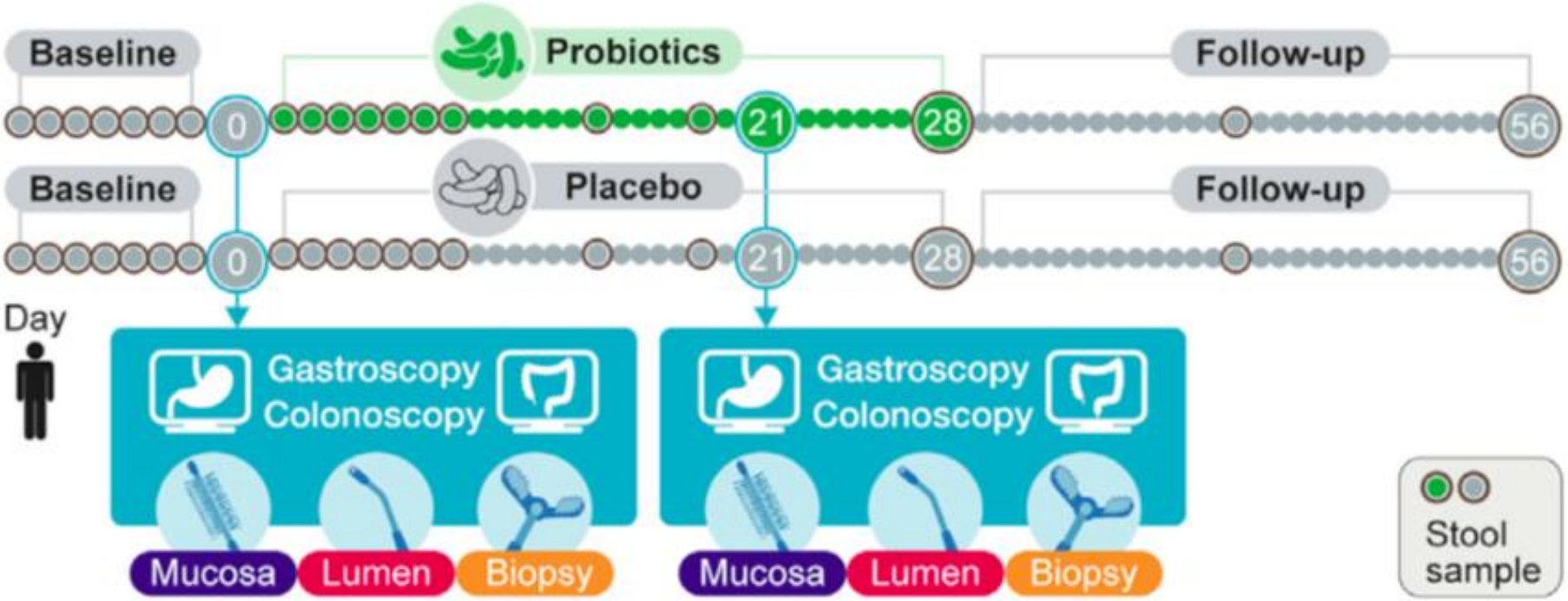
Levi et al., in preparation

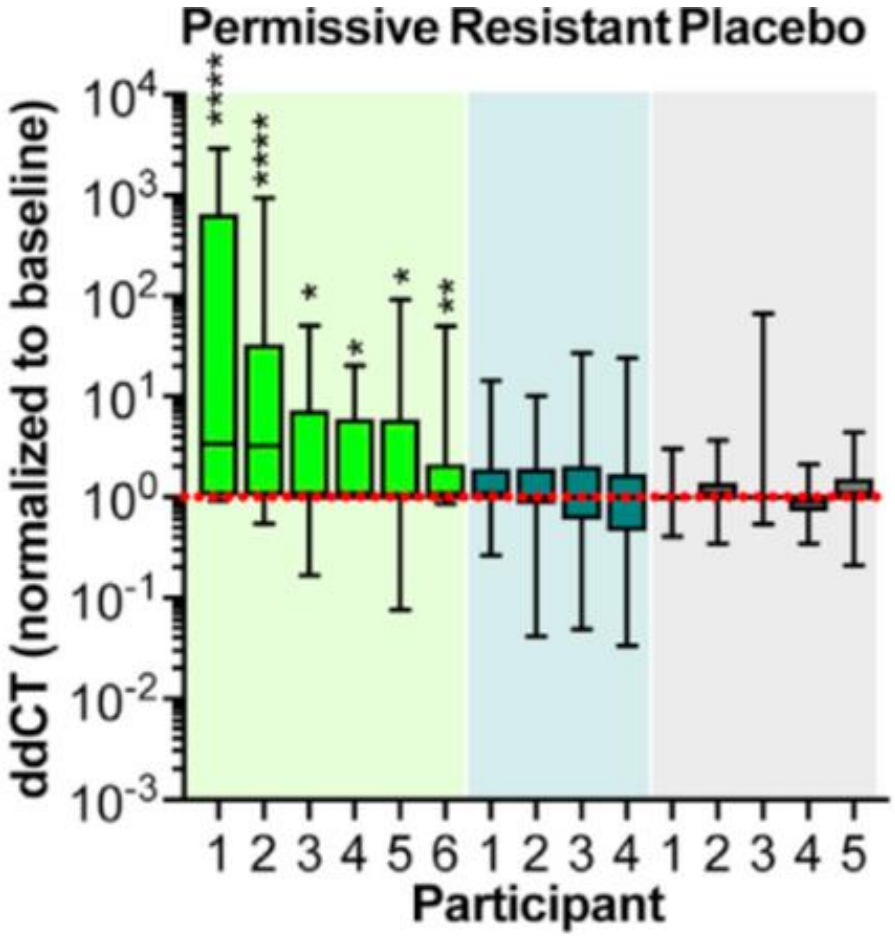
Do probiotics colonize the human gut?

Invasive microbiome profiling along the human gut following probiotic intake



Zmora *et al.*, Cell 2018

Probiotic colonization differs across individuals



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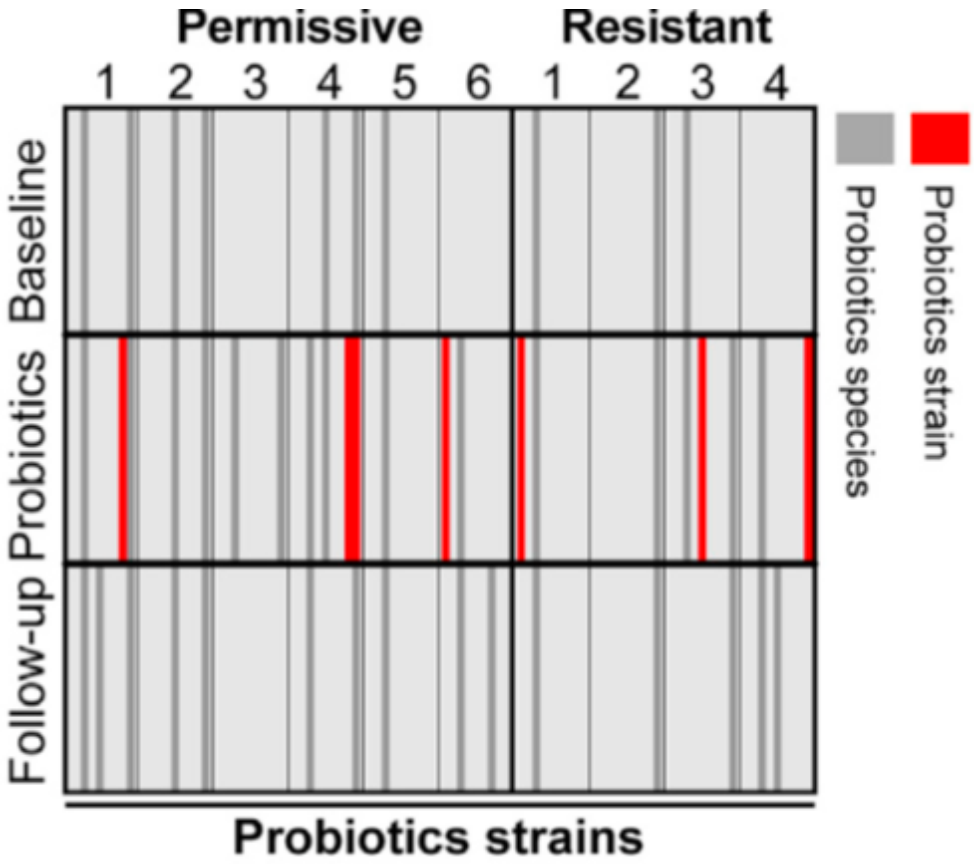
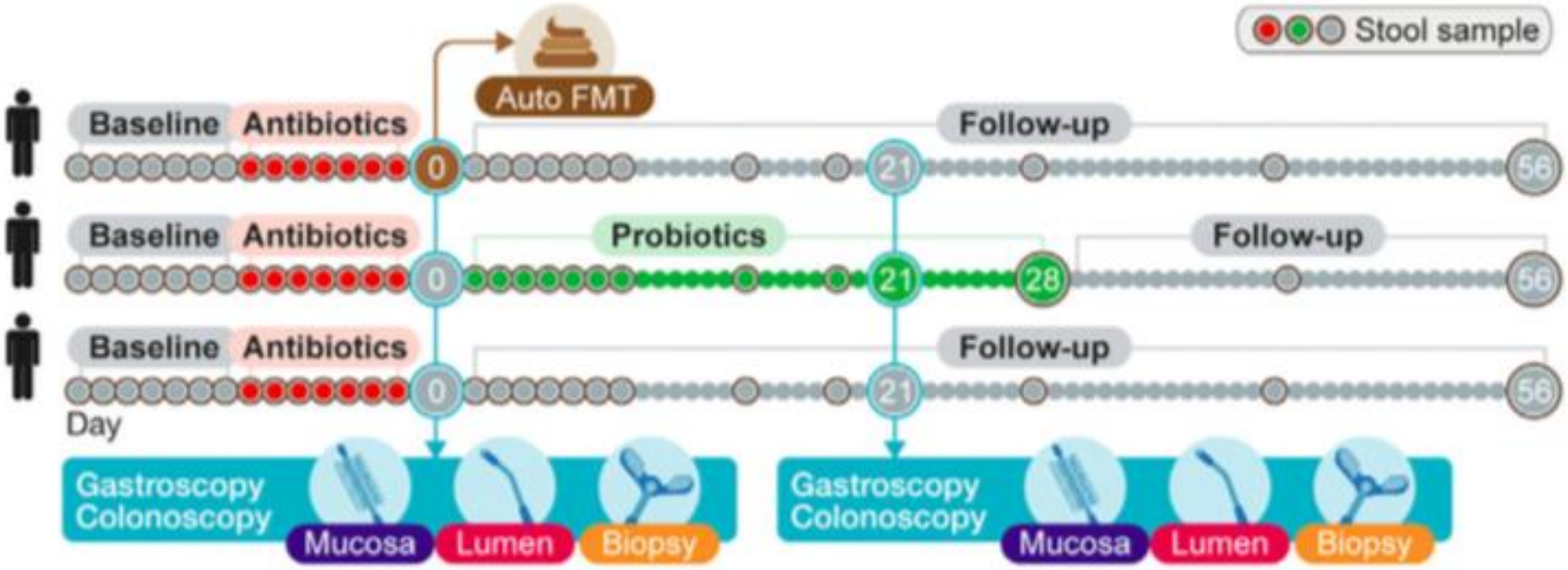


Zmora *et al*., Cell 2018

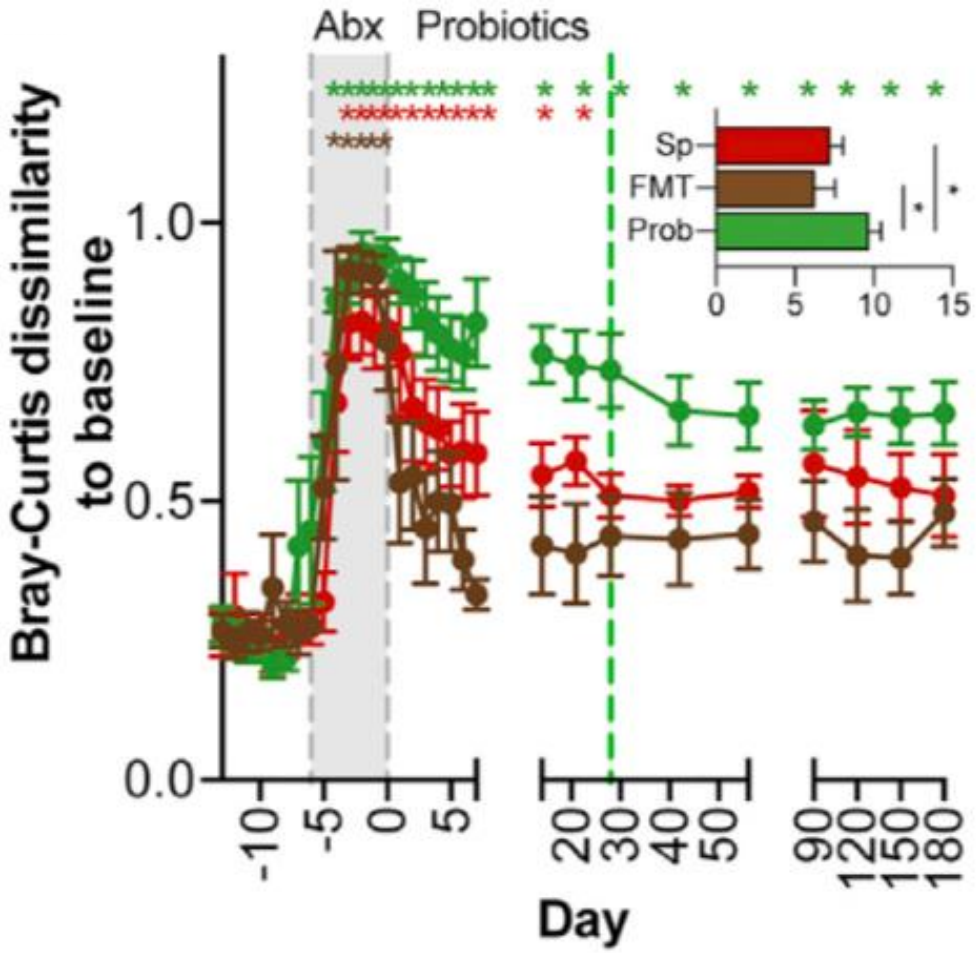
Do probiotics impact microbiome reconstitution after antibiotics?

Invasive microbiome profiling along the human gut following recovery from antibiotics



Suez *et al*., Cell 2018

Probiotics delay microbiome return to baseline after antibiotics



Suez *et al*., Cell 2018

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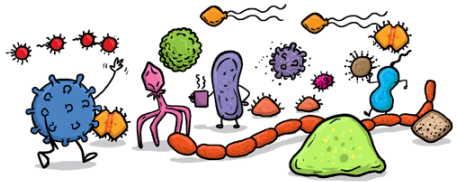

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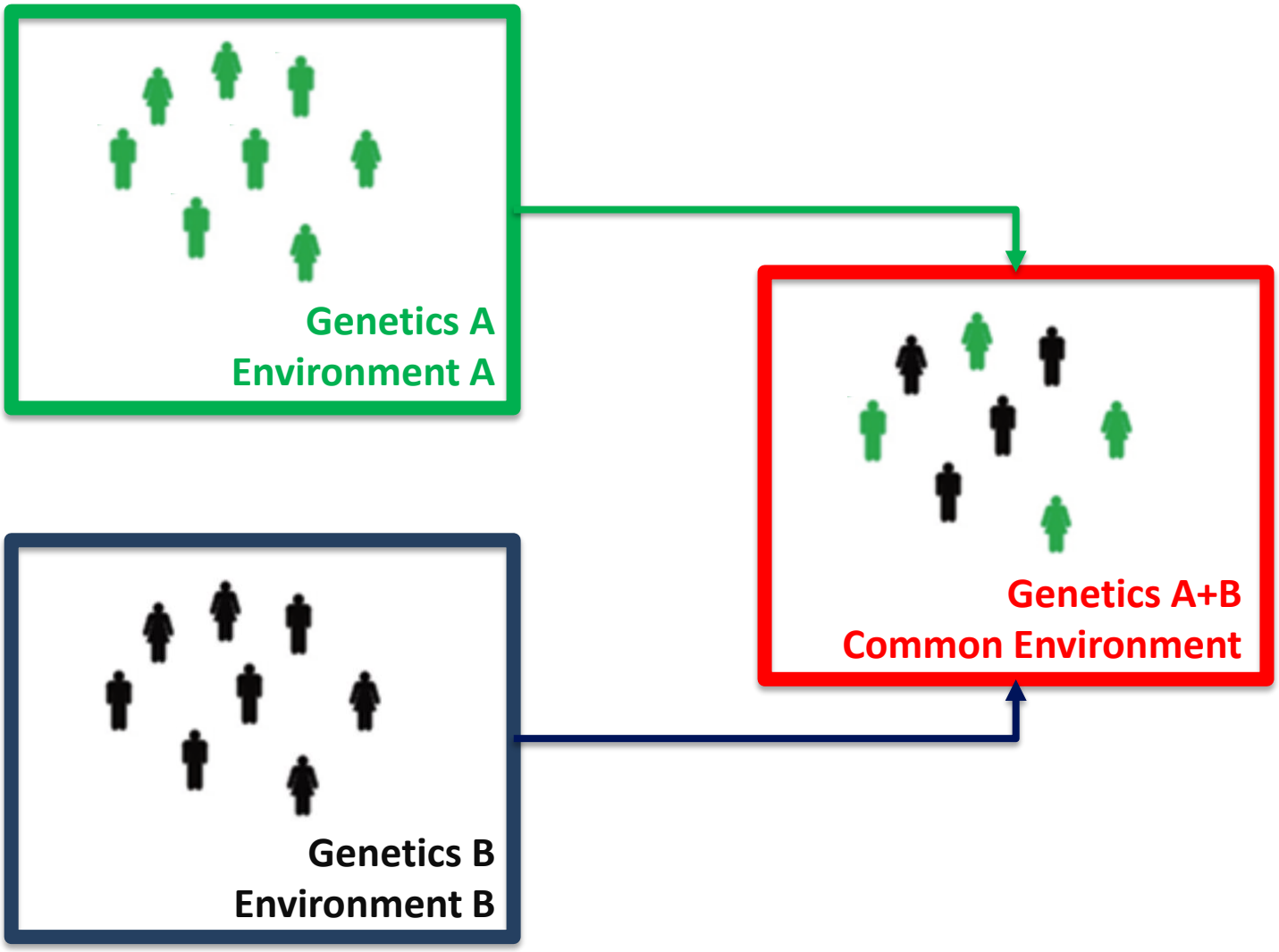
Levi et al., in preparation

Nature or Nurture: What determines our microbiome composition?

Idealized experimental setting for distinguishing the effect of genetics and environment



Rothschild, Weissbrod, and Barkan *et al*., Nature, 2018

Israel is ideal for experiments aimed at distinguishing the effect of genetics and environment

- **Genetically diverse (**most Jewish population arrived over last 100 years)
- **Environmentally homogeneous** (relatively)

Ashkenazi

Sephardi

North African

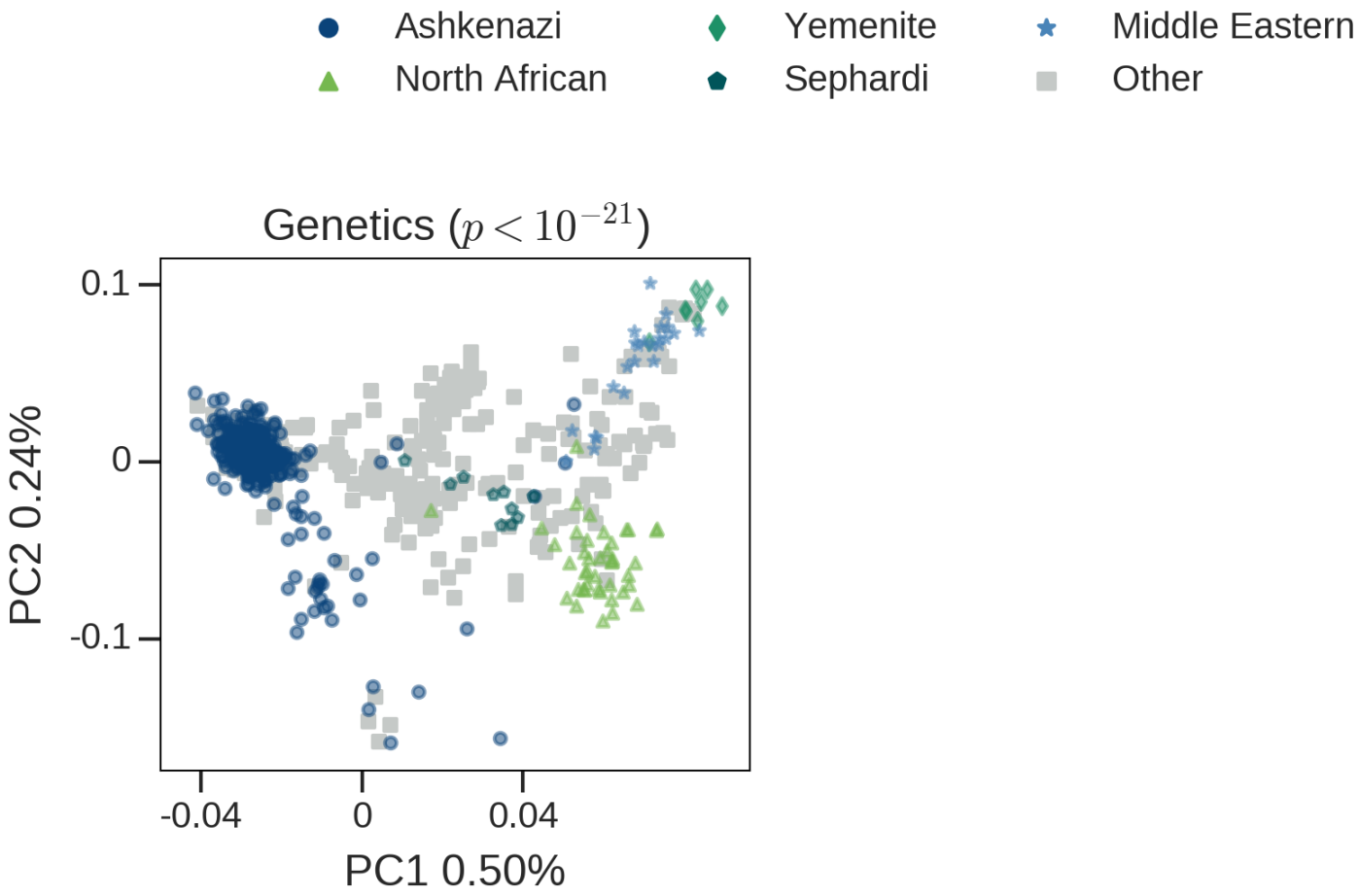
Middle Eastern

Yemen

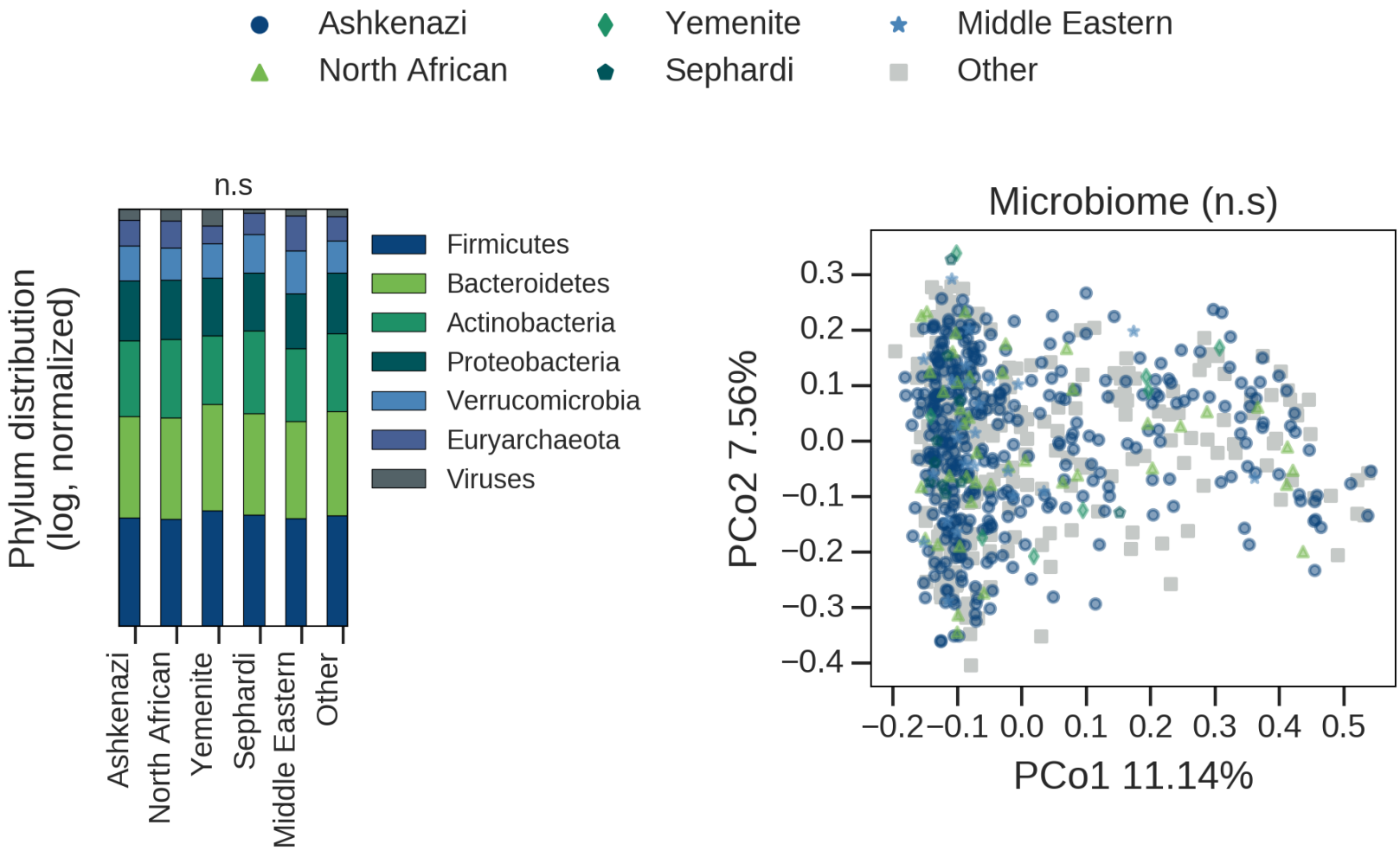
Rothschild, Weissbrod, and Barkan *et al*., Nature, 2018

Do ancestrally similar individuals have more similar microbiome compositions?

Ancestry is not associated with microbiome composition



Ancestry is not associated with microbiome composition



Rothschild, Weissbrod, and Barkan *et al.*, Nature, 2018

Biome-Association Index: Association of microbiome and host phenotypes after accounting for host genetics

Phenotype = genotype effect + microbiome effect + environmental effect (noise)

Phenotype	Biome-explainability Israeli cohort |	Genetic heritability (literature)
HDL	35.9% ***	23.9% - 48%
Lactose cons.	35.5% ***	N/A
Waist circ.	28.8% ***	15% - 24%
Hip circ.	27.1% ***	10.6% - 27%
Glycemic status	24.5% ***	N/A
BMI	24.5% ***	14% - 32%
WHR	23.9% ***	12% - 14%
Fasting glucose	21.9% ***	9% - 33%
HbA1c%	16.1% *	21% - 32%
Creatinine	12.3% *	19% - 25%
Height	3.2%	33% - 68%
Total Cholesterol	0%	14% - 53%

Biome-association levels are comparable to genetic heritability estimates based on thousands or tens of thousands of individuals

Rothschild, Weissbrod, and Barkan *et al*., Nature, 2018

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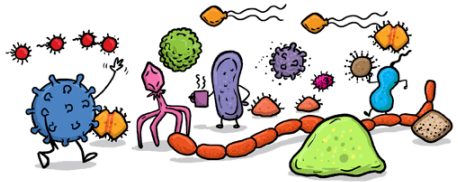

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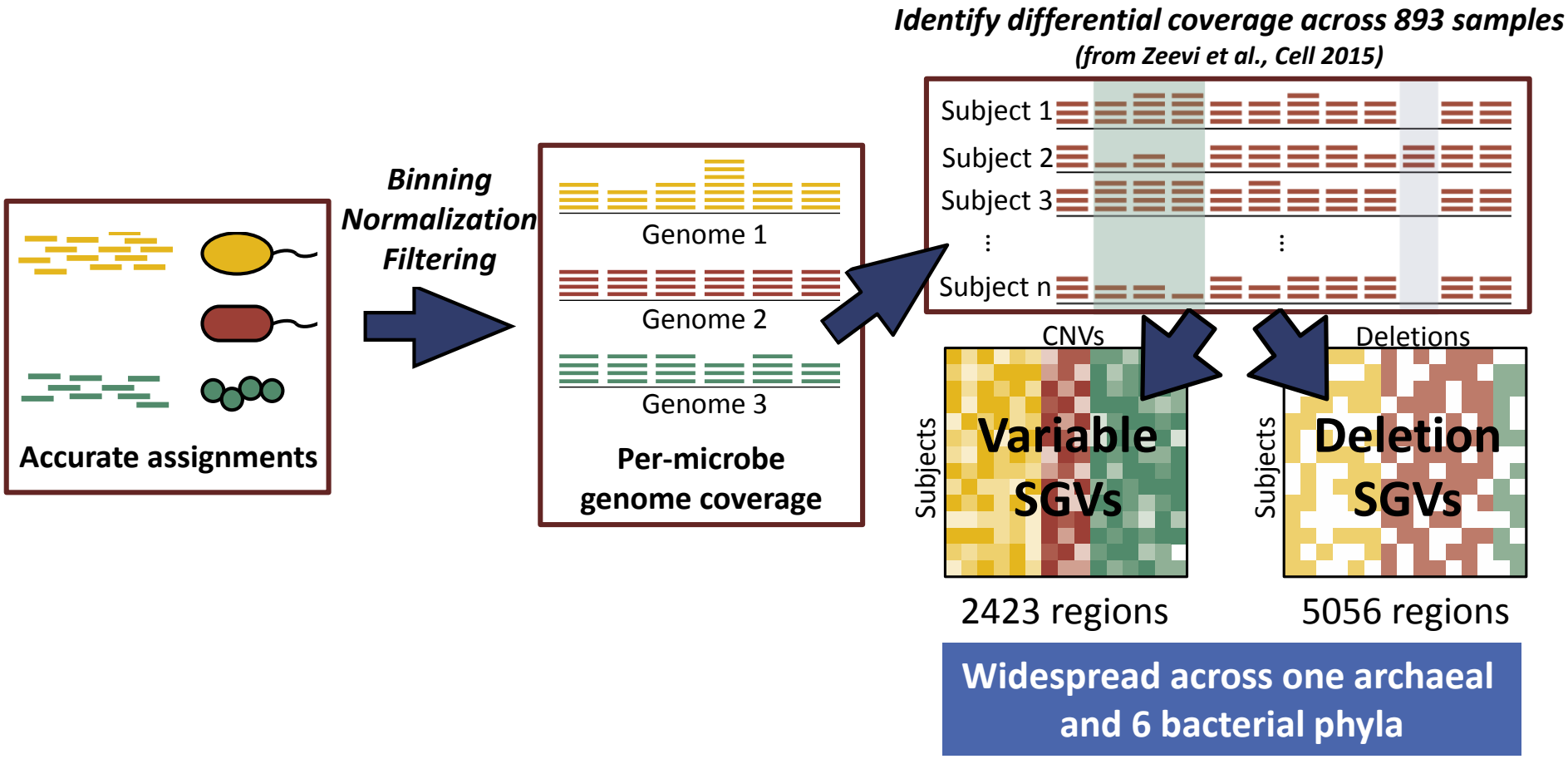
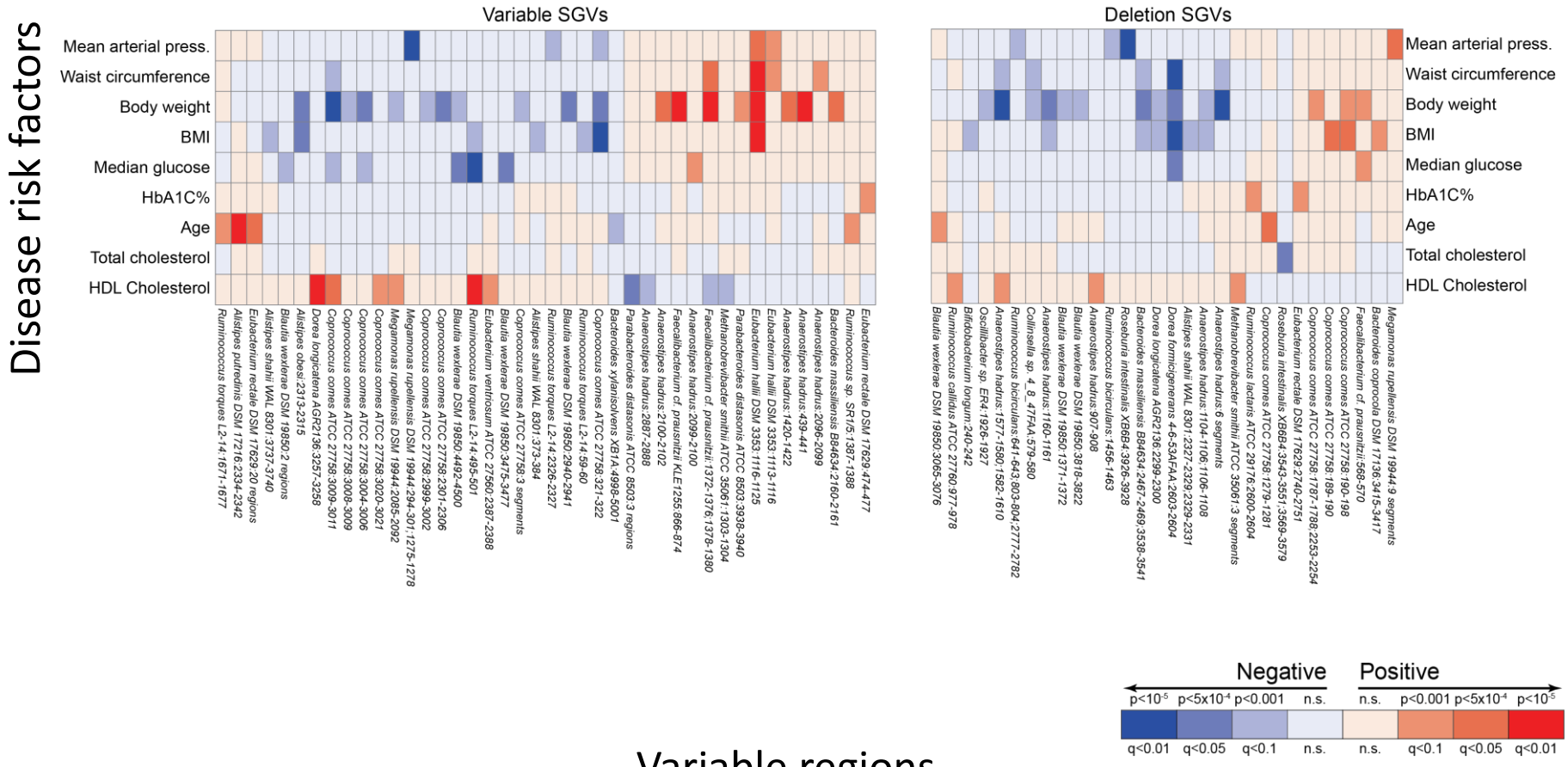
Detecting microbiome Sub-Genomic Variability (SGV)



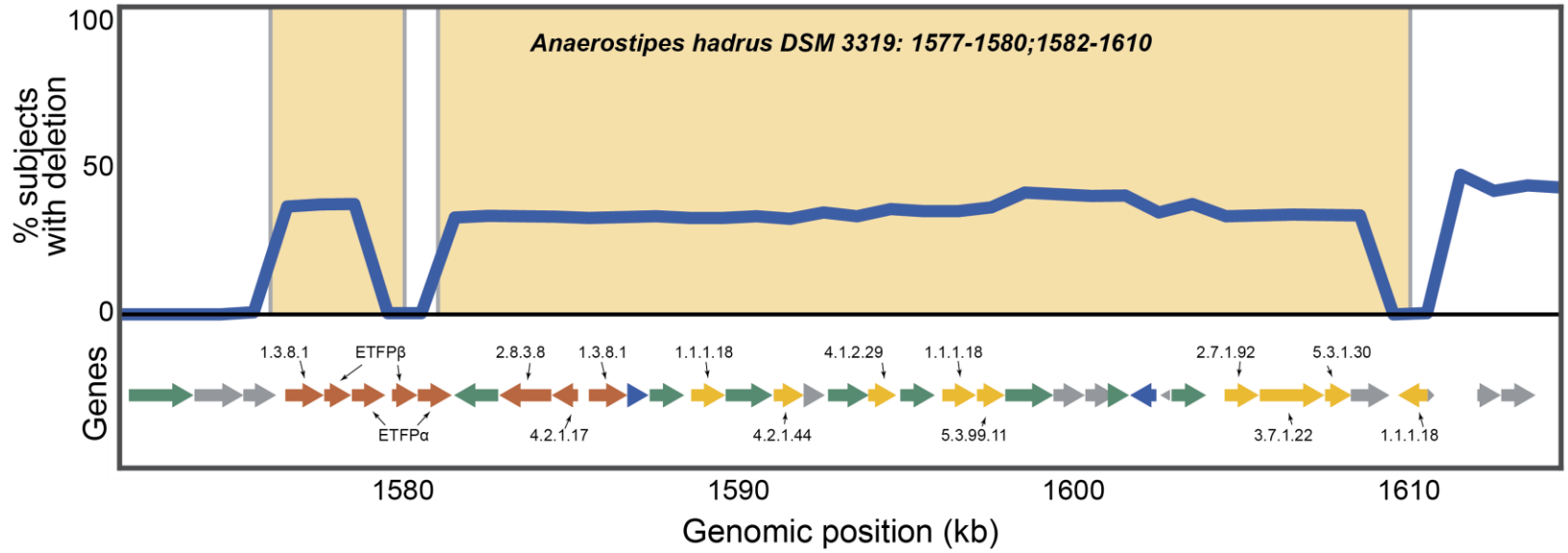
Zeevi and Korem *et al.*, unpublished

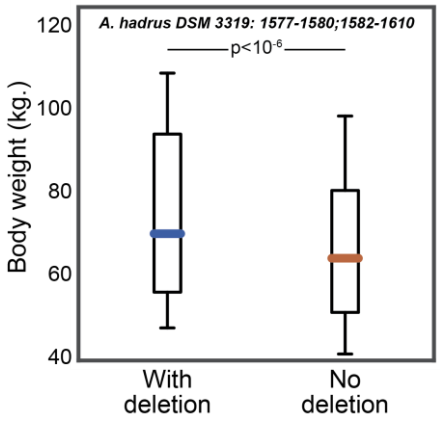
Variable regions associate with disease risk

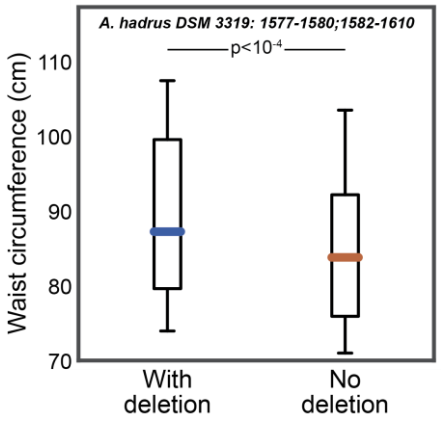


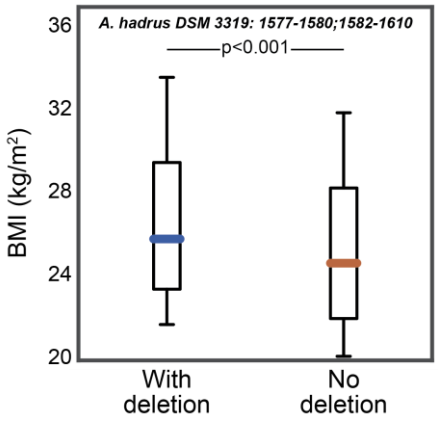
Zeevi and Korem *et al.*, unpublished

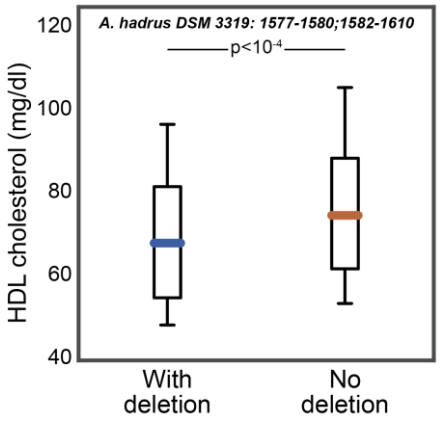
Deletion of a single region involved in butyrate production associates with an increase of 6kg in body weight











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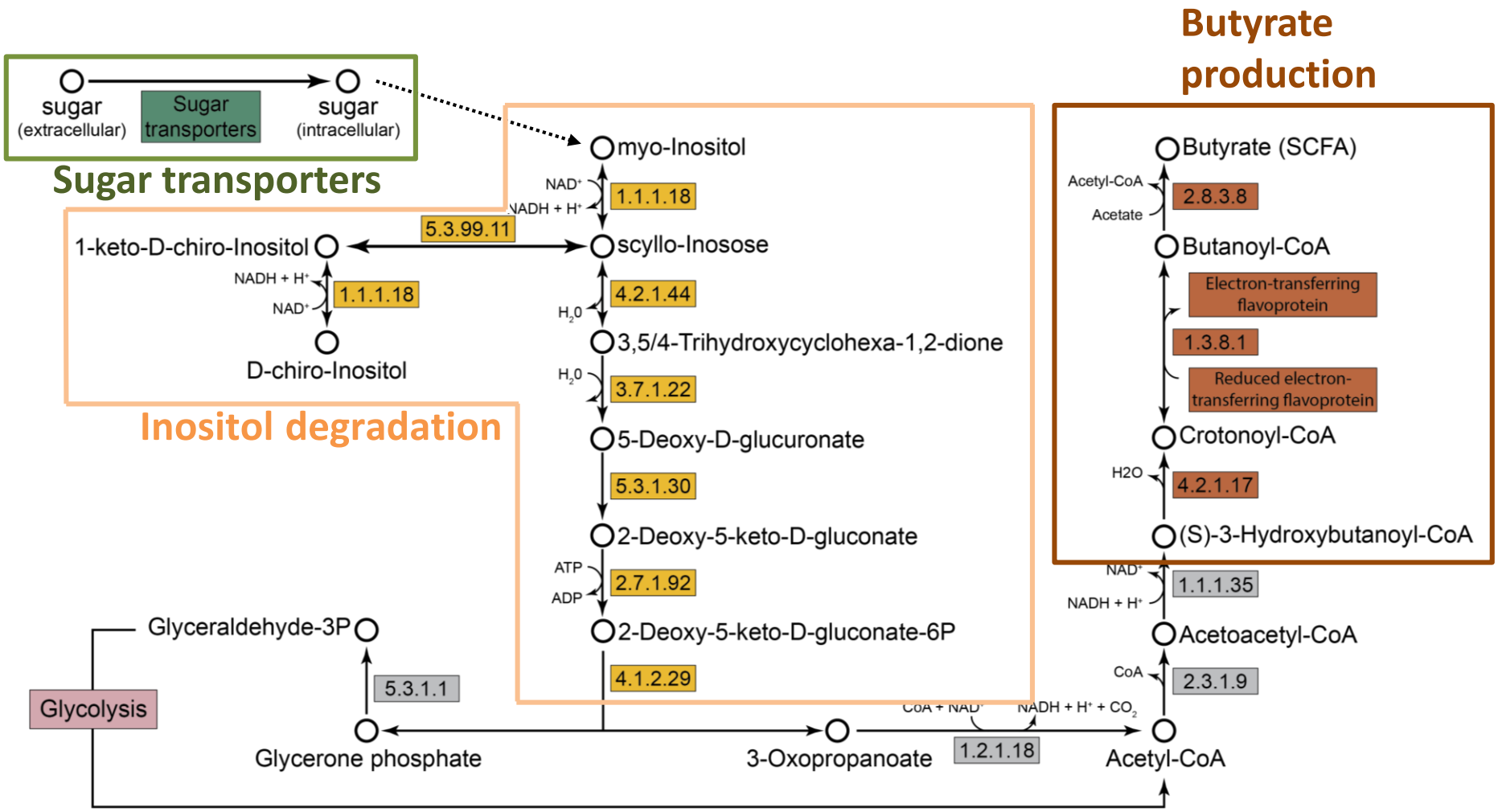
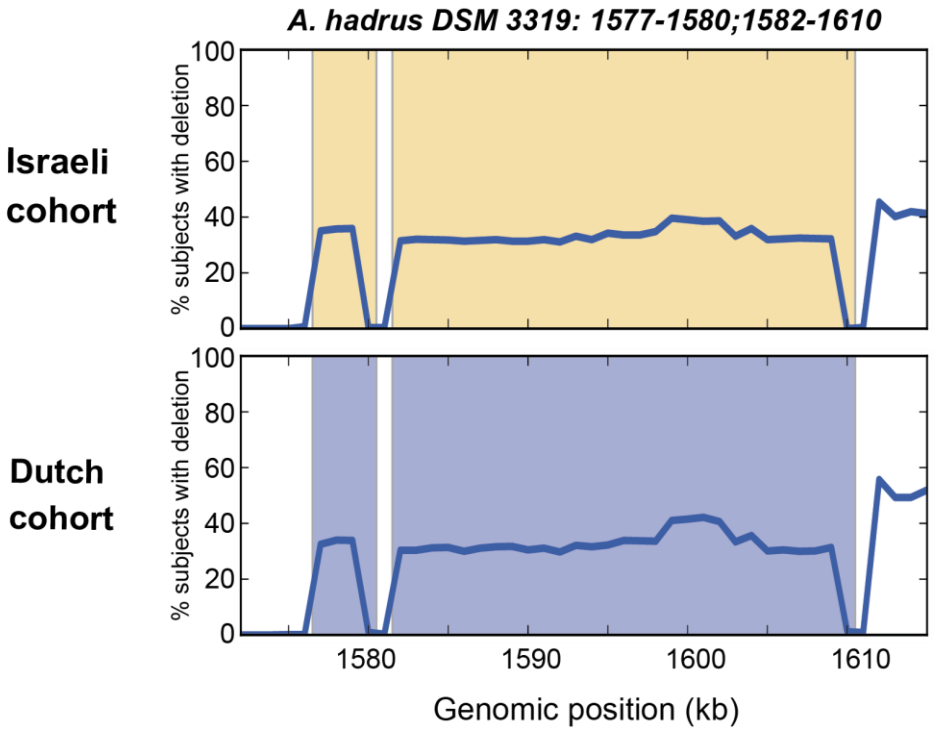
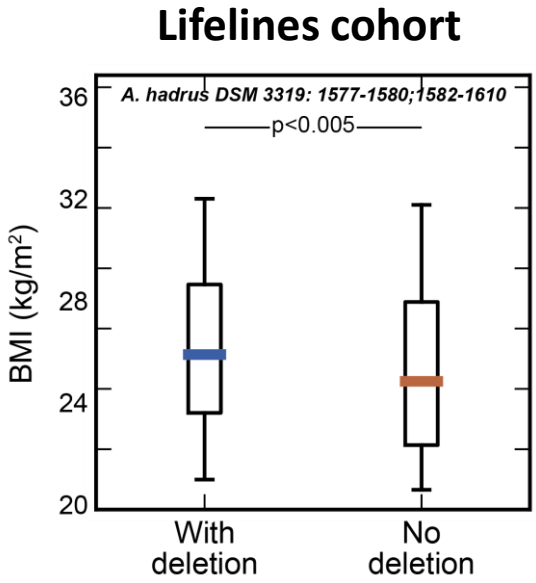


Zeevi and Korem *et al.*, unpublished

Association of butyrate producing region with BMI fully replicate in Dutch Lifelines cohort

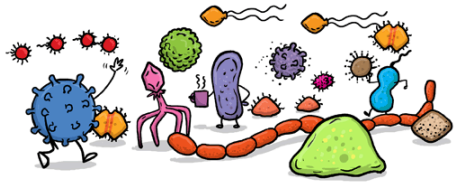




Zeevi and Korem *et al.*, unpublished

Lifelines cohort: Zhernakova et al., Science 2016

MICROBIOME ORIGIN



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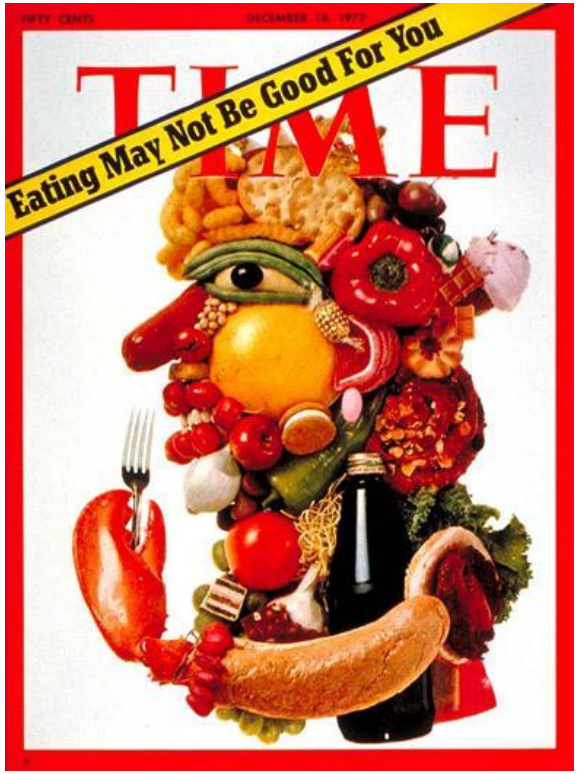
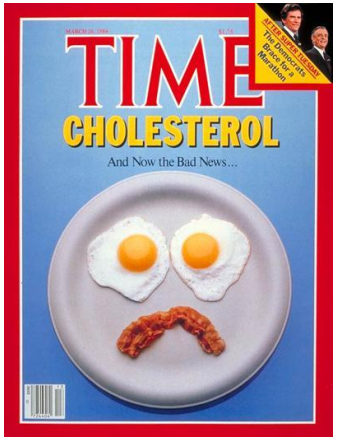
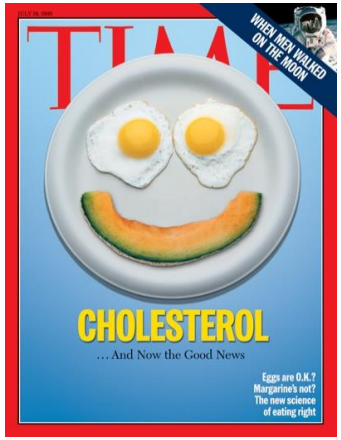
What is healthy nutrition?



1972



1984



1999

2002

2003

2011

2014

Is cholesterol good for you?

Is cholesterol bad for you?

Should you eat less fat?

Is a low carb diet healthy?

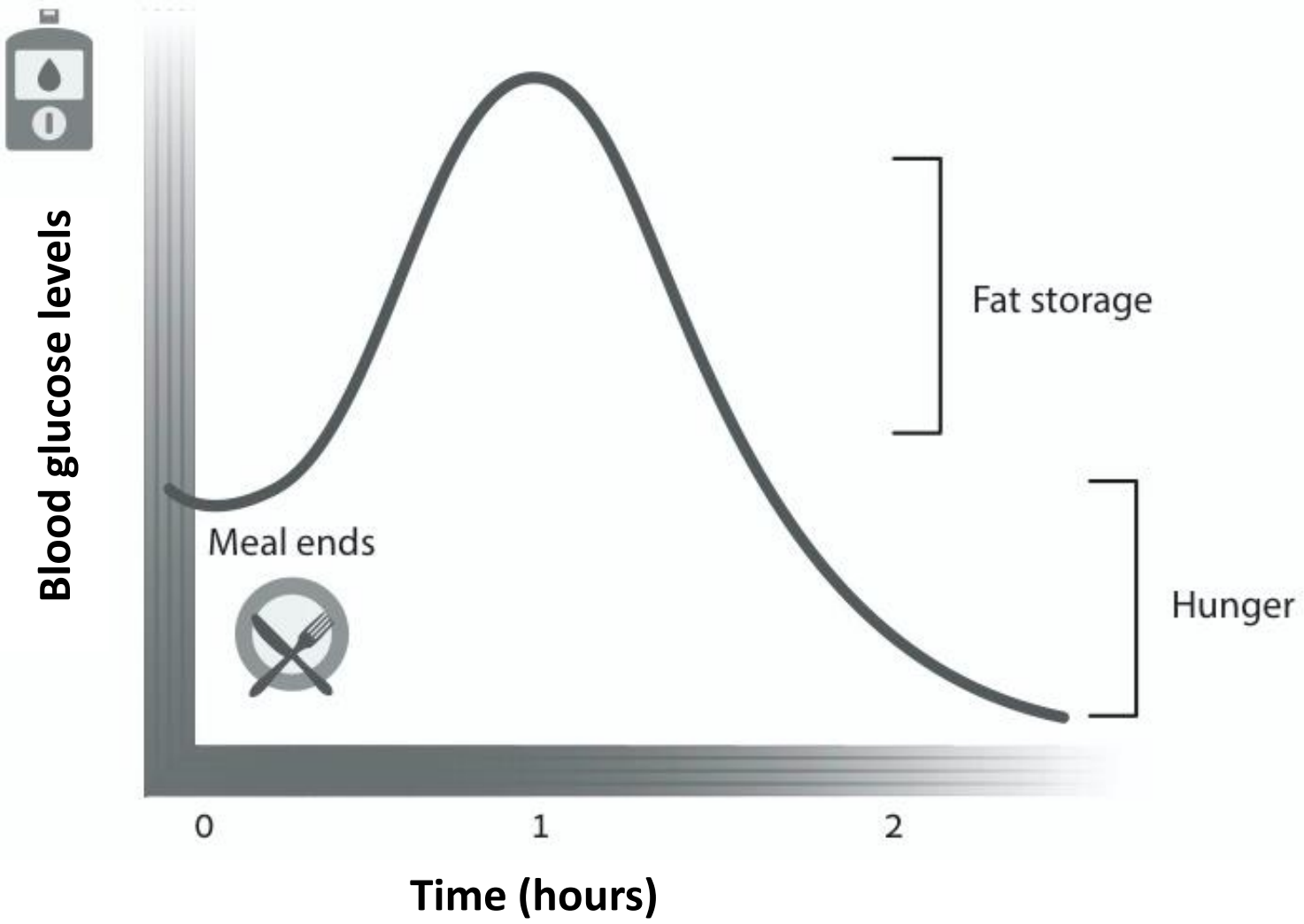
Should you be a vegetarian?

Should you eat butter?

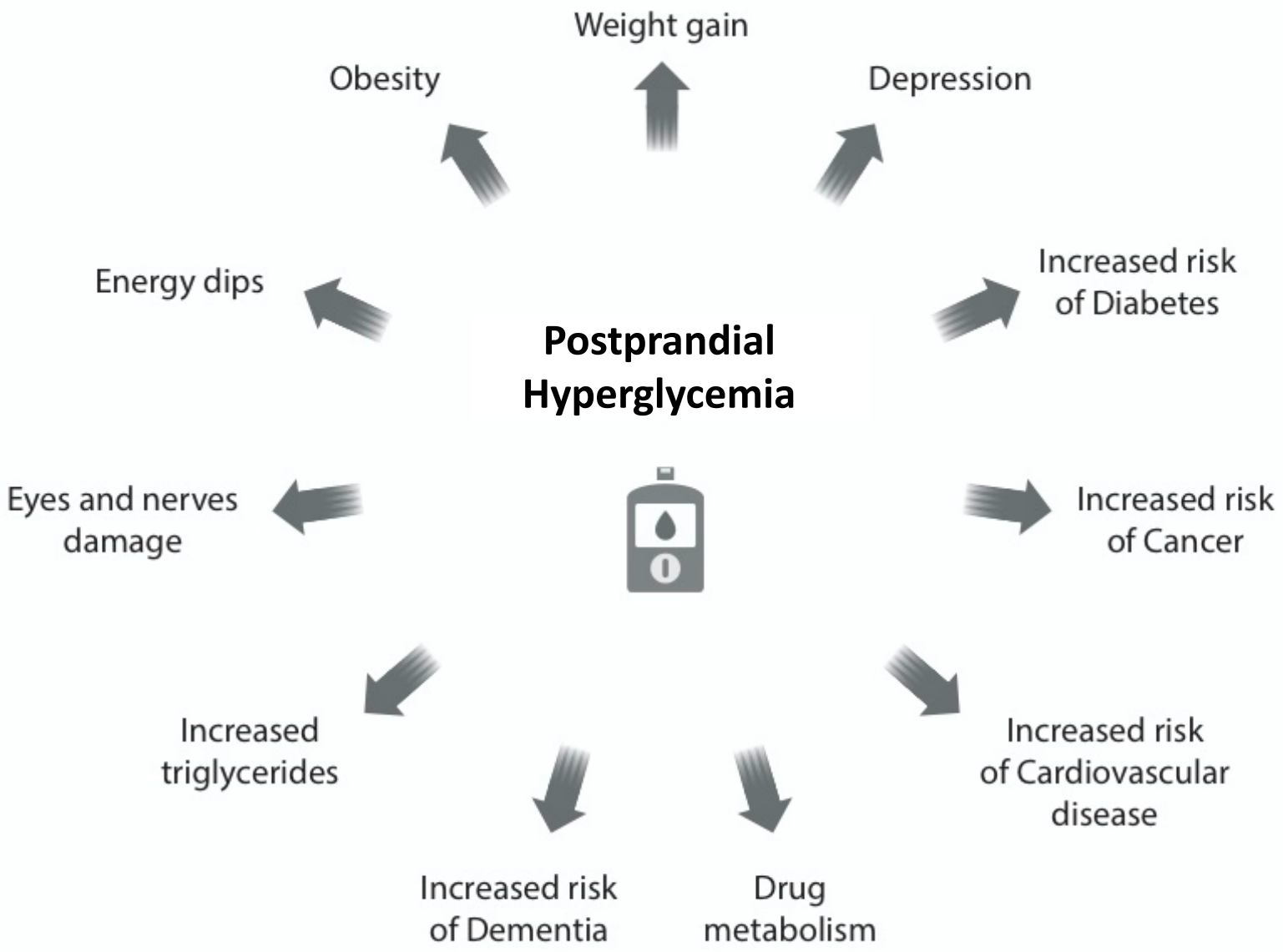
Are dairy products good?

How much sugar should you eat?

Postprandial (post-meal) glucose response



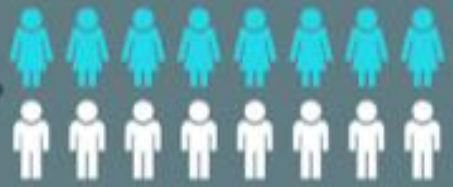
Zeevi *et al.*, Cell 2015



Zeevi *et al.*, Cell 2015

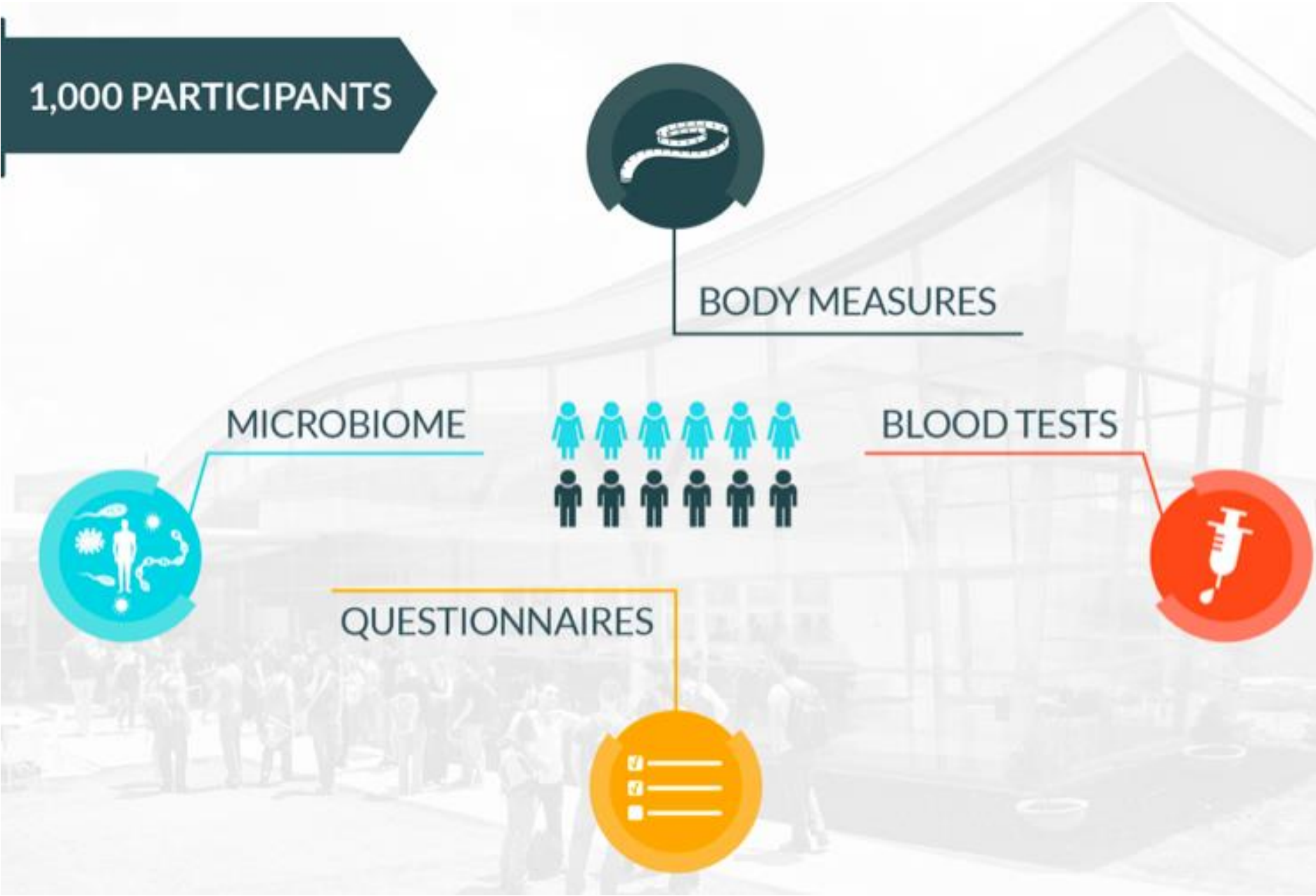
THE PERSONALIZED NUTRITION PROJECT

1,000 PARTICIPANTS



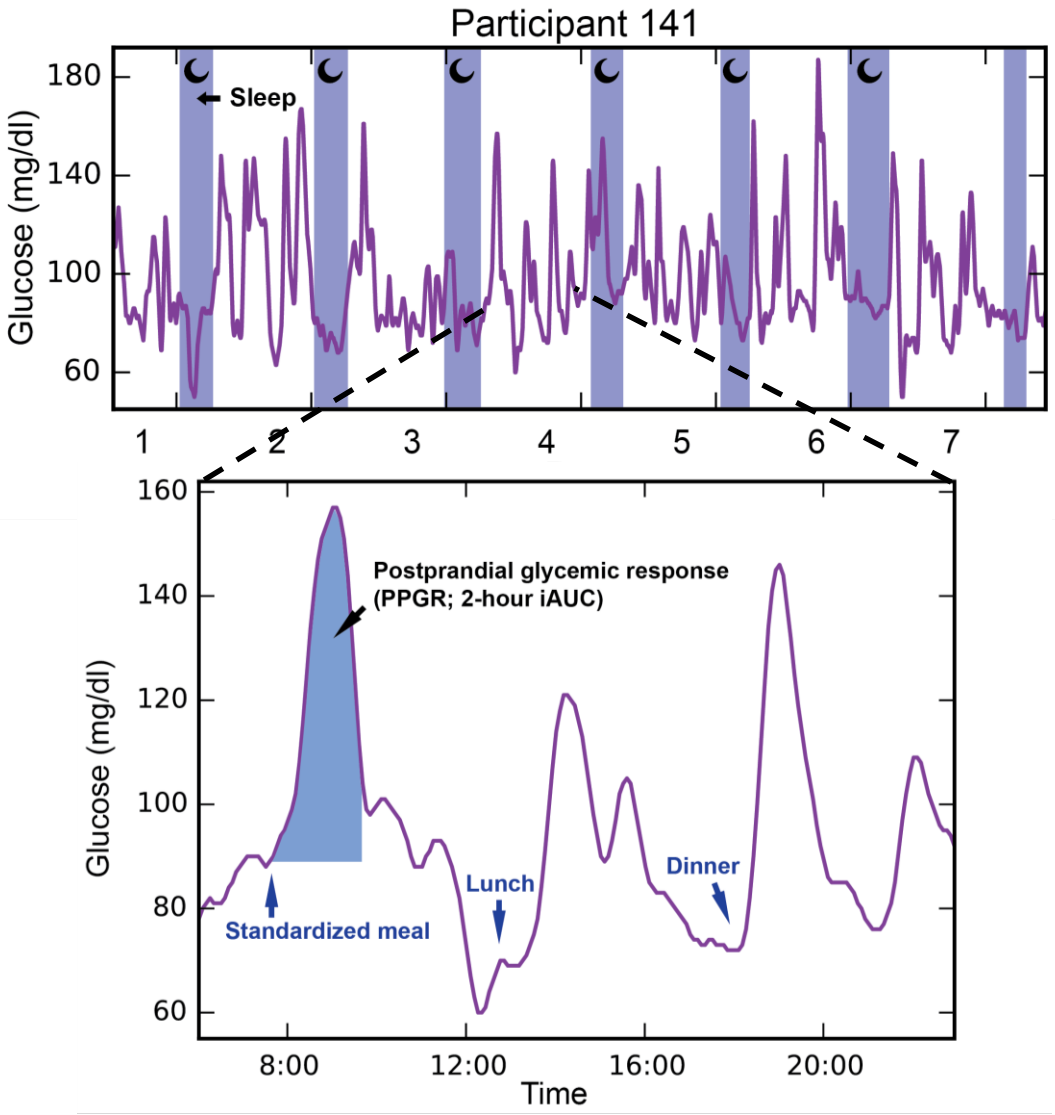
50,000 MEALS

2,000,000 GLUCOSE MEASUREMENTS



Zeevi *et al.*, Cell 2015

Continuous glucose monitoring

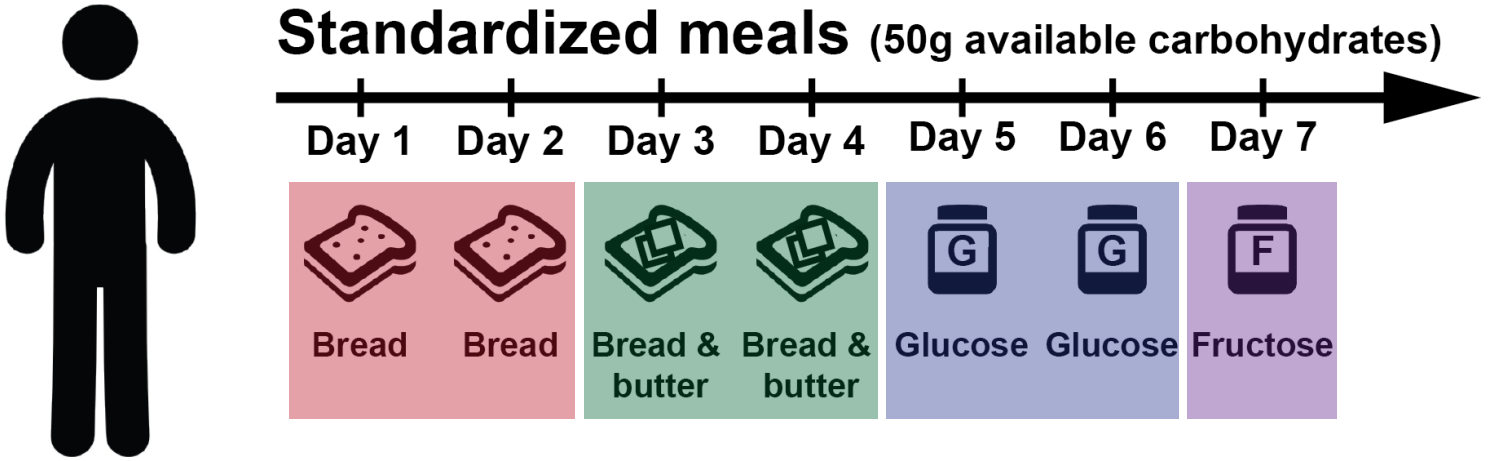


Zeevi *et al.*, Cell 2015

What is the response of different people to the same food?

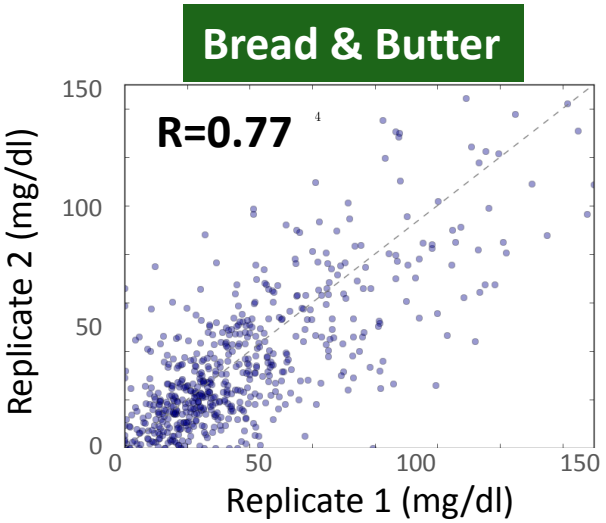
Testing the cohort response to standardized meals

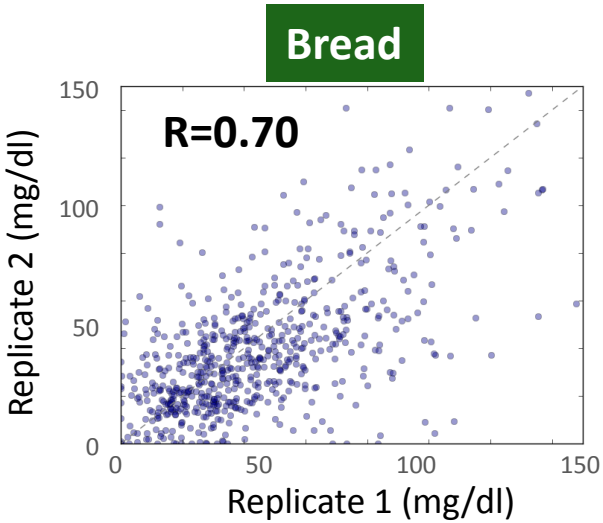
800 x

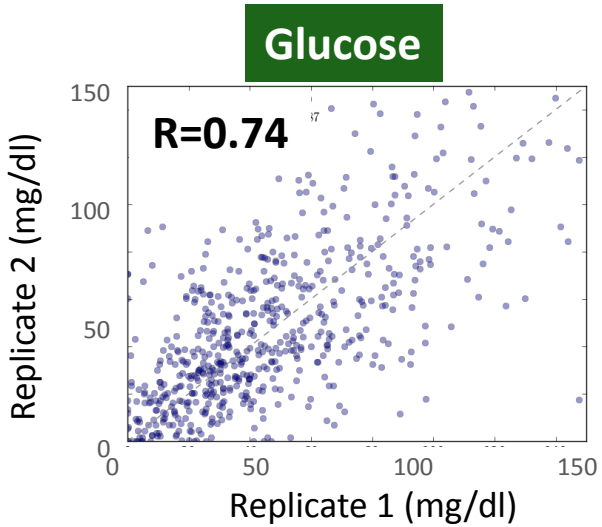


Zeevi *et al.*, Cell 2015

The same person has a highly similar post-meal response to identical meals across different days



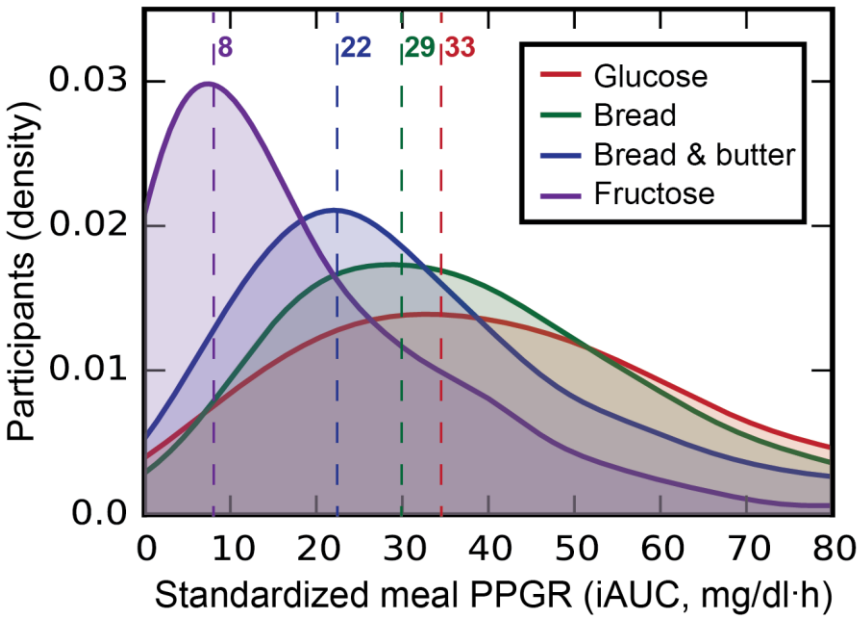




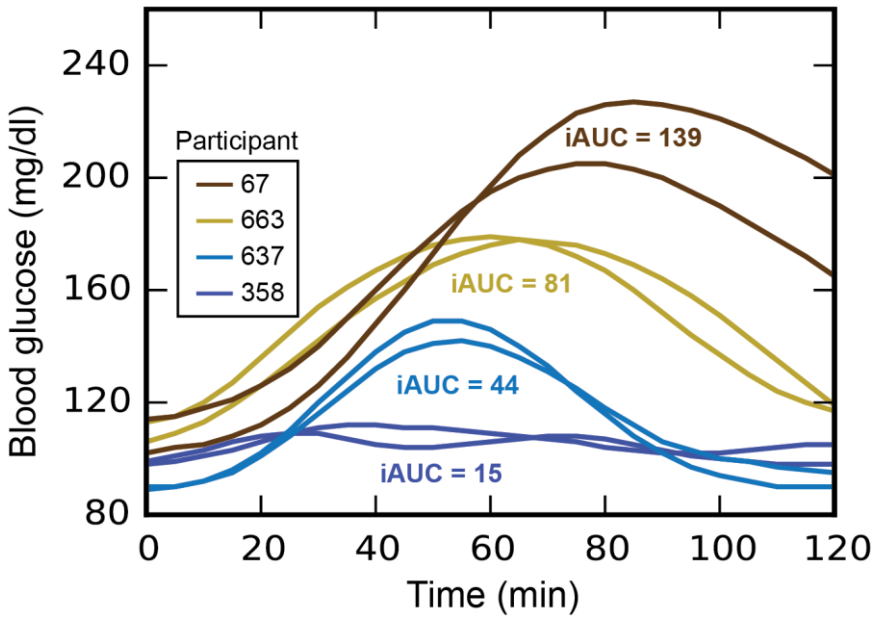
Zeevi *et al.*, Cell 2015

Different people have widely different post-meal responses to identical meals

Population Responses to Standardized Meals



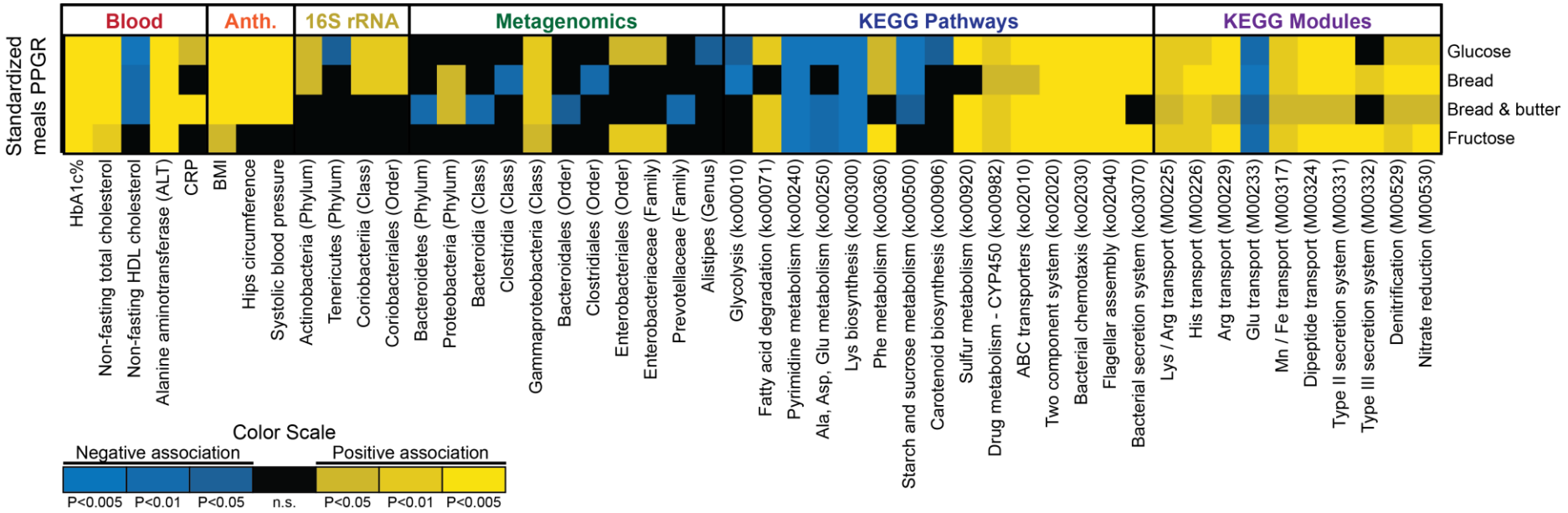
Four Individual Responses to Bread



Zeevi *et al.*, Cell 2015

What explains the variability in people's response to the same food?

Variability in post-meal glucose response across people associates with microbiota composition and function

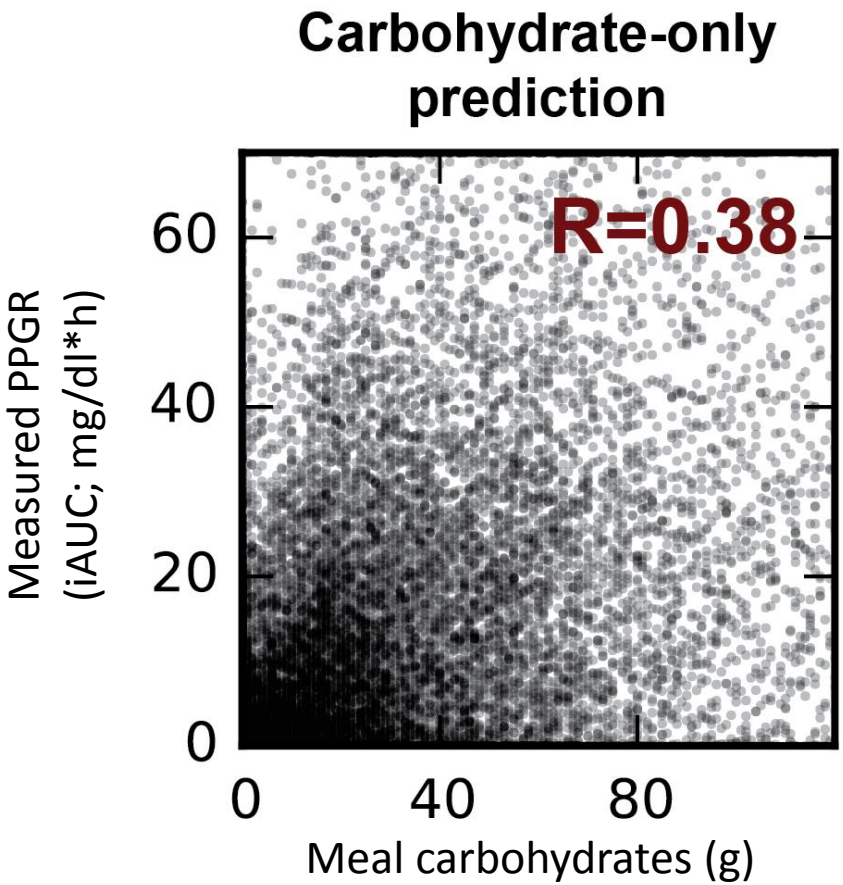


Zeevi *et al.*, Cell 2015

Can we predict the personal post-prandial glucose response to any complex meal?

Meal Carbohydrates: State of the art in predicting post-meal glucose responses

State of the art



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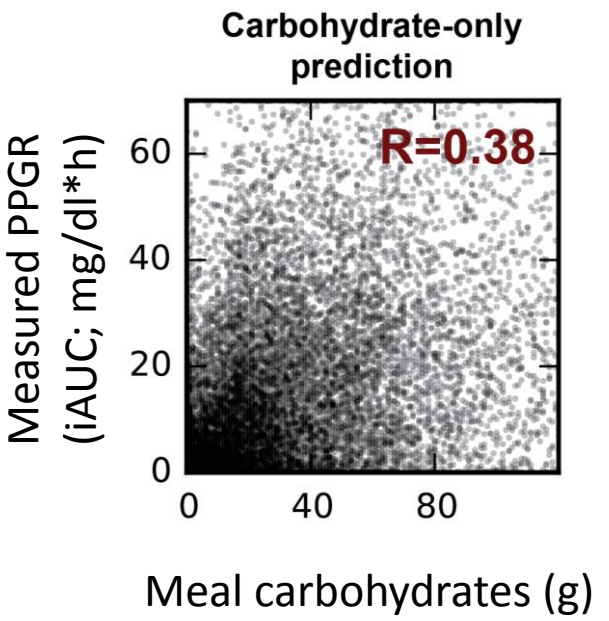
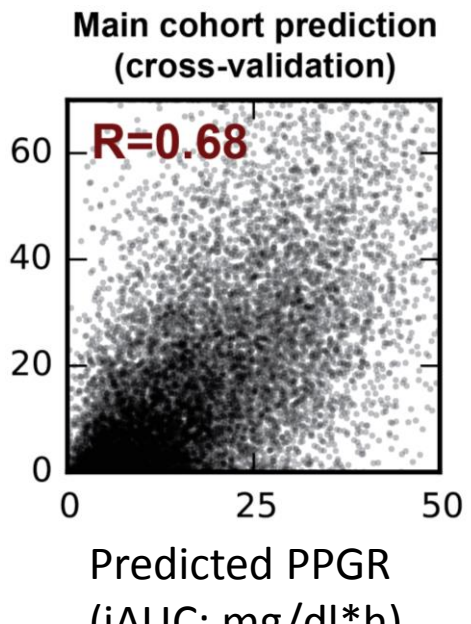
Accurate predictions of personalized glucose responses

State of the art



Our prediction
800 participants



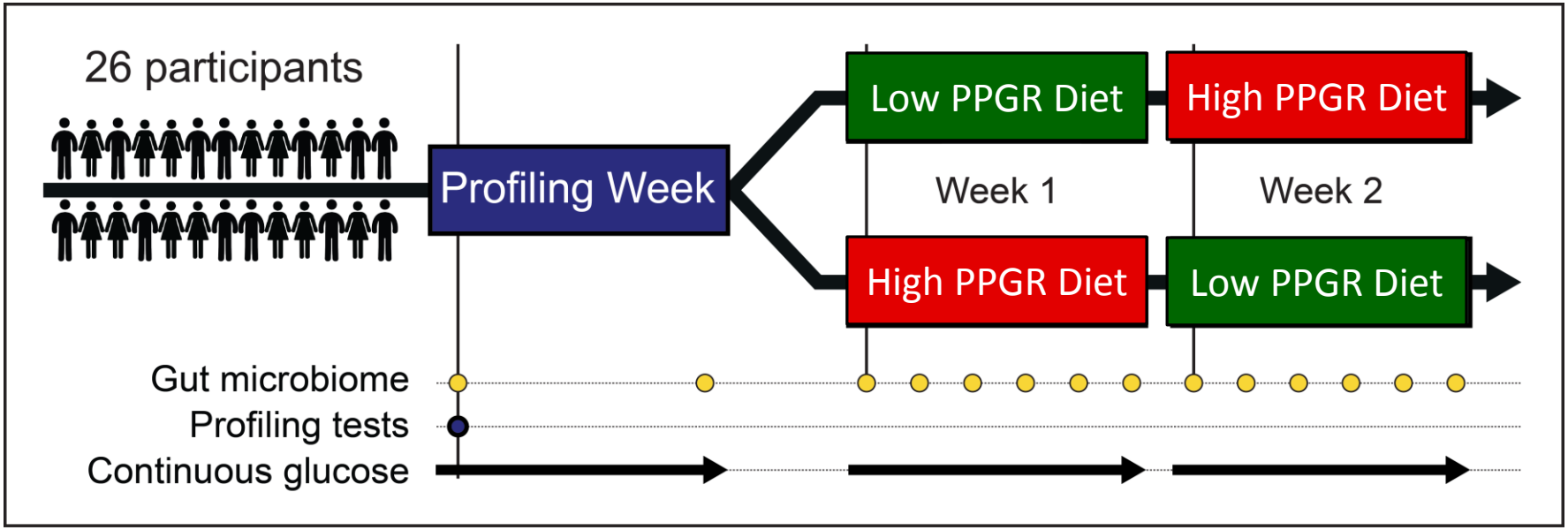
Prediction validation
100 participants

Predicted PPGR
(iAUC; mg/dl*h)

Zeevi *et al.*, Cell 2015

Can personally tailored dietary interventions improve post-prandial glucose responses?

Constructing personally tailored diets that target postprandial glucose responses (PPGR)



Zeevi *et al.*, Cell 2015

Can you distinguish between the high and low PPGR diets?

	High PPGR Diet / Low PPGR Diet ?	High PPGR Diet / Low PPGR Diet ?
Breakfast	 Muesli	 Egg with bread and coffee
Lunch	 Sushi	 Hummus and pita
Snack	 Chocolate	 Edamame
Dinner	 Corn and nuts	 Vegetable noodles with tofu
Night snack	 Chocolate and coffee	 Ice cream

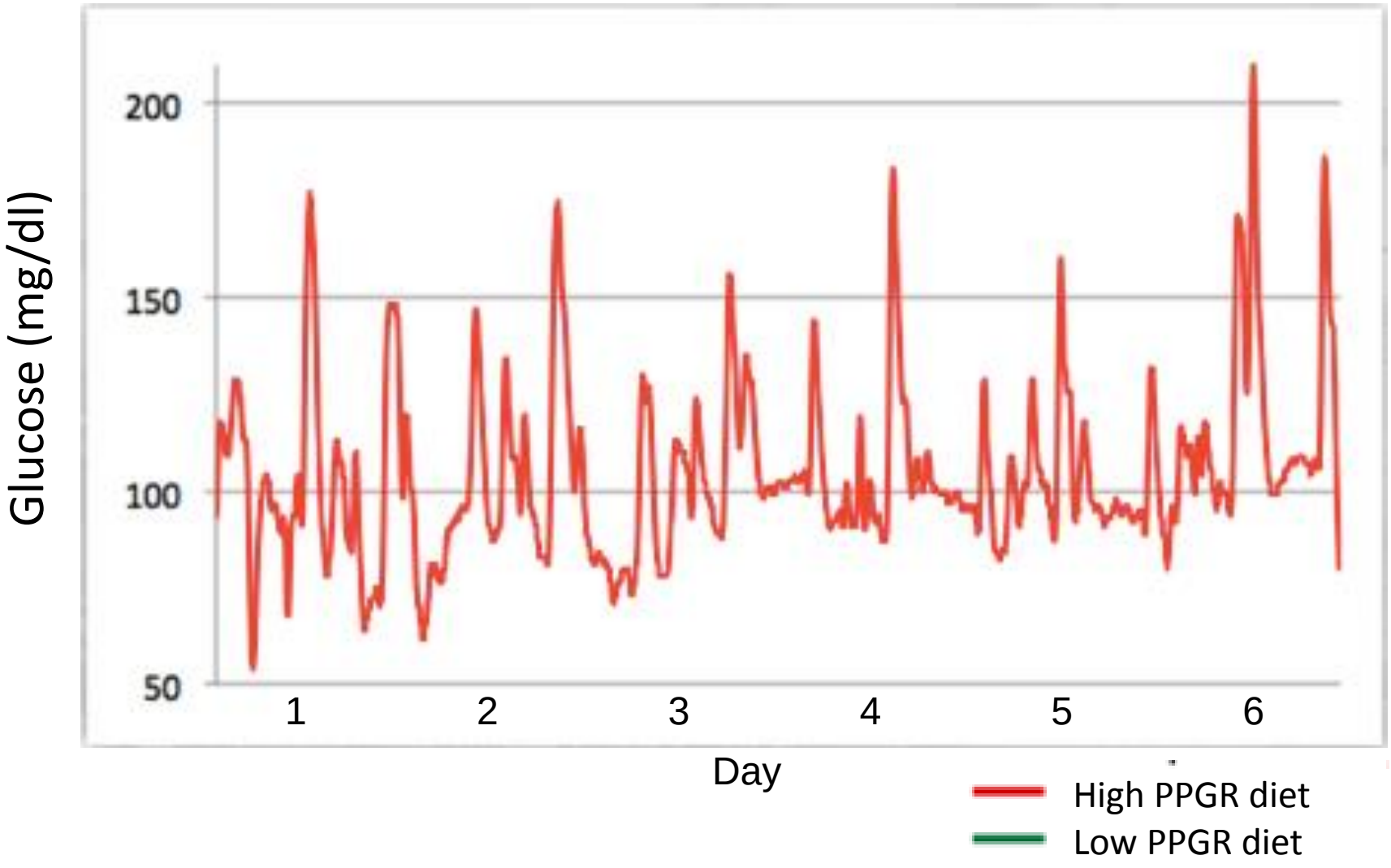
Zeevi *et al.*, Cell 2015

Can you distinguish between the high and low PPGR diets?

	High PPGR Diet	Low PPGR Diet
Breakfast	Muesli	Egg with bread and coffee
Lunch	Sushi	Hummus and pita
Snack	Chocolate	Edamame
Dinner	Corn and nuts	Vegetable noodles with tofu
Night snack	Chocolate and coffee	Ice cream

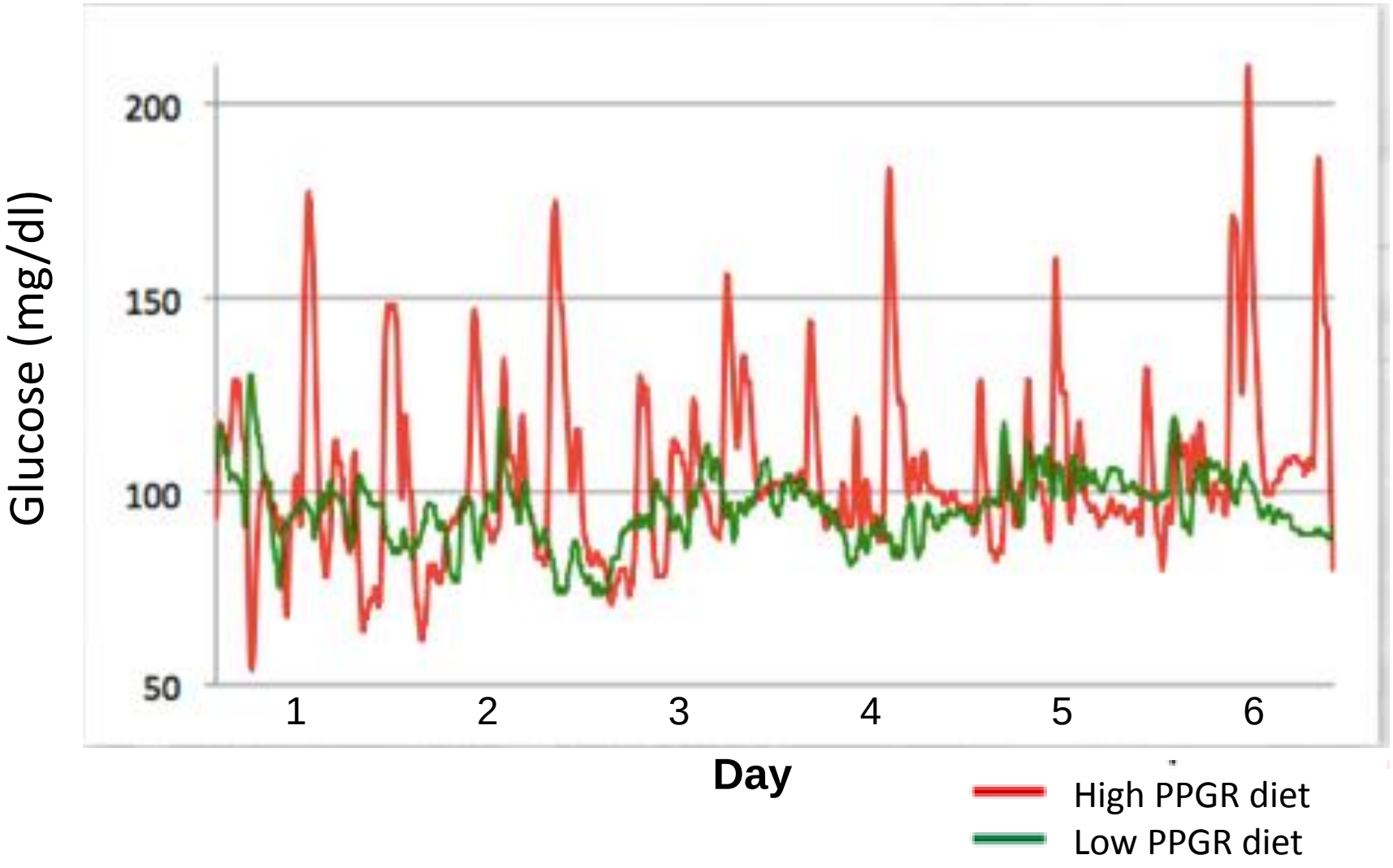
Zeevi *et al.*, Cell 2015

Personally tailored diets lower the post-prandial glucose response



Zeevi *et al.*, Cell 2015

Personally tailored diets lower the post-prandial glucose response



Zeevi *et al.*, Cell 2015

Can you distinguish between the high and low PPGR diets?

	High PPGR Diet	Low PPGR Diet	?	High PPGR Diet	Low PPGR Diet	?
Breakfast		Orange juice			Croissant	
Lunch		Schnitzel			Goulash with rice	
Snack		Peach			Halva	
Dinner		Bread with butter			Hummus	
Night snack		Grapes			Red wine	

Zeevi *et al.*, Cell 2015

Can you distinguish between the high and low PPGR diets?

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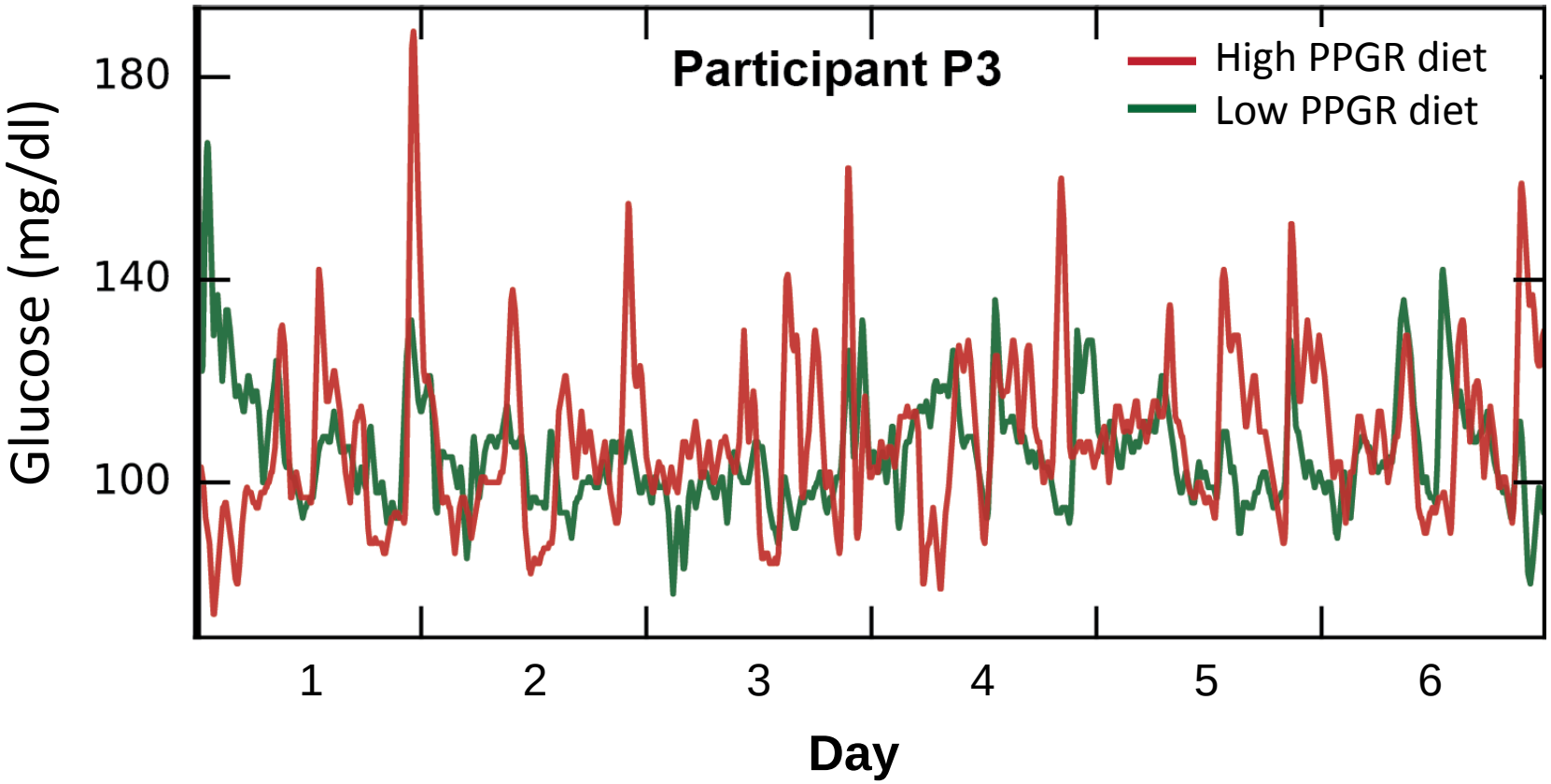
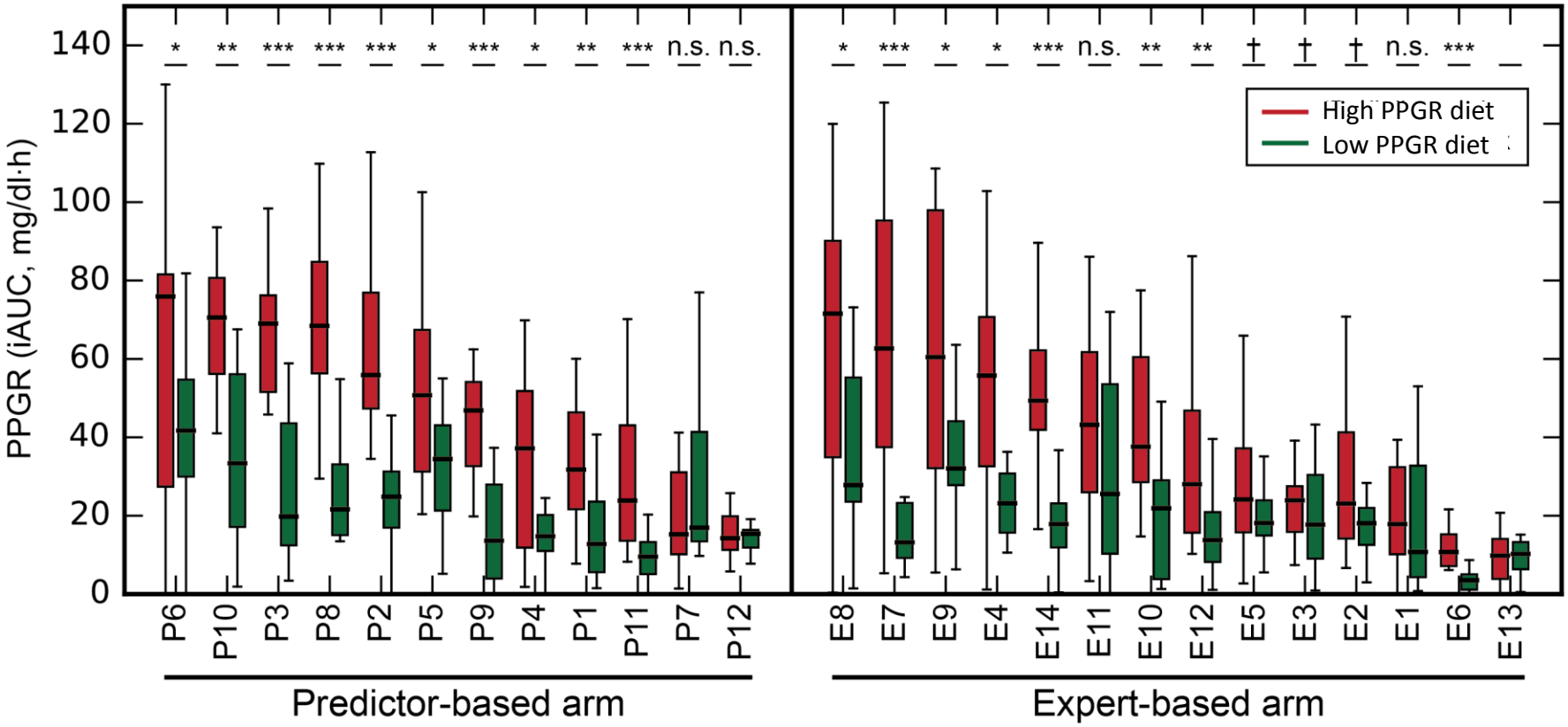
Zeevi *et al.*, Cell 2015

Personally tailored diets lower the post-prandial glucose response



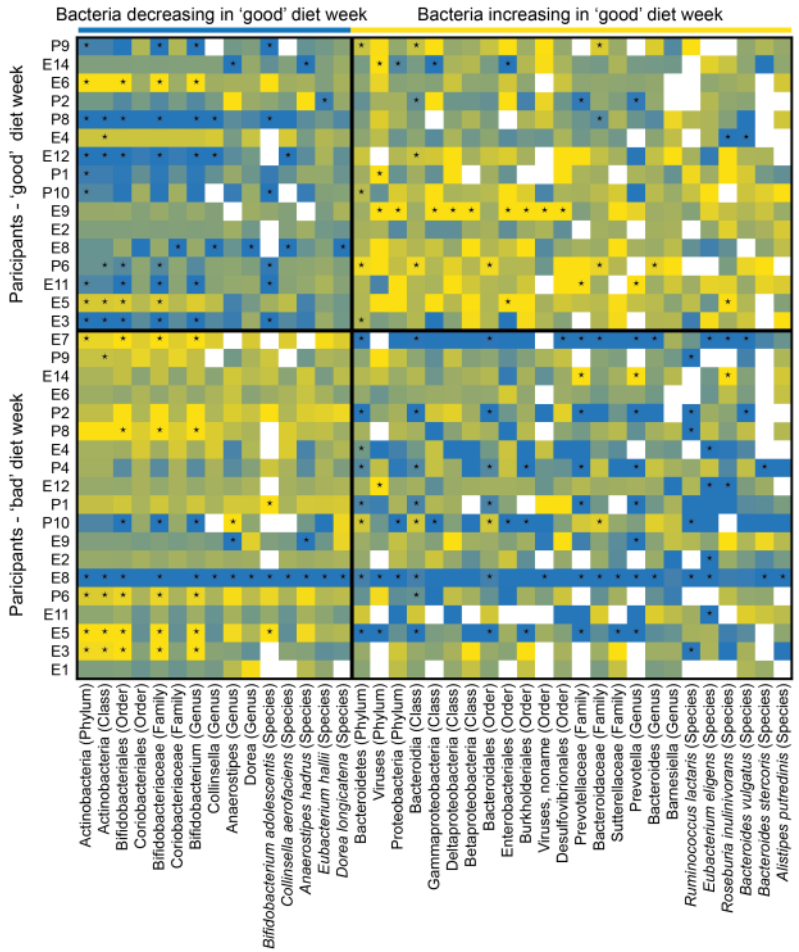
Zeevi *et al.*, Cell 2015

Personally tailored diets lower the post-prandial glucose response



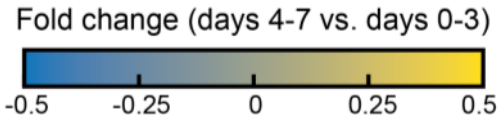
Zeevi *et al.*, Cell 2015

Dietary interventions targeting post-meal glucose responses induce consistent changes in microbiota



- Bifidobacterium adolescentis decreases following the low PPGR diet week
- Low levels associate with greater weight loss (Santacruz et al., 2009)

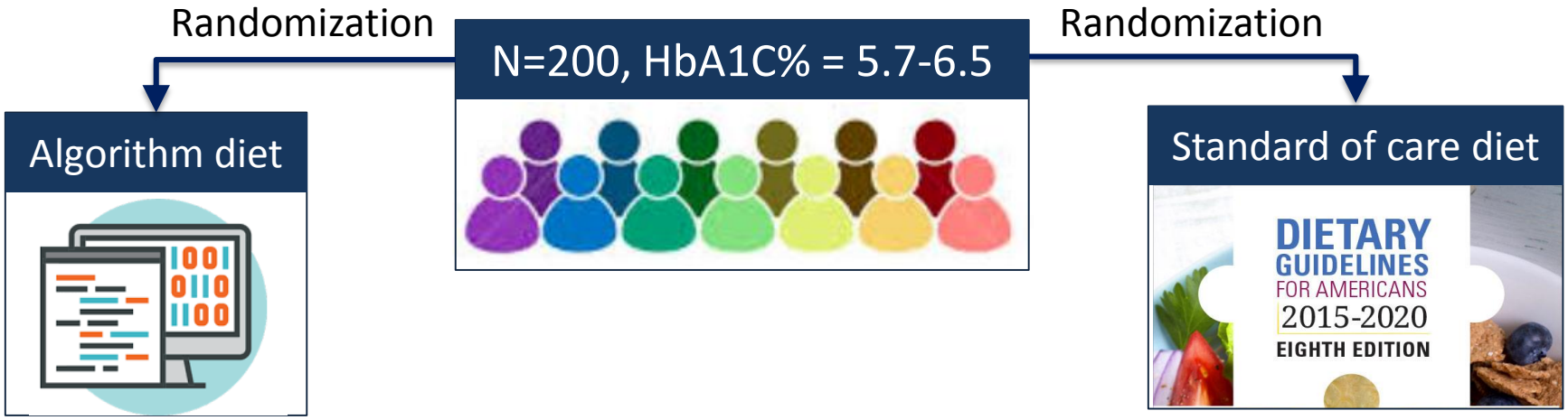
- Roseburia inulinivorans increases following the low PPGR diet week
- Low levels associate with T2DM (Qin et al., 2012)



Zeevi *et al.*, Cell 2015

What is the long-term clinical impact of personally tailored dietary interventions?

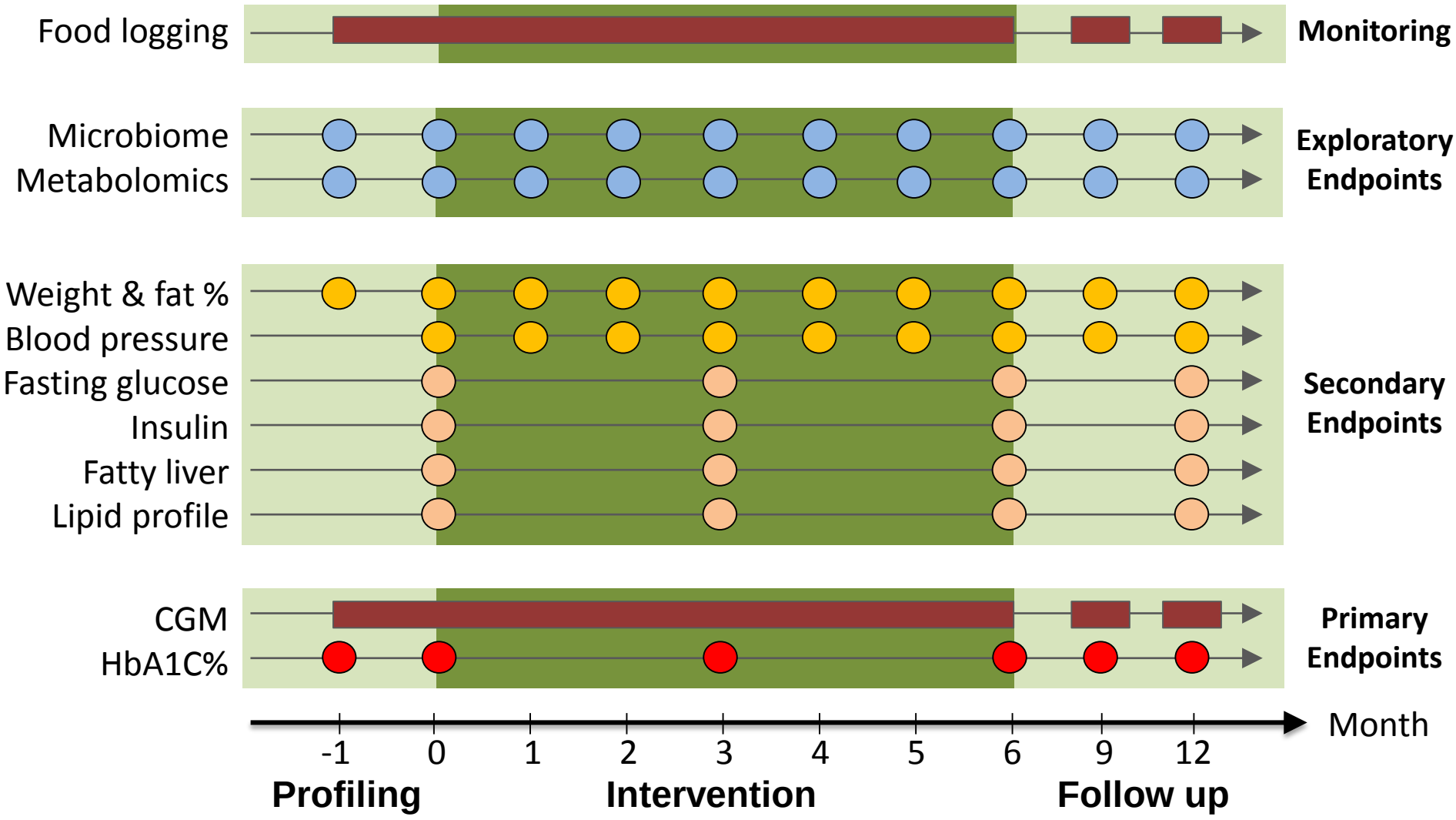
Randomized Clinical Trial (NCT03222791) to test the long-term (6M) effect of a personalized algorithm diet



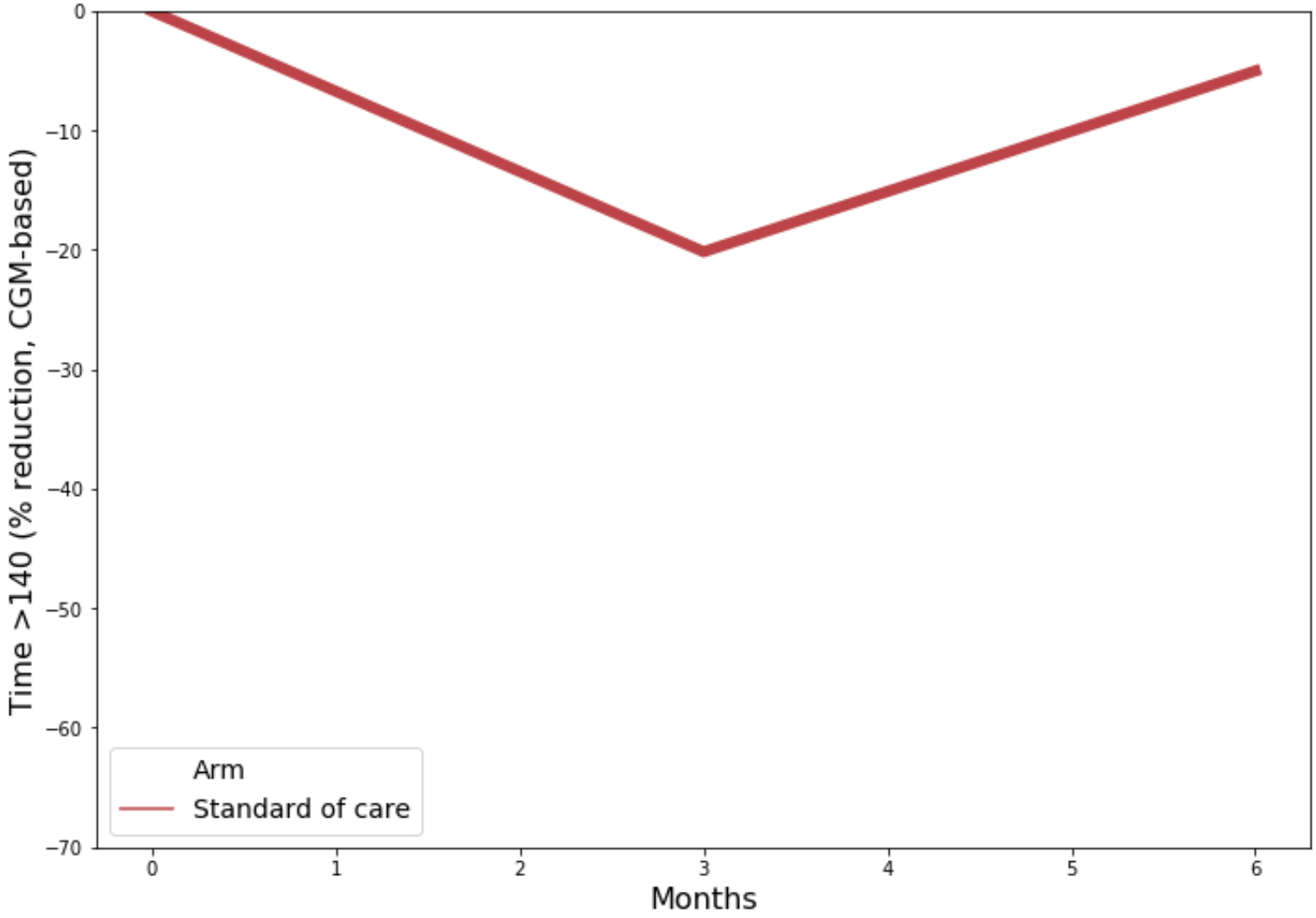
Primary outcomes

- Reduction in average glucose levels (based on HbA1C% and CGM)
- Reduction in time below 140 mg/dl (based on CGM)

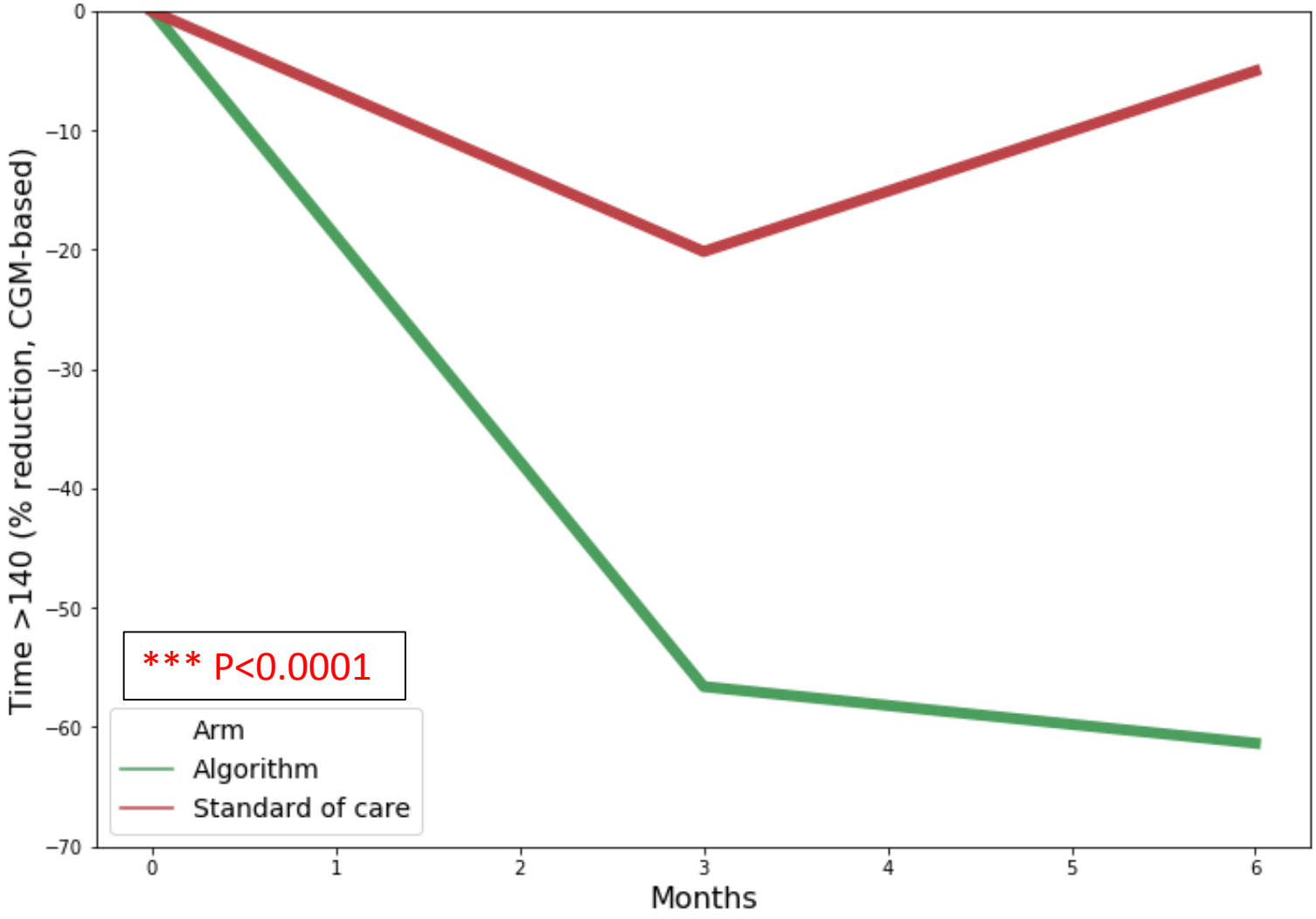
Randomized Clinical Trial (NCT03222791) to test the long-term (6M) effect of a personalized algorithm diet



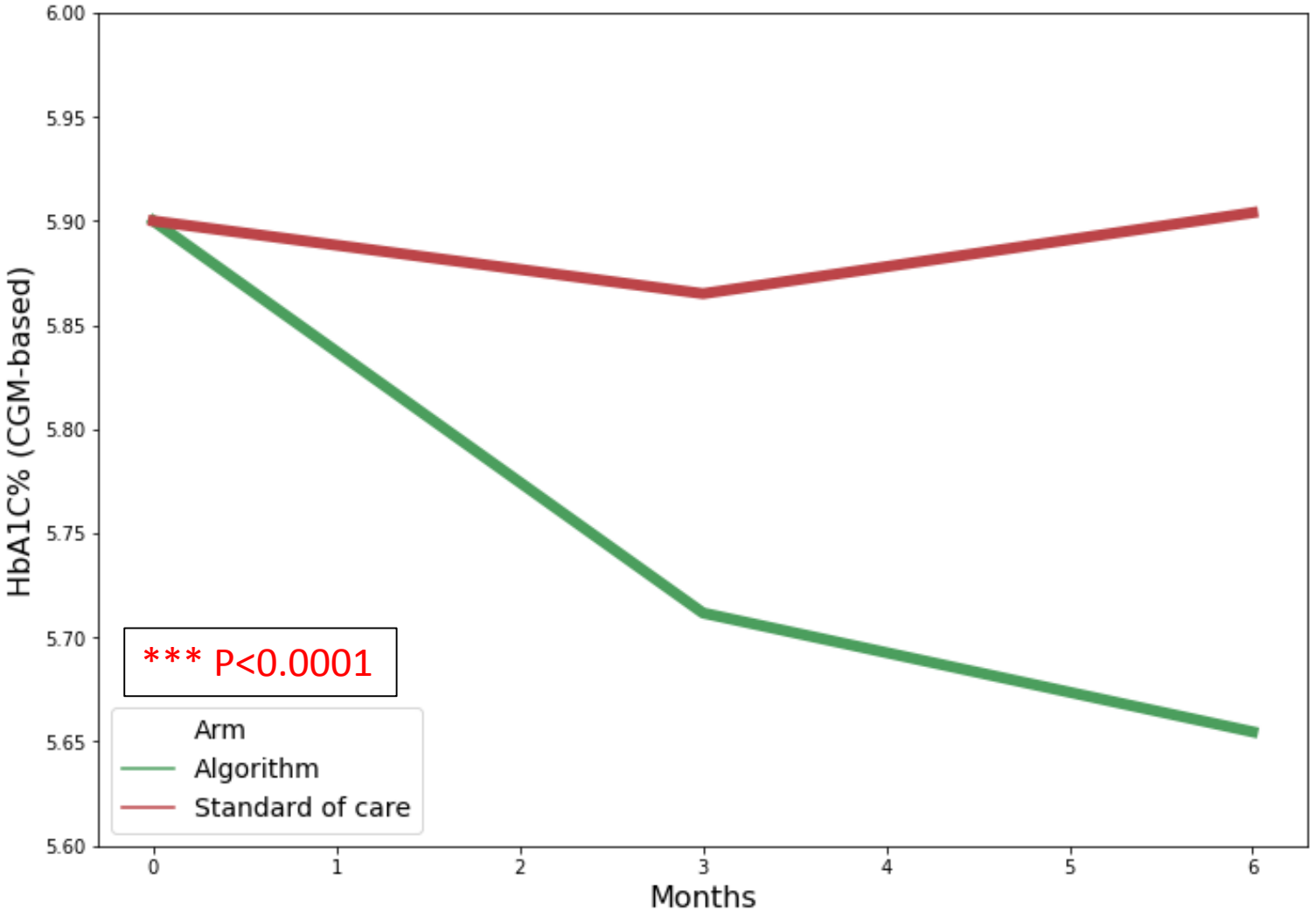
Algorithm diet reduces post-meal glucose levels



Algorithm diet reduces post-meal glucose levels



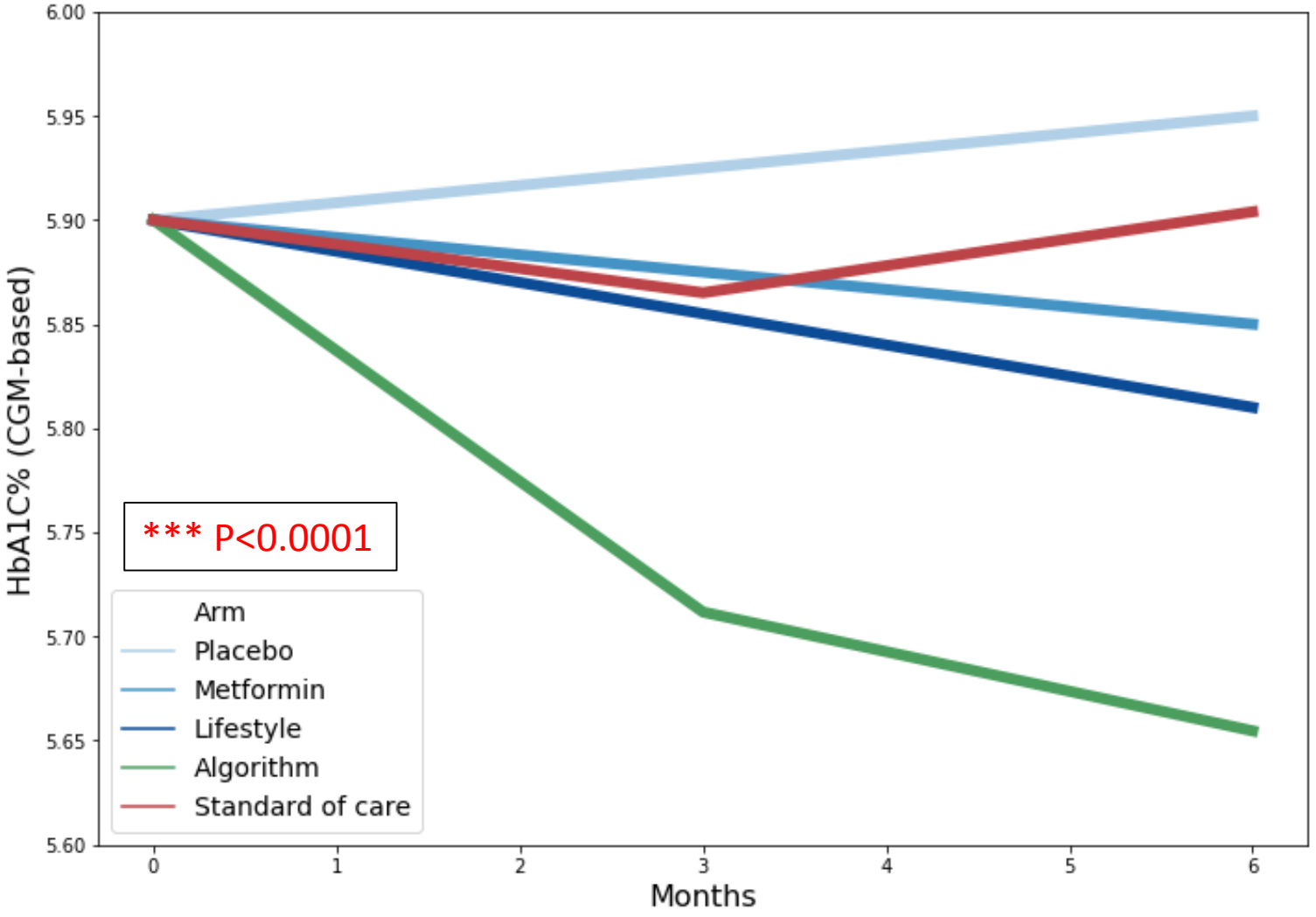
Algorithm diet reduces average glucose levels



Placebo, Metformin, Lifestyle from
Diabetes Prevention Program, NEJM 2002

CGM-based HbA1c% estimate from
Nathan et al., Diabetes Care 2008

Algorithm diet reduces average glucose levels



Placebo, Metformin, Lifestyle from
Diabetes Prevention Program, NEJM 2002

CGM-based HbA1c% estimate from
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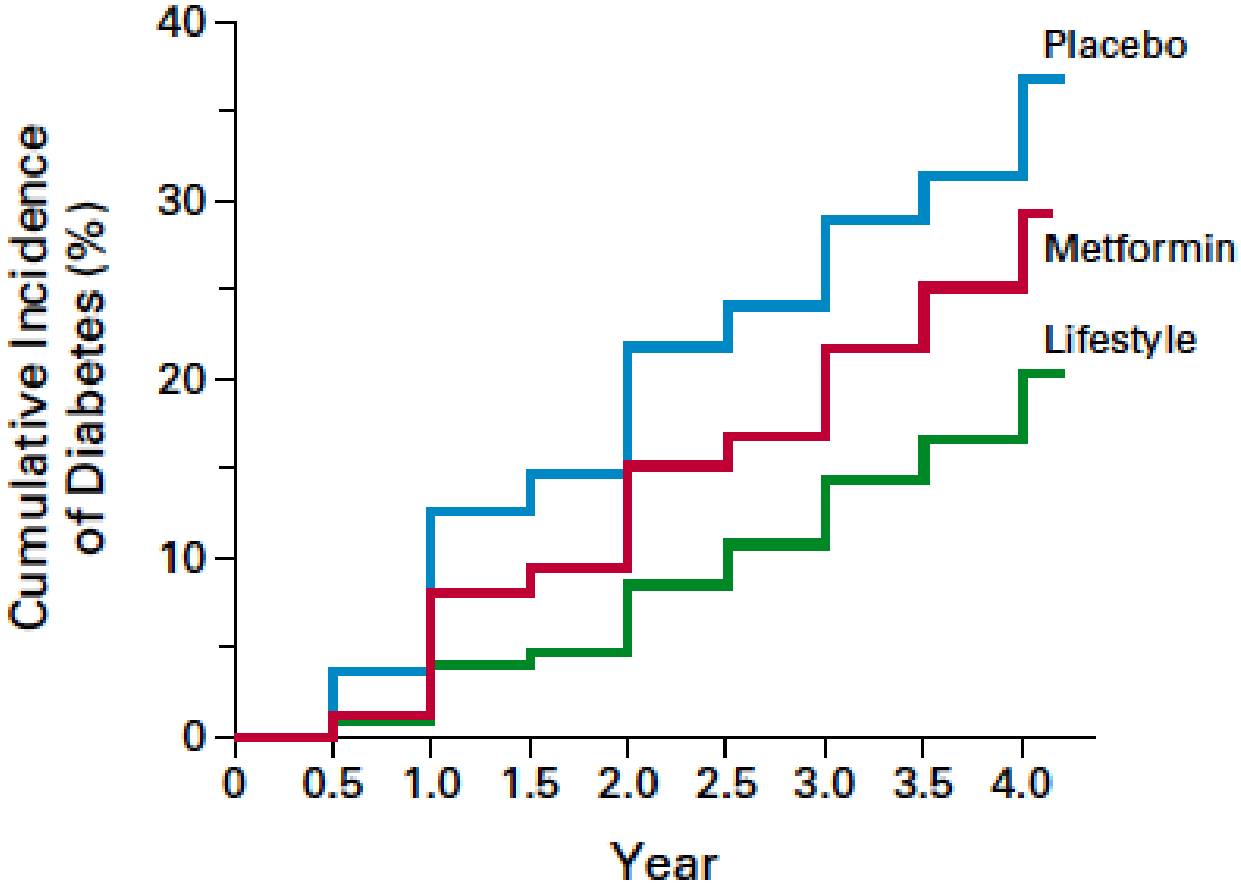
Algorithm diet may reduce incidence of diabetes



Summary and take home messages

- People have unique post-meal glucose responses to identical meals
- An algorithm accurately predicts post-meal glucose responses
- Personalized diets successfully lower post-meal glucose response
- Findings replicated in the U.S. (Hall et al., 2018, Stanford study)
- Algorithm tested and validated in >2,000 subjects

Segal Lab

Nitzan Arzi
Noam Bar
Elad Barkan
Shani Ben-Ari
Orly Ben Yaakov
Noa David
Yochai Edlitz
Nastya Godneva
Tal Karady
Shelley Klompus
Dmitry Kolobkov
Yulia Kogan
Noa Kossower
Eran Kotler
Netta Koren
Izhak Levi
Martin Mikl
Sigal Peled-Livyatan
Gal Perlman
Maya Pompan
Michal Rein
Hagai Rossman
Daphna Rothschild
Ira Shavitt
Smadar Shilo
Ilya Slutskin
Tamara Travinsky
Yaara Unger
Thomas Vogl
Adi Watzman
Adina Weinberger
Bat-Chen Wolf
Liron Zahavi

Collaborators

Weizmann Institute
Eran Elinav
Niv Zmora
Jotham Suez
Christoph Thaiss

Uni. of Groningen
Alexander Kurilshikov
Jingyuan Fu
Cisca Wijmenga
Alexandra Zhernakova

Rockefeller Uni.
David Zeevi

Columbia Uni.
Tal Korem

Tel-Aviv Uni.
Prof. Zamir Halpern

Twitter: **@segal_eran** Website: **http://genie.weizmann.ac.il**