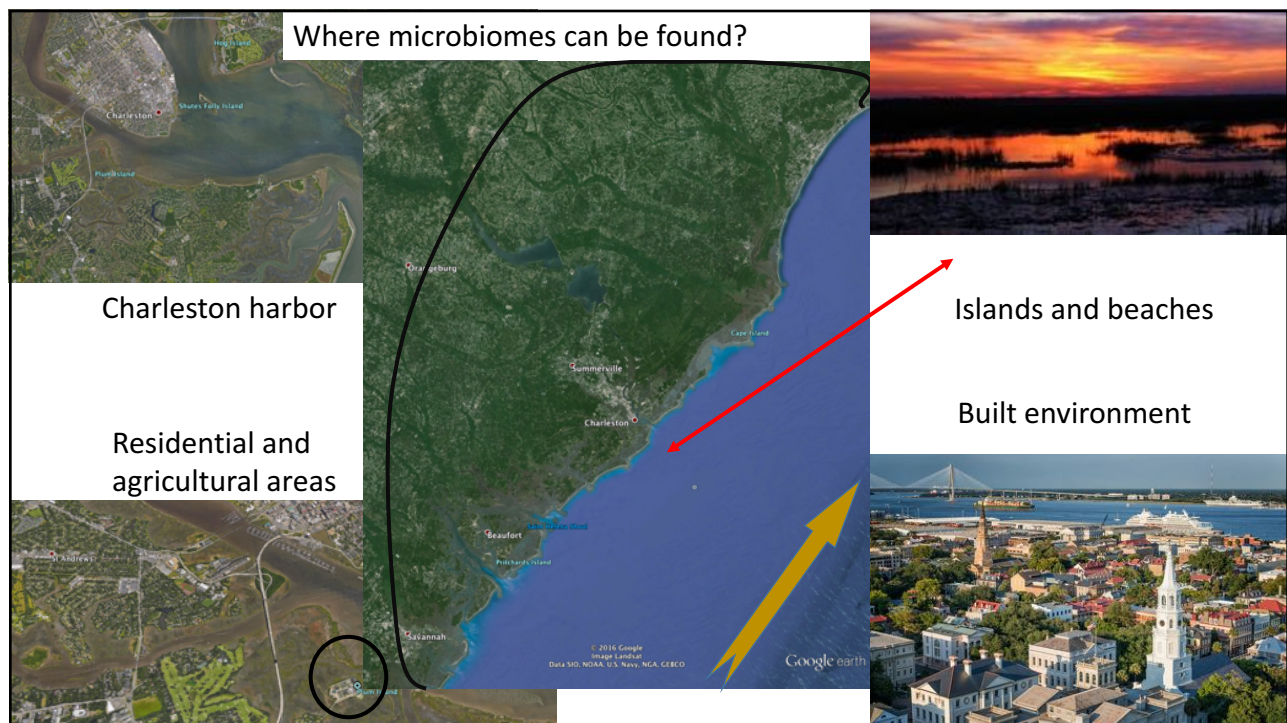
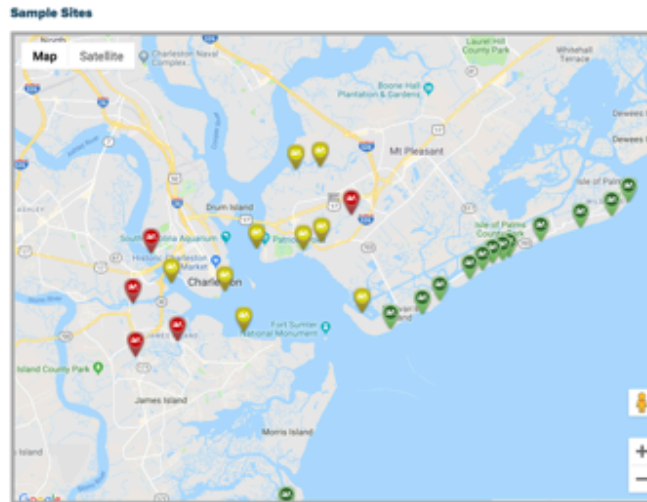


Introduction: Metagenomics in Biology and Medicine



Charleston Waterkeeper: monitor bacteria levels at fifteen of the most frequently used recreational locations around Charleston so you can splash safely.



3

Medical University of South Carolina



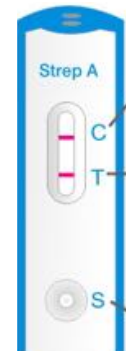
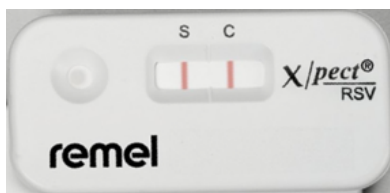
4

Modern precision medicine decision support tools



5

So are these!

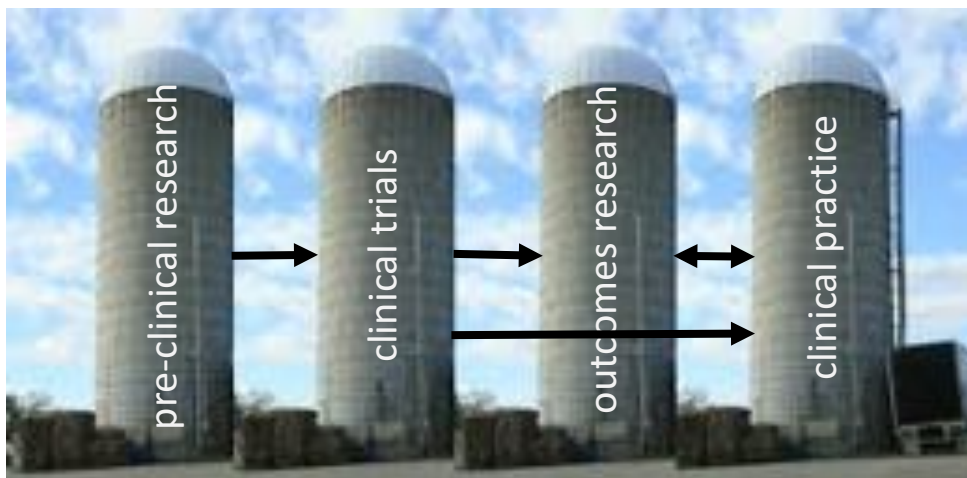


Major challenge: Silo-ing of clinical practice and research



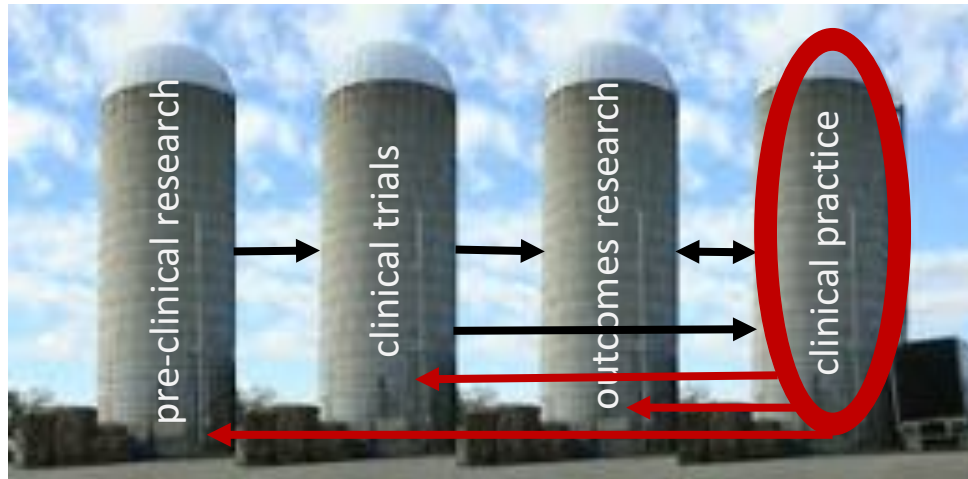
9

Major challenge: Silo-ing of clinical practice and research



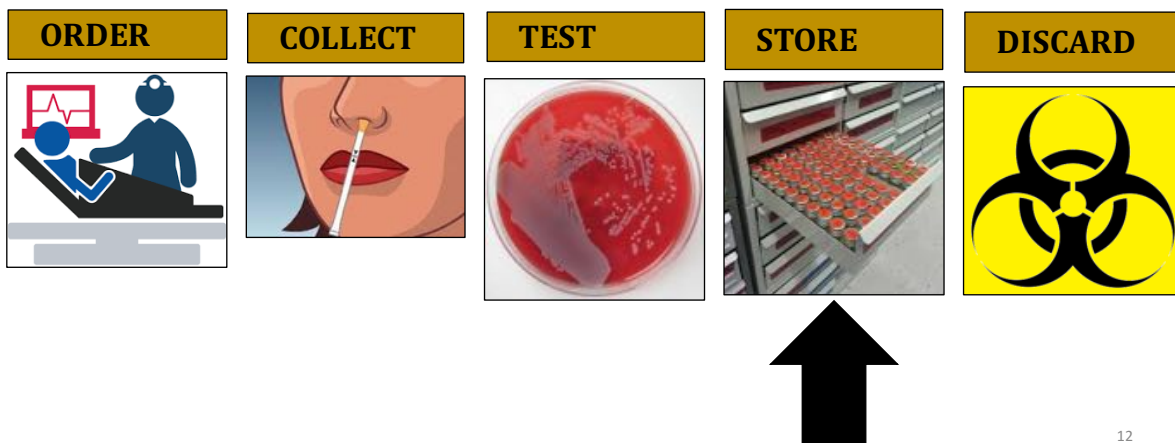
10

Major challenge: Silo-ing of clinical practice and research



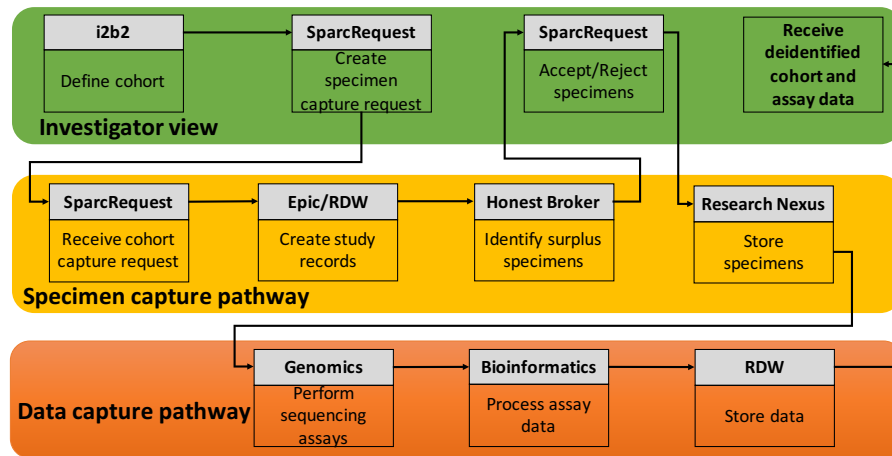
11

Microbiology specimen lifecycle



12

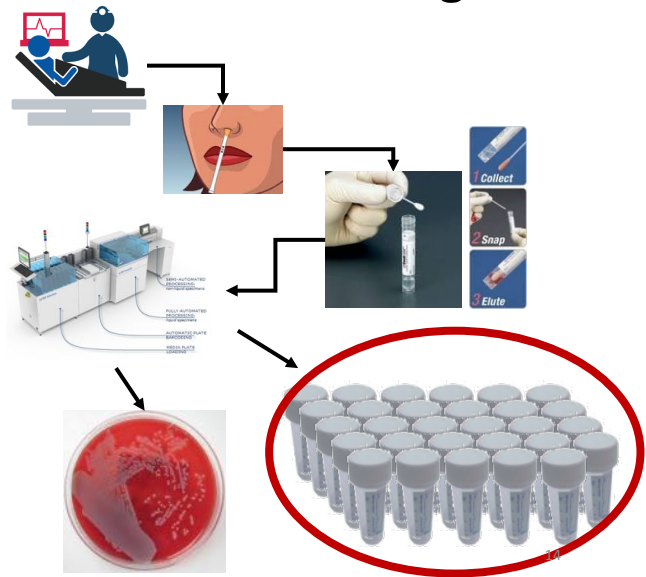
Living μ Biome Bank



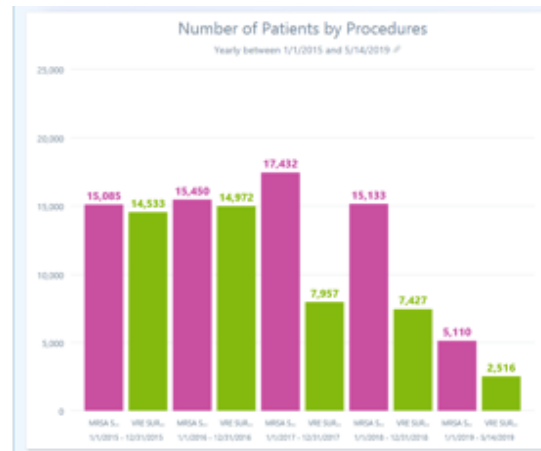
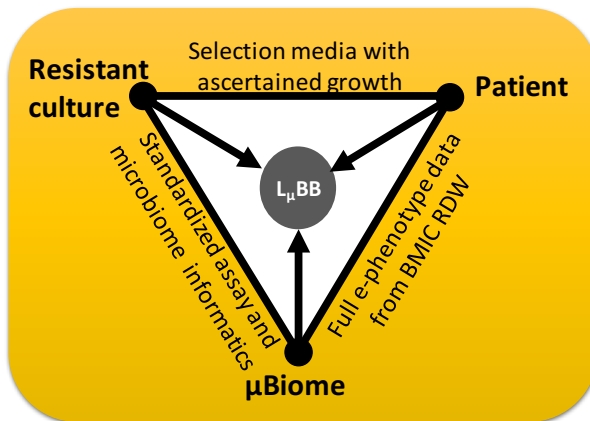
13

MUSC Infection Surveillance Culture Program

- Every inpatient admitted to the hospital is subject to the program
- Swabs for MRSA and VRE are obtained as soon as possible after admission
- Samples are processed within 24-48 hours to determine colonization
- BD auto-streaking instrument is used to minimize bias
- **75% of the specimen volume remains in excess and is discarded within a week of collection**
- Thousands of specimens pass through this program every month



Specimen sources for L_μBB



15

Why infection use surveillance specimens?

- **Sampling uniformity**
- Limited number of nurses collect the swabs, minimizing collection biases.
- Sample handling is semi-automated, minimizing handling bias.
- **Participation reach**
- All patients are subject to the program.
- ~15,000/year patients swabbed for MRSA.
- ~7,500/year patients swabbed for VRE (select units, e.g. surgery, etc.)
- **Impact potential**
- Specimens are collected early in the course of providing care.
- Specimens are collected throughout care provision timeline.
- Outcomes available in EHR for correlative research.

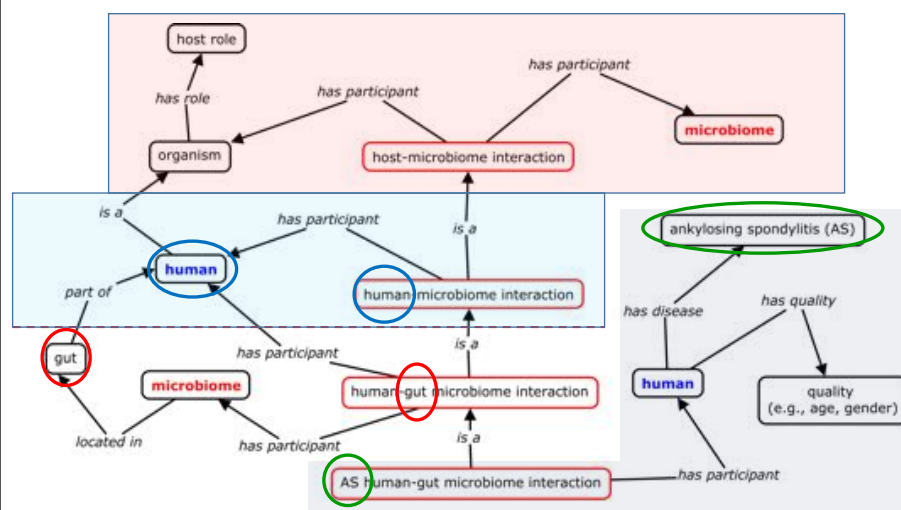
16

What is a microbiome after all?

Informally define it

17

Ontology for Host-Microbiome Interactions (OHMI) terms



<https://github.com/OHMI-ontology/OHMI>

University of Michigan

- Yongqun “Oliver” He
- Haihe Wang
- Hong Yu
- Jiahao Wang

UPenn

- Jie Zheng
- Daniel P. Beiting

Duke

- Anna Maria Masci

MUSC

- Jihad S. Obeid
- Alexander V. Alekseyenko

Unique aspects of microbiome analysis

- Expression Analysis
 - Unit of analysis: Transcript (an isoform of mRNA produced from a gene)
 - Measurement: Quantitative
- Variant Analysis
 - Unit of analysis: Variant (a version of a genomic segment)
 - Measurement: number of copies, usually 0, 1, or 2; or 0 vs 1+
- Microbiome Analysis
 - Unit of analysis: Abundance of variants of a 16S rRNA gene amplicon region
 - Measurement: Count of observed sequence variants in the specimen
 - Analogy: variant analysis in an omniplod organism

19

Additional caveats

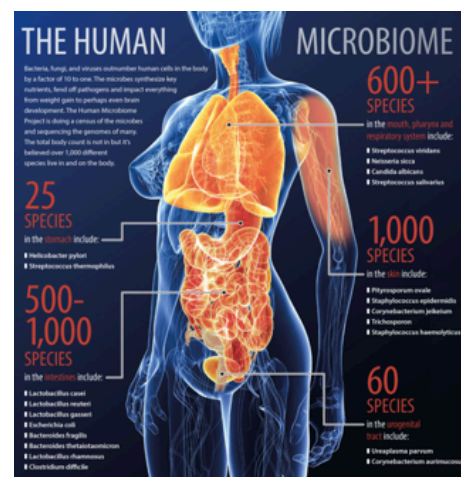
- Sequencing errors
 - A big problem when you need to get 100x coverage of a gene in a diploid organism;
 - A huge problem, when the coverage is 10,000x in an omniplod microbiome.
- Functional multiplicity
 - Many microbes fill the same role
- Compositional effects
 - Inference about absolute quantity of microbes is hard with amplicon data
- Causal considerations

20

What is the role of microbiome in human health?

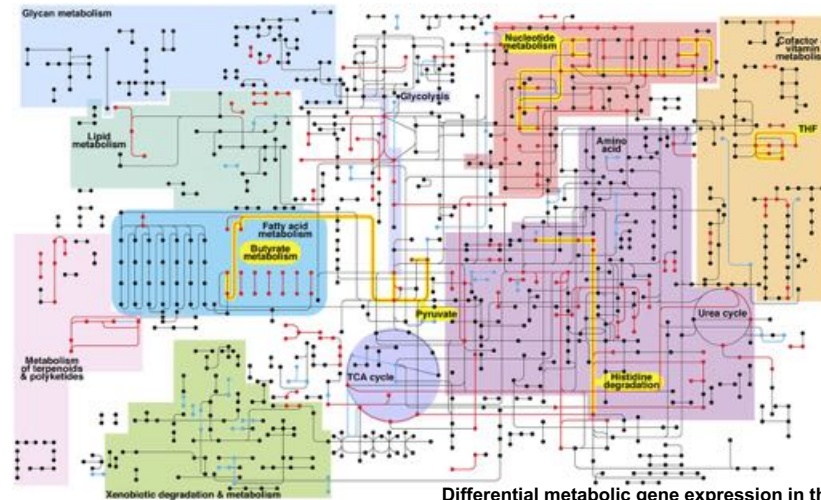
We are more microbes than we are humans?

- Human shelter 10 trillion microbes (10^{13}) in their gut alone, (we are made of 10 trillion cells).
- Only 1 in 10 cells in your body carries 'your' DNA. Recent evidence suggests as many bacterial cells as human.
- It is estimated that there are 1000 species of bacteria living in the human gut.
- Compare also the number of human genes (~25,000) to the number of genes and variants that bacterial communities may carry (~4,000,000, see e.g. doi:10.1038/ncomms3151).



22

Mechanisms for host-microbe interactions



Peter Jorth et al. mBio 2014; doi:10.1128/mBio.01012-14

Differential metabolic gene expression in the diseased periodontal microbiome.

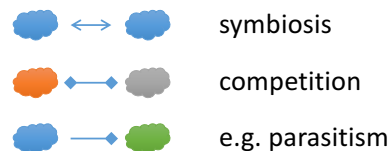


Journals.ASM.org | CC BY-NC-SA This work is licensed under a Creative Commons Attribution-Noncommercial-Share Alike 3.0 Unported license.

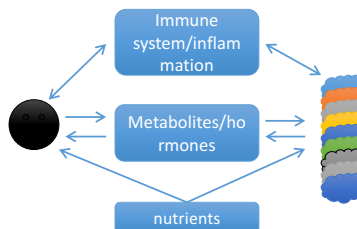
23

Mechanisms for host-microbe interactions

- With each other
 - Via regular ecological mechanisms (competition)



- With the host/environment
 - Produce and metabolize hormones and common nutrients
 - Host immune system

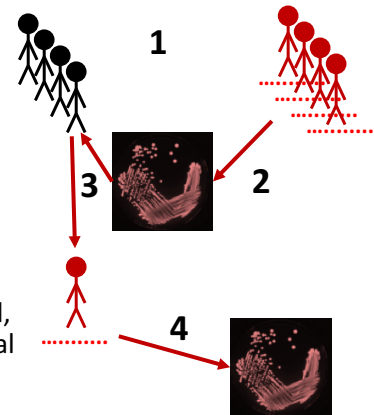


24

A conceptual role of the microbiome in human disease, an infectious disease approach

- Robert Koch's (1843 - 1910) postulates:

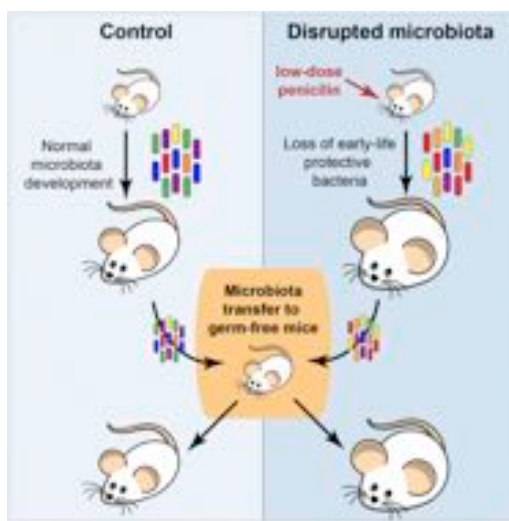
1. The microorganism must be found in abundance in all organisms suffering from the disease, *but should not be found in healthy organisms.*
2. The microorganism must be isolated from a diseased organism and grown in pure culture.
3. The cultured microorganism should cause disease when introduced into a healthy organism.
4. The microorganism must be reisolated from the inoculated, diseased experimental host and identified as being identical to the original specific causative agent.



- Do these apply to specific microbiota?

25

Causality via germ-free experiments (postulate 3)



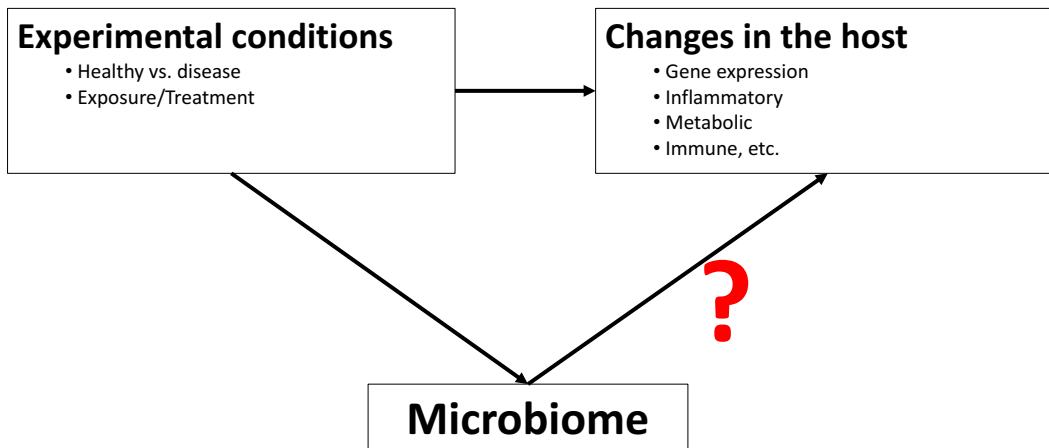
Altering the Intestinal Microbiota during a Critical Developmental Window Has Lasting Metabolic Consequences

Laura M. Cox,^{1,2} Shingo Yamanishi,² Jiho Sohn,² Alexander V. Alekseyenko,^{2,3} Jacqueline M. Leung,¹ Ilseung Cho,² Sungheon G. Kim,¹ Hulin Li,² Zhan Gao,² Douglas Mahana,¹ Jorge G. Zarate Rodriguez,² Arlin B. Rogers,² Nicolas Robine,¹ Ping Loke,¹ and Martin J. Blaser^{1,2,3,4}

Cell

26

Microbiome as a mediator in human health



27

The American Journal of Pathology, Vol. 189, No. 2, February 2019



See related Commentary on page 229

MUSCULOSKELETAL PATHOLOGY

Antibiotic Perturbation of Gut Microbiota Dysregulates Osteoimmune Cross Talk in Postpubertal Skeletal Development

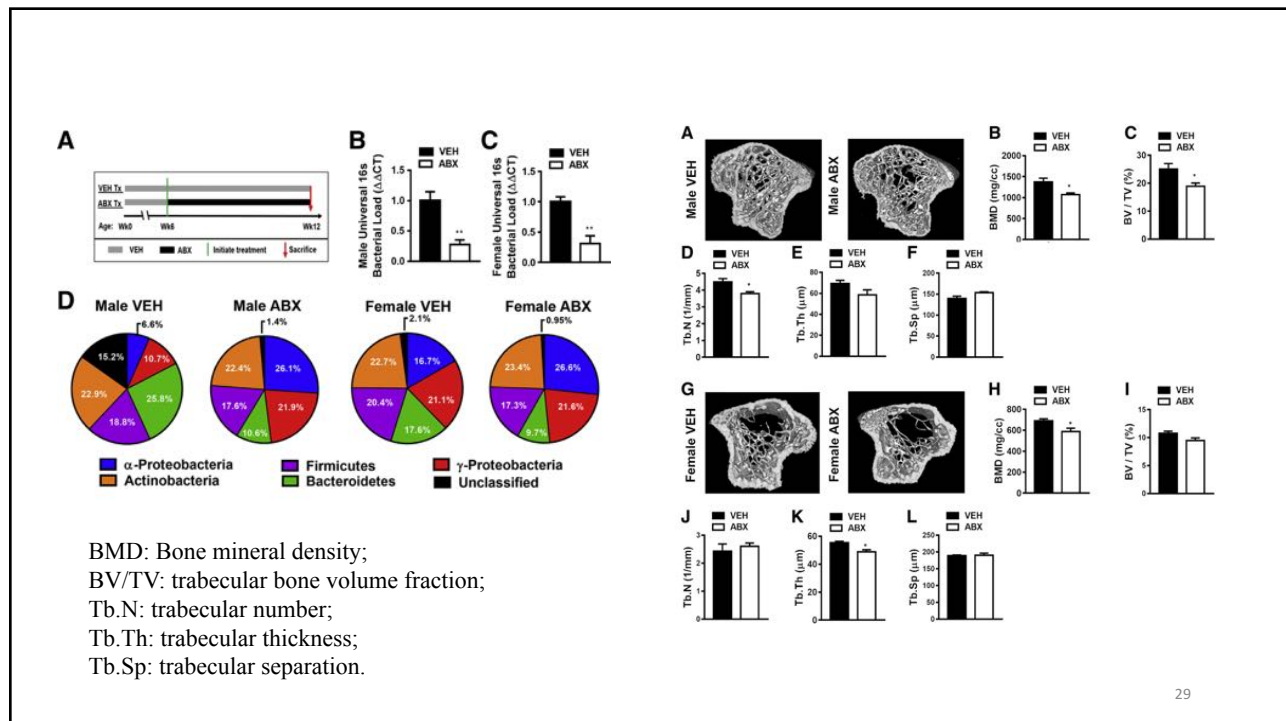
Jessica D. Hathaway-Schrader,^{*†} Heidi M. Steinkamp,^{*‡} Michael B. Chavez,^{*§} Nicole A. Poulides,^{*†} Joy E. Kirkpatrick,^{*} Michael E. Chew,^{*} Emily Huang,^{*} Alexander V. Alekseyenko,^{*¶} Jose I. Aguirre,^{||} and Chad M. Novince^{*†}

The American Journal of
PATHOLOGY

ajp.amjpathol.org



28



'New' ways to 'look' at microbiomes

