


The Human Microbiome



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Main topics of today's talk

- ✓ NIH Human Microbiome Project
- ✓ What characterizes the human microbiome?
 - Universal properties
 - Personalized properties
- ✓ Lessons learned from the HMP
- ✓ NIH research investments in human microbiome
 - Current
 - Future



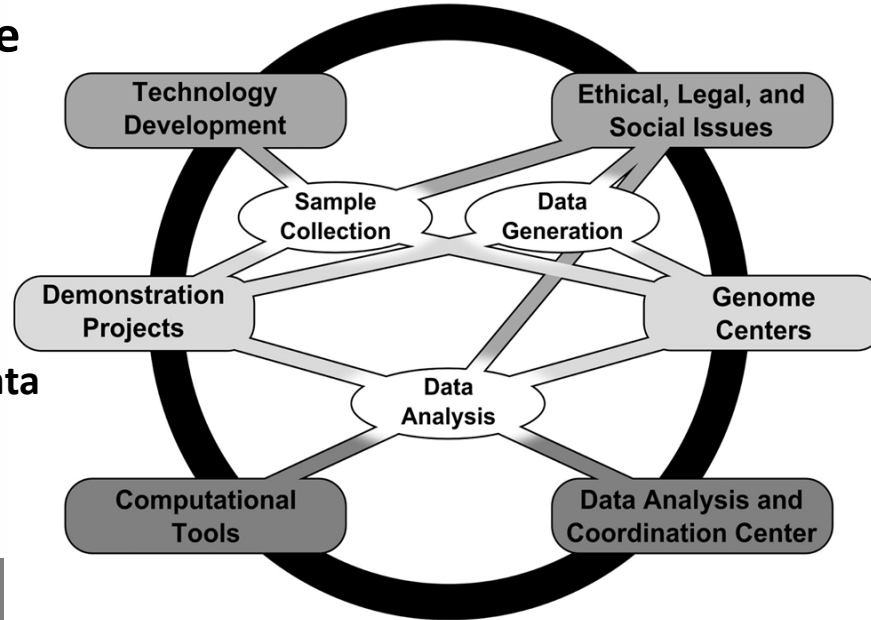
NIH Common Fund Human Microbiome Project

<http://commonfund.nih.gov/hmp/>

Community resource

Repositories:

- sequence data
 - microbiome
 - human
- strains
- clinical/phenotype data
- nucleic acid extracts
- cell lines

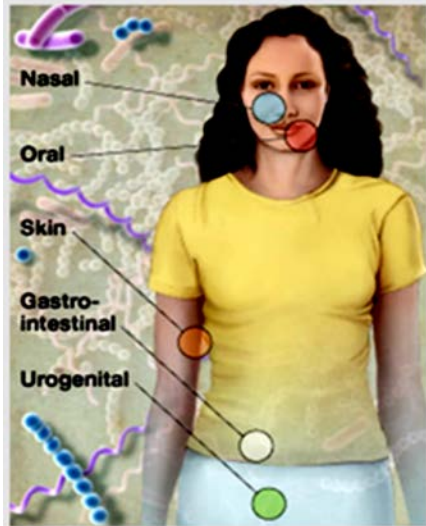


6 Initiatives in HMP

Interact through DACC and 200+ member consortium

www.hmpdacc.org

Healthy cohort study



Clinically healthy

300 male/female

18-40 y.o.

18 body sites

Up to 3 visits in 2 yrs

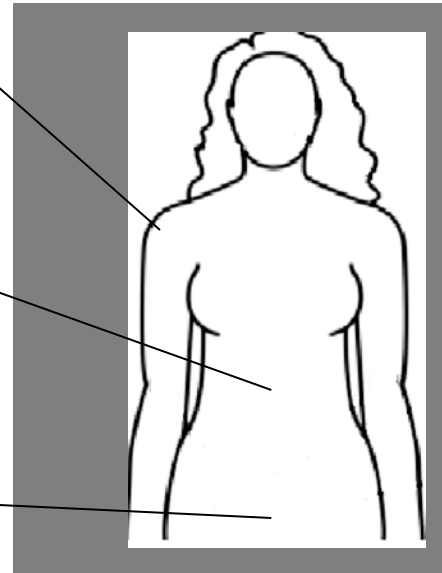
16S rRNA, WGS metagenomes

Skin: eczema, psoriasis

GI: Crohn's disease, esophageal adenocarcinoma, neonatal necrotizing enterocolitis, pediatric IBD, ulcerative colitis

Urogenital: bacterial vaginosis, circumcision, sexual histories

Demonstration Projects



Best place to start for exploring HMP data, tools and protocols: www.hmpdacc.org

Go to "Get Data" to get started

The screenshot shows the HMP DACC website. At the top left is the HMP logo and the text "NIH HUMAN MICROBIOME PROJECT". A navigation menu includes "REFERENCE GENOMES", "MICROBIOME ANALYSIS", "IMPACTS ON HEALTH", "TECHNOLOGY DEVELOPMENT", "ETHICAL IMPLICATIONS", and "OUTREACH". A central banner reads: "Welcome to the Data Analysis and Coordination Center (DACC) for the National Institutes of Health (NIH) Common Fund supported Human Microbiome Project (HMP). This site is the central repository for all HMP data. The aim of the HMP is to characterize microbial communities found at multiple human body sites and to look for correlations between changes in the microbiome and human health. More information can be found in the menus above and on the NIH Common Fund site." Below this are "GET DATA" and "GET TOOLS" buttons. A section titled "Areas of Interest" features a circular genomic visualization with tracks for "1.4Mb" and "0.2Mb" and labels for "Human Microbial Sampling", "DACC Member Organizations", and "Related Sites".

Current News

- January 2012
New DACC Data Browser Released
- July 2011
Expansion of the HMP Project Catalog
- May 2011
New Datasets available

[More News Items](#)

Publications

- The genome of th17 cell-inducing segmented filamentous bacteria reveal...
- Genetic basis for in vivo deplomyicin resistance in enterococci....
- Linking long-term dietary patterns with gut microbial enterotypes....

[More Publications](#)

Data Resources

- Tools & Protocols
- BLAST against Reference Genomes
- Project Catalog
- Access to Strains

Human Microbial Sampling
16S RNA and whole metagenome sequencing of samples collected from 300 healthy human participants, to characterize complexity of microbial communities at individual body sites and to provide insights into functions performed by the human microbiome...

DACC Member Organizations

Related Sites





NIH HUMAN MICROBIOME PROJECT

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And all the data from
the healthy cohort
study

Data Resources

- Tools & Protocols
- BLAST against Reference Genomes
- Project Catalog
- Access to Strains
- Clinical Sampling
- 100 Most Wanted Resource

Register | Login

REFERENCE GENOMES | TECHNOLOGY DEVELOPMENT | ETHICAL IMPLICATIONS | DATA

home

The HMP DACC Data Browser provides access to all publicly available HMP data sets. If this is your first time to this page, please read the Tour Guide to HMP Sequence Data and the Data Use Agreement Text.

The HMP Data Flow Chart is available for...

Ref Genomes

Tools & Protocols

Here are the reference genome data

Reference Genomes

- HMRGD HMP Reference Genome sequence data
- HMREFG Reference genome database for read mapping
- 100 Most Wanted genome project
- HMMDA16S Single cell MDA 16S rRNA Sanger sequencing
- Reference genome data at NCBI

And don't forget the Demonstration Project data

Mock Community A

HMMC Mock community

Demonstration Project Data

Demonstration project data at NCBI

Other Data

- HMFUNC Functional databases used for
- RSEQ RNAseq expression analysis of dental

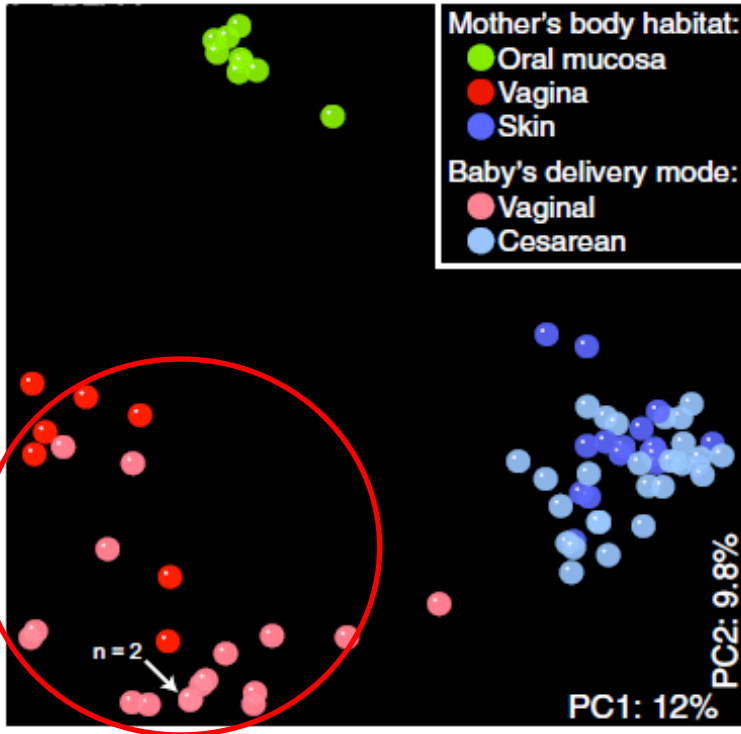
And much more....

Universal properties of the microbiome

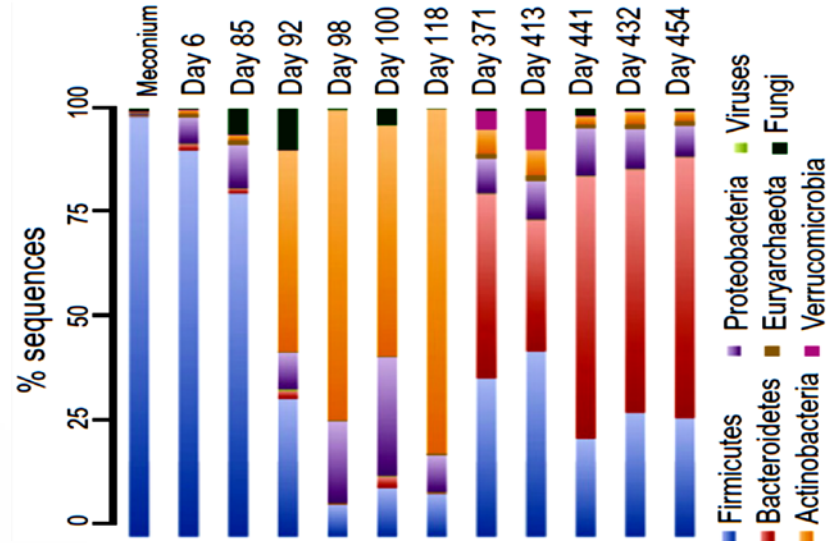


Microbiota acquired anew each generation.

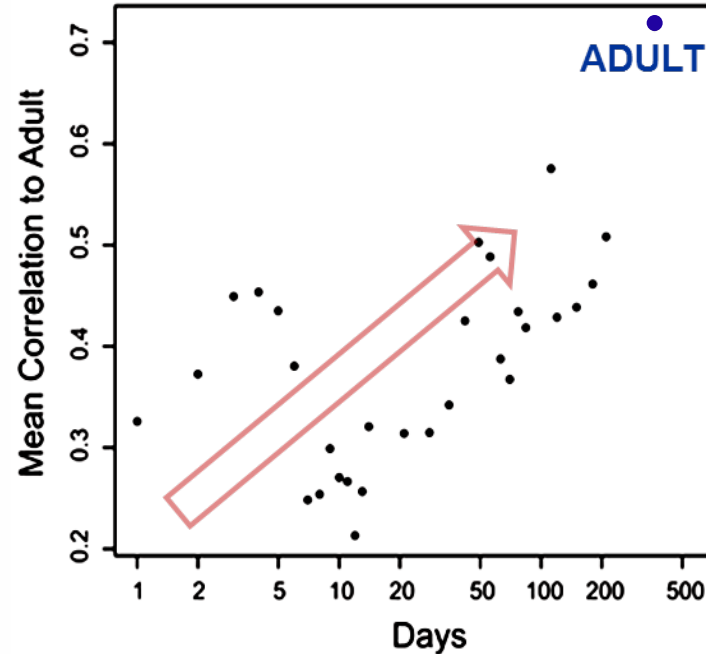
Dominguez-Bello et al. (2010).



- 1) Infants obtain inoculum from mother or environment.
- 2) Microbial succession over ~1-2 yrs.
- 3) Microbiome becomes "adult-like" in ~1-2 yrs.



Koenig et al. (2010)

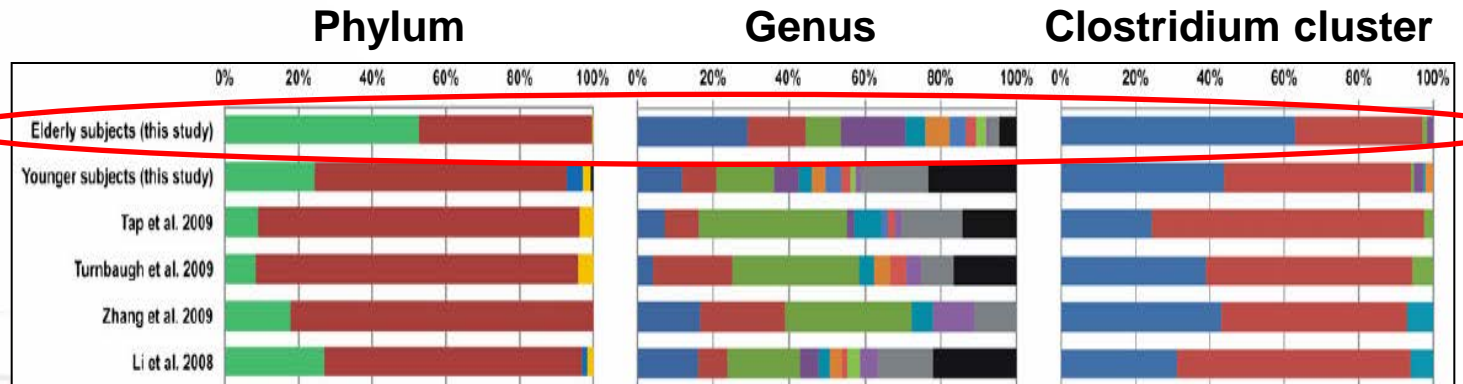


Palmer et al. (2007)

The gut microbiome changes over a lifetime.

Elderly

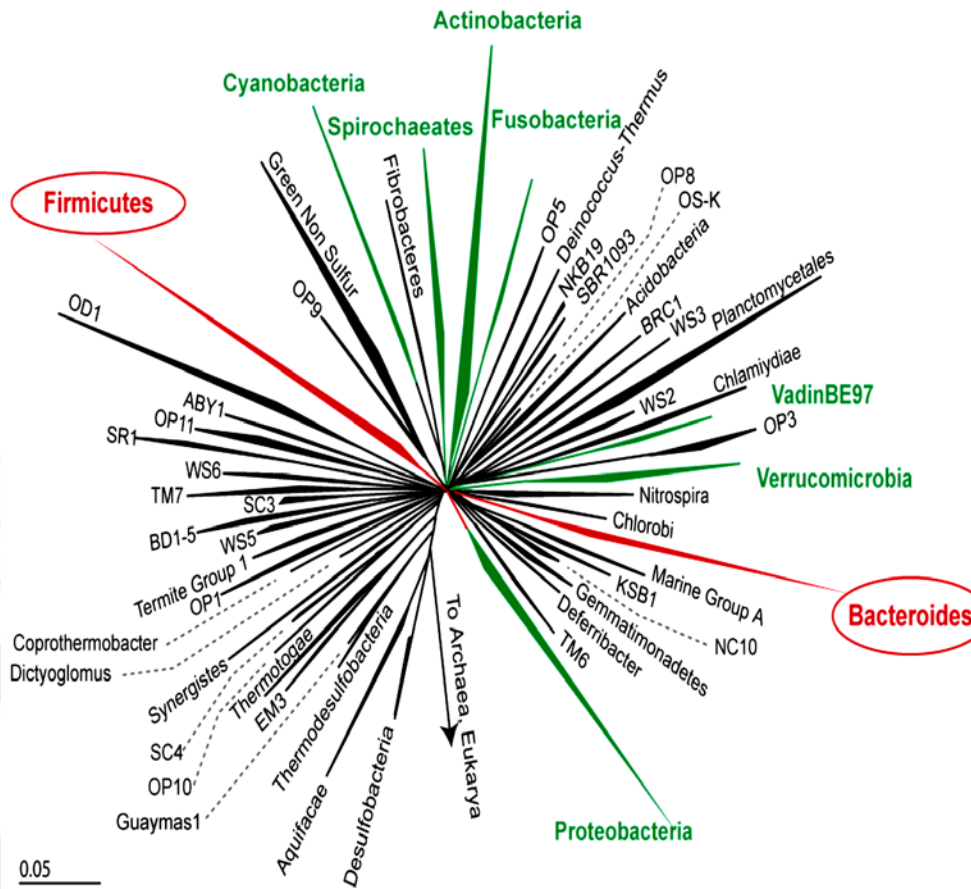
**Mid-age
Adults**



Elderly (> 65 y.o.) have distinct microbiota:

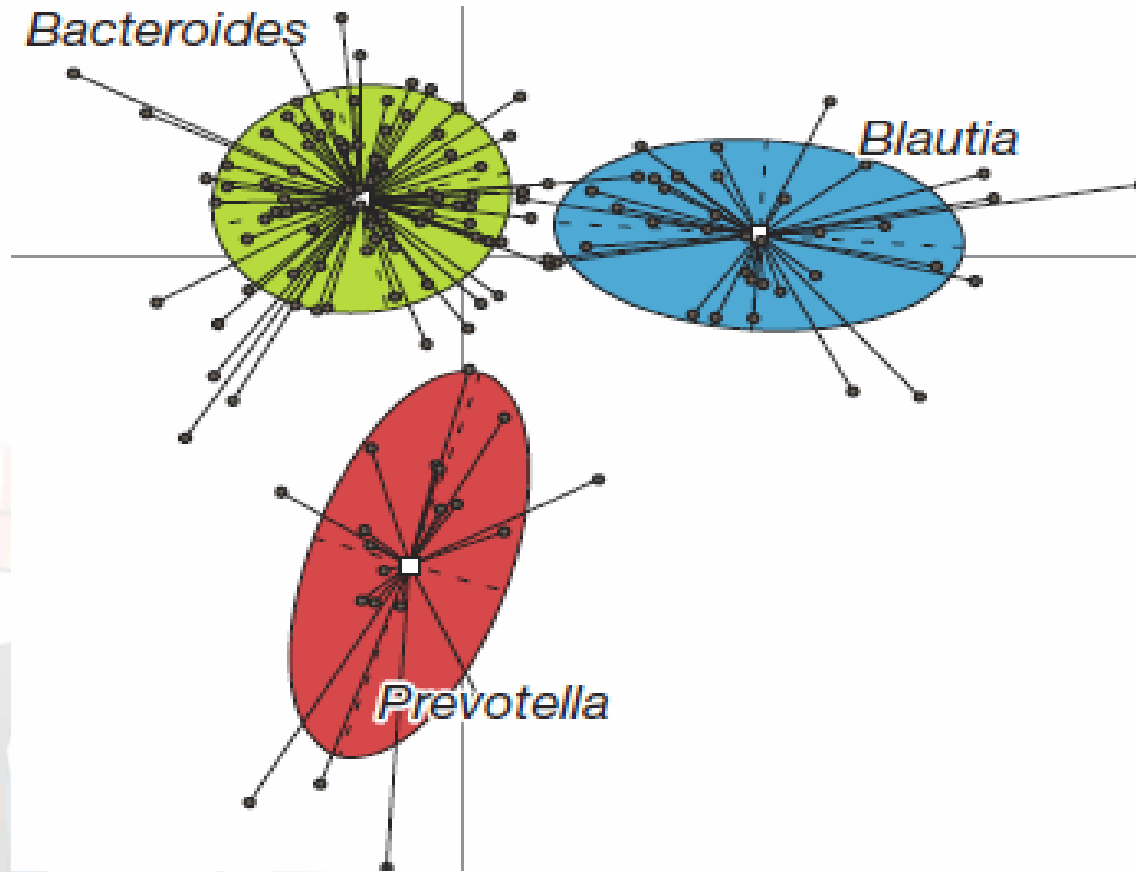
- ✓ Increase in Bacteroidetes, decrease in Firmicutes
- ✓ More diversity
- ✓ More overall instability in composition

Presence of a “core” microbiome?



Yes at Phylum level, and even down to Genus level

Grouping of microbiome (enterotypes)?



But apparently enterotypes not always a constant property,
ex. HMP healthy cohort study, Wu et al. (2011)

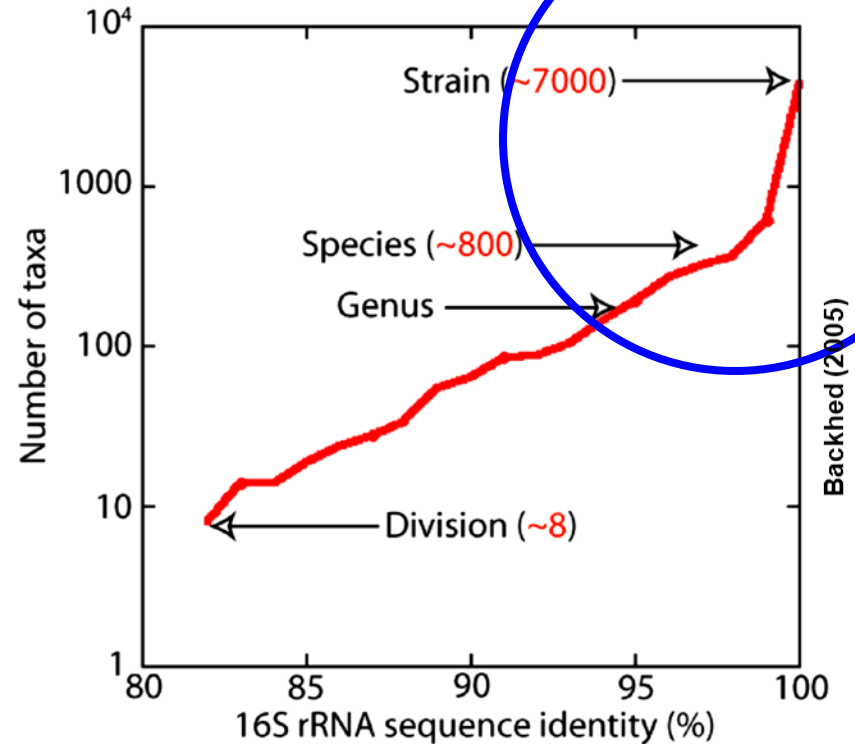
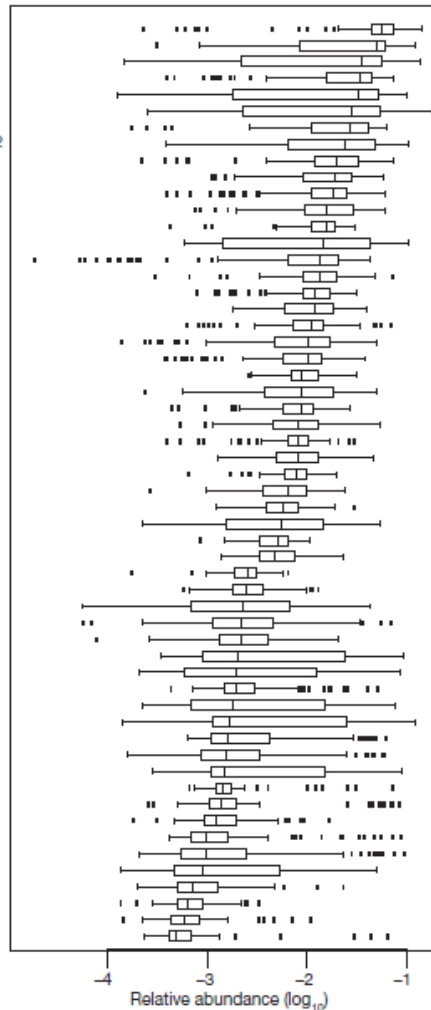
Personalized properties of the microbiome



Diversity at species, strain level is host-specific.

Qin et al. (2010)

Bacteroides uniformis
Alistipes putredinis
Parabacteroides merdae
Dorea longicatena
Ruminococcus bromii L2-63
Bacteroides caccae
Clostridium sp. SS2-1
Bacteroides thetaiotaomicron VPI-5482
Eubacterium hallii
Ruminococcus torques L2-14
 Unknown sp. SS3 4
Ruminococcus sp. SR1 5
Faecalibacterium prausnitzii SL3 3
Ruminococcus lactaris
Collinsella aerofaciens
Dorea formicigenerans
Bacteroides vulgatus ATCC 8482
Roseburia intestinalis M50 1
Bacteroides sp. 2_1_7
Eubacterium siraeum 70 3
Parabacteroides distans ATCC 8503
Bacteroides sp. 9_1_42FAA
Bacteroides ovatus
Bacteroides sp. 4_3_47FAA
Bacteroides sp. 2_2_4
Eubacterium rectale M104 1
Bacterioides xylanisolvens XB1A
Coprococcus comes SL7 1
Bacteroides sp. D1
Bacteroides sp. D4
Eubacterium ventriosum
Bacteroides dorei
Ruminococcus obeum A2-162
Subdoligranulum variabile
Bacteroides capillosus
Streptococcus thermophilus LMD-9
Clostridium leptum
Holdemania filiformis
Bacteroides stercoris
Coprococcus eutactus
Clostridium sp. M62 1
Bacteroides eggerthii
Butyrivibrio crossotus
Bacteroides finegoldii
Parabacteroides johnsonii
Clostridium sp. L2-50
Clostridium nexile
Bacteroides pectinophilus
Anaerotruncus colihominis
Ruminococcus gnavus
Bacteroides intestinalis
Bacteroides fragilis 3_1_12
Clostridium asparagiforme
Enterococcus faecalis TX0104
Clostridium scindens
Blautia hansenii



Abundance of a bacterial species/strain can vary > 1000-fold between individuals.
 (Also unique metabolic properties contributed by each species/strain)

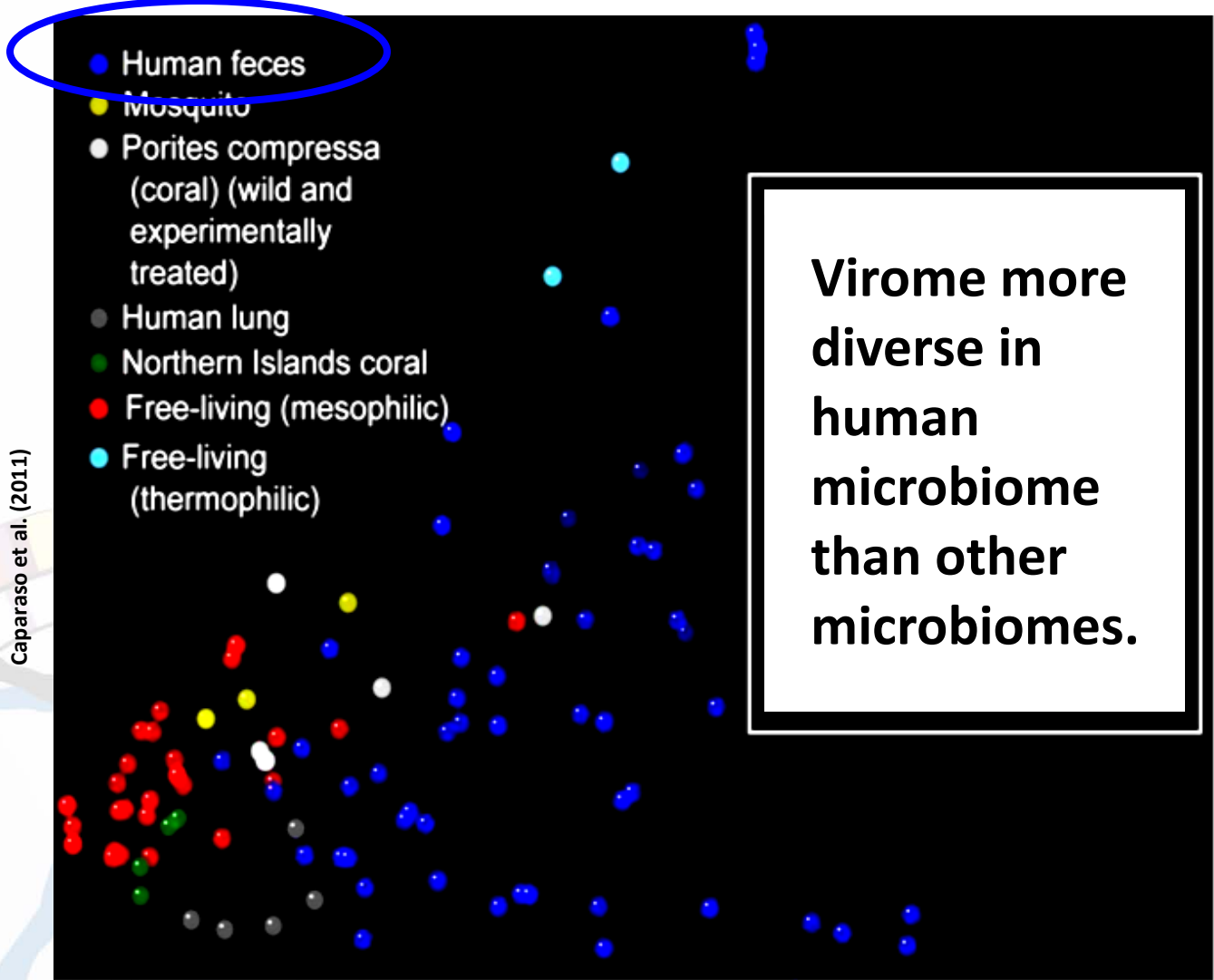


Role of host genetics and microbiome?

Gene	Role of protein	Putative effect on microbiome
MEFV	Proposed cytoskeletal/inflammation factor	Gene mutations affects microbiome composition
APOA1	Main HDL protein	Gene absence affects microbiome composition
MYD88	Signaling molecule for bacterial products in innate immunity	Equivocal results: One study showed gene absence affects microbiome composition; another study showed no apparent effect.
NOD2	Pattern recognition receptor for peptidoglycans	Gene absence affects microbiome composition
Defensin genes	Host antimicrobial peptides	Gene absence affects microbiome composition
RELMB	Cytokine for innate immunity; regulates antimicrobial peptide (REGIII γ)	Gene absence affects microbiome composition
IgA locus	Antibodies in mucosal immunity	Gene absence affects microbiome composition
HLA genes	Major histocompatibility complex (cell surface antigen-presenting proteins)	Gene variation affects microbiome composition

Almost unknown; these candidate genes have been postulated.

Human virome: phage, eukaryotic viruses



Role of virome in human microbiome almost completely unknown.



Lessons learned from the HMP



1) *Not clear how to define a healthy microbiome.*

“Core” microbiome is not a fixed property.

Pathogens are present in healthy microbiome.

Role of host genetics?

2) *Analysis of functional properties of microbiomes needed.*

5,200,000 nonredundant ORFs (HMP) vs 3,300,000 (MetaHIT)

Majority (~80-90%) of annotated genes in HMP microbiomes could not be assigned a function.

Majority (~75-85%) of predicted proteins in HMP microbiomes could not be functionally characterized.

3) *Robust bioinformatics environments/computational tools needed.*

Need infrastructure/tools which can operate on terabases/petabases of microbiome data.

Need infrastructure/tools for diverse data types (DNA, RNA, protein, small molecules).

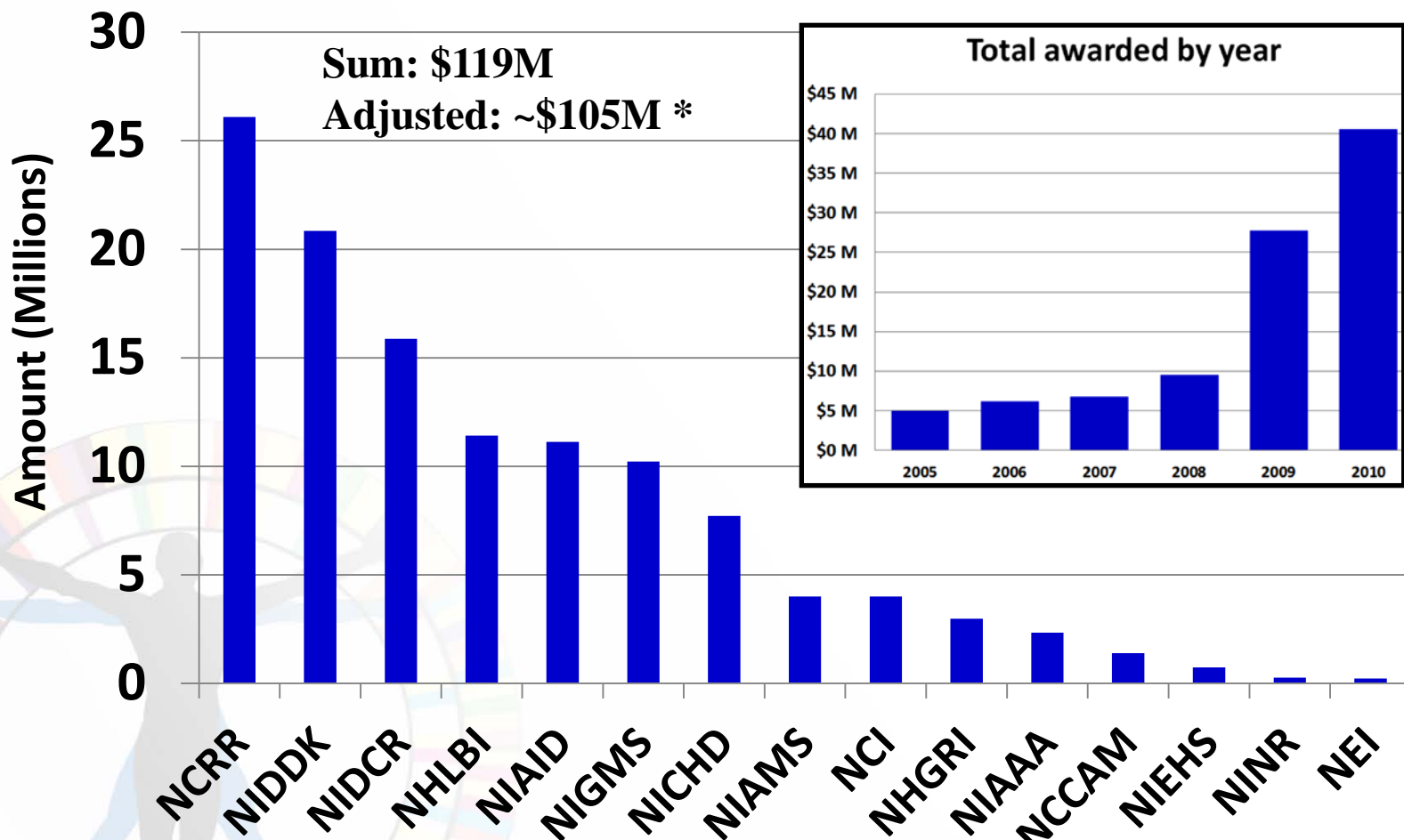
4) *HMP needed better training/outreach to the larger community.*



Research investments in human microbiome science



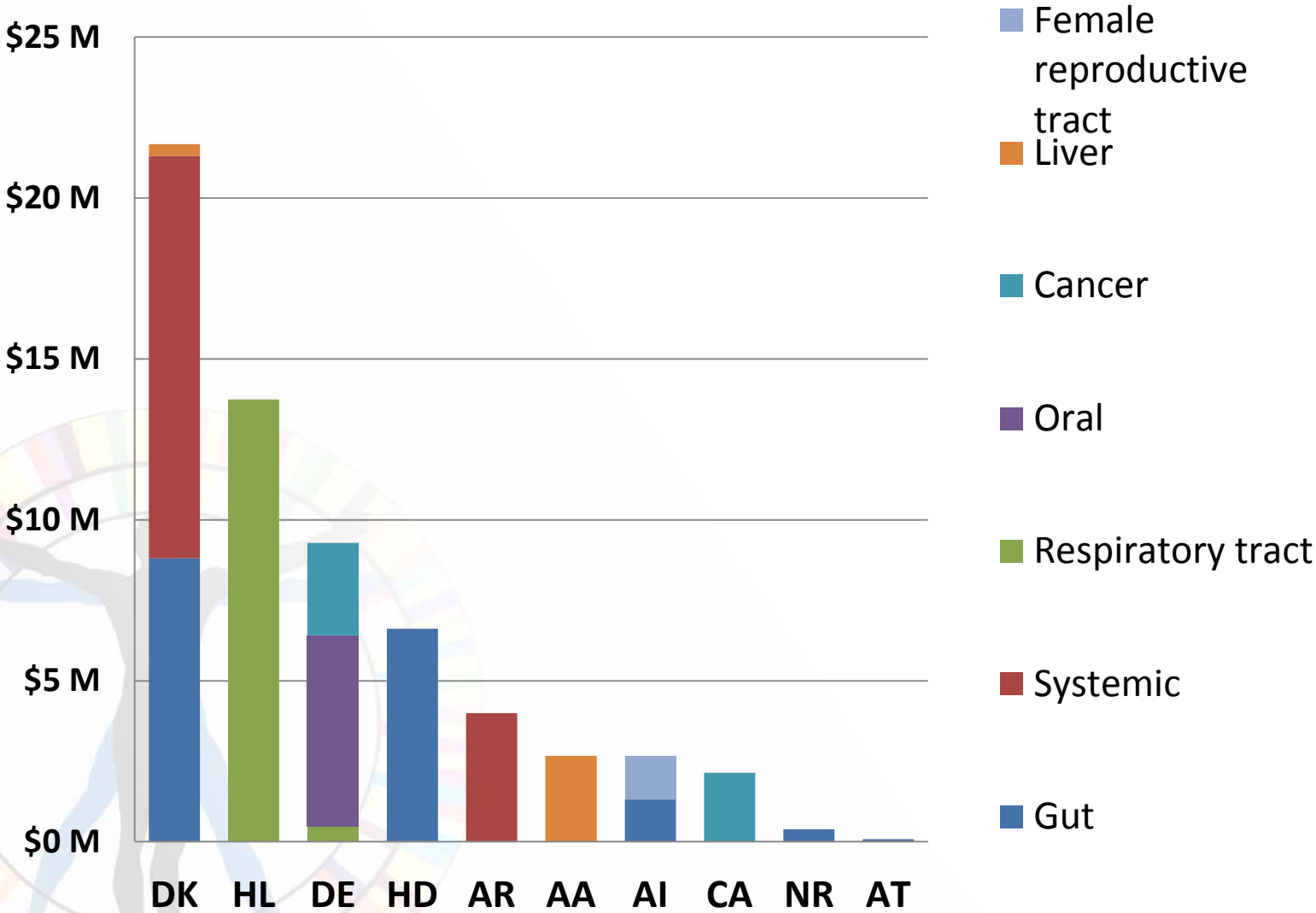
Amount awarded by NIH ICs (FY05-FY10)



* Research core/DCC/center & equipment so not all related to microbiome.



Projects by disease or body site (FY05-FY10).



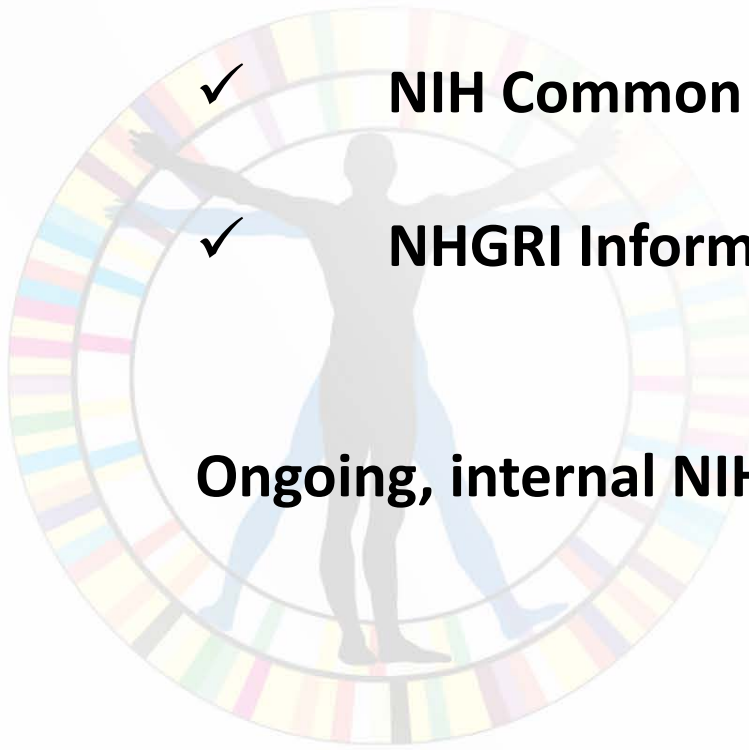
Microbiome 2 Initiative?

Planning Activities

Extramural community input (April-October, 2011):

- ✓ **NIH Common Fund Innovation Brainstorm**
- ✓ **NIH Common Fund Social Media Public Comment Site**
- ✓ **NHGRI Informal Brainstorm Meeting**

Ongoing, internal NIH discussions (2010-2011)



Community recommendations

Scientific questions:

- ✓ What are the mother-child-environment and microbiome interactions?
- ✓ What are the universal drivers in microbe-microbe interactions?
- ✓ What are the universal drivers in host-microbe interactions?
- ✓ What are the local vs systemic roles of the microbiome in health? In disease?

Needed resources:

- ✓ Bioinformatics/computational tools, especially for community-level analyses.
- ✓ Flexible, user-friendly infrastructure for all microbiome data, microbial and host – linked to analytical, visualization tools.
- ✓ New and high throughput technologies to assay microbiome activities, host/microbe interactions.
- ✓ Large cohorts (ex. birth, elderly, nonEuropean, animal models).
- ✓ Training/outreach for tools, techniques for the larger community.



Questions?

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