

**Interagency Strategic Plan for Microbiome Research
FY 2018-2022**

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About this Document

This plan was developed by the Microbiome Interagency Working Group (MIWG), an interagency working group under the Life Sciences Subcommittee (LSSC) of the National Science and Technology Council (NSTC) Committee on Science (CoS). The MIWG is a successor to the Fast Track Action Committee on Mapping the Microbiome (FTAC-MM).

About the Fast Track Action Committee on Mapping the Microbiome

The Fast Track Action Committee on Mapping the Microbiome (FTAC-MM) was established in February 2015 by action of the LSSC. The FTAC-MM released a report in November 2015 identifying areas of current Federal investment, research needs, and resource gaps for the development of an integrated Federal plan for microbiome research. The report identified priority areas for Federal agency coordination and cooperation on achieving a predictive understanding of microbiomes and their functions.

About the Microbiome Interagency Working Group

The Microbiome Interagency Working Group (MIWG) serves as part of the internal deliberative process of the NSTC and provides overall guidance and direction for microbiome research across the Federal government agencies. The MIWG was chartered in February 2016 to develop a Federal Strategic Plan for microbiome research. Using the FTAC-MM report as a foundation, the MIWG developed the Interagency Strategic Plan for Microbiome Research, taking into account how future Federal actions could benefit from an understanding of and engagement with current international activities. The Interagency Strategic Plan provides recommendations for improving coordination of microbiome research among Federal agencies and between agencies and non-Federal domestic and international microbiome research efforts. The Plan promotes enhancement of the Federal R&D enterprise by embracing diversity, recognizing that inclusion of a broad range of backgrounds and perspectives is critical to achieving robust intellectual dialogue.

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Executive Summary

Microbiome science aims to advance understanding of microbial communities (microbiomes) for applications in areas such as health care, food production, and environmental restoration to benefit individuals, communities, and the planet.

Microbiomes—the communities of microorganisms (such as bacteria, viruses, or fungi) that live on, in, and around people, plants, animals, soil, oceans, and the atmosphere—contribute to our health and livelihoods. Microbiomes are key to maintaining healthy function of diverse ecosystems. They have positive influences on human health, they are responsible for global climate cycles, and benign communities improve food security and have other impacts such as enabling effective wastewater treatment. Dysfunctional microbiomes are associated with numerous problems, including chronic human diseases such as obesity, diabetes, and asthma; disruption of beneficial ecosystem services caused by ecosystem imbalance, such as the hypoxic zone in the Gulf of Mexico; and reductions in agricultural productivity, such as increases in antimicrobial resistance in livestock and poultry. A multitude of industrial processes, such as biofuel production and many food processing operations, depend on healthy microbial communities. Several global ecosystem services, such as nutrient cycling, soil organic matter formation, soil aggregation, and water purification depend on fully functional soil microbiomes. Our nation’s food and fiber production likewise depend on soil health—a complex combination of microbes and their mediated functions. Contamination or alteration of the active soil microbiome communities can lead to reduced efficiency or lost productivity. New technologies in genetics, genomics, and other fields have enabled exciting discoveries about the importance of microbiomes. The next steps—to further understand and then manage microbiome systems to maintain health, prevent imbalance or dysfunction, and restore function when damaged—require additional knowledge and tools.

Given the connection between microbiomes and a broad spectrum of important issues, Federal agencies have converged on three recommended areas of focus to transform microbiome discoveries to solutions:

1. **Supporting interdisciplinary and collaborative research** to enable a predictive understanding of the function of microbiomes in diverse ecosystems to enhance public health, food, and environmental security and grow new bioeconomy product areas.
2. **Developing platform technologies** to generate critical insights and to improve access to and sharing of microbiome data across ecosystems.
3. **Expanding the microbiome workforce** through educational opportunities, citizen science, and public engagement.

This five-year Strategic Plan coordinates microbiome research activities across 21 U.S. government agencies, describing the interagency objectives, structure and operating principles, and research focus areas. This plan demonstrates commonalities that can be leveraged and thus represents an opportunity to increase Federal efficiency.

A Microbial World

Microbiomes are microbial communities existing within greater systems that are organic (including human, animal, plant, insect) or inorganic (soil, water, manufactured products, and the built environment) in nature.

Recent discoveries have generated a new view of the biological world, one that recognizes that plants, animals, and humans are actually meta-organisms containing one or many microbial species. Even inanimate surfaces, from rocks to computer keyboards, are homes to surprisingly complex microbial communities. These microbial communities, called microbiomes, help define the health and integrity of their living or inanimate hosts.

A growing body of research has shown that microbiomes play essential roles in a wide range of biological processes and functions, including human nutrition and disease, nutrient acquisition and stress tolerance in plants, and the stability of soil and aquatic environments. Microbiomes are important to addressing the shared global challenges of maintaining clean water, ensuring adequate food supply, meeting energy needs, and preserving human and ecosystem health. In addition, microbiome profiling could potentially serve as a useful tool in various human endeavors; for example, microbiome profiles may complement human DNA profiling in criminal investigations.

Imbalanced microbiomes have been associated with a number of problems, including human chronic diseases such as obesity, diabetes, and asthma; regional ecological disruptions such as the “dead zone” in the Gulf of Mexico; and reductions in agricultural productivity caused by livestock antimicrobial resistance or poor soil health. Despite the exciting progress that led to these discoveries, the knowledge and tools necessary to manipulate or control microbiomes are still lacking.

Early discoveries in the human, livestock, and crop microbiome areas have already led to investments in start-up companies as well as increased investments by large corporations in this field. The Wall Street Journal¹ and Fortune Magazine² reported in 2016 that investments in microbiome-based products and interventions have been increasing more rapidly than overall venture funding; in 2016, microbiome investment continued to surge when overall funding actually decreased. These investments in microbiome-based companies contribute to thousands of new jobs in this expanding high-tech field. Thus, the Interagency Strategic Plan for

¹ <https://www.wsj.com/articles/microbiome-companies-attract-big-investments-1474250460>

² <http://fortune.com/2016/11/02/gut-bacteria-microbiome-investment/>

Microbiome Research supports recommendations made by the President’s Task Force on Agricultural and Rural Prosperity for coordinated action by federal agencies to promote agriculture and rural prosperity in America through research and technological innovation.³

Key Environments Influenced by Microbiomes

Research has shown that the microbiome is intimately associated with many aspects of human health and disease. From birth when the initial inoculum of microbes is transferred from mother to child, to the development of the microbiomes of various organ systems along with the development of the immune system in childhood, to the synthesis of neurotransmitters in the gut microbiome, these microbial communities regulate many aspects of human health. Further, formula feeding, frequent antibiotic use, high fat diets, and other modern practices which lead to dysfunctional microbiomes have been implicated in the development of many autoimmune diseases and compromised physical, mental, and cognitive resilience, as well as the exacerbation of other diseases.

As with humans, the microbiomes of plants and animals play an important role in plant and animal growth and development. They confer protection against abiotic and biotic stress. For example, drought resistance in plants has been linked not only to plant physiology, but also to benefits provided by the soil microbiome, especially associated root endophytes such as mycorrhizal fungi and rhizobacteria. Plant and animal microbiomes are being investigated and manipulated along with modern agricultural practices to increase productivity and yield.

All terrestrial and aquatic habitats contain microbial communities, from those that live in the deep sea to microbial communities in the water pockets in the ice sheet of the Antarctic to those found in the snow and ice on the tops of the highest mountain ranges—and their dynamics provide highly valuable ecosystem services. The breadth of all of these communities form the base of the global food web and thus support all commercial food production, such as fisheries, which have tremendous economic, social, and cultural significance. In addition to their key roles in human health, agriculture, and ecosystems services, microbiomes play major roles in global cycling of many elements, with carbon and nitrogen among the most important. Their influence is far-reaching—the detoxification of hazardous chemicals and the degradation of waste matter such as sewage are carried out by microbial communities. Microbial communities even affect global climate processes, such as the seeding of clouds in the atmosphere.

Microbiomes change and adapt; for example, the Deepwater Horizon oil spill altered the diversity of microbes in the Gulf of Mexico allowing for microbes capable of degrading oil to flourish. Further research on these microorganisms may potentially provide ecological and economic benefits as a silver lining to this destructive event. Some microbiomes associated with

³ <https://www.usda.gov/sites/default/files/documents/rural-prosperity-report.pdf>

coral reefs have been shown to enable the reefs to resist bleaching and disease. These are being studied so that we can better understand the coral reef ecosystem and conserve this important resource. The study of microbiome dynamics across a variety of ecosystems is being undertaken to investigate and potentially reveal common responses to environmental parameters and to apply the knowledge gained to solving suites of societal challenges.

Microbiomes have also been leveraged for key functions in a unique environment—that of industrial production. Microbiomes play a critical role in many areas relevant to energy research, whether converting natural materials into renewable sources of biofuels, bio-products or electricity, converting waste carbon dioxide to important chemical products, or promoting the growth, productivity, and adaptability of bioenergy feedstock crops. Greater understanding of the interactions and physiological compositions of these microbial communities will elucidate critical functional traits essential to a “healthy” microbiome, and in turn allow us to accurately predict and potentially manipulate consortia properties towards energy production and utilization.

Table 1. Key environments and processes whose functions depend on microbiomes binned into eight microbiome research Target Areas.

Microbiome Target Area	Key Environments and Processes
Agriculture	Crops, soils, food animals, food safety, insects, disease, fisheries, aquaculture, pollinators, energy crops.
Aquatic	Oceans, lakes, streams, reservoirs, sediments, estuaries, coastal, coral reefs, extreme environments, oil spills, marine animals, marine sediments, lake sediments, invasive species, ice, service animals.
Human	GI tract, respiratory tract, oral, urogenital, brain, skin, cardiovascular system, blood, immune system. Applications include addressing many diseases associated with organ systems and body regions; forensics.
Laboratory	Animal model, plant model, soil, synthetic microbiome, biofilms, bioinformatics, and/or in silico, but not directly involving humans.
Built Environment	Water and sewage treatment, water and sewage lines, hospitals, daycare facilities, assisted living facilities, home plumbing and air handling systems, offices, ships, airplanes, International Space Station.
Terrestrial (non-agricultural)	Soils, forest, desert, mountains, grasslands, invasive species, nutrient cycling, contaminated sites, caves, wild plants, insects and animals, Arctic and Antarctic.
Energy (non-agricultural)	Feedstock development for bioenergy, coal/oil/natural gas recovery, conversion and synthesis of bio-products, biofuels, microbial electrochemical systems.
Atmospheric	Aerosols, clouds, dust events (local and intercontinental).

Existing Agency Investments in Microbiome Research

In 2015, the National Science and Technology Council’s Fast Track Action Committee on Mapping the Microbiome (FTAC-MM) was tasked with taking inventory of current Federal investment and identifying research needs, resource gaps, and priority areas for microbiome research. The FTAC-MM reported broad interest and Federal support for microbiome research from Fiscal Year 2012 through Fiscal Year 2014.⁴

More than 21 Federal agencies were connected to topic areas in which microbiomes are known to play a critical role. Figure 1 illustrates an array of agency roles in coordinating microbiome research in each of the eight Target Areas summarized in Table 1. This data illustrates an opportunity for agency coordination and cooperation to expedite predictive understanding of microbiome function.

Table 2. Agency roles in eight microbiome research Target Areas, as described in Table 1.

	USAID	NIST/DOC	NOAA/DOC	DOD	SC/DOE	EPA	CDC/HHS	FDA/HHS	NIH/HHS	DHS	NPS/DOI	USGS/DOI	FBI/DOJ	NIJ/DOJ	NASA	NSF	SI	ARS/USDA	FS/USDA	NIFA/USDA	NRCS/USDA	VA
Agriculture	X	X	X	X	X		X		X		X			X	X	X	X	X	X	X	X	X
Aquatic		X	X	X		X					X			X	X	X		X	X			
Atmosphere			X						X		X			X	X		X		X			
Built Environment		X		X		X	X		X	X		X	X	X	X					X		X
Human	X	X		X		X	X	X	X		X		X	X	X	X	X	X		X		X
Energy				X	X						X									X		
Laboratory			X	X		X	X	X	X		X			X	X	X	X	X	X	X	X	
Terrestrial				X	X	X			X		X	X	X	X	X	X	X	X	X	X	X	X

⁴ Stulberg et al. (2016) doi:10.1038/nmicrobiol.2015.15.

Recent Microbiome Research Workshops

For several years, federal agencies supported workshops to gather input from the research community on the anticipated impacts of microbiome research and strategic research needs. Appendix V lists several of those workshops. For example, the NIH-sponsored workshop, “The Human Microbiome: Emerging Themes at the Horizon of the 21st Century” held in August 2017 sought input from a trans-disciplinary group of scientists to identify (1) knowledge gaps, (2) technical hurdles, (3) new approaches, and (4) research opportunities to inform the development of novel prevention and treatment strategies based on host/microbiome interactions over the next 10 years. The workshop closed with a Joint Agency Panel that identified areas of common interest and possible collaboration, touching on all three of the Interagency Microbiome Strategic Plan focus areas.

Objectives of an Interagency Microbiome Strategic Plan

The goal of this Interagency Strategic Plan for Microbiome Research is to identify and prioritize research needs across Federal agencies to efficiently promote understanding of how microbiomes function and how to manipulate those functions to address societal problems. The aim is to accelerate the development of new products and services that improve human health and nutrition, the health and safety of crop and animal production, ecosystem services, and industrial applications of microbiomes. To that end, the plan focuses on the study of microbiomes across different ecosystems to seek organizing principles that shape all microbiomes, with the ultimate objective of developing predictive capabilities of microbiome function and the effects of disruptions in a wide range of environments. The plan advances efforts across three key Research Objectives, outlined below. These objectives reflect commonalities across agencies and thus represent an opportunity to increase Federal efficiency through leveraging and coordination.

1. Support Interdisciplinary Research

Since microbiomes are communities existing within greater natural systems, analysis of microbiome functions and the function of the greater system is, by nature, multidisciplinary and integrative. Human health, for example, is dependent on healthy gut, oral, lung, and skin microbiome functions, among others. Crop health is dependent on microbiomes on plant surfaces, in inter- and intra-cellular spaces, in the soils, and on other associated organisms, like pollinating insects. The soil microbiome has a crucial role in the delivery of nutrients, vitamins, minerals, and other chemicals that have profound effects on plant, animal, and human health. In addition, many discoveries such as antibiotics were derived from soil organisms. Similarly, when considering ecosystem services, community-level studies of microbiome function must be

integrated with the basic biology, chemistry, and dynamics of the oceans, soils, forests, and atmosphere. Thus, Federal agencies should encourage:

- Coordination of research investments across Federal agencies to maximize efficiency, reduce duplicative efforts, and disseminate advances;
- Research partnerships with the private sector and the international community to leverage non-Federal investments and accelerate translation from the laboratory to needed applications;
- Development of networks, tools, and technologies for improving access to and distribution of microbiome datasets.
- Multidisciplinary research, including integration of biological, computational, physical, and chemical sciences as well as mathematics and statistics.

Expected outcomes of this national effort include greater efficiencies and cost savings for data generation and analysis, increased pace of technological innovation towards the improvement of human health and agricultural productivity, and the development of consistent practices in the Federal Government regarding the use of genetic, organismal, and data resources.

2. Develop Platform Technologies

Advanced DNA sequencing technologies have illuminated unanticipated complexity and diversity in vast networks of microorganisms, leading to questions about how microbiomes function as communities, how they interact with the environments and hosts they inhabit, and how microbiomes can be leveraged to improve health and ecosystem services. Due to the diversity and the scale at which microorganisms function, answering such questions has been hampered by numerous technical, technological, and conceptual challenges, including effective standardization for collection of samples and metadata, lack of capacity to store and analyze sequencing results, and lack of effective, wide-ranging collaboration and integration among researchers studying different ecosystems. Overcoming these barriers to address the fundamental questions about microbiomes may elucidate universal principles governing microbial communities, enabling predictive models of the communities' robustness and resilience in supporting the essential ecosystem services on which we rely. This knowledge can lead directly to system designs and interventions that positively impact health, food systems, manufacturing, renewable energy production, and the environment. A key component to addressing these broad challenges is proposed herein: development of technologies, strategies, and standards that maximize our ability to understand microbiomes and their processes and that also maximize the utility of generated data.

Technology development is required to sustain rapid advances in understanding the core principles that underlie microbiome functions for biomedical, agricultural, environmental, and industrial use. The Interagency Microbiome Strategic Plan recommends continued support for research in three strategic areas of technological need:

1. **Develop robust and consistent standards.** The plan advocates for development of standards, protocols, and reference materials for the microbiome research community that address the challenges of biomedical, agricultural, environmental, and industrial microbiome research. Collaboration between disciplines is recommended for the development of standards that enable the sharing of information. The National Institute of Standards and Technology will continue to facilitate and encourage cooperation in microbiome standards development between the agencies.
2. **Support open and transparent data.**⁵ Develop a user-friendly, interoperable system of databases that includes microbiome metagenomes, metabolomes, transcriptomes, proteomes, lipidomes, and associated metadata. Federal, academic, and other public sector microbiome research efforts will generate significant quantities of data that must be analyzed, curated, stored, and made accessible to the public and private research communities. A robust, integrated federation of open access microbiome databases and associated software tools is needed, as is access to high performance and cloud computing. Along with open access data resources, resources such as reference samples, reference genome sequences, and open access sample repositories must be developed, maintained, and distributed. Moreover, to achieve maximum impact, microbiome data systems must be integrated with biomedical, agricultural, industrial, and environmental data systems. Examples of microbiome and related databases are listed in Appendix IV. Microbiome knowledge-based and curated database systems must have sustainable long-term funding support with expert curation. Moreover, data and software that is deposited in federally-sponsored databases must be open and freely available to all researchers to the extent possible while IRB consents and national security concerns are also recognized. This will enable more rapid advancement of the field and transition of research to applications.
3. **Further develop analytical technologies.** Development of accessible, high-throughput tools for characterizing microbiomes easily and cheaply at multiple scales for medical, agricultural, environmental, and industrial uses. The plan must also support the development of a wide range of computational, biostatistical, visualization, and modeling tools needed to enable analysis and visualization of the large and complex multi-omic

⁵ https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/NSTC/iwgodsp_principles_0.pdf

data generated by microbiome studies. New technologies must democratize microbiome research, thus enabling small and large laboratories to contribute and ultimately benefit public health, agriculture, and our economy.

3. Expand the Microbiome Workforce

The ultimate success of the Interagency Microbiome Strategic Plan will be determined by its positive impacts on medical, agricultural, environmental, and industrial research, and on innovative applications of this research. Bioinformaticians and computational modelers—newly recruited or trained from the current pool of researchers—are needed to analyze the microbiome data gathered and to develop testable hypotheses. This in turn will spur the development of a predictive understanding of microbiome functions under various conditions, resulting in biomedical, agricultural, industrial, and environmental applications.

The plan will offer excellent training opportunities for young scientists to contribute to this exciting enterprise, including members of under-represented groups. Federal resources must be made available to support the education, training, and recruitment of experts in target fields deemed critical by the research community, e.g., bioinformatics, programming, data analytics, and modeling. Professionals with the computational expertise and the biology background necessary to understand systems biology will be critical.

Finally, to ensure the rapid transfer of microbiome information and technologies to end users, outreach must be an integral element in the overall Interagency Microbiome Strategic Plan. Examples of outreach activities include workshops and tutorials on how to access and utilize the resources, tools, and data on microbiomes and workshops that bring together microbiome researchers with biomedical, agricultural, computer, ecological, and industrial scientists. Collaborative problem-solving forums will allow programmers to meet with users to develop new software solutions.

Structure and Operating Principles of the Interagency Microbiome Strategic Plan

The Interagency Microbiome Strategic Plan will follow four broad Operating Principles:

1. The plan is an effort by the Federal Government to advance and coordinate microbiome research across agencies. It should be guided by an Interagency Strategic Plan for Microbiome Research (this document), to be updated every five years to review progress

toward goals and revised as needed to reflect up-to-date science and unmet research needs.

2. The Plan is coordinated by an interagency working group with inclusive representation.
3. All resources, including data, software, microbial stocks, and other biological materials, should be made openly accessible while in compliance with Institutional Review Board (IRB) consents and national security concerns.
4. Extramural awards should be made on a competitive basis with peer review.

The Plan will also pursue collaborations with non-Federal bodies (such as universities, research foundations, and businesses), as well as with other nations, to advance its objectives and increase its impact. Such collaborations may include:

Data Access and Management

Microbiome research often makes use of so-called “Big Data”, and requires databases that can house the large and complex sequence and other “omic” datasets produced from this research. Appendix IV lists some widely used US databases and cyberinfrastructure that support federally-funded microbiome research in specific areas; the list is not exhaustive and does not capture many private microbiome research databases or important databases from associated scientific areas (e.g., chemistry, structural biology, plant science, geosciences). Consistent and reliable database and resource coordination to facilitate data collection, analysis, interoperability, and data sharing is a long-term priority issue for the Federal agencies involved.

International Coordination and Collaboration

Microbiomes are central to the global challenges of maintaining sustainable water and food supplies, improving human health and nutrition, sustaining ecosystem services, and meeting our renewable energy needs. Indeed, microbiome research supports our National Security Strategy through collaborations with allies and partners and investments in early-stage research and development⁶ as well as the goals and objectives laid out in the US Global Food Security Strategy.⁷ These fundamental resource issues (and the microbiomes associated with them) are not limited to the domestic sphere. Thus, there is much to be gained from international collaboration and coordination to advance our knowledge and application of microbiome research. Additionally, coordinating with allies and partners can be a cost-effective way to advance research that will be beneficial for U.S. national security and economic prosperity. Topics for collaboration might include:

⁶ <https://www.whitehouse.gov/wp-content/uploads/2017/12/NSS-Final-12-18-2017-0905.pdf>

⁷ <https://www.usaid.gov/sites/default/files/documents/1867/USG-Global-Food-Security-Strategy-2016.pdf>

- Data-sharing and access to global communities, unique birth cohorts, and individuals from all socioeconomic backgrounds. This will enhance scientists’ understanding of human microbiomes, which are heterogeneous yet reflective of specific regions and environments.
- International collaboration on disease research, surveillance, and treatment, both from the perspective of microbe-caused human and agricultural diseases (e.g. tuberculosis, cholera, plant rusts, and rots) and the applicability of microbes as treatments (e.g., bacteriophage therapy cocktails). Plant pathogens, for example, travel the globe via several mechanisms, including international freight and storm winds, potentially devastating crops in regions without natural resistance mechanisms. Microbes may also be used as therapeutics for non-communicable diseases that profoundly affect the health of people in developing countries.
- Partnerships between researchers in advanced and developing countries. These are integral to efforts to improve global food security. Smallholder farmers working in resource-poor environments have much to gain from microbiome-informed guidance on soil amendments, for example. Optimizing soil microbiomes may allow farmers to grow crops on marginal lands, helping them feed their families and contribute to their local economy.

The international community recognizes that countries have sovereign rights over many genetic resources found within their national jurisdiction. Countries may have established domestic processes—commonly referred to as “access and benefit-sharing regimes”—to manage access to genetic resources and sharing of benefits derived from their utilization that may apply to microbiomes. U.S. researchers utilizing microbiomes from other countries are responsible for ensuring that they are following all applicable domestic laws and regulations regarding collection and utilization of genetic resources.

Interactions with the Private Sector

The private sector has already begun to invest in market-oriented microbiome research, including microbial therapeutics for many human diseases. Microbiome-based therapeutics are being developed and used to treat infectious disease (like that caused by the bacterium *Clostridium difficile*), and the same rationale is being applied to the development of microbiome-based treatments for other microbiome-related human diseases. Some large pharmaceutical companies are creating new R&D efforts that are focused on the development of microbial therapeutics.

Microbiome-based drug discovery and therapeutics will require coordinated effort across sectors. For instance, the private sector is increasingly committing to supporting the development of new antimicrobial drugs, and public-private partnerships can help with drug repurposing in academic research. Many current drugs used or re-purposed to treat disease are metabolized by the gut microbiome, but there are no organized efforts to determine 1) which classes of drugs are metabolized by the microbiome, 2) which microbiomes, and in particular which specific microbial communities within a microbiome, are most bio-active in metabolizing drugs, or 3) whether the metabolized drugs are made more potent, neutralized, or made more toxic by the microbiome. Public-private partnerships are needed to resolve the role of the microbiome in drug metabolism.

There exist numerous consortia to encourage international collaboration on “antibiotic resistance breakers” and discovery of new antimicrobial drugs. The microbiome, both in the gut as well as in other body regions, defends against invading pathogens and against microbial competitors in their own ecosystem by producing substances with antibacterial and antifungal activity. Much has been discovered about these underexplored antimicrobials through the computational analysis of the genomes in a microbial community—so-called “metagenomic data.” Analyses of metagenomes have revealed a diverse array of different classes of antimicrobials. This approach holds great promise to the discovery of new antimicrobial drugs, which may replace those drugs we are losing to the rise of antimicrobial resistance. Similar public and private initiatives are coalescing in agricultural microbiomes including soil, crop, animal, and insects.

Finally, the federal government recognizes there are future opportunities to engage the broad community and leverage citizen science initiatives to address gaps in microbiome knowledge.

Strategic Research Areas

The following Strategic Research Areas support the Interagency Microbiome Strategic Plan Research Objectives, fit into each agency’s Target Areas, and are supported by Federal agencies. Opportunities for cooperation and coordination of research efforts will be pursued in a manner that recognizes the responsibility of specific agencies to support their distinct missions as well as their national laboratories. Some selected examples of priority microbiome-related strategic research areas are listed below. Appendix III provides a high level summary of microbiome research activities supported by a number of Federal agencies.

1. Human Health and Safety

Microbial communities live in and on all epithelial surfaces of the human body, and play a role in virtually all aspects of human health and development including digestion, immune system function, and defense against infectious disease. Though much has been learned about the vast and diverse roles of the human microbiome, we have only begun to understand how these microbial communities interact with the human host. Such understanding will result in a new perspective on human health because of the role of the microbiome in human health and disease and may produce novel strategies for microbiome-based therapeutic intervention and treatments for disease.

1.1. Human Health and Disease

- 1.1.1. Investigate proper functioning of the microbiomes of healthy people in order to understand what is altered in the microbiomes of people with disease.
- 1.1.2. Investigate the emergence of modern diseases that are related to common modern practices and that result in a disturbed or malfunctioning microbiome.
- 1.1.3. Harness the microbiome for the treatment of disease, or to enhance resilience or performance.
- 1.1.4. Understand how pre- or pro-biotics aid in treatment and prevention of disease, or enhance resilience or performance.
- 1.1.5. Investigate how the human microbiome interacts with toxic and/or xenobiotic chemicals from sources in the environment, food, and drinking water to transform or metabolize these chemicals and mitigate or enhance their effects.
- 1.1.6. Investigate how members of the gut microbiome interact with particular classes of cancer drugs to stimulate the patient's immune system and utilize them in the fight against cancer.
- 1.1.7. Develop microbiome-based treatments for diseases that involve the immune system, such as diabetes and inflammatory bowel disease.

The loss of traditional antimicrobial drugs and discovery of new antimicrobial drugs in the human microbiome. Antimicrobial resistance (AR) can emerge and spread through many paths, from hospital



stays or from incomplete consumption of courses of antimicrobial drugs, which can promote AR spread from person to person; livestock and poultry, which contain bacteria with AR genes; and from the environment. AR spread prompted the White House to announce the 2015 National Action Plan for Combatting Antibiotic Resistant Bacteria.⁸ Better data on the impact of antimicrobial drugs on human, animal, and environment-located microbiomes is needed to develop and implement effective strategies throughout the world to address the emergence and spread of drug resistance. With the loss of our current arsenal of antimicrobial drugs, perhaps the human microbiome can be the source of new ones? Amongst many roles, the microbiome helps to defend us against

pathogens. Part of this defense involves the use of antimicrobials made by these microbes. Researchers have found that a class of novel and potent antimicrobials was widely distributed in the NIH's Human Microbiome Project data.⁹ These studies demonstrate that the human microbiome is a treasure trove of new and novel antimicrobials that may supplant those we are losing to the rise of AR.

1.2. Antimicrobial Resistance

- 1.2.1. Understand the impact of antimicrobial drug use on the emergence of antimicrobial resistance and microbial dynamics in humans, terrestrial and aquatic farm animals, and the environment.
- 1.2.2. Understand the mechanisms that drive the spread of antimicrobial resistance in the hospital and between livestock, poultry, aquaculture, and humans in order to develop strategies for reducing this spread.
- 1.2.3. Discover new and novel antimicrobial drugs isolated from the human and other microbiomes that can replace those drugs that are no longer effective.
- 1.2.4. Develop microbiome-based antimicrobial resistance monitoring.
- 1.2.5. Develop novel microbiome-altering therapeutics to block colonization by resistant microbes or treat refractory infections.

1.3. Human Nutrition

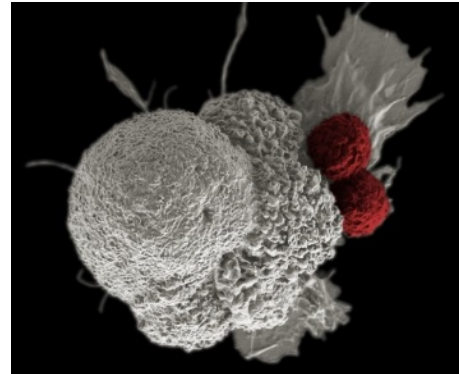
- 1.3.1. Illuminate the functions the gut microbiome and its metabolites have in modulating nutritional status and human health through their interaction with diet.

⁸ https://obamawhitehouse.archives.gov/sites/default/files/docs/national_action_plan_for_combating_antibiotic-resistant_bacteria.pdf

⁹ Donia et al. (2014). doi: 10.1016/j.cell.2014.08.032

- 1.3.2. Evaluate the effect of specific foods in the diet on the microbiome and its metabolites, and the impact on obesity, heart disease, and cancer. Identify whether metabolites produced serve as biomarkers for health and disease.
- 1.3.3. Investigate the effect of fermented foods on the human gut microbiome.

The human microbiome and cancer treatment. Cancer overwhelms a patient's immune system, which engages in fighting the disease. Checkpoint immunotherapy uses a drug to slow down the overactive immune system so that it can recover. However, not all cancer patients respond the same way to this drug; the patient's microbiome seems to be an important factor in treatment success. Specific gut microbiome members must be present for the drug to rejuvenate the immune system.¹⁰ Should the microbiome be sequenced alongside immunotherapy? Image: A pseudo-colored micrograph of an oral squamous cancer cell (white) being attacked by two T cells (red), part of the immune response. Specific gut bacteria are needed to work with the checkpoint drug in order to rejuvenate the patient's immune system to fight the cancer. Credit: NCI/NIH



2. Food Production

Global demands for food, feed, and fiber are expected to double in the next 35 years while the amount of arable land and water is expected to decrease, creating a huge challenge for agricultural productivity. One emerging approach to increase global crop productivity is through manipulating the plant microbiome; indeed, managing soil microbiomes for agricultural benefit has been occurring for centuries via processes like crop rotation. Additionally, scientists are beginning to exploit the animal and aquaculture microbiomes to enhance animal health and productivity for sustained livestock and fish production and to meet the global increase in demand of livestock and fish products.

2.1. Soil Health

- 2.1.1. Advance the knowledge of complex soil microbial communities in agricultural soils in general—and in and around roots of high-yielding, disease and drought resistant crops in particular—to accelerate the development and use of these crops.
- 2.1.2. Understand the interactions among soil microbes within the soil ecosystem and how these interactions contribute to healthy, productive, resilient, and sustainable systems.

¹⁰ Sivan et al. (2015). doi: 10.1126/science.aac4255

2.1.3. Understand the impacts of applied amendments to soils, especially manures, to elucidate practices that can reduce antimicrobial resistant bacteria and genes.

2.2. Crop Health

2.2.1. Explore individual microbes and their interactions in agriculturally important microbiomes in order to enhance food, feed, and fiber production.

2.2.2. Understand the signaling pathways between plant-associated microbes and between microbes and plants and how these communications contribute to plant yield, nutrient acquisition, and stress tolerance, thereby enhancing overall health and productivity.

Soil microbiome-mediated crop immunity to disease. Disease-suppressive soils provide microbiome-mediated protection of crop plants against infections by soil-borne pathogens and pests—plant pathogenic fungi, fungal-like oomycetes, bacteria, nematodes, and parasitic weeds. Specific suppression requires time for a pathogen reaction to develop, is pathogen specific, and establishes a pathogen memory in the soil microbiome; analogous to the adaptive immune response in animals.¹¹ Mechanistic understanding of the plant metabolites and pathogen effectors that trigger the adaptive immune response of soil microbiomes will provide a means to engineer better soils for agriculture.



2.3. Animal Health

2.3.1. Determine the mechanisms by which the microbiota supports the development and maintenance of the immune system.

2.3.2. Develop veterinary medical interventions to modulate the microbiomes of animals to enhance disease resistance and prevent or treat infectious diseases.

2.3.3. Develop countermeasures to reduce/mitigate exposure of non-target free ranging species to antibiotics intended for agriculture.

2.3.4. Investigate the microbial ecology of animals to decipher the mechanisms that promote antimicrobial resistance.

2.3.5. Develop alternatives to antimicrobial drugs to reduce the use of medically important antimicrobial drugs.

2.3.6. Investigate the synergistic use of prebiotics and probiotics to enhance digestibility and thereby animal production.

2.4. Food Safety

¹¹ Raaijmakers and Mazzola (2016). doi: 10.1126/science.aaf3252

- 2.4.1. Investigate food microbiomes for foodborne pathogen detection and authentication, and to potentially use metagenomics approaches in routine regulatory testing of foods.
- 2.4.2. Survey the microbiome of the built environment and the farm environment, which impact the farm to fork continuum.
- 2.4.3. Evaluate the safety of veterinary antimicrobial drug residues and pesticides in food and harmonize guidelines used by national and international regulatory agencies to assess the effects of animal drug residues in animal-derived foods as part of the risk assessment for humans consuming food containing antimicrobial drug residues.
- 2.4.4. Investigate the effects of contaminants such as arsenic, lead and mercury, and organic substances such as low levels of pesticides or endocrine disrupting compounds in food, water, and incidentally ingested soils or dusts on the gut microbiome and its metabolites, and the subsequent impact on human health.
- 2.4.5. Evaluate the effect of pre- and pro-biotics on microbial human pathogens such as *Salmonella*.
- 2.4.6. Investigate the impact of the plant microbiome on pathogenic bacteria such as *Salmonella* on food crops such as lettuce and tomato. Can normal microflora prevent colonization by pathogenic bacteria?

Poultry microbiome and food safety. *Salmonella* affects more than 1.4 million people in the United States each year, resulting in about 15,000 hospitalizations and 400 deaths. Researchers are studying the development of the chick microbiome from hatch to 28 days, including the role of prebiotics and vaccination on the persistence of *Salmonella*. These studies found that both vaccination and prebiotic use (i.e., microbial nutrients) with the chick diet are beneficial in reducing the persistence of *Salmonella* in the challenged birds.¹² Similar approaches with other poultry and livestock may help prevent other food-borne diseases.



3. Energy

Understanding microbial communities and their interactions with the environment has profound implications for energy production and utilization as well as for creating and maintaining a healthy environment. Microbiome research will play a key role in developing high-yielding, sustainable, and domestic sources of feedstock for renewable energy and bioproducts. Investigation of microbiomes in a variety of environments – from thawing permafrosts to deep

¹² Ballou et al. (2016). doi: 10.3389/fvets.2016.00002

ocean methane seeps – will provide insight into the role microbes play in nanoscale biogeochemistry, ecosystem level carbon and nitrogen cycling, and global earth system processes. Studies of the composition and structure of these microbial communities along with their physiological processes and interactions allow for a better understanding of the characteristics that make up ecosystems with functional, “healthy” microbiomes.

3.1. Waste Conversion and Utilization

3.1.1. Enable optimization and scale up of processes that utilize waste materials to generate high-value products by exploiting the ability of bacterial consortia to convert wastes or CO₂ into high-value chemical products or electricity.

3.2. Sustainable Bioenergy Crop Production

3.2.1. Accelerate development of sustainable bioenergy feedstocks that are highly productive on marginal lands by elucidating how plant-associated microbiomes contribute to biomass yield, nutrient acquisition, stress tolerance, and resilience.



Tree microbiomes and energy. Many sources of energy are being explored for future use. The soil microbiomes of the roots of the bioenergy feedstock plant *Populus* (cottonwood) are being studied to understand the molecular mechanisms regulating this tree-microbiome association. This research revealed the presence of a genetic “symbiosis toolkit” among mycorrhizal fungi, containing mycorrhizal-induced genes that contribute to tree development and immunity and a reduced complement of plant cell wall-degrading enzymes.¹³ This knowledge may lead the way to strategies for sustainable production of biomass feedstocks for bioenergy.

3.3. Production of Renewable Resources

3.3.1. Discover degradative enzymes isolated from environmental microbiomes that are useful for conversion of natural materials into renewable sources of biofuels and bioproduct components.

3.3.2. Manipulate natural and synthetic microbial communities for synthesis of specific metabolic compounds in order to produce biofuels and bioproducts.

3.3.3. Manipulate natural and synthetic microbial communities to directly produce electricity.

3.4. Fossil Fuels

3.4.1. Explore microbial processes in oil and gas wastewaters, coal seams, and crude oils to increase recovery of energy resources.

¹³ Kohler et al. (2015). doi: 10.1038/ng.3223

- 3.4.2. Harness microbial community abilities to mitigate contaminants from energy development

4. Ecosystem Services

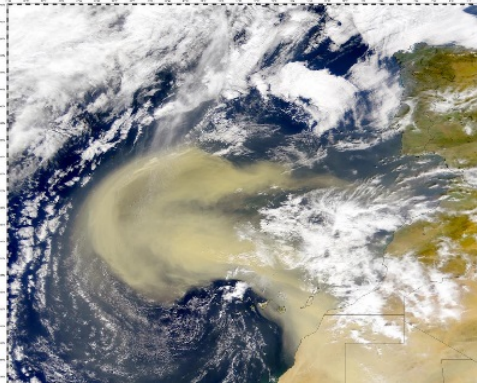
Ecosystem services are the contributions that a biological community and its habitat provide to the physical and mental well-being of the human population and directly impact the national economy. For example, commercial and recreational fishing activities generate \$208 billion in U.S. sales and support 1.6 million jobs.¹⁴ Microbes can be transported across oceans and continents via desert dust events and have the potential to affect human health (e.g., asthma, allergies, infectious disease) and agriculture (e.g., plant and animal pathogens). Microbial communities have critical roles in nanoscale biogeochemistry, ecosystem-level carbon and nitrogen cycling, and global climate processes. Additionally, knowing the natural background aerosol microbiome and normal soil microbiomes is critical to detecting the intentional release of select agents.

4.1. Wildlife Health and Conservation & Natural Resource Management

- 4.1.1. Enable development of practical methods for wildlife disease diagnosis and mitigation of wildlife losses, a critical component of effective wildlife management.
- 4.1.2. Allow effective management and conservation of coral ecosystems by characterizing associated microbiomes, providing baseline information against which their sensitivity to events like oil spills, mud plumes, or climate can be assessed.
- 4.1.3. Investigate the basic biology of the microbiomes of invasive species in order to facilitate the development of molecular monitoring tools, determine potential for biological control, and characterize effects of invasive species on ecosystem function, thus restoring a healthy habitat.
- 4.1.4. Translate microbiome science to impacts on ecosystem services, such as fisheries and aquaculture.

¹⁴ <https://www.fisheries.noaa.gov/feature-story/fisheries-economics-united-states-2015>

Atmospheric microbiome and microbial movement. The atmospheric microbiome is at the intersection of



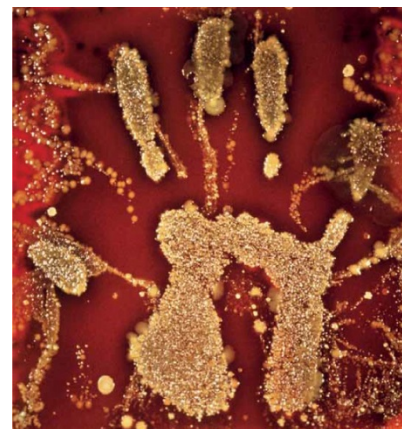
the biosphere, climate, and health. Biological aerosols influence climate and the hydrological cycle by nucleating clouds, ice crystals, and precipitation.¹⁵ Winds aerosolize several billion tons of desert-derived dust each year, including concentrated seasonal pulses from Africa and Asia. These transoceanic and transcontinental dust events inject microbes and pollen into the atmosphere and could have a role in transporting pathogens or expanding the biogeographical range of some microbes. Such dispersal may have human-health effects, impacts on agriculture, and the need to

distinguish natural background aerosols from intentional bioterror threats.

4.2. “Built” Environments

- 4.2.1. Determine the extent and makeup of the microbiomes within buildings, particularly hospitals and day care centers, and determine which microbes remain active and/or infectious after shedding, in order to enhance public safety in these environments.
- 4.2.2. Evaluate where microbes might accumulate in buildings to facilitate development of new architectural or engineering approaches to designs that minimize or eliminate microbial contamination, thus providing a new approach to improve public health.
- 4.2.3. Understand impact of microbial communities on degradation of anthropogenic products or structures (e.g., corrosion).

Forensics using the human microbiome. Our microbiomes can be used as forensic tools. The microbes we shed and that accumulate in our clothes and what we touch are a potential means to associate people with evidence and environments.¹⁶ The necrobiome — the microbiome found on or around decomposing remains — can be used as an indicator of time-since-death in the investigation of these remains. Even soil microbiomes from different parts of the country or the world can be used to link a victim, suspect, or evidence to a particular environment.



¹⁵ Fröhlich-Nowoisky et al. (2016). doi: 10.1016/j.atmosres.2016.07.018

¹⁶ Lax et al. (2015). doi: 10.1186/s40168-015-0082-9

4.3. Chemical, Metal, Water, and Carbon Cycles

- 4.3.1. Develop genetic tools and predictive models of metabolic and regulatory processes for key microbes to understand microbial community roles in environmental processes such as carbon cycling.
- 4.3.2. Investigate biogeochemical processes mediated by microbial communities in order to better understand their roles in the fate and transport of metals, contaminants, and nutrients in subsurface environments.
- 4.3.3. Understand the role of the aerosol microbiome in seeding of clouds and water cycling.

4.4. Bioremediation and Phytoremediation of Contaminated Areas

- 4.4.1. Apply focused metagenomic/microbiome analysis tools to further explore the roles of microbial communities in the degradation and mineralization of pollutants to optimize these processes.
- 4.4.2. Investigate the key microbiome assemblages and processes that can be manipulated to enhance the role of the plant microbiome in growth of plants in contaminated soils.
- 4.4.3. Investigate and elucidate the key members of wastewater treatment microbiomes to enhance and improve wastewater treatment.

Oceanic microbiome and ecosystem services. Each drop of ocean water contains one million bacteria and



10 million viruses in addition to microscopic plankton. This marine microbiome contributes to half the oxygen we breathe, supports oceanic food webs that ultimately produce the fish and shellfish we eat, removes carbon from the atmosphere, and cleans up many pollutants. International efforts, such as Ocean Sampling Day,¹⁷ are part of efforts to understand the vast reservoirs of genetic, enzymatic, and biogeochemical capabilities that underlie this microbiome and how to best manage it to maintain a healthy ocean and planet.

¹⁷ Kopf et al. (2015) doi: 10.1186/s13742-015-0066-5

Conclusion

Planet Earth is a microbial world. Microorganisms contribute to all key essential ecosystem processes, including the health and productivity of soils, plants, animals, and humans. Recognition of the critical role of microorganisms in all aspects of life has grown rapidly due to recent technological advances that have revealed previously hidden connections and complexities. Although appreciation for microbiome function has deepened, controlling mechanisms are not yet well understood. Collaborative research, new technology, and workforce development are key to developing predictive understanding of microbiome function. Expected outcomes include resolution of problems in pressing areas such as antimicrobial resistance, food production and safety, chronic disease, and conservation of ecological resources. Microbial communities do not stop at borders or boundaries but instead act as links between organisms and ecosystems. Likewise, this Federal Strategic Plan promotes interagency coordination and is intended to maximize concrete outcomes derived from research investment. By leveraging the foci of the agencies involved, the United States will be positioned to take advantage of the transformative opportunities of microbiome science.

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*former affiliation

Appendix II. Summary of Federal Agency Contributions to the Interagency Microbiome Strategic Plan Research Objectives, Fiscal Years 2018–2022

This table summarizes each agency’s plan to support research in each of the Microbiome Strategic Research Objectives: (1) Promote multi-agency interdisciplinary collaborations, public-private partnerships, and virtual centers for innovation for microbiome research; (2) Develop (i) key standards and reference materials, (ii) new methods and tools, and (iii) enhance open data; (3) Build a workforce to bridge experimental and computational biology. A ‘+’ in each box indicates that the agency (listed in the same order as in Table 2) contributes to that Objective.

	Interagency Microbiome Strategic Plan Research Objectives				
	Promote interdisciplinary collaboration	Support key technology development			Support human resource development
		(i)	(ii)	(iii)	
USAID	+			+	+
NIST/DOC	+	+	+	+	
NOAA/DOC	+		+	+	+
DOD	+	+	+	+	+
SC/DOE	+		+	+	+
EPA	+	+	+	+	+
CDC/HHS	+	+	+	+	+
FDA/HHS	+	+	+	+	+
NIH/HHS	+	+	+	+	+
DHS	+	+	+		
NPS/DOI	+				
USGS/DOI	+	+	+	+	+
NIJ/FBI/DOJ	+		+	+	+
NASA	+	+	+	+	+
NSF	+	+	+	+	+
SI	+	+	+		+
ARS/USDA	+	+	+	+	+
FS/USDA	+	+	+	+	+
NIFA/USDA	+	+	+	+	+
NRCS/USDA	+	+	+	+	
VA		+	+	+	+

Appendix III. Current Microbiome Research Activities Supported by the Interagency Microbiome Strategic Plan Agencies

Agency for International Development (USAID)

USAID partners to end extreme poverty and promote resilient, democratic societies, in part through inclusive, sustainable, agriculture-led economic growth and improved global health and nutrition. USAID supports microbiome research aimed at improving crop productivity, maternal and infant nutrition, and human and animal health. This work includes studies of the gut microbiomes of infants and toddlers as they respond to improved diets, the relationship between the gut microbiome and environmental enteropathy in households with peridomestic animals, mapping of the global virome, and mapping of the African soil microbiome. Additionally, USAID has supported the proof of concept work for the Global Virome Project (an effort to map all viral threats to human and animal health) as well as steps to build a partnership to scale up the project globally. USAID also supports human and institutional capacity development.

Department of Commerce (DOC)/ National Institute of Standards and Technology (NIST)

NIST has recently implemented a new strategic program in microbial metrology. A major driver of this new strategic plan is the development of novel microbiome measurement technologies, standards, and reference materials. The biosciences programs at NIST have historically focused on human clinical applications such as diagnostics and therapeutics. However, with regard to microbiome measurements, we recognize that any novel measurements or standards that are developed can be applied across many microbial ecosystems, such as agriculture (phytobiomes), food safety, built environment, and, of course, the human microbiome. NIST is very stakeholder driven and works closely with industry, government, and academic partners to deliver state-of-the-art measurement science.

Department of Commerce (DOC)/ National Oceanic and Atmospheric Administration (NOAA)

NOAA microbiome studies include metagenomic and metatranscriptomic work to support ecosystem understanding and fisheries assessment; coral holobiont studies to enhance protection and recovery from thermal, acidification, nutrient, and disease stress; eDNA research to garner intelligence on higher trophic levels via ocean microbiome assessment; and development of in-situ and mobile technologies for microbiome assessment.

Department of Defense (DOD)

DOD microbiome research seeks to enhance human performance through improved nutritional status and mitigation of psychological and physiological stressor-related effects; to produce energy and materials; and to minimize deleterious effects on platforms. Biomedical microbiome research is aimed at understanding host-microbiome bidirectional relationships in health and performance; shielding personnel from the effects of environmental, physical, and psychological

stress, wound healing, and exposure to toxic chemicals; and treating gastrointestinal distress and inflammation. This research is also exploring tools, models, and interventions to analyze and restore the microbiome to its pre-stress condition. Non-biomedical microbiome research includes the study of corrosive biofilms for corrosion mitigation or prevention, for assessing environmental impacts, and engineering of microbiomes for material synthesis or embedded sensing, and the development of electroactive biofilms for power generation.

Department of Energy (DOE)/ Office of Science (SC)

The DOE Office of Science, Office of Biological and Environmental Research (BER) supports a broad systems biology research portfolio focused on environmental and bioenergy relevant microbiome work. Knowledge of the processes of the plant root-soil-microbe interface can inform predictive control of interface components, thereby increasing understanding of the stability of soil carbon pools and plant productivity while reducing energy, nutrient, and water inputs needed for sustainable biomass production or regional ecosystem resilience. Specific focus areas include sustainable bioenergy production in natural and artificial microbiomes, environmental process understanding of carbon cycling and biological transformation of materials such as nutrients and contaminants in the environment, and the contribution of the microbiome to representation of primary carbon sink drivers in global earth system models.

Environmental Protection Agency (EPA)

Current research within the Office of Research of Development (ORD) is evaluating the potential use of microbiome signatures as indicators of nutrient enrichment as well as broader markers of ecosystem state, linked to nationwide mapping of the microbiome of rivers and streams as part of the National Aquatic Resource Survey. Deep sequencing of wastewater is also on-going to define both improved indicators of fecal contamination of ambient waters and novel targets to monitor water reuse systems.

Health and Human Services (HHS)/Centers for Disease Control and Prevention (CDC)

The mission of the CDC is to prevent infections and protect the health of the public. As part of these efforts, CDC supports and conducts studies to better understand the role of the microbiome as it impacts health, ranging from the human microbiome to the environmental microbiome. An important focus of CDC's microbiome work is on antibiotic resistance—a growing threat to public health and modern medicine. Examples of current extramural and intramural efforts to protect patients and slow antibiotic resistance, include 1) understanding how antimicrobial drugs disrupt a healthy microbiome and can lead to infection caused by both community and healthcare-associated pathogens; 2) developing and testing microbiome measures predictive of a patient's risk of disruption, risk of carriage (colonization), and risk of infection; and 3) research that might lead to the development of novel microbiome interventions

to prevent infection with and transmission of antimicrobial resistant pathogens, for example, through decolonization.

Health and Human Services (HHS)/ Food and Drug Administration (FDA)

The FDA is responsible for ensuring the safety, efficacy, and quality of foods, new human and veterinary drugs, biologics, medical devices, cosmetics, tobacco products, and many other consumer goods. Thus, the FDA has invested in numerous microbiome research projects related to food safety, safety and efficacy of drugs, and novel biologics (such as fecal transplants, live biotherapeutic products, and bacteriophage therapy), as well as changes induced by various therapeutics, cosmetics, and tobacco products. FDA scientists are also examining the role of the microbiome in antimicrobial resistance in both humans and animals as well as how antimicrobials and other chemicals can alter the microbiome of these species.

Health and Human Services (HHS)/ National Institutes of Health (NIH)

NIH is the largest U.S. biomedical research agency and is made up of 27 Institutes and Centers (ICs), 20 of which currently support human microbiome research through their extramural programs. The longest running program, the 10-year Common Fund's Human Microbiome Project, is designed as a community resource to catalyze this field and is producing reference microbial genome sequences and metagenomic sequences and other microbiome 'omic data, as well as microbial cultures, computational tools, clinical protocols, and methodologies for sampling and analyzing the microbiome in five major body regions, gut tract, skin, nasal cavity, oral cavity and urogenital tracts of men and women. As a community resource, the HMP is also releasing all data into public repositories. The ICs support microbiome-related research related to their missions, and this includes the role of the microbiome in causing many complex diseases (cancer, autoimmune diseases such as type 2 diabetes, rheumatoid arthritis, multiple sclerosis, and gut, lung, and heart diseases to name a very few) as well as approaches to harness the microbiome for treating disease or staving off disease. These include the development of microbiome-based interventions and devices. Animal model, human cohort, and *in silico* model studies are used to carry out this research.

Department of Homeland Security (DHS)

DHS is exploring the environmental microbiome in an attempt to better understand the microbial components present in the unique urban and rural environments across the country, primarily focused on aerosolized particles. This information will better inform biodefense and biosurveillance efforts and will enable DHS to implement systems and capabilities to better detect, identify, and characterize changes in the presence or abundance of the local microbiome that are due to intentional manipulation or release of biological agents.

Department of the Interior / United States Geological Survey (USGS) and National Park Service (NPS)

The Department of the Interior (DOI) protects and manages natural resources on 500 million acres of public lands and 1.7 billion acres on the Outer Continental Shelf (submerged marine lands). USGS microbiome research is a cross-cutting priority embedded within its mission to provide science about our Nation's water, energy, minerals, and other natural resources, ecosystem health, and the impacts of land-use resources. Key research areas include work to support clean water resources, optimizing bioremediation of contaminated environments; understanding how environmental factors such as geochemistry impact the health of humans; studying microbial processes that can enhance energy production; developing microbial-control based strategies for invasive species; mitigation of wildlife diseases; understanding climate effects on soil and permafrost; and aquatic ecosystem services in outer continental shelf environments like deep-sea corals and cold seeps. Extramural funding of microbiome research sometimes occurs via other DOI bureaus such as the U.S. National Park Service, U.S. Fish and Wildlife Service, and Bureau of Ocean Energy Management.

Department of Justice (DOJ)/National Institute of Justice (NIJ)/Federal Bureau of Investigation (FBI)

NIJ-funded microbiome research addresses challenges in forensic science. This includes research to determine if it is possible to derive information from the progression of microbial communities in human decomposition – to more accurately determine time since death for human remains; analyzing human skin microbiome to determine the stability and forensic value of the human microbiome; and understanding the variability of the terrestrial microbiome in trace soil samples recovered as forensic evidence; improving bioinformatic tools for the interpretation of microbiome data.

National Aeronautics and Space Administration (NASA)

NASA supports research in a wide variety of microbiome-related research areas including the probable first common ancestor; reconstructing microbiomes from early days on Earth, and characterizing microbiomes from extreme environments; genetic inventories of the microbiome in space assembly facilities and outbound space craft and instruments; technologies for assessing microbiomes in extreme environments and deep oceans; analyzing the microbiome of plants, and demonstrating the roles of microbial-plant systems in long-term life support systems. Finally, NASA's astronaut microbiome experiment has investigated the impact of space travel on both the human immune system and an individual's microbiome. In addition, DOI (USGS) is collaborating with NASA in several research areas including life in the ancient permafrost; microbial processes in a contaminated mine; and a transoceanic aerobiology biodiversity study to characterize microorganisms in Asian and African dust plumes reaching North America.

National Science Foundation (NSF)

The NSF supports research on the microbiome across the biological, physical, geological, and social sciences as well as engineering and education. The Biology Directorate funds projects on the role of the microbiome in ecological, evolutionary, and physiological processes, including the genomics of rice-microbiome interactions, a systems approach to the role of the microbiome in plant growth promotion, links between the skin microbiome and disease risk in amphibians, the moss microbiome in rapidly changing Alaskan ecosystems, the role of bacterial viruses in structuring animal microbiomes, and the rules that govern the assembly of the microbiomes of plant roots. The Engineering Directorate support includes research on microbiomes in human influenced environmental contexts: examples include the effects of ingestion of manufactured nanoparticles on the microbiome and pathogen resistance in rainbow trout, and the microbiomes aerosolized by shower units. The Geosciences Directorate, particularly through its Ocean Sciences Division, is a major funder of microbiome research on the role of microbiomes in the physiology, health and disease of corals. The Social, Behavioral & Economic Sciences Directorate provides support for the role of microbiomes in social contexts. In addition, tool development is supported in the Engineering directorate and in the Biology Directorate. The Computer & Information Science & Engineering Directorate supports efforts to analyze the data generated by research into microbiomes. Finally, the NSF mission to promote the training of the next generation of scientists and extend public understanding of science is carried out through the broader impacts of all microbiome related awards from the research directorates as well as education-focused projects funded by the Education & Human Resources Directorate.

Smithsonian Institution (SI)

The Smithsonian Institution has been characterizing and assessing interspecies interactions and functionality of microbiomes in environmental contexts in tropical and temperate terrestrial and marine ecosystems, and in species of conservation concern or special ecological contexts. This includes research programs on microbiomes of tropical insects, plants, and soils at the Smithsonian Tropical Research Institute; of coral reefs and in wild vultures at the National Museum of Natural History; in ship ballast water, marine and terrestrial ecosystems, and fungal symbionts at the Smithsonian Environmental Research Center; and in amphibian skin in relation to chytrid fungal infection, as biomarkers of carrion in diet analysis, in primate milk, and in intestinal tracts of bamboo-consuming mammals (with Duke University) at the Smithsonian Conservation Biology Institute and National Zoo. These programs are often collaborative with other institutions and depend upon internal and often external gift and grant funding. The Smithsonian Institution, as the nation's primary repository of classically and cryopreserved biological specimens, also offers retrospective views of microbiomes and serves as a site for retention of vouchers for future study. The massive public side of the Smithsonian also provides

an excellent resource for public engagement and education about microbiomes and their contributions to society.

Department of Agriculture (USDA)/ Agricultural Research Service (ARS)

USDA ARS conducts basic and applied microbiome research to enhance the productivity, health, nutrition, and safety of farming systems (e.g., soils, water supplies), crop plants, animals, and humans. USDA ARS research targets critical knowledge gaps that are key to solving the several major challenges facing agriculture today: i) to prolong the effectiveness of antimicrobial drugs for treating people and animals by developing effective antimicrobial resistance mitigation strategies, ii) to enhance crop and animal yields, health, nutrition, and tolerance to environmental extremes—heat, cold, drought, flooding—as well as disease and pests, iii) to understand and protect the soils, water sinks and sources, and atmosphere from pollution and degradation through innovation in agricultural production, and iv) to enhance the economic efficiency, productivity, and sustainability of US agriculture for future generations.

Department of Agriculture (USDA)/ Forest Service (FS)

USDA FS conducts microbiome research to support the agency's goal of sustaining the health, diversity and productivity of the Nation's forests and grasslands to meet the needs of present and future generations. This includes microbiome research related to tree and plant health, as well as research related to maintaining healthy wildlife populations in aquatic and terrestrial environments. At the ecosystem level, USDA FS conducts microbiome research related to ecosystem functions, including carbon sequestration and the maintenance of healthy water systems. USDA FS also supports the development of tools to help standardize the collection and analysis of microbiome data, with the goal of being able to better understand and predict how different management actions and climate may affect the ability of our nation's forest to continue to provide critical ecosystem services.

Department of Agriculture (USDA)/ National Institute of Food and Agriculture (NIFA)

USDA/NIFA supports microbiome research on microbial communities associated with plants, animals, humans, soil, water, and air. This microbiome research includes work on 1) how agricultural production systems can alter plant and animal microbiomes, 2) how microbial communities affect animal protection and production, and crop protection and production, including how microbiomes influence drought, heat and salt tolerance in plants, 3) signaling between the microbiome and host, including host genome X microbiome interaction, 4) factors influencing development, spread, and control of anti-microbial resistance, 5) microbial communities involved in human food safety, nutrition, and health, 6) microbial communities involved in nutrient cycling in soils, and 7) the effect of microbial communities on greenhouse gases. NIFA supports development of tools and technologies that enable microbiome research

and training of students (undergraduate, graduate and postdoctoral) in areas needed to advance microbiome research.

Department of Agriculture (USDA)/ National Resources Conservation Service (NRCS)

The Natural Resources Conservation Service leverages microbiome research related to improving the health of our nation's soil, water, air, plant, and animal resources to then incorporate findings that are ready for application in the voluntary, incentive-based conservation planning process. Although the NRCS is not a research-based agency, the NRCS collaborates with public and private partners to address critical resource concerns. Specific to the microbiome effort, the NRCS leverages through partnerships efforts to address: 1) how land use management impacts the soil microbiome, 2) importance of soil health principles on shaping the soil microbiome and associated functions, 3) relationships between land use decisions and arbuscular mycorrhizal populations, 4) soil microbiome or biological components relevant to the microbiome as part of a soil health assessment, 5) how the soil microbiome helps build resiliency and resistance into the landscape against disease pressures and environmental disturbances. The NRCS has the unique ability to translate and then apply these research/scientific discoveries to on-the-ground conservation planning efforts.

Department of Veteran Affairs (VA)

The Department of Veterans Affairs Veterans Health Administration's Office of Research and Development (VHA ORD) supports microbiome research related to improving the health and care of our nation's Veterans. VHA ORD-supported microbiome research spans a spectrum of diseases and medical conditions including investigating the role of the microbiome in alcoholic liver disease and cirrhosis, characterizing components of the nasal microbiome that could prevent transmission of methicillin-resistant *Staphylococcus aureus* (MRSA) in VA hospitals, and determining the role of the microbiome in preventing or reducing infection at the implant sites of Veterans receiving osseointegrated prosthetic lower limb implants. In addition, the VHA ORD Cooperative Studies Program is sponsoring a pivotal clinical trial, CSP #2004- Microbiota vs. Antimicrobial Therapy for recurrent *Clostridium difficile* at Home (MATCH), beginning in mid-2017. The primary study goal is to assess the efficacy of fecal microbiota transplantation (FMT) for the prevention of subsequent recurrent *C. difficile* infection (CDI) when administered after successful treatment of recurrent CDI. FMT in this trial will be compared to standard antimicrobial therapy in a total of 390 participants. The majority of VHA ORD supported intramural microbiome research is investigator initiated and based at VA medical centers across the country. The breadth and scope of microbiome research has increased steadily over the last decade as more advance tools in next-generation sequencing and bioinformatics have become more widely available to VA researchers and academic affiliates. The magnitude of microbiome research within the VA is anticipated to continue to increase in the coming years as more VA

investigators gain expertise in molecular and genomic science methods and bioinformatics data analysis techniques through their ongoing training and research activities.

Appendix IV. Widely Used Microbiome and Related Databases

Database	Website	Support
Coral Microbiome Portal	https://vamps.mbl.edu/portals/coral_microbe/coral.php	NASA, NSF, Sloan Foundation
GenBank	https://www.ncbi.nlm.nih.gov/genbank	NIH
Genomes Online Database	https://gold.jgi.doe.gov/index	DOE
Germplasm Resources Information Network: National Microbial Germplasm Program	https://www.ars-grin.gov/nmg/	USDA
Green Genes	http://greengenes.lbl.gov/	NSF
HMP Data Analysis Coordination Center	www.hmpdacc.org	NIH
Integrated Microbial Genomes and Microbiomes	https://img.jgi.doe.gov/	DOE
Joint Genome Institute	http://jgi.doe.gov	DOE
KBase	http://kbase.us	DOE
Mass Spectral Library and Related Tools	http://chemdata.nist.gov	NIST
Metabolomics Workbench	http://www.metabolomicsworkbench.org	NIH
Metagenomics-RAST	https://metagenomics.anl.gov	NIH, NSF
Phytoplasma Database	https://plantpathology.ba.ars.usda.gov/cgi-bin/resource/phytoclass.cgi	USDA
Ribosomal Database Project	https://rdp.cme.msu.edu/	DOE, NIH

Appendix V. Meetings, Workshops and Whitepapers Used to Gain Scientific Insight and Stakeholder Input

A. Meetings and Workshops Organized by MIWG Members and Used to Gain Scientific Insight and Stakeholder Input

- *AgMicrobiomes*. Mar. 2016, Asilomar, CA. <http://www.agmicrobiomes.org/2016-meeting/>
- *Cellular & Molecular Fungal Biology Gordon Research Conference*, Jun. 19-24, 2016, Holderness School, Holderness, NH. <https://www.grc.org/programs.aspx?id=11335>
- *DOD Tri-Service Microbiome Consortium Meeting*. May 10-11, 2017, Rockville, MD. http://mrmc.amedd.army.mil/index.cfm?pageid=media_resources.articles.tri-service_microbiome_consortium
- *DOD U.S. Air Force Academy DOD Microbiome Symposium*. Apr. 6-7, 2017. URL not available.
- *DOD U.S. Air Force Research Laboratory Workshop on Microbiome for Health and Human Performance*. Apr. 11-12, 2016. URL not available.
- *DOD U.S. Army Center for Environmental Health Research, State of the Science Workshop to Discuss Environmental Health and Protection: "Personalized Tools to Support Potential and Actual Health Hazards in the Megacity Operational Environment."* Oct. 27-28, 2015, Ft. Detrick, MD. http://mrmc.amedd.army.mil/index.cfm?pageid=media_resources.articles.USACEHR_hosts_workshop
- *DOD U.S. Army Natick Soldier Research, Development & Engineering Center Workshop on DOD Microbiome R&D*. Nov. 16-17, 2015. URL not available.
- *DOD U.S. Army Public Health Center & Army Center for Environmental Health Research Workshop on Microbiome Risk Assessment*. Apr. 20, 2016, Falls Church, VA. URL not available.
- *DOE Joint Genome Institute (JGI) User Meeting, Genomics of Energy & Environment Meeting*, Mar. 21–24, 2016, Walnut Creek, CA. <https://usermeeting.jgi.doe.gov/past-meetings/2016-agenda/>
- *FDA/CBER and NIH/DMID Public Workshop on Bacteriophage Therapy*. Jul. 10-11, 2017, Rockville, MD. <https://www.fda.gov/downloads/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/UCM579441.pdf>
- *FDA/CFSAN Linking the Microbiome to Health, Safety, and Regulation*. Sep. 29-30 2015, College Park, MD. URL not available.
- *International Congress on Molecular Plant-Microbe Interactions*. Jul. 17-21, 2016. Portland, OR. <https://www.ismpmi.org/Congress/2016/Pages/default.aspx>
- *NAS Workshop Microbiomes of the Built Environment*, Co-sponsored by the EPA and the Sloan Foundation, NIEHS/NIH, and NASA. Dec. 1, 2016, Washington, DC. <http://nas-sites.org/builtmicrobiome/meeting-4/>

- NAS Workshop *Microbiome and Human Health*, Co-sponsored by EPA and NIEHS/NIH. Jan. 29-30, 2017, Washington, DC. <http://www8.nationalacademies.org/cp/projectview.aspx?key=49795>
- NCI/NIH *Modulation of Anti-tumor Immune Responses by Diet- and Microbiome-derived Metabolites*. Aug. 31-Sep. 1, 2016, Bethesda, MD. <https://academic.oup.com/jnci/article-abstract/109/6/djx040/3806188>
- NCI/NIH *Next Steps in Studying the Human Microbiome and Health in Prospective Studies*. May 16-17, 2017, Bethesda, MD. <https://epi.grants.cancer.gov/events/human-microbiome/>
- NHLBI/NIH *The Role of Microbiota in Blood Pressure Regulation*. Jun. 10, 2016, Bethesda, MD. <https://www.nhlbi.nih.gov/events/2016/role-microbiota-blood-pressure-regulation-executive-summary>
- NIAID/NIH *Workshop on Best Practices in Studies of Diet and the Intestinal Microbiome*. Jun. 13-14, 2017, Bethesda, MD. <https://www.niddk.nih.gov/news/events-calendar/Pages/workshop-best-practices-studies-diet-intestinal-microbiome.aspx>
- NIH-wide Obesity Research Taskforce *The Gastrointestinal Microbiome and Energy Balance: Obesity Development and Treatment—Beyond Metagenomic Associations*. Dec. 14-15, 2015, Bethesda, MD. URL not available.
- NIH-wide *The Human Microbiome: Emerging Themes at the Horizon of the 21st Century*. Aug. 16-18, 2017, Bethesda, MD. <https://commonfund.nih.gov/hmp/meetings/emerging>
- NIST-NIH *Standards for Microbiome Measurements*. Aug. 9-10, 2016, Gaithersburg, MD. URL not available.
- NIST-Phytobiomes Alliance Workshop *Standards for Phytobiomes Measurement*. Aug. 12, 2016, Gaithersburg, MD. <https://www.eventbrite.com/e/nist-phytobiomes-alliance-workshop-on-standards-for-phytobiomes-measurement-tickets-25822009325>
- NOAA *Marine Microbes Workshop*. Nov. 29-30, 2011, Charleston, SC. <http://oceanexplorer.noaa.gov/about/what-we-do/news-room/marine-microbes-workshop-report.pdf>
- Office of AIDS Research/NIH *2nd International Workshop on the Microbiome in HIV Pathogenesis, Prevention, and Treatment*. Nov. 17-18, 2016, Bethesda, MD. <http://www.virology-education.com/event/previous/international-workshop-microbiome-hiv-pathogenesis-prevention-treatment-2016/>
- *Phytobiomes 2015: Designing a New Paradigm for Crop Improvement*. Jun. 30-Jul. 2, 2015, Washington, DC. <http://www.phytobiomes.org/activities/pages/phytobiomes-2015.aspx>
- Society for Industrial Microbiology and Biotechnology (SIMB) *Annual Meeting*. Jul. 24-28, 2016, New Orleans, LA. <https://sim.confex.com/sim/2016/webprogram/meeting.html>

B. Microbiome-related Meetings and Workshops Organized Outside of the MIWG and Used to Gain Scientific Insight

- *2nd International Symposium on Alternatives to Antibiotics: Challenges and Solutions in Animal Production*, World Organization for Animal Health (OIE). Dec. 12-15, 2016, Paris, France. <http://www.ars.usda.gov/alternativestoantibiotics/Symposium2016/index.html>
- *6th ASM Conference on Beneficial Microbes*, American Society for Microbiology. Sep. 9-12, 2016, Seattle, WA. <https://www.asm.org/index.php/asm-conferences-resources/past-conferences/item/6195-6th-asm-conference-on-beneficial-microbes-2016>
- *5th International Human Microbiome Congress*. Mar. 31-Apr. 2, 2015, Luxembourg. URL not available.
- *OECD Workshop on the Microbiome, Diet, and Health: Assessing Gaps in Science and Innovation*. May 30-21, 2016, Brussels. <https://www.innovationpolicyplatform.org/project-better-food-better-health-oecd-bnct/workshop-microbiome-diet-and-health-assessing-gaps>
- *6th International Human Microbiome Congress*. Nov. 9-11, 2016, Houston, TX. <http://ihmc2016.org>
- *International Coral Reef Symposium*. Jun. 19-24, 2016, Honolulu, HI. <https://sgmeet.com/icrs2016/>
- *Keystone Symposia: Phytobiomes: From Microbes to Plant Ecosystems*. Nov. 8-12, 2016, Santa Fe, NM. <http://www.keystonesymposia.org/16S2>
- *14th Annual Symposium in Plant Biology: Phytobiomes: The Social Networks of Plants and Microbes*. Oct. 1, 2016. Amherst, MA. URL not available.
- *2015 Applied and Environmental Microbiology Gordon Research Conference*, Jul. 12-17, 2015, Mount Holyoke College, South Hadley, MA. <https://www.grc.org/programs.aspx?id=10899>

C. MIWG Whitepapers and NSTC Reports

- *Report of the Fast-Track Action Committee on Mapping the Microbiome*, Life Science Subcommittee, NSTC, 2016. https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/NSTC/ftac-mm_report_final_112015_0.pdf
- *Phytobiomes: A Roadmap for Research and Translation*, American Phytopathological Society, 2016, <http://www.phytobiomes.org/Roadmap/Documents/PhytobiomesRoadmap.pdf>
- *National Action Plan for Combating Antibiotic-Resistant Bacteria*, NSTC, 2015, https://obamawhitehouse.archives.gov/sites/default/files/docs/national_action_plan_for_combating_antibiotic-resistant_bacteria.pdf
- *USDA Antimicrobial Resistance Action Plan*, USDA, 2014, <http://www.usda.gov/documents/usda-antimicrobial-resistance-action-plan.pdf>
- *National Plant Genome Initiative Five-Year Plan 2014-2018*, Life Sciences Subcommittee, NSTC, https://obamawhitehouse.archives.gov/sites/default/files/microsites/ostp/NSTC/npgi_five-year_plan_5-2014.pdf

D. Interagency Microbiome Strategic Plan-relevant Agency, Interagency and International Working Groups

- NIH/FDA Joint Agency Microbiome (JAM) Working Group, formed in 2016. JAM is an interagency forum for discussing human microbiome research advances with potential for products or interventions.
- NIAID special interest group. The Microbiome SEAL (Scientific Exploration and Leadership) Team, formed in 2014.
- NHLBI special interest group. Develop strategic plan for microbiome research on heart, lung and blood diseases/disorders. Forming in 2017.
- NOAA Marine Microbes Working Group. The aim of the group is to exchange information, inventory, coordinate, and leverage NOAA capabilities and to identify gaps. Ultimately, the group, in collaboration with external experts, will develop a NOAA-wide vision for marine microbe research priorities and strategies.
- US-EC Task Force on Biotechnology Research. The US-EU Taskforce on Biotechnology Research was established in 1990 to promote information exchange and coordination between biotechnology research programs funded by the European Commission and Government of the United States. The TF was revived in 2016 with the US signing onto the EC's Horizon 2020 (<https://www.neweurope.eu/article/sky-not-limit-us-eu-sign-implementing-arrangement-horizon-2020/>). One of four pillars of Horizon 2020 includes the microbiome (the other three are precision agriculture, forestry, and plant health). An international Bioeconomy Forum will coordinate these research areas.
- DOD Tri-Service Microbiome Consortium (TSMC), chartered in Dec 2016, established to enhance collaboration, coordination, and communication of microbiome research among DoD organizations.