Gut Microbiome

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Jacksonville, Florida

15th Annual Internal Medicine Conference
Boca Raton Regional Hospital
Objectives

• Understand the microbial ecology of the gut

• Appreciate the role of the human intestinal microbiota in both normal and abnormal gut and systemic function

• Explore various disorders associated with microbiome alterations

• Assess the possible impact of modulating the bacterial milieu in various disease states
Gut Microbiome

• Surge of interest, with almost 95% of over 9,500 articles published in the last 5 years (2,857 in 2017)

• Culture-independent techniques (e.g., 16S rRNA sequencing) have revolutionized our understanding of the microbial diversity of the gut

• Growing realization of the role that our commensal microbiota plays in human health and disease

• Diagnostic and therapeutic role in personalized medicine
• Human body contains trillions of microbial cells (microbiota)
  — Most within gut (100 trillion)
  — Bacteria (Firmicutes, Bacteroidetes, Actinobacteria and Proteobacteria)
  — Archaea, Viruses, Fungi

• Aggregate microbial genome (microbiome) contains >100 fold more genes than human genome (gene transfer)

• Crucial to our health and well-being

Modified from DiBaise
Microbiota Development and Ecology

>1,000 Microbial Species

**WHAT IS KNOWN**

- Colonization begins at birth
- Develops in early life (feeding and play)
- Unique to each individual
- General stability throughout life
- Affected by internal and external factors
- Alterations in disease

**Colon**
$10^{10-12}$ cfu/mL
pH 5-7

**Ileum**
$10^{7-9}$ cfu/mL
pH 6-7

**Jejunum**
$10^{3-4}$ cfu/mL
pH 6-7

**Duodenum**
$10^{1-3}$ cfu/mL
pH 6-7

**Stomach**
$<10^2$ cfu/mL
pH 1-2

**Modified from DiBaise MCP 2008**
Actions of the Gut Microbiota

- Intestinal development
- Epithelial turnover, motility, blood flow
- Immune system development/modulation
- Energy utilization and storage
- Micronutrients and SCFA
- Block colonization with pathogenic bacteria
- Drug metabolism
- Affect behavior?

Modified from Parkes *Am J Gastroenterol* 2008
Microbiome is Influenced by Multiple Factors

- Maternal vertical transmission
- Host genetics
- GI infections
- Hygiene
- Stress
- Prebiotics
- Probiotics
- Diet
- Fecal microbiota
- Surgery
- Medications
- Lifestyle
- Diet

Modified from Kashyap *MCP* 2017
Genetic Determinants of the Gut Microbiome

Association between host genetics and select bacterial taxa

- Microbiome analysis (16S rRNA-based) of 1,126 twin pairs in the UK

- More than a dozen microbes with known links to health that are heritable

- Lactase non-persistence was linked to higher levels of Bifidobacteria; other gene/microbe links relate to diet, blood pressure and barrier defense

- Although the microorganisms are environmentally acquired, the genome also plays a part by determining which microorganisms are more dominant than others

Goodrich et al. *Cell Host & Microbe* 2016
Prolonged use of a PPI reduces microbial diversity
Implications for *Clostridium difficile* susceptibility

- Observational studies associate PPI use and CDI incidence
- 9 healthy and 5 treatment-naïve CDI subjects
- Random assignment to PPI for 28 days
- Stool microbiome samples collected/analyzed/compared
- PPI usage
  - Decreased operational taxonomic unit (OTU) counts
  - Similar to treatment-naïve CDI group
- Partly reversible after a 1-month drug withdrawal
Westernization of the Microbiome

- Traditional vs. Industrialized
  - Prevotellaceae, Treponema, Clostridiaceae
  - Vitamins, Amino acids, Virulence
  - Carbohydrates, Xenobiotics

- BaAka pygmies: Rainforest hunter-gatherers
- Bantu: Agricultural
- US Americans: Western diet

Microbiome changes over time

Duncan & Flint/Maturitas 2013
Intestinal Microbiota
The organ analogy

• Like a postnatal acquired organ that performs different functions for the host

• Maximal diversity during adolescence

• Remains stable until later stages of life, where the microbiota becomes comparatively less diverse with reduced stability (associated with “inflamm-ageing”)

• Lack of diversity, dysbiosis associated with disease states
Microbiome Assault Over the Past Six Decades
Explanations for Increase in Human Disease

- Hygiene hypothesis
- Antibiotic overuse
- Lifestyle changes
  - Diet
  - Exercise
- Aging

Courtesy John DiBaise
Potential Role in Human Disease

Gut Microbiota

- Metabolic syndrome
- Cardiovascular diseases
- Endotoxemia/septicemia
- Rheumatoid arthritis
- NAFLD/NASH/HS
- Hypertension
- Endocrinial imbalance
- Asthma
- Colorectal cancers
- Diarrhea/constipation
- Celiac disease/Gastroenteritis
- Diabetes/Insulin resistance
- Obesity/Adiposity
- IBD/IBS/UC/Crohn’s disease

Nagpal Front Med 2014
*Clostridium difficile* Infection (CDI)

Pseudomembranous Colitis

Normal colonic mucosa

Pseudomembranes
Gut Microbiota is Altered in Patients with IBS

* Decreased diversity and Bacteroidetes
Gut Microbiota and Mechanisms in IBS

Gut microbiota

Brain gut axis

Altered permeability

Visceral hypersensitivity

Altered gastrointestinal motility

Neurotransmitter release

Kashyap World Summit 2014
Microbiome differences in IBD
Individual dynamics of each subtype vs. healthy control

- Gut microbiota findings in IBD
  - Reduced species diversity
  - Lower temporal stability
  - Structural disruption of the secreted mucus layer
- Cause versus effect
- Fecal diversion, antibiotics, probiotics
PSC is characterized by intestinal dysbiosis independent from IBD

- PSC is associated with alterations in intestinal microbiota

- Three genera (Enterococcus, Lactobacillus and Fusobacterium) are overrepresented in patients with PSC

- An OTU belonging to the Enterococcus genus is positively correlated with the levels of alkaline phosphatase

- Intestinal microbiota modulation through diet, FMT, antibiotics or probiotics may be used in the treatment or prevention of PSC

Diet and Microbiota in IBD
The gut in disharmony
Altered Duodenal Microbiota Composition in Celiac Disease Patients Suffering From Persistent Symptoms on a Long-Term Gluten-Free Diet

Wacklin, et al. AJG 2014
Gut Dysbiosis and Metabolic Disease States

- **Metabolic syndrome**
  - Healthy state: Normal microbiota
  - Diseased state: Fewer Bacteroidetes and Lachnospiraceae phyotypes

- **Type 1 diabetes**
  - Diseased state: Typical NOD mouse microbiota
  - Protected state: More Porphyromonadaceae and Rikenellaceae phyotypes

Colon Cancer and the Microbiota

- Tumor tissue from colon cancers has less microbial diversity.
- Long-term and repeated antibiotic exposure might increase colorectal cancer risk.
- Biofilm associated with colorectal cancer:
  - 89% (13/15) of right-sided tumors
  - 12% (2/15) of left-sided tumors
  - None of the normal mucosa
  - Associated with a reduced or redistributed colonic epithelial cell E-cadherin
- Increased permeability → direct access of bacterial antigens/mutagens → promote procarcinogenic tissue inflammation.

Boursi *ASCO Mtg* 2015
Dejea *PNAS* 2015
Allergic Diseases

• Prevalence increased over last several decades

• Asthma, eczema, food allergies

• Hygiene hypothesis – microbial exposures during childhood are crucial to the development of the immune system

• Developmental alterations predispose to loss of self-tolerance

• Altered microbial colonization (perinatal, early childhood; especially recurrent antibiotics) → dysregulated immune responses → allergic and atopic conditions
Rheumatoid Arthritis and Autoimmunity

- Genes are insufficient to explain rheumatoid arthritis

- Presence of bacteria in mucosal surfaces alter local and systemic host immune responses and elicit joint inflammation

- Theory of bacteria sharing similar pro-inflammatory properties serving as a trigger in various mucosal sites in genetically predisposed individuals
  - Peridontal disease strongly linked to RA
  - Gut microbiome altered in mouse models of inflammatory arthritis and human patients with RA
  - Airway inflammation and autoimmunity present at preclinical stages

Brisca et al Curr Opin Rheumatol 2014
Gut bacteria/bacterial products can influence CNS function

- Altered blood brain barrier
- Binding to cross-reactive epitopes
- Altered gut microbiota

Collins et al. Nature Reviews Microbiology 2012
Hornig Curr Opinion Rheumatol 2013
Bi-directional interactions within the gut microbiota/brain axis

Is there a role for modulation of the bacterial milieu in gastrointestinal or other disorders?
Lawn Care and the Microbiome

• Lawn
  – Types of grass, weeds and bugs
  – Collective is the microbiota/microbiome

• Treatment (e.g., pesticides/antibiotics)
  – Intended and unintended consequences
  – Weeds can overgrow

• Replenishment
  – Fertilizer (prebiotics)
  – Seeds (probiotics)
  – Planting new sod (FMT)
Potential Interventions
Microbiota restorative/manipulative therapies

- Diet modification
- Antibiotics
- Prebiotics, probiotics and synbiotics
- Fecal microbiota transplantation
- Ecobiotics, designer probiotics
We are what we eat
We are what our microbiome is

• Type of food we eat selects for specific microbes

• Microbes alter taste receptor expression and signaling

• Further impacts our intake

• In turn, this impacts our behavior and food habits
Long Term and Short Term Dietary Effects on Gut Microbiome

Wu et al. Science 2011
David et al. Nature 2013
Dietary sources of prebiotics

- Whole grains
- Apples
- Leaks
- Onions
- Garlic
- Bananas
- Asparagus
- Honey
- Avocados
- Nuts
- Seeds
- Artichokes
- Root vegetables
- Beans
- Lentils
- Chickpeas
- Green tea extracts
- Cocoa extracts
- Red wine extracts
- Sauerkraut

Modified from Ruairi Robertson
Antibiotics
A man-made catastrophe?!

- Human use – smallest impact
- Meat industry/farm animals – 19,000 tons/year
- Excreted and contaminate the food chain

- United States
  - By 2 yrs old, most kids have had 3 courses of antibiotics
  - Increased risk for obesity if antibiotics during the first 6 months of life
  - 19,000 people/year killed secondary to MRSA
Probiotics
Probiotics

• Live organisms that confer potential health benefits
• Wide use in Europe and Asia
• Increasing popularity in US
• Interest in scientific credibility
• Easily available without a prescription
• Proposed use in inflammatory, infectious, neoplastic, allergic GI and non-GI conditions
Proposed Probiotic Mechanisms

1. Physical barrier
2. Altered epithelial surface glycosylation pattern
3. Increased mucus production
4. Secretion of anti-microbial peptides
5. Modulation of the immune system
# Recommendations for Probiotic Use

Modified from Floch *J Clin Gastroenterol* 2011

<table>
<thead>
<tr>
<th>CLINICAL CONDITION</th>
<th>EFFECTIVENESS</th>
<th>ORGANISM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diarrhea</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Acute infection</td>
<td>A</td>
<td><em>S. boulardii, Lactobacillus GG, L. reuteri SD2112</em></td>
</tr>
<tr>
<td>• Prevention of infection</td>
<td>B</td>
<td><em>S. boulardii, LGG</em></td>
</tr>
<tr>
<td>• Ab-assoc (prevention)</td>
<td>A</td>
<td><em>S. boulardii, LGG, combination of L. casei, L. bulgaricus and S. thermophilus</em></td>
</tr>
<tr>
<td>• C. difficile (treat/prevent)</td>
<td>B/C</td>
<td><em>S. boulardii, LGG, bacteriotherapy</em></td>
</tr>
<tr>
<td><strong>IBD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Crohn’s disease</td>
<td>C</td>
<td><em>E. coli Nissle, S. boulardii, LGG</em></td>
</tr>
<tr>
<td>• UC (induce rem/maintain)</td>
<td>B/A</td>
<td><em>E. coli Nissle, VSL#3</em></td>
</tr>
<tr>
<td>• Pouchitis (prevent/induce)</td>
<td>A/C</td>
<td><em>VSL#3</em></td>
</tr>
<tr>
<td><strong>IBS</strong></td>
<td>B/C</td>
<td><em>B. infantis, VSL#3; B. animalis, L. plantarum</em></td>
</tr>
</tbody>
</table>
# Recommendations for Probiotic Use

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<th>CLINICAL CONDITION</th>
<th>EFFECTIVENESS</th>
<th>ORGANISM</th>
</tr>
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<tbody>
<tr>
<td>Immune Response</td>
<td><strong>A</strong></td>
<td><strong>LGG, L. acidophilus LAFT1, L. plantarum, B. lactis, L. johnsonii</strong></td>
</tr>
</tbody>
</table>

**Allergy**

Atopic exema associated with cow’s milk allergy

- **Treatment**  
  - **A**  
  - LGG, *Bifidobacterium lactis*

- **Prevention**  
  - **A**  
  - LGG, *Bifidobacterium lactis*

**Radiation enteritis**  

- **C**  
  - VSL#3, *L. acidophilus*

**Vaginosis and vaginitis**  

- **C**  
  - *L. acidophilus, L. rhamnosus GR-1, L. reuteri RC14*
Indications, Dosage Forms and Clinical Evidence to Date

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Download PROBIOTIC GUIDE mobile app for free

http://usprobioticguide.com/
Probiotic Use

Advice to patients

1. Check the label (group, species and strain, number)
2. Call the company
3. Beware of the internet
4. Stick to well-established companies
5. Store properly
6. Cost and side-effects vary
7. Dietary supplements are not FDA-regulated
8. Not all claims on the label are true
Probiotic Health Benefits May Be Overstated
No Proof Supplements Do Anything For Healthy Adults' Gut Microbiota

Probiotic Use
Has our enthusiasm outpaced the science?

• Several probiotic preparations show promise in various conditions (~20 organisms used)
• Most studies have important methodologic limitations
• Difficult to assess significance/applicability
• Preparations are different in composition, dose, biologic activity (strain-specific outcomes)
• No preparation is FDA-approved
• Most probiotics not covered by insurance carriers
• Cost to be considered
Exploring an illness is like looking for Waldo . . .

Not as simple as one microbe; Ecosystem interaction is key
Fecal Microbiota Transplant (FMT)
FMT – The Origins

- China, 4th century AD
- Physician Ge Hong described fecal solutions for the treatment of food poisoning and severe diarrhea

- Ming dynasty of the 16th century AD
- Li Shizhen used fecal solution for treatment of abdominal diseases with severe diarrhea, fever, pain, vomiting
- Called “yellow soup”
How Does FMT Work?

- Transfer gut microbiota from a healthy donor into a recipient
- 4 *C. difficile* patients in the 1950s

Goal is engraftment/re-establishment of a normal, stable microbial community within the gut

*Eiseman et al. Surgery 1958*
Clinical resolution rates of rCDI with FMT

90% patients with clinical resolution (245/273 pts)

Dysbiosis and Disease
More studies with FMT

- Ulcerative colitis
- Crohn’s disease
- IBS
- Chronic constipation
- Obesity
- Diabetes mellitus
- Multiple sclerosis
- Parkinson disease
- Atopy
- Rheumatoid arthritis
- Depression
- Eosinophilic disorders
- ITP
- Chronic fatigue
- Autism
Fecal transplant beneficial in UC
Multicenter, DB, randomised, placebo-controlled trial

- 85 UC patients in 3 centers across Australia
  - 42 FMT
  - 43 placebo

- Study details
  - FMT #1 via colonoscope
  - Self-administered enemas (5 days/week for 8 weeks)
  - FMT consisted of a stool from at least 3 donors

- Primary outcome
  - Steroid-free clinical remission with endoscopic remission or response at 8 weeks

Fecal transplant beneficial in UC
As effective as steroids

<table>
<thead>
<tr>
<th></th>
<th>FMT (n=41)</th>
<th>Placebo (n=40)</th>
<th>Risk ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid-free clinical remission and endoscopic remission or response</td>
<td>11 (27%)</td>
<td>3 (8%)</td>
<td>3.6 (1.1–11.9)</td>
<td>0.021</td>
</tr>
<tr>
<td></td>
<td><strong>NNT = 4</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid-free clinical remission</td>
<td>18 (44%)</td>
<td>8 (20%)</td>
<td>2.2 (1.1–4.5)</td>
<td>0.021</td>
</tr>
<tr>
<td>Steroid-free clinical response</td>
<td>22 (54%)</td>
<td>9 (23%)</td>
<td>2.4 (1.3–4.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>Steroid-free endoscopic remission</td>
<td>5 (12%)</td>
<td>3 (8%)</td>
<td>1.6 (0.4–6.4)</td>
<td>0.48</td>
</tr>
<tr>
<td>Steroid-free endoscopic response</td>
<td>13 (32%)</td>
<td>4 (10%)</td>
<td>3.2 (1.1–8.9)</td>
<td>0.016</td>
</tr>
</tbody>
</table>

FMT Effective for Refractory Crohn’s Disease
Pilot study of mid-gut FMT

- 49 CD patients
- 86.7% (26/30) improved, 76.7% (23/30) in remission

Cui, et al. J Gastro Hepatol 2015
FMT for Inflammatory Bowel Disease
Systematic Review and Meta-analysis

METHODS
• Review through January 2017
• Clinical remission was established as the primary outcome

RESULTS
• 53 studies were included (41 UC, 11 CD, 4 pouchitis)
• Overall clinical remission – 36% UC, 50.5% CD, and 21.5% pouchitis
• UC improved with increased number of FMT infusions and lower GI tract administration
• Most adverse events were transient gastrointestinal complaints
• Increased diversity and shift to donor microbiota profile post-FMT

CONCLUSIONS
• FMT appears effective in UC remission induction, but long-term durability and safety remain unclear
• Additional well-designed controlled studies of FMT in IBD are needed, especially in CD and pouchitis.

Paramsothy, et al. J Crohns Colitis 2018
FMT Beneficial in IBS
Results of a DB, Placebo-controlled, RC Trial

Study participants
90 patients (IBS-D, IBS-M)

Treatment
FMT (fresh or frozen) via colonoscopy

Primary Endpoint
Symptom relief at 3 months by IBS-SSS

Results
65% (FMT) vs 43% (placebo), p=0.049
FMT and Metabolic Syndrome

Obese

Lean

Relative amount of two bacteria

Firmicutes

Bacteroidetes
Transfer of Intestinal Microbiota From Lean Donors Increases Insulin Sensitivity in Individuals With Metabolic Syndrome
Think Safety First!
Potential Long-Term Adverse Effects of FMT

Think of your selection criteria

- Immune status
- Nutritional status
- Body weight
- Diabetes risk
- Cardiovascular risk
- Cognition/mood
- Personality
- Cancer risk
- Host genomics
- What else is in there?
What does the future hold for FMT?
FMT Suitable for Mainstream Medicine

• Identifying a suitable donor

• Material processing
  – Take the smell out of it
  – Separate the microbial fraction from fecal matter
  – Freeze microbial fraction
  – Less aesthetically challenging
  – Bank material to allow testing (versus fresh)

• Development of a lyophilized preparation
  – Stored at room temperature
  – Encapsulated

• Reimbursement issues

Khoruts et al. *Clin Gastro Hepatol* 2015
Fresh is as good as frozen FMT
Results of a RCT

Table 2. Number of Fecal Microbiota Transplantations and the Proportion With Clinical Resolution at 13 Weeks After Last Transplantation

<table>
<thead>
<tr>
<th>No. of FMTs</th>
<th>mITT Population</th>
<th>Per-Protocol Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frozen (n = 108) Fresh (n = 111)</td>
<td>Frozen (n = 91) Fresh (n = 87)</td>
</tr>
<tr>
<td>1</td>
<td>57 (52.8)</td>
<td>56 (50.5)</td>
</tr>
<tr>
<td>2</td>
<td>24 (75.0)</td>
<td>22 (70.3)</td>
</tr>
<tr>
<td>3-5</td>
<td>13 (87.0)</td>
<td>12 (81.1)</td>
</tr>
<tr>
<td>&gt;5</td>
<td>4 (90.7)</td>
<td>5 (85.6)</td>
</tr>
<tr>
<td>Total</td>
<td>98/108 (90.7)</td>
<td>95/111 (85.6)</td>
</tr>
</tbody>
</table>

Advantage of frozen
Immediate access to already screened stool

Primary endpoints
• Clinical resolution of diarrhea without relapse at 13 weeks
• Adverse events

Results
• Fresh and frozen are equivalent
• No difference in adverse or serious adverse events
FMT Diner
Daily Specials

• The Traditional (lower endoscopy)

• From the Top (EGD, nasoenteric/gastric tubes)

• The Repeat Customer (enema)

• Take Out (capsules)

Please let your server know how you’d like your selection prepared
- Single, multiple, fresh or frozen; personality options available
Ecobiotics and Designer Probiotics
Beyond Probiotics
A new paradigm

- Ecobiotic
  - Combinations of a small number of selected discrete organisms
  - Work by enabling a shift from a disease state to one of health

- Capture breadth of phylogenetic diversity that occurs in the GI microbiome (versus just 1 bug)

- Impact specific metabolic or inflammatory pathways

- Development for rCDI (109), primary CDI (262), Infection and GVHD (155), IBD (287,301), Immuno-oncology (401)
A Novel Microbiome Therapeutic Increases Gut Microbial Diversity and Prevents Recurrent *C. difficile* Infection

- 26/30 patients (**86.7%**) met the primary efficacy end point (absence of *C* diff + diarrhea).
- Gut microbiota rapidly diversified.
- **Durable engraftment** of spores and no outgrowth of non–spore-forming bacteria.
- Adverse events included mild diarrhea, abdominal pain, and nausea.
A Look into the Future of Probitoics

• Genetically modified organisms
  • Deliver therapeutic agents
  • Deliver vaccines
  • Modify metabolic and other processes
    – TMAO
    – Increase conjugated lineoleic acid in the liver
    – Chemotherapy

• Role of dead (versus living) organisms
Cardiometabolic and Thrombotic Disease

Gut Microbial Metabolite TMAO Enhances Platelet Hyperreactivity and Increases Thrombosis Risk

Plasma TMAO levels in subjects (n > 4,000) independently predicted incident (3 years) thrombosis (heart attack, stroke) risk.

Drugging the microbiome may treat heart disease

Wang et al. Cell 2015
Alleviating cancer drug toxicity by inhibiting a bacterial enzyme
Programming a Human Commensal Bacterium, Bacteroides thetaiotaomicron, to Sense and Respond to Stimuli in the Murine Gut Microbiota

Creating the Designer Microbiome
Creating the Designer Microbiome

Bacteroides thetaiotaomicron (white) living on cells in the gut (large pink spheres), being activated by chemical signals (small green dots) to express specific genes. The glowing bacteria are encoding light-generating proteins.

Microbes as more than pathogens
Some concepts and a small sampling of recent literature
Quote of the Day

“Medicine sometimes gets trapped in dogma and embraces the conventional escalator to clinical impact. But sometimes a new, bold path pops up serendipitously, and a few brave optimists take the elevator and change the way we think about medicine.”

Zain Kassam, chief medical officer at OpenBiome
Your microbiome extends beyond yourself, into the air around you. It hovers in a cloud around your body and leaves bits of itself on surfaces wherever you go. In short, you have an aura, except it isn’t made of purplish light; it’s your personal cloud of dead skin cells, fungus and many, many microbes . . . And researchers are learning to be able to identify you by it.
Is obesity contagious?

Ingesting Gut Microbes Living Outside The Body May Potentially Trigger Disease

- A large study of human microbiome has found that one third of species produce spores which survive in the open air and can potentially move between people.

- Study suggests that those microbes can live outside of the body and be ingested, potentially upsetting populations of healthy bacteria in the gut and triggering disease.

- Perhaps it could explain why some illnesses run in families. Far from being simply genetic, **family members could be picking up conditions through close contact or sharing bathrooms.**

- Raises the question of whether conditions like obesity and IBD can be passed on.

- People who live in the same house share a similar microbiome, and genetics only really accounts for between 7–13% of the risk.

Intestinal removal of free fatty acids from hosts by *Lactobacilli* for the treatment of obesity

Gut Microbiome Predicts Response to Cancer Immunotherapy

- Abx compromised efficacy of PD-1 immunotherapy
- Microbiome predicted 3-month response to cancer therapy
- FMT from responsive patients led to improved response to anti-PD-1 therapy in mice versus those who received FMT from nonresponders
Consumption of Fermented Milk With Probiotic Modulates Brain Activity

Tillisch, et al. *Gastroenterology* 2013
Analysis of gut microbiota diversity and auxiliary diagnosis as a biomarker in patients with schizophrenia

Shen et al. Schizophr Res 2018
Antibiotics cause gut dysbiosis and negatively influence cognition in mice

**Challenge**
- Adult mice were treated in parallel with antibiotic mix or vehicle by oral gavage for 11 days
- Various markers analyzed

**Antibiotic treatment**
- Strongly disrupted and diminished the colonic microbial community
- Decreased microbial metabolite levels in the colonic luminal content as well as circulating metabolite levels
- Impaired novel object recognition (also termed non-spatial memory), evaluated with the memory index
- Altered tight junction protein mRNA expression both in the amygdala and hippocampus, and the cerebral expression of neural signaling-related molecules that are involved in learning and memory
- Cognitive effect was associated with a disruption of the microbial communities in the colon, a depletion of bacteria-derived metabolites in the colon, and particular changes of neurochemical brain activity.

Pancreatic Cancer
Differences in the Microbiome

- Mouth bacteria samples from 140,000 healthy individuals (collected by the NCI and ACS for larger, longer term cancer-risk studies)
- 361 developed pancreatic cancer over a 10-year period
- **Two oral bacteria were elevated in the pancreatic cancer patients compared to controls**
  - *Porphyromonas gingivalis* – 59% greater risk of developing pancreatic cancer
  - *Aggregatibacter actinomycetemcomitans* – 50% more likely to develop the disease

- **Pancreatic ductal adenocarcinoma (PDA) microbiome promotes oncogenesis by induction of innate and adaptive immune suppression**
- Microbiome in PDA was distinct and more abundant (mice and human)
- Drives suppressive monocytic cellular differentiation in pancreatic cancer via selective Toll-like receptor ligation leading to T-cell anergy
- Ablation of microbiome was protective against PDA
- Transfer of bacteria from PDA-bearing hosts (but not controls) reverses that tumor protection

Fan et al. *Gut* 2018
Pushalkar et al. *Cancer Discovery* 2018
Clinical implications of recent studies exploring ‘microbial restoration procedure’ for caesarian-born infants

  Vaginal seeding of infants born by caesarian section

  Partial restoration of the microbiota of caesarian-born infants via vaginal microbial transfer

  First microbial encounters
Interesting Headlines (1)

- Aberrant IgA responses to the gut microbiota during infancy precede asthma and allergy development

- **Antibiotic-induced decrease in neurogenesis and cognitive function rescued by probiotics**

- Age-associated microbial dysbiosis promotes intestinal permeability, systemic inflammation and macrophage dysfunction
  Thevarunjum, et al. *Cell Host & Microbe* 2017

- Gene-microbiota interactions contribute to the pathogenesis of IBD

- Duodenal bacteria from patients with **Celiac disease** versus healthy subjects affect gluten breakdown differently
Interesting Headlines (2)


- Probiotic supplementation can positively affect anxiety and depressive symptoms: a systematic review of randomized controlled trials. Pirbaglou *Nutr Res*. 2016

Interesting Headlines (3)

- Gut microbiome remodeling induces **depressive-like behaviors** through a pathway mediated by the host’s metabolism

- Fiber-mediated nourishment of gut microbiota protects against diet-induced obesity by restoring IL-22-mediated colonic health
  Zou et al. *Cell Host & Microbe* 2018

- Fecal transplant improves metabolic syndrome in patients with greater initial microbial diversity
  Kootte et al. *Cell Metab.* 2017

- Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson’s disease
  Sampson *Cell* 2016

- **Gut microbiome markers show promise for colorectal cancer diagnosis**
Interesting Headlines (4)

• High-Fat Diets Alter Gut Microbiota, Leading to Increased Choroidal Neovascularization

• Infant Gut Microbiome Associated With Cognitive Development
  Carlson et al. *Biological Psychiatry* 2017

• **Probiotic supplementation improves cognitive function** and metabolic status in Alzheimer’s disease in a randomized, DB controlled trial

• Serologic microbial associated markers can predict Crohn’s disease behavior years before disease diagnosis

• **Fecal profiling may predict dietary response in IBS**
  Rossi *Clinical Gastroenterology and Hepatology* 2018
Companies pursuing diagnostics that mine the microbiome

- Microbial ecosystem contributions in disease
- Microbial patterns in IBD, Type II DM, obesity
- IBD diagnostics and therapeutics
- Sequencing to predict colon cancer from stool or mucosal samples
- Caution needed in light of system complexity
So, where do we go from here?
Gut Microbiome and Us

• Rapid environmental transition and modern lifestyles are likely driving changes in the biodiversity of the human gut microbiota
• Clear effects on physiologic, immunologic and metabolic processes
• Aberrations in gut microbiome have capacity for multisystem effects; disease-associated dysbiosis
• Causality question
• Need a better understanding of the normal environment
• Diagnostic and therapeutic opportunities
Microbiome as a Determinant of Human Therapeutics

• Both a modulator and target for therapies (personalized medicine)

• Inter-individual variability in treatment response/adverse events beyond host genetics

• Role in drug transformation
  – Acetaminophen
  – Chemotherapy agents
  – Statin therapy
  – Digoxin
  – Metformin
Personalized Medicine Clinics of the Future
Using the microbiota for management of health and illness

• Genome assessment
• Microbiome assessment (matched with human genome)
• Prophylactic, diagnostic and therapeutic targets for various health issues
• Therapeutic manipulation → better profiles to improve health
  – Functional foods (microbiome diet) and prebiotics
  – Probiotics and ecobiotics
  – Probiotic modulation of pharmacologic therapy
  – Updated fecal transplantation
  – Designer probiotics ("bugs as drugs")
USA Today reports that the White House is set to launch a new national initiative Friday to **study microbiomes found in the human body and the ecosystem.**

The initiative is “**part of an effort to fight disease, grow more food and even reduce the greenhouse gases fueling climate change.**”

The new National Microbiome Initiative will start with “**$121 million in federal dollars and $400 million in private funds,**” bringing “together researchers from a variety of disciplines.” Government researchers “will be joined by organizations such as the Bill and Melinda Gates Foundation, the University of Michigan and JDRF, formerly known as the Juvenile Diabetes Research Foundation.”

The New York Times reports, “The federal government has been sponsoring research into the microbiome for decades,” mentioning that the **National Institutes of Health began the Human Microbiome Project in 2007** to “create a comprehensive dictionary of these micro-organisms.”
Mayo Clinic joins the National Microbiome Initiative
May 16, 2016

The Mayo Clinic Center for Individualized Medicine has joined the National Microbiome Initiative sponsored by the White House Office of Science and Technology Policy. Through this initiative, more than 100 institutions have committed to advance microbiome research in areas such as health care, food safety and security, environmental protection, and bioenergy production.

In support of the National Microbiome Initiative, Mayo Clinic is establishing a Microbiome Clinic, offering clinical services, diagnostics and patient education. “The new clinic will focus on improving the care of the individual patient through knowledge of the human microbiome,” says Purna Kashyap, M.B.B.S., Gastroenterology/Physiology and Biomedical Engineering, who is associate director of the Mayo Clinic Microbiome Program.

According to Dr. Kashyap, new diagnostics based on next-generation sequencing will allow the Microbiome Clinic to individualize treatment of undiagnosed infections and conditions, as well as to perform hospital surveillance. These will include:

- Bacterial whole genome sequencing to track and identify source of outbreaks and determine susceptibility to antibiotics
- Clinical metagenomic profiling to identify unculturable bacteria causing infections
- Microbial community profiling as biomarkers of disease outcomes and response to treatment

In addition to the already established fecal microbiota transplant program, Mayo will offer new therapies emerging from clinical trials. Patient education will focus on helping patients navigate the complex options that promote health and wellness, including diet and nutritional supplements and probiotic foods.

"The Center for Individualized Medicine’s Microbiome Program will continue to support a discovery, translational and clinical research portfolio that ensures continued success of the Microbiome Clinic,” says Heidi Nelson, M.D., Colon and Rectal surgery, who is program director of the Microbiome Program, and the Fred C. Andersen Professor.