

“microbiome”

“metagenome”

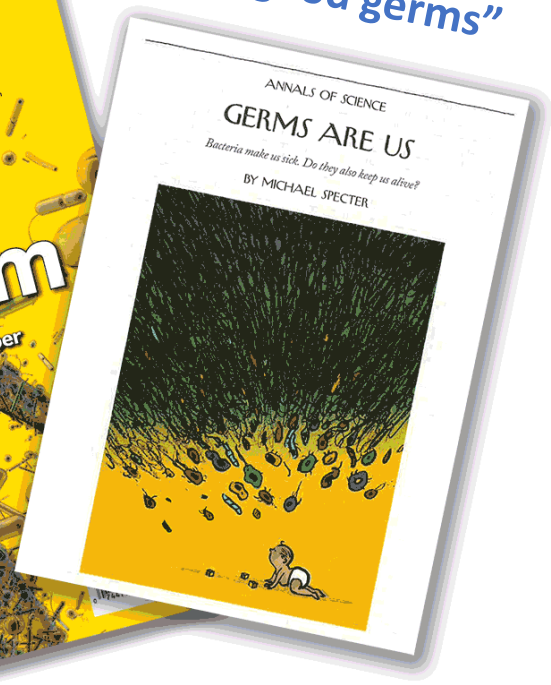
“microbial organ”

“our second genome”

“holobiont”

“human ecosystem”

“good germs”



Lita M Proctor, NHGRI/NIH
September 25, 2019

What are microbes?

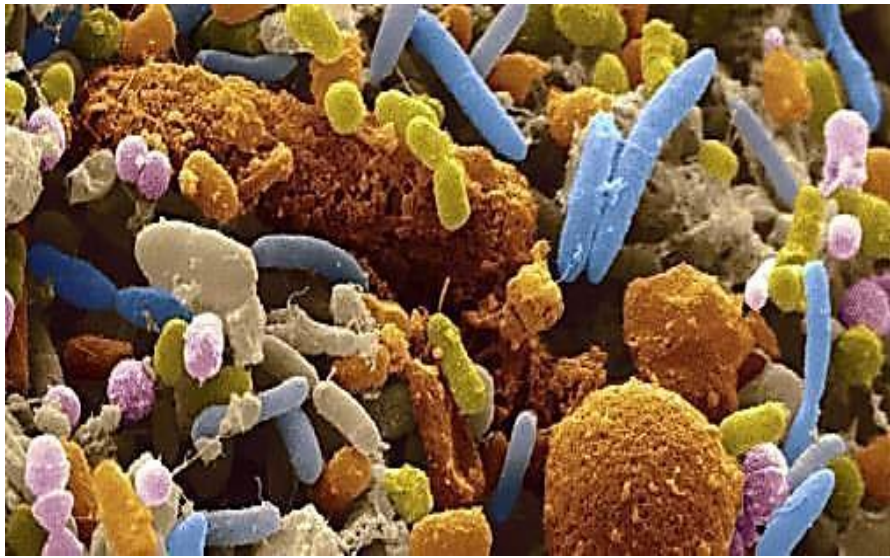
- ▶ often used to mean bacteria
- ▶ broader meaning: microscopic lifeforms
- ▶ many kinds (bacteria, archaea, viruses, bacteriophage, fungi, protozoa)
- ▶ in nature, key principles: don't live alone, interact as communities



Society's war against infectious disease

(bubonic plague, smallpox, scarlet fever, yellow fever, tuberculosis, malaria, diphtheria, dysentery, leprosy, typhoid fever...)





~1400 human pathogenic microbes

vs.

~1 trillion microbial species on Earth

43%



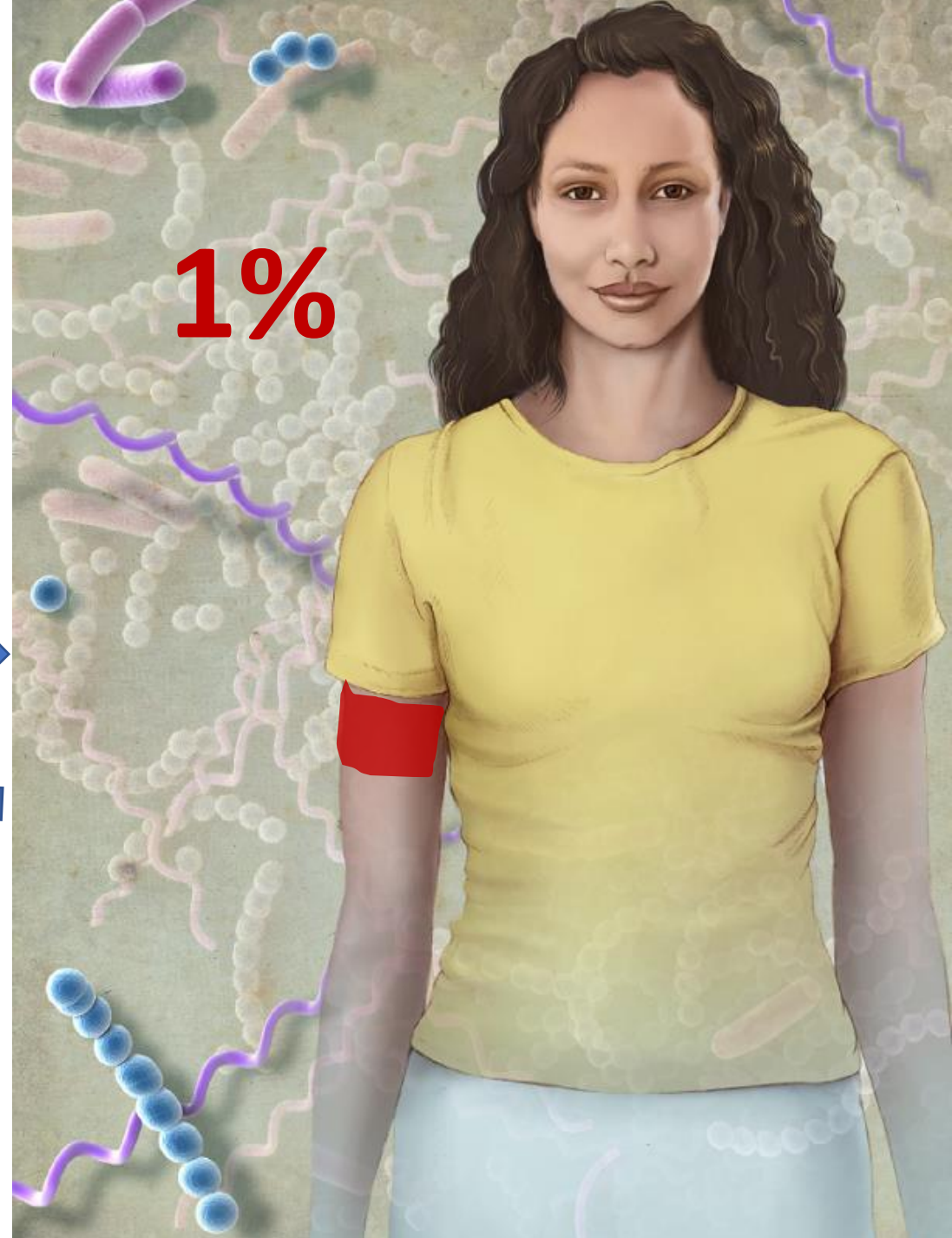
**30 trillion
human cells
vs
39 trillion
microbes**



**~20,000
human
genes
vs
2-20 million
microbial
genes**



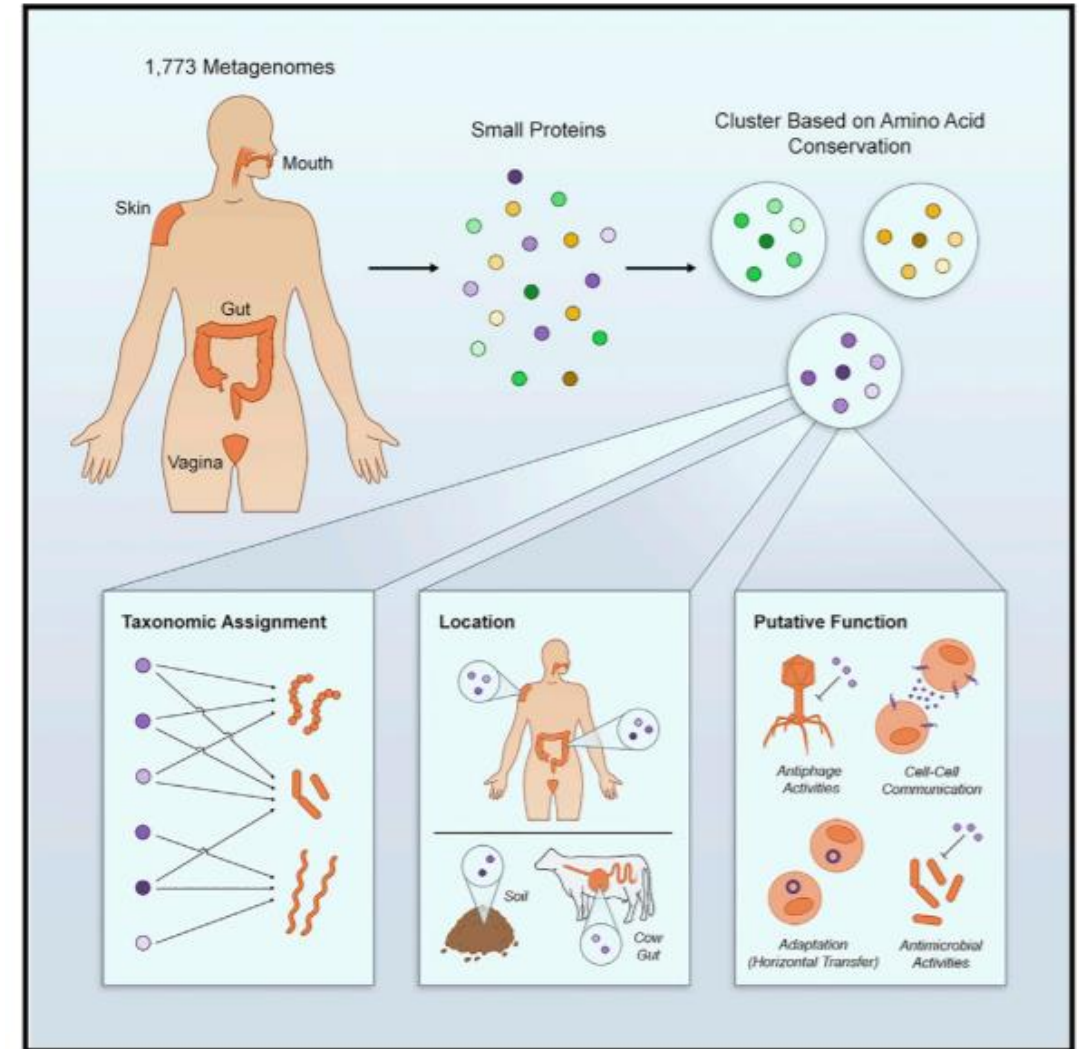
1%



What do these microbial genes code for?

Many kinds of vitamins, anti-microbials, anti-inflammatories, neurotransmitters, signaling molecules, host energy sources, etc, etc

But also, thousands of new-to-medicine microbial proteins...



Large-Scale Analyses of Human Microbiomes Reveal Thousands of Small, Novel Genes

Hila Sberro,^{1,2} Brayon J. Fremin,¹ Soumaya Zlitni,¹ Fredrik Edfors,² Nicholas Greenfield,³ Michael P. Snyder,² Georgios A. Pavlopoulos,^{4,5} Nikos C. Kyrpides,^{4,6} and Ami S. Bhatt^{1,2,7,*}

¹Department of Medicine (Hematology; Blood and Marrow Transplantation) and Genetics, Stanford University, Stanford, CA, USA

²Department of Genetics, Stanford University, Stanford, CA, USA

³One Codex, San Francisco, CA, USA

⁴Department of Energy, Joint Genome Institute, Walnut Creek, CA, USA

⁵Institute for Fundamental Biomedical Research, Biomedical Sciences Research Center Alexander Fleming, Vari, Greece

⁶Environmental Genomics and Systems Biology Division, Lawrence Berkeley National Laboratory, Berkeley, CA, USA

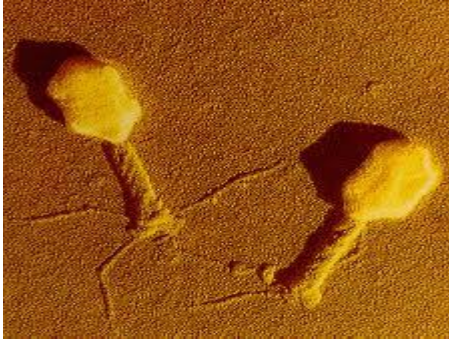
⁷Lead Contact

*Correspondence: asbhatt@stanford.edu

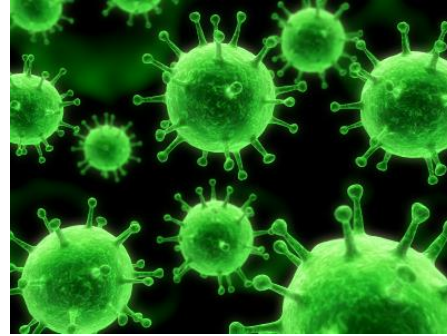
<https://doi.org/10.1016/j.cell.2019.07.016>

Beneficial role(s) of non-bacterial members of microbiome

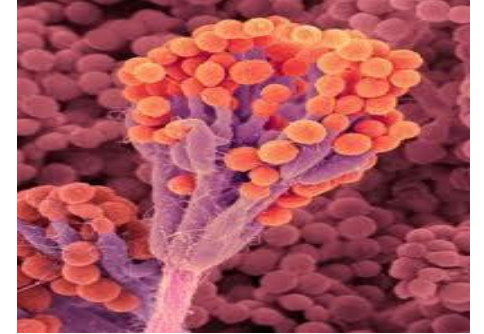
Bacteriophage

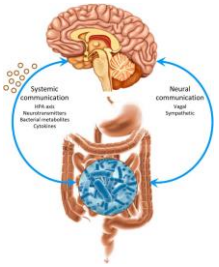


Eukaryotic viruses

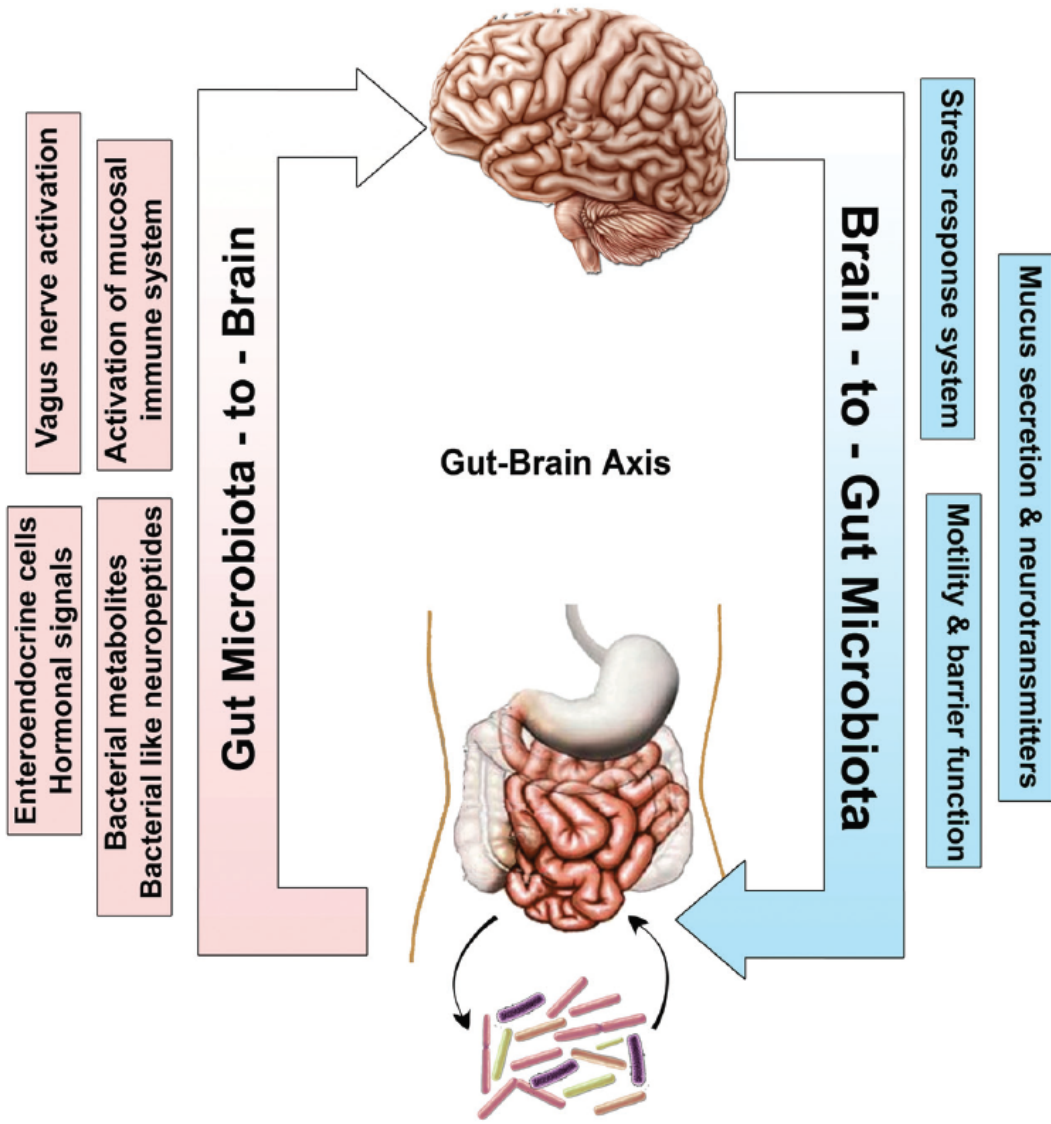


Fungi





Gut-microbiome-brain axis & human health and disease



Gut microbiota modulate CNS:

- vagus nerve activation
- hormonal system
- immunological system

Brain-gut-microbiota linkages:

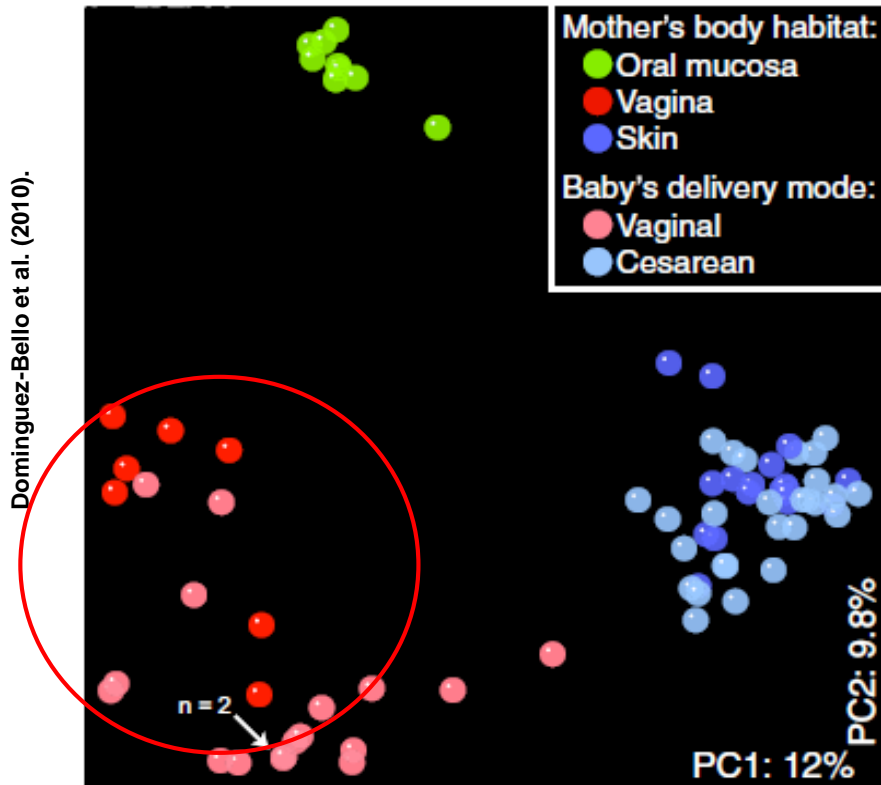
- stress factors
- gut permeability changes
- neurotransmitter release

ex. serotonin synthesis by gut cells depends on gut bacteria

doi:10.1016/j.cell.2015.02.047

Neurological/mental conditions: *epilepsy, autism spectrum disorders, Alzheimer's, psychiatric disorders, Parkinson's, schizophrenia, Multiple Sclerosis, etc*

Microbiota are acquired anew each generation.

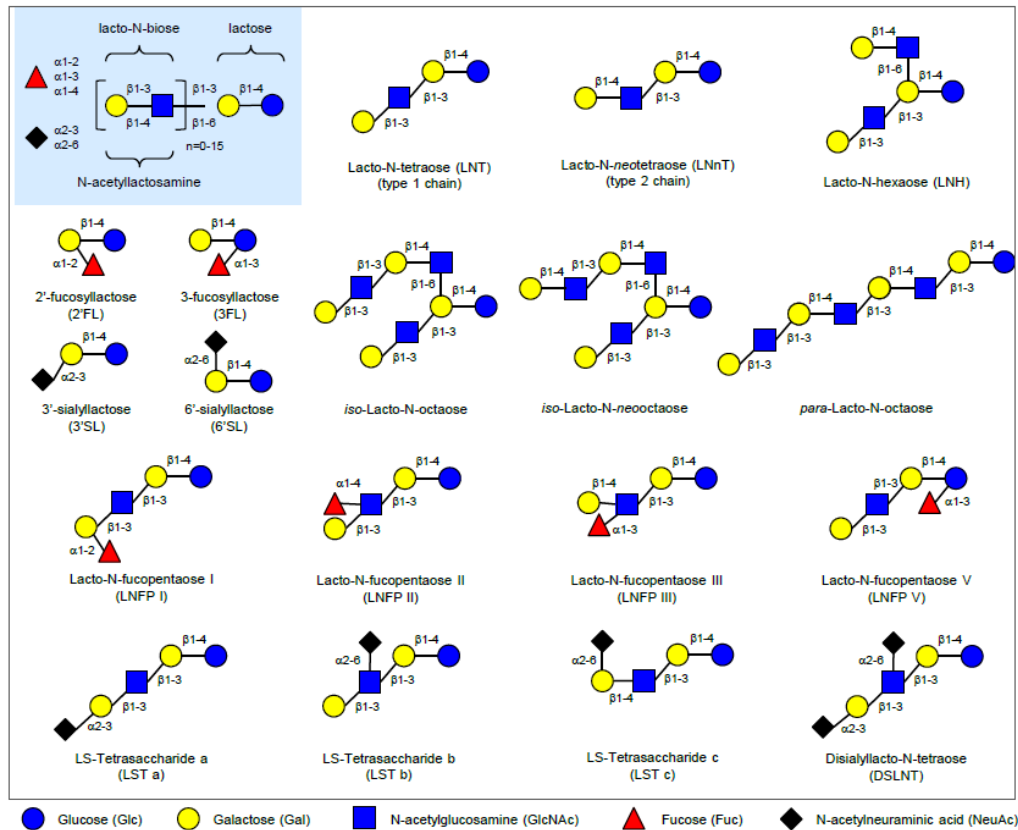


- 1) Infants obtain inoculum from mother or environment.
- 2) Microbial succession over ~1-2 yrs of life.
- 3) Microbiome becomes “adult-like” in ~2-3 yrs of life.

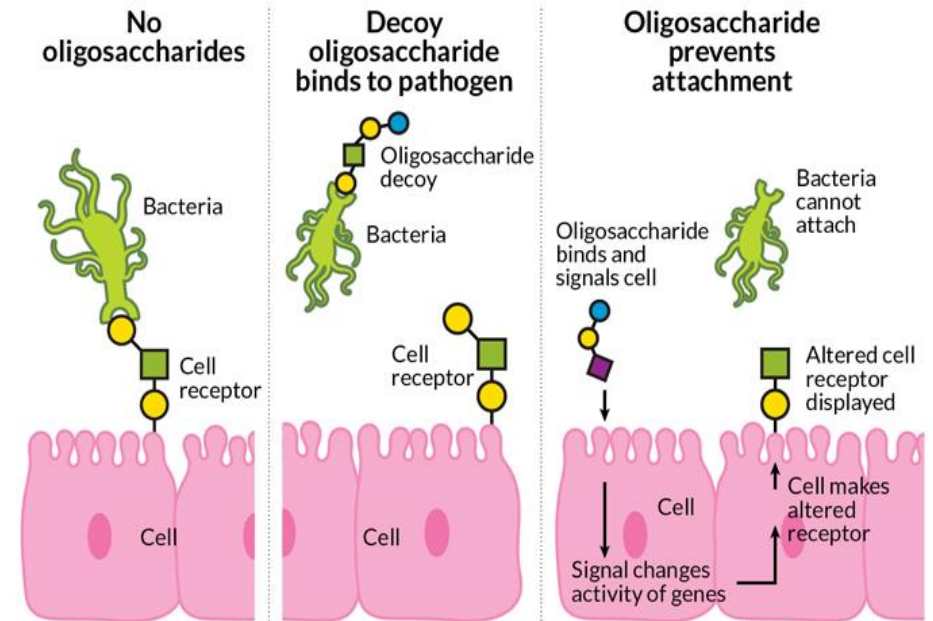
Human milk oligosaccharides (HMOs)*:

- 1) microbial food for the developing microbiome
- 2) protects against invading pathogens

100s of different kinds of HMOs

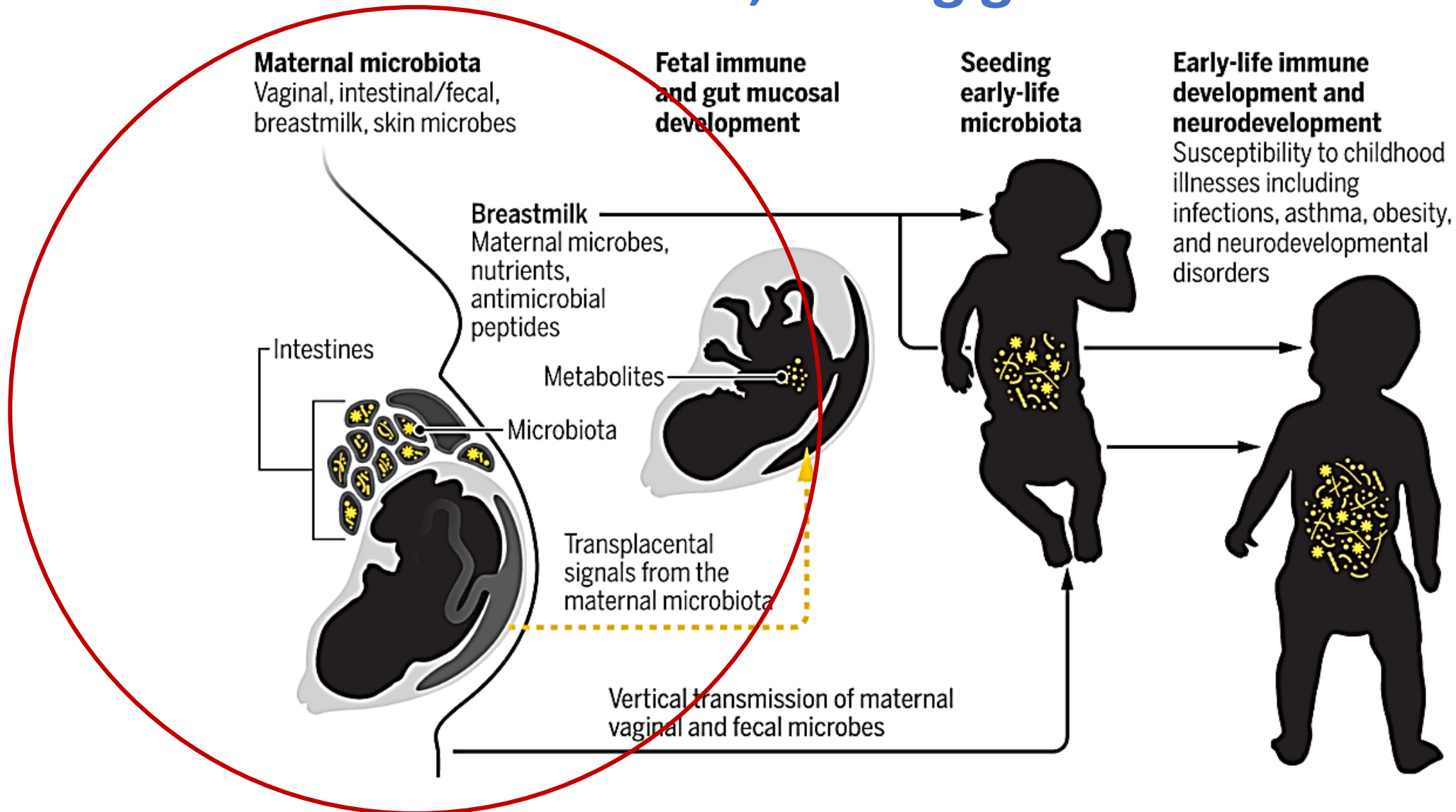


HMOs as molecular decoys

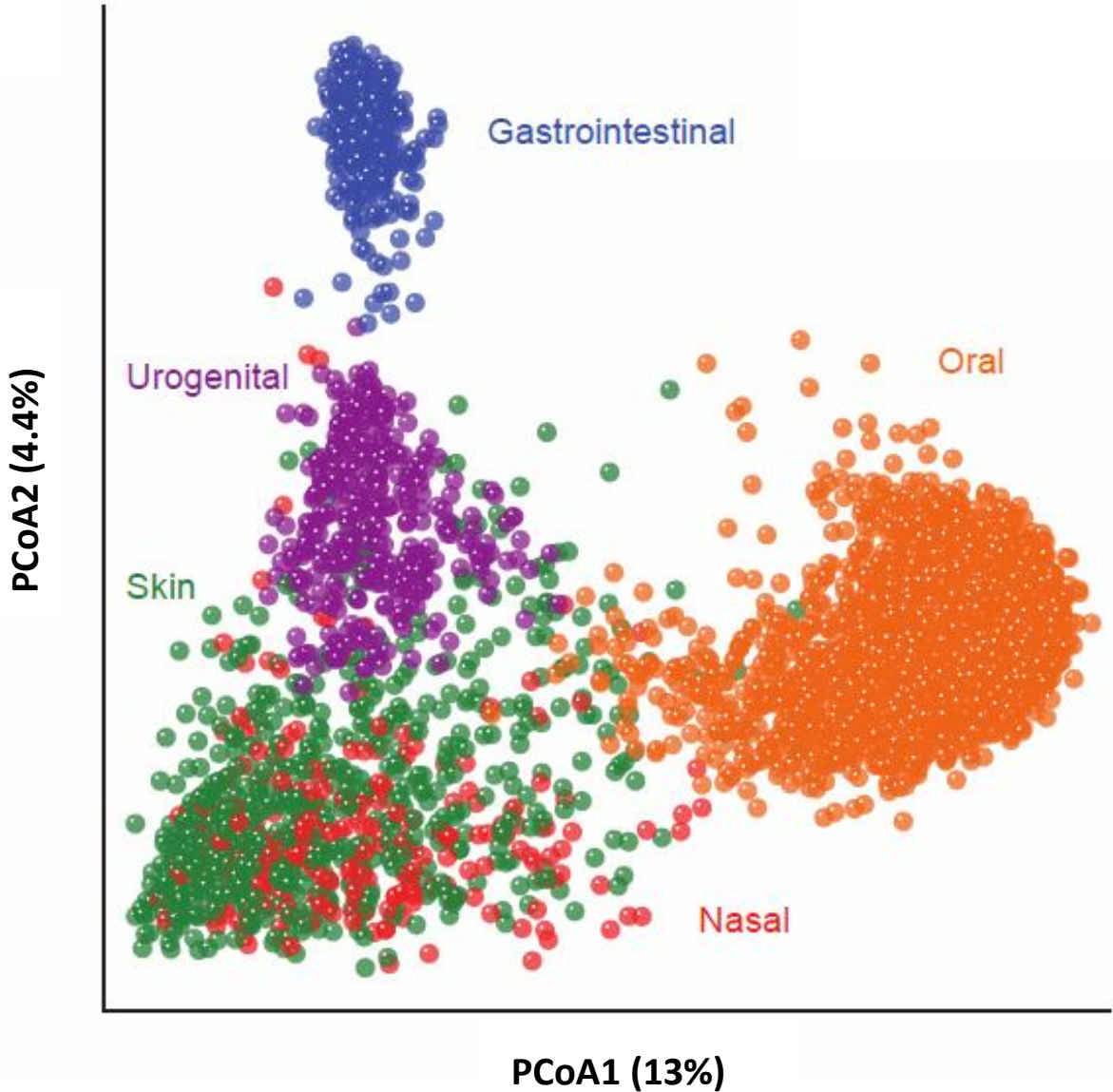
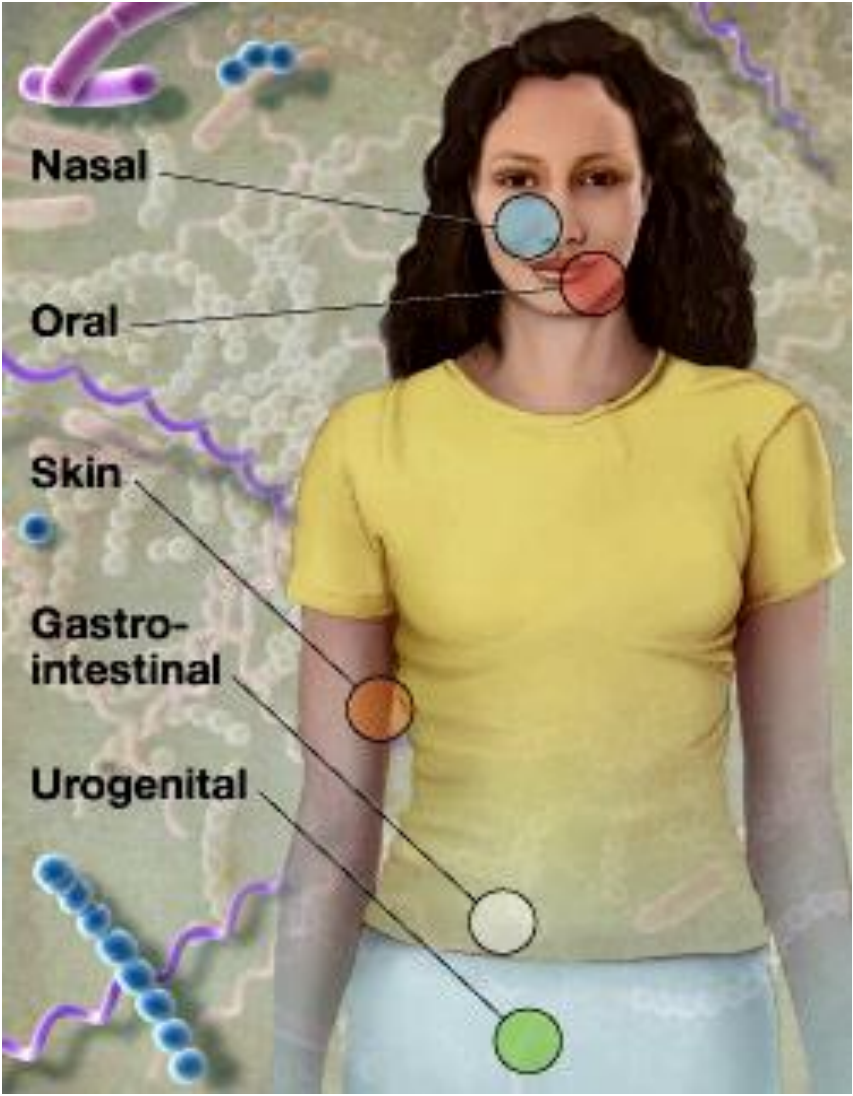


[Breastmilk (per 100 mls): Proteins = 2.5 g, Fats = 5 g and *HMOs = 0.5 g]

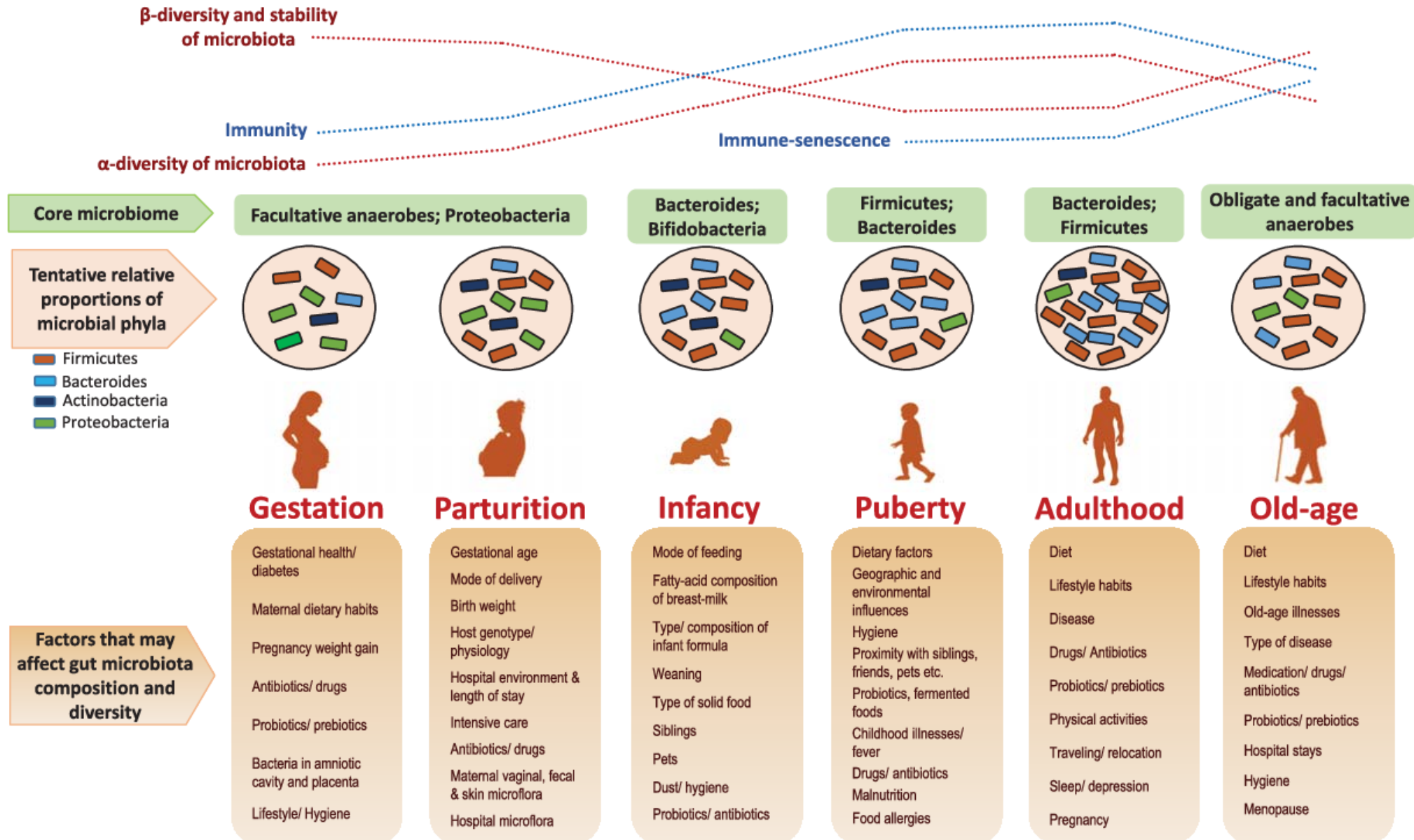
Does microbiome developmental period start at birth or before, during gestation?



The human body matures into an ecosystem of microbial habitats.



But the microbiome is mutable and naturally changes over our lifetimes.



Timing and Opportunity: Human Microbiome Project



"All the News That's Fit to Print"

The New York Times

Late Edition
New York: Today, afternoon thunderstorms, high 85. Tonight, showers end, low 67. Tomorrow, partly cloudy with showers late, high 81. Yesterday, high 88, low 74. weather map, page D8.

VOL. CXLIX . . . No. 51,432 Copyright © 2000 The New York Times NEW YORK, TUESDAY, JUNE 27, 2000 \$1 beyond the greater New York metropolitan area 75 CENTS

Genetic Code of Human Life Is Cracked by Scientists

JUSTICES REAFFIRM MIRANDA RULE, 7-2; A PART OF 'CULTURE'

By LINDA GREENHOUSE

WASHINGTON, June 26 — The Supreme Court reaffirmed the Miranda decision today by a 7-to-2 vote that erased a shadow over one of the most famous rulings of modern times and acknowledged that the Miranda warnings "have become part of our national culture."

The court said in an opinion by Chief Justice William E. Rehnquist that because the 1966 Miranda decision "announced a constitutional rule," a statute by which Congress had sought to overrule the decision was itself unconstitutional.

Miranda had appeared to be in jeopardy, both because of that long-ignored but recently rediscovered law, by which Congress had tried to overrule Miranda 32 years ago, and because of the court's perceived hostility to the original decision.

The chief justice said, though, that the 1968 law, which replaced the Miranda warnings with a case-by-case test of whether a confession was voluntary, could be upheld only if the Supreme Court decided to overturn Miranda. But with Miranda intact,

Justices Antonin Scalia and Clarence Thomas cast the dissenting votes.

The decision overturned a ruling last year by the federal appeals court in Richmond, Va., which held that Congress was entitled to the last word because Miranda's presumption that a confession was not voluntary unless preceded by the warnings was not required by the Constitution.

The decision today — only 14 pages long, in Chief Justice Rehnquist's typically spare style — brought an abrupt end to one of the oddest episodes in the court's recent history, an intense and strangely delayed re-lighting of a previous generation's battle over the rights of criminal suspects. Miranda v. Arizona was a hallmark of the Warren Court, and Chief Justice Rehnquist, despite his record as an early and tenacious critic of the decision, evidently did not want its repudiation to be an imprint of his own tenure.

There was considerable drama in the courtroom today as the chief

The Book of Life
The three billion base pairs ...

... of the intertwining double helix of DNA ...

... that make up the set of chromosomes in our cells, have been sequenced.

BASE PAIRS
Rungs between the strands of the double helix

BASES
A adenine
C cytosine
G guanine
T thymine

A SHARED SUCCESS
2 Rivals' Announcement Marks New Medical Era, Risks and All

By NICHOLAS WADE

WASHINGTON, June 26 — In an achievement that represents a pinnacle of human self-knowledge, two rival groups of scientists said today that they had deciphered the hereditary script, the set of instructions that defines the human organism.

"Today we are learning the language in which God created life," President Clinton said at a White House ceremony attended by members of the two teams, Dr. James D. Watson, codiscoverer of the structure of DNA, and, via satellite, Prime Minister Tony Blair of Britain. [Excerpts, Page D8.]

The teams' leaders, Dr. J. Craig Venter, president of Celera Genomics, and Dr. Francis S. Collins, director of the National Human Genome Research Institute, praised each other's contributions and signaled a spirit of cooperation from now on, even though the two efforts will remain firmly independent.

The human genome, the ancient script that has now been deciphered, consists of two sets of 23 chromosomes.

By ordering the base units, scientists hope to locate the genes and determine their functions.

Francis S. Collins, head of the Human Genome Project, left, with J. Craig Venter, head of Celera Genomics, after the announcement yesterday that they had finished the first survey of the human genome.

Section F

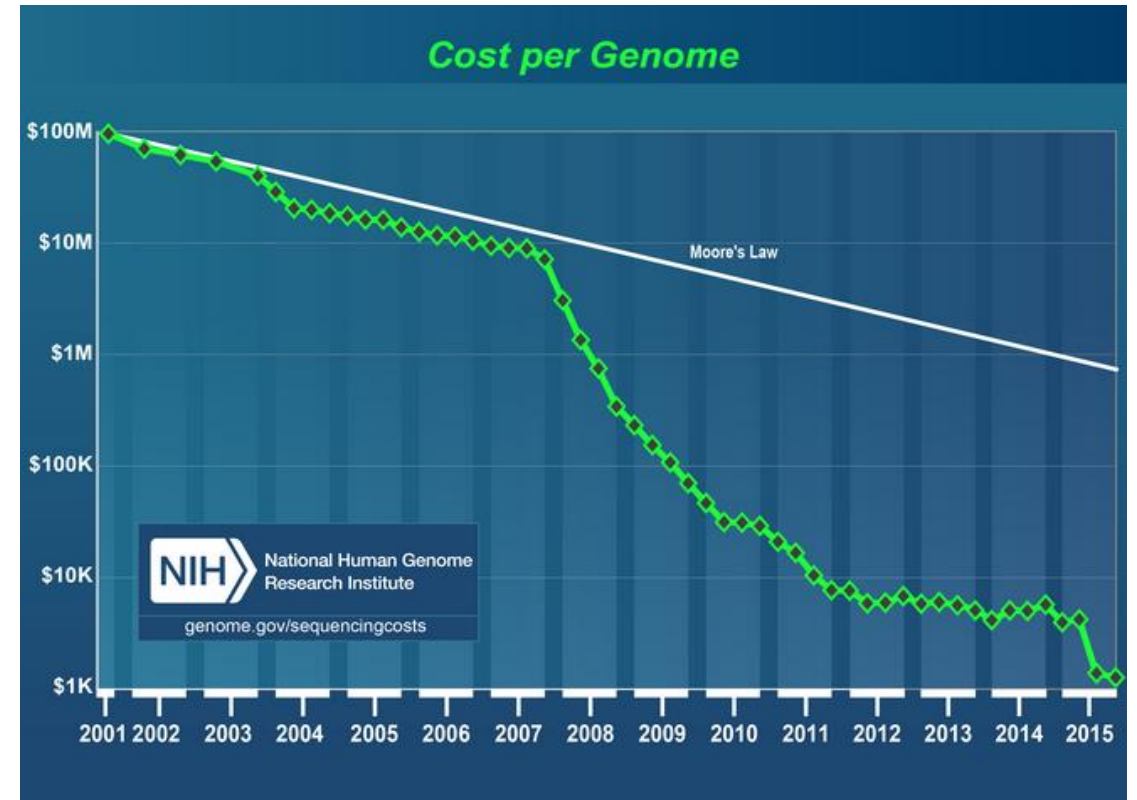
- Putting the genome to work.
- Some information has already paid research dividends.
- Two research methods, two results.
- From Mendel to helix to genome.
- More articles, charts and photos of the genome effort.

2006/2007 →

- NIH Common Fund established
- Sequence the 'other genome'
- HMP: \$215M, 10-yr program
- Create research toolbox

2000 →

- Human genome sequence announced
- Four (4) US Genome Centers
- Sequencing technologies improving
- Cost/genome begins dropping



Ten-year (FY2007-2016) Human Microbiome Project

\$215M to build research 'toolbox' and network



HMP program goals

1) *Develop research resources:*

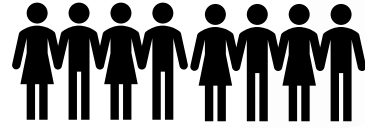
e.g. reference datasets, clinical & analytical methods, statistical & computational tools and pipelines

2) *Rapidly release resources:*

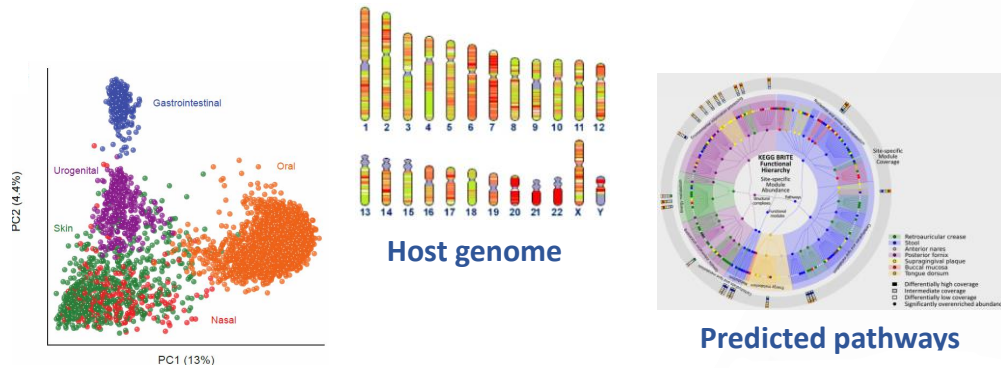
e.g. public repositories & community databases, HMP Data Analysis Coordination Center (DACC), GitHub & meetings/webinars

HMP one

Benchmark Healthy Cohort Study

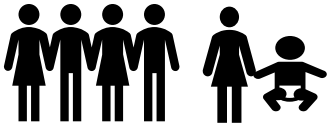


- Characterize microbiomes
- Correlate with phenotypes



“Who’s there?”

Demonstration Projects (12)



HMP two collection of papers (3 flagship and ~20 companion)
published in *Nature* in 2019



HMP research toolbox

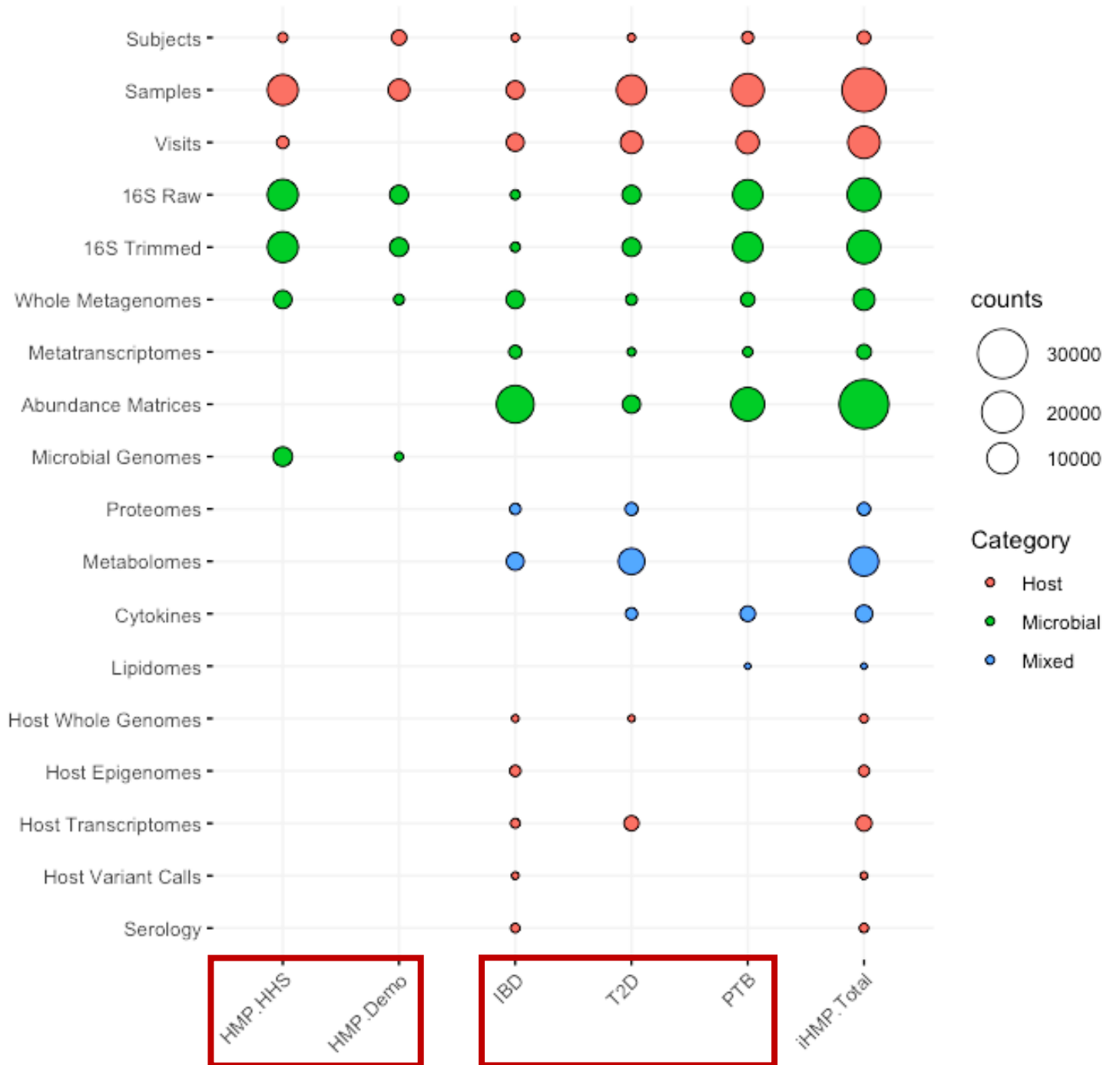
www.hmpdacc.org

HMP one

~10 Tb data (sequence)

HMP two

~30 Tb data (multi omic)

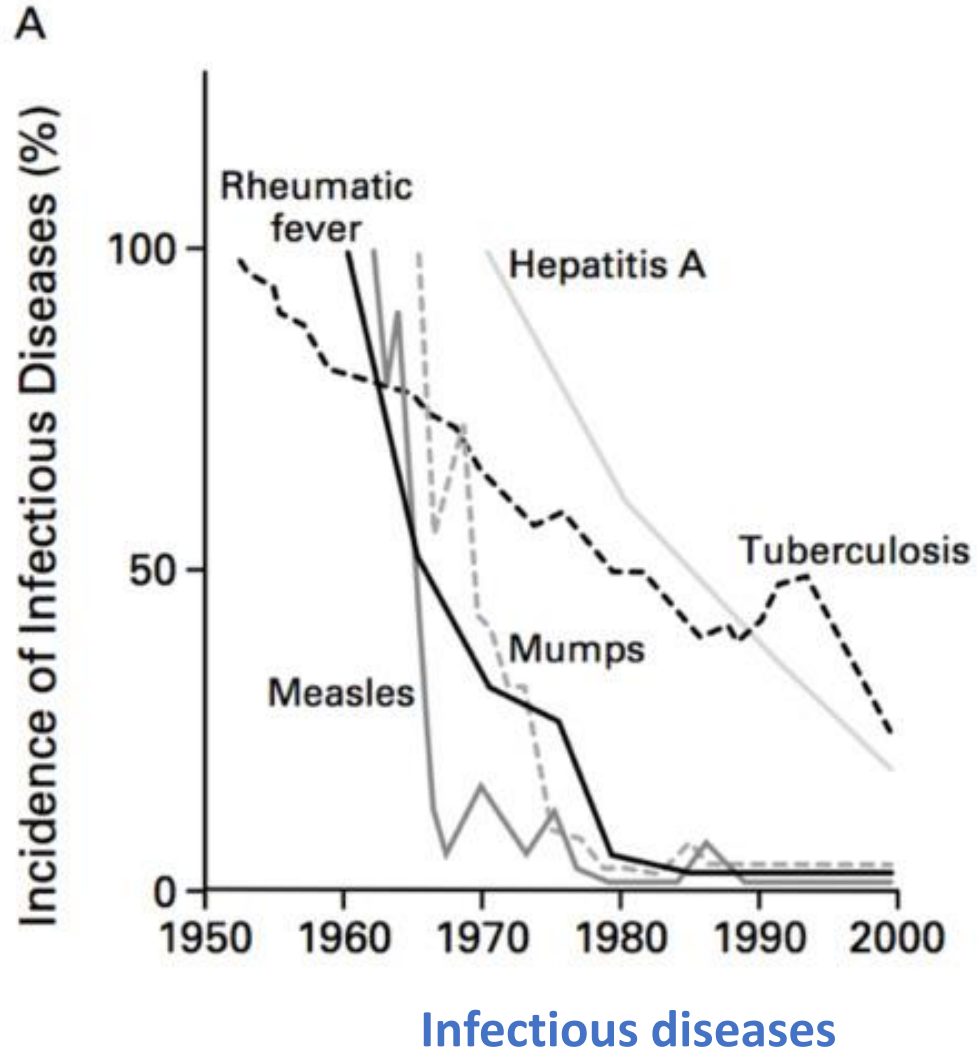


Microbiota and host *interact* to regulate human health.

- ✓ digests the 'indigestibles'
(ex. plant material, host cells, mucous)
- ✓ 'educates' the immune system
- ✓ produces energy substrates
(ex. SCFAs such as acetate)
- ✓ metabolizes drugs
- ✓ produces beneficial compounds
(ex. vitamins, antimicrobials)
- ✓ communicates with the brain
- ✓ regulates organ development/function



Is the appearance of chronic disease related to changes in the microbiome?

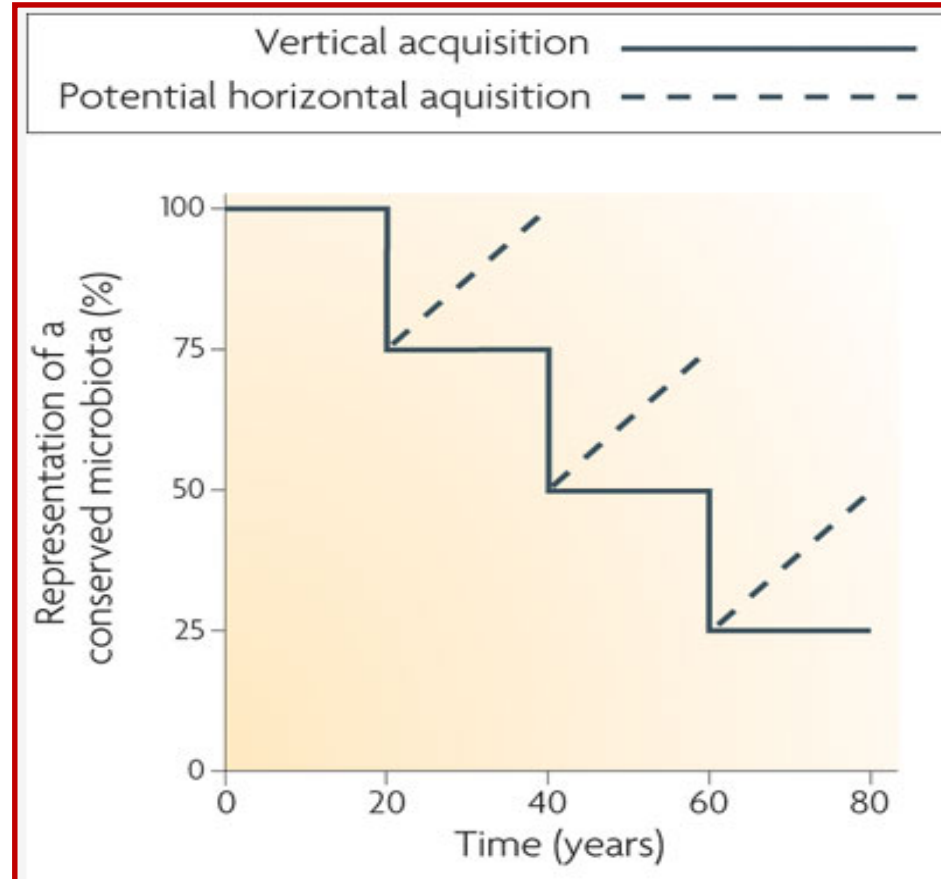


Increase in immune disorders over last ~ 75 yrs

Is the appearance of chronic disease related to changes in the microbiome?

Contemporary practices:

- Excessive hygiene
- Caesarean birth
- Antibiotic overuse
- Processed foods/additives
- Formula feeding
- Hg amalgams
- Other factors?



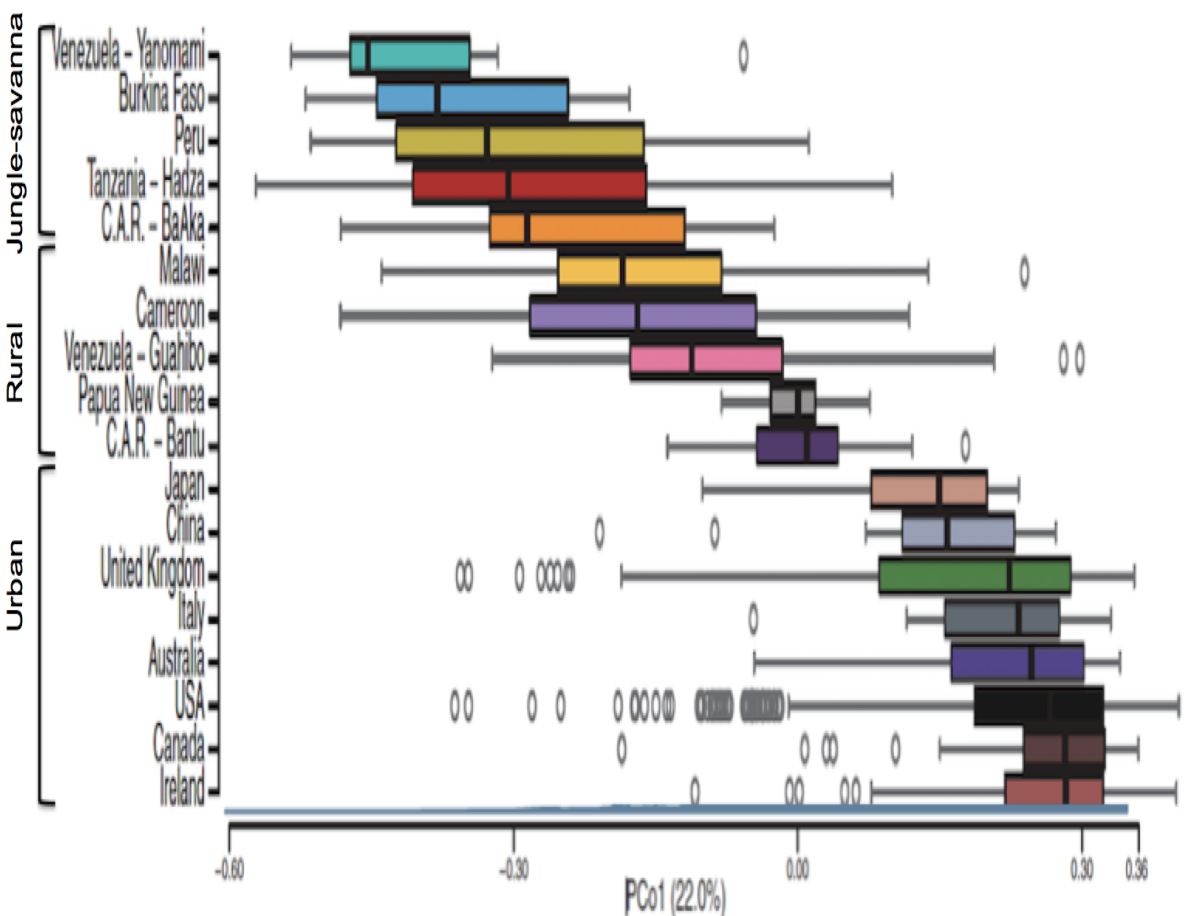
Blaser and Falkow (2009)



Postulated systematic loss of microbiota inocula each generation.

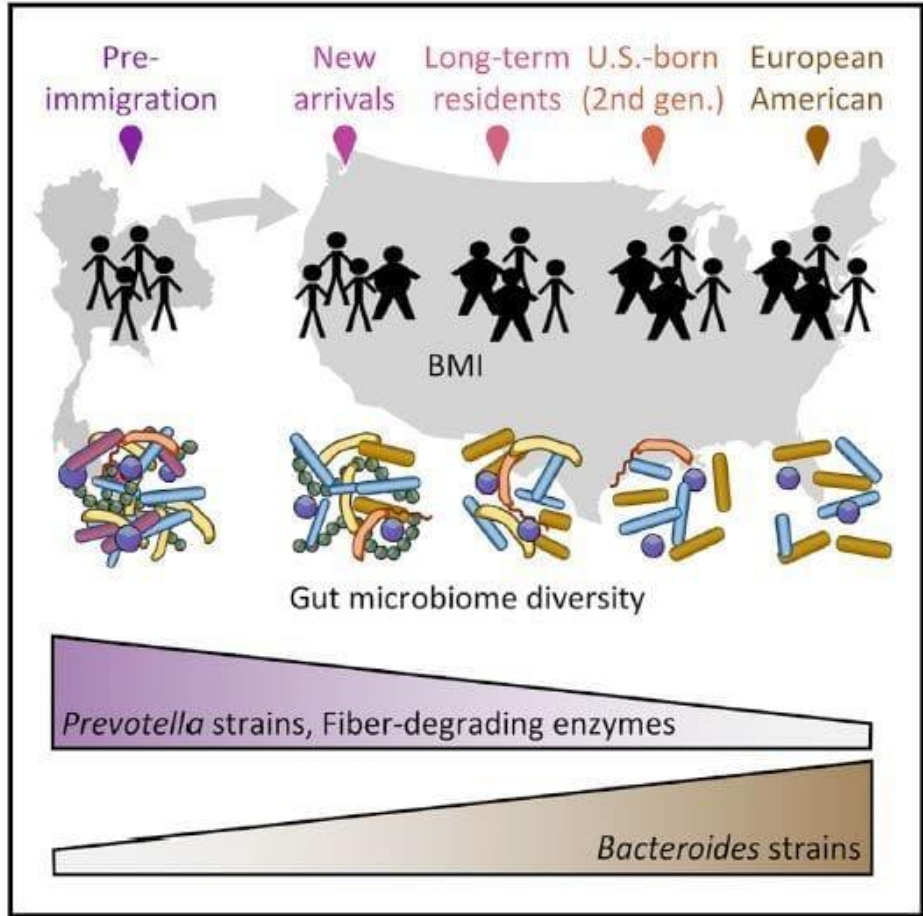
Microbiome diversity appears to be decreasing across populations and across generations

across populations

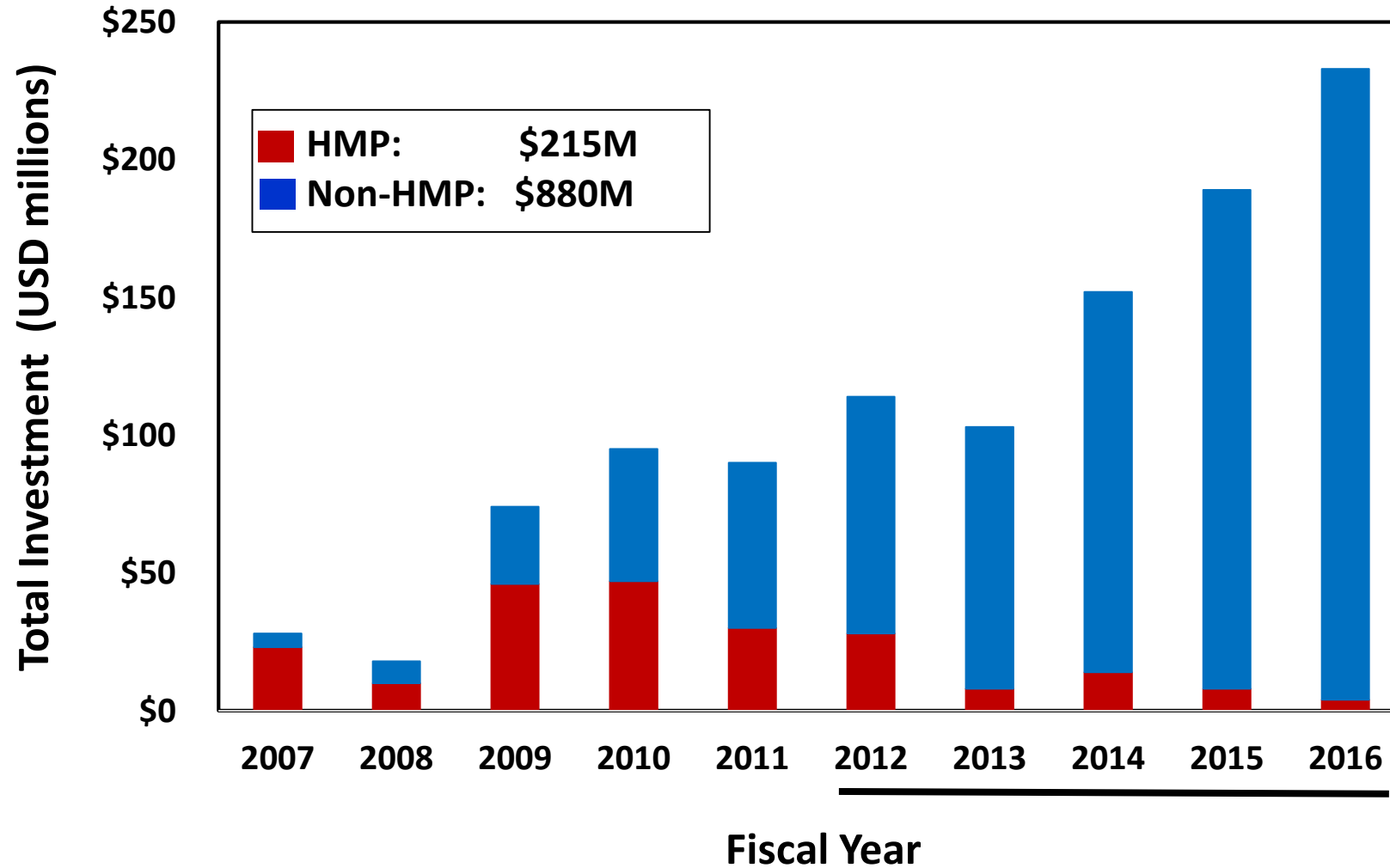


Decreasing gut microbiota diversity

across generations

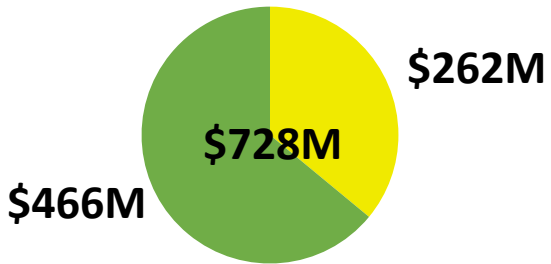


HMP catalysed human microbiome research at NIH*



* "A review of 10 years of human microbiome research activities at the US National Institutes of Health, Fiscal Years 2007-2016" NIH Human Microbiome Portfolio Analysis Group. *BMC Microbiome*. doi: 10.1186/s40168-019-0620-y

FY12-16



Microbiome(s) and disease(s)

NIH funds studies in 100+ classes of disease

Neurological/mental: *epilepsy, Alzheimer's, psychiatric disorders*

GI tract: *irritable bowel disease (IBD), ulcerative colitis, Crohn's disease, GERD, necrotizing enterocolitis (NEC)*

Heart:
cardiovascular diseases



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

Lungs: *asthma, cystic fibrosis*

Skin: *eczema, psoriasis, acne, rheumatoid arthritis*

Vagina/Uterus:
bacterial vaginosis, preterm birth

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

Systemic: *Obesity, Type 1 and type 2 diabetes, lupus, multiple sclerosis, autism, etc.*

Recent advances in human microbiome research

(postulated mechanisms of disease initiation/exacerbation)

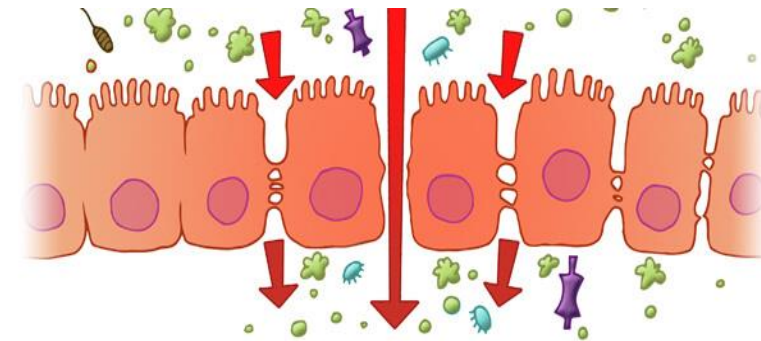
- ✓ Environmentally-derived microbes (ex. dental caries)



- ✓ Commensal microbes becoming pathogenic (ex. IBD)



- ✓ Gut translocation of microbes or microbial products (ex. lupus)

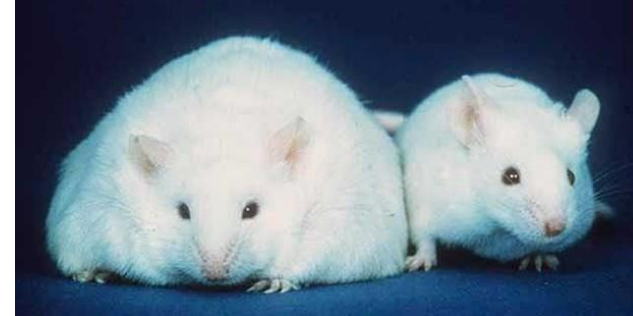
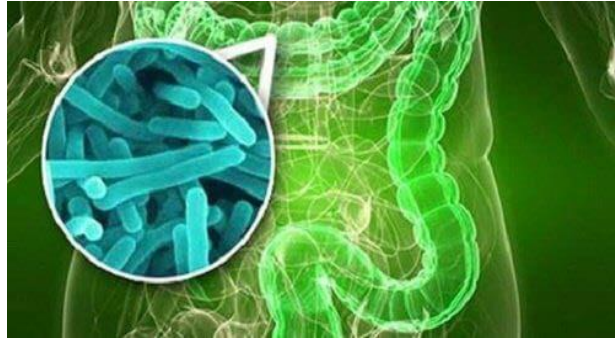


Each mechanism will inform specific interventions.

Recent advances in human microbiome research

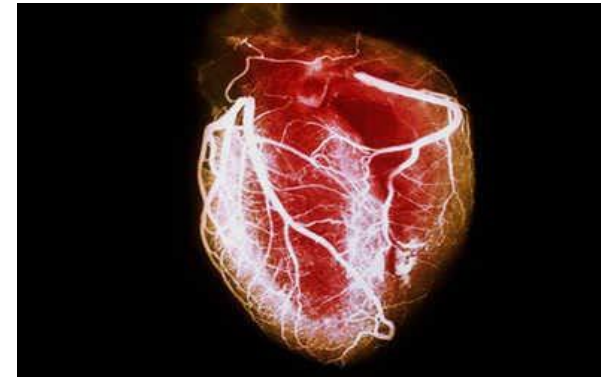
(microbiome-based biomarkers for disease risk)

- ✓ Gut bacteria/bacterial metabolites and obesity



- ✓ Bacterial epigenetic effects on colorectal cancer

- ✓ Bacterial metabolites and cardiovascular disease

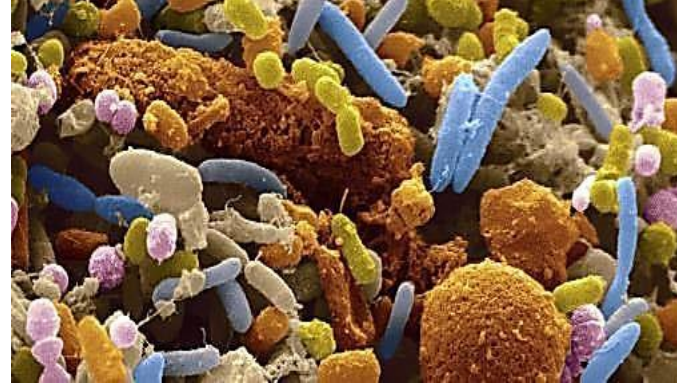


Recent advances in human microbiome research

(microbiome-based interventions and products)

Microbiome-based therapeutic interventions

- Fecal microbiota transplantation
- Microbiome-derived microbial consortia
- Live biotherapeutic products
- Therapeutic bacteriophage
- Microbial augmentation of treatment



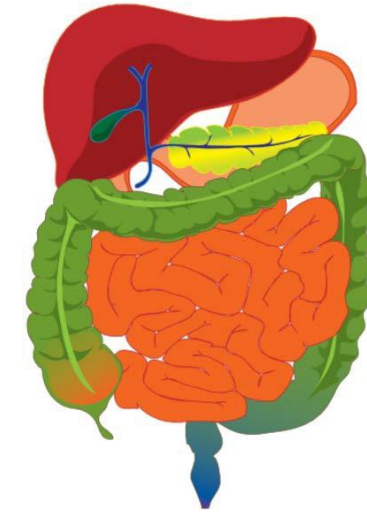
Gaps/challenges in human microbiome research

model system(s)?



cause or effect?

microbiome = organ system?



interventions for health?



role of host genetics?



Microbiome Centers (not all focused on human)

36+ Microbiome Centers around the country



Microbiome Centers Consortium (MCC) under development:

**1st workshop: UC Irvine, June 25-26, 2019
(white paper upcoming in *Nature Microbiology*)**

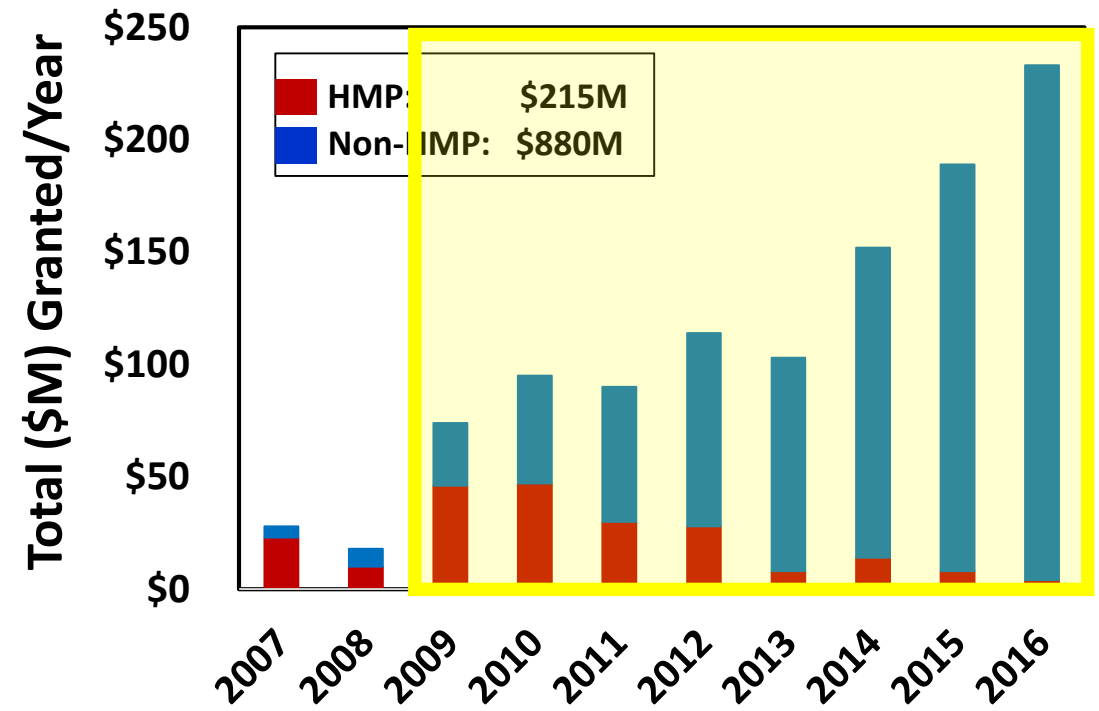
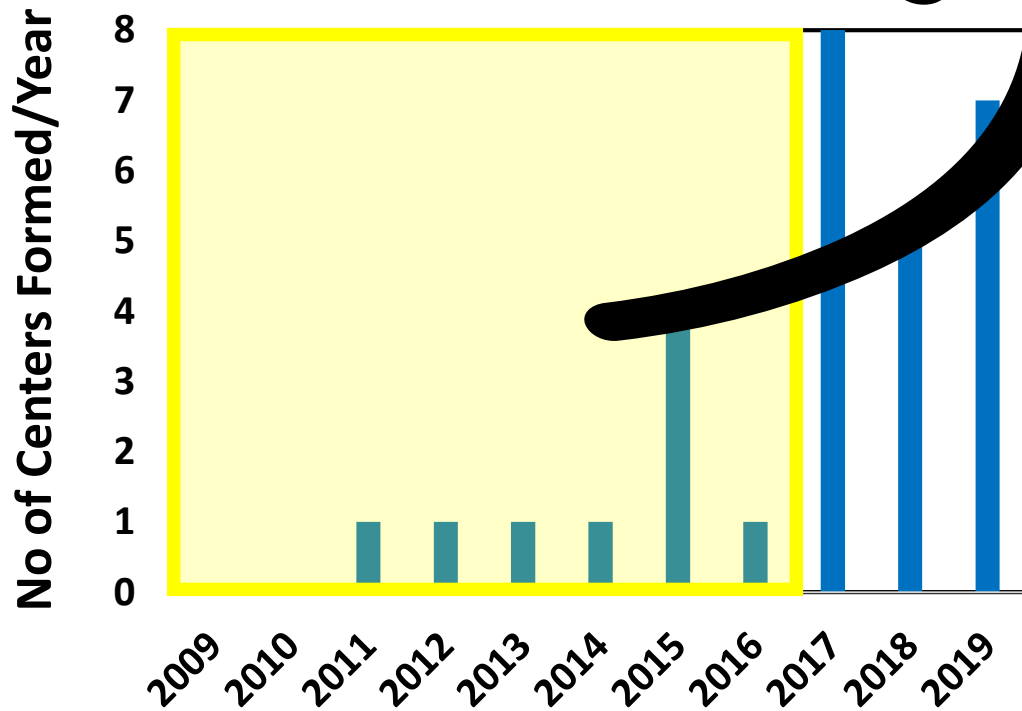
2nd workshop: Univ Chicago, May 16-17, 2020

	University	Director
1	ASU	Garcia-Pichel, Ferran
2	BCM	Petrosino, Joseph
3	CalTech	Newman, Diane
4	Colorado State	Metcalf, Jessica
5	Cornell	Lazzaro, Brian
6	Duke	Rawls, John
7	George Mason	Gillevet, Patrick
8	John Hopkins	Sears, Cynthia
9	LBNL	Brodie, Eoin
10	Med College Wisconsin	Salzman, Nita H.
11	MIT & Mass General	Alm, Eric
12	Northern Arizona Univ	Caporaso, Greg
13	PNNL	Jansson, Janet
14	Penn State	Bull, Carolee
15	Rutgers	Blaser, Martin
16	Stanford	Sonnenburg, Justin
17	SUNY Buffalo	Genco, Robert
18	UC Berkeley	Brodie, Eoin
19	UC Davis	Eisen, Jonathan
20	UC Irvine	Martiny, Jennifer
21	UCLA	Jacobs, Jonathan
22	UC Riverside	Sachs, Joel
23	UC San Diego	Knight, Rob
24	Univ Chicago	Gilbert, Jack
25	UConn - Storrs	Maas, Kendra
26	Univ Hawaii	McFall-Ngai, Margaret
27	UMass Med - Worcester	McCormick, Beth
28	Univ Michigan - Ann Arbor	Schmidt, Tom
29	Univ Oregon	Bohannon, Brendan
30	Univ Penn	Baldassano, Robert N.
31	Univ Pittsburgh	Morris, Allison
32	Univ Toledo	Vijay-Kumar, Matam
33	Univ Washington	DePaolo, William
34	Univ Wisconsin	McMahon, Katherine
35	Vanderbilt	Bordenstein, Seth
36	Yale	Jacobs-Wagner, Christine



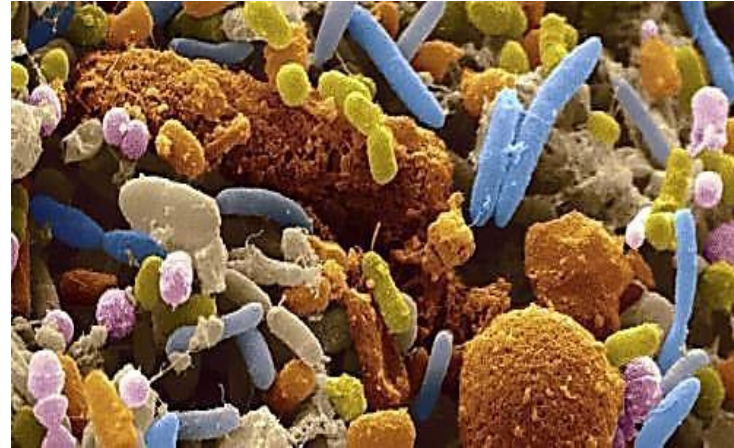
Growth of Microbiome Centers

(not all focused on human)



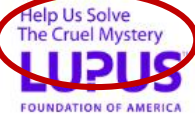
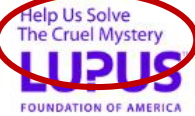
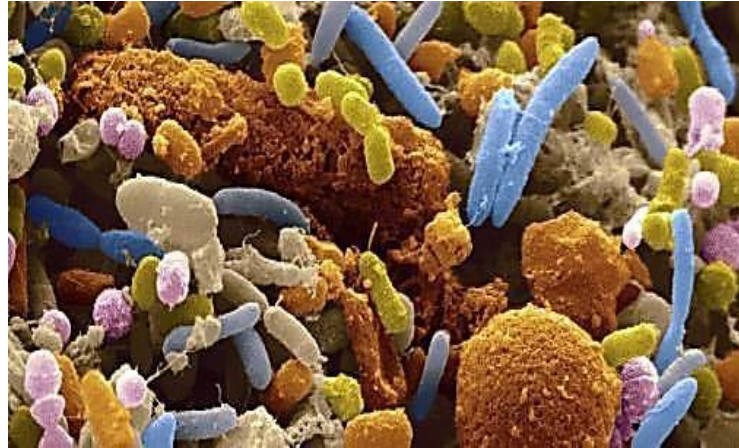
Growth of microbiome research and centers has just begun.

How can HRA engage?



alzheimer's association





Proposed HRA Cross-Cutting Initiatives

I. Create National Microbiome Cohort Registry



Gestation



Parturition



Infancy



Puberty

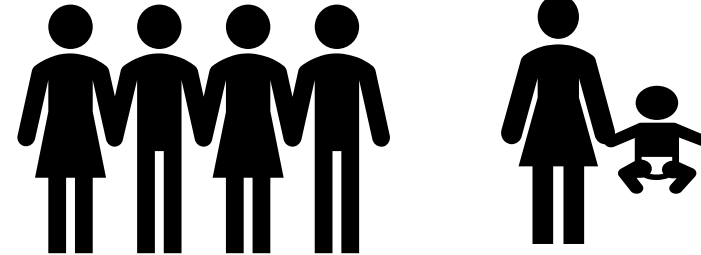


Adulthood



Old-age

1. Create a cohort registry for ongoing and upcoming cohort studies which could incorporate a microbiome component.



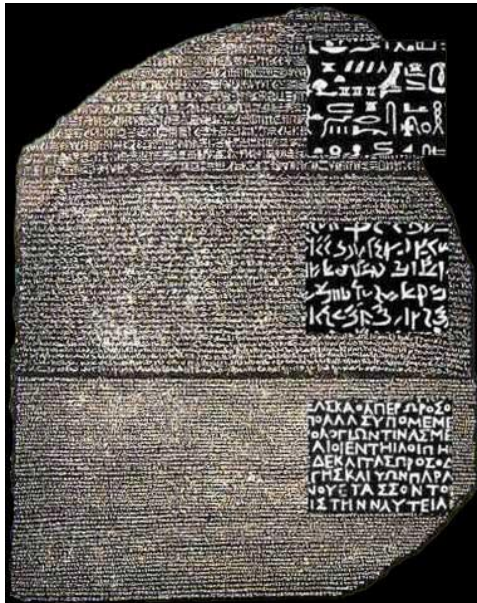
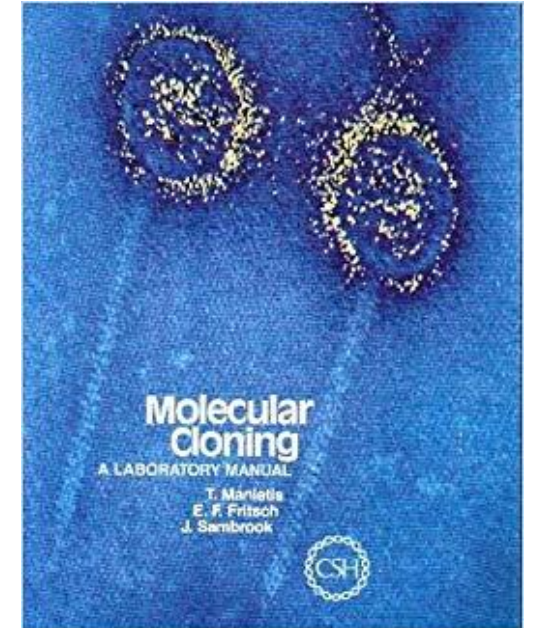
2. Establish a stool/tissue biobank from cohort studies which already include a microbiome component.



Proposed HRA Cross-Cutting Initiatives

II. Spearhead Standardization Efforts for Microbiome Datasets

- microbiome standards (mixed DNA, proteins stds)
- technology comparisons
- cross-lab blinded ‘round robins’
- ‘Maniatis-style’ manual of microbiome methods



Goal: curation of gold-standard publically-accessible clinical research datasets

‘Rosetta Stone’ for the microbiome

Proposed HRA Cross-Cutting Initiatives

III. Support Microbiome Technology Development & Innovation

Analytical

- blood microbiome protocol
- room temp protocols for tissue collection/storage
- *in situ* sampling device for gut microbiome
- HTP cultivation of novel microbes
- HTP analysis of novel microbial products



Proposed HRA Cross-Cutting Initiatives

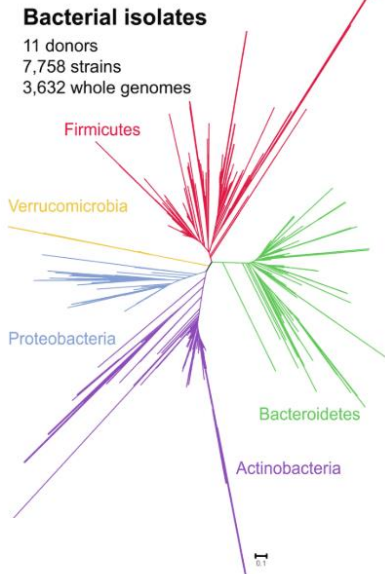
IV. Build Microbiome-Based Isolate and Microbial Products Resource

nature
medicine

Resource | Published: 02 September 2019

A library of human gut bacterial isolates paired with longitudinal multiomics data enables mechanistic microbiome research

M. Poyet, M. Groussin, S. M. Gibbons, J. Avila-Pacheco, X. Jiang, S. M. Kearney, A. R. Perrotta, B. Berdy, S. Zhao, T. D. Lieberman, P. K. Swanson, M. Smith, S. Roesemann, J. E. Alexander, S. A. Rich, J. Livny, H. V. ... R. J. Xavier & E. J. Alm

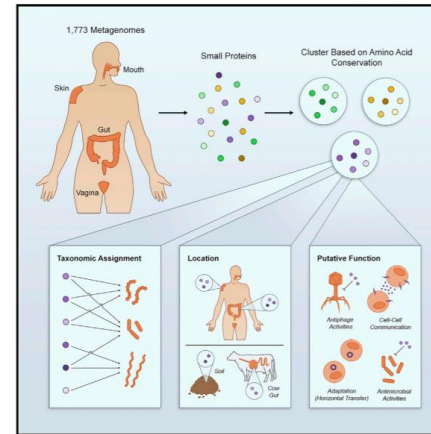


Perspective | Published: 09 August 2016

Sharing and community curation of mass spectrometry data with Global Natural Products Social Molecular Networking

nature
biotechnology

Mingxun Wang, Jeremy J Carver [...] Nuno E



Cell

Large-Scale Analyses of Human Microbiomes Reveal Thousands of Small, Novel Genes

Hila Sberro,^{1,2} Brayon J. Fremin,¹ Soumaya Zlithi,¹ Fredrik Edfors,² Nicholas Greenfield,³ Michael P. Snyder,² Georgios A. Pavlopoulos,^{4,5} Nikos C. Kyrpides,^{4,6} and Ami S. Bhatt^{1,2,7,*}

¹Department of Medicine (Hematology; Blood and Marrow Transplantation) and Genetics, Stanford University, Stanford, CA, USA

²Department of Genetics, Stanford University, Stanford, CA, USA

³One Codex, San Francisco, CA, USA

⁴Department of Energy, Joint Genome Institute, Walnut Creek, CA, USA

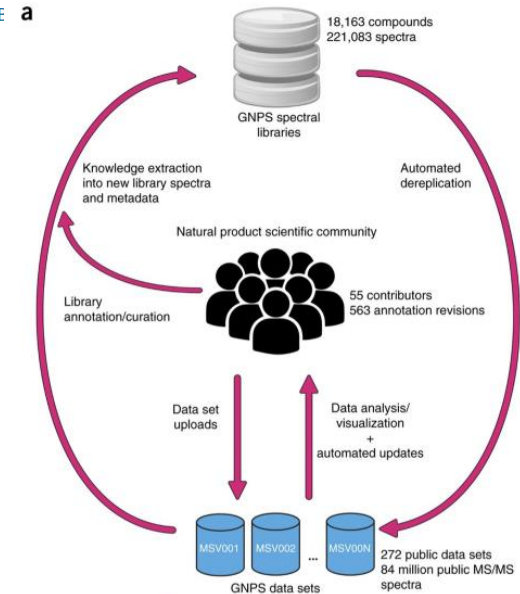
⁵Institute for Fundamental Biomedical Research, Biomedical Sciences Research Center Alexander Fleming, Vari, Greece

⁶Environmental Genomics and Systems Biology Division, Lawrence Berkeley National Laboratory, Berkeley, CA, USA

⁷Lead Contact

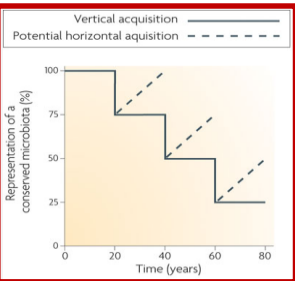
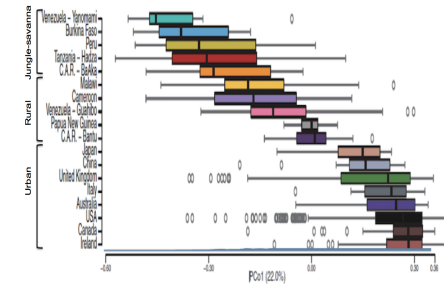
*Correspondence: asbhatt@stanford.edu

<https://doi.org/10.1016/j.cell.2019.07.016>

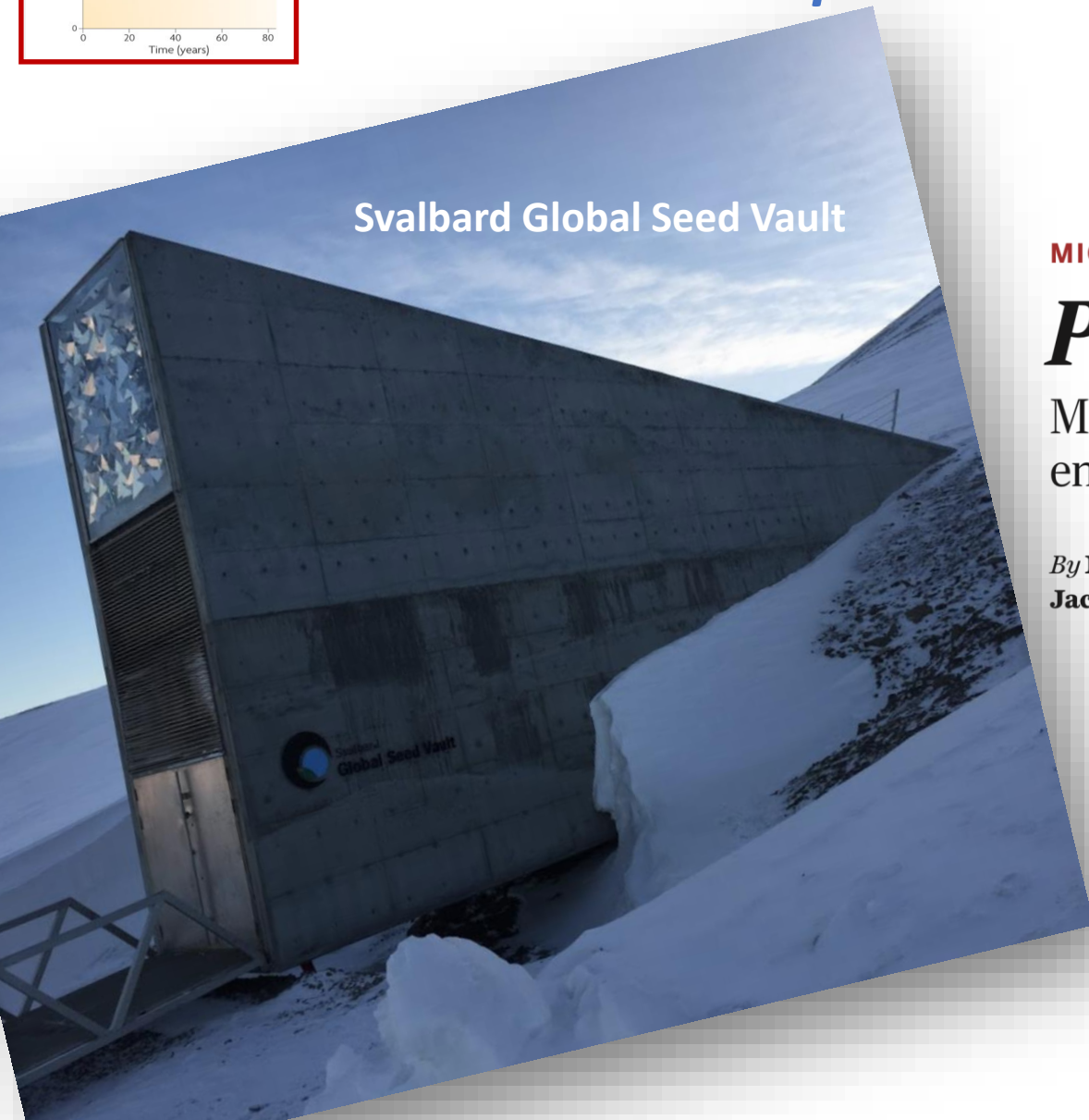


Proposed HRA Cross-Cutting Initiatives

V. Develop a Global Microbial Isolate Vault



Svalbard Global Seed Vault



MICROBIOLOGY

Preserving microbial diversity

Microbiota from humans of all cultures are needed to ensure the health of future generations

By Maria G. Dominguez Bello¹, Rob Knight²,
Jack A. Gilbert³, Martin J. Blaser⁴

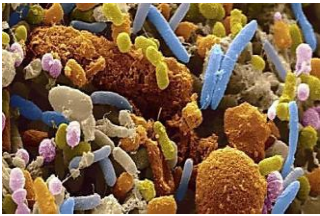
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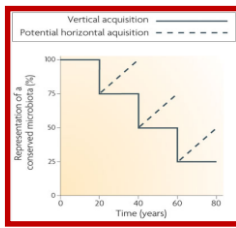
Support to date:

Rutgers University, Karolinska Institutet, Seerave Foundation, Norwegian Institute of Public Health, New England Biolabs, Kiel Life Science, Calonste Gulbenkian Foundation

 **Feasibility study currently underway**



Summary



1. Thousands of different kinds of microbial species*, possessing millions of genes, known as the microbiome or metagenome, live with humans.

<u>Body region</u>	<u>Abundance (approx.)</u>
Breastmilk	~10e3-6
Lungs	~10e3-5
Vagina	~10e8-9
Skin	~10e9-10
Oral	~10e10-11
GI tract	~10e14



2. The microbiome develops like an organ system over first few years of life and maintains our immune system and our organs throughout our lifetimes.

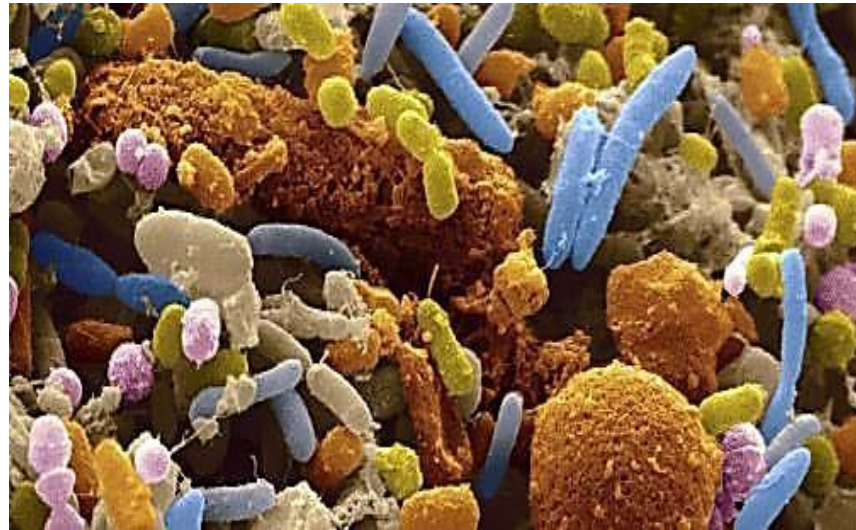


*bacteria, fungi, viruses, phage, archaea, protozoa, (helminths)

3. Changes in the microbiome due to modern practices may be associated with disease and the role of the microbiome is now being studied in 100+ disease classes.

4. HRA cross-cutting initiatives could involve a. developing research resources, b. creating cohort registries, c. building stool/tissue biobanks, d. funding technology development and innovation, e. supporting standardization activities (and so on) to catalyse microbiome research and treatments.

Questions?



lita.proctor@nih.gov