

The NIH Human Microbiome Project: Catalyst for an emerging field in biomedical research



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NHGRI Council
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Topics for this talk

- ✓ **The human microbiome**
- ✓ **NIH Human Microbiome Project, FY2007-2016**
- ✓ **Recent advances in human microbiome research**

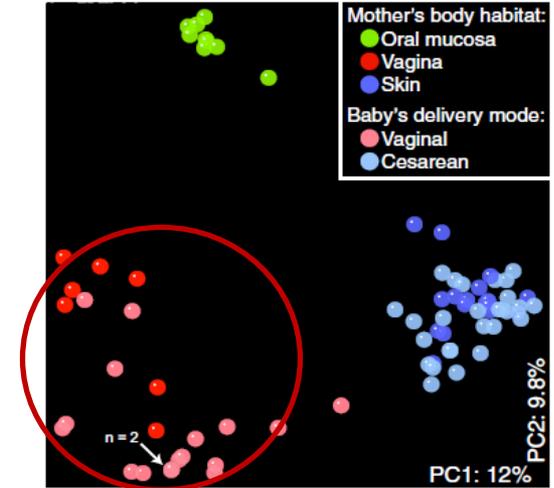
The Human Microbiome

1. Thousands of microbial species*, possessing millions of genes, live with humans.
2. Known as the microbiome, most are not culturable.

<u>Body region</u>	<u>Numbers</u>
Mouth (total)	10^{10}
Lungs (est.)	$\sim 10^9/\text{ml}$
Breastmilk (est.)	$\sim 10^9/\text{L}$
Skin (total)	10^{12}
GI tract (total)	10^{14}
Vagina	$10^9/\text{ml}$

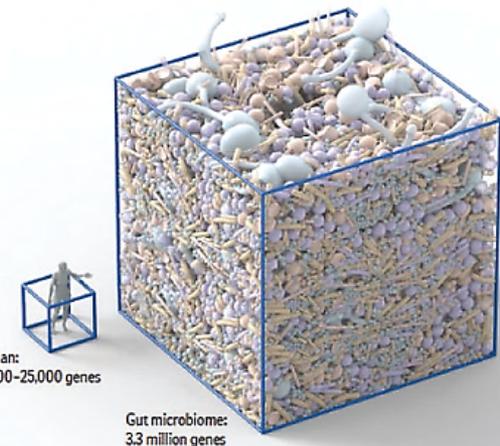


*bacteria, fungi, viruses, phage, archaea, protozoa, (helminths)



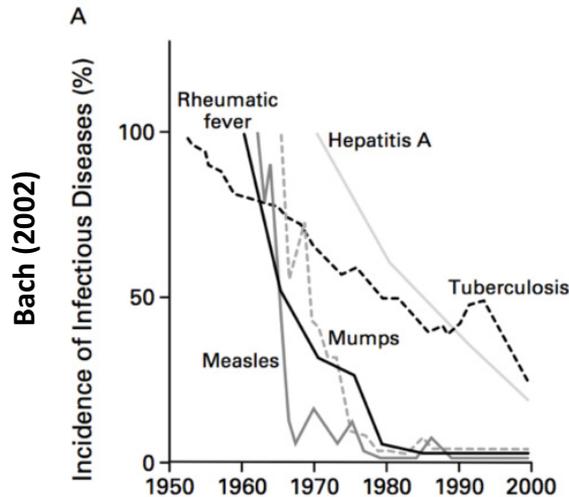
3. These microbes are acquired each generation.

4. Microbiome maturation continues to age 2 or 3, along with immune system development.
5. These microbial genes encode myriad metabolic capabilities.
6. The human microbiome augments/extends capabilities encoded in the human genome.

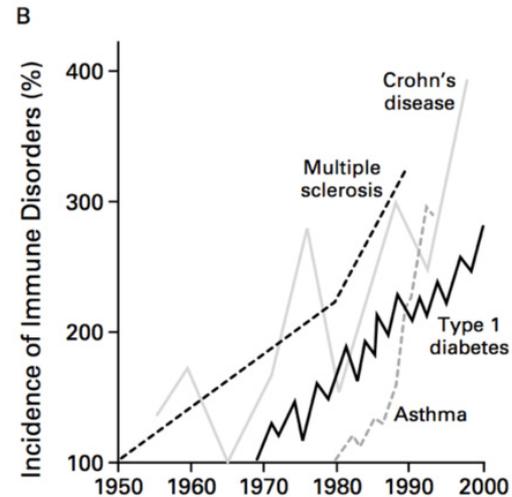


Rationale for Human Microbiome Project

Changes in the microbiome and appearance of 'modern' diseases?



Infectious diseases



Allergic/autoimmune diseases

Next generation sequencing technology enabled microbiome analysis



Ten-year (FY07-16) Human Microbiome Project

\$215M community resource program



HMP program goals

- 1) *Develop research resources:*
e.g. reference datasets, clinical & analytical methods, statistical & computational tools and pipelines
- 2) *Rapidly release resources:*
e.g. public repositories & community databases, HMP Data Analysis Coordination Center (DACC), GitHub & meetings/webinars

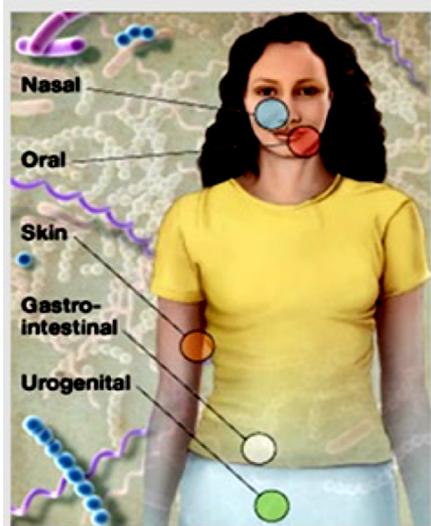
HMP Phase One (2007-2012)

Phase One (\$180M): Survey of microbiome in humans

(funding from Common Fund + NIAID, NCI, NIDDK, NIDCR, NCCIH, NHGRI, ORWH, ODS)

“Who’s there?”

Healthy cohort study



Clinically healthy

300 male/female

18-40 y.o.

5 major body regions
(18 body sites)

Up to 3 visits in 2 yrs

No antibiotics, probiotics,
immunomodulators

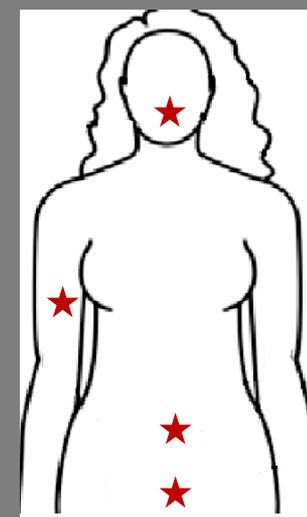
Microbiome-associated conditions

Skin: eczema, psoriasis, acne

GI/oral: esophageal
adenocarcinoma, necrotizing
enterocolitis, pediatric IBS,
ulcerative colitis, Crohn’s
Disease

Urogenital: bacterial vaginosis,
circumcision, sexual histories

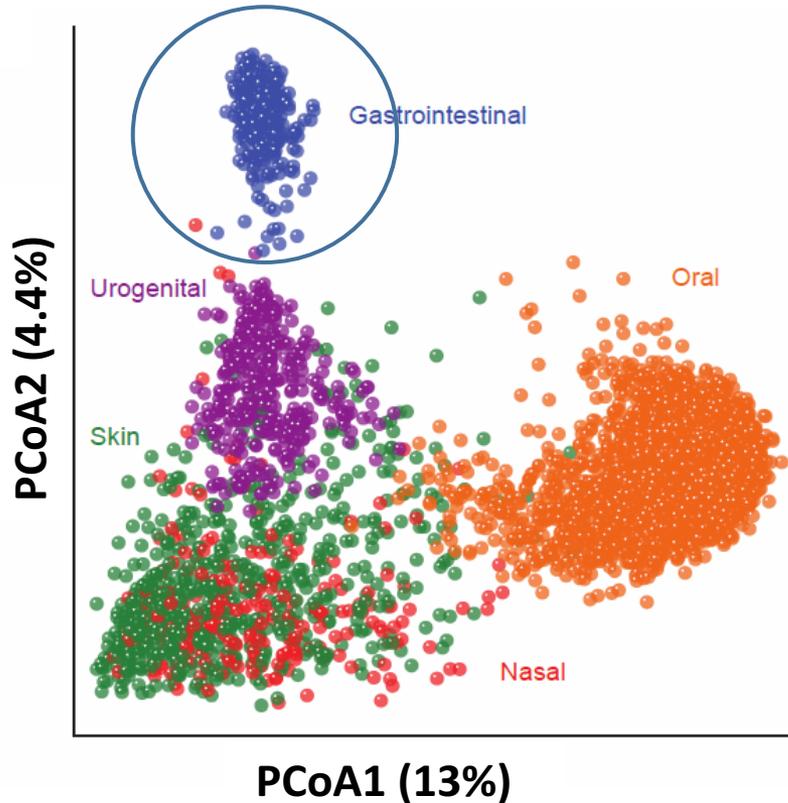
Demonstration Projects



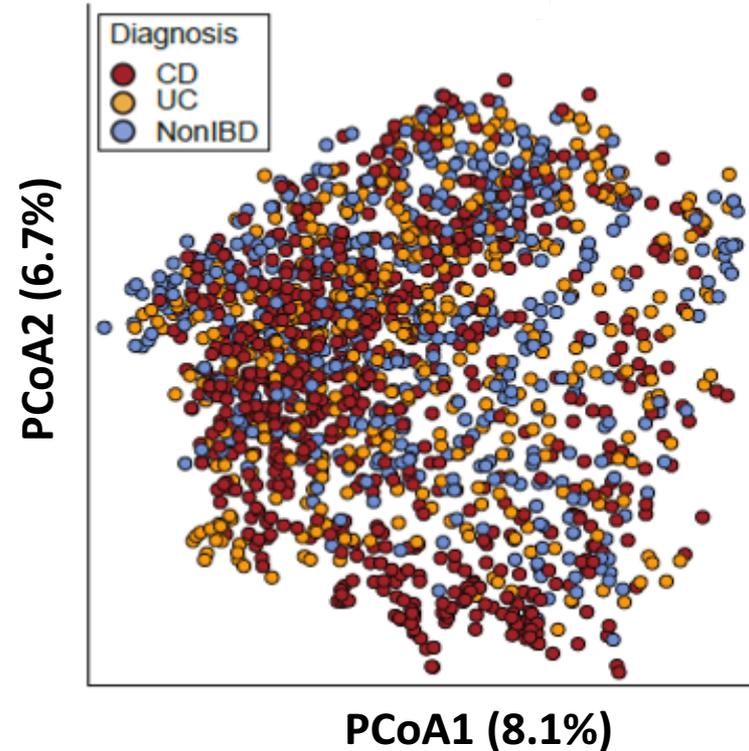
HMP Phase One (2007-2012)

metagenomic analysis of microbial community composition

Human Microbiome Project Consortium (2012a)



Microbial community composition in each body region is distinct.



But large-scale community composition alone cannot differentiate host phenotypes.

Huttenhower et al. (in review)

HMP Phase Two (2013-2016)

Phase Two (\$35M): Integrative HMP “iHMP”

(funding from Common Fund + NIDDK, NICHD, ORWH, NCCIH, ODS)

“What are they doing?”

Analyze multi ‘omic functional properties:

- both microbiome & host
- over time

Interrogate these integrated datasets

Three “model” microbiome-associated conditions:



Pregnancy & Preterm Birth

Multi-Omic Microbiome Study: Pregnancy Initiative (MOMS-PI)



Inflammatory Bowel Disease

Characterizing the gut microbial ecosystem for diagnosis and in therapy in IBD

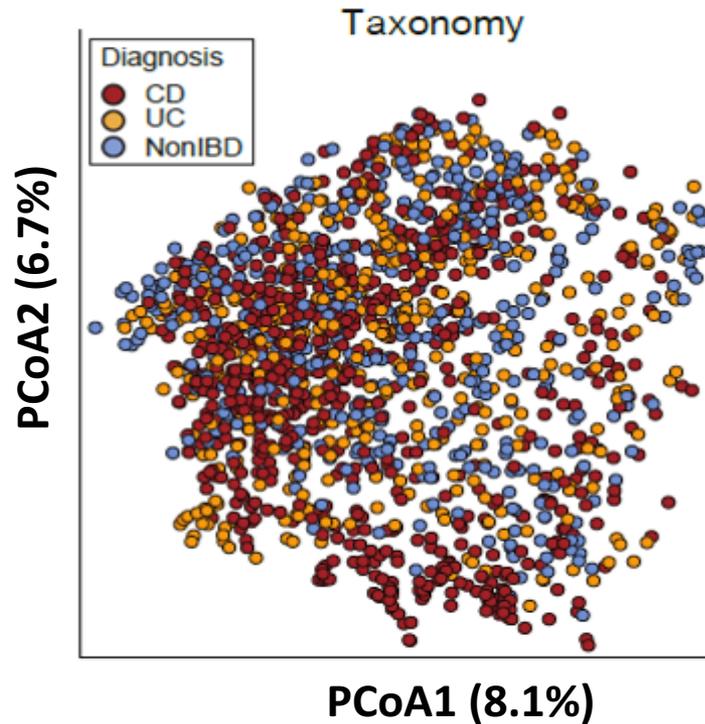
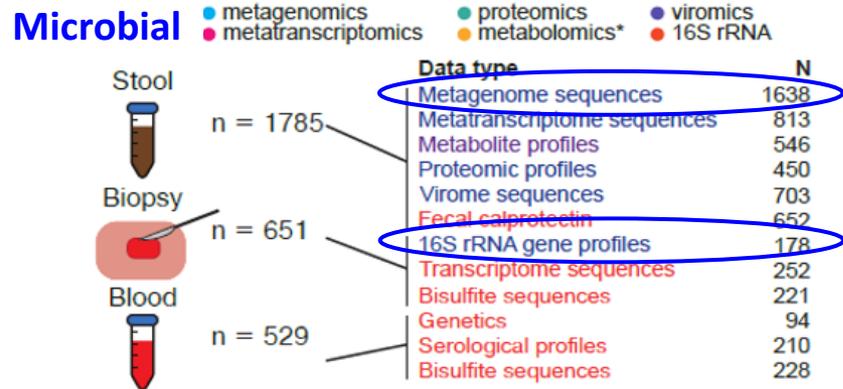
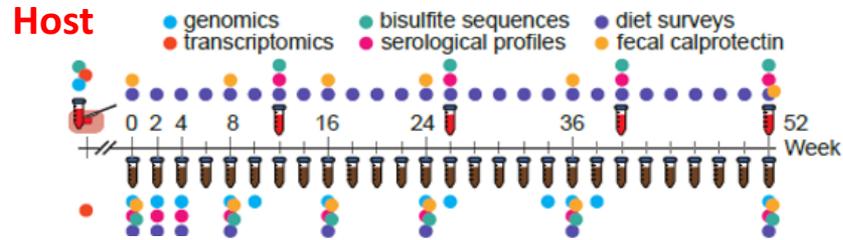


Prediabetes

Microbiome and host changes during respiratory and other stress conditions in individuals at risk for type 2 diabetes

HMP Phase Two (2013-2016)

Ex. IBD host/microbiome properties



Huttenhower et al. (in review)

But large-scale community composition alone cannot differentiate host phenotypes.

Loss/gain of specific microbes and/or specific microbial metabolic pathways are characteristic of disease patients vs healthy controls

HMP Data Analysis and Coordination Center (www.hmpdacc.org)

NIH Human Microbiome Project



Characterization of the microbiomes of healthy human subjects at five major body sites, using 16S and metagenomic shotgun sequencing

Enter HMP1



Characterization of microbiome and human host from three cohorts of microbiome-associated conditions, using multiple 'omics technologies.

Enter iHMP

2018

- ✓ **iHMP paper collection**
 - 4 major mss
 - 35 companion mss
- ✓ **HMP DACC:**
 - **multi-omic datasets**
 - **associated tools**
 - **pipelines**

All primary and derived datasets, tools, and analytical pipelines

HMP resources developed in both phases

1) Sequence and other 'omic reference datasets of microbiome and host

- 16S rRNA & metagenome sequences from five major body regions of 300 adult men and women [*>2,000 metagenomes (10 TB) of sequence data. ~20-30 TB total for Phase One and Two.*]
- Human genome sequences from subjects
- Multi-omic profiles (e.g. transcript, protein, metabolite) from hosts and microbiomes

2) Computational and statistical tools & pipelines for microbiome multi-omic data analyses

- Sequence analysis, including meta-transcriptomic analysis
- Composition, metabolic pathway, network analysis
- Meta-proteomic analysis
- Meta-metabolomic analysis
- Cloud-based analyses

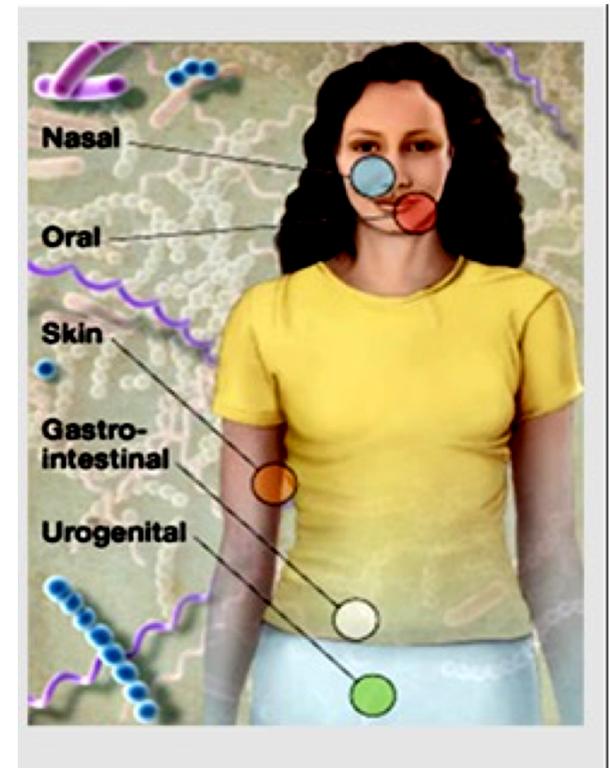
3) Analytical protocols for microbiome sample analysis

4) Clinical protocols for collection/storage of samples

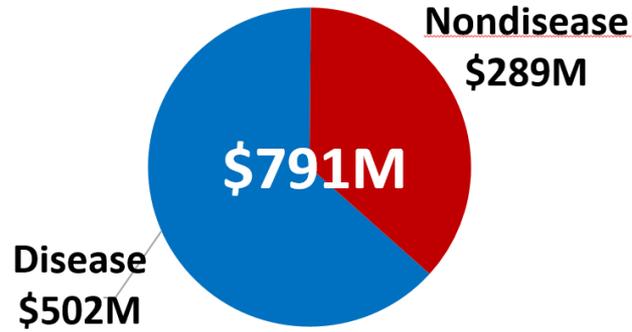
- Skin
- Oral
- GI tract
- Urogenital tract (both vagina and penis)
- Nares

5) IRB protocols for clinical studies of microbiome

6) Evaluation of ELSI issues related to the microbiome



Microbiome(s) and disease(s)



100+ classes of disease over FY12-16

GI tract: irritable bowel disease (IBD), ulcerative colitis, Crohn's disease, GERD, necrotizing enterocolitis (NEC) obesity, metabolic syndrome, type 1 and type 2 diabetes

Heart: cardiovascular diseases

Brain/mental: multiple sclerosis, epilepsy, Alzheimer's, autism, psychiatric disorders



Cancers: Hodgkins' lymphoma, liver, gastric esophageal, colorectal, cervical

Lungs: asthma, cystic fibrosis

Skin: eczema, psoriasis, acne, rheumatoid arthritis

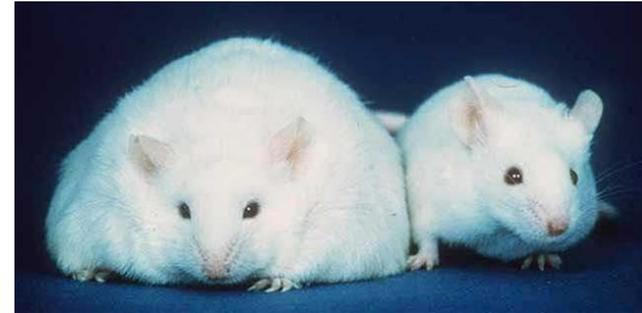
Vagina: bacterial vaginosis, preterm birth

Liver: non-alcoholic liver disease (NAFLD), alcoholic steatosis

Recent advances in microbiome research*

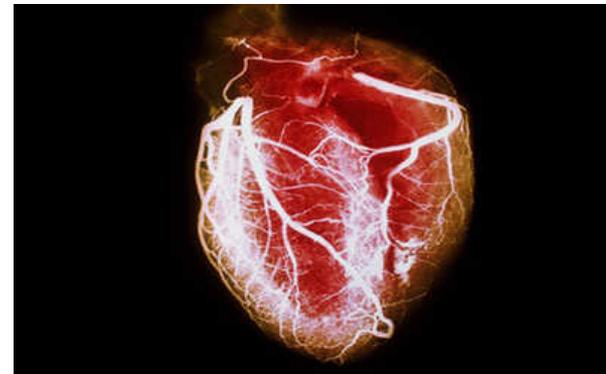
Microbiome-based biomarkers related to disease

- ✓ Gut bacteria/bacterial metabolism and obesity



- ✓ Bacterial epigenetic effects on colorectal cancer

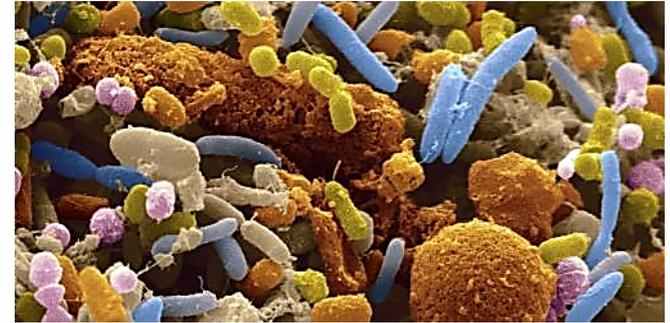
- ✓ Bacterial metabolism and cardiovascular disease



Recent advances in microbiome research*

Microbiome-based therapeutic interventions

- Fecal microbiota transplantation
- Microbiome-derived microbial consortia
- Live biotherapeutic products
- Bacteriophage
- Pharmacobiotics



Microbiome as a source of new pharmaceuticals

NIH Council of Councils

January 27, 2017

“Small Molecules from the
Human Microbiota”

Michael Fischbach (UCSF)

2010 NIH New Innovator awardee

*Mined HMP metagenomic data to
discover and develop novel
antimicrobials*

Current gaps/challenges in microbiome research*

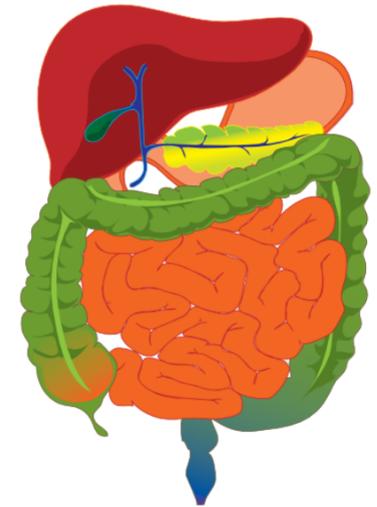
model system(s)?



cause or effect?



microbiome = organ system?



interventions for health?



role of host genetics?



Conclusions

The human microbiome

- 1000s of microbial species, millions of microbial genes
- Metabolically diverse, active, mutable 'microbial organ(s)'

NIH Human Microbiome Project, FY2007-2016

- \$215M invested in rapidly deployed research resources
- Supported 35 institution/50 PI research consortium

Recent advances in human microbiome research

- NIH extramural support expanded to over \$1B over 10 yrs
- Extensive research on host/microbiome biology
- Role of microbiome being studied in 100+ disease classes
- Microbiome-based interventions and drug development

Main challenge: The microbiome is far more than the sum of its microbial members.

Acknowledgements

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Trans-NIH Microbiome Working Group

HMP advisors: Julian Davies (UBC), Francis Ouellette (GenomeCanada), Eugene Chang (Univ Chicago), Stan Falkow (Stanford), Rick Stevens (ANL)

HMP Research Consortium!





HMP and related resources

1) Common Fund HMP website: <https://commonfund.nih.gov/hmp>

2) HMP Data Analysis and Coordination Center (DACC):
<https://www.hmpdacc.org>

3) Trans-NIH Microbiome Working Group (TMWG):
https://commonfund.nih.gov/hmp/related_activities

4) “Emerging Themes” 2017 NIH-wide microbiome workshop:
<https://commonfund.nih.gov/hmp/meetings/emerging>

5) International Human Microbiome Consortium (IHMC):
<http://www.human-microbiome.org/>