The Gut Microbiome and Cardiometabolic Health

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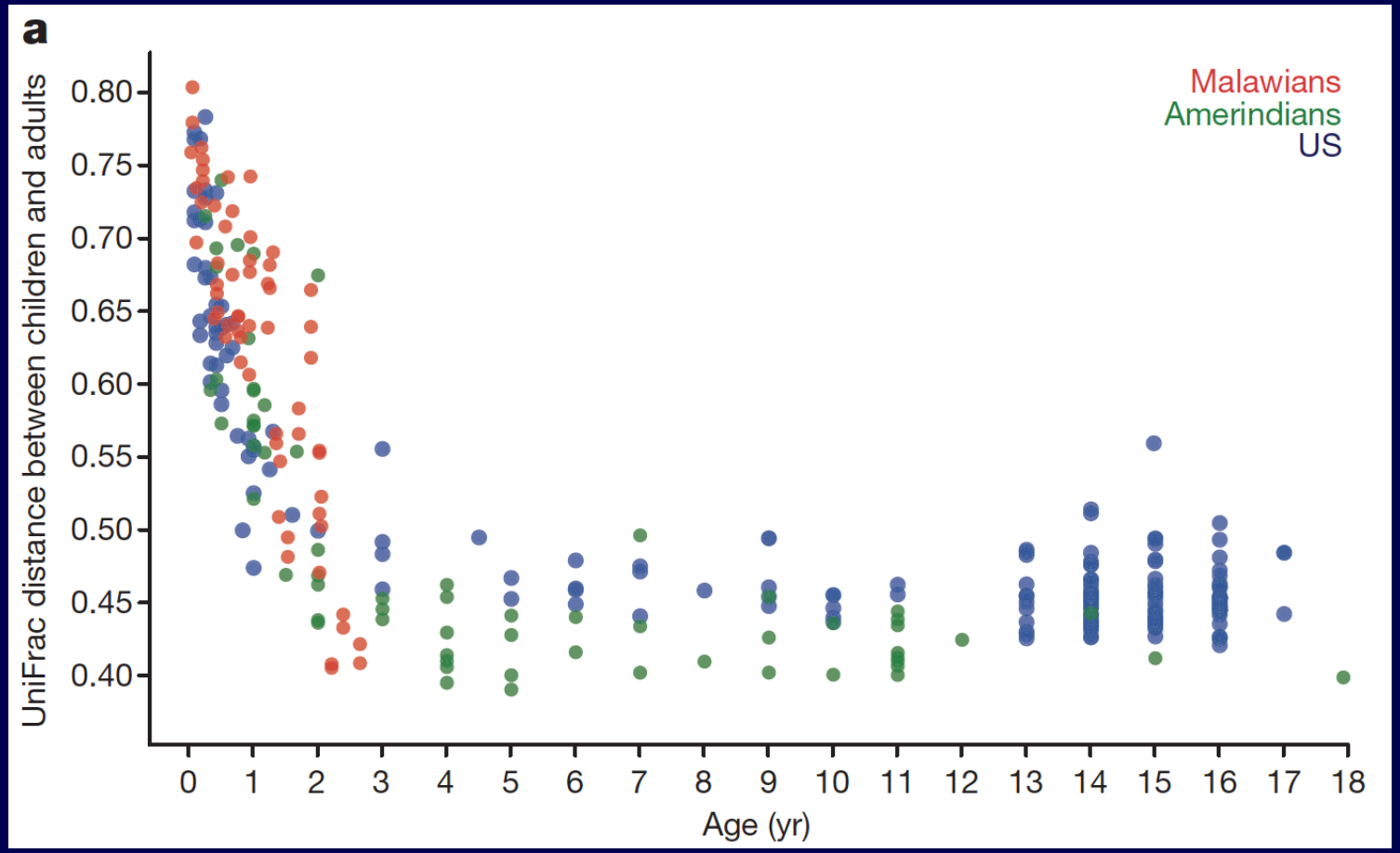
Humans are home to trillions of microbes

Image credit: Suzy Parker, USA Today

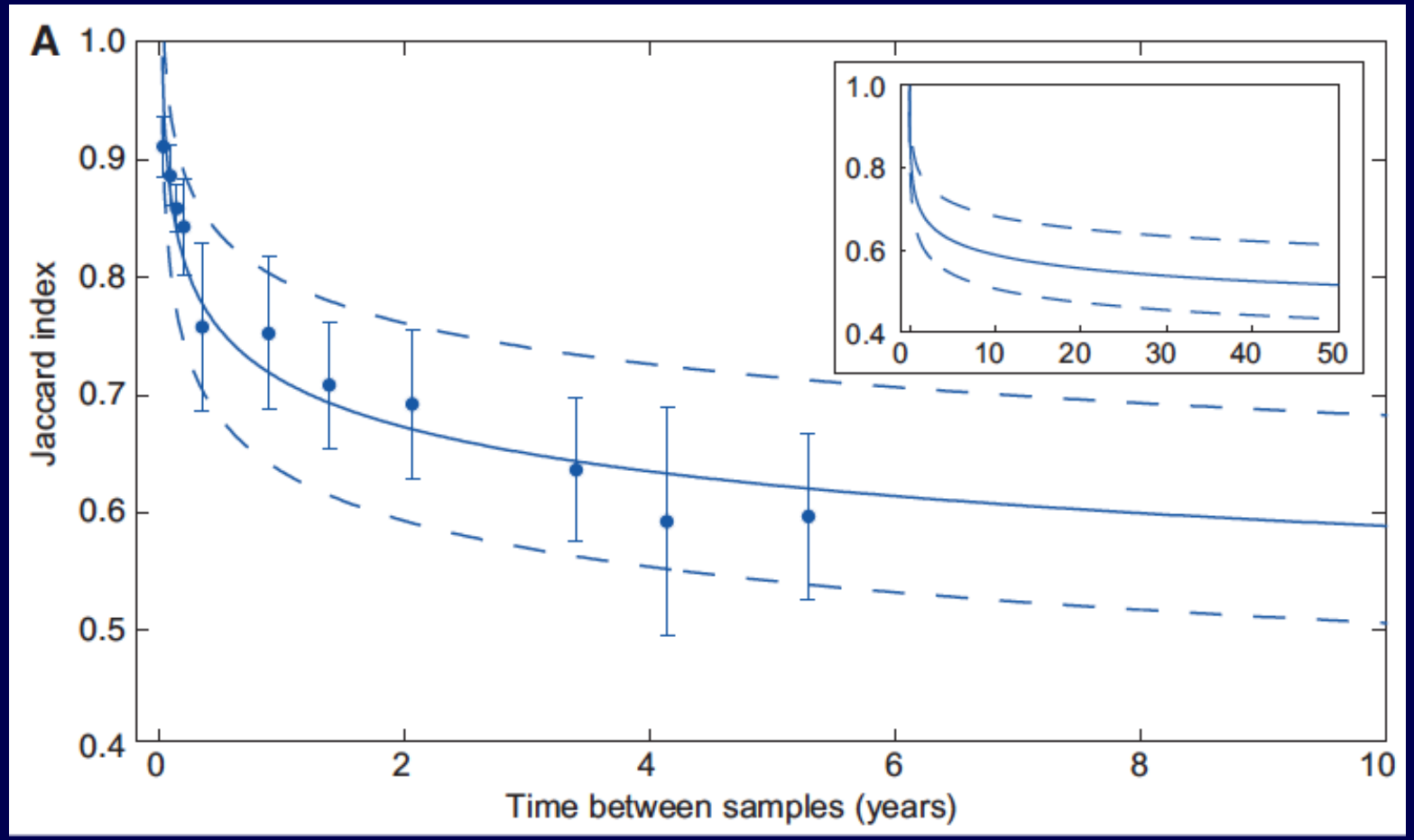
- Bacteria, archaea, microscopic fungi, parasites, and viruses (the **microbiota**)
- Colonize multiple body habitats: gut, skin, mouth
- Combined, the **microbiome** has >100X more genes than the human genome

The microbiota rapidly "matures" in the first 3 years of life



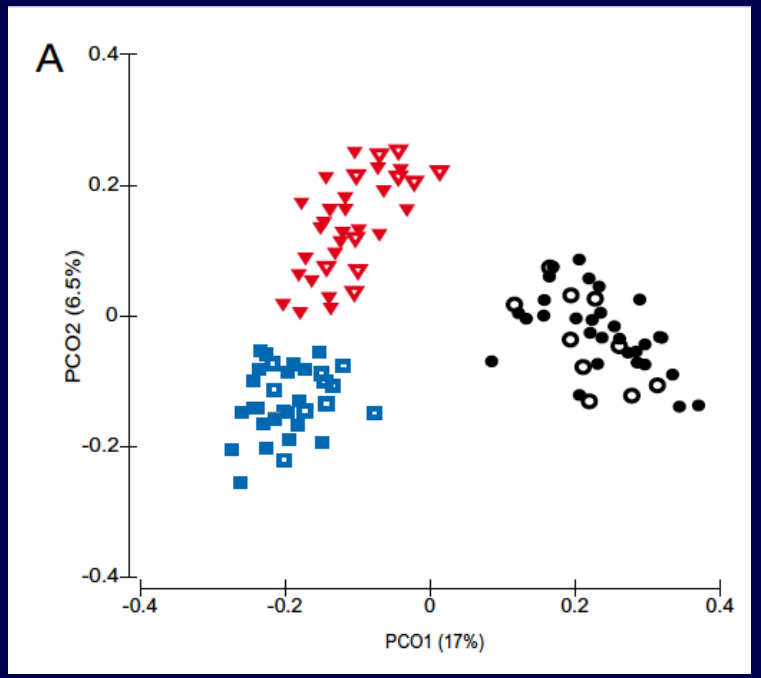
Yatsunenko et al. Nature 2012;486:222-27.

Most bacterial strains can stably colonize the adult GI tract for years



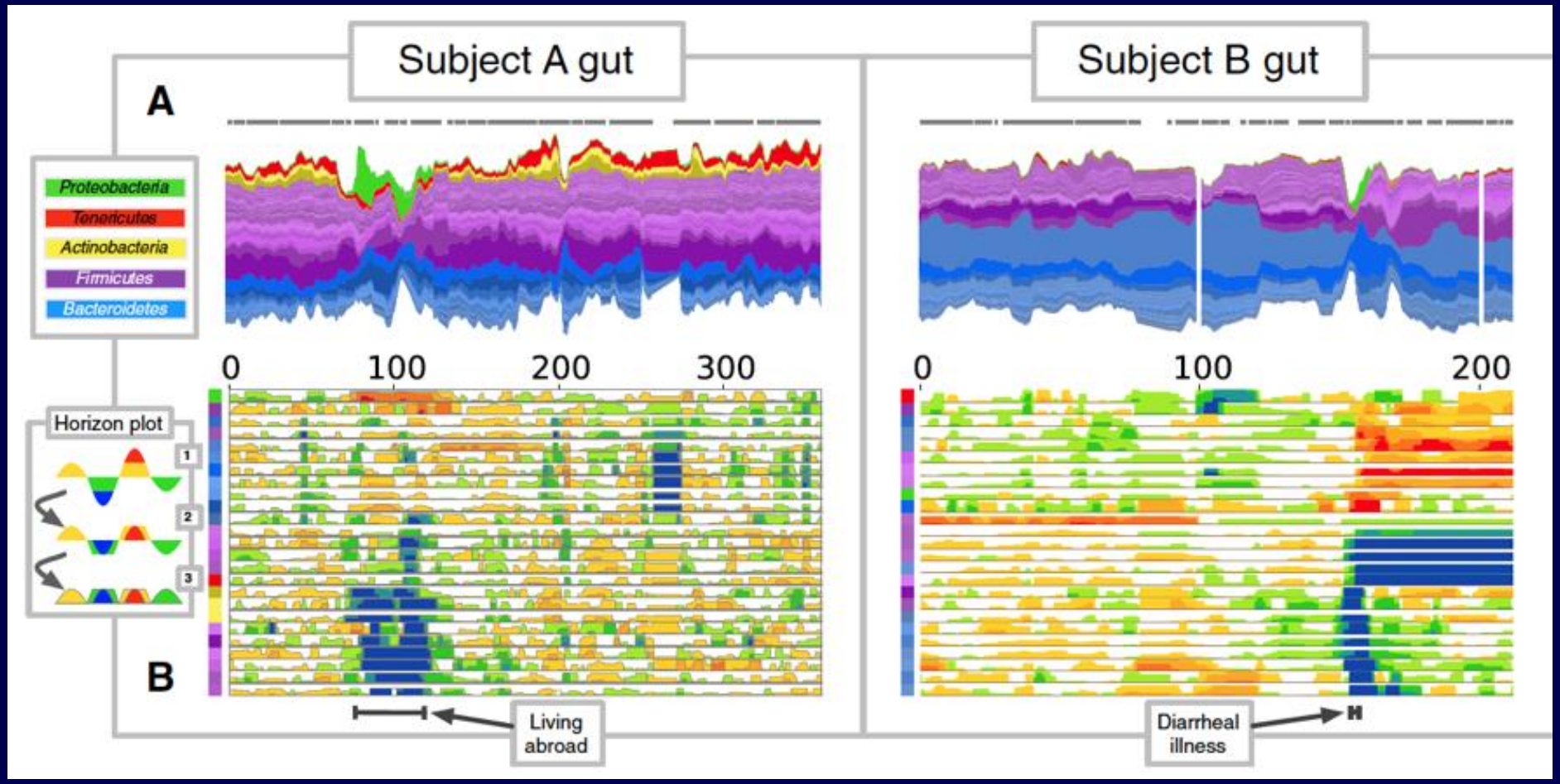
Faith et al. Science 2013.

The microbiota is a unique fingerprint



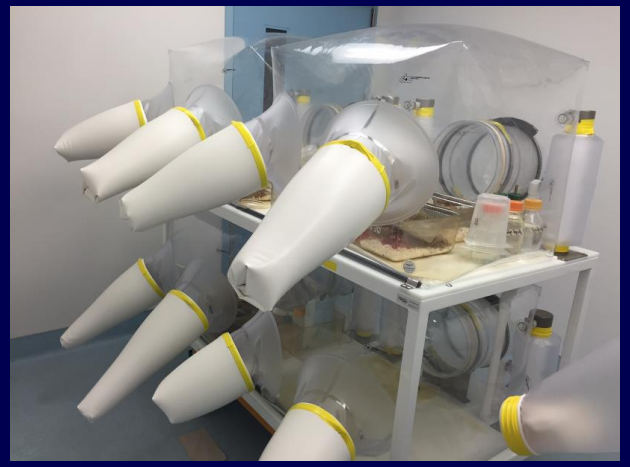
Fierer et al. PNAS. 2010;107:6477-81.

Rapid changes in abundance are possible



David et al. Genome Biology 2014;15:R89.

The microbiota is not a passive bystander



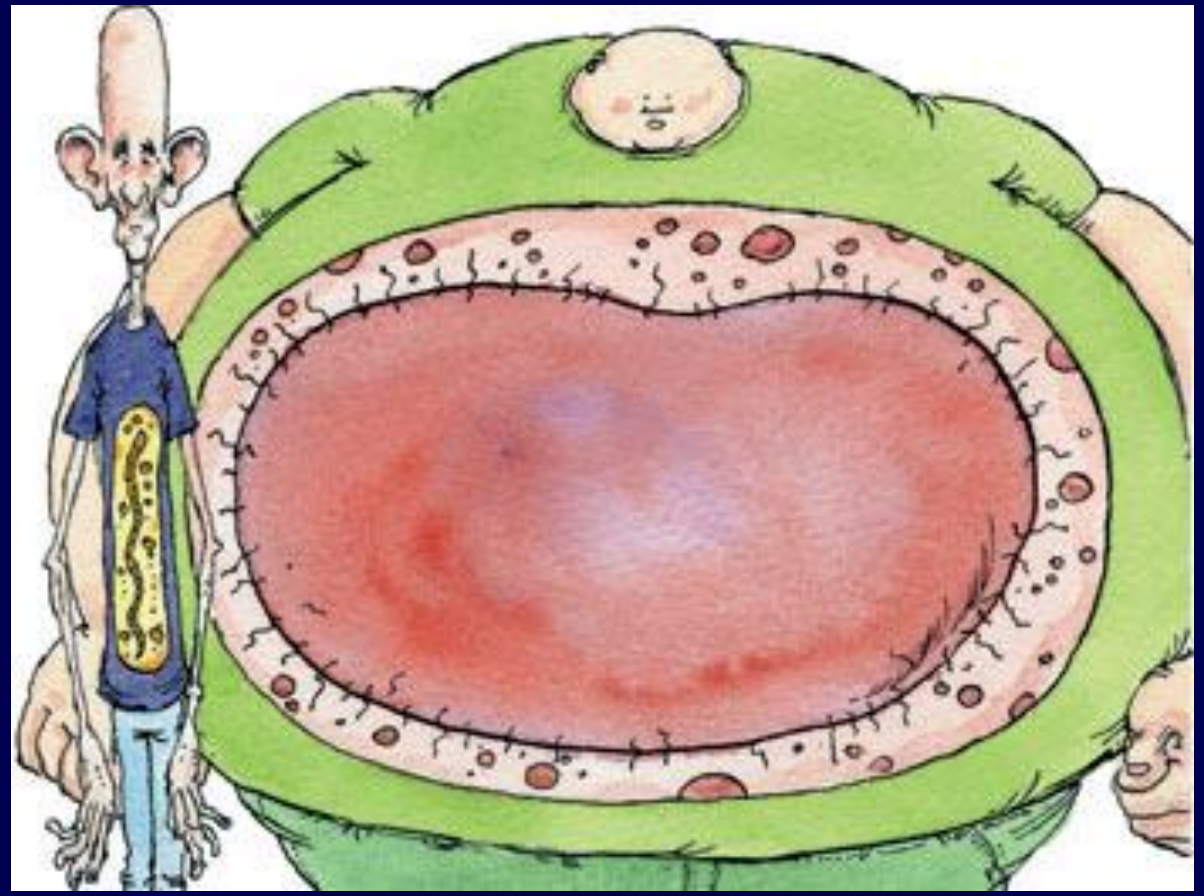
Definitions:

- Gnotobiotic = “known life”
- Germ-free = no microbes
- Conventionalized = GF mice colonized with donor microbiome
- Conventional = colonized from birth

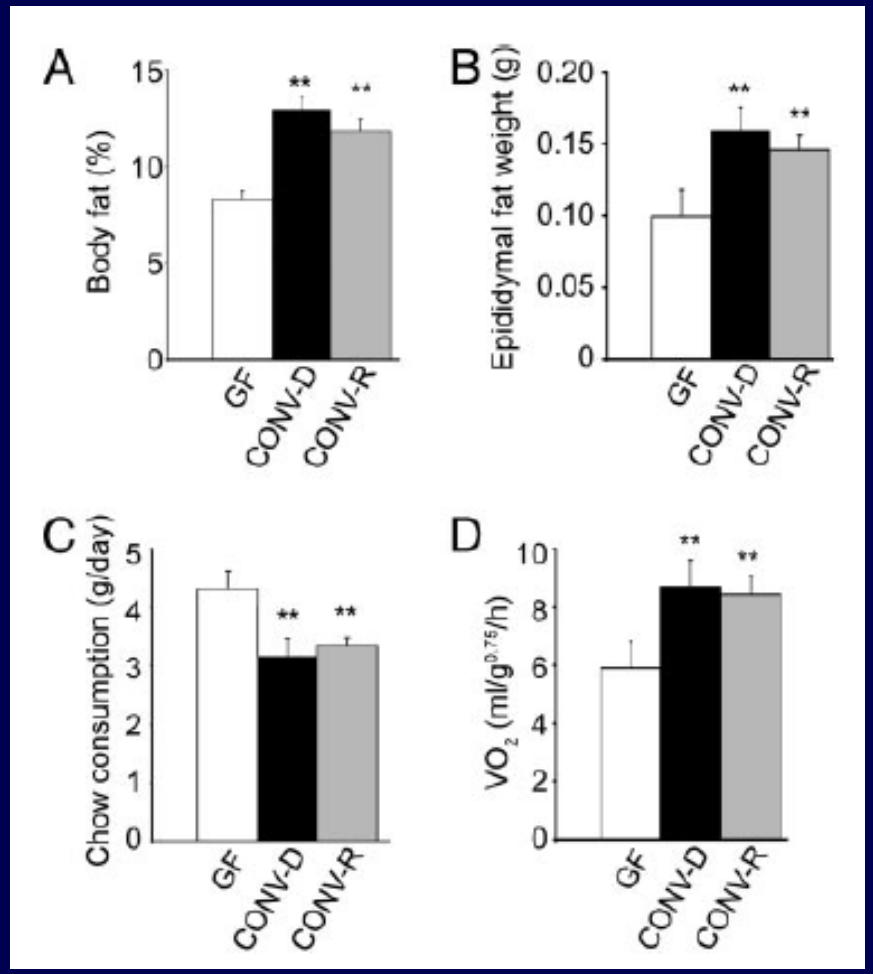
Have implicated the microbiome in many areas of science typically considered to be independent of microbes:

1. Host metabolism, immunity, behavior, development
2. Disease etiology
3. Treatment outcomes

Links to obesity



Germ-free mice have decreased body fat

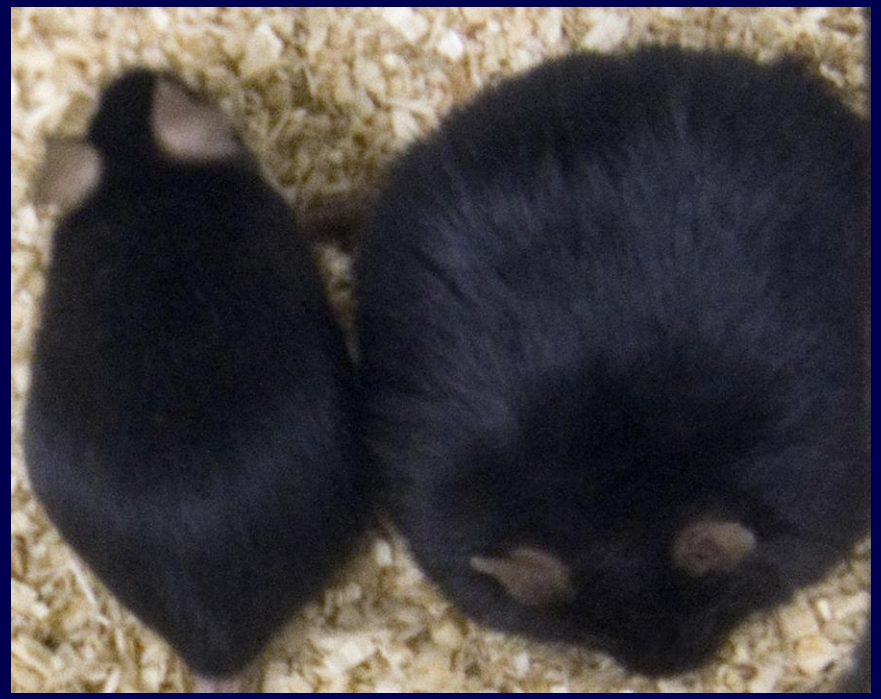


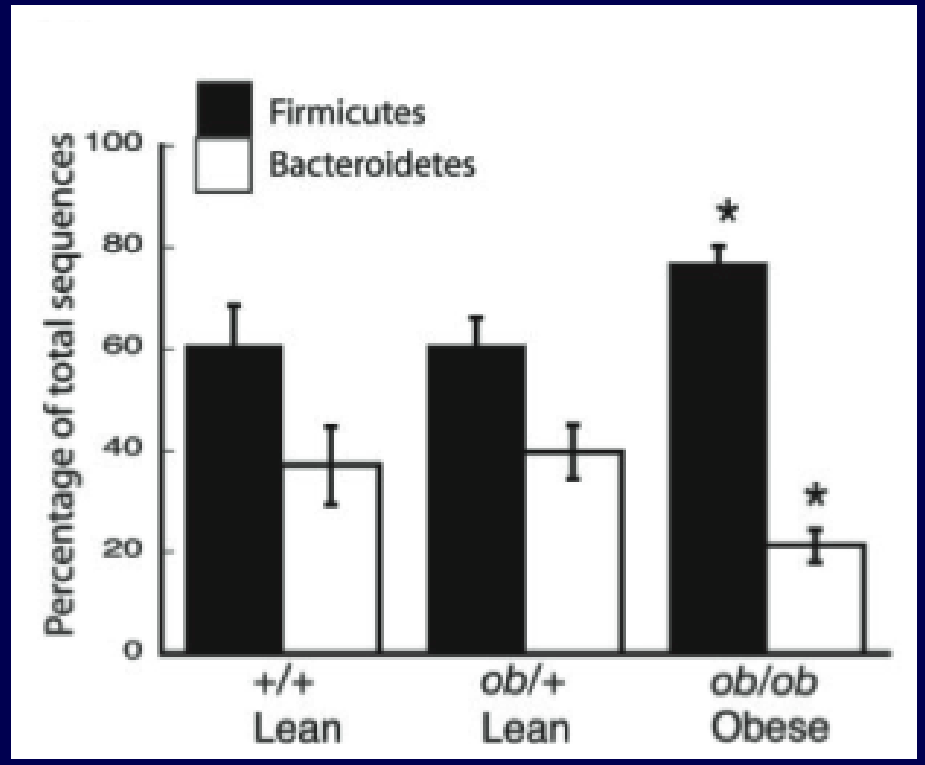
- Males and females have similar response
- Found across multiple mouse strains
- Runs counter to traditional energy balance equation (**more** caloric intake and **less** expenditure)

Backhed et al. PNAS 2004;101:15718-23.

Obese mice have an altered gut microbiota

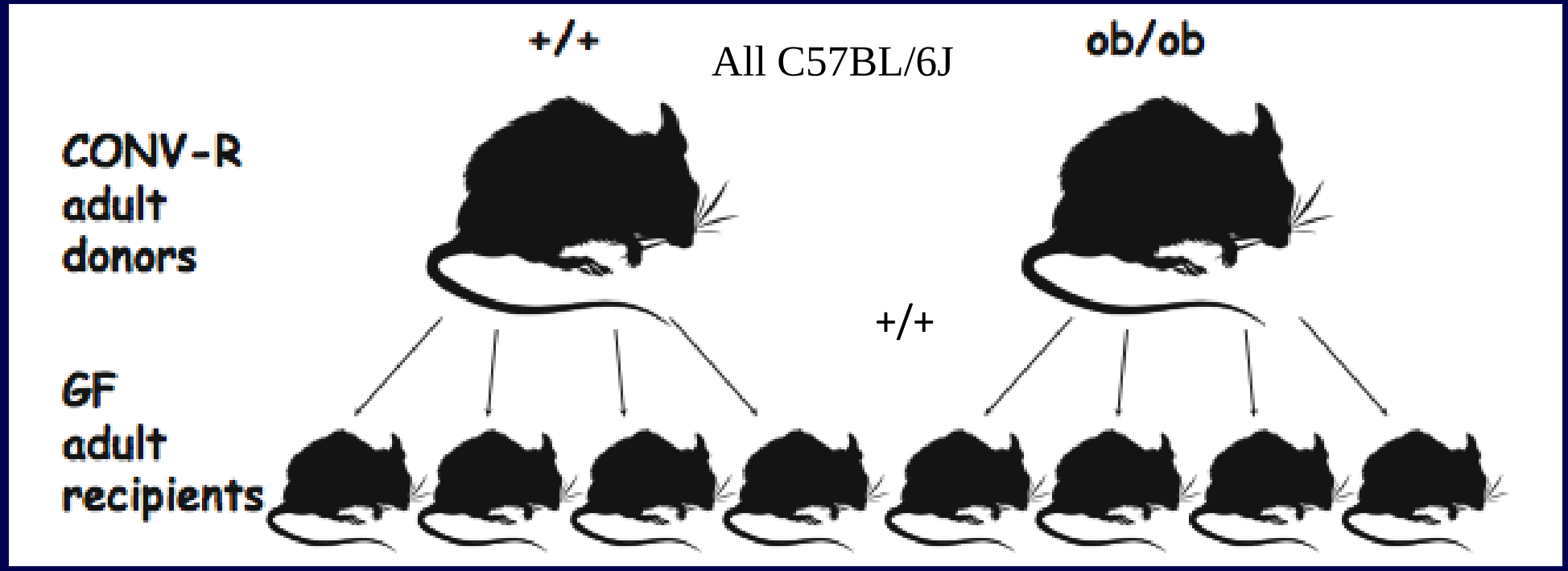
ob/ob mice are genetically deficient for leptin (they **overeat**)



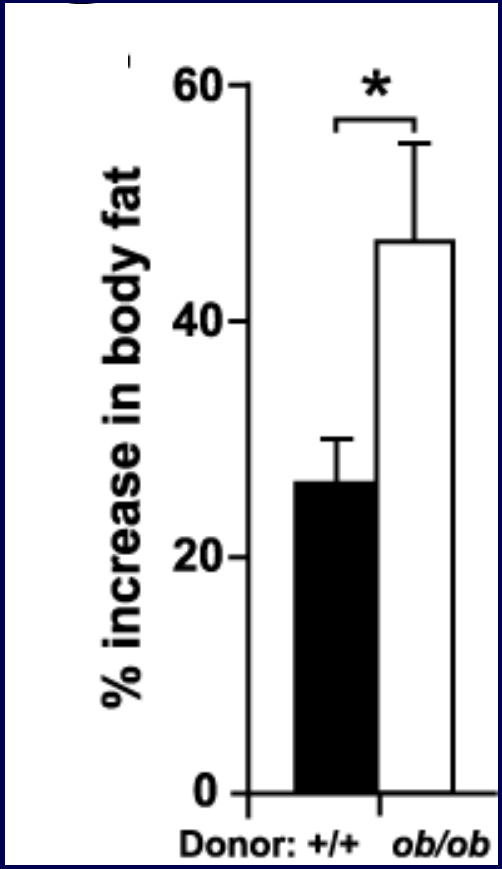


Ley et al. PNAS 2005;102:11070-75.

Fecal Microbiota Transplantations (FMT) for mice



Recipients of “obese” microbiota gain twice as much body fat



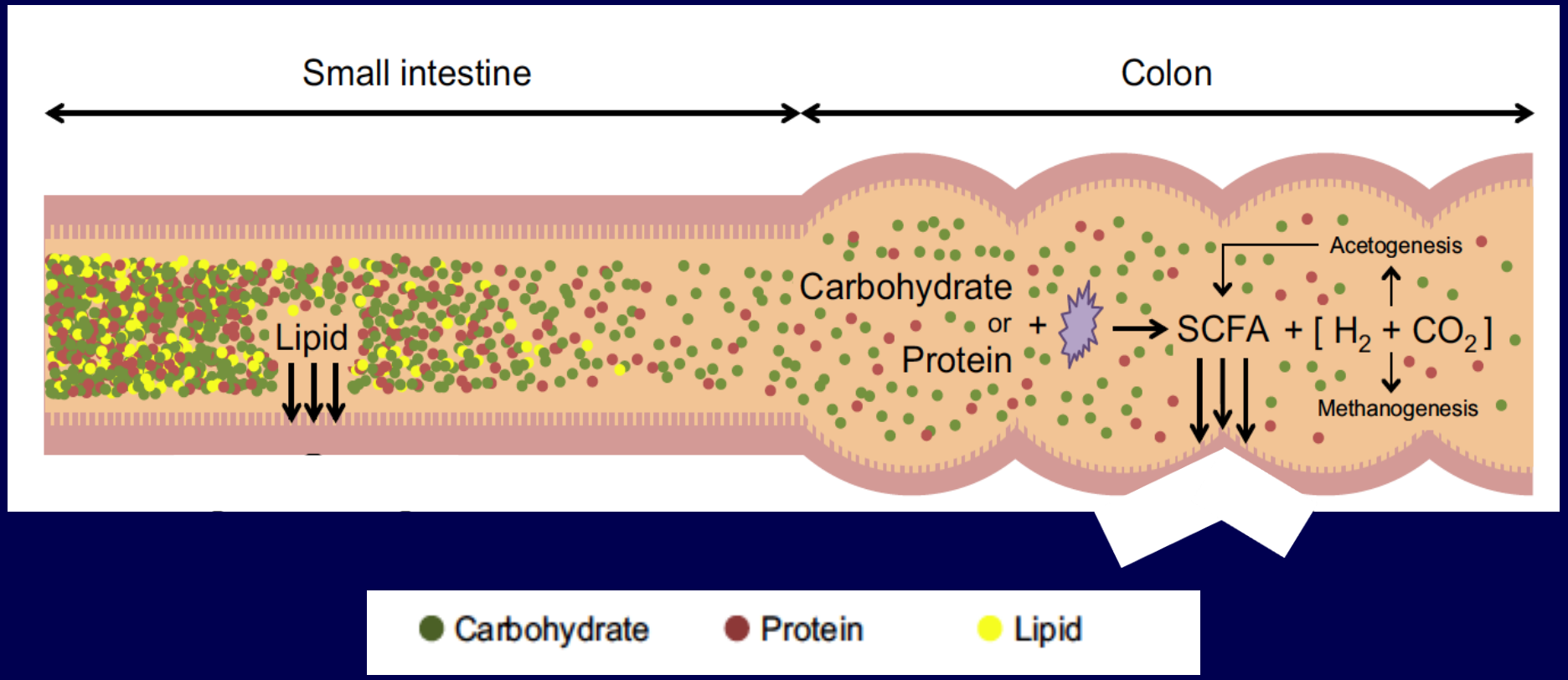
■ Mice colonized with a microbiota from a lean donor

□ Mice colonized with a microbiota from an obese donor

No significant difference in chow consumption, initial body fat, or initial weight

Turnbaugh et al. Nature 2006;444:1027-31.

Gut microbes increase dietary energy harvest

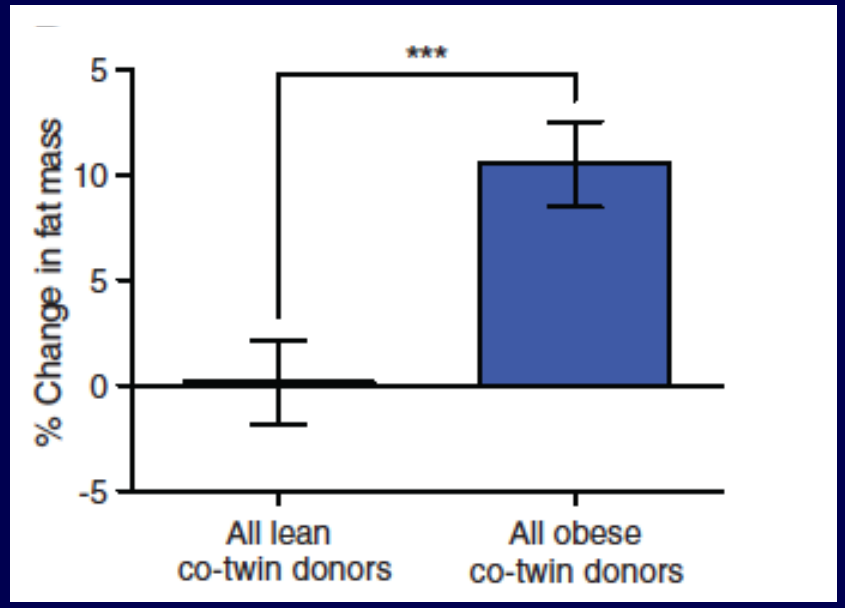


Turnbaugh et al. Nature 2006;444:1027-31.
Carmody and Turnbaugh, Cell Host Microbe 2012;12:259-61.

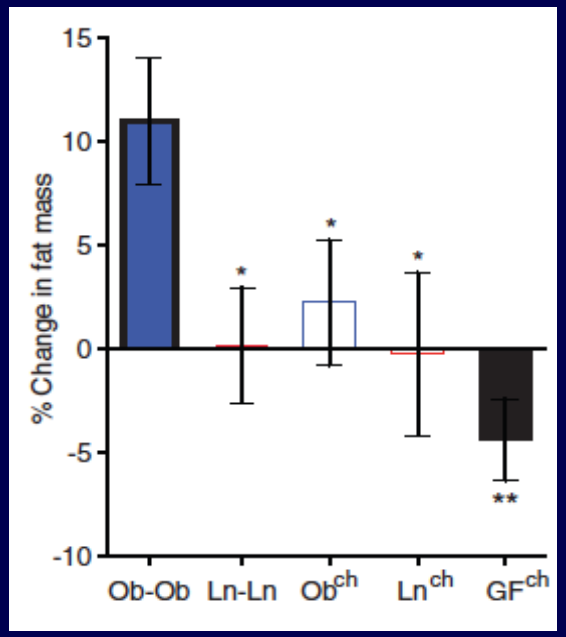
Multiple indirect mechanisms have been proposed

1. Microbial metabolites signal to the host to **increase fat storage** (Backhed et al. PNAS 2004; Samuel et al. PNAS 2008)
2. Microbial products **"leak" into circulation** inducing an inflammatory immune response (Cani et al. Diabetes 2008; Fei and Zhao. ISME J 2012)
3. Microbial products signal to the immune system to prevent the **"browning"** of white adipose tissue (Suarez-Zamorano et al. Nature Medicine 2015)

Adiposity can be transmitted from humans to mice



Discordant human twins can transmit phenotype to germ-free mice



Mice are rescued by exposure to the “lean” gut microbiota

Ridaura et al. Science 2013.

Initial FMTs in humans have been unsuccessful…

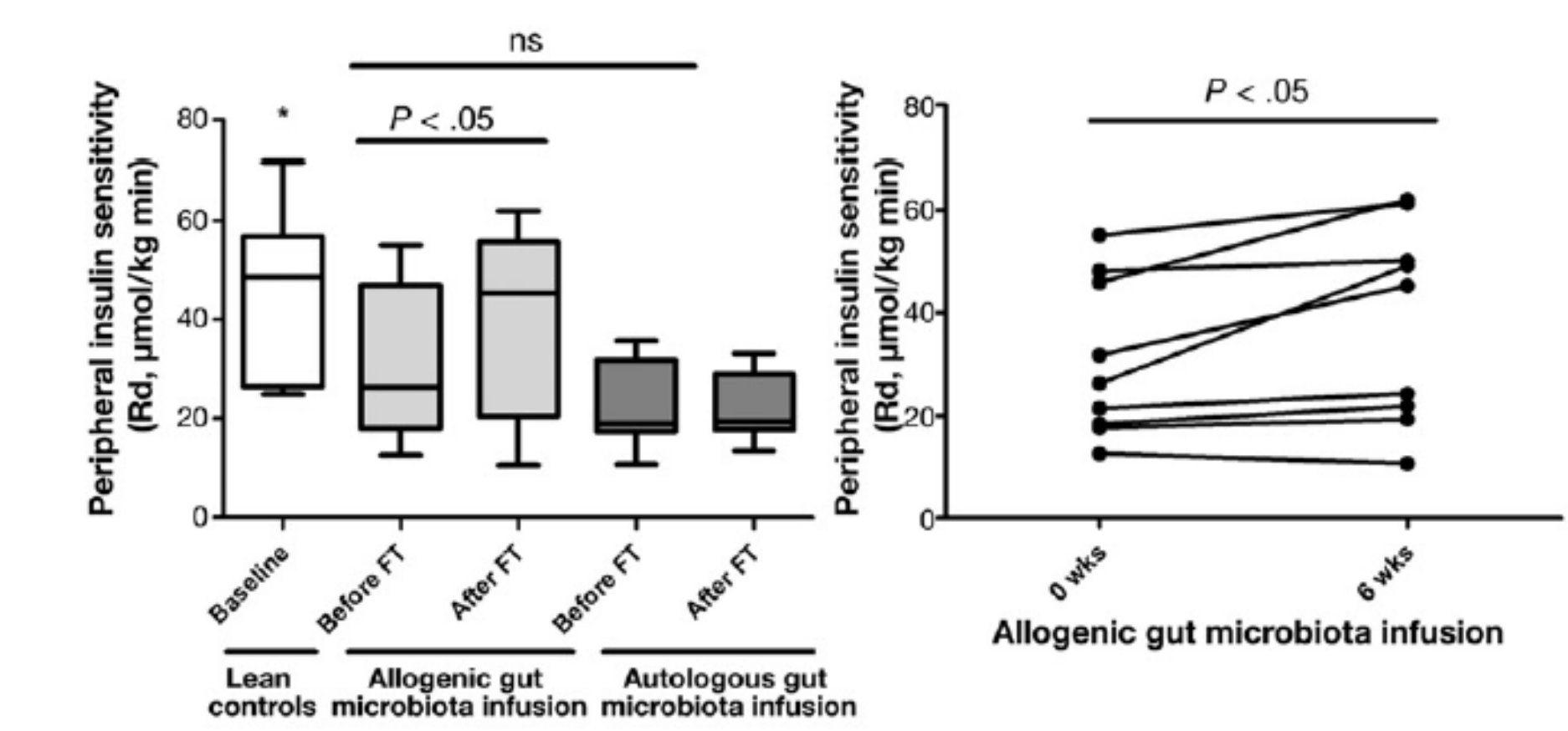
Supplementary Table 1. Characteristics of Study Subjects at Baseline and After 6 Weeks

	Allogenic group (N = 9)		Autologic group (N = 9)	
	Baseline	6 weeks	Baseline	6 weeks
Age, *y*	47 ± 4		53 ± 3	
Length, *cm*	185 ± 2		178 ± 2	
Weight, *kg*	123 ± 6	122 ± 6	113 ± 7	113 ± 7
Body mass index, *kg/m²*	35.7 ± 1.5	35.6 ± 1.4	35.6 ± 1.5	35.7 ± 1.6
Body fat mass, *%*	40 ± 1	40 ± 1	39 ± 2	39 ± 1
Fasting plasma glucose, *mmol/L*	5.7 ± 0.2	5.7 ± 0.2	5.7 ± 0.2	5.7 ± 0.2
Glycated hemoglobin, *mmol/mol*	39 ± 1.1	38 ± 1.2	40 ± 1.5	39 ± 3
Cholesterol, *mmol/L*	4.5 ± 0.4	4.6 ± 0.4	4.8 ± 0.3	4.8 ± 0.2
HDLc	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	0.9 ± 0.1
LDLc	3.1 ± 0.4	3.0 ± 0.3	2.9 ± 0.2	2.9 ± 0.2
TG	1.4 ± 0.3	1.5 ± 0.4	1.6 ± 0.3	1.8 ± 0.4
Plasma free fatty acid, *mmol/L*	0.5 ± 0.1	0.5 ± 0.1	0.7 ± 0.2	0.5 ± 0.1
Systolic blood pressure, *mm Hg*	138 ± 3	132 ± 6	140 ± 2	142 ± 8
Diastolic blood pressure, *mm Hg*	85 ± 2	83 ± 5	84 ± 2	86 ± 6

NOTE. Values are expressed as mean ± standard error of the mean. The body mass index is the weight in kilograms divided by the square of the height in meters. No significant differences in clinical variables were found between baseline and 6 weeks in both treatment groups.
HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; TG, triglycerides.

Vrieze et al. Gastroenterology 2012;143:913-16.

…Although insulin sensitivity was improved



Vrieze et al. Gastroenterology 2012;143:913-16.

Case report: transfer of obesity via FMT

Weight Gain After Fecal Microbiota Transplantation

Neha Alang[1] and Colleen R. Kelly[2]

[1]Department of Internal Medicine, Newport Hospital, and [2]Division of Gastroenterology, Center for Women's Gastrointestinal Medicine at the Women's Medicine Collaborative, The Miriam Hospital, Warren Alpert School of Brown University, Providence, Rhode Island

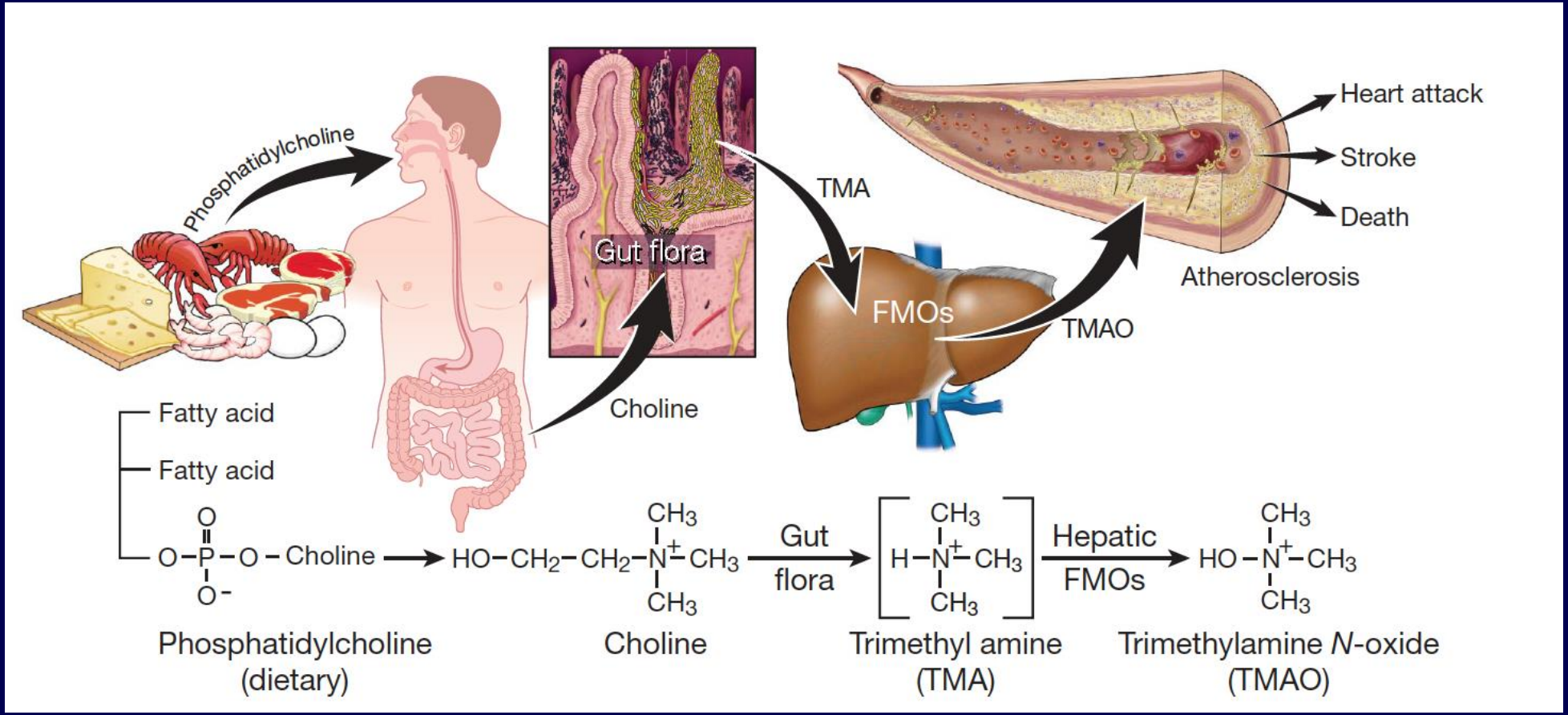
Fecal microbiota transplantation (FMT) is a promising treatment for recurrent *Clostridium difficile* infection. We report a case of a woman successfully treated with FMT who developed new-onset obesity after receiving stool from a healthy but overweight donor. This case may stimulate further studies on the mechanisms of the nutritional-neural-microbiota axis and reports of outcomes in patients who have used non-ideal donors for FMT.

Keywords. *Clostridium difficile* infection; fecal microbiota transplantation; gut microbiota; obesity.

- 32 year-old female diagnosed w/recurrent *Clostridium difficile* infection
- 10 days oral metronidazole, 14 days oral vancomycin, triple therapy (amoxicillin, clarithromycin, PPI), 12 weeks tapering course of vancomycin, rifaximin
- Opted for FMT from daughter (slightly overweight; initial BMI=26.4 increased during study to 32)
- Patient had been **weight stable** during antibiotic treatment
- 16 months later – patient had gained 34 lbs, BMI=33
- 36 months later – BMI=34.5

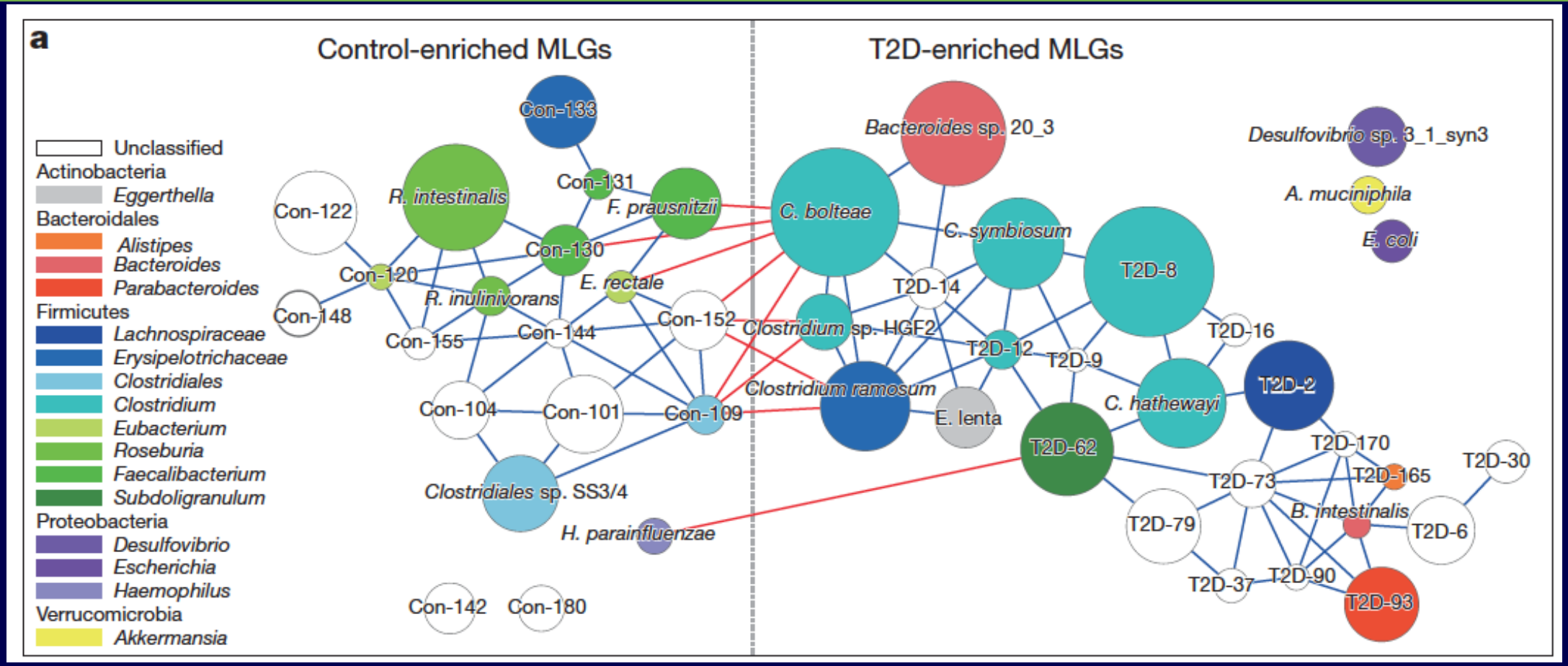
Alang and Kelly. Open Forum Infect Dis 2015; doi: 10.1093/ofid/ofv004

Broader relevance to cardiometabolic disease: atherosclerosis



Wang et al. Nature 2011;472:57-63.

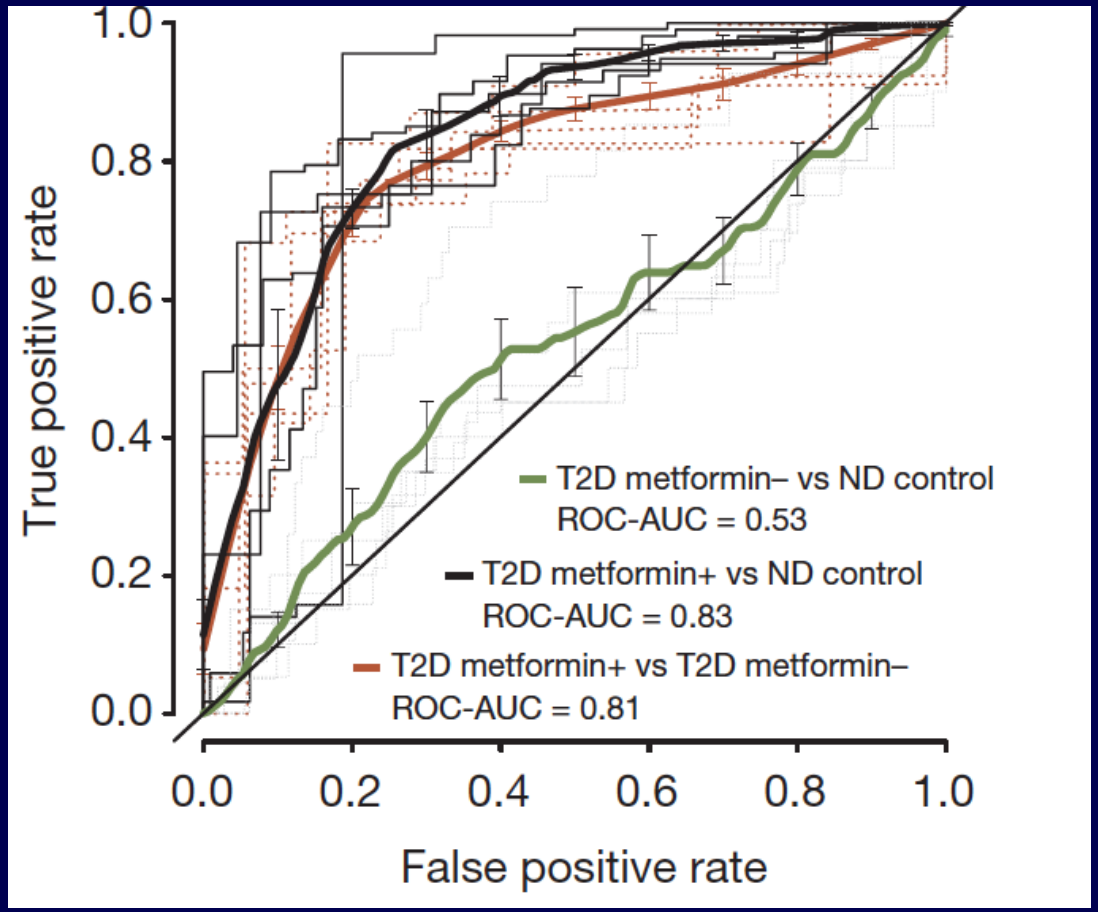
Broader relevance to cardiometabolic disease: type 2 diabetes



No overlap in an independent Swedish cohort! (Karlsson et al. Nature 2013)

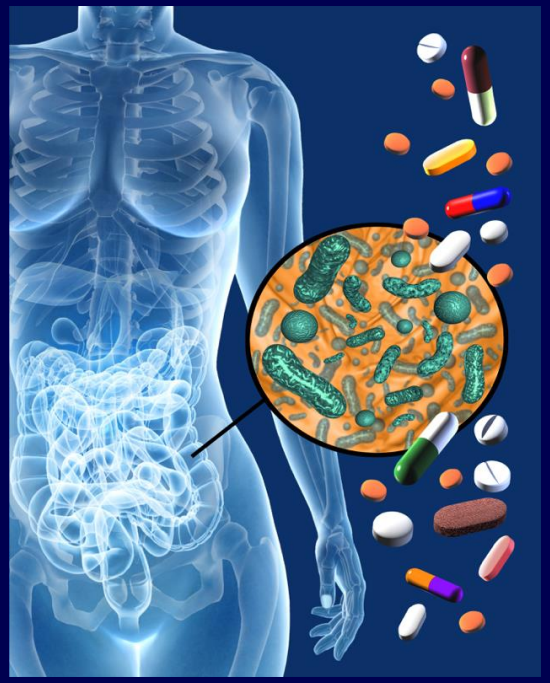
Qin et al. Nature 2012;490:55-60.

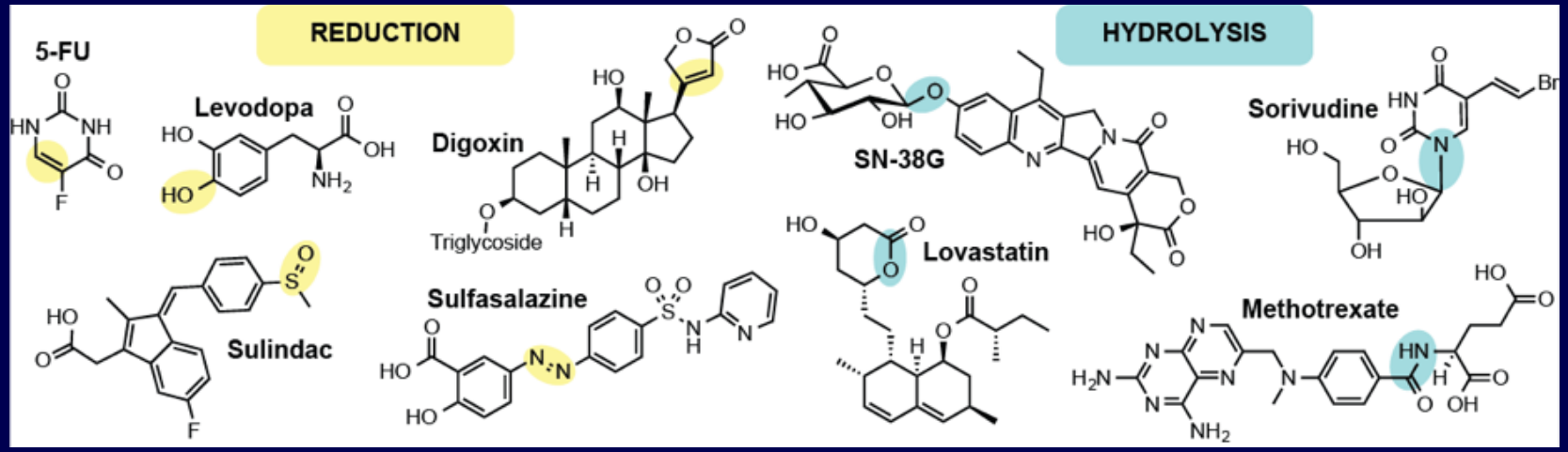
A cautionary tale: treatment confounds microbiome associations



Forslund et al. Nature 2015; doi:10.1038/nrendo.2015.222

The microbiome impacts drug response

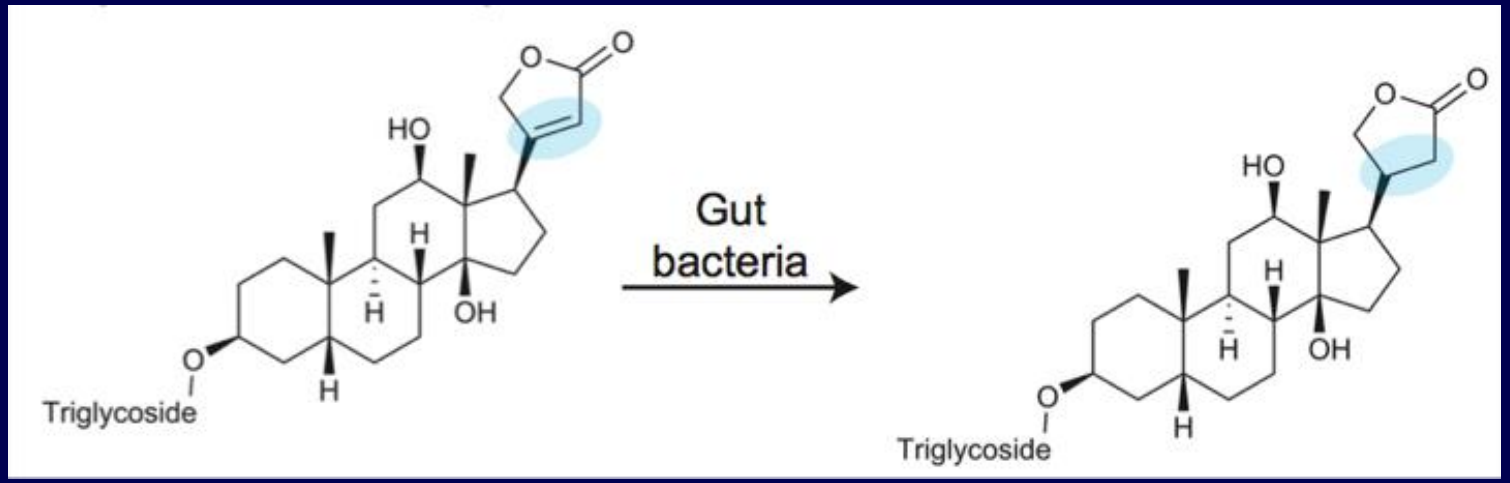




- Most of the genes responsible are **unknown**
- Cannot **predict** which patients are at risk or prevent these biotransformations
- May contribute to the **high cost** of new drugs ($5 billion)

Spanogiannopoulos et al. Nature Rev Micro. In press.

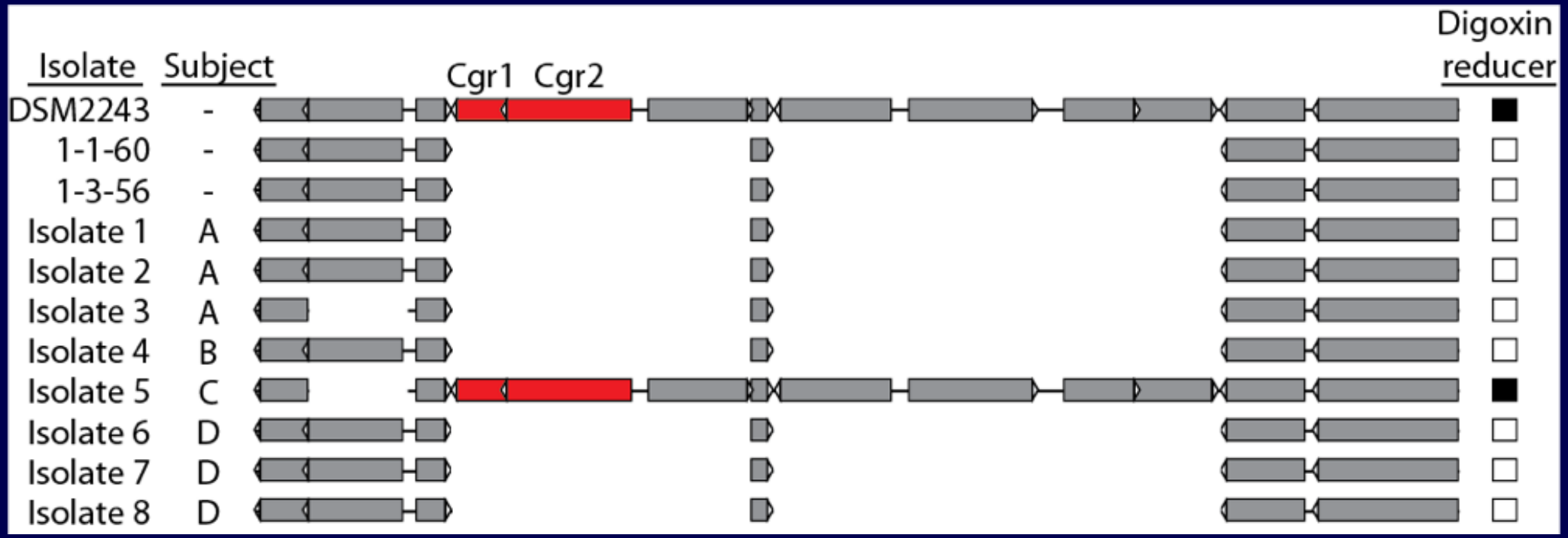
Identifying microbial genes for drug inactivation



- Narrow therapeutic range due to **high toxicity**
- **~3 million** heart failure and arrhythmia patients/year
- In development for **cancer** and **autoimmune disease**

Haiser et al. Science 2013; doi: 10.1126/science.1235872

Finding and validating genes unique to metabolizers



Haiser et al. Science 2013; doi: 10.1126/science.1235872

Immediate clinical implications

Diagnostics

Therapeutics

Spanogiannopoulos et al. Nature Rev Micro. In press.

Not ready for prime time

- **Findings** from the microbiome field have not been translated into clinical practice yet
- Good news = microbiome is plastic, rapid pace of basic research findings, lots of start-ups and established companies entering this area now
- Bad news = we don't know what the **optimal** microbiome looks like and we don't know **how** to get there
- What is clear is that to understand and improve human medicine we can no longer **ignore** our microbial partners

Acknowledgements

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