

## Is Your Gut Microbiome Making You Fat?

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## Disclosures

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### Siesta Medical

Minor stock holder – sleep apnea device

### Patent Pending 61/624,105

Sinus diagnostics and therapeutics



## What is Microbial Ecology?

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The study of micro-organisms and their relationship to each other and their environment

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## The Great Plate Count Anomaly

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0.1 – 1 %

Microscopy vs culture isolates

Staley JT Annu Rev Microbiol.1985

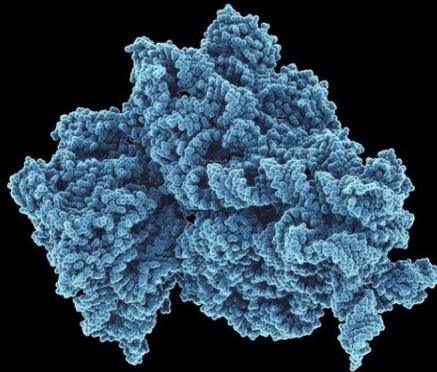
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# Culture Independent Techniques

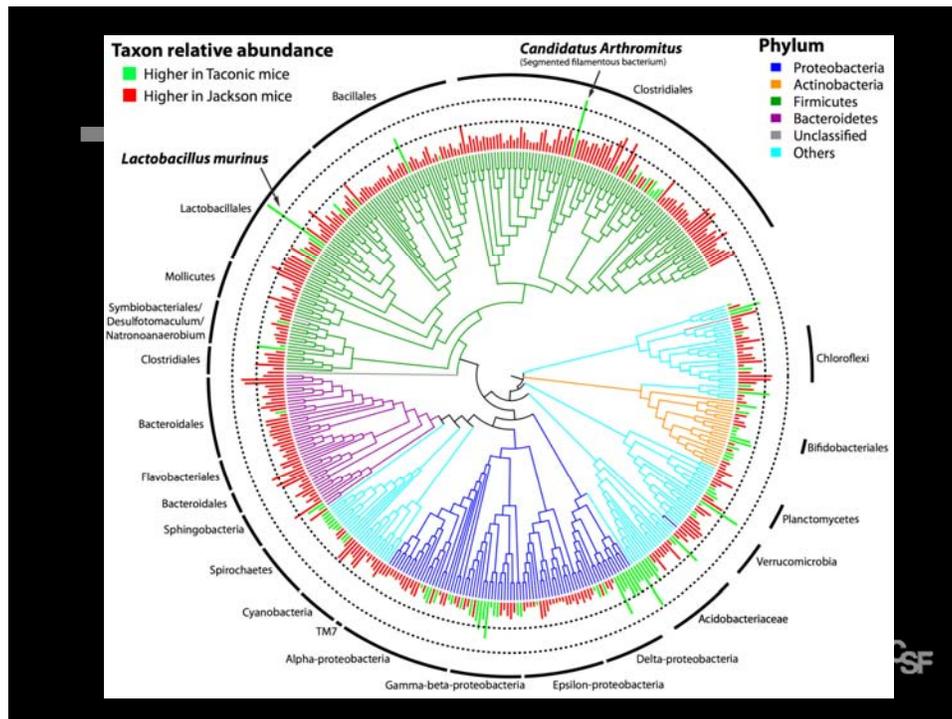
## 16S rRNA PhyloChip



## 16s rRNA subunit

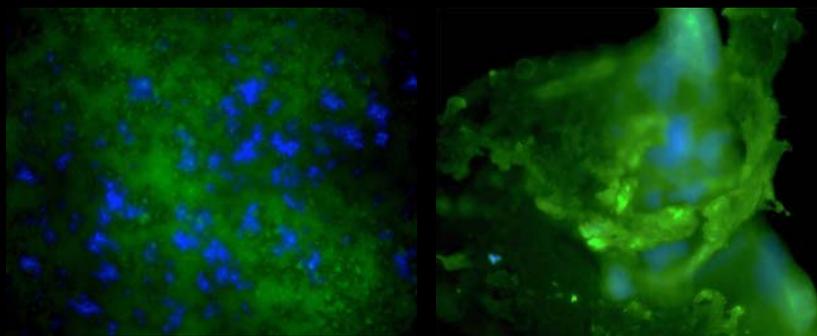


**CONSERVED REGIONS:** unspecific applications  
**VARIABLE REGIONS:** group or species-specific applications



## Normal Flora on Mucosal Surfaces

- Ethmoid Mucosa biopsy in a healthy patient
  - Bacteria Green (16-s probe)
  - Human Nuclei Blue (DAPI stain)





“Humans represent a scaffold on which diverse microbial ecosystems are established”

Round Nature Reviews Immunology 2009

## Nature

1 7 4 | N A T U R E | V O L 4 7 3 | 1 2 M A Y 2 0 1 1

### Enterotypes of the human gut microbiome

Manimozhayan Arumugam<sup>1\*</sup>, Jeroen Raes<sup>1,2\*</sup>, Eric Pelletier<sup>3,4,5</sup>, Denis Le Paslier<sup>3,4,5</sup>, Takuji Yamada<sup>1</sup>, Daniel R. Mende<sup>1</sup>, Gabriel R. Fernandes<sup>1,6</sup>, Julien Tap<sup>1,7</sup>, Thomas Bruls<sup>3,4,5</sup>, Jean-Michel Batto<sup>7</sup>, Marcelo Bertalan<sup>8</sup>, Natalia Borrue<sup>9</sup>, Francesc Casellas<sup>9</sup>, Leyden Fernandez<sup>10</sup>, Laurent Gautier<sup>8</sup>, Torben Hansen<sup>11,12</sup>, Masahira Hattori<sup>13</sup>, Tetsuya Hayashi<sup>14</sup>, Michiel Kleerebezem<sup>15</sup>, Ken Kurokawa<sup>16</sup>, Marion Leclerc<sup>7</sup>, Florence Levenez<sup>7</sup>, Chaysavanh Manichanh<sup>9</sup>, H. Bjørn Nielsen<sup>8</sup>, Trine Nielsen<sup>11</sup>, Nicolas Pons<sup>7</sup>, Julie Poulain<sup>3</sup>, Junjie Qin<sup>17</sup>, Thomas Sicheritz-Ponten<sup>8,18</sup>, Sebastian Tims<sup>15</sup>, David Torrents<sup>10,19</sup>, Edgardo Ugarte<sup>3</sup>, Erwin G. Zoetendal<sup>15</sup>, JunWang<sup>17,20</sup>, Francisco Guarner<sup>9</sup>, Oluf Pedersen<sup>11,21,22,23</sup>, Willem M. de Vos<sup>15,24</sup>, Søren Brunak<sup>8</sup>, Joel Dore<sup>7</sup>, MetaHIT Consortium<sup>†</sup>, Jean Weissenbach<sup>3,4,5</sup>, S. Dusko Ehrlich<sup>7</sup> & Peer Bork<sup>1,25</sup>

Our knowledge of species and functional composition of the human gut microbiome is rapidly increasing, but it is still based on very few cohorts and little is known about variation across the world. By combining 22 newly sequenced faecal metagenomes of individuals from four countries with previously published data sets, here we identify three robust clusters (referred to as enterotypes hereafter) that are not nation or continent specific.

## Where does our gut microbiome come from?

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- Fetal intestines are sterile and colonized at birth
- Bacteroidetes /Firmicutes dominate the gut flora

Bull 2014

- C-Section neonates colonize the gut differently and are predisposed to obesity

Mueller 2015

- Bacteroides populations in obese children and C-section children are similar

Ravussin 2012

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## What does the gut microbiome do?

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- Energy / metabolism of components of foods
- Protection of a host from pathogenic invasion
- Modulation of the immune system

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## Is our gut microbiome stable?

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- Fecal samples were collected over the course of 5 years from individuals, family members, and unrelated individuals
- Unrelated donors not similarly concordant
- >96% of the genome were maintained over time for an individual and family members
  - Early colonizers appear to persist for many years

Faith 2013



## Clostridium Difficile infection

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*The* **NEW ENGLAND**  
**JOURNAL of MEDICINE**

ESTABLISHED IN 1812

JANUARY 31, 2013

VOL. 368 NO. 5

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.,  
Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D.,  
Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D.,  
Marcel G.W. Dijkgraaf, Ph.D., and Josbert J. Keller, M.D., Ph.D.



## Clostridium Difficile and the Microbiome

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- Rise in incidence of C.diff – antibiotic use
- Recurrence is common (expected?)
  - 25% of patients after an initial bout of CDI
  - 65% of patients who experience one recurrence
- Fecal Bacteriotherapy (Fecal Transplant)
  - Instillation of fecal material via enteric tube or enema
- Success rate 90%, complication rate low

Eiseman Surgery 1958  
Bakken Clin GI Hepatology 2011  
Bakken Anaerobe 2009  
Nood NEJM 2013

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## Does our gut microbiome influence obesity?

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- Ratio of Bacteroides and Firmicutes is decreased in obese versus lean individuals Turnbaugh 2009
- Use of fecal material from human twins discordant for obesity were transplanted to mice
  - Mice exposed to the microbiome of the obese twin developed obesity (No change in chow consumption)Ridaura 2013

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## Is the altered flora transmissible?

- Lean mice given feces from obese mice became obese (they're coprophagic...)
- Lean mice could breakdown and ferment polysaccharides better than obese twins
- Transplants of fecal microbiota from healthy human donors to recipients with metabolic syndrome ameliorate insulin resistance!

Ridaura 2013

Vrieze 2012



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**The Root of All Stomach Problems? CHANGE YOUR DIGESTION, NOT YOUR DIET**

Recent studies are linking a large number of health problems to a single condition, one that affects up to 70 percent of Americans.

Leading health professionals are linking this condition to dozens of symptoms, including:  
**Gas and Bloating Diarrhea, Constipation, and IBS Allergies Headaches Lack of Energy Yeast Infections**



### Data in Humans are Messy!

- Gut flora in mice demonstrate systematic differences in lean/fat mice, humans inconsistent  
Walters Febs Let 2014
- Small differences in taxonomic composition exists, not in larger data sets in lean/obese humans  
Finucane Plos One, 2014
- Before therapeutic manipulation of the microbiome in humans, studies are needed to prove causation  
Rosenbaum 2015

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## How has the gut microbiome changed?

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- Microbiome transitions
  - Foraging, rural farming, industrialized life
  - Host genetics, environmental factors, diet
  - Loss of dietary diversity over the past 50 years
    - Decreased agrobiodiversity, varied plants, animal breeds
    - Decline in fiber intake, and MAC in dietary fiber
    - Not recoverable!
  - Antibiotics, c-section, water treatment, sanitation

Requena Roy Soc Chem 2018

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## Microbiome Comparisons

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- “Neolithic” versus industrialized
  - Burkina Faso versus Florence, Italy; age 1-6
- BF children –Bacteroidetes ↑, Firmicutes ↓
  - Prevotella, Xylanibacter ↑↑
  - Short chain fatty acids ↑↑
- Gut microbiota evolved to max energy from fiber and protect from inflammation, other dis.

De Filippo PNAS 2010

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## Conclusions

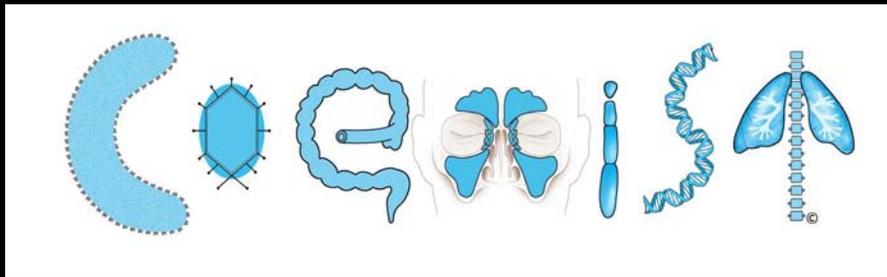
- The human microbiome is important to normal function throughout body surfaces
- Alterations in the microbial community can be associated with disease or altered function
- Manipulation of the microbiome in mice can induce obesity independent of energy consumption and caloric intake
- Changes in diet and environment alter the microbiome – industrialization seems bad!

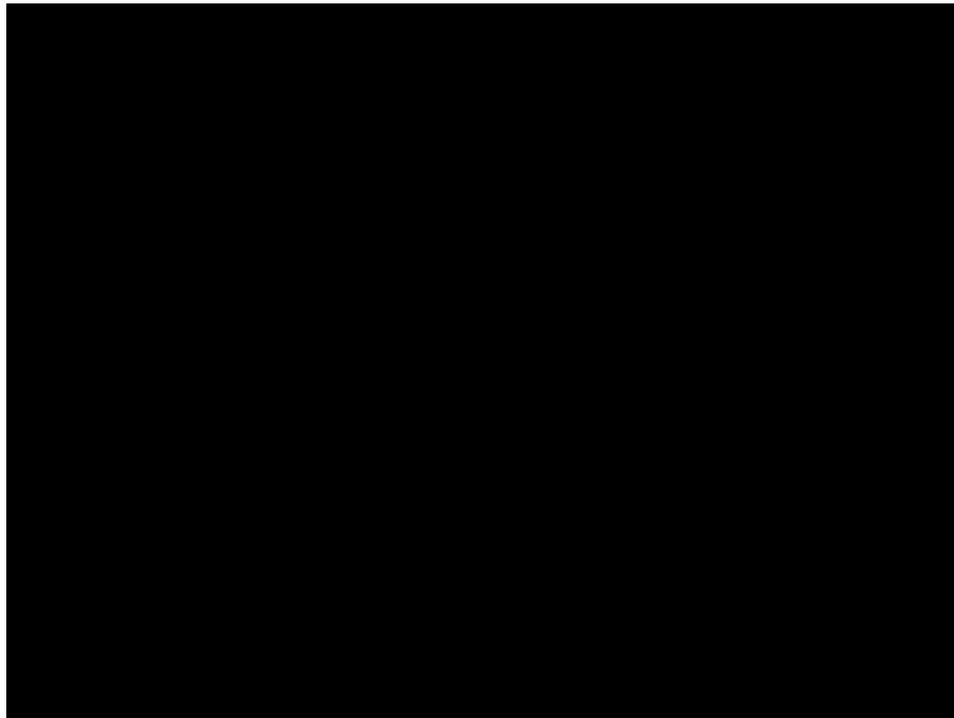
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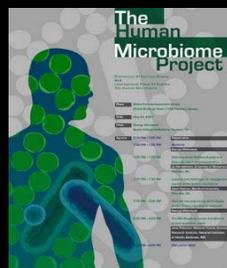


## The Human Superorganism

10 x more bacterial cells ( $10^{15}$ ) than human cells  
100 times as many bacterial genes



1990 - 2003



2008 - 2012