The Human Microbiome and [Faecal] Microbial Transplantation

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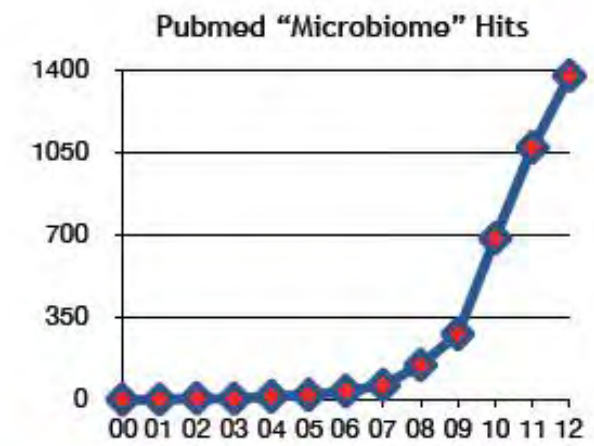
Why?

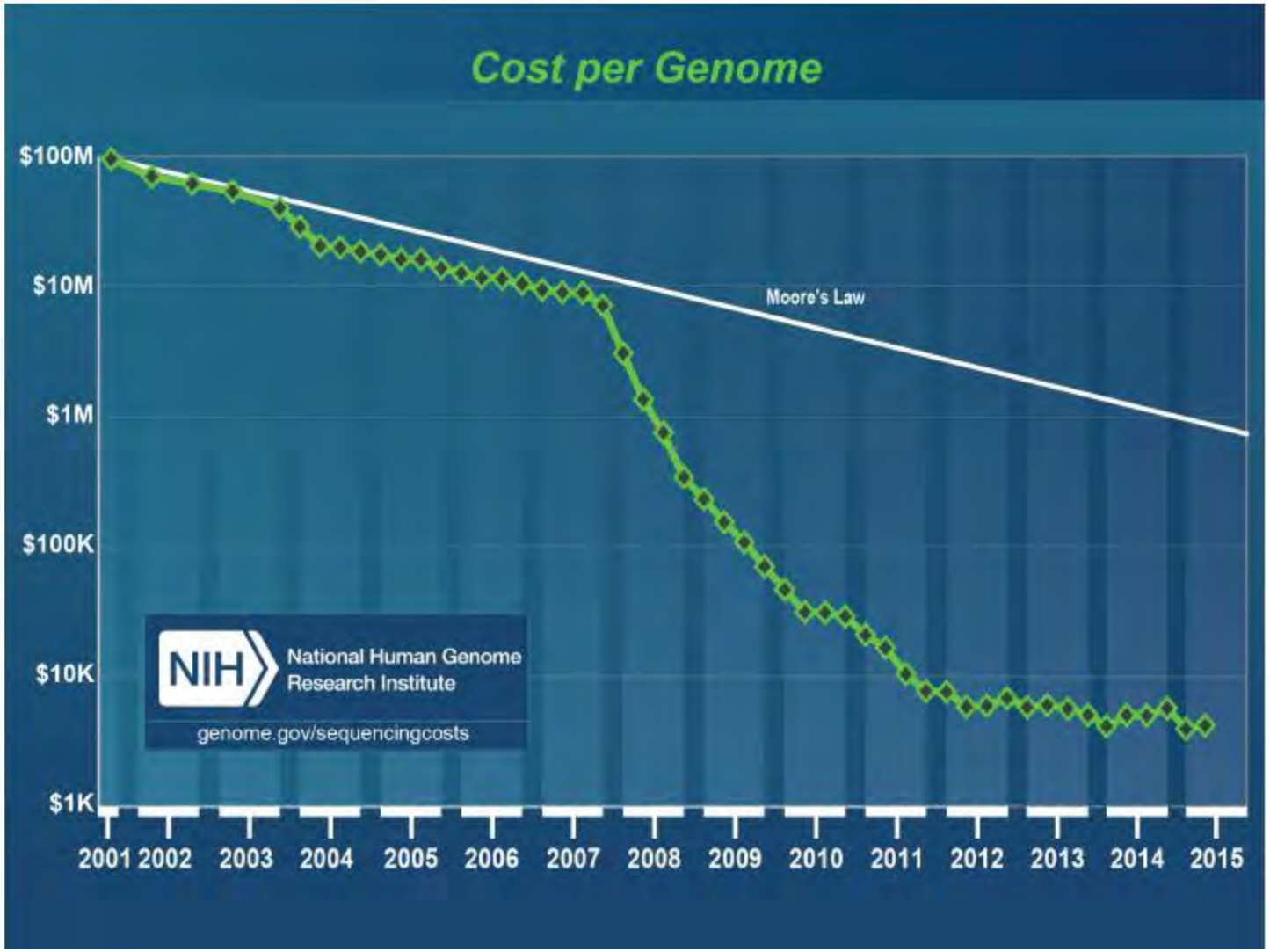
- Increasing interest in the role of the microbiome in shaping health and disease
- Rapid technological advances
- Stand-out example of a therapeutic effect
- Tsunami of chronic disease fuelled by obesity

What?

- Definitions and technology
- Microbial functions
- Age-related change
- Factors that influence the microbiome
- Microbial imbalance – “dysbiosis”
- Therapeutic strategies



NIH HUMAN MICROBIOME PROJECT


Cost per Genome
$100M
$10M
$1M
$100K
$10K
$1K
Moore's Law
NIH
National Human Genome Research Institute
genome.gov/sequencingcosts
2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015

Definitions

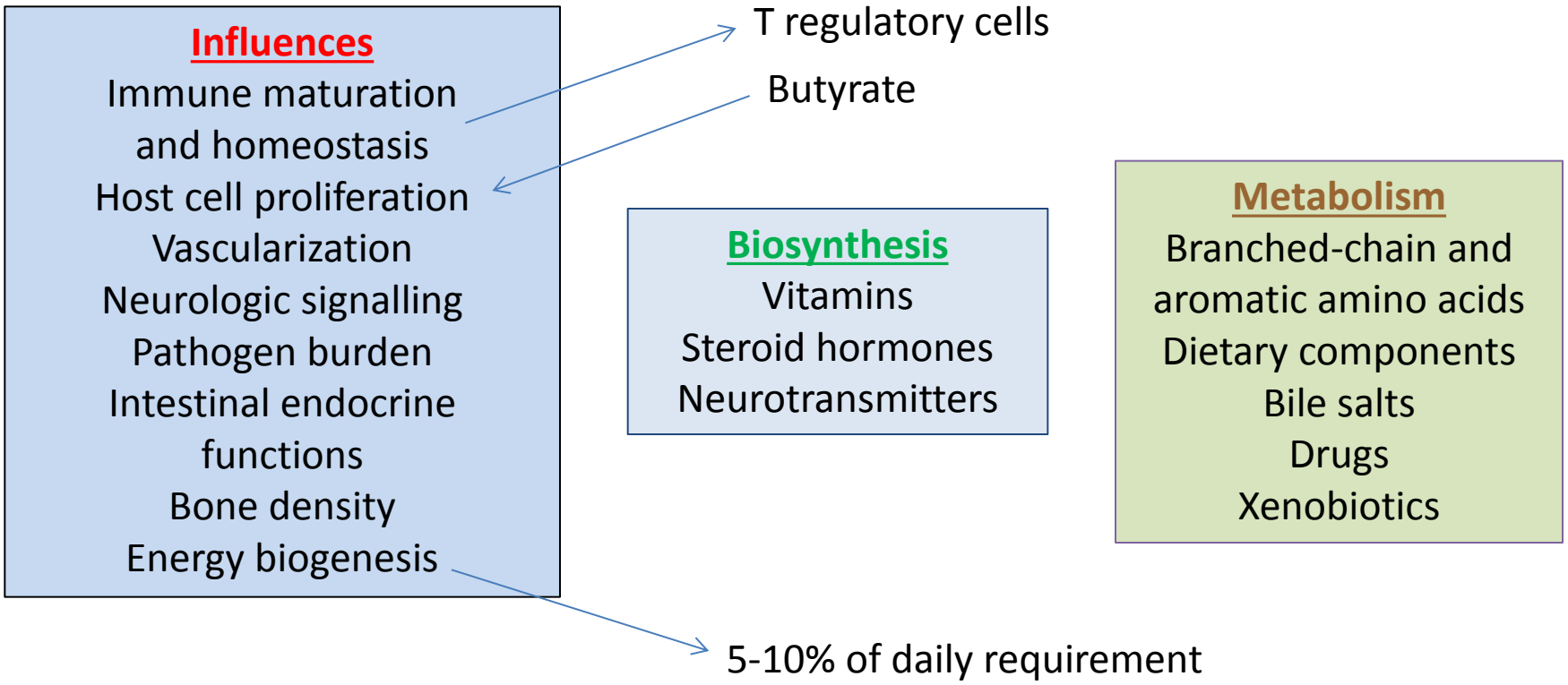
- Microbiome – microbial encoding genes
- Microbiota – micro-organisms
- Hologenome – Host and microbial genes
- Holobiont – an individual host and its microbial community
- Metagenome – all the genetic material in a given sample (eg faecal sample)
- Pathobiont – a benign commensal microbe that can elicit pathogenesis under certain environmental conditions

Technology

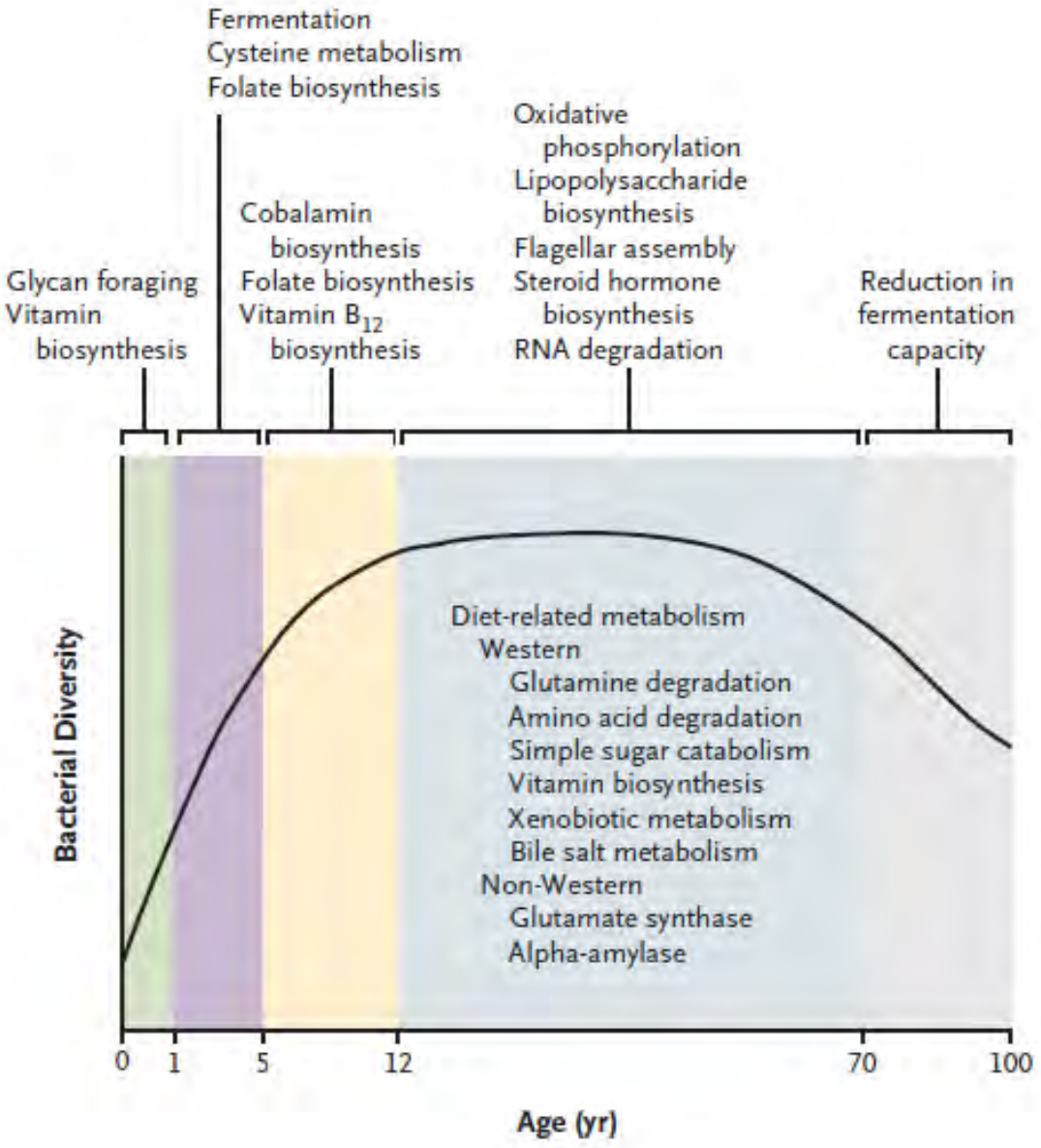
Approach	Data	Platform
Biomarker sequencing (e.g., 16S rRNA gene or internal transcribed spacer region)*	Community composition	Next-generation sequencing Semi-quantitative, genus level resolution
Metagenomics	Generation of draft genomes, functional capacity, growth dynamics	Next-generation sequencing Strain-level, quantitative, functional data
Metatranscriptomics (RNA sequencing)	Gene expression	Next-generation sequencing Highly expressed genes favoured
Metaproteomics	Protein expression	Liquid or gas chromatography–mass spectrometry
Metabolomics	Metabolic productivity	Liquid or gas chromatography–mass spectrometry or magnetic resonance spectroscopy

Detects metabolites from microbes, diet, host; depends on data dictionary

Microbial functions

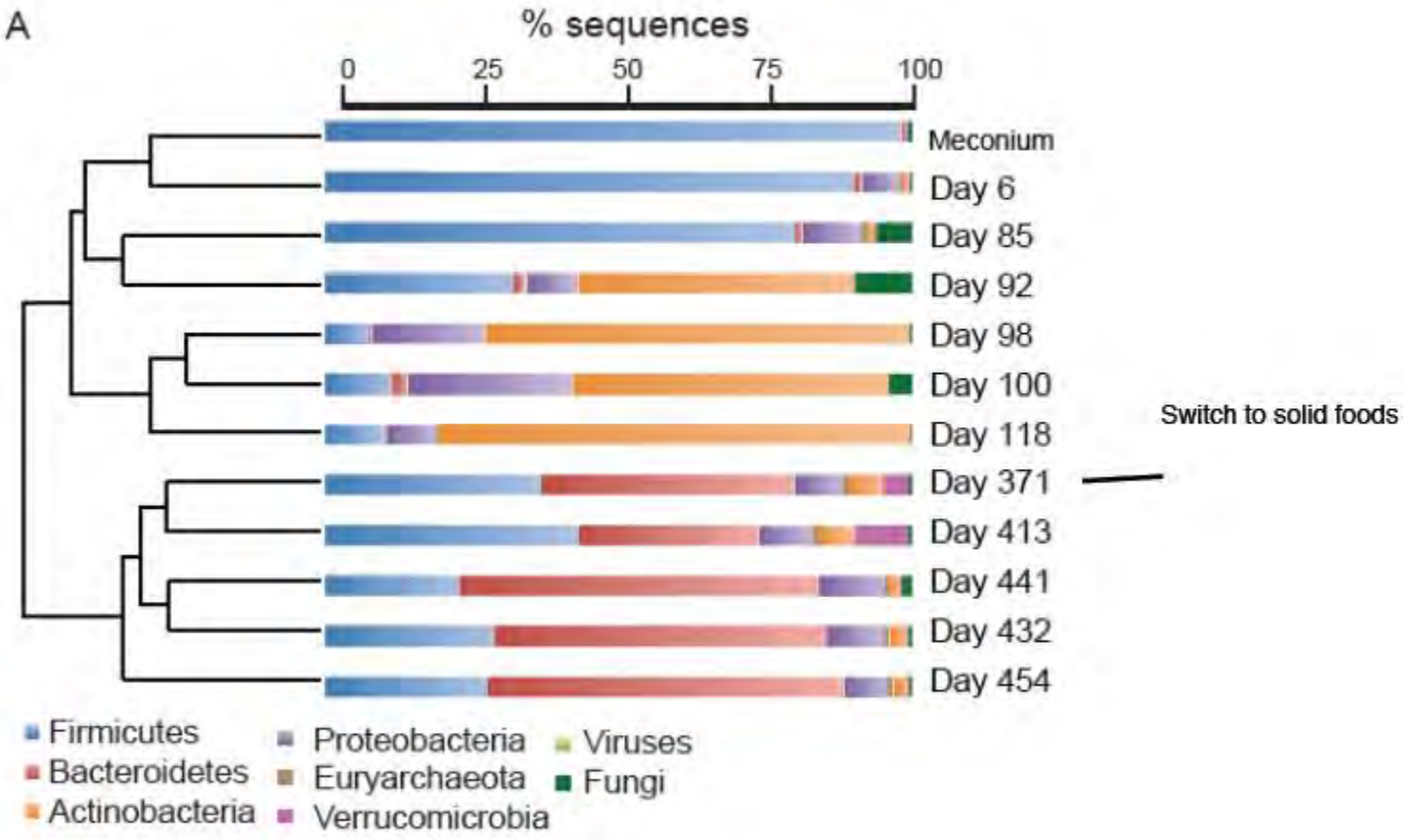


Age-related development of the intestinal microbiome



- Mode of delivery
- Major adult microbiota are Bacteroidetes and Firmicutes
- Enormous variation between individuals
- Functionally similar

Microbiome changes after birth



Cesarean delivery and childhood disorders

Cesarean Delivery Associated Childhood Diseases[1,2]	
Allergic Rhinitis	
All Cesareans	1.37 (1.14-1.63)
Repeat Cesareans Only	1.78 (1.34-2.37)
Asthma	
All Cesareans	1.24 (1.01-1.53)
Female	1.53 (1.10-2.10)
Female & Repeat Cesarean [3]	1.83 (1.13-2.97)
Celiac Disease	1.80 (1.13-2.88)
Diabetes Mellitus (Type 1)	1.19 (1.04-1.36)
Gastroenteritis [4]	1.31 (1.24-1.38)
Gastroenteritis AND Asthma	1.74 (1.36-2.23)

Cesarean delivery in US increased 48% between 1996 and 2007 – to 31.8%

From Neu J, Rushing J. Clinical Perinatology 2011

Influences on the microbiome

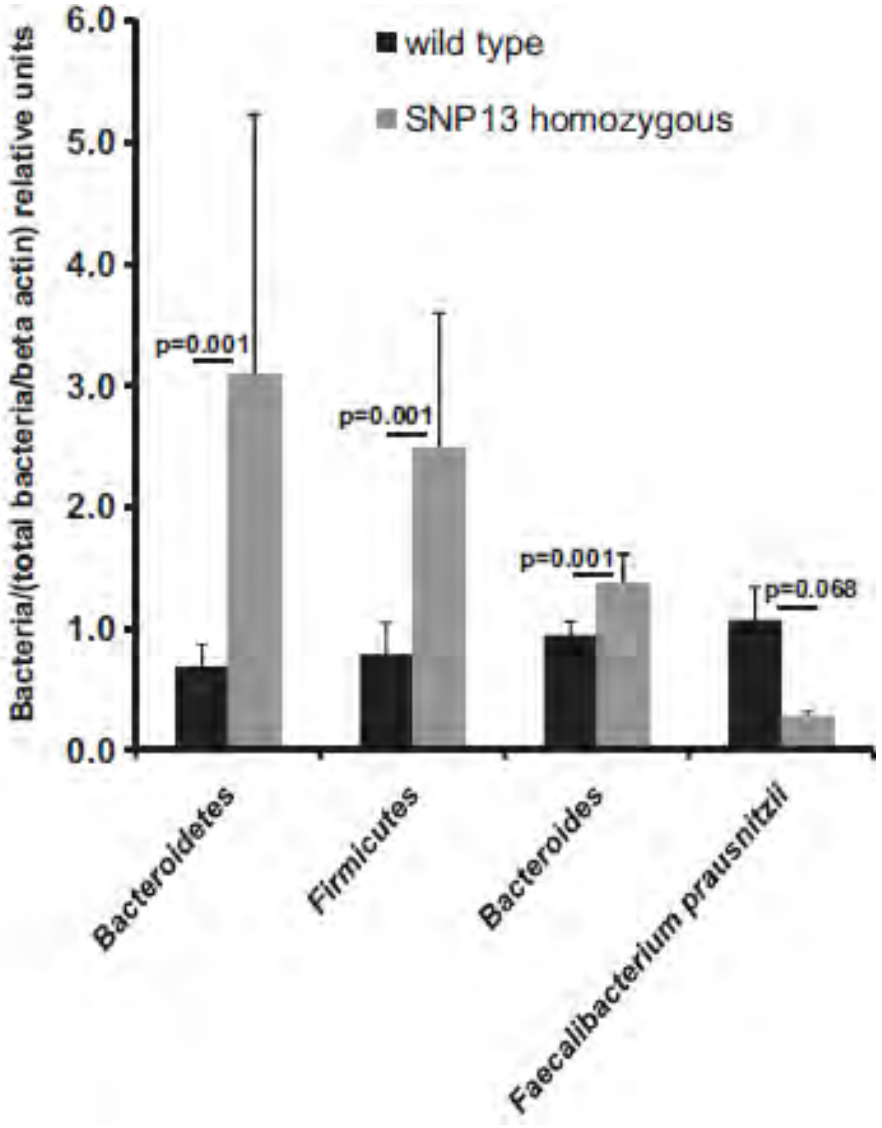
- Host genetic factors
- Diet (including infant feeding, supplements)
- Host immune response
- Smoking
- Antibiotics and other drugs
- Infections
- Diurnal rhythm
- Environmental microbial exposures

Nod2 is essential for temporal development of intestinal microbial communities

Ateequr Rehman,[1] Christian Sina,[2] Olga Gavrilova,[1] Robert Häsler,[1] Stephan Ott,[2] John F Baines,[3,4] Stefan Schreiber,[1,2] Philip Rosenstiel[1]

- Nod2 is an intracellular sensor of muramyl dipeptide, a component of bacterial cell walls
- It is a major susceptibility gene for Crohn's disease – homozygotes for a disease-associated mutation carry a 20-40 fold increased disease risk
- Both mouse models and human studies show a significantly increased load of commensal bacteria in those carrying Nod2 mutations

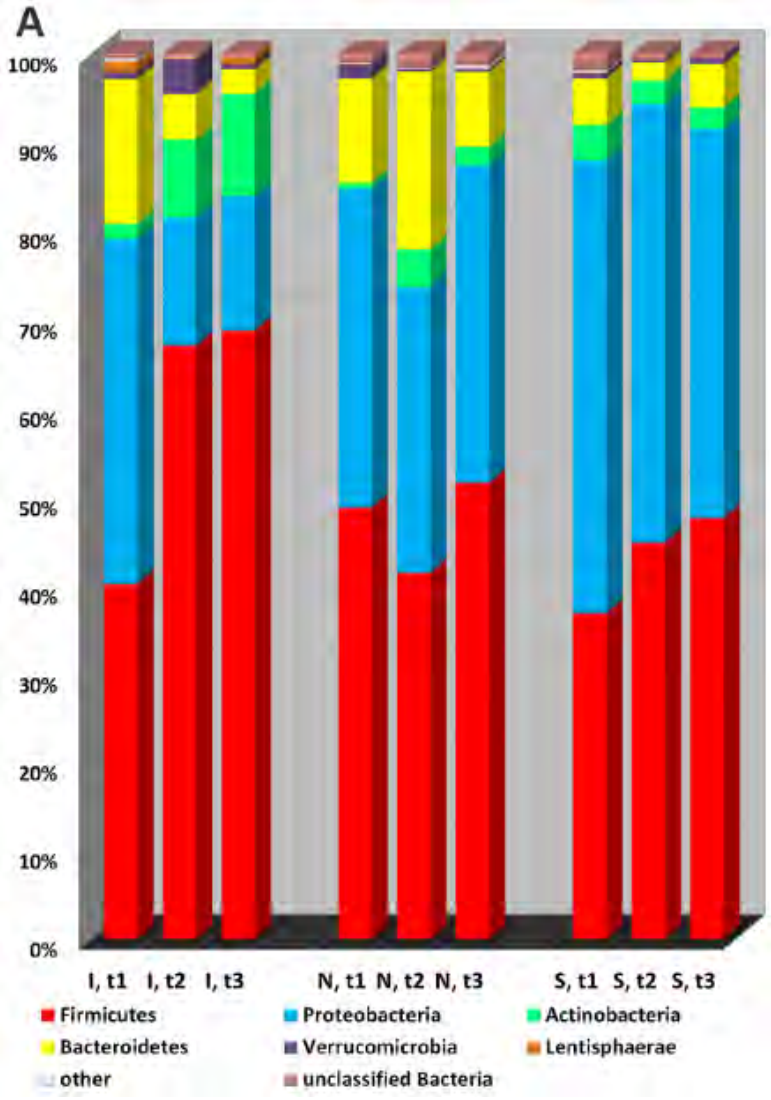
Relative abundance of microbiota in human subjects with or without Nod2 mutations



Results for the mucosa-associated microbiota using tissue biopsies taken from the terminal ileum

Smoking Cessation Induces Profound Changes in the Composition of the Intestinal Microbiota in Humans

Luc Biedermann[1], Jonas Zeitz[2], Jessica Mwinyi[1,3], Eveline Sutter-Minder[4], Ateequr Rehman[5¤],



- Stool samples
- 9 week period
- Small numbers (10 + 10)
- Increased microbial diversity with smoking cessation
- Similar shifts to obese→lean

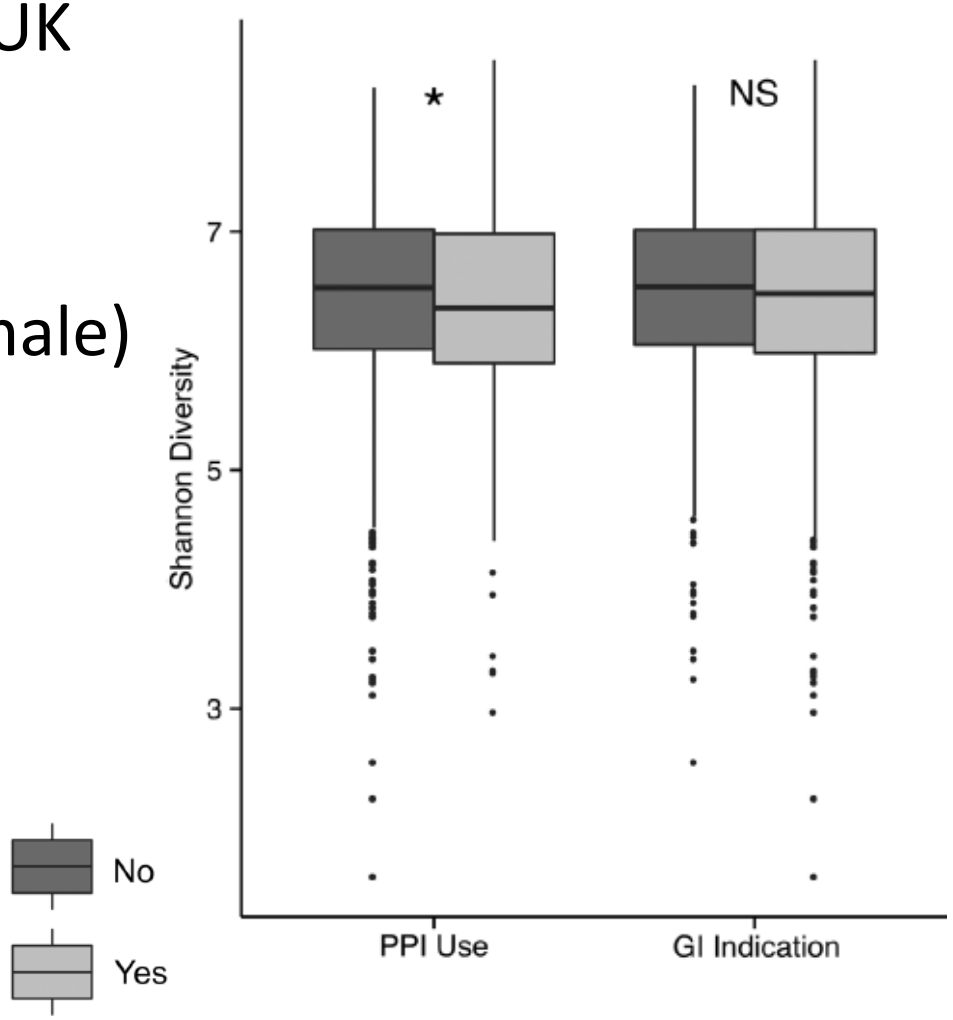
PPIs alter the intestinal microbiome

- PPI data within the TwinsUK cohort
- Self-reported
- 1827 individuals (90% female)
- Average age – 62 years
- PPI users significantly:

  Older ($p<10^{-6}$)

  Frailer ($p<10^{-15}$)

  Higher BMI ($p=0.0003$)



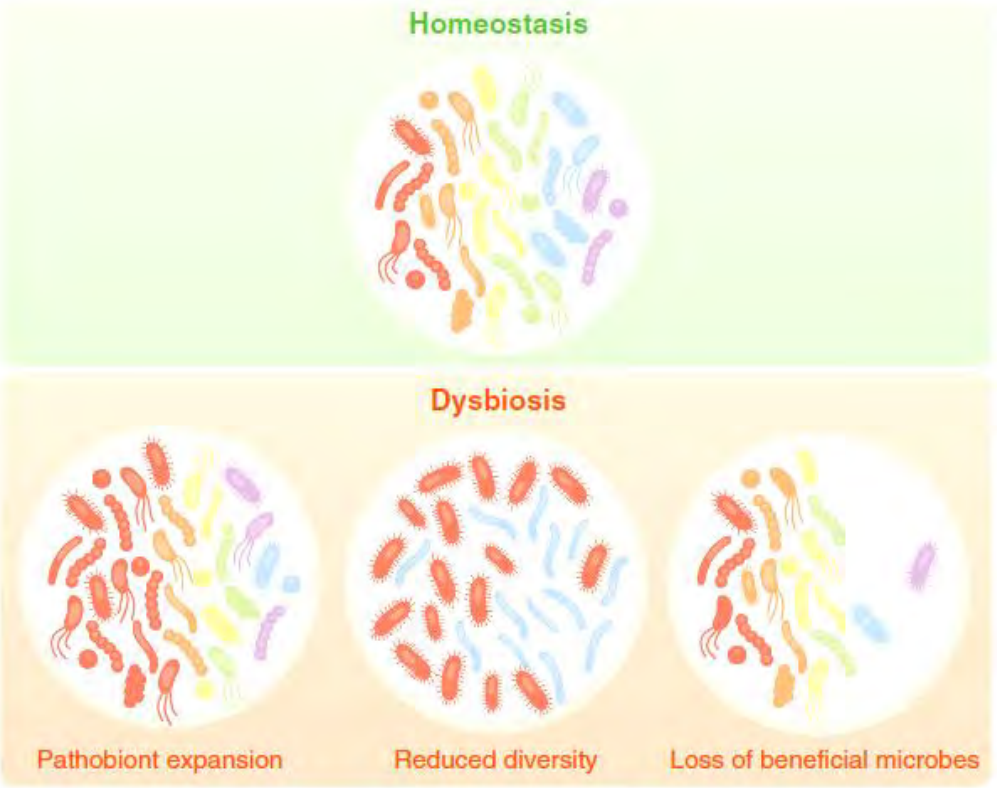
From Jackson MA, et al. Gut 2016

Major findings in PPI users as compared to not:

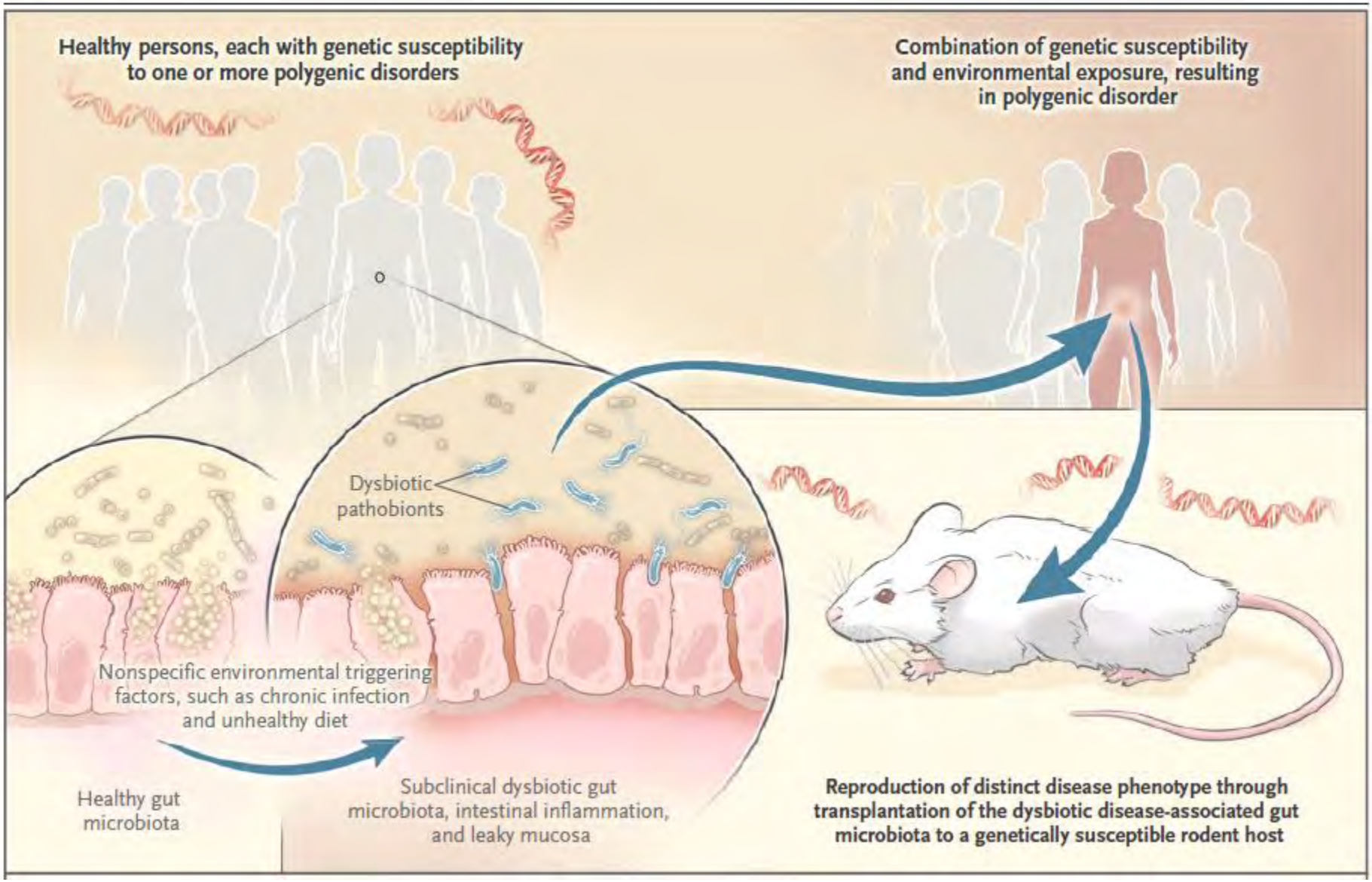
- Lower abundance of commensals
- Reduced microbial diversity
- Increased oral and pharyngeal commensals
- ↑ Streptococcaceae
- Replicated in independent study of MZ twins discordant for PPI use

Dysbiosis – microbial imbalance ± maladaptation

- Change in microbial composition relative to healthy individuals
- What is a healthy human microbiome?



Terms	Publications	
	All	2011–2016
Gut | colon | intestinal	17,546	10,707
Oral | mouth | tongue | tooth | subgingival | supragingival	4843	2089
Urogenital | vaginal | penile	1477	706
Skin | cutaneous	1372	754
Airway | lung	764	524
Placenta | breast milk	702	426
Ocular | eye	152	82



The "Common Ground" Hypothesis of disease attributed to dysbiotic intestinal microbiota (from: Lynch S 2016)

Disease associations

- Atherosclerosis
- Metabolic disorders (obesity, Type II diabetes)
- Asthma
- Autism spectrum disorder
- Inflammatory Bowel Diseases

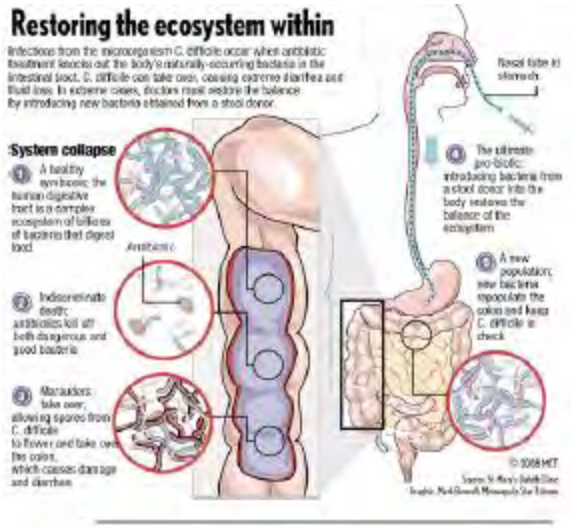
Human studies

- Majority used 16S ribosomal RNA sequencing

- Useful insights but multiple issues:
  variability within and across individuals
  lifestyle factors – diet, smoking
  reproducibility
  sampling
  statistical power
  heterogeneity within and between cases/controls
  adjustment for drug effects
  need for longitudinal and interventional studies

Coprophagia

Fecal “transplants”



Fecal transplant: Sounds gross but saves lives

ERIK ORTIZ

Thursday, September 27, 2012

An Atlanta-area woman found relief from a bacterial infection in her colon when her mom provided a life-saving transplant — involving fecal matter.

While a fecal-matter transplant sounds stomach turning, it ensured 20-year-old Kaitlin Hunter a normal life again after a devastating car accident that nearly killed her.

“I’ve been so happy,” Hunter, of Marietta, told CNN on Wednesday after the July surgery. “I’m cured.”

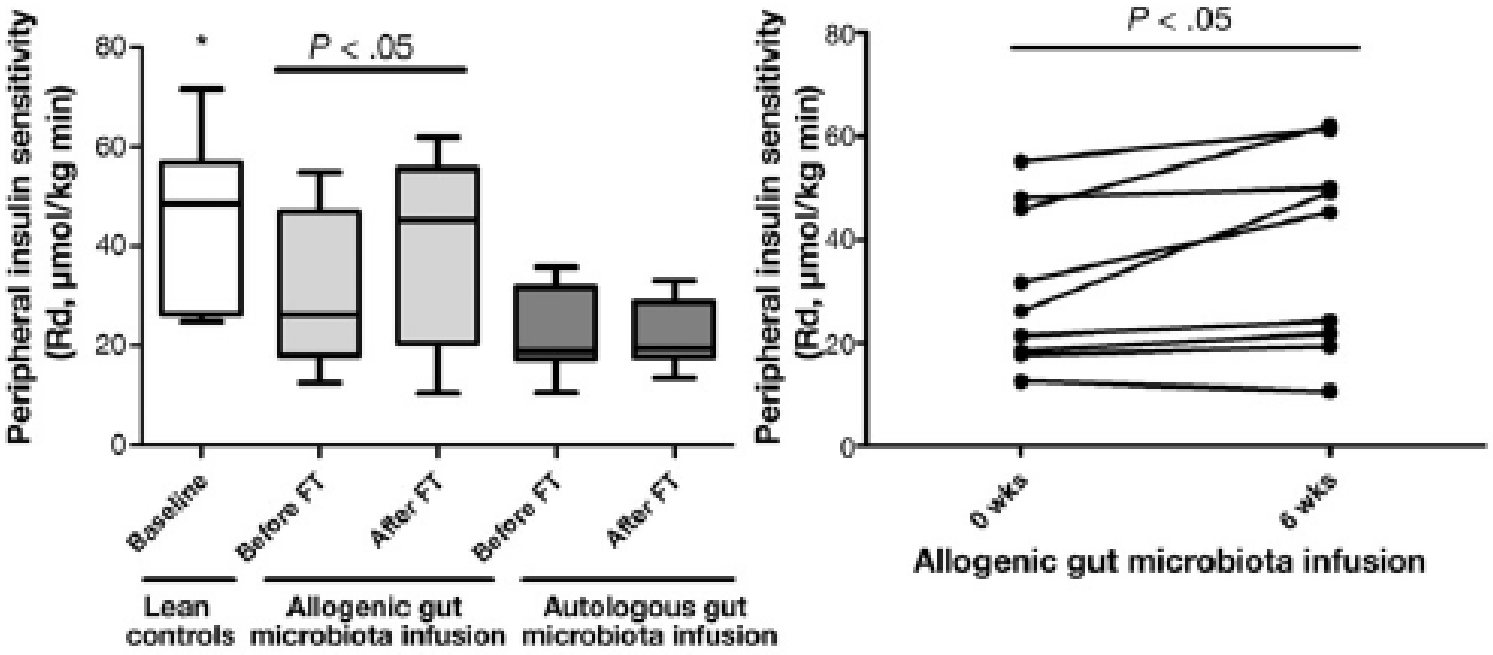
Hunter’s ordeal began after a June 2011 car accident in California that left her with a fractured spine and damaged liver and colon, CNN said.

Kaitlin Hunter of Marietta, Ga., who underwent a fecal transplant from...

Longitudinal studies

Transfer of Intestinal Microbiota From Lean Donors Increases Insulin Sensitivity in Individuals With Metabolic Syndrome

ANNE VRIEZE,* ELS VAN NOOD,* FRITS HOLLEMAN,* JARKKO SALOJÄRVI,‡ RUUD S. KOOTTE,§



Interventional studies - FMT

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D.,

- Established role in Clostridium difficile dysbiosis
- Success rate close to 90% [CI, 84-93%]
- Three randomized, controlled trials (to 2016)
- 127 CDI cases – NNT = 2!

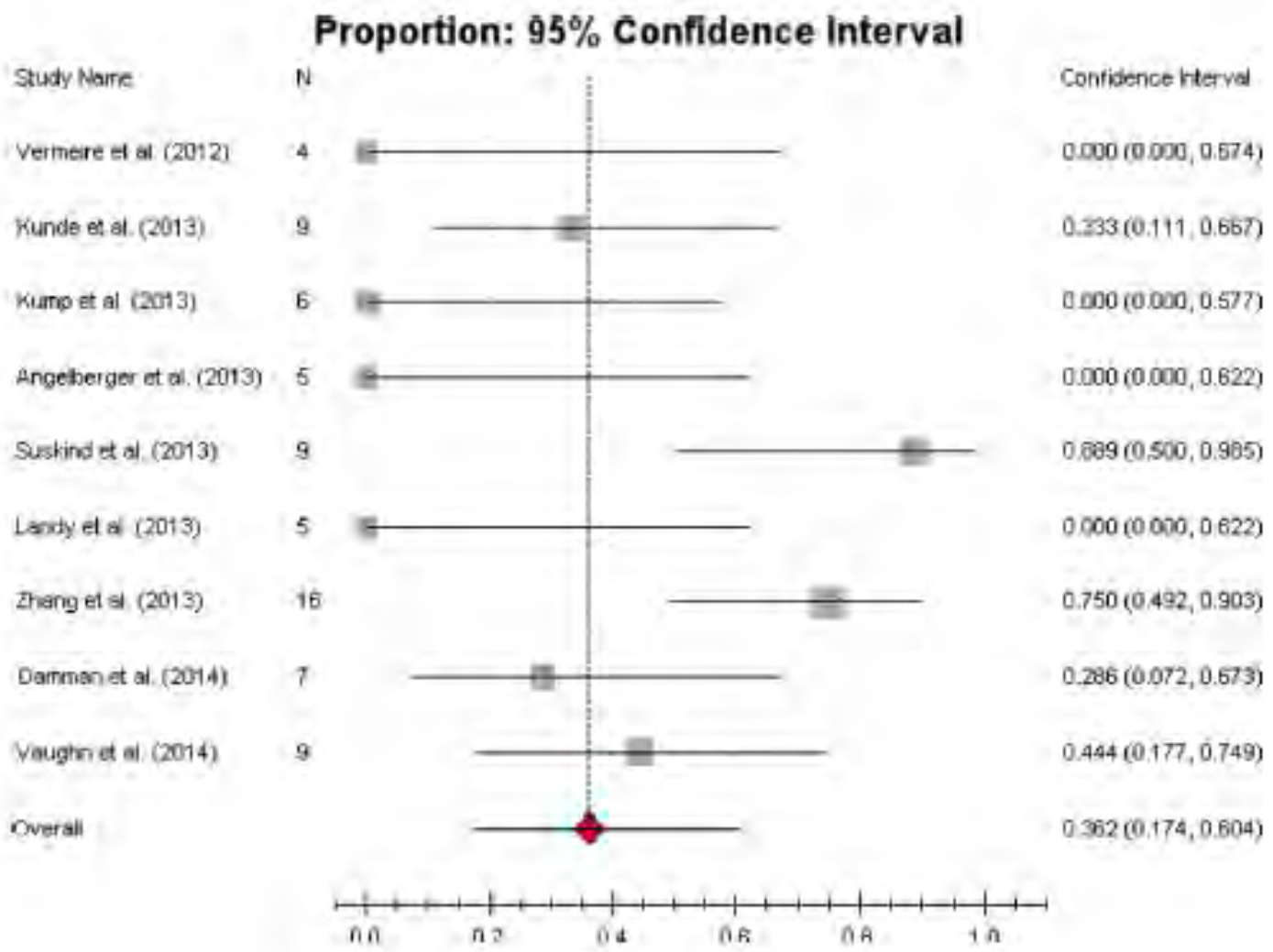
FMT in IBD – meta-analysis

- 18 studies to Q4 2014
- 79 UC and 39 CD described
- 45% of cases achieved clinical remission (CR)
- 36.2% CR in 9 cohort studies
- 24% CR in UC
- 60.5% CR in CD

- Limited data on mucosal healing

Colman RJ, Rubin DT. JCC 2014

Forest plot of 9 cohort studies



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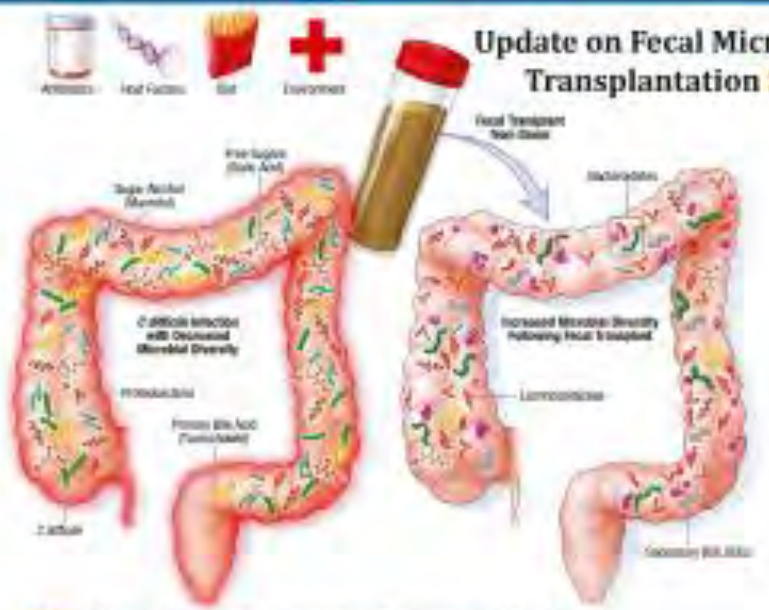


RCTs

Fecal Microbiota Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial

Paul Moayyedi,[1] Michael G. Surette,[1] Peter T. Kim,[2,3] Josie Libertucci,[1] Melanie Wolfe,[1]

Findings From a Randomized Controlled Trial of Fecal Transplantation for Patients With Ulcerative Colitis

Noortje G. Rossen,[1] Susana Fuentes,[2] Mirjam J. van der Spek,[1] Jan G. Tijssen,[3]

Multi-Donor Intense Faecal Microbiota Transplantation for Resistant Ulcerative Colitis: A Randomised Controlled Trial (The FOCUS Study)

Sudarshan Paramsothy

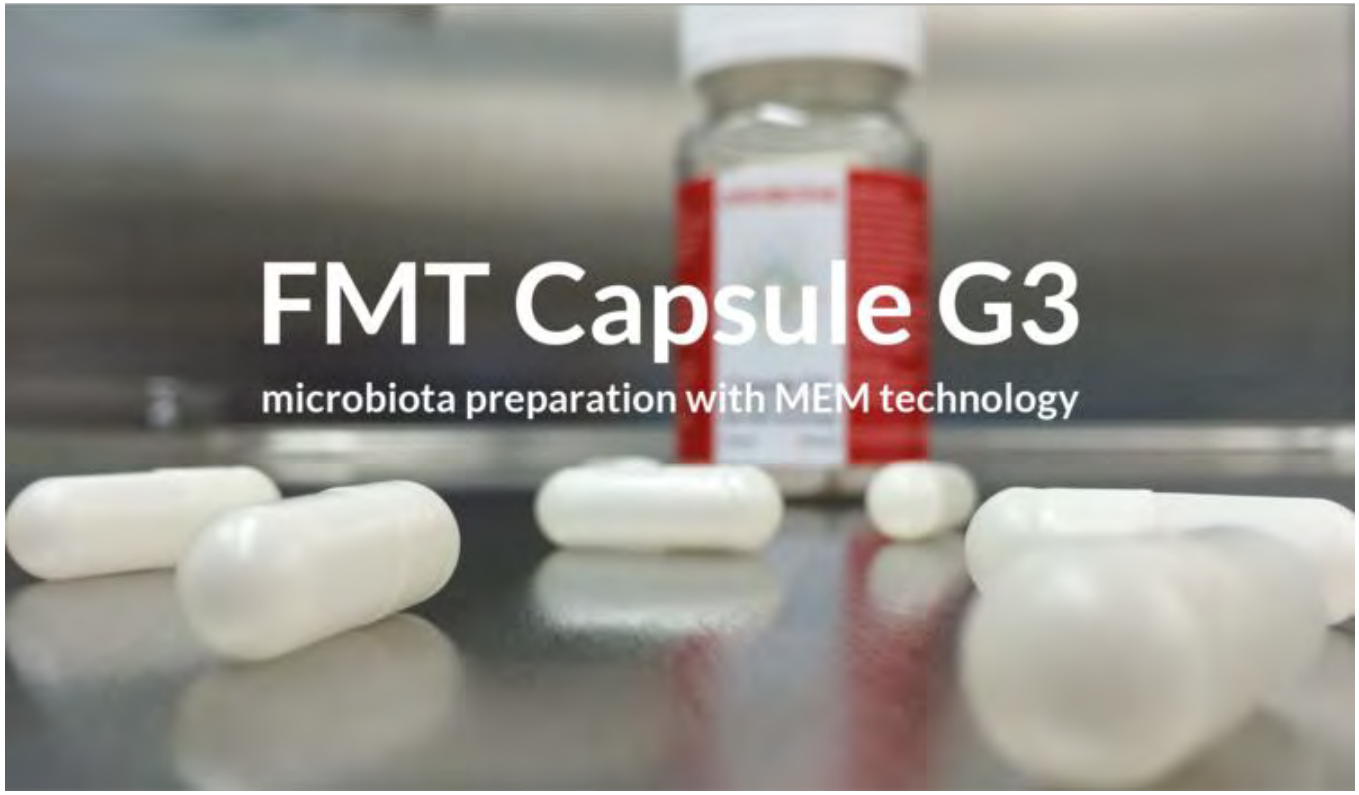
on behalf of the FOCUS Study Group

Factor	Canada	Netherlands	Australia
Disease severity	All-comers	Mild-moderate	Mild-moderate
Concomitant meds	Any – stable doses	Not biologic	Not biologic
Sites	1	1	3
Number of cases	75	48	81
Donors	Single HV	Known or HV	Mixed HV
Preparation	None	Bowel lavage	None
Route	Enema	NG	Scope, then enemas
Volume	50 ml	120 ml	150 ml
Frequency/duration	OW – 6 weeks	Weeks 0 and 3	5/week – 8 weeks
Primary outcome	Total Mayo≤2, Endo 0	SCCAI≤2, Endo improved by ≥1	Total Mayo≤2, Endo improved by ≥1
Time point	Week 7	Week 12	Week 8

Meta-analysis of 3 RCTs

- Based on clinical remission
- RR = 0.81 [95% CI = 0.71-0.92]
- NNT = 6 [95% CI = 4-14]
- All 3 studies had similar RR – Dutch study lacked sufficient power
- Safe approach – AEs related to deterioration in UC, one C.difficile

Other strategies



- OpenBiome – capsule technology

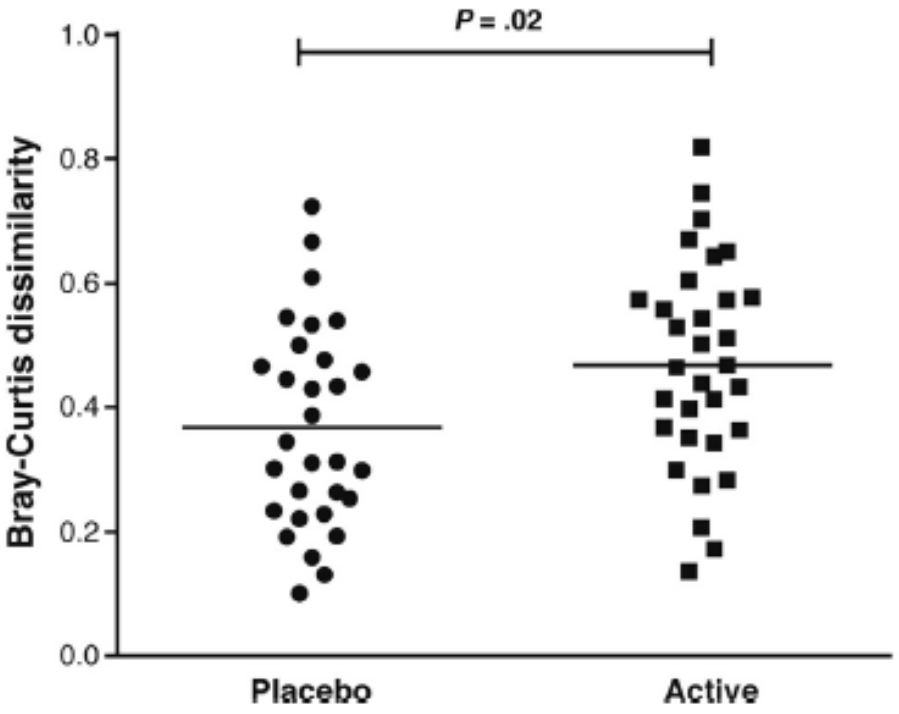
DIY – “the power of poop”

- Stool by stool instructions…..

Future work

- Further RCT including CD
- Capsules for CD (ileum)
- Enemas for UC – twice a week
- For 6-8 weeks
- HV
- Single donor – 7 of 9 cases in remission received FMT from one donor

Predictors:
Disease duration
Immunosuppression
Corticosteroids at baseline
Disease severity



Summary

- Understanding of the human microbiome rapidly advancing
- Increasing attention being given to study design
- Key roles for diet and other lifestyle interventions that can occur in primary care