The Integration of Microbiological Health (Microbiome) Into Occupational Health – Then and Now

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Presentation Caveats

- The presentation is intended to provide a brief overview of core aspects of the microbiome
  - Origin, development, and impact of human health and disease
  - Current connections to occupational health, gaps, and limitations in the research

- This is field of study requires multiple non-clinical and clinical disciplines
  - Technologies that are relatively new and novel
  - There is both an overabundance of available data and, yet not enough…*a mile wide, but an inch deep*

- This presentation is focused on the human microbiome, not the envirobiome
  - Collection of biological exposures (e.g., workplace microbiome or indoor microbiome)

- Part 1 of this presentation will provide the fundamental understanding of the microbiome and how it applies to occupational health
  - Part 2 will focus on the current sampling/monitoring efforts and future directions of this field


Let's Journey Into the World of the Human Microbiome

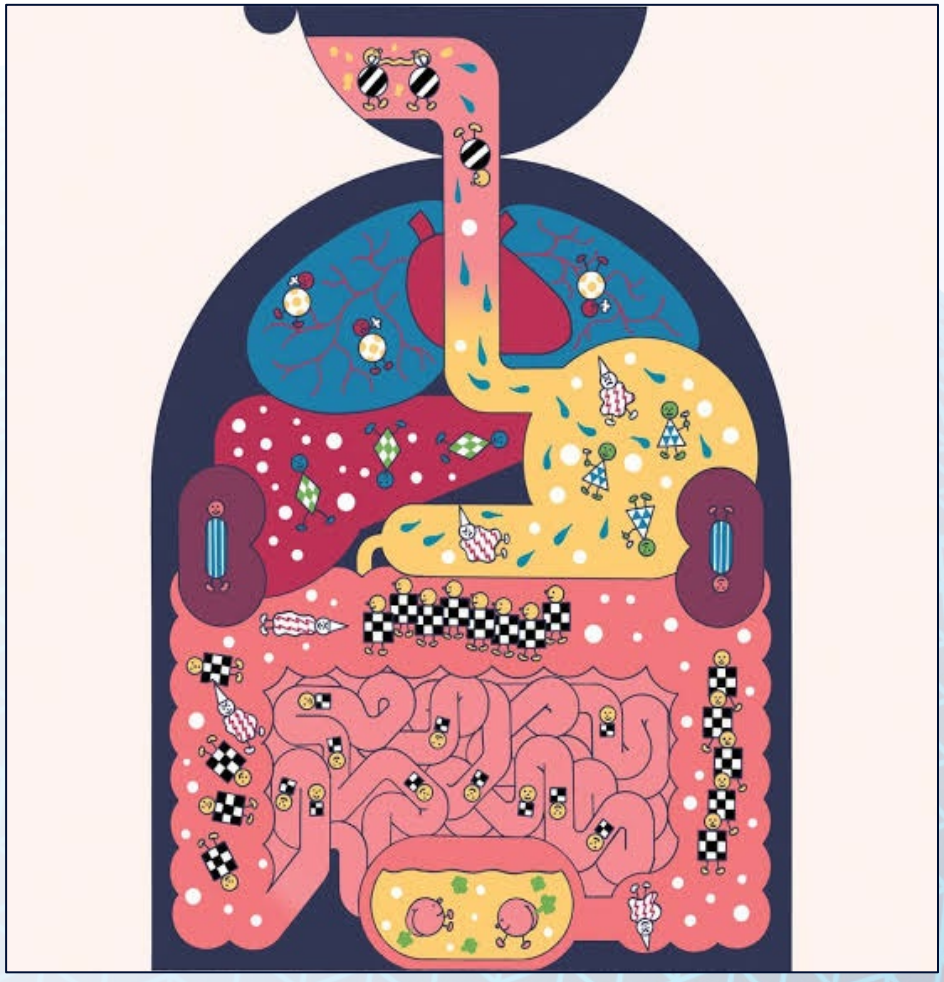
Outline

- The human microbiome and its origin
- The role of the human microbiome
- The link between the microbiome, health, and disease
- Current understanding of the relationship between the microbiome and occupational health
- Gaps and complications of occupational health research
- Current applications
- Summary

The Human Microbiome

What Is the Human Microbiome?

- The microbiome is the environment where microbiota reside
  - Human microbiome (HM) encompasses all of these
- The human microbiota is the collection of all the microbes living in association with the human body
  - Includes archaea, bacteria, viruses, and some unicellular eukaryotes
- The collection of microbes that constitute the HM is not random
  - The HM is made up of particular microbiota that complement each other and the human host



The Guardian 2018

Many Different Biomes…

- Microbiomes have been identified in different organs, regions, and habitats within the human body
  - Largest concentration of the human microbiome is found in the gut
- Within these regions, varying locations can have unique microbial profiles
  - Microbial neighborhoods within diverse communities!
- This diversity allows for varying and specialized functionality unique to that region of the body

Human microbiota composition across the five most extensively studied body sites. Interestingly, the oral and gut microbiota have the highest microbial diversity, while the urogenital tract has the smallest bacterial diversity [See references 1–4].

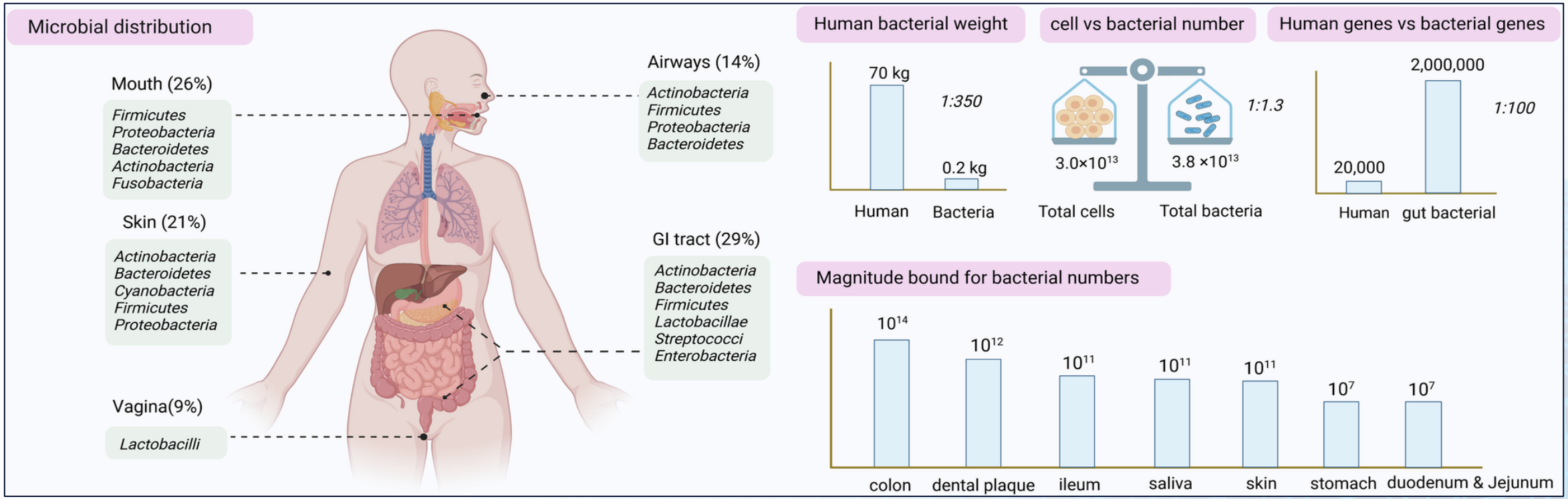
Human microbial habitats	Human microbiota (10 times more microbial than human cells: 10^{14} vs 10^{13}) Most represented Phyla and their relative abundance (%)	Number of species
Oral cavity	*Firmicutes* (36.7), *Bacteroidetes* (17.3), *Proteobacteria* (17.1), *Actinobacteria* (11.9), *Fusobacteria* (5.2)	>500
Skin	*Actinobacteria* (52), *Firmicutes* (24.4), *Proteobacteria* (16.5), *Bacteroidetes* (6.3)	~300
Airways	*Actinobacteria* (55), *Firmicutes* (15), *Proteobacteria* (8), *Bacteroidetes* (3)	>500
Gut	*Firmicutes* (38.8), *Bacteroidetes* (27.8), *Actinobacteria* (8.2), *Proteobacteria* (2.1)	>1000
Urogenital tract[a]	*Firmicutes* (83), *Bacteroidetes* (3), *Actinobacteria* (3)	~150

[a] Mainly female.

D'Argenio and Salvatore 2015

Note: Several regions have microbiota, such as the eyes, breast, and ears

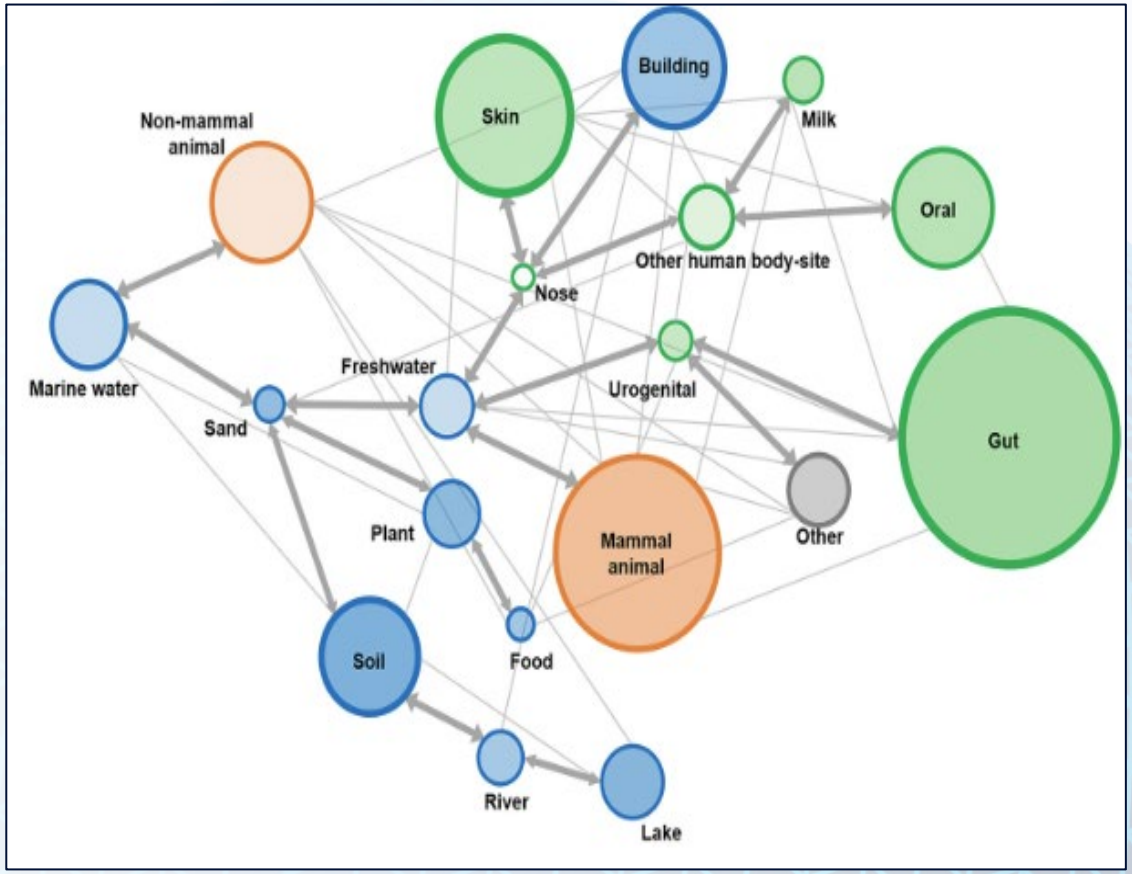
The Microbiome Is BIG



- This microbial imbalance suggests that the human body is a collection of human and microbial cells and genes
  - Thus, we are a blend of human and microbial traits

A Truly Global Network

- Partnerships between animals and plants and their microbes are just beginning to be explored
  - It is important to recognize that these associations are not random
- Each organism has evolved to have intimate associations with microbes
- Humans are no exception
  - Of the hundreds of thousands of microbes on Earth, only a small portion have been found associated with humans



Jing et al. 2021

The Field Is Still Young

- Systematic study of the human microbiome is a very young science compared to other fields
  - Ecology, marine biology, and even evolutionary biology
- Scientists are just beginning to address fundamental questions, including:
  - What constitutes a normal microbiome,
  - How the microbiome changes over time, and
  - How the composition and activity of the microbiome affect health and disease
- It is already clear that the effect of HM is profound and multifaceted
  - It is reasonable to characterize the microbiome as a newly recognized organ, with a great range of metabolic activities

Origins of Human Microbiome Research

- As early as the mid-1880s, it was noted that microbes were a part of the human system
  - *E. coli* was observed among healthy children and those with GI disease
- More microbes in connection with various regions of the human body were isolated in the following years
- Whipps et al. first coined “microbiome” in their 1988 publication as:
  - *…microbial community occupying a reasonably well-defined habitat which has distinct physio-chemical properties. The term thus not only refers to the microorganisms involved but also encompasses their theatre of activity*
  - Some debate around the origin of the word

Human Microbiome Research

- Microbiome research accelerated in the 21st century with the more efficient, accurate, and cost-effective analytical tools

- Relman and Falkow (2001) published an inventory of microbial genes and genomes from four major locations in the body
  - These researchers began to call for the use of more sophisticated analytical methods, and
  - Investigation into the HM connection with health and disease

- Within the decade, the Human Microbiome Project would begin
  - Other substantial works included Integrative Human Microbiome Project (Phase 2), MetaHIT (European), American Gut Project (AGP), Dutch Microbiome Project (DMP), and Chinese diabetes cohort

Complications with Early Research

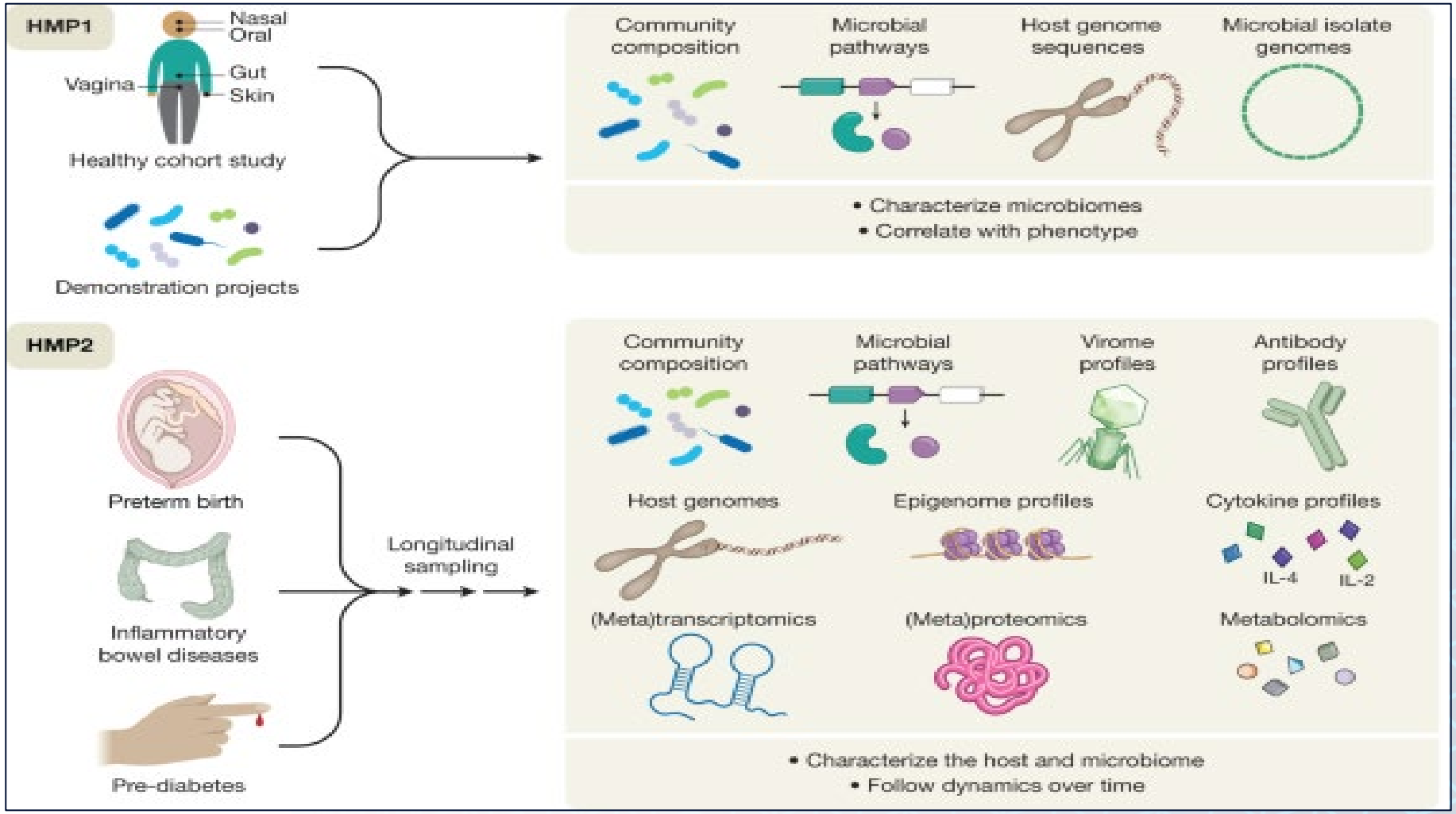
- Early studies were either cross-sectional or did not control for important confounders (medications, diet, smoking)
  - Led to issues related to causation vs. correlation:
    - Did changes in the microbiome occur because the disease led to changes in immunity favoring certain microbes, or
    - Do microbiome changes precede and lead to disease development?

- Sequencing technology and standards have rapidly evolved
  - Complicates the usefulness and comparative potential of past data due to collection and method of analysis

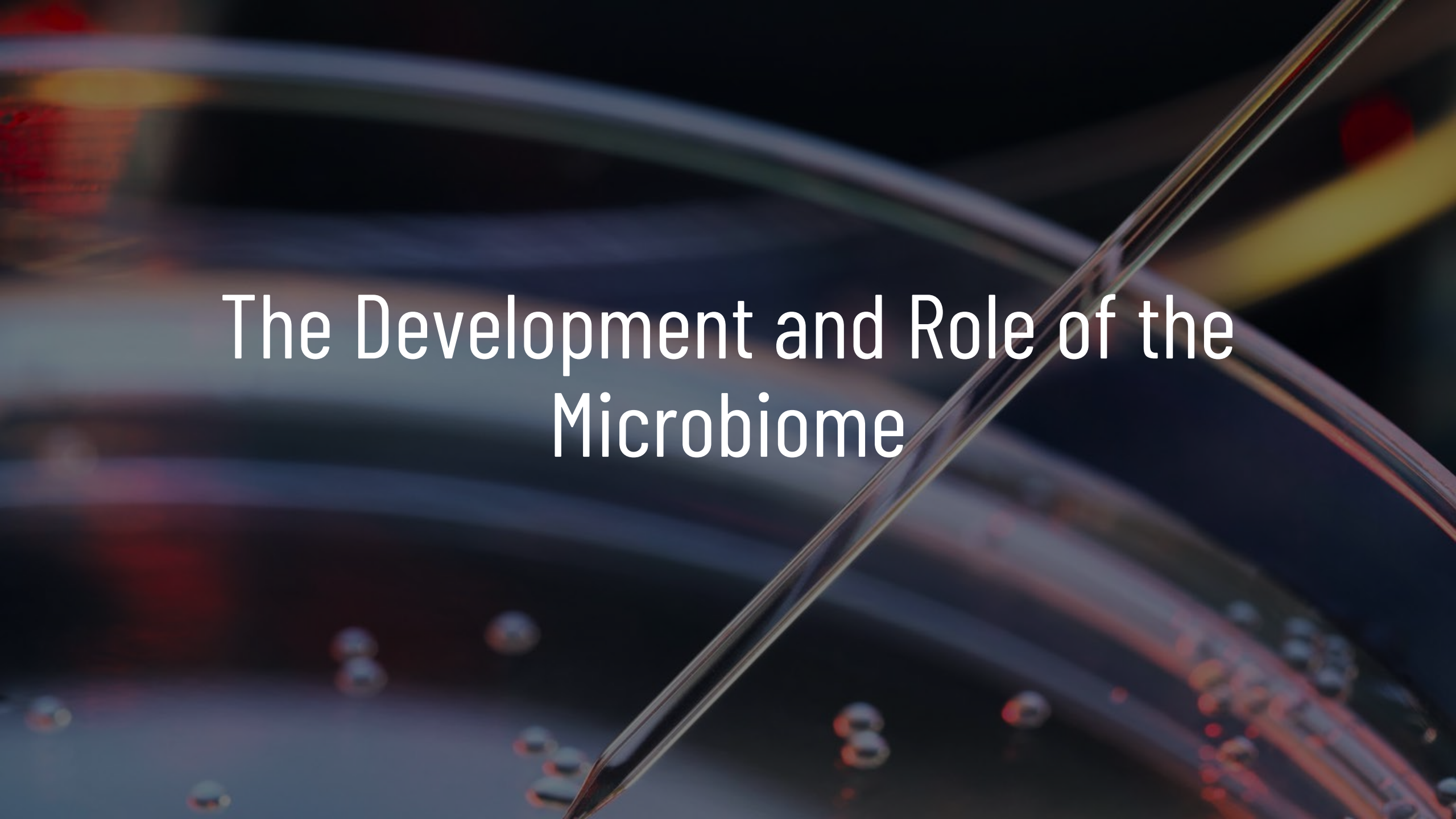
The Human Microbiome Project

- Human Microbiome Project (HMP) was one of the first large scale projects to comprehensively assess the microbiome
  - Supported by the NIH and involved individuals and groups
- Goal of developing resources for the characterization of the HM and analysis of its role in human health and disease
- Utilized a combination of varying analytical methods
- Divided into two phases
  - Discussed on the next slide

The Human Microbiome Project



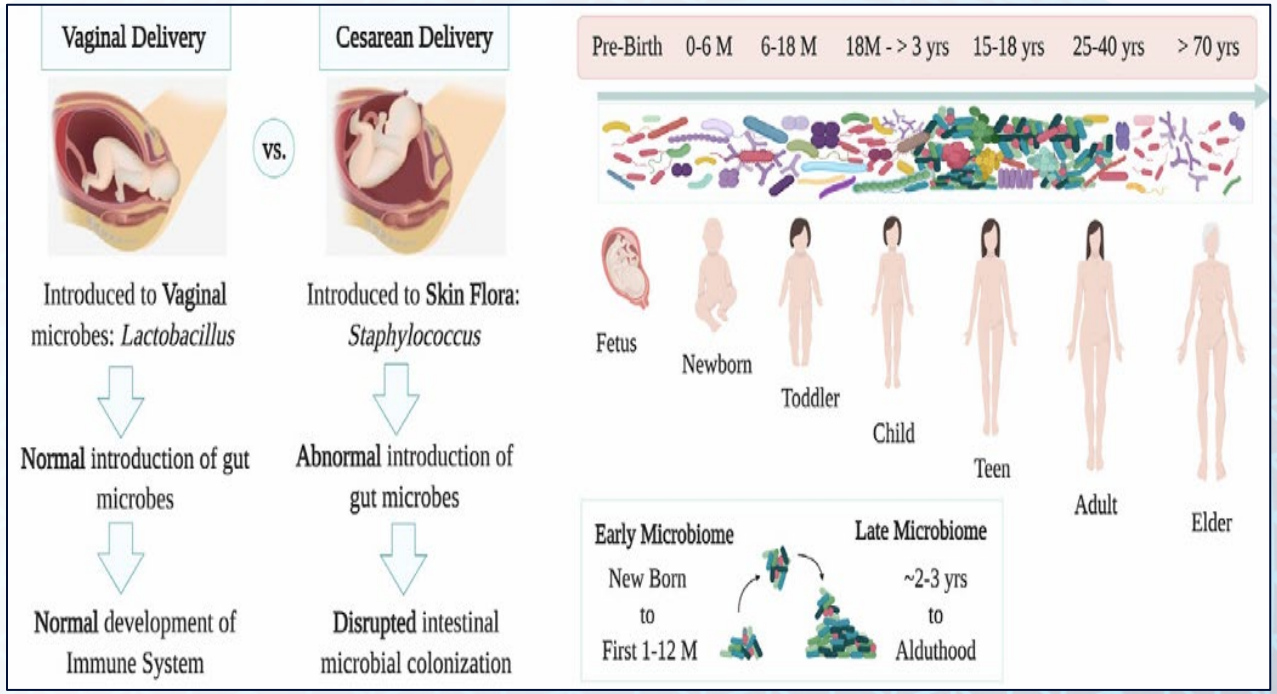
iHMP Research Network Consortium 2019



The Development and Role of the Microbiome

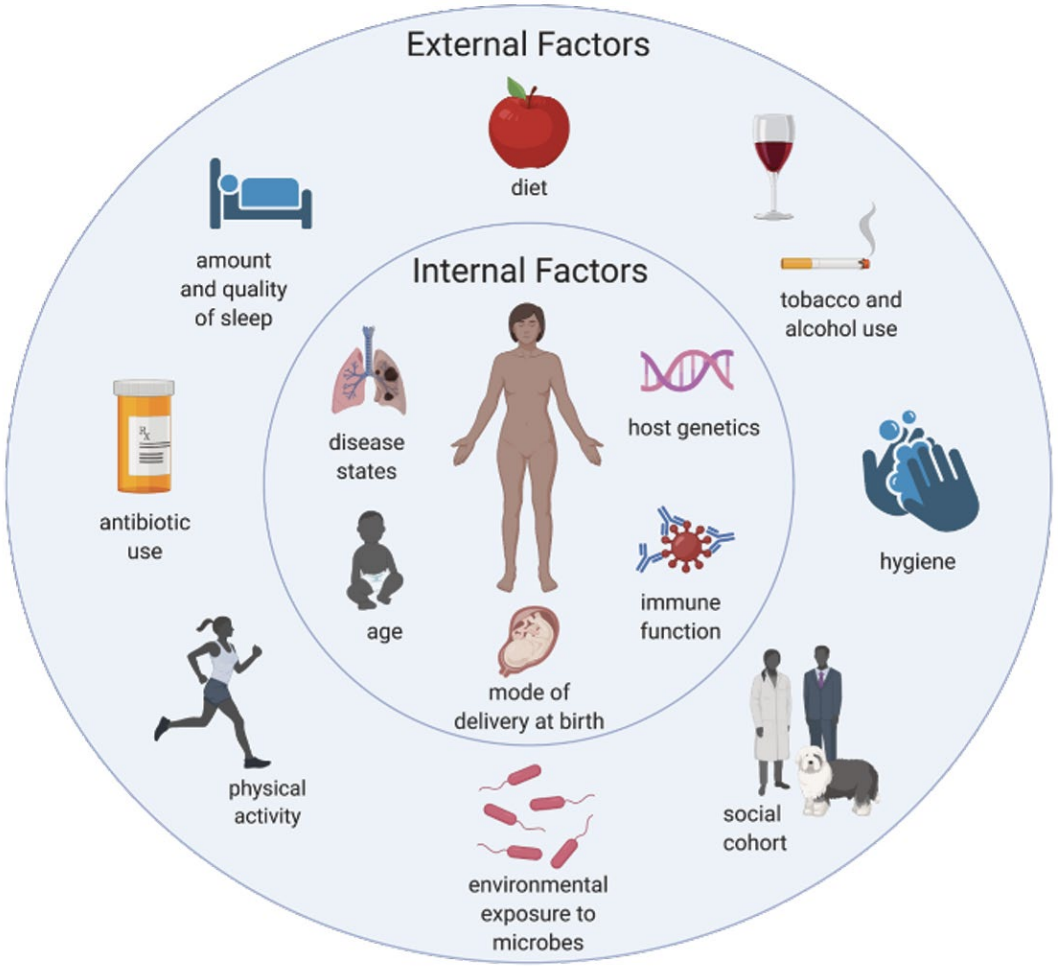
Development of the Human Microbiome

- Bacterial transfer from mother to infant occurs when:
  - Babies go through the vaginal canal, or
  - Via skin contact by C-section at birth, and
  - By skin-to-skin contact during breastfeeding
- Only a group of the microbes to which the newborn is initially exposed at birth will permanently colonize various body regions
- The mode of transmission is likely to be part of a response to protect and promote fetus health before exposure to other environmental conditions and microbes



Reynoso-Garcia et al. 2022

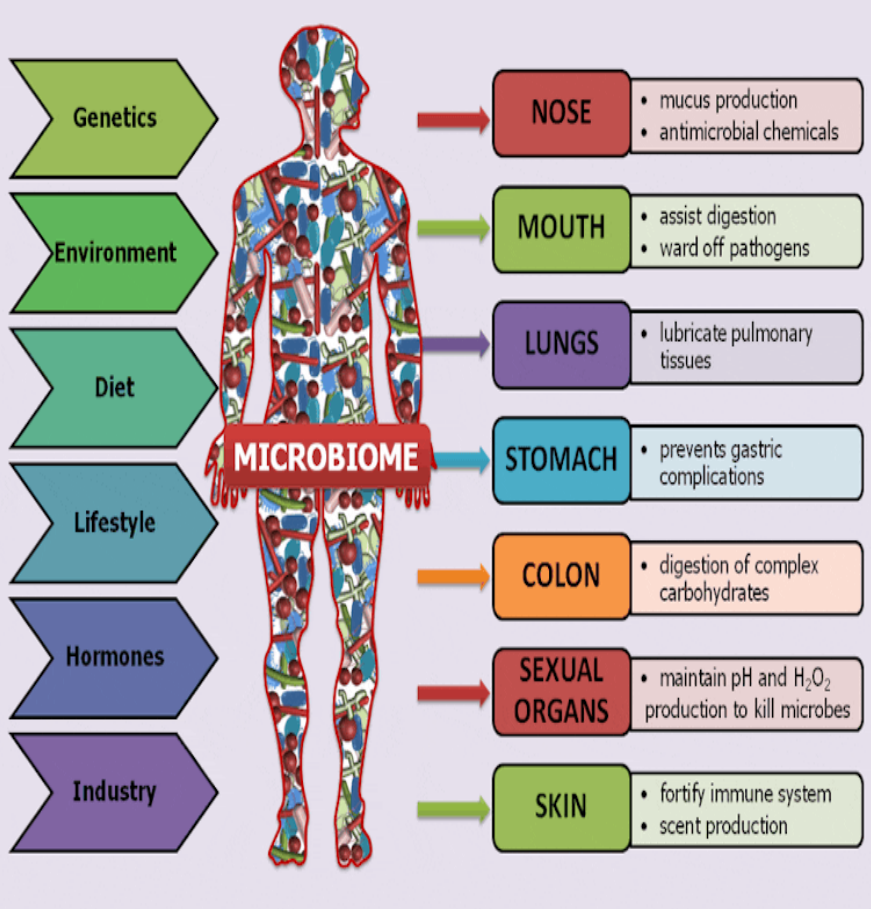
Factors Influencing the Human Microbiome



Waynick and Carmichael 2021

Microbiome and Health

- The HM has several positive effects on the human body
  - The human-microbiome interaction is still being studied with regards to health
- Scientific consensus of positive effects include:
  - Digestion, nutrients supply, and xenobiotic degradation
  - Immune system maturation and function
  - Brain development and behavior
  - Protection and clearance from pathogen invasion

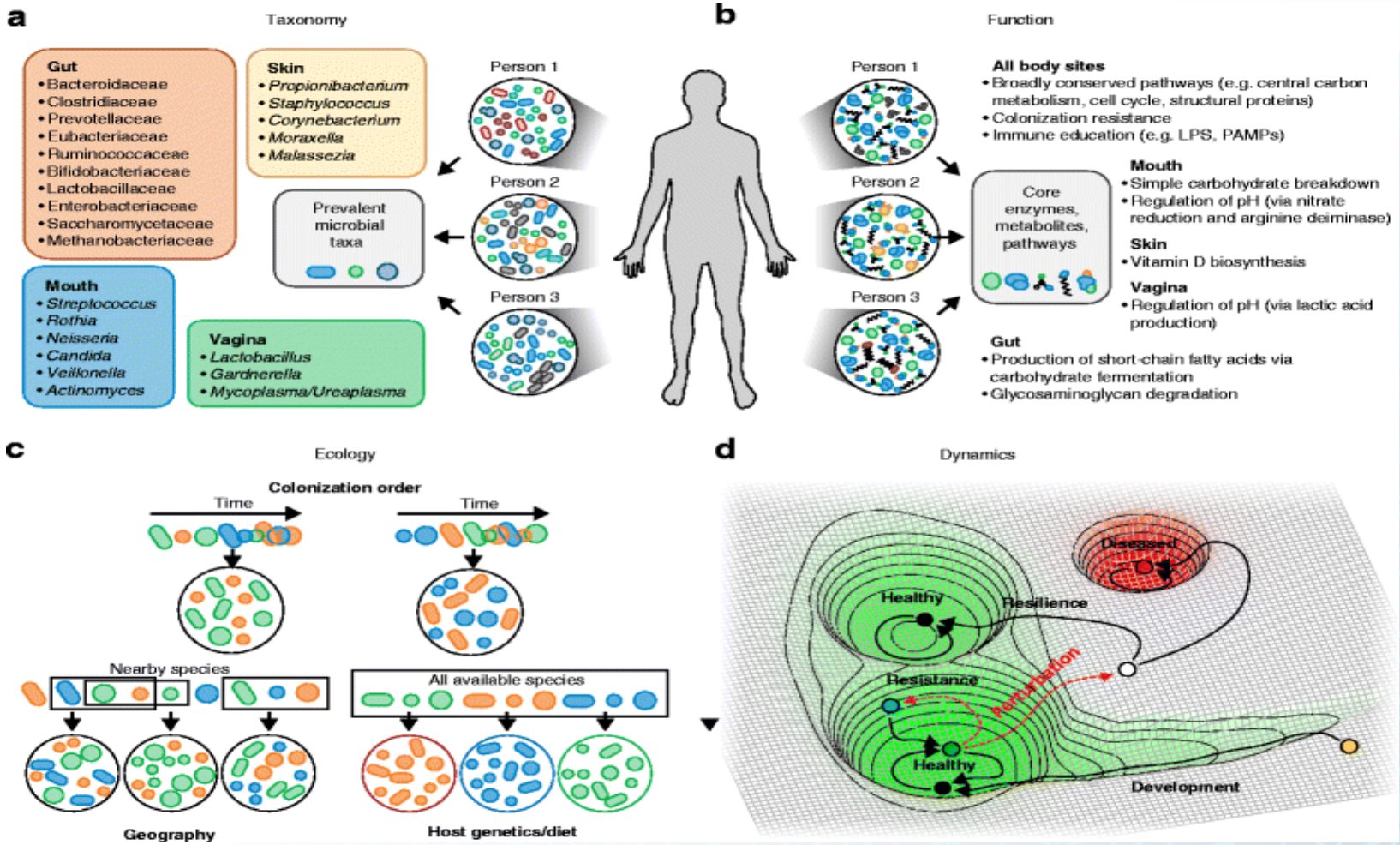


Appanna 2018

So, What Does a "Healthy" Microbiome Look Like?

- We are not quite sure…
- Prior to defining "healthy" we must determine baseline
  - From baseline, we can begin to draw associations with health and disease outcomes
- Large scale population-based studies have been limited
  - Those that have been carried out are limited in their generalizability
  - Large scale military studies do not include non-military personnel
  - HMP was limited to a few hundred samples
- "Health" is also dictated by life stage, geography, and body site

How Should We Define "Healthy"?



Lloyd-Price et al. 2016


Microbiome and Disease

Prevailing Theories Dictating Assessment Approach

- Scientists from diverse disciplines have converged on exploring microbiomes associated with host organisms using certain theories
  - The *holobiont* and *metaorganism*

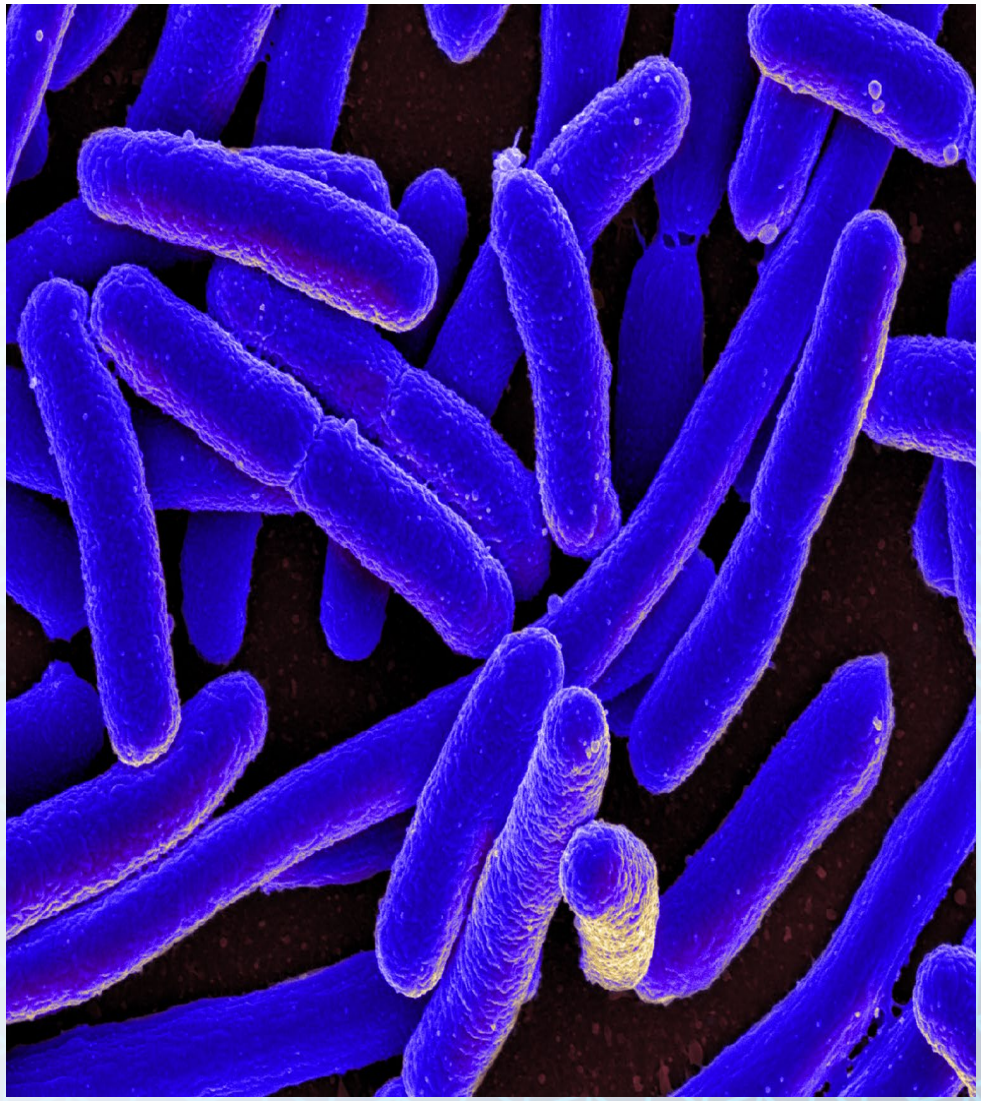
- *Holobiont* is the eukaryotic host with all external and internal associates – long-term relationship
  - Does not necessarily consider function

- *Metaorganism* is the sum of a eukaryotic host and its associated species with the focus on those associates for which function is required
  - A narrower context as compared to the holobiont
  - *Function* can be defined differently

Microbiome and Disease

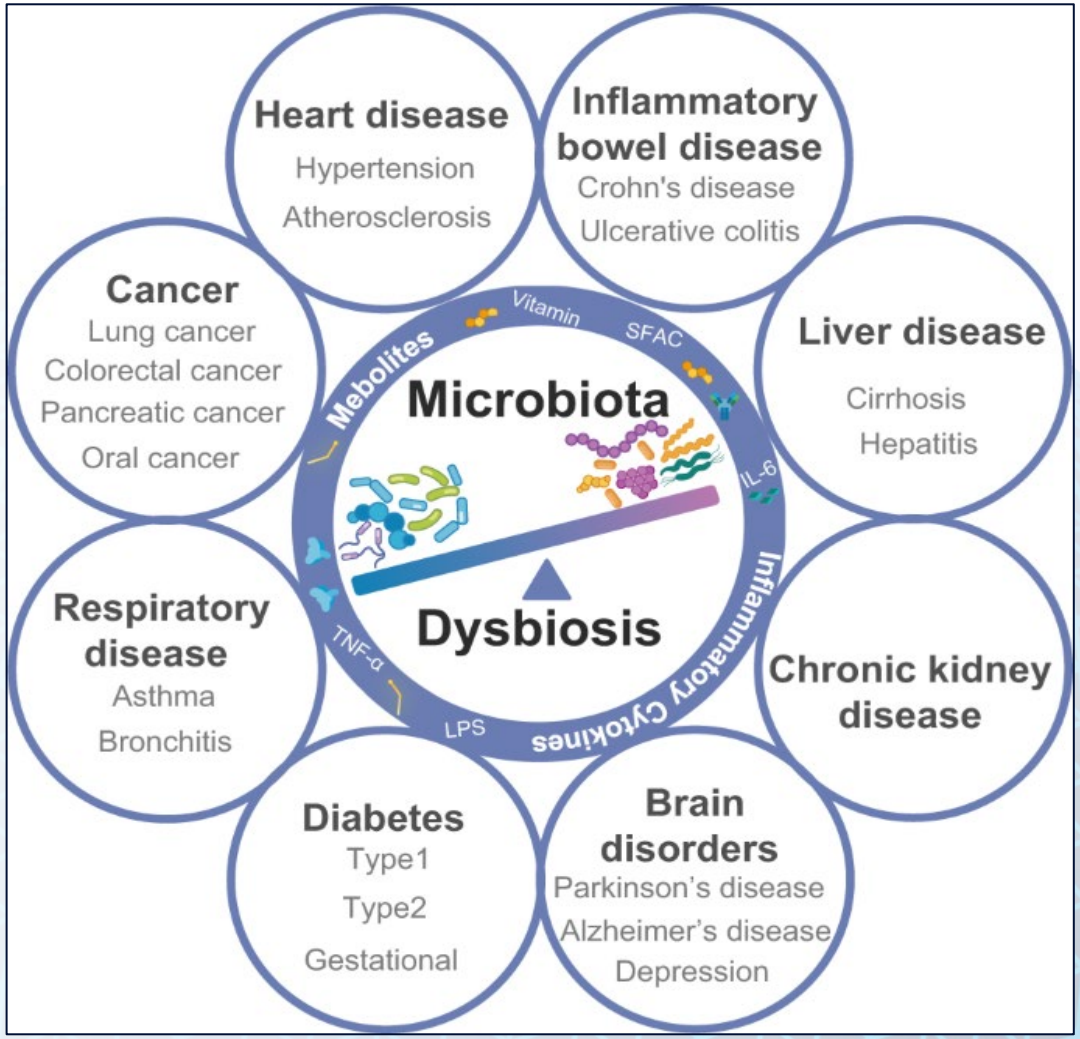
- It has become clear that not all microbially-associated diseases are “infectious” in the traditional sense

- Some diseases are caused by microbes that are normal constituents of the microbiome
  - *E. coli*, *S. aureus*, and *C. diff* are examples of potential pathogens
  - Found in healthy individuals, but cause disease only when:
    - The microbiome is disturbed, or the microbes gain access to a part of the body where they do not normally reside



Microbiome and Disease

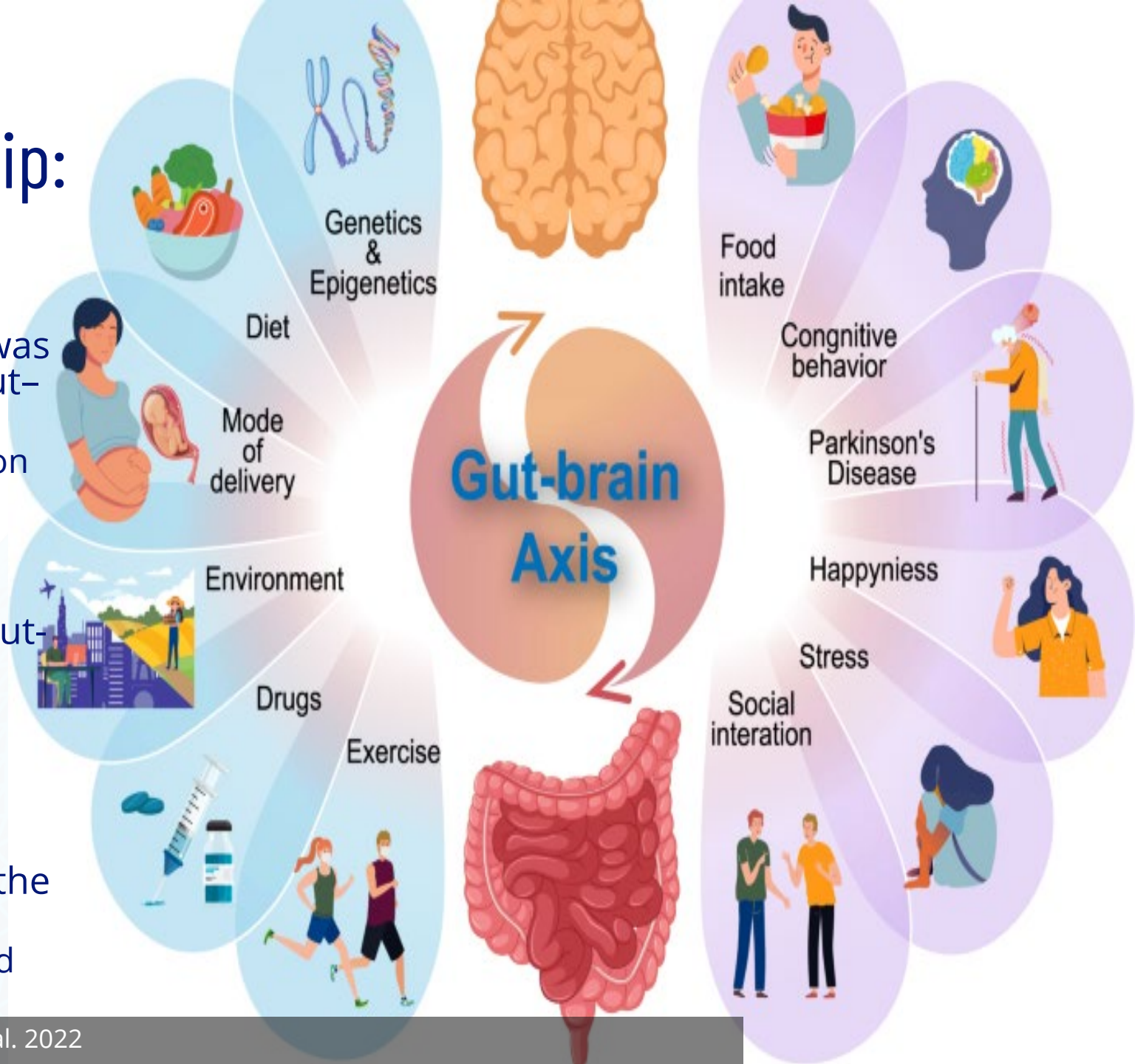
- The HM inhibiting pathogens is another reason that the presence of a pathogen does not mean disease
  - A pathogen may not cause disease if it is introduced to a healthy HM, or,
  - A smaller dose of the pathogen may result in disease if the microbiome is disturbed
- Some diseases may be the result of disturbance of the microbial “community” that makes up the HM
  - E.g., Antibiotic resistance and stewardship programs
- This disturbance in microbial communities can lead to dysregulation of bodily functions and diseases
  - Through wide ranging, and at times, overlapping pathways



Hou et al. 2022

Long Distance Relationship: Gut-Brain Axis

- In the past decades, gut microbiota was identified as a key regulator of the gut–brain axis
  - How the gut can impact brain function and vice versa
- Pathways have been proposed that mediate communication within the gut-brain axis
  - Nervous, immune, and endocrine systems
- Studies have reported factor that influence the gut-brain axis through the gut microbiome
  - Mechanisms are not fully understood



Hou et al. 2022

Microbiome and Occupational Health

History of Occupational Health-Microbiome Research

- Studies investigating microbiome impacts in the workplace are limited compared to the overall field
- In a recent (2021) systematic review, only ~26 original articles were identified investigating the topic
  - Study design varied and were concentrated in the US
  - The number of identified studies align with a similar reports published in 2020, 2023, and 2024
- These occupational exposures represent biological agents, chemical agents, and stress factors/microclimate
- Some animal and *in vitro* studies are referenced, but not typically relied upon due the unique properties of the HM and dynamic effects/impacts on the body

Exposure to Biological Agents and the Microbiome

- Majority of studies were focused on exposure to biological agents
  - This included workers in contact with livestock and animals (i.e., farmers, slaughters, zookeepers, lab personnel) and healthcare workers
- Agriculture workers are the most widely studied population
  - Likely due to biosecurity concerns related to food security which has national security implications
- An important finding was the similarity between the envirobiome and the HM among this population
  - This was also accompanied by less microbiota diversity
  - Unfortunately, these findings also extended to the prevalence of MRSA

Exposure to Chemical Agents and the Microbiome

- Studies assessing the impacts from chemical exposures have also been published
  - This included exposure to metalworking fluid (which itself may contain biological agents), dust, silica, pesticides, burn pits, and cotton/flax
- Microbiota from the gut, lung, skin, nasal, and oro-buccal regions were evaluated following chemical exposure(s)
- One study analyzed gut microbiota characteristics in patients with early-stage pulmonary fibrosis due to silica exposure in the workplace
  - Abundances of certain phyla were lower in patients with silicosis compared to controls

Exposure to Chemical Agents and the Microbiome

- Symptomatic MWF exposed workers noted an increase in the abundance of *Pseudomonas*
  - Increase was observed from lung, skin, and nasal samples
  - The microbe was identified MWF samples but not air samples

- One study evaluated agricultural pesticide exposure-associated changes in the oro-buccal microbiota
  - A seasonally persistent association between the detected blood concentration of the insecticide and the taxonomic composition of the microbiome was reported
  - Persistence of this association from the spring/summer to winter suggests that long-lasting effects on the microbiota do occur

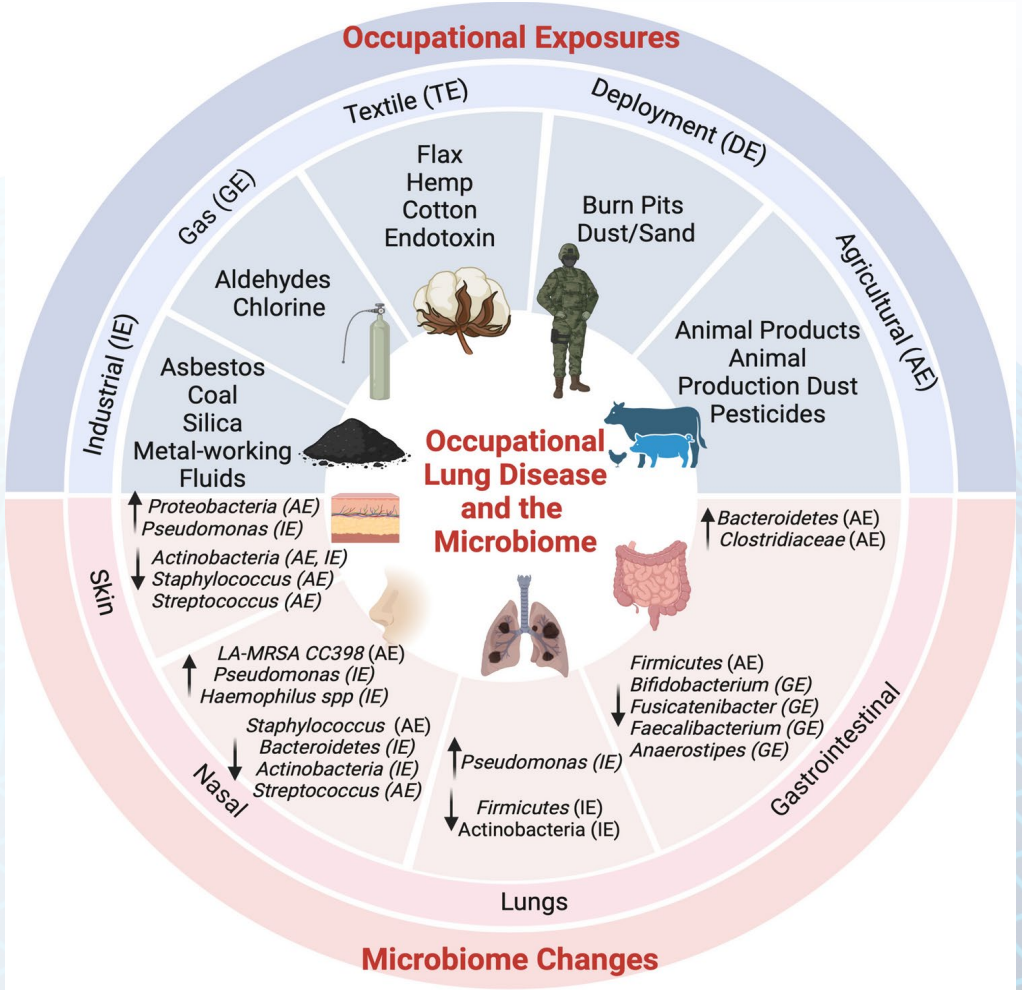
- A longitudinal study to evaluate the microbiota of the respiratory tract in health military personnel
  - Unfortunately, the results are not often referenced due the absence of control group(s)

Occupational Stress Factors and the Microbiome

- Impact of occupational stress factors on the HM centered around unique or specialized occupations and workplaces
  - I.e., military personnel, sailors, tunnel workers, and diving sub-sea workers
- Studies focused on the work environment and stressors that may impact the HM
  - Overall, specific species of the microbiota contained within the HM were impacted in various ways
  - However, there is a lack of connection or discussion regarding the potential health implications of these findings
- Interestingly, a study of tunnel workers correlated microbiota variations with altered mental status after exposure to stressful work conditions
  - Tunnel workers after 3 weeks underground demonstrated gut microbial diversity significantly lower with respect to baseline
  - Self-evaluations reported that at least half of the tunnel workers experienced one or more symptoms of mental distress (inattention, sleeplessness, loss of appetite, headache or dizziness, irritability)

Overall Findings

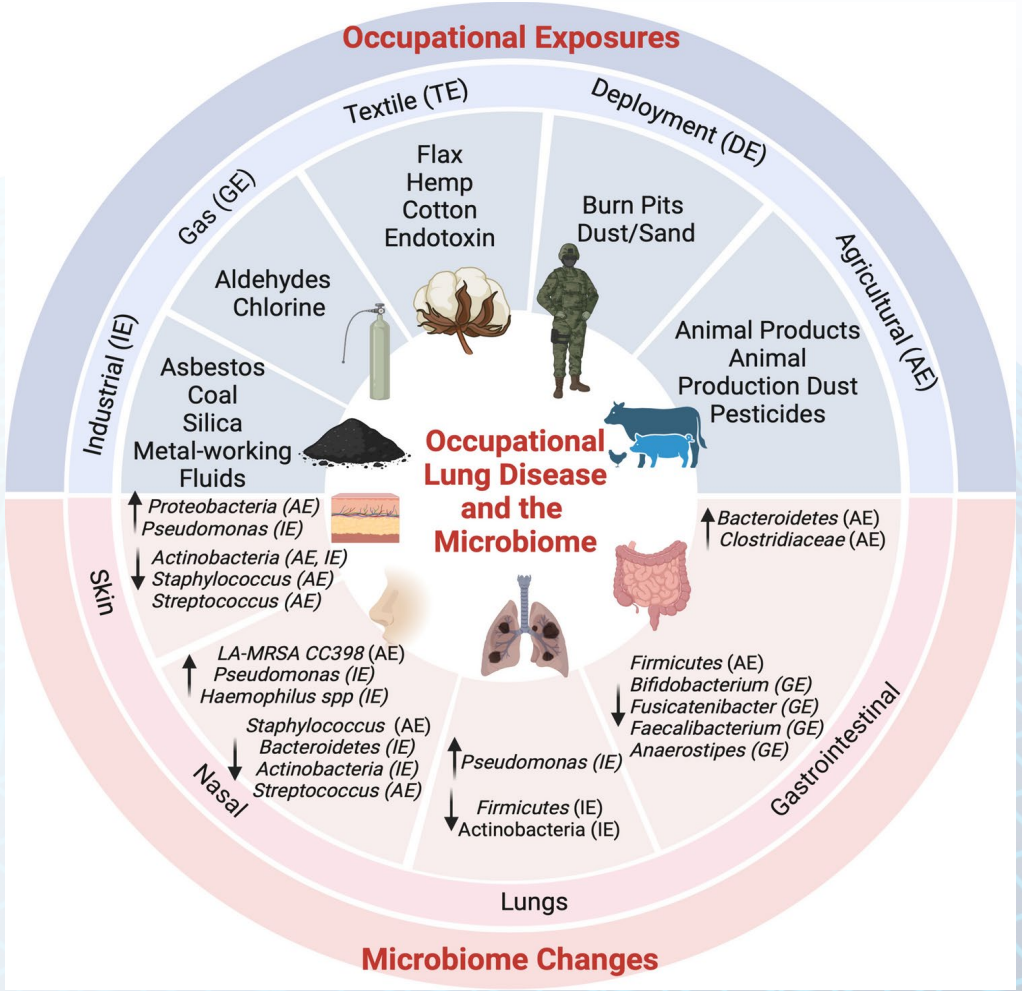
- There are overall impressions
  - Growing recognition that biological, chemical, psychosocial stress factors and exposures can impact the HM
  - Direct and indirect contact with animals and livestock and influence the HM
- Unfortunately, it is difficult to take away any direct or indirect health implications
  - While changes in microbiome are noted, what does that mean for “health”?
- Specific conclusions are not available
  - Given the limited amount of research and focus on cross-sectional study designs



Peer and Samuelson 2024

Overall Findings

No studies *have examined the functional consequences of the changes in the microbial communities with the development of occupational lung disease or occupational diseases in general.*



Peer and Samuelson 2024

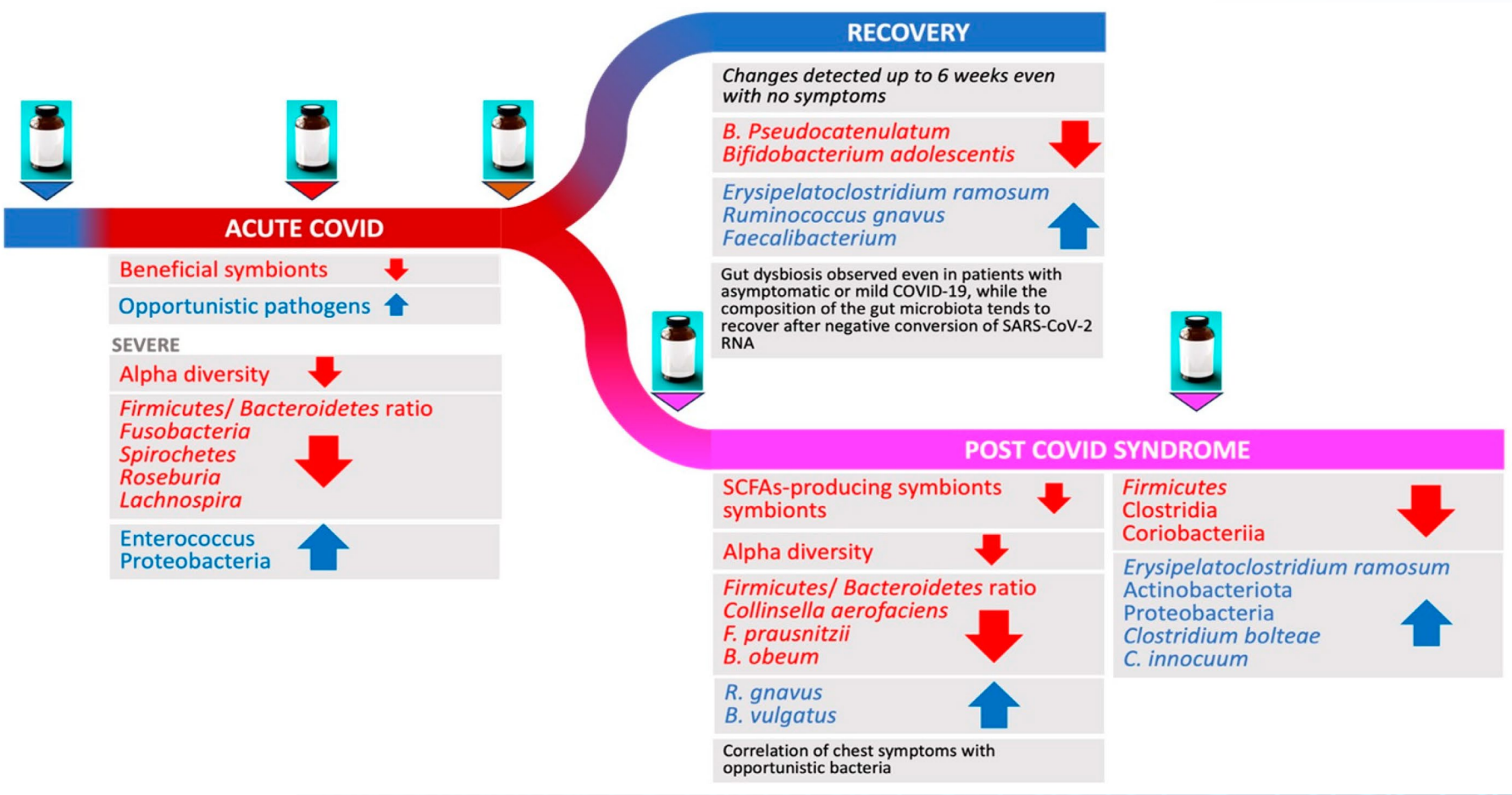
SARS-CoV-2 and COVID-19

- Several studies have assessed disruption of the gut microbiome following COVID-19
  - One recent (2024) study analyzed several of these studies
  - Majority of the samples were from patients, but the authors also included samples from an occupational cohort

- In acute COVID-19, rapid alteration of the gut microbiome composition was observed
  - On one side a reduction in beneficial microbes and on the other side an increase in opportunistic pathogens
  - This can be common with initial symptom onset and hospital admission, easily influenced by confounders (e.g., medication, immune response)

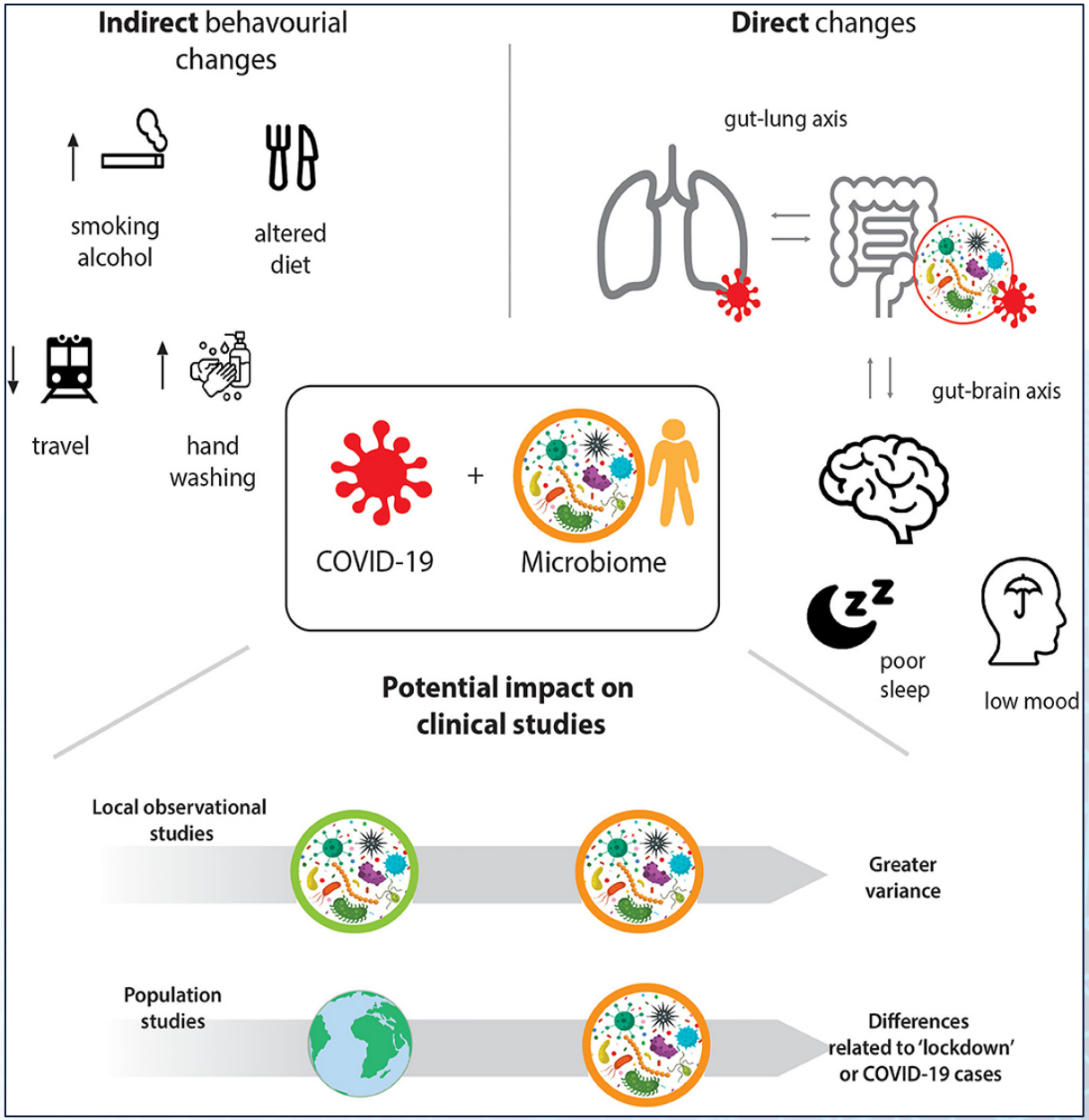
- Patients with COVID-19 post-acute syndrome were impacted by changes in gut microbiome composition
  - Specific microbes associated with respiratory symptoms up to 12 months following acute disease

SARS-CoV-2 and COVID-19



Righi et al. 2024

Questions Remain Around The Long-Term Impact(s) of COVID-19

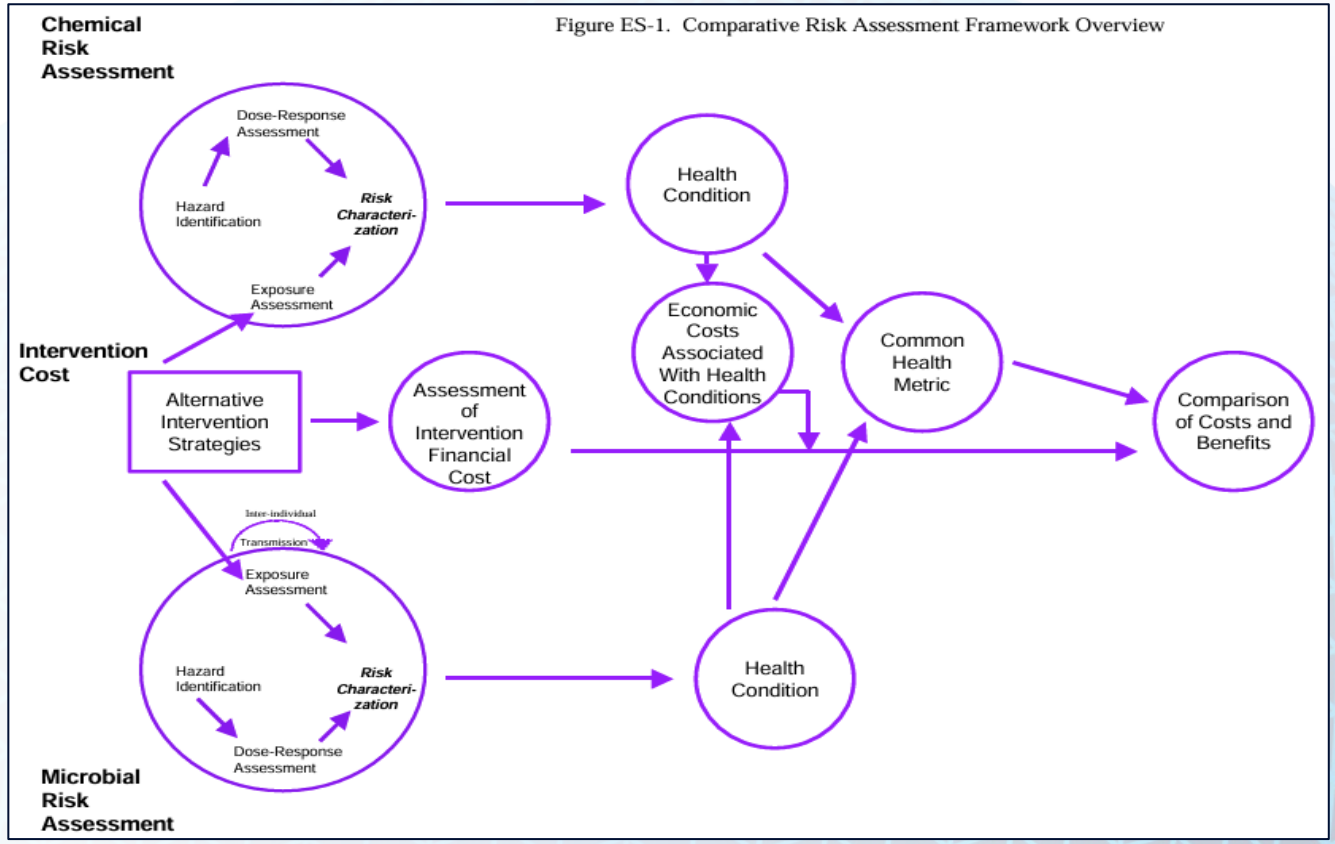


Burchill et al. 2021

Given the Hygiene Hypothesis, Perhaps Comparative Risk Assessments Are Needed…

Comparative Risk Assessments

- Perhaps the risk of exposure to biological agents should be considered alongside risks posed by interventions
  - Applied within the context of the Hygiene Hypothesis
- EPA proposed a comparative risk assessment framework
  - 1998 for drinking water
- Allows for simultaneous risk assessment



EPA 1998

Comparative Risk Assessment

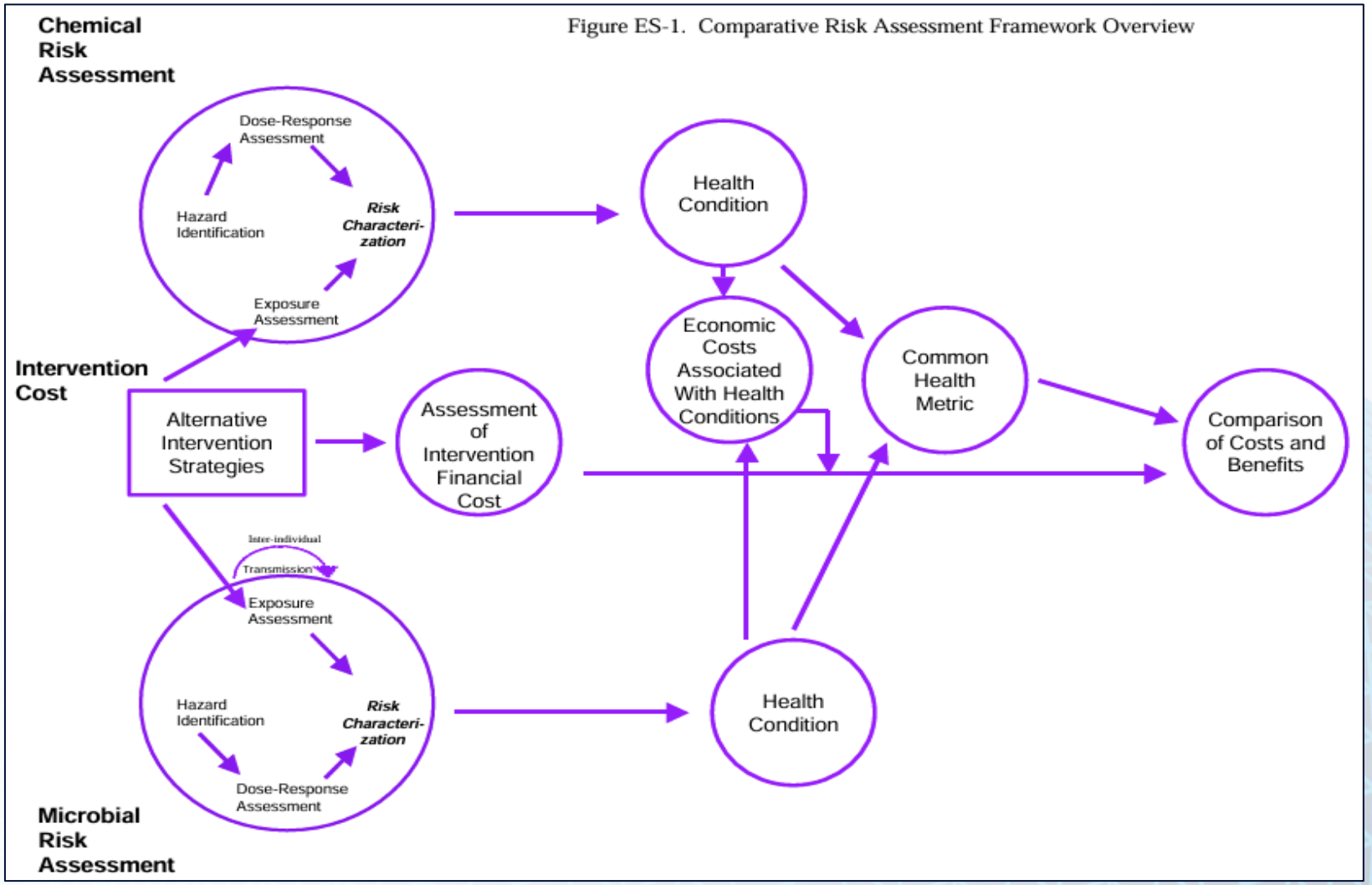


Figure ES-1. Comparative Risk Assessment Framework Overview

EPA 1998

Comparative Risk Assessment

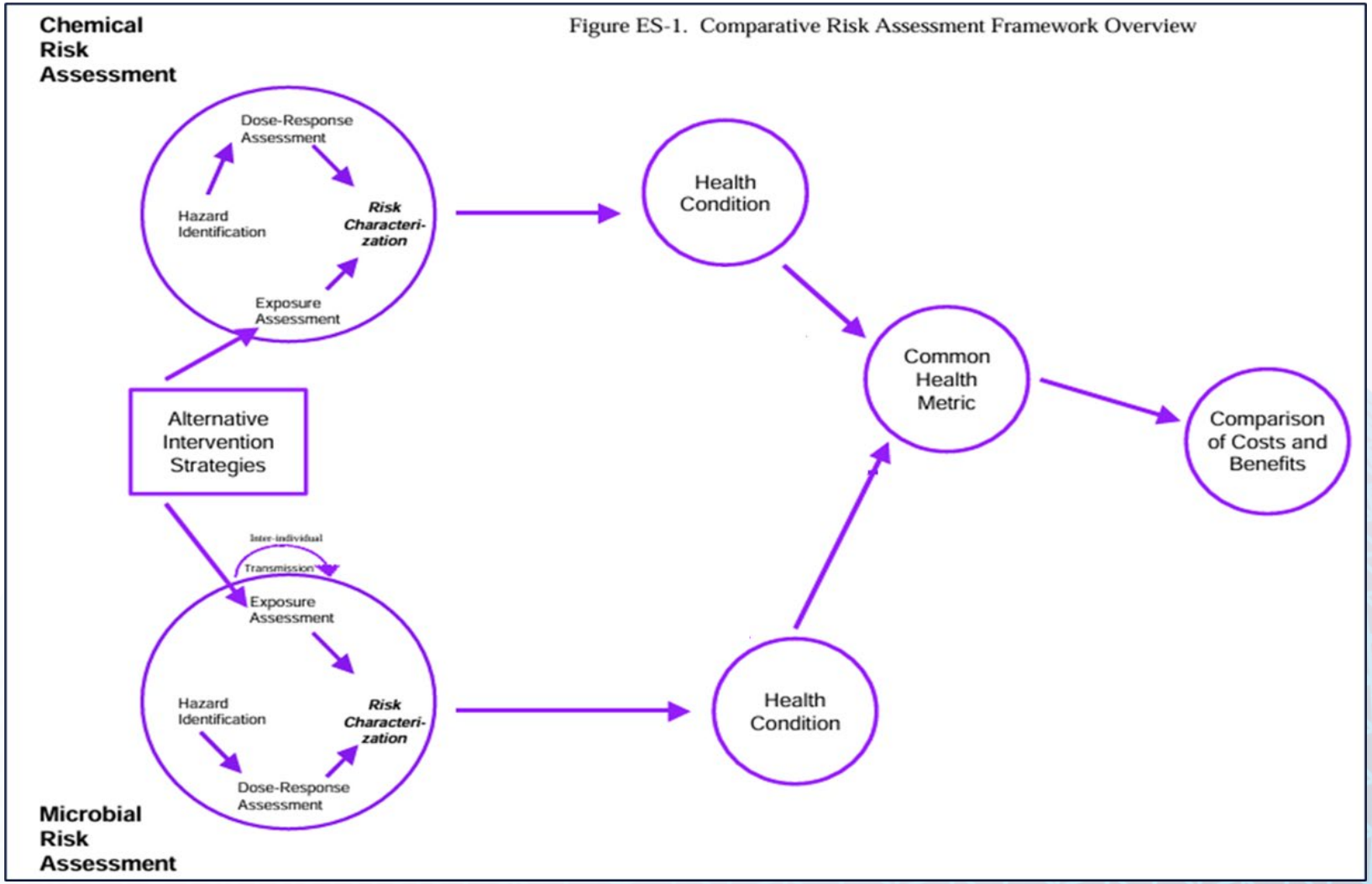
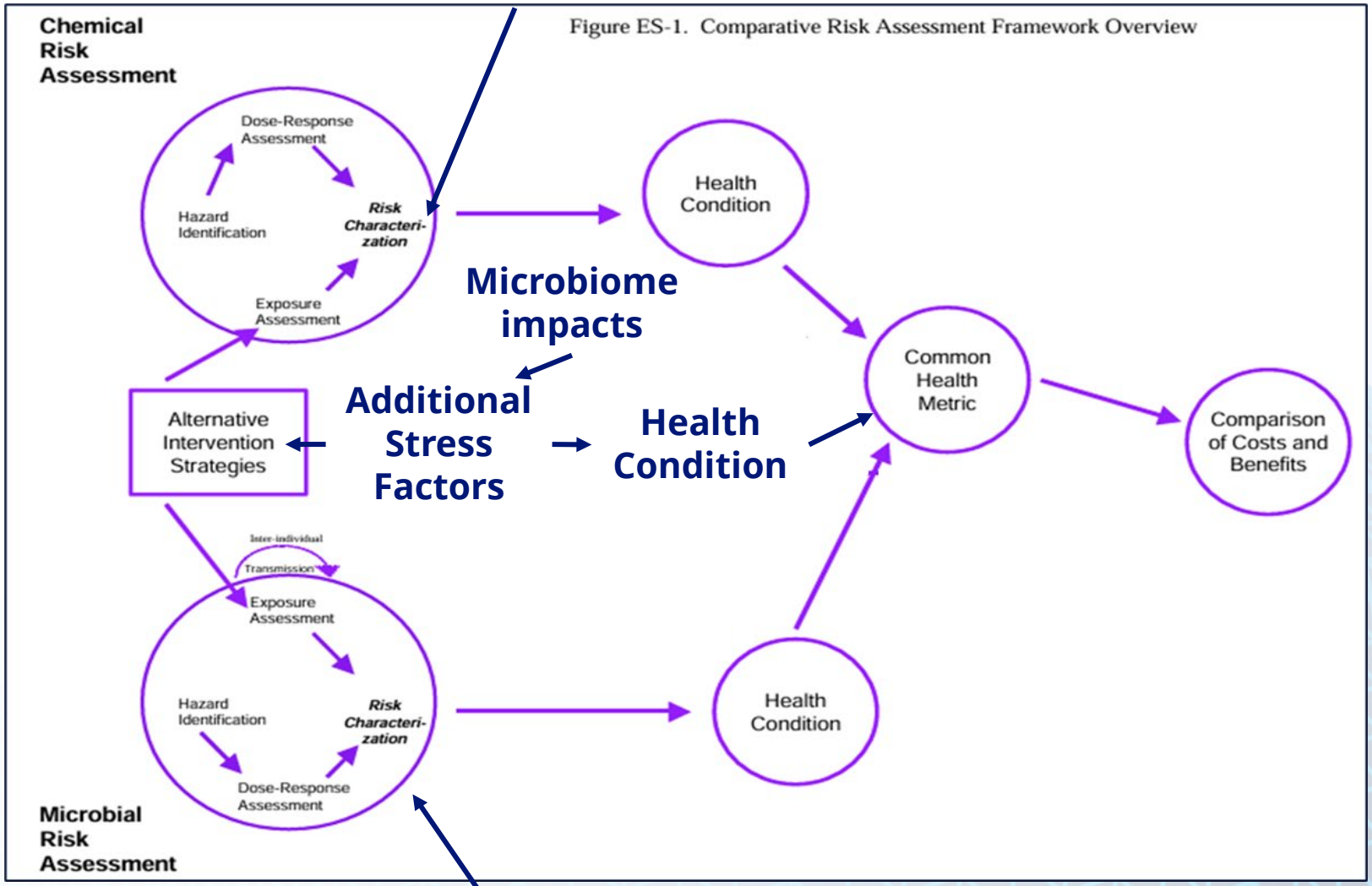


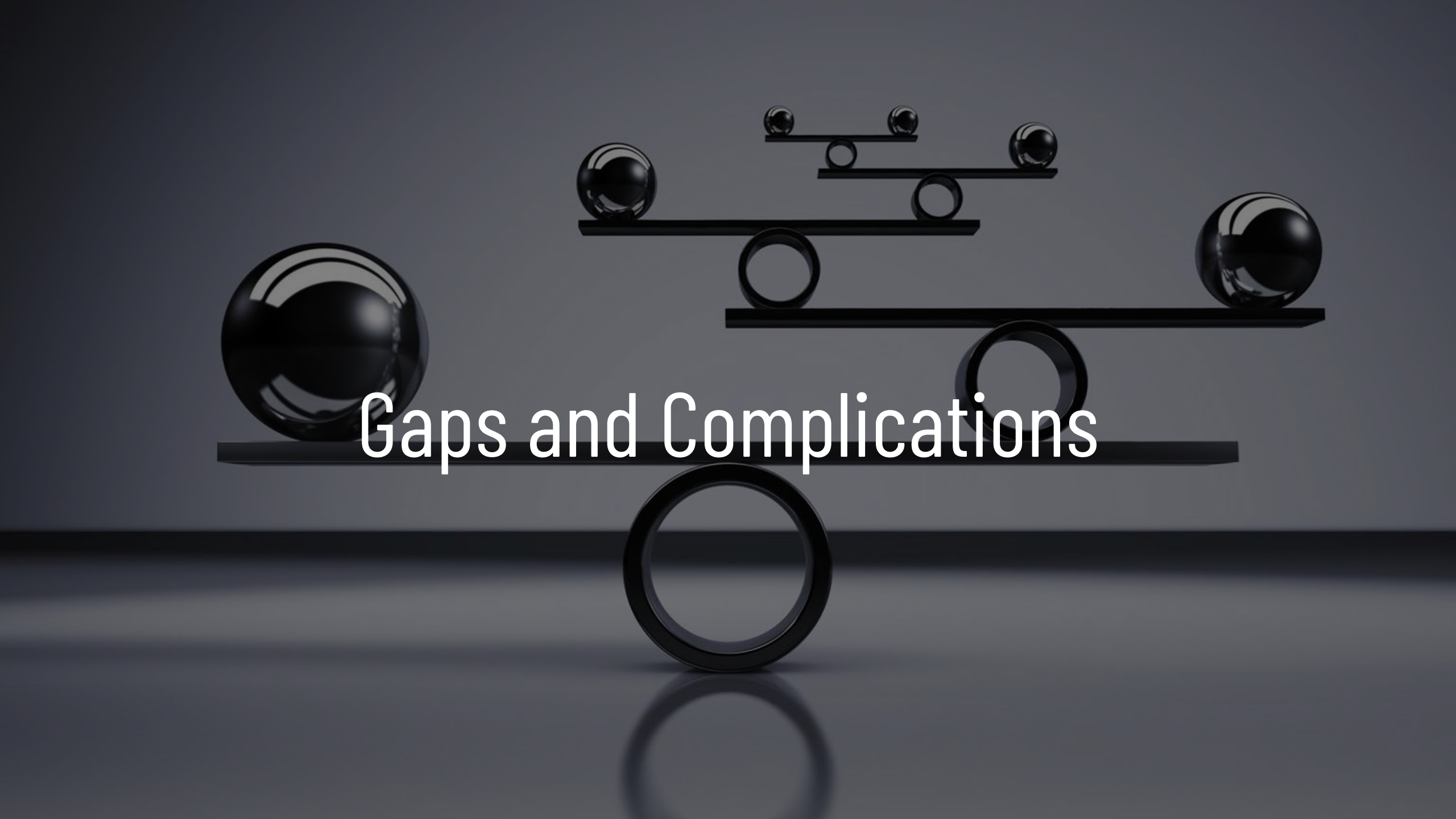
Figure ES-1. Comparative Risk Assessment Framework Overview

EPA 1998

Comparative Risk Assessment

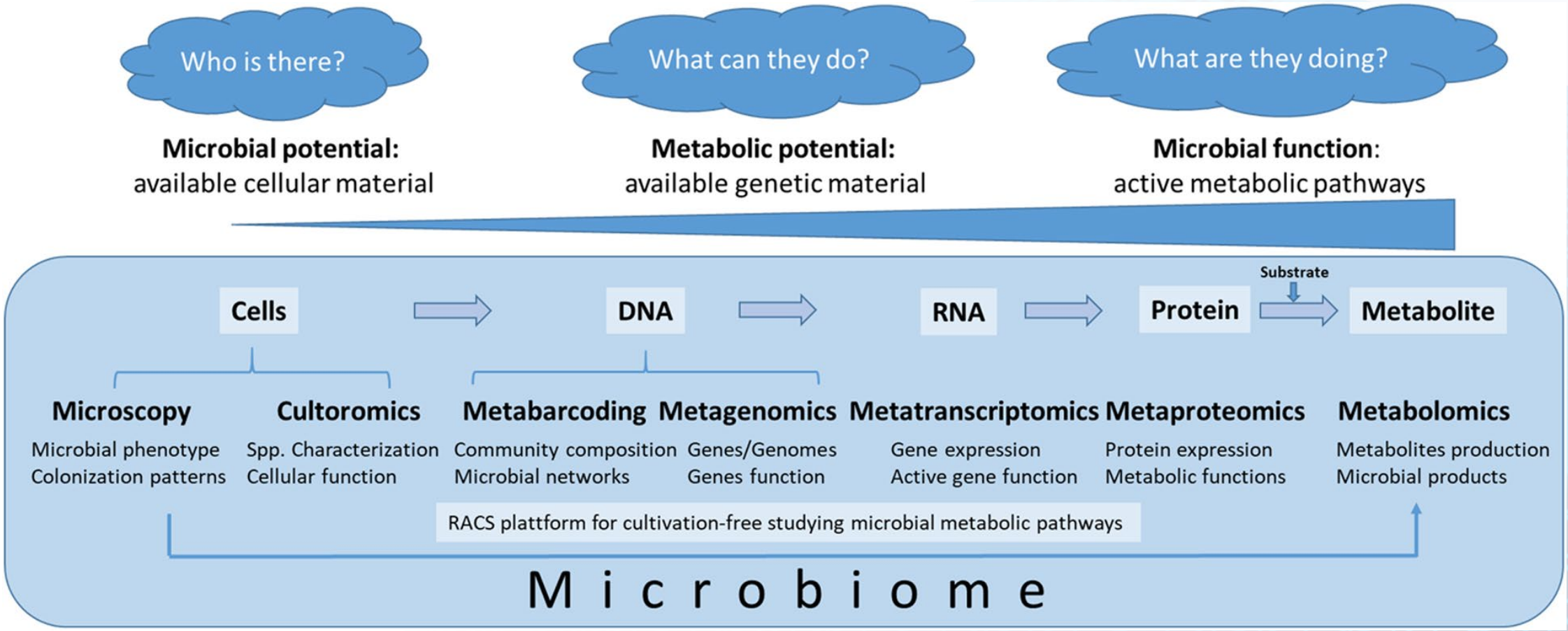


EPA 1998



Gaps and Complications

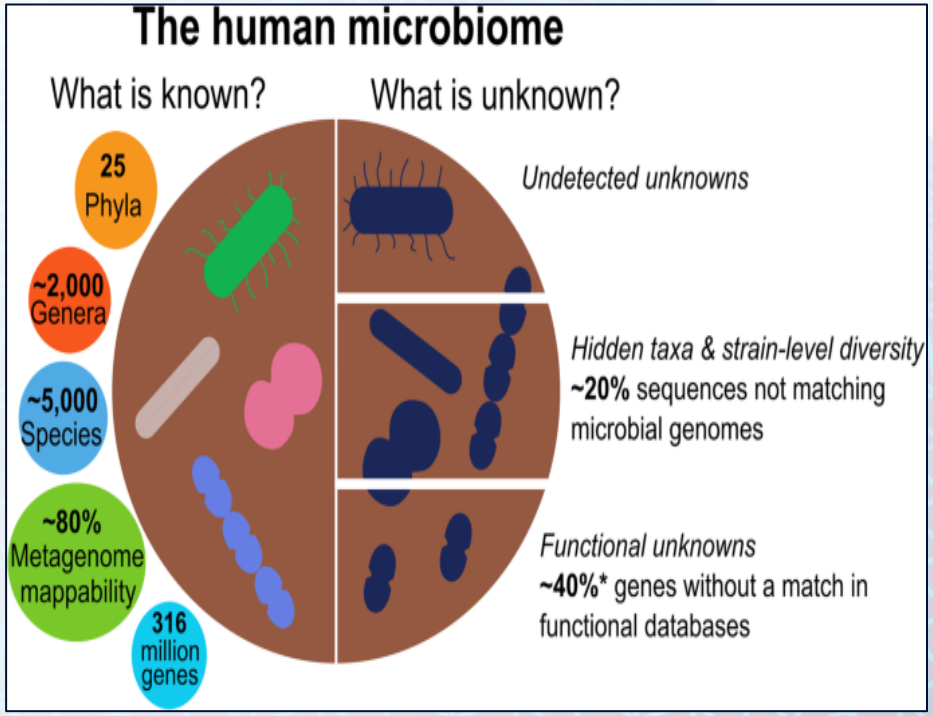
Fundamental Gaps In Data and Approaches



Berg et al. 2020

Did You Notice Something Missing During Our Discussion?

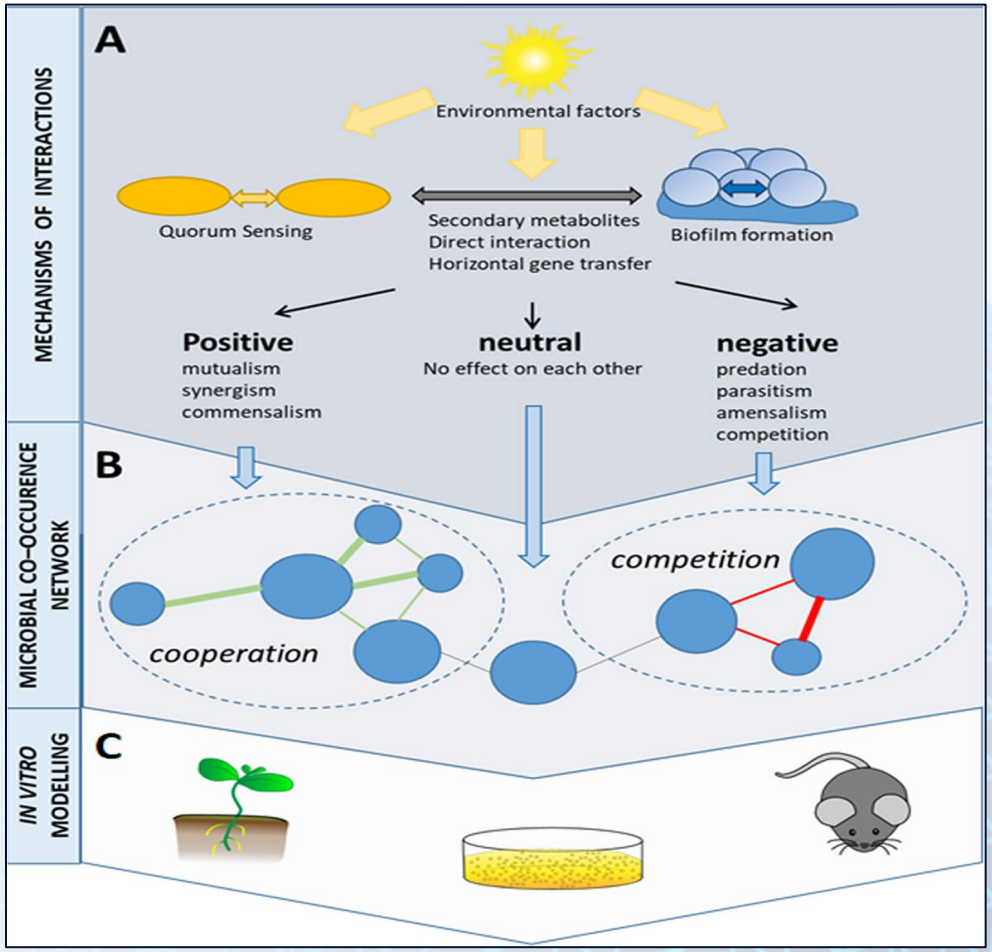
- We primarily focus on the bacterial element of the microbiota
  - Due to the limited studies on non-bacterial species in disease development
- A small number of archaea have been identified in the healthy human microbiome, primarily in the gut
- Human virome is extensive and is recognized as an integral part of the HM
  - However, they are under-characterized
- Direct mutualistic relationships between humans and fungi have been found
  - The best-characterized involves the probiotic yeast



Thomas and Segata 2019

Microbial Networks and Communication

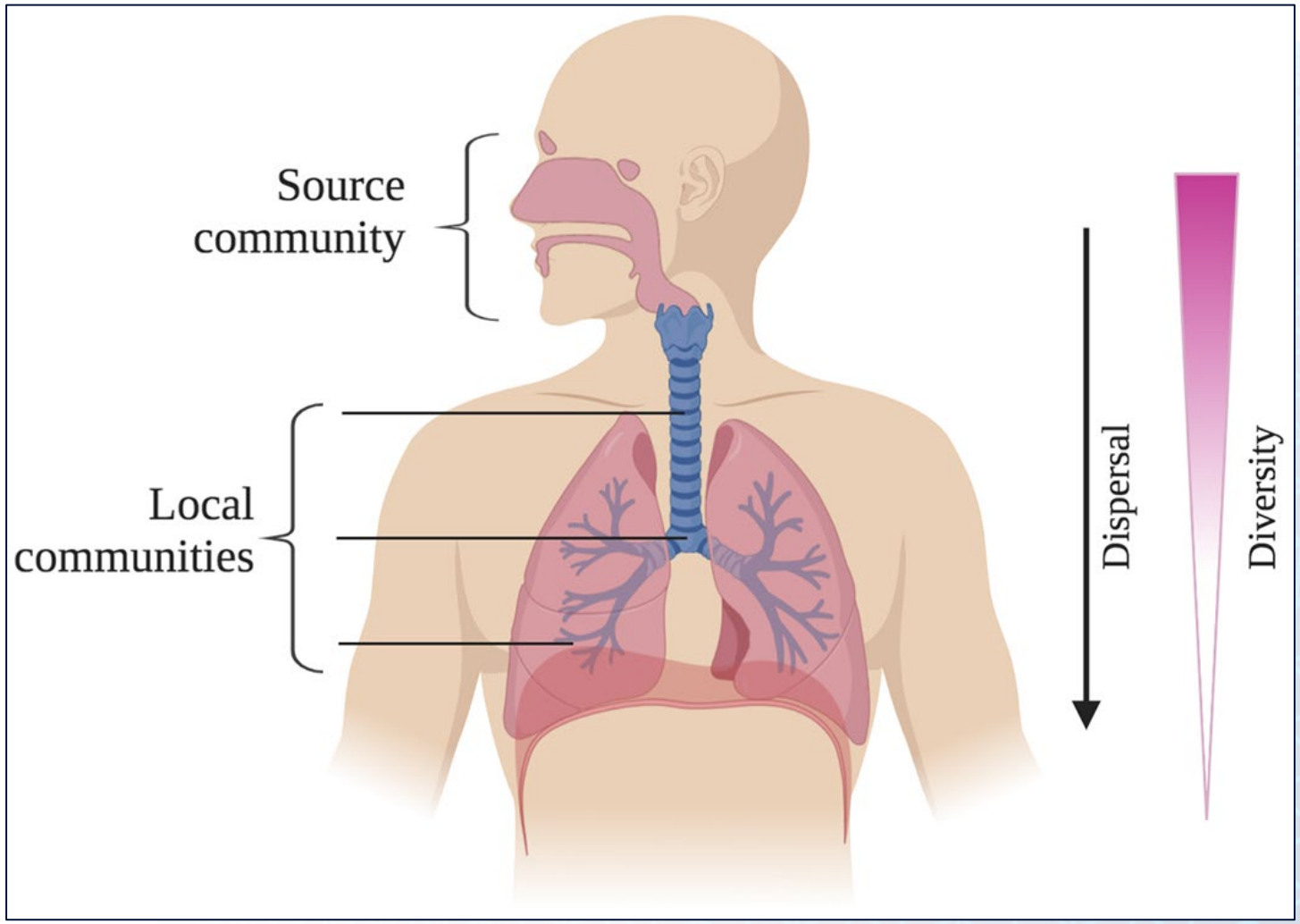
- Microbes interact with one another
  - These interactions have diverse consequences for microbial fitness, population dynamics, and functional capacities within the HM
- Interactions can be between the same species or between different species, families, and domains of life
  - The interactive patterns within these webs may be positive, negative, or neutral
- These microbial social interactions are so far understudied
  - Recent approaches have involved application of social network mapping



Berg et al. 2020

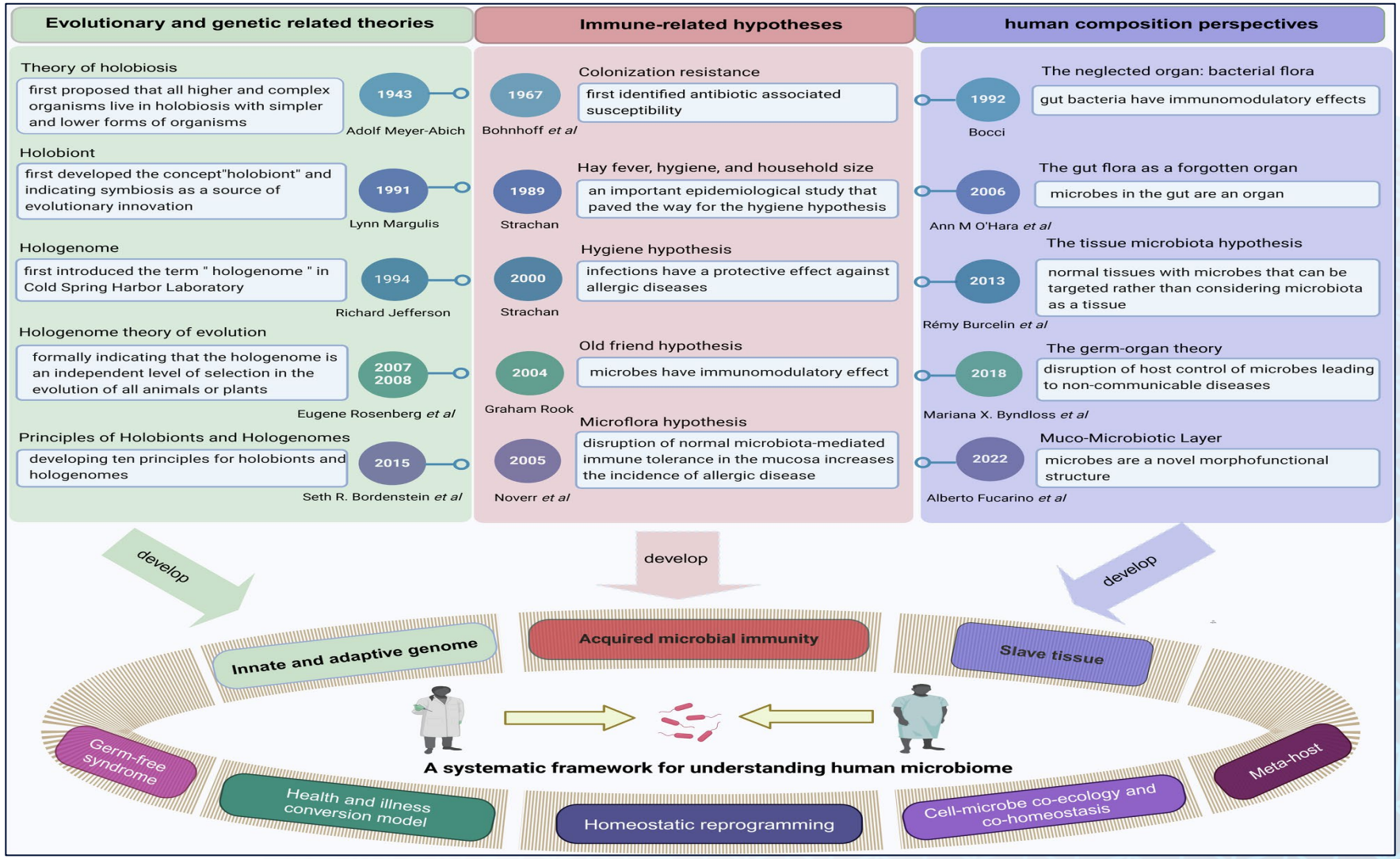
Many Hypotheses That May Impact Occ. Health…

Adapted Island Theory



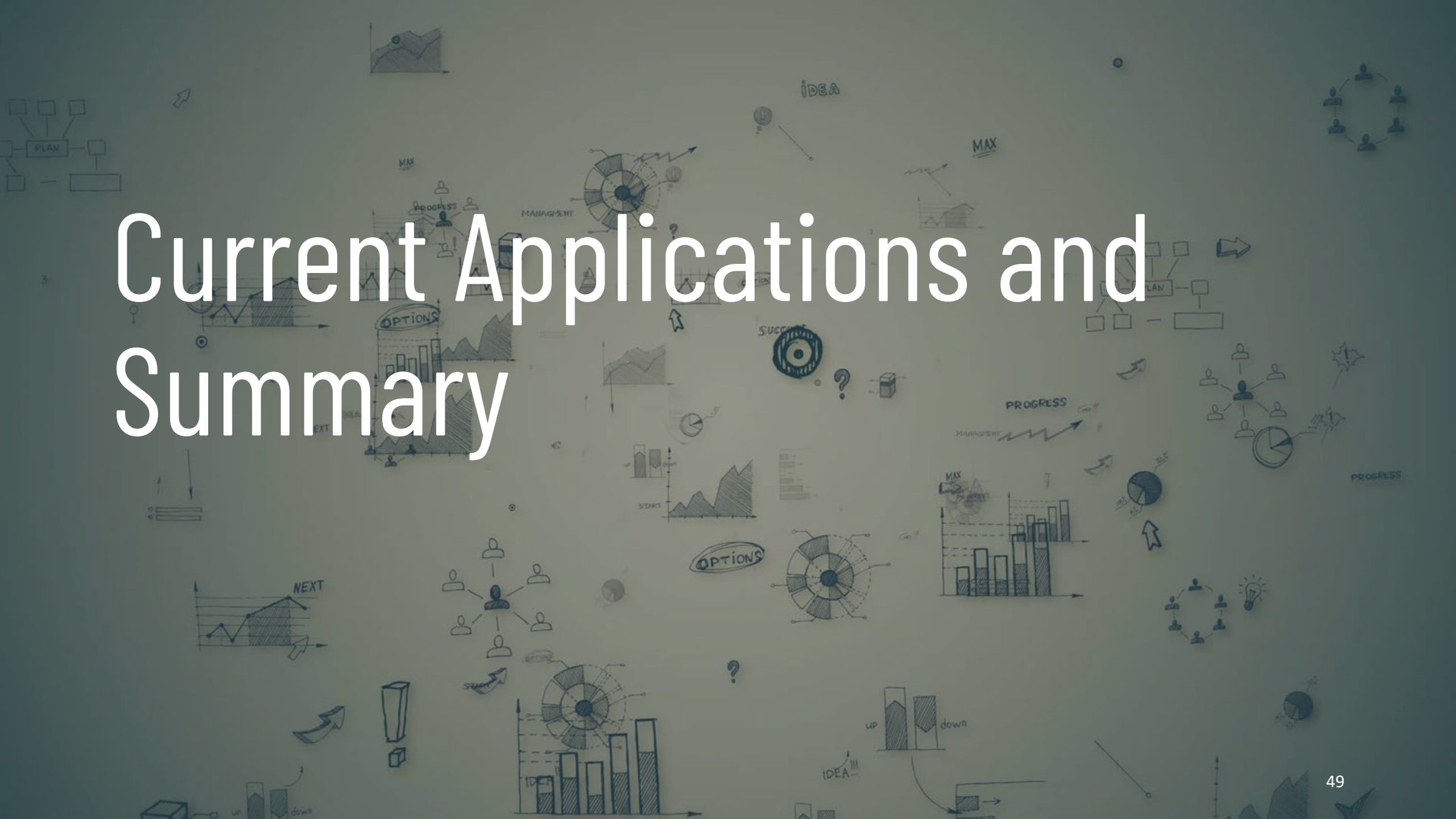
Kennedy and Chang 2021

Many Hypotheses That May Impact Occ. Health…



Kennedy and Chang 2021

Current Applications and Summary



Potential Occupational Health Applications

There are immediate applications and considerations towards workers

- Those interacting with animals and livestock
- Healthcare professionals

Integration of a holistic, comprehensive approach towards human health risk assessment

- Applying an exposome mindset is a necessity for fully understanding the effects of the HM
- EU is currently pursuing to characterize the “working-life” exposome through their EPHOR project
  - However, there is no mention of capturing exposure to the envirobiome

The Total Worker Health platform is well suited for integration of HM data and assessments

- It is already designed to apply a holistic, comprehensive assessment

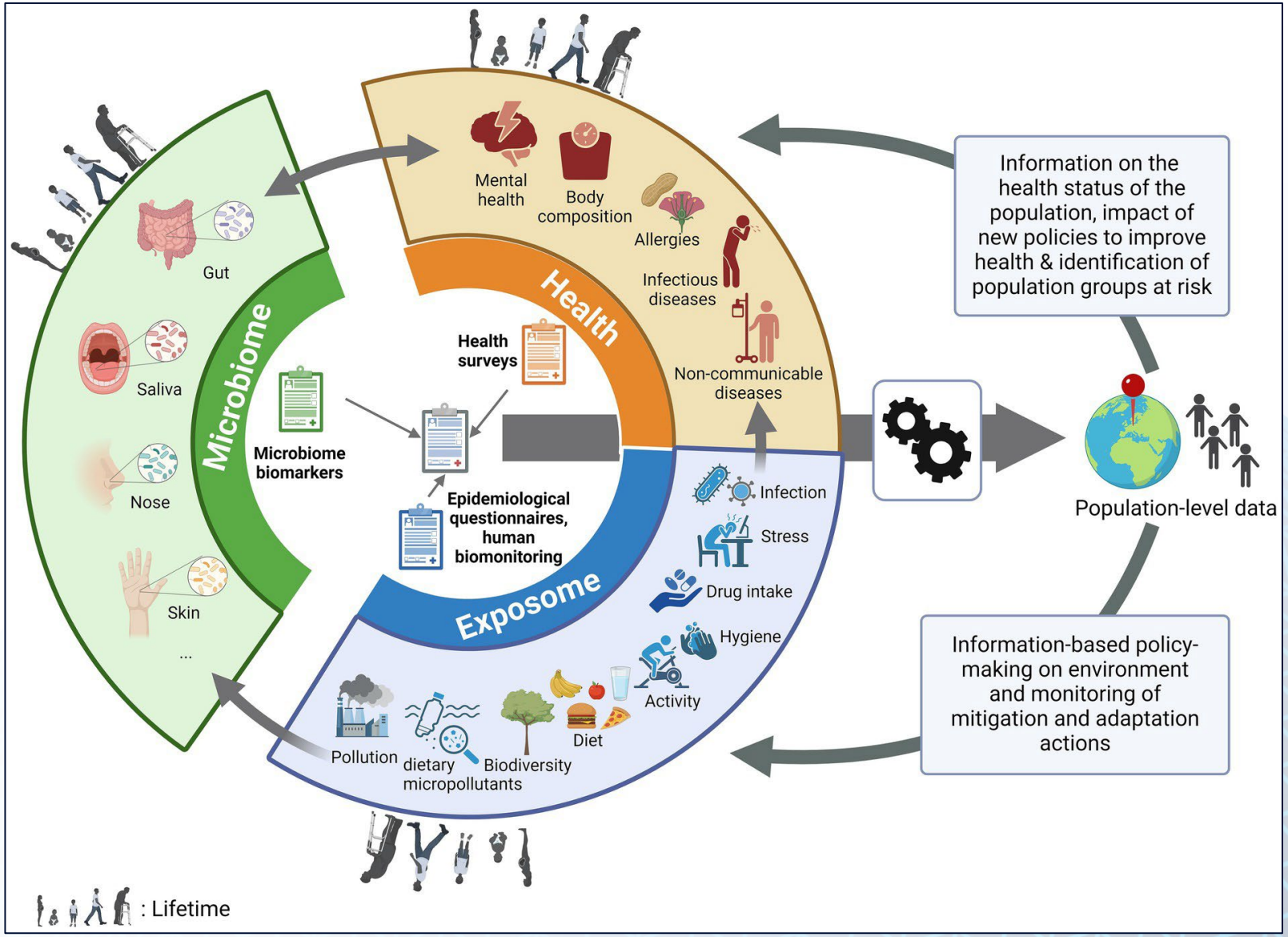
Potential Occupational Health Applications

The [exposome] and its interplay with the human microbiome may one day serve as a leading indicator of disease and illness risk for workers and contribute to the TWH tapestry of worker health and well-being.

Buerger et al. 2023

Let's Apply The Metaorganism and Exposome Frameworks to Occupational Health

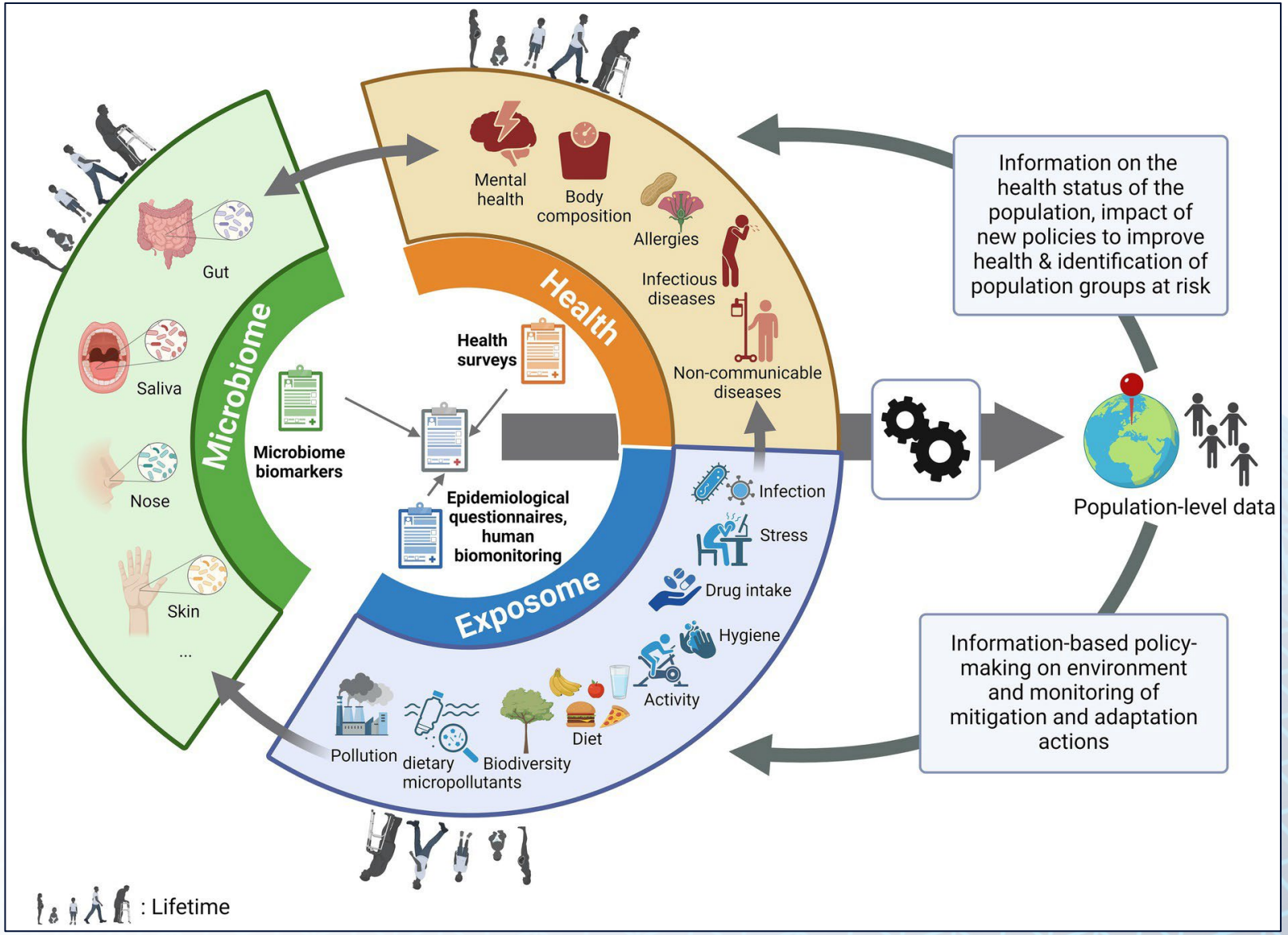
Metaorganism + Exposome



Buytaers et al. 2024

Do you notice what is missing?

Metaorganism + Exposome



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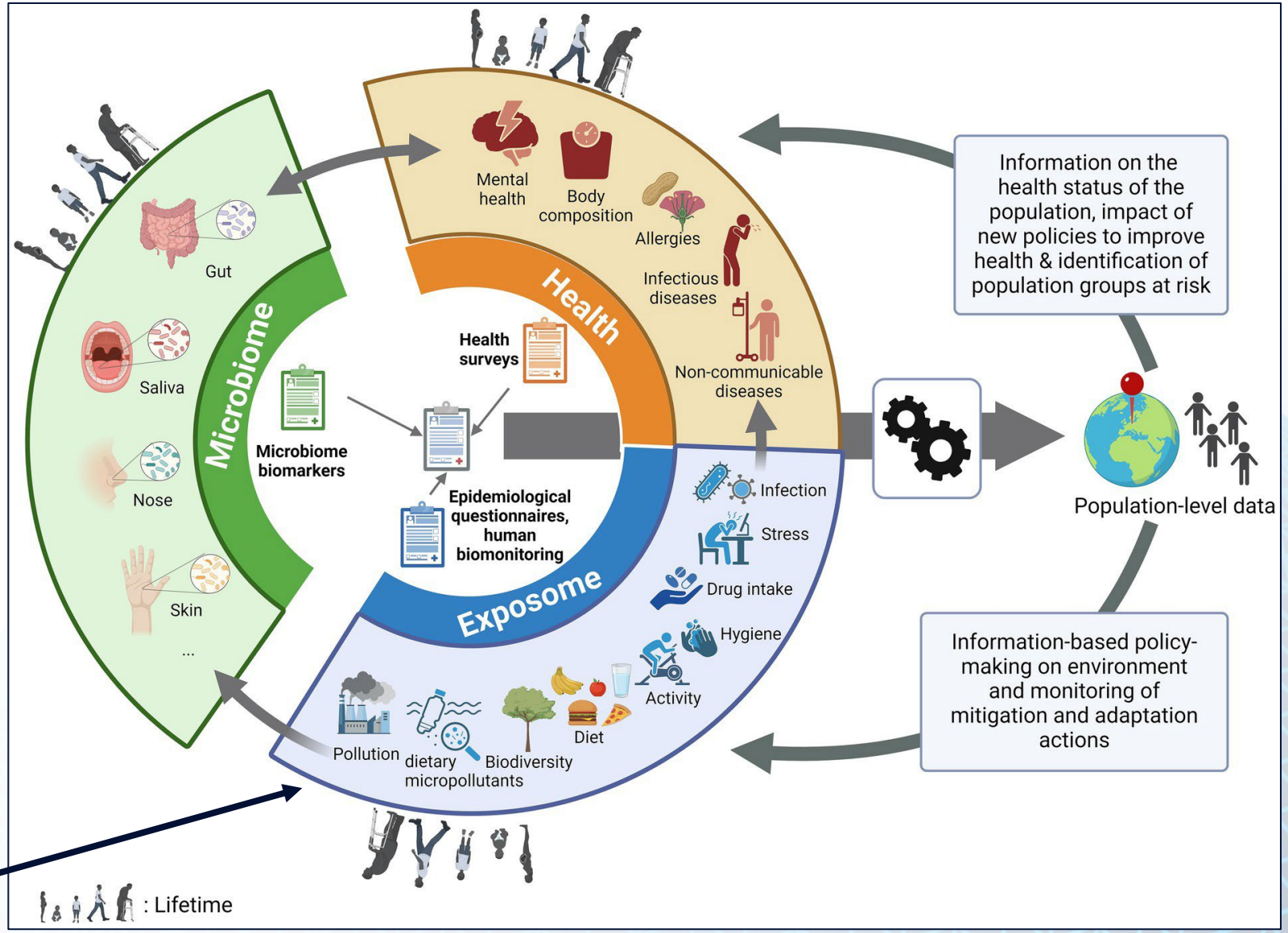

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No mention of workplace exposures!

So, What Does This Mean for the OEHS Professional?

- Holistic, comprehensive approaches are needed
  - An exposome mindset combined with TWH platform allows for this
  - We must begin thinking more holistically about the exposure-effect connection
- Microbiome research of the occupational population is comparatively limited
  - We ***must*** advocate for a seat at the table and emphasize the importance of workplace exposures and their impact on the microbiome
- We have many of the sampling and analytical tools needed
  - However, more information is needed to understand how to use these tools strategically

Summary

- The HM is being increasingly recognized as critical element of human health
  - Growing consensus that a wide range of diverse factors can impact the microbiome
  - It's an exciting time to be involved!

- The field is still young, and research is limited
  - Focused on specific questions of direct impacts to the HM
  - However, we know little about HM-mediated health effects

- The lack of research is exacerbated among occupational health research
  - Some specific studies have been conducted, but is difficult to generalize or apply this data
  - TWH provides an ideal platform to address these gaps

- The OH perspective ***must be*** integrated into these discussions and research

- There are several paths forward, which will be covered in Part 2


Questions

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