The microbiome and personalized nutrition

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The microbiome is a signaling hub
Studying host-microbiome interactions

Circadian rhythmicity
- Thaiss et al, *Cell* 2014
- Thaiss et al, *Cell* 2014, in press

Nutrition
- Zeevy et al, *Cell* 2015

Immunity
- Wladarska et al, *Cell* 2014
- Levy et al, *Cell* 2015

Relapsing obesity

Microbial Drivers of disease

Eran Segal
The obesity pandemic

1990

2000

2010

<table>
<thead>
<tr>
<th>No Data</th>
<th>&lt;10%</th>
<th>10%–14%</th>
<th>15%–19%</th>
<th>20%–24%</th>
<th>25%–29%</th>
<th>≥30%</th>
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37.5%

78 million

Adults

17%

12.5 million

Children

The obesity pandemic

37.5%

78 million

Adults

17%

12.5 million

Children
The obesity paradox

Williams et al., Obesity Reviews, 2015
Our dieting failure

Time following weight loss
Months

Average weight loss
Kilograms

Exercise

Diet
Exercise+diet
Meal replacement
Very low energy diet

Source: McKinsey Global Institute
November 2014
Current paradigm: defining diets by the food
Current paradigm: defining diets by the food
Current paradigm: defining diets by the food

**GLYCEMIC INDEX CHART**

<table>
<thead>
<tr>
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<td>Yogurt, Plain</td>
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<td>White Rice</td>
<td>38</td>
<td>Pepper</td>
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<td>Yogurt, Low Fat</td>
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<td>Pound Cake</td>
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<td>Skim Milk</td>
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<td>Soda</td>
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<td>Baked Potato</td>
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<td>Onions</td>
<td>75</td>
<td>Dates</td>
<td>103</td>
<td>Ice Cream</td>
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</table>
People have widely different glucose responses to the same food.
People have widely different glucose responses to the same food.
‘one size fits all diet’ cannot be effective
Diet must be tailored to the individual.
Factors driving personalized dietary responses can be measured:

- Genetics
- Lifestyle
- Microbes
A novel science-based approach to nutrition: The Personalized Nutrition Project

Zeevi et al, Cell, 2015
The Personalized Nutrition Project: Experimental Setup

Register online
www.personalnutrition.org

Log activities & food
Measure glucose response to food

Analyze your bacteria

Study Week Start

Study Week End

View Bacteria

Personal Diet

Genetics
Glucose
Microbes

Blood tests
Questionnaires

Connection meeting

Study week analysis

Plan personal diet
The Personalized Nutrition Project: Understanding personal glucose responses

- 1000 people profiled
- 50,000 meals measured
  - 9,000,000 Kcal
  - 12,000 Kg
  - 5,000 standardized meals
- 2,000,000 glucose measures
  - 150,000 hours
- 10 Billion metagenome reads
- 5,000 more people registered

http://www.personalnutrition.org
The Personalized Nutrition Project: Cohort statistics

- 25-70 years of age
- ~50% overweight
- ~20% obese
- ~25% pre-diabetic
Microbiome features overlap with HMP & MetaHIT
Postprandial (post-meal) response is correlated with multiple clinical markers.
Postprandial (post-meal) response is correlated with multiple clinical markers.

Maximal post-meal response (mg/dl) correlated with...

- HbA1c% (R=0.56)
- Wakeup glucose (mg/dl) (R=0.65)
Postprandial (post-meal) response is correlated with multiple clinical markers

Maximal post-meal response (mg/dl)

R=0.45  Age

R=-0.22  HDL Cholesterol (mg/dl)
Testing the cohort response to standardized meals

Standardized meals (50g available carbohydrates)

Day 1: Bread
Day 2: Bread
Day 3: Bread & butter
Day 4: Bread & butter
Day 5: Glucose
Day 6: Glucose
Day 7: Fructose
Testing the cohort response to standardized meals

- **Graph 1:**
  - X-axis: Glycemic response - iAUCmed (mg/dl·h)
  - Y-axis: No. of participants (Density)
  - Graph shows distributions for Glucose, Bread, Bread & Butter, and Fructose.

- **Graph 2:**
  - X-axis: Time (min.)
  - Y-axis: Blood glucose (mg/dl)
  - Graph shows individual responses to bread with iAUC values: 139, 81, 44, 15.

- **Legend:**
  - Participant 123
  - Participant 864
  - Participant 834
  - Participant 485
Major inter-personal variability in the response to test foods
Major inter-personal variability in the response to real-life foods
Prediction scheme: current state of the art

Meal carbohydrates (g)

Measured $i$AUC (mg/dl h)

$r=0.37$
New prediction scheme

Training cohort
800 participants
40,000 meals

Validation cohort
100 participants
5,000 meals

Personal features
Meal features

Glycemic meal responses

Meal Response Predictor

Boosted decision trees

Train predictor

Cross-validation
Leave-one-person-out

Use predictor to predict meal responses

Predicted = Measured
Model Features

Prediction scheme

R

0.37

0.4

0.5

0.6

0.7
Prediction scheme

Model Features

Meal features
Nutrient weights, water

R

0.37 0.41
Prediction scheme

Model Features

Meal features
Nutrient weights, water

Logged features
Time of day, sleep, exercise
Prediction scheme

**Model Features**

- **Meal features**
  - Nutrient weights, water

- **Logged features**
  - Time of day, sleep, exercise

- **Microbiome features**
  - Gene levels, bacteria levels, 16S

---

![Graph showing correlation coefficients](image)

- $R = 0.37$
- $R = 0.41$
- $R = 0.55$
- $R = 0.64$
Prediction scheme

Model Features

- **Meal features**
  - Nutrient weights, water
- **Logged features**
  - Time of day, sleep, exercise
- **Microbiome features**
  - Gene levels, bacteria levels, 16S
- **Personal features**
  - Blood tests, questionnaires

<table>
<thead>
<tr>
<th>Feature Type</th>
<th>R Value</th>
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<tbody>
<tr>
<td>Meal features</td>
<td>0.37</td>
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<tr>
<td>Logged features</td>
<td>0.41</td>
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<tr>
<td>Microbiome features</td>
<td>0.55</td>
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<tr>
<td>Personal features</td>
<td>0.64</td>
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<tr>
<td>Overall</td>
<td>0.68</td>
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Accurate predictions of personalized glucose responses

State of the art

Carbohydrate-only prediction

\[ R = 0.38 \]

Meal carbohydrates (g)

Our prediction
800 participants

Main cohort prediction
cross-validation

\[ R = 0.68 \]

Predicted PPGR
(iAUC; mg/dl*h)

Prediction validation

Measured PPGR
(iAUC; mg/dl*h)

Predicted PPGR
(iAUC; mg/dl*h)
Microbiome features affect the post-meal glucose response
Constructing personally tailored diets that achieve normal post-prandial glucose responses

One week profiling

**“Good” Diet: Low predicted responses**
- Food diary
- Continuous glucose monitoring
- Daily microbiota profiling

**“Bad” Diet: High predicted responses**
- Food diary
- Continuous glucose monitoring
- Daily microbiota profiling

Expert (n=14)

Algorithm (n=12)
Foods that appear in the ‘good’ diet of one person may appear in the ‘bad’ diet of another.
Can you distinguish between the good and bad menus?

### Breakfast
- **“Bad” Diet:** Muesli
- **“Good” Diet:** Egg with bread and coffee

### Lunch
- **“Bad” Diet:** Sushi
- **“Good” Diet:** Hummus and pita

### Snack
- **“Bad” Diet:** Marzipan
- **“Good” Diet:** Edamame

### Dinner
- **“Bad” Diet:** Corn and nuts
- **“Good” Diet:** Vegetable noodles with tofu

### Night snack
- **“Bad” Diet:** Toblerone and coffee
- **“Good” Diet:** Ice cream
Can you distinguish between the good and bad menus?

Bad Diet
- Muesli
- Sushi
- Marzipan
- Corn and nuts
- Toblerone and coffee

Good Diet
- Egg with bread and coffee
- Hummus and pita
- Edamame
- Vegetable noodles with tofu
- Ice cream
Personally tailored diets reduce the post-prandial glucose response

![Graph showing glucose levels over time for good and bad diets.](image)
Can you distinguish between the good and bad menus?

Breakfast
- Orange juice
- Peach
- Bread with butter
- Grapes

Lunch
- Schnitzel

Snack
- Croissant
- Goulash with rice
- Halva
- Hummus
- Red wine

Dinner

Night snack

Can you distinguish between the good and bad menus?

**Bad Menu**
- Breakfast: Orange juice
- Lunch: Schnitzel
- Snack: Peach
- Dinner: Bread with butter
- Night snack: Grapes

**Good Menu**
- Croissant
- Goulash with rice
- Halva
- Hummus
- Red wine
Personality tailored diets reduce the post-prandial glucose response

**Graph 1:**
- **X-axis:** Days (1 to 7)
- **Y-axis:** Glucose levels (mg/dl)
- **Legend:**
  - Good (green)
  - Bad (red)

**Graph 2:**
- **X-axis:** Time (hr) (0 to 3)
- **Y-axis:** Glucose rise (mg/dl)
- **Legend:**
  - Good (green)
  - Bad (red)

**Statistical Significance:**
- \( P < 10^{-6} \)
Personally tailored diets reduce the post-prandial glucose response
Personally tailored diets reduce the post-prandial glucose response.
Personalized dietary interventions induce consistent changes in microbiota.
The diet- microbiome- metabolism axis can be diagnostically and therapeutically exploited.
Thanks

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