Microbiome and Medical Disease: Ready for Prime Time?

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The future is now...
The future is now...

Gut Time Lapse $199

Sample three times: before, during and after a diet or lifestyle change.

Our most popular bundle goes a step further with multiple samples, to see how your microbiome changes over time.

It's a 25% discount off the normal Gut Kit, and you get three timepoints for comparison.

4,618 results for Health & Household: Vitamins & Dietary Supplements: Digestive Supplements: "probiotics"
Lots of coverage in lay press

Human Microbiome May Be Seeded Before Birth

Say Hello to the 100 Trillion Bacteria That Make Up Your Microbiome

>23,000 articles in PubMed

In Good Health? Thank Your 100 Trillion Bacteria

New York Times
Outline

• Background on the microbiome
• Current clinical scenarios
• Future clinical scenarios
Definitions

• **Microbiota:**
  – The collection of microbial organisms from a defined environment.

• **Microbiome:**
  – The totality of microbes, their genetic information, and the milieu in which they interact.

• **Metagenome:**
  – The genetic information of a complex population that is constituted by the genomes of many individual organisms.
Study of the Microbiome

Microbiology

Microbiome

![Culture vs. Uncultured](chart.png)

- 1% cultured
- 99% uncultured
NIH Human Microbiome Project

- Started in 2007
- 242 healthy adults
- Women: 18 body sites
- Men: 15 body sites
- 4,788 specimens overall

3.3M microbial genes (changeable, 10% identical)

22K human genes (fixed, 99.9% identical)

95% of microbes in the intestinal tract

~ 2kg

Exteriorized organ
Functions of the microbiome

• Metabolism
  – Vitamin production
  – Amino acid synthesis
  – Short chain fatty acid production

• Host protection and immune development
  – Anti-microbial compounds
  – Competition with other organisms
  – Protective or dysregulated immune response
    • Allergy, asthma, autoimmunity

• Gut-brain axis: bidirectional
Potential disease links

- Autoimmune/inflammatory diseases
- Obesity
- Inflammatory bowel disease
- Skin disease: acne, psoriasis
- Dental caries
- Lung disease
- Cardiovascular disease
- Psychiatric disease
- Flatulence
- Halitosis
- Mating preference
- Alterations in systemic diseases
Influences on the microbiome

• Age
• Diet
• Environment
• Smoking
• Genetics
• Pregnancy
• Pets
• Family members
-Diagnostics
-Therapeutics
-Impact on disease susceptibility/prevention, response to therapy, adverse effects
-Biomarkers
Promise for microbiome-directed therapeutics

A Targeting microbiome structure

- Probiotics
- Prebiotics, e.g., fiber
- Bioengineered commensals
- Bacterial transplantation
- SCFA

B Targeting microbiome function

- Bacteriocin isolation (test in lab)
- Receptor agonists (test in lab)
- Enzyme inhibition
- Postbiotics

Immune regulation
Energy provision

Kitsios et al. in revision
16s Ribosomal RNA gene

- Present in all bacteria
- Highly conserved DNA sequences allow detection of all bacteria
- Several highly variable regions act as bacterial “fingerprint”
- Allows differentiation between organisms

Differences in the microbiome by anatomical site

No taxa present in every body site or in every individual

100 phyla exist in biology; human microbiomes are dominated by 4 phyla: Actinobacteria, Firmicutes, Proteobacteria, Bacteroidetes

Presence or absence of certain species can lead to changes in community composition

Alpha diversity: diversity in a single sample

Richness

Evenness

Loss of diversity is bad…

Dominance

Day 1

Day 3

Staph aureus
Beta diversity: differences in groups of samples

Sample A  Sample B

Doctor, I can’t get rid of my C. diff, what should I do?

– Eat a lot of yogurt
– Take *Lactobacillus*
– Get a fecal transplant
Fecal microbiotic transplantation (FMT)

Feces from healthy donor
- Intestinal tube
- Coloscopy
- Gastroscopy/Enteroscopy
• 43 patients with recurrent C. diff
• Compared donor feces to oral vancomycin and vancomycin bowel lavage
• Donors screened for parasites, other infections
• Infused through nasoduodenal tube

Nood E et al, NEJM, 2013

[Graph showing percentage cured without relapse for different treatments: First Infusion of Donor Feces (N=16) 81.3%, Infusion of Donor Feces Overall (N=16) 93.8%, Vancomycin (N=13) 30.8%, Vancomycin with Bowel Lavage (N=13) 23.1%.]
Microbiota Diversity in Patients before and after Infusion of Donor Feces, as Compared with Diversity in Healthy Donors.

Future of fecal transplant for C. diff

• Increasing popularity
• Auto-transplant, relative?
• Are there particular donors or recipients that are better matches, like blood types?
• Particular species?
• Ecospor trial of Ser-109
• Ecology of bacterial spores enriched and purified
• Strains of bacteria from healthy, screened human donors, but does not need recurrent donation
• Promising Phase I results, in recent Phase II recurrence rates at 8 weeks same as placebo
We are transplanting more than bacteria...

Jeremy Teaford / Vanderbilt
A woman who received gut bacteria from an overweight donor – for the treatment of recurrent C. difficile infection – rapidly gained 34 pounds in the 16 months after the procedure.
<table>
<thead>
<tr>
<th>Date</th>
<th>Milestone</th>
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<tbody>
<tr>
<td>July 2013</td>
<td>FDA guidance on FMT issued</td>
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<tr>
<td>October 2013</td>
<td>ID and GI decide to collaborate on FMT program</td>
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<tr>
<td>July 2014</td>
<td>UPMC secures lab space for FMT</td>
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<td>SRC support for medical director of FMT</td>
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<td></td>
<td>IRB approval for FMT registry</td>
</tr>
<tr>
<td>September 2014</td>
<td>ID and GI agree on FMT protocol</td>
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<td></td>
<td>UPMC finance agrees to $500 cost for donor screening</td>
</tr>
<tr>
<td>October 2014</td>
<td>PA Department of Health approves FMT lab occupancy</td>
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<tr>
<td>December 2014</td>
<td>First colonoscopic FMT performed at UPMC</td>
</tr>
<tr>
<td>February 2015</td>
<td>First ND tube FMT performed at UPMC</td>
</tr>
<tr>
<td>April 2016</td>
<td>Volunteer stool bank opens at UPMC</td>
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FMT: Results (Dec 2014-April 2016)

<table>
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<tr>
<th>Endpoint</th>
<th>Route</th>
<th>n/N (%)</th>
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<tr>
<td>Diarrhea at 12 weeks</td>
<td>ND tube</td>
<td>6/12 (50)</td>
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<tr>
<td></td>
<td>C-scope</td>
<td>5/7 (71)</td>
</tr>
<tr>
<td>C. diff testing sent after FMT</td>
<td>ND tube</td>
<td>5/12 (42)</td>
</tr>
<tr>
<td></td>
<td>C-scope</td>
<td>4/7 (57)</td>
</tr>
<tr>
<td>Positive C. diff testing after FMT</td>
<td>ND tube</td>
<td>1/12 (8)</td>
</tr>
<tr>
<td></td>
<td>C-scope</td>
<td>1/7 (14)</td>
</tr>
</tbody>
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Composite success rate: 17/19 (89%)
Future directions of FMT at UPMC

• Continue existing directed donor program
• Build Volunteer (frozen) Stool Donor Bank
  – Time-to-treatment shortened to 1-2 days
  – Possible treatment of inpatients
  – Treatment of patients coming from a distance
• Frozen versus fresh stool
• Encapsulated stool
• FMT clinic: Tatiana Bogdanovich, MD
  – 412-647-7228
  – bogdanovicht@upmc.edu or FMT@upmc.edu
Future directions of FMT at UPMC

- Expansion of FMT indications
  - CDI (for 1\textsuperscript{st}-2\textsuperscript{nd} episodes, severe/fulminant CDI, primary/secondary prevention of CDI)
  - Primary/secondary prevention of multi-drug resistant organisms
  - Inflammatory bowel disease
  - Oncology (augmented responses to anti-PD-L1 Ab, post-tx C. diff)
  - Metabolic diseases (insulin resistance, DM, obesity)
  - Neuropsychiatric disorders (MS, PD, autism, CFS)
Doctor, I just had a heart attack, but I really like steak, can’t you just give me something for my microbiome?
Metabolomics, microbiota, & CV disease

- Metabolites reflect small molecules generated by cellular metabolic activities
- Byproducts of microbes, communities
  - GI tract
  - Other sites
- Products of inflammation stimulated by microbial communities
Gut bacteria break down red meat to TMAO that leads to CVD

trimethylamine-N-oxide = TMAO
Metabolomics, microbiota, & CV disease

- High levels TMAO from GI bacteria associated with CV disease
- Suggest that gut microbiota are important in CV disease pathways

- 4007 participants
- Followed for major cardiac event for 3 years
- Linked levels of TMAO to CV outcomes

Dietary study

• 40 healthy adults
• Ate 2 large hard-boiled eggs with deuterium-labeled phosphatidylcholine
• Six treated with metronidazole and cipro for one week
• Egg challenge repeated
• Off abx for 1 month
• Egg challenge repeated
• Serial blood and urine

• TMAO in plasma and urine elevated after eggs
• TMAO decreased after antibiotics
• Increased after d/c of antibiotics
Therapeutic implications

- Change diet
- Suppressive probiotics
- 3,3-dimethyl-1-butanol (DMB): structural analog of choline that suppresses microbial TMAO production under investigation
- Fecal transplantation likely less helpful
Doctor, I think my gut microbiome is making me fat.

Do it yourself sequencing!

YOUR AMERICAN GUT SAMPLE

MICHAEL POLLAN

What's in your American Gut sample?

How do your gut microbes compare to others?
Obesity and the microbiome

• Gut microbiome proposed to play role in obesity
• Diet can rapidly alter gut microbiome
• Metabolic effects/efficiency of nutrient utilization
• Different profiles of obese and lean individuals
Obesity and the microbiome

- 4 twin pairs discordant for obesity
- Collected fecal samples
- Transplanted into germ free mice

Ridaura VK et al, Science, 2013
Mice with obese twin microbiome gained more fat.
Future directions: Can we treat obesity via the microbiome?

• What are key bacteria and/or key functions?
• How could these be manipulated to treat obesity?
  – Fecal transplant
  – Probiotics
  – Metabolic products
  – Antibiotics
• Recent study casts doubt on sample size needed
Personalized nutrition by glycemic response prediction

- Found high variability in glucose response to identical meals
- Machine learning algorithm including gut microbiome to predict glycemic response
- Used the algorithm in blinded, controlled dietary intervention
- Led to decreases in postprandial glucose and alterations in microbiomes

*Can we use a patient’s genome and microbiome to prescribe dietary interventions?*

Zeevi D et al, Cell, 2015
Microbiome and chemotherapy

• Can identify patients at risk for complications and infections
• Immune checkpoint blockade: anti CTL4, anti PD1
  – Work by increasing host immune response to tumor
  – Ineffective in antibiotic or germ-free mice with melanoma
  – Certain microbiome characteristics can improve anti-tumor effect
Microbiome and diagnosis

- Diagnosis of infections:
  - Faster, more detailed ID of pathogens compared to cultures
  - Early warnings of dysbiosis for preventive measures

Warhurst et al HTA 2015
Summary

• Microbial cells/DNA outnumber human
• Complex impact on health and disease
• Fecal transplant currently approved for recurrent C. diff
• Potential to impact many facets of disease diagnosis, progression, prevention, and therapy
IT'S GONNA BE THE FUTURE SOON

Is the Microbiome