REPORT OF THE FAST TRACK ACTION COMMITTEE ON MAPPING THE MICROBIOME

PRODUCT OF THE

Life Sciences Subcommittee

OF THE NATIONAL SCIENCE AND TECHNOLOGY COUNCIL

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About the Fast Track Action Committee on Mapping the Microbiome

The Fast Track Action Committee on Mapping the Microbiome (FTAC-MM) was formed in February 2015. The purpose of the FTAC-MM was to identify areas of current Federal investment, research needs, and resource gaps for the development of an integrated Federal plan for microbiome research, and to identify priority areas for Federal agency coordination and cooperation on achieving a predictive understanding of microbiomes and their functions.

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COMMITTEE ON SCIENCE
SUBCOMMITTEE ON LIFE SCIENCES
FAST TRACK ACTION COMMITTEE ON MAPPING THE MICROBIOME

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Executive Summary

New technologies enabling rapid and inexpensive gene sequencing have enabled scientists from all fields and disciplines to explore the microbial world. Scientists are finding communities of microorganisms performing essential ecosystem services even in places previously thought to be sterile, and new science is uncovering an unprecedented potential for the application of microorganisms to human, plant, animal, and environmental health; renewable energy production; water treatment; and manufacturing. The study of these communities of microorganisms, or microbiomes, has left researchers with even more questions, such as "*What is a healthy microbiome?*" "*What makes a microbiome resilient to perturbations?*" "*How can we harness the huge potential of these microbial communities?*"

With these questions in mind, the Life Sciences Subcommittee (LSSC) of the National Science and Technology Council (NSTC) chartered the Fast Track Action Committee on Mapping the Microbiome (FTAC-MM) to survey Federally-supported microbiome research and make recommendations for Federal investments that would target cross-cutting challenges and areas of need. Fourteen Federal departments and independent agencies participated in the FTAC-MM's survey, answering sweeping questions about their investments over the previous three fiscal years (FY12-14) and where the most important research gaps for advancing this field exist.

The survey found a total Federal investment in microbiome research of approximately $922 million disbursed to 2,784 projects over the course of three fiscal years, FY12 through FY14. This corresponds to an average of about $307 million each year, and support of microbiome research has increased each year since FY12. Federal microbiome research investments are dominated by the National Institutes of Health, which funded 59 percent of the investments in microbiome research from FY12-14. Research investments in the human microbiome were larger than any other category, at 37 percent of the total from FY12-14. The FTAC found less activity than expected in agricultural microbiome research, particularly in food-based studies, viral microbiome research, and applied microbiome research and tool development, compared to basic microbiome research.

Recommendation

The FTAC-MM identified three specific areas of need based on the results of its survey. First, the committee found that food-related microbiome research, representing just 4 percent of the total investment, is underinvested relative to its likely impact on increased food production for a growing population. Viral communities, which have been shown to play important roles in plant and animal health, currently represent only 3 percent of the total investment. Lastly, basic research funding has steadily increased at the expense of the fractions of the total focused on the translational research and tool development that are necessary for bringing the success of microbial discoveries to bear on pressing global challenges.

In addition to highlighting these three areas of need, the FTAC-MM makes three policy recommendations based on the results of its survey. First, microbiome research would greatly benefit from virtual Centers of Microbiome Innovation that would enable interdisciplinary, interagency collaborations among a diversity of scientists. Such cross-cutting research programs would be more likely than traditional, siloed research to elucidate the fundamental principles governing microbiomes, thereby accelerating progress in all fields. Second, the Federal Government should support the development of three key tools and technologies: protocol standards and reference materials to allow comparison of experiments; a flexible, open-access database for broad, interdisciplinary analysis of microbiomes; and widely available high-throughput tools for measuring microbiome data. Third, the Federal Government should support education, training, and recruitment of experts in the fields of bioinformatics and modeling who can interpret the existing, vast microbiome datasets already gathered to pose new hypotheses.

Introduction

The vast potential of microbiome research to improve plant, animal, and human health, to mitigate climate change, and to promote industrial innovation, coupled with its interdisciplinary underpinnings, demand an interagency approach for assessment and facilitation. The Fast Track Action Committee on Mapping the Microbiome (FTAC-MM) was chartered in February 2015 under the Life Sciences Subcommittee (LSSC) of the National Science and Technology Council (NSTC) to describe the current portfolio of Federally-supported microbiome research, to identify and prioritize cross-cutting challenges and areas of need with regard to enabling a predictive understanding of microbiomes, and to outline a coordinated plan for future Federal Investment (Appendix 1).

Advanced DNA sequencing technologies have illuminated unanticipated complexity and diversity in vast networks of microorganisms. These networks connect and underpin all life on Earth and are found performing essential environmental processes even in places long thought to be sterile. The study of these communities of microorganisms, or microbiomes, is poised for breakthrough discoveries, with a unique opportunity for major scientific advancement. Modern sequencing and computational biology have illuminated the communities of microorganisms telling us what is there, but what remains are the essential questions about how microbiomes function as communities, how they interact with the environments and hosts they inhabit, and how they can be leveraged to improve health and ecosystem services. These questions come from all fields of life sciences, arising from the study of microbiomes in humans and in homes and workplaces, in domesticated animals and plants in agriculture, and in natural environments as diverse as oceans, soils, and permafrost. Thirteen major Federal agencies and the Smithsonian Institution perform or support microbiome research (Appendix 2).

The Microbiome and Ecosystem Services

The potential of microbiome research is enormous – it could create revolutionary technologies such as:

- a probiotic to treat health conditions, such as obesity, heart disease, or autoimmune disorders;
- "living" buildings that promote healthy immune system development or reduce the spread of viruses and allergens;
- improved agricultural practices based on understanding relationships between plants, their associated microbiomes, and soil systems to improve crop production;
- growth-promoting animal feed that eliminates the need for antibiotics;
- bacteria that reduce methane emissions from cows;
- high-efficiency biological systems for the conversion of plant biomass to biofuels and bioproducts;
- bioreactors that convert waste to energy or new chemicals;
- tracking tools for invasive species; and
- better predictive models of ecosystem-scale processes mediated by microbiomes that could serve as sentinels for disease or ecosystems under stress.

These functions are commonly known as ecosystems services and the role of microbiomes as providers of these services is now being recognized. In fact, significant medical, environmental, agricultural, and industrial contributions from microbiome research are already being realized. For example, half a million people are infected in the United States each year with the dangerous, diarrhea-causing *C. difficile* pathogen, but in a clinical trial, extremely ill patients with recurrent infections were successfully treated with transplants of a donor's healthy gut microbiome. In the next five years, Federal agencies plan to explore the impacts of the microbiome on:

- vaccine efficacy and the immune system;
- disease transmission;
- exposure to toxic chemicals;
- marine mammal health and coral reef preservation;
- bat and pollinator decline;
- livestock, plant, and soil health;
- behavior and cognitive function;
- malnutrition and obesity prevention; and
- the many other ecosystem services that the microbiome can provide.

Biogeochemists, toxicologists, health care workers, astronauts, engineers, and agronomists all agree that staggering advancements in molecular techniques make this the perfect time to invest in dedicated microbiome research. Although the researchers observing microbiomes are diverse, their research questions are remarkably similar, including such fundamental questions as: What is a healthy microbiome? What are the key genes, proteins, and metabolites active in the microbiome, and what are their functions? How does a community assemble? How can we predict what effect a disturbance will have? How do the members of a microbiome sense and respond to each other and to their environment? Due to their 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, insufficient capacity to store and analyze sequence data, and minimal 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 community robustness and resilience which are necessary for continuous delivery of essential ecosystem services. This knowledge will lead directly to system designs and interventions that influence health, food systems, manufacturing, renewable energy production, and the environment. This knowledge will lead directly to system designs and interventions that influence health, food systems, manufacturing, renewable energy production, and the environment.

Methods

The FTAC-MM issued a data call in April 2015 that consisted of a spreadsheet to be completed by each participating Agency with fields for research funding source, microbiome system, level of support, research theme (such as basic or applied), and notes. The spreadsheet included definitions and examples. Participating agencies also were asked for short answers to a series of questions on the nature of their current support of microbiome research, technology and training needs, and future outlook. The FTAC-MM distributed a set of explanatory slides that outlined the purpose of the data call and provided specific definitions for each type of research delineated in the spreadsheet.

Microbiome research was defined as the study of multi-species communities of microorganisms in a specific environment with regard to phylogenetic and genetic composition, structure and function, and interactions with their hosts or in ecosystems. This definition includes communities of all kinds of microorganisms, not only bacteria, but also Archaea, microeukaryotes, phytoplankton, and viruses. We also included mobile genetic elements. Specifically excluded were studies focused on a single species. Thirteen major agencies and the Smithsonian Institution participated in the data call (*Appendix 2*).

Although each Department recognized the essential role microbiome research will play in advancing its mission, few agencies presented stand-alone projects for microbiome research. In the attempt to be as comprehensive as possible, the data call accepted projects that included some microbiome research even if a portion of the projects' funding was not necessarily used for microbiome research; agencies were asked to report funding only for the microbiome portion, rather than the total funding for the project. This made some direct comparisons among agencies challenging, but the broad strokes of each agency's support of microbiome research and areas of study were accessible.

Summary of Results from the Data Call

The FTAC-MM identified approximately $922 million disbursed to 2,784 projects involving microbiome research over the course of three fiscal years, FY12 through FY14. Projects were counted each year in which the project was active, regardless of when funding was disbursed. This enabled us to include multi-year projects that may have received some of their funding outside the three years examined in this data call. The funding data are broken down by fiscal year (*Appendix 4*), by subject or ecosystem (*Appendices 3 and 6*), and by microorganism or microbial category studied (*Appendix 14*). Subject and ecosystem categories include agriculture, aquatic, atmospheric, built environment, human microbiome, energy, laboratory-based non-human, terrestrial, and conference. Large categories such as agriculture, aquatic, human, and terrestrial are further sub-divided to illuminate funding for specific habitats or purposes (*Appendices 7-12*).

Of the total funding for microbiome research for FY12-14, approximately 72 percent supported extramural research, while the remaining 28 percent was allocated for intramural research (*Appendix 5)*. Research involving human microbiomes garnered the most dollars, at 37 percent of the total ($342 million). Laboratory-based research not directly involving humans, for example using animal or plant models, developing tools, or investigating biofilms, captured another 29 percent of total funds ($268 million). An additional 14 percent of funding ($128 million) supported the "terrestrial" microbiome, which includes environmental research in specific habitats, like forests and deserts, the microbiomes of wild plants and animals, contaminated sites such as near mines with acid drainage-induced sediments, and the study of microbial communities involved in nutrient cycling. Agricultural and aquatic microbiome research each accounted for about 8 percent of the total ($705 million and $721 million, respectively). Energy crops accounted for 47 percent of agricultural microbiome research ($33 million), and other types of energy microbiome research, such as fuel cell and bioenergy development, accounted for 2 percent of the total

funds ($24 million). The remaining funds, about 2 percent, supported atmospheric research and the built environment, which includes studies of microbiomes in hospitals, for example, hardware on the International Space Station, and home plumbing systems. There was also some funding for microbiome conference support, though it is unclear if all conference data were captured in the data call.

Across the 14 participating agencies, most microbiome research funding (51 percent, $470 million) was invested in studies of the basic biology of microbiomes, such as community structure and function, the role of the microbiome in host, habitat, or ecosystem health, and the relationship between microbiome properties and the properties of the host or surrounding community. An additional 28 percent ($258 million) was invested in applied studies of the microbiome, and the remaining 21 percent ($194 million) was invested in the development of tools, technologies, methods, resources, and practices for microbiome research. These proportions remained relatively stable over FY12-14, with perhaps an increase in basic research (45 percent in FY12 and 54 percent in FY14).

Approximately 70 percent ($645 million) of the microbiome research funding for FY12-14 supported community-level studies of the microbiome, which include metagenomic analyses and other studies that include all members of a microbial community. Approximately 23 percent ($212 million) of the total supported microbiome studies that focused only on the bacterial members of the microbiome. The remainder (7%, $64.5M) supported studies of Archaea, microeukaryotes, mobile genetic elements, phytoplankton, viruses, and other microbial components of the microbiome.

Needs and Gaps Identified by the Data Call

The FTAC-MM also asked agencies to provide short answers to targeted questions, such as "What microbiome research area is your program emphasizing currently (in FY15-16)? Where do you see your program going in five years?" and "Over the next ten years, what crucial type of scientific and technical training will be needed?" Agencies also provided the "one scientific or technological advance that would enable microbiome research to leap forward quickly" and a "listing of priority needs in technology, tools, and infrastructure." Based on the answers to these questions, the FTAC-MM identified needs and gaps common to a minimum of four and up to all 14 of the agencies surveyed. These needs and gaps are illustrated in Appendix 15 and summarized below.

Disparities in Microbiome Research Areas

The FTAC-MM found that microbiome research related to food, either in the field or in the lab, in plants, animals, or soil, represents 4 percent of the total investment, which is an underinvestment relative to the importance of food production to a growing global population. Total plant and soil microbiome research in both natural and agricultural environments, while greater than and partly encompassing total food-related research, is nevertheless also currently under-resourced in light of the importance of these systems in food and fiber production, ecosystem services, and response to climate change variables.

Another obvious disparity relative to need is the level of support for viral research. Researchers have demonstrated the important role of the virome in human health,[1,2] and viruses are the most prevalent

[1] Norman, Jason M. et al. "Disease-specific alterations in the enteric virome in inflammatory bowel disease." *Cell*. 2015; 160: 447-460. http://www.cell.com/cell/abstract/S0092-8674(15)00003-3

[2] Cadwell, K. "The virome in host health and disease." *Immunity*. 2015; 42: 805-813. http://www.cell.com/immunity/abstract/S1074-7613(15)00183-1?_returnURL=http%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS1074761315001831%3Fshowall%3Dtrue

biological entities in the oceans[3] and abundant in soil, which may contain 10^8 virus particles per gram.[4] Yet Federal investments in the study of viral communities make up only 3 percent of microbiome research, compared to whole-community studies, which may or may not include viruses, at 70 percent, and bacteria exclusively at 23 percent (*Appendix 14*).

Also of note is the high level of support for basic research as compared to applied, translational research and tool development (*Appendix 13*). While basic research is a necessary component of microbiome investigation, the FY12-14 trend for a higher fraction of basic research at the expense of the fraction of the total focused on translational research and tool development is of concern. Basic research lays the foundation for mechanistic and translational studies, but the time is now ripe for investments in building upon that foundation.

Acquiring Data

Most responding agencies have been supporting the collection of microbiome data at least since FY12, but despite their experience, many still identified a pressing need for better data collection methods. Eleven of the 14 responding agencies specifically mentioned cheaper, long-read sequencing and better software for assembly of genetic sequences as a priority need. The Smithsonian best explained that access to such sequencing capabilities "would eliminate the taxonomic biases associated with PCR and other capture methods" to enable a more accurate assessment of the microbial community.

Importantly, genetic sequences of microbial samples were not the only data deemed necessary to collect. Ten agencies specifically recognized the need for widely available tools that measure multiple aspects of a microbiome, or what the Department of Defense (DOD) described as "community data," which includes genomics but also proteomics, lipidomics, and metabolomics in a spatial and temporal context. DOE also stressed the importance of developing high-resolution analytical technologies that would allow quantitative measurements of microbiome activities at the nano-, micro-, and meso-scale. When paired with multi-omics datasets, these tools would provide new approaches for dynamic analysis of microbiome functional attributes and scaling of information to the level of the host or environment. The National Aeronautics and Space Administration (NASA) described a desire for such a tool as a "robust, mobile, high-throughput diagnostic instrument," which could be used to identify the basis for "dysbiosis, disease, and environmental fouling."

Twelve agencies also emphasized the need for collection protocol standards and reference genomes. The U.S. Agency for International Development (USAID) listed "standardized protocols" as its most highly prioritized technical need, and the National Oceanic and Atmospheric Administration (NOAA) underscored this need by explaining that "resolving differences in method biases for sequencing would permit honest comparisons between studies and for longitudinal studies." The National Institute of Standards and Technology (NIST) reported that such standards are needed since "the interlab comparability of measurements on microbiomes is generally poor. Biases exist along every step of the measurement process, including sample collection, extraction techniques, measurement technology employed (NGS, mass spec, NMR), and, finally, data analysis and interpretation. There is a need for the adoption of reference materials, reference data, and reference protocols in order to identify and eliminate measurement bias."

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[3] Angly, Florent E. et al. "The marine viromes of four oceanic regions." *PLoS Biol*. 2006; 4: e368. http://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.0040368

[4] Reavy, Brian, et al. "Viruses in soil." *Biodiversity, Community and Ecosystems*. 2014; 1:163-180. http://link.springer.com/chapter/10.1007/978-94-017-8890-8_8

In addition to sample collection protocols, many agencies reported a need for baseline data with which to compare new microbiome data. The Department of the Interior (DOI) highlighted "robust reference genomes" and "vouchered specimens" as necessary for advancing the field, and DOD prioritized support for "tissue and sample storage" capability. Also, along with NIST, NIH, and the Food and Drug Administration, DOD noted a need for "improved methods for cultivating uncultivable bacteria and *in vitro* platforms to cultivate simple or complex communities."

Just as important as collecting data in a standardized, reproducible fashion, a few agencies reported the need for more hypothesis-driven research that will move the field from descriptive to predictive. NSF reported that "although many are expert at generating sequence data," the field needs more "investigators asking functional and biological questions about microbiomes. Training needs to move the focus away from data and method towards biological inquiry." Ten agencies described a pressing need for interdisciplinary research, education, and training, with suggestions that comparative microbiome research would benefit all fields.

Data Storage and Analysis

Once data are collected, how they are stored and analyzed becomes paramount. Nine agencies agreed with the FDA about the need for "high performance computation resources that are flexible to accommodate a rapidly evolving analytical pipeline" and "cloud computing solutions that overcome confidentiality and privacy concerns." The NIH, Environmental Protection Agency (EPA), and DOD in particular agreed that there was a dearth of open-source, supervised, quality-controlled software for data analysis. NSF wrote more specifically about this need, arguing that "the most pressing priority continues to be well-curated databases that are interoperable and easy to use." In total, eleven agencies identified a need for comprehensive, publically available data sets within a single data repository.

Importantly, many agencies connected the need for a database with the potential for data integration of community data across diverse ecosystems. Such software would tag genetic sequences with phenotype and function, enabling high-level comparisons and analysis.

Human Resource

Every agency surveyed identified education and training in Big Data and bioinformatics as crucial for advancing the field through growing workforce capacity. As NIH reported, "There is a desperate need for individuals who can develop creative approaches to bioinformatics problems," and the U.S. Department of Agriculture (USDA) wrote that "students should be trained to use "big data" and computer modeling to describe various networks within microbiomes, such as chemical signaling between microbes and their hosts (plant or animal) or the flow of genetic material."

Training biologists in bioinformatics is key, but agencies also repeatedly described a need for interdisciplinary education and training in general. DOE explains that "multidisciplinary training opportunities will be critical, particularly in developing a larger pool of researchers that more effectively bridge experimental and computational biology." NIH took this a step further and suggested that a diversity of education and training should be mirrored in a diversity of scientists, and listed the encouragement of "more diversity in the field as it relates to access for underserved populations in research training" as crucial.

Recommendations

Collaborative Microbiome Research

Knowledge gained at the intersection of fields is likely to have the most significant impact on all fields, but current funding structures may impede collaborative efforts across fields and ecosystems to find the common principles governing all microbiomes. Furthermore, collaborations are needed not just among microbiome experts, but among microbiome research, systems-level measurements, and modeling of life processes. For example, answering the fundamental questions that lie at the heart of microbiome dynamics, such as "*What is a healthy microbiome?"* and *"What makes a microbiome resilient?"* require a coordinated, interdisciplinary effort that should include geochemists, statisticians, environmental engineers, mathematical modelers, medical professionals, and others. Diverse collaborations are more likely to elucidate the truly fundamental principles governing microbiomes, enabling the acceleration of progress in all microbiome-related inquiry.

Current efforts to integrate microbiome research include the Earth Microbiome Project, which suggests a "massively multidisciplinary effort to analyze microbial communities across the globe."[5] Creating virtual Centers of Microbiome Innovation would improve collaboration at the Federal level. These could be supported through a variety of mechanisms, including each agency's internal (in-kind) research efforts, agency solicitations, or interagency solicitations, in which collaborative efforts among multiple agencies would fund interdisciplinary, multi-institution projects that tackle questions and themes that correspond to the missions of multiple agencies. The agencies could assess the project proposals through a unified review system, and each agency could choose to fund proposals that are germane to the agency's mission while still supporting solutions for fundamental questions at hand.

Microbiome Research and Sequence Analysis

Advanced study of the microbiome, whether human, animal or environmental, is possible because key tools are now available and affordable. One of these tools is DNA, or genetic, sequencing. When the Human Genome Project was completed in 2003, it cost about $54 million to sequence and analyze one human genome[1]. In the last five years, because of advances in DNA sequencing technologies, the cost has dropped to $4,000 for a eukaryotic genome, and about one tenth of that for a bacterial genome.[1] Metagenomics is the simultaneous sequencing and analysis of multiple genomes, such as those found in a microbiome.[2] It can now cost less than $1,000 for a high level analysis of a metagenome, making this kind of data within reach of many laboratories, but for a number of important reasons, analyzing a microbiome's composition, is not the same as understanding its properties. Metagenomes require extensive computational analysis to decipher which species are present and to determine what metabolic properties and pathways these communities possess. This kind of analysis can be cost prohibitive and is technically difficult to execute. Additional analysis of metabolites is also needed to understand which properties and pathways are active in the microbiomes and under what conditions. Although DNA sequencing has opened the door to microbiome research across a wide range of fields, similar advances in other "-omic" technologies, and in the development of tools to analyze these complex data, are still needed in order to move the field forward.

[1]National Human Genome Research Institute, NIH (https://www.genome.gov/27541954)

[2]National Research Council. *The New Science of Metagenomics.* The National Academies Press (2007)

[5] Jack A. Gilbert, Janet K. Jansson, and Rob Knight. "The Earth Microbiome project: successes and aspirations." *BMC biology* 12.1 (2014): 69.

Multi-agency collaborations are another approach that could be utilized for collaborative, intramural, or extramural research. DOI and NSF, for example, have been successfully collaborating since 2010 to control the invasive weed phragmites in wetland habitats, partially through the study of its microbiome. Similarly, DOE and NIH collaborated in 2007 to create the bioinformatics pipeline MG-RAST (the "Metagenomics Rapid Annotations using Subsystems Technology"), an open-source web application server that provides quantitative information on microbial populations and which now has over 12,000 registered users and 182,758 data sets.[6] Other formal joint activities include the NSF and USDA Microbial Genome Sequencing Program[7] and the NIH and NSF Ecology of Infectious Diseases Programs.[8]

The Microbiome, Horizontal Gene Transfer, and Antibiotic Resistance

A microbiome is the community of microorganisms that inhabit an ecosystem. Microbes can move from ecosystem to ecosystem by various means, which brings them into contact with other microorganisms and communities. Microorganisms are particularly adept at acquiring and exchanging genes between even unrelated species and have a variety of mechanisms at their disposal for this purpose. For example, some gene exchange may involve direct microbe-to-microbe contact while other forms of genetic exchange may involve:

- the exchange of accessory genomes, such as plasmids or other mobile genetic elements;
- mediation by viruses, such as bacteriophage; or
- acquisition of naked DNA found in the environment.

These types of gene exchange are called horizontal gene transfer (HGT), and the most well-known example of HGT has resulted in the emergence of wide-spread antibiotic resistance in pathogens. Recent studies have demonstrated that the human microbiome supports the greatest frequency of HGT of all microbial ecosystems studied to date, seconded by what is occurs in livestock and poultry[1], and much of this HGT involves antibiotic-resistance genes [2]. How and under what conditions HGT occurs in human and livestock microbiomes and how it can be regulated is an area of intense study. Emerging research on the structure and function of microbiomes and on the factors that drive horizontal gene transfer will be crucial in helping to mitigate and even reverse the growth of antibiotic resistant pathogens.

[1]Smillie et al., (2011). Ecology drives a global network of gene exchange connecting the human microbiome. Nature, 480: 327-336.

[2]Sommer and Dantas (2011). Antibiotics and the resistant microbiome. Curr. Opinions in Microb., 14: 556-563.

Through these and other mechanisms, Federal agencies would coordinate to maximize the impact of resources, minimize duplicative infrastructure investment, and share expertise and lessons learned.

Certainly not all efforts can or should be centralized, but agencies with smaller investments in microbiome research will surely benefit through coordination and leveraging of efforts with other agencies. In addition, Federal agencies should establish strategic partnerships with academic and industrial partners. **Expected outcomes include efficiencies and cost savings for sequencing, computing, and bioinformatics; increased data sharing and data usability; increased pace of technological innovation and research-to-application transitions for the Federal Government; and consistency in the Federal approach for the use of genetic resources.**

[6] metagenomics.anl.gov

[7] http://www.nsf.gov/funding/pgm_summ.jsp?pims_id=5688

[8] http://www.fic.nih.gov/programs/Pages/ecology-infectious-diseases.aspx

Key Techniques and Technologies

Second, we suggest funding three key technical and technological needs identified as priorities by at least ten of the fourteen agencies surveyed.

(1) Protocol standards and reference materials. NIST may be most suitable to lead such efforts, but preliminary protocol development is already taking place in a variety of agencies, from development of protocols for sampling ocean sediments at DOI to standards for dietary effects at USDA. Collaborations to achieve standards in all relevant ecosystems should be prioritized.

(2) A comprehensive, adaptable, user-friendly database that includes the meta-genomes, metabolomes, proteomes, lipidomes, and meta-data, and the flexibility to include other, as yet unidentified information. The Federal Government, with its support of research in so many ecosystems, is uniquely qualified to sponsor such a database. Moreover, in 2013, a Presidential Memorandum required nearly all data from federally-funded research to be made publically available.[9] Therefore, data deposited in federally-sponsored databases would be open and freely available to all researchers, enabling more rapid advancement of the field. The database and associated software would be available for use by all agencies, enabling continuity and quality-control, issues specifically raised in the FTAC-MM data call. DOD "identified a challenge in loading certain types of software (to support analysis of –omics data), which may be restricted" on government servers, but federally-sponsored resources could potentially overcome these restrictions.

(3) Widely available, high-throughput tools for measuring microbiomes cheaply and easily and at a variety of scales. Such technologies would democratize microbiome research, enabling agencies with smaller investments in this field to benefit as greatly as the others.

Education and Training

Federal resources should be made available to support the education, training, and recruitment of experts in the fields of bioinformatics and modeling. Because the current flood of data is expected to increase, every agency participating in the data call expressed a need for professionals with both the biology background necessary to understand the ecosystems in question and the computational expertise required to assess the vast data gathered from these systems. Bioinformaticians and computational modelers, whether newly recruited or trained from the current pool of microbiology researchers, are needed to pose testable hypotheses from the microbiome data already gathered, which will spur the development of a predictive understanding microbiome function under various conditions.

[9] https://www.whitehouse.gov/sites/default/files/microsites/ostp/ostp_public_access_memo_2013.pdf

Conclusions

With annual Federal Government spending on microbiome research now over $300 million (*Appendix 4)*, the United States is at the leading edge of research and development in this area. This position may not last as other countries rapidly expand their investments. Although a comprehensive survey of international microbiome research is not available, there are a myriad programs and proposals worldwide directed at microbiome research.

The first applications of microbiome research are already beginning to emerge in human health, but others will likely follow. The 2014 World Economic Forum listed human microbiome therapeutics as one of the "top-ten emerging technologies that can reshape the future."[10] Some areas of microbiome research are already yielding large economic returns. Probiotics are currently a $35 million industry, projected reach $650 million by 2023.[11] Although more difficult to quantify, the impact of microbiome research on the health care industry could be even more substantial. A 2015 Nature Biotechnology News Feature, "Drugging the Gut Microbiome," estimated that there are currently almost 20 companies conducting clinical trials with microbiome-targeted products.[12] If better predictability in treatment outcomes and increased understanding of the microbiome interaction with diet reduces even a fraction of the annual economic cost of obesity ($147 billion),[13] foodborne illness ($14.6 billion),[14] antimicrobial resistance ($55-70 billion),[15] or cancer ($90 billion),[16] the country may save significantly in health care costs. Biomanufacturing of microbial therapeutics is advancing with one product, a bacterial mixture to treat recurrent *C. difficile* infections, which is in Phase 2/3 clinical trials.

The potential for applied microbiome research to impact the health care industry is substantial, but understanding the basic mechanisms of microbiome assembly and communication within the context of any system, human or otherwise, will provide benefits to many additional areas, such as energy, agriculture, manufacturing, and environmental health. To capitalize on microbiome research and keep pace with other countries' increased awareness of the importance of the microbiome, the United States should sustain investments in microbiome research while addressing research gaps and needs, encouraging collaborations and interdisciplinary research, incentivizing the development of key tools and platform technologies, and supporting the education, training, and recruitment of a data-savvy workforce. With the right tools and an interdisciplinary focus on the fundamental questions of microbiome science, researchers may find new, technologically sophisticated and precise therapeutic approaches for disease prevention and treatments for plant, animal (including human), and environmental health.

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[10] http://www3.weforum.org/docs/GAC/2014/WEF_GAC_EmergingTechnologies_TopTen_Brochure_2014.pdf

[11] http://www.marketsandmarkets.com/Market-Reports/human-microbiome-market-37621904.html

[12] http://www.nature.com/nbt/journal/v33/n3/pdf/nbt.3161.pdf

[13] Hammond, Ross A. and Ruth Levine, (2010). The economic impact of obesity in the United States. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, 2010(3): 285-295.

[14] http://www.ers.usda.gov/amber-waves/2013-november/recent-estimates-of-the-cost-of-foodborne-illness-are-in-general-agreement.aspx#.VYwJvflVhBc

[15] PCAST Report to the President on Combating Antibiotic Resistance, (September 2014). https://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST/pcast_carb_report_sept2014.pdf

[16] http://www.cancer.org/cancer/cancerbasics/economic-impact-of-cancer

Appendix 1: The Mapping the Microbiomes Fast Track Action Committee Charter

CHARTER
of the
FAST-TRACK ACTION COMMITTEE ON MAPPING THE MICROBIOME
SUBCOMMITTEE ON LIFE SCIENCES
COMMITTEE ON SCIENCE
NATIONAL SCIENCE AND TECHNOLOGY COUNCIL

A. Official Designation

The Fast-Track Action Committee on Mapping the Microbiome (FTAC-MM) is hereby established by action of the National Science and Technology Council (NSTC), Committee on Science (CoS), Subcommittee on Life Sciences (LSSC).

B. Purpose and Scope

A microbiome is the assemblage of microorganisms that live in a particular environment. Research has shown that microbiomes play a dynamic and essential role in human health, environmental processes, and agriculture. In recent years, Federal investments have led to extraordinary growth in the understanding of the components and dynamic nature of microbiomes in human, plant, and animal environments. Microbiomes are emerging as important influences in all Earth habitats, governing an astounding array of biological processes, ranging from nutrition and disease in humans to nutrient acquisition and stress tolerance in plants and stability of soil and aquatic environments.

There is still much to learn about microbiomes. Little is known, for example, about how microbiomes protect their plant and animal hosts from disease, how higher-order microbiome interactions drive outcomes relevant to zoonotic diseases and food safety, what factors contribute to shifts in microbiome composition, and what new benefits and outcomes might derive from changing the composition of a microbiome to influence its function.

The purpose of the FTAC-MM is to identify areas of current Federal investment, research needs, and resource gaps for the development of an integrated Federal plan for microbiome research, and to identify priority areas for Federal Agency coordination and cooperation on achieving a predictive understanding of microbiomes and their functions.

C. Functions

To achieve its goals, the FTAC-MM will:

1. Describe existing federally supported research and development activities in microbiome research, including a clear description of current investments and individual agency priorities;
2. Identify and prioritize technology needs and cross-cutting challenges common to all microbiome research, with a specific focus on enabling predictive understanding and modeling of microbiomes; and
3. Outline a coordinated plan for Federal investment to address research and development gaps for microbiome research required to achieve a predictive understanding of microbiomes and their functions.

D. Membership

The following NSTC departments and agencies are represented on the FTAC-MM:

Department of Agriculture;
Department of Commerce;
Department of Defense;
Department of Energy;
Department of Health and Human Services;
Department of Interior;
Environmental Protection Agency;
National Aeronautics and Space Administration; and
National Science Foundation.

The following organizations in the Executive Office of the President shall also be represented on the FTAC-MM:

Office of Management and Budget; and
Office of Science and Technology Policy.

Cooperating departments and agencies shall include other such Executive organizations, departments, and agencies as the FTAC-MM Co-chairs may, from time to time, designate.

E. Private-Sector Interface

The FTAC-MM may seek advice from the President's Council of Advisors on Science and Technology (PCAST) and will recommend to the CoS and/or the Assistant to the President for Science and Technology the nature of any additional private-sector[17] advice needed to accomplish its mission. The FTAC-MM may also interact with and receive *ad hoc* advice from various private-sector groups as consistent with the Federal Advisory Committee Act (FACA).

[17] The Federal Advisory Committee Act, 5 U.S.C. App., as amended, does not explicitly define "private sector," but the phrase is generally understood to include individuals or entities outside the Federal government such as, but not limited to, the following: non-Federal sources, academia, State, local or Tribal governments, individual citizens, the public, non-governmental organizations, industry associations, and international bodies.

F. Termination Date

Unless renewed and approved by the Co-chairs of the CoS prior to its expiration, the FTAC-MM shall terminate no later than 120 days from the date of approval.

G. Determination

I hereby determine that the establishment of the Fast-Track Action Committee on Mapping the Microbiome is in the public interest in connection with the performance of duties imposed on the Executive Branch by law and that such duties can best be performed through the advice and counsel of such a group.

Approved:

2/9/15

Kathy Hudson — Date
Co-chair of Subcommittee on Life Sciences, and
Deputy Director for Science, Outreach, and Policy
National Institutes of Health
Department of Health and Human Services

2/9/15

Chavonda Jacobs-Young — Date
Co-chair of Subcommittee on Life Sciences, and
Administrator, Agricultural Research Service
Department of Agriculture

2/9/15

James Olds — Date
Co-chair of Subcommittee on Life Sciences, and
Assistant Director for Biological Sciences
National Science Foundation

2/9/15

Sharlene Weatherwax — Date
Co-chair of Subcommittee on Life Sciences, and
Associate Director of Science for Biological and Environmental Research
Office of Science
Department of Energy

Appendix 2: Participating Departments and Independent Agencies

Department of Commerce (DOC)
- National Institute of Standards and Technology (NIST)
- National Oceanic and Atmospheric Administration (NOAA)

Department of Defense (DOD)
Department of Energy (DOE)
Department of the Interior (DOI)
Environmental Protection Agency (EPA)
Department of Health and Human Services (HHS)
- Centers for Disease Control and Prevention (CDC)
- Food and Drug Administration (FDA)
- National Institutes of Health (NIH)

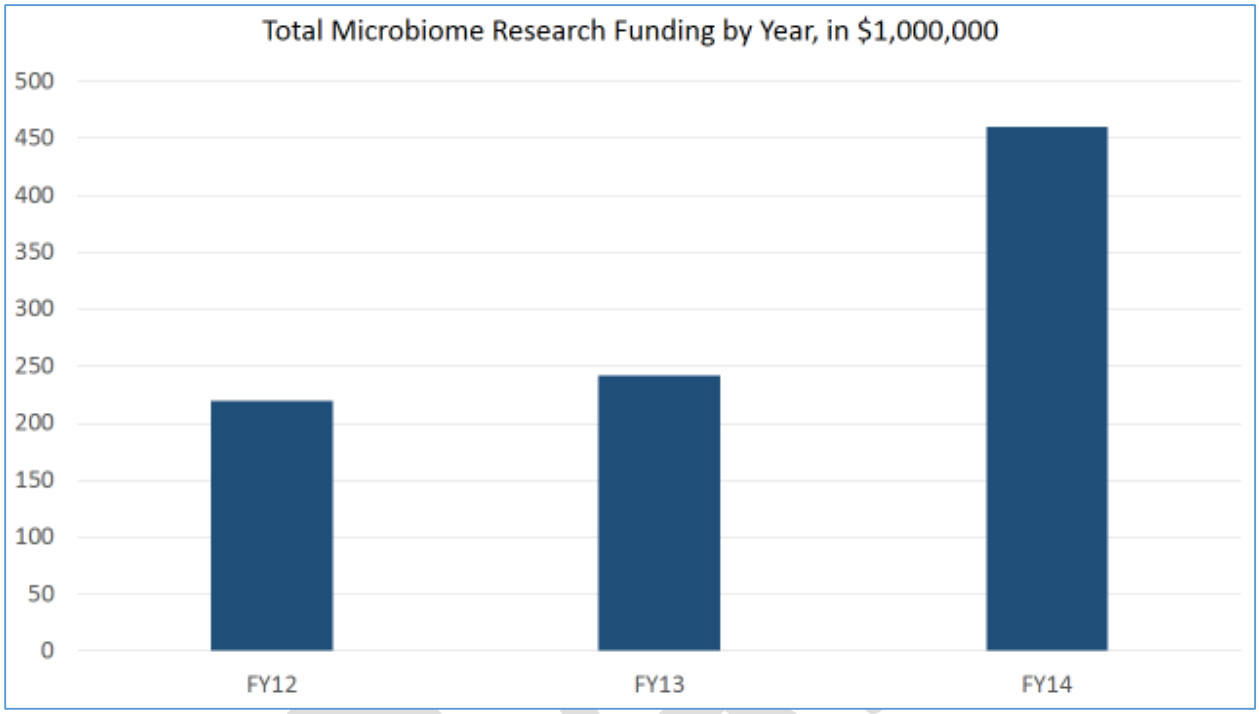
National Aeronautics and Space Administration (NASA)
National Science Foundation (NSF)
Smithsonian Institution
U.S. Agency for International Development (USAID)
U.S. Department of Agriculture (USDA)

Appendix 3: Categories of Microbiome Research Funded or Performed by Department or Independent Agency in FY12-14

	Agriculture	Aquatic	Atmospheric	Built Environment	Human	Energy, Non-Agriculture	Lab Based	Terrestrial
CDC				✓	✓			
DOD	✓	✓		✓	✓	✓	✓	✓
DOE	✓					✓		✓
DOI		✓					✓	✓
EPA		✓		✓				
FDA	✓		✓	✓	✓		✓	
NASA		✓		✓	✓		✓	✓
NIH					✓		✓	✓
NIST		✓			✓			
NOAA	✓	✓						
NSF	✓	✓	✓		✓	✓	✓	✓
Smithsonian	✓	✓					✓	✓
USAID	✓				✓			
USDA	✓				✓		✓	✓

Appendix 4: Total Microbiome Research Funding by Fiscal Year, in $1,000,000

Total funding for microbiome research in each Fiscal Year surveyed.



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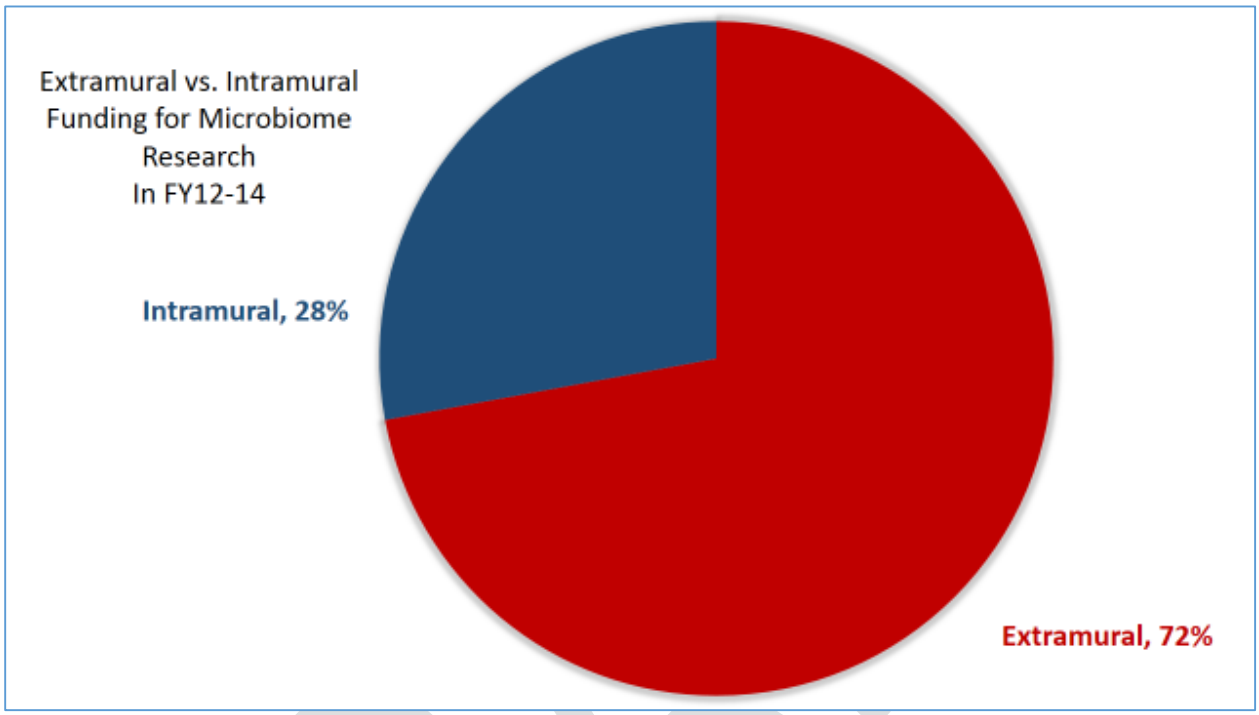
Appendix 5: Extramural vs. Intramural Funding for Microbiome Research in FY12-14



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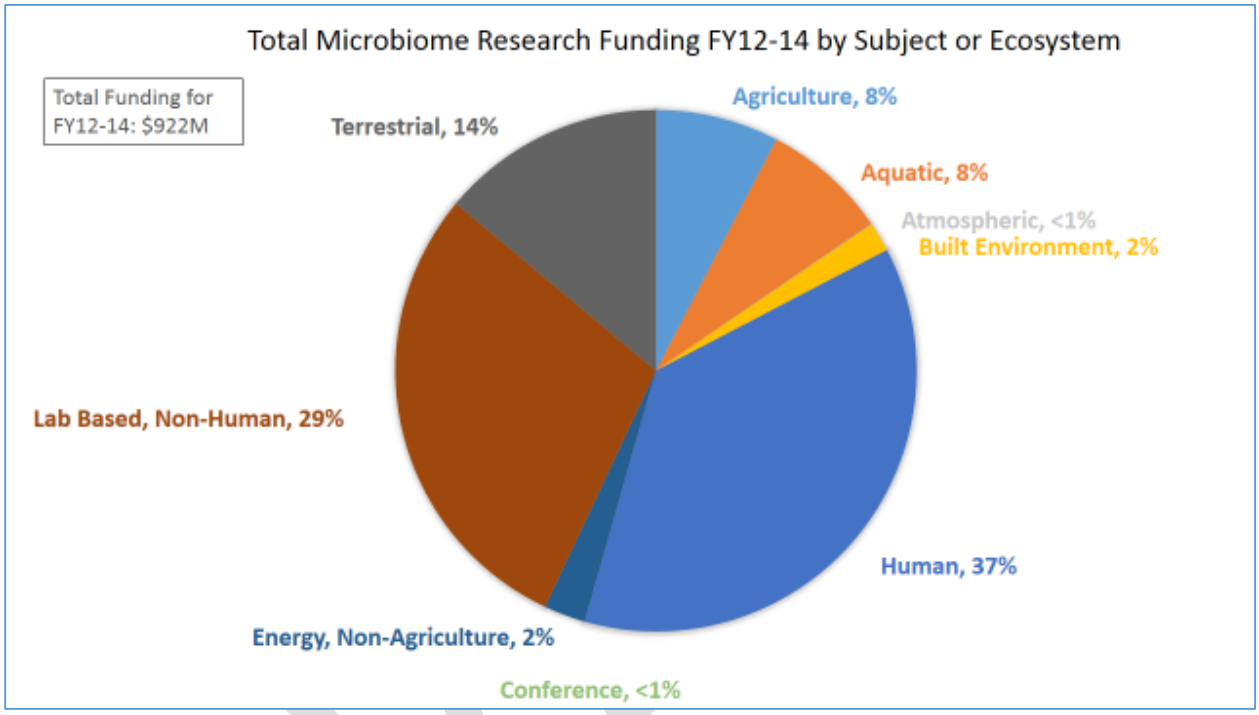
Appendix 6: Total FY12-14 Funding for Microbiome Research by Subject or Ecosystem

Total funding across FY12-14 for microbiome research with percentages given for nine general categories.



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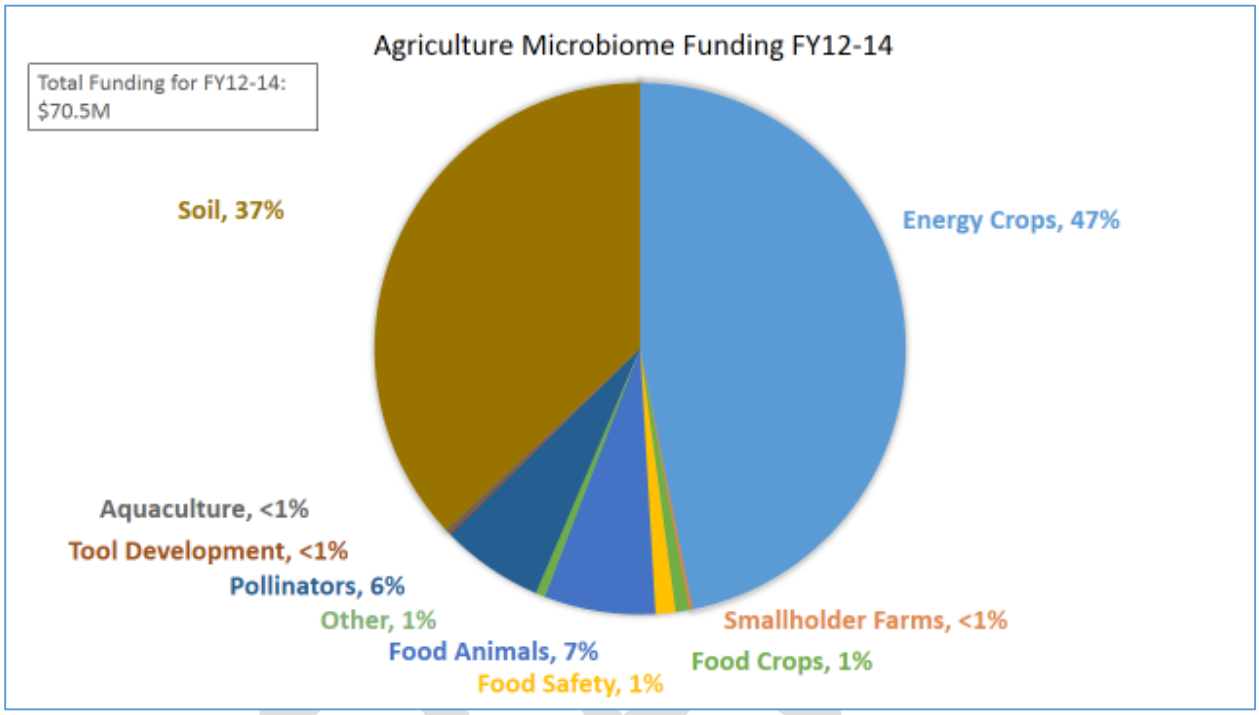
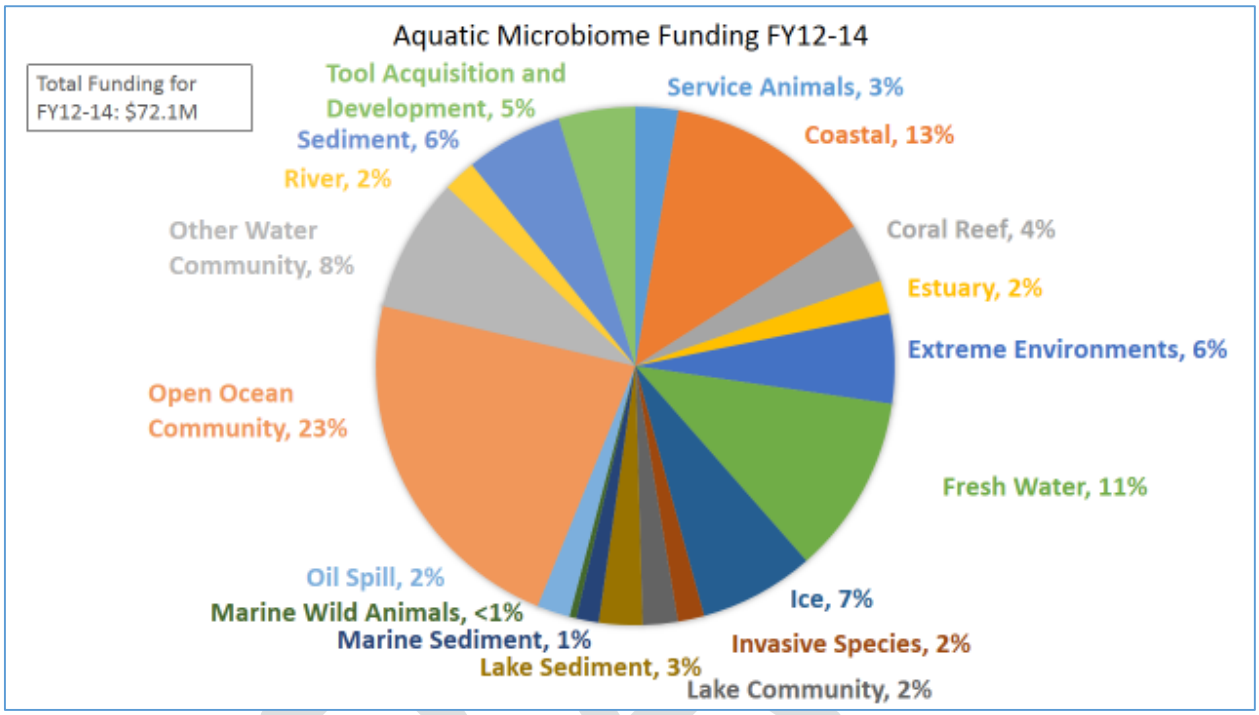
Appendix 7: Agriculture Microbiome Research Funding FY12-14

Total investment in agricultural research focusing on the microbiome. This includes animal, crop, and soil research on smallholder and large, industrial farms, aquaculture, domesticated pollinators like bees, and food safety research.



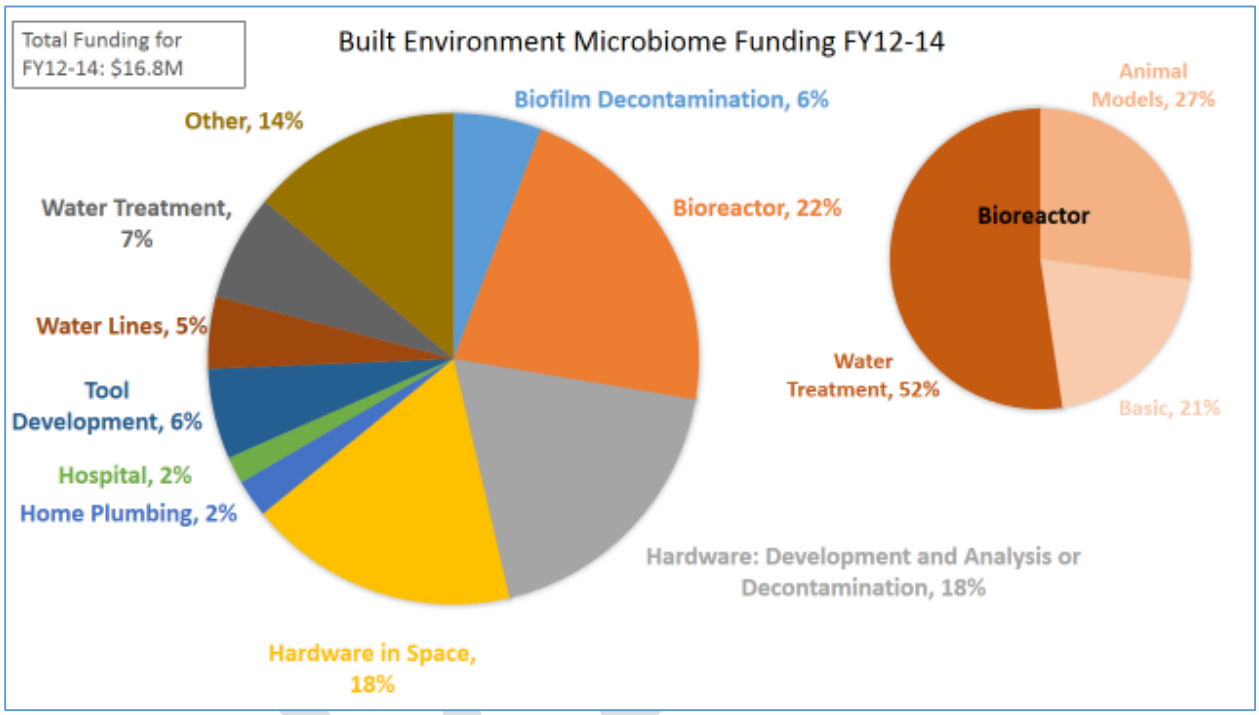
Appendix 8: Aquatic Microbiome Research Funding FY12-14

Total investment in microbiome research in waterborne microbiomes, including microorganisms inhabiting a variety of aquatic environments, such as coasts, oceans, rivers and lakes, and the microbiomes of auatic and marine plants and animals.



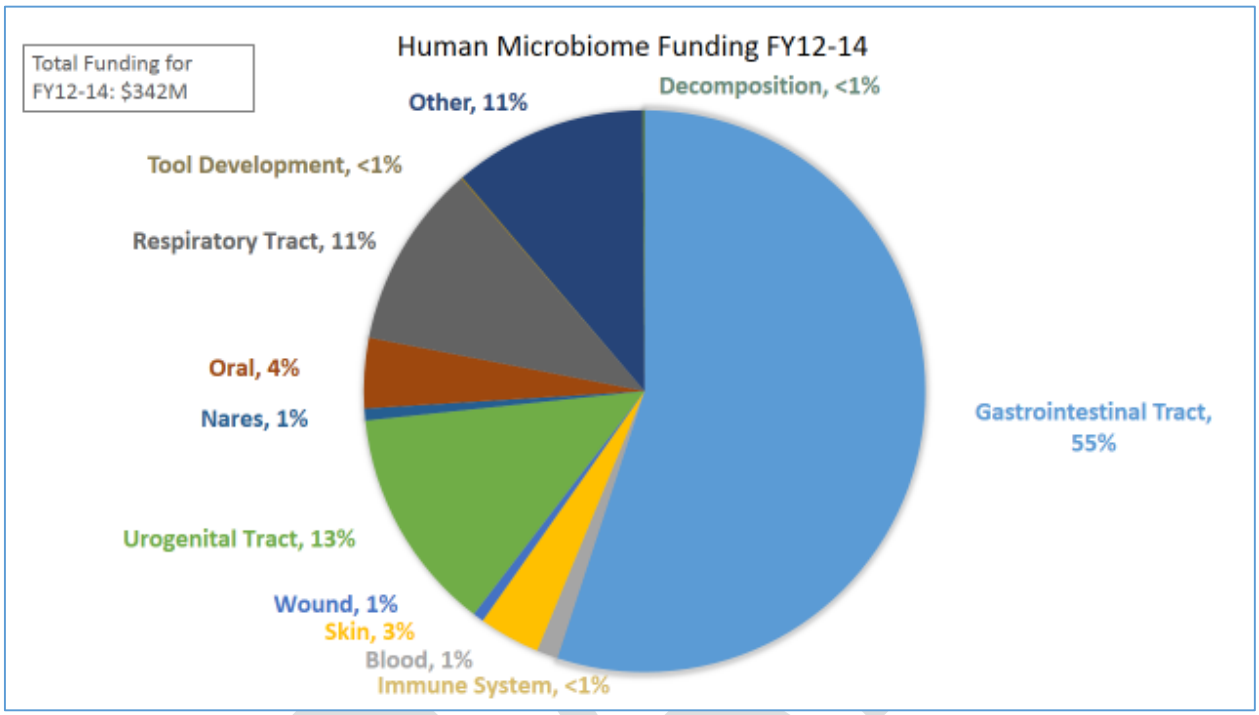
Appendix 9: Built Environment Microbiome Funding FY12-14

Total investment in microbiome research projects investigating artificial environments and systems, including water treatment facilities, public water lines, home plumbing systems, bioreactors, and hardware used in places like hospitals and on the International Space Station. Bioreactor funding is further broken down to show the research purpose.



Appendix 10: Human Microbiome Research Funding FY12-14

Total investment in microbiome research in humans with percentages given for the system, organ, or type of research.



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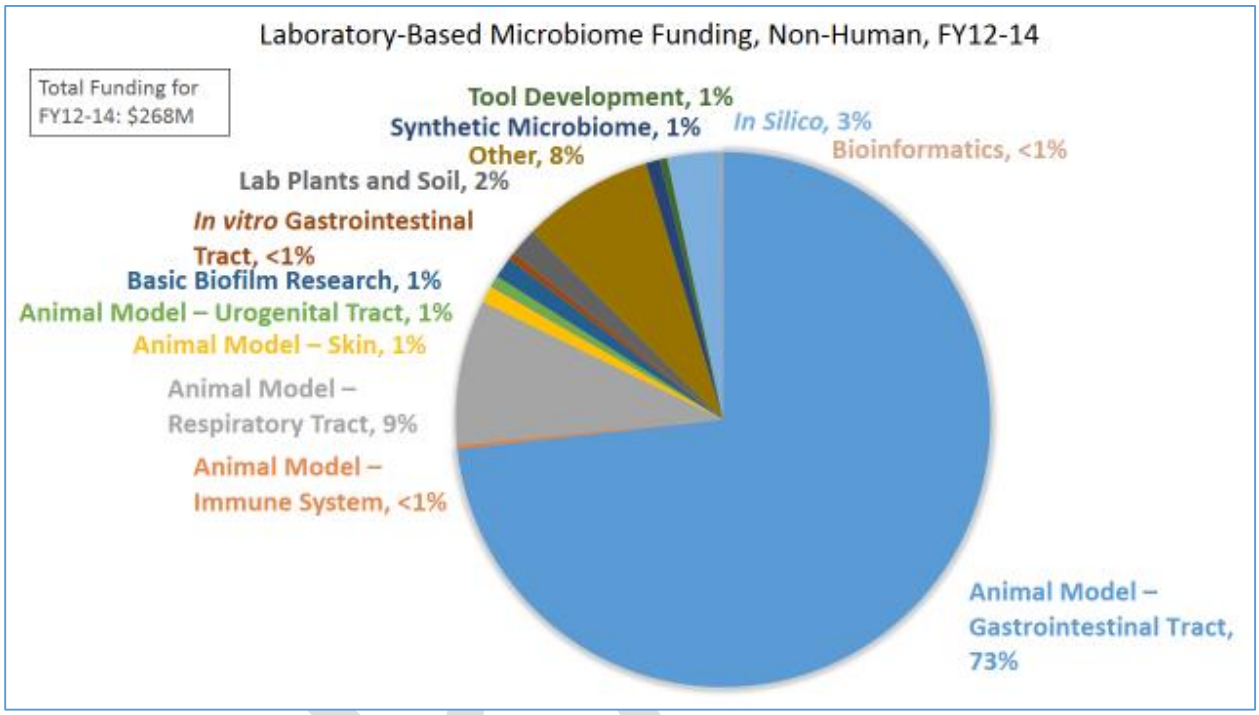
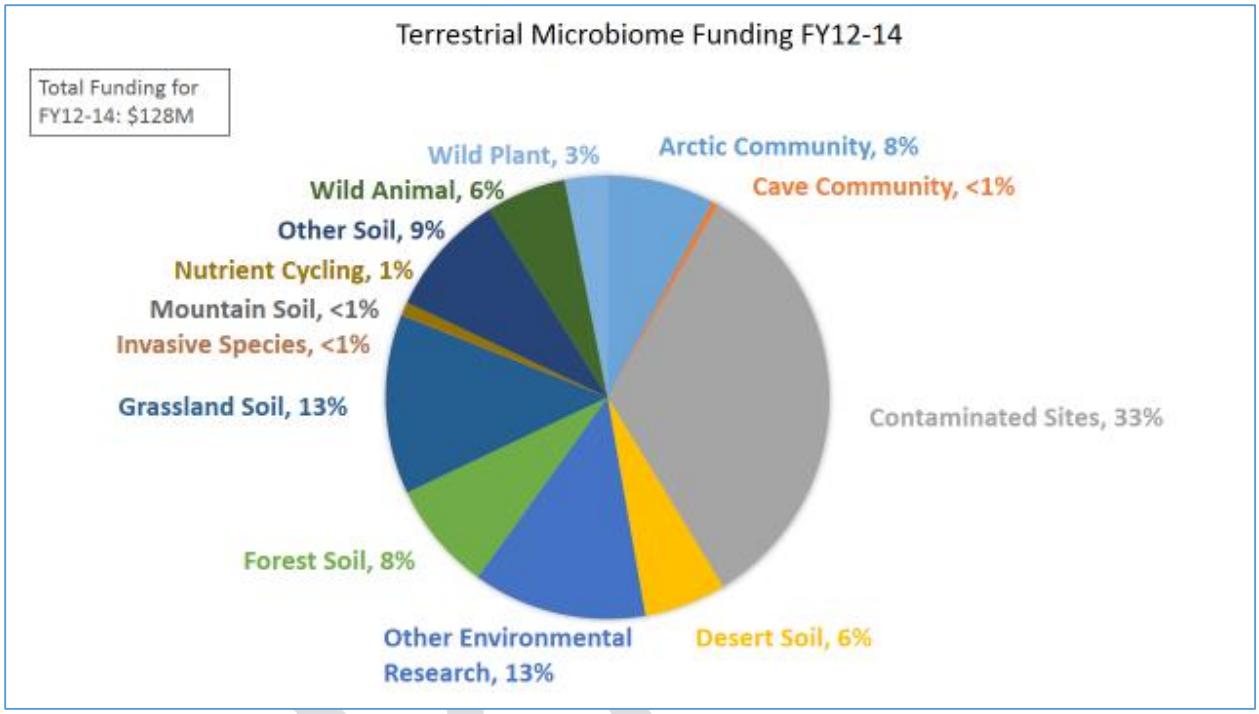
Appendix 11: Laboratory-Based Microbiome Research Funding, Non-Human, FY12-14

Total funding for laboratory-based microbiome research not directly involving humans, such as research using animal or plant models, tool development, basic biofilm research, computer based ("*in silico*") research, and the study of synthetic communities.



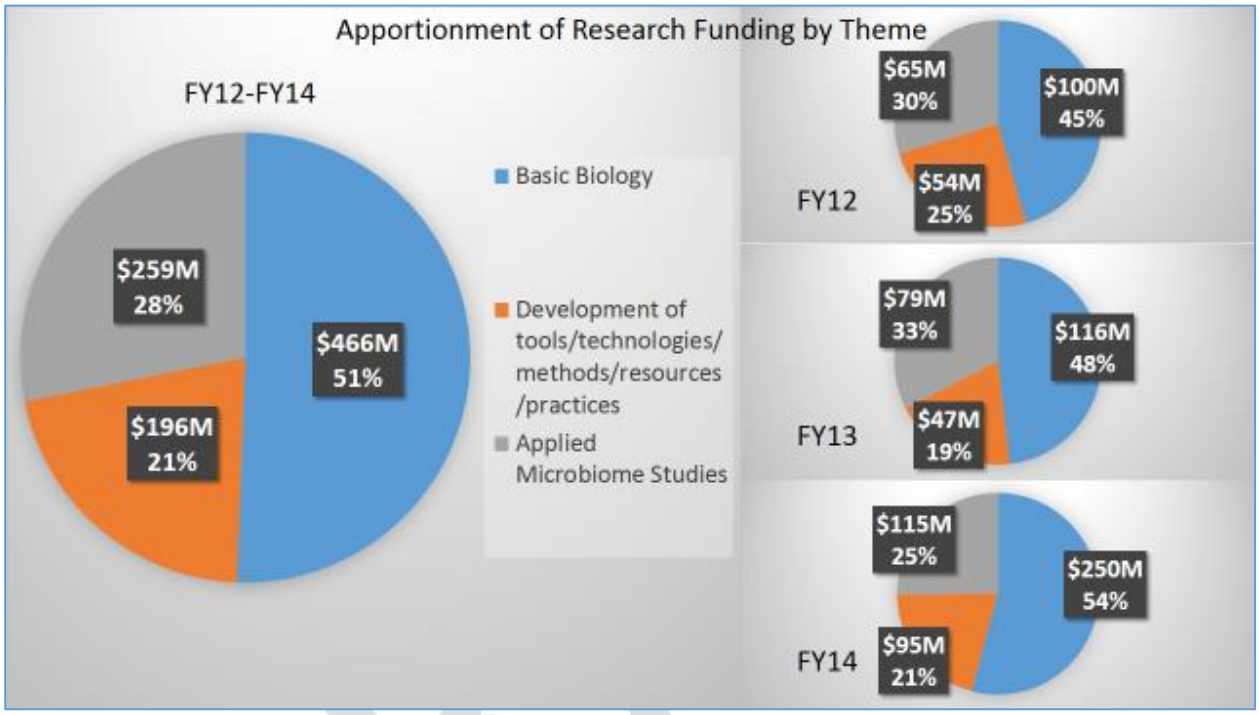
Appendix 12: Terrestrial Microbiome Research Funding FY12-14

Total funding for terrestrial microbiome research includes projects investigating the microbiomes of specific habitats, like forests and deserts, the microbiomes of wild plants and animals, contaminated sites such as near mines with acid drainage-induced sediments, and the study of microbial communities involved in nutrient cycling.



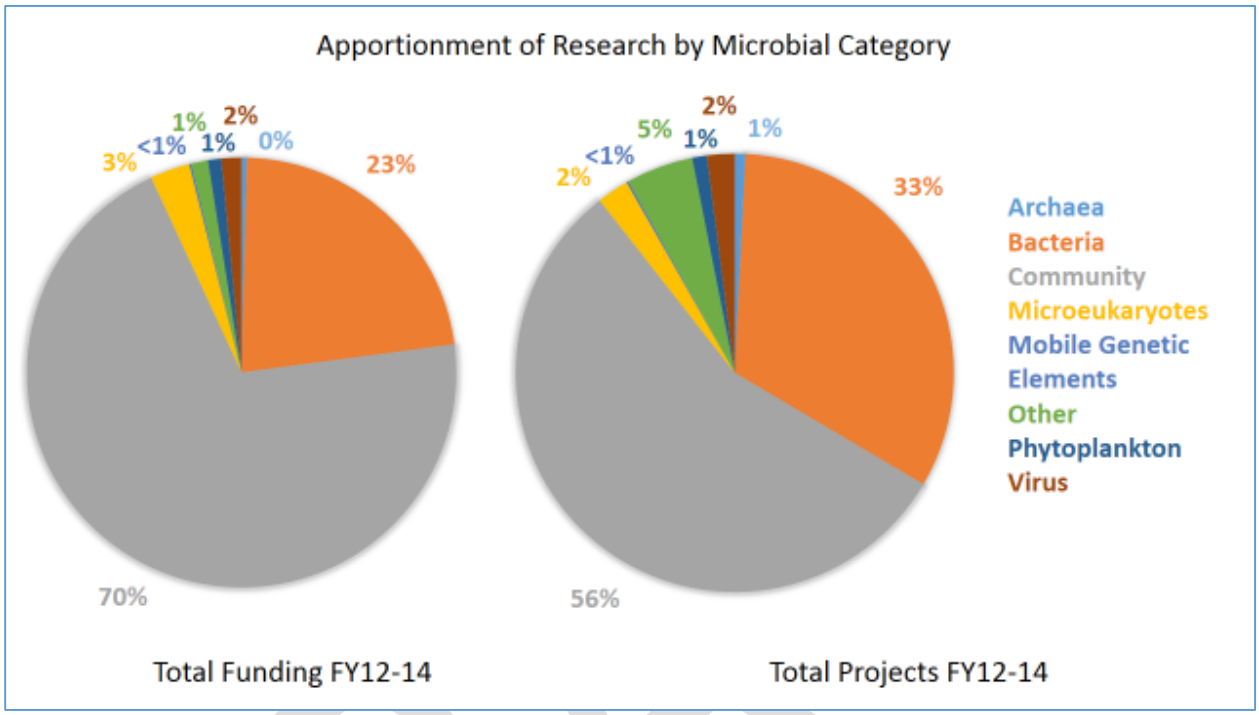
Appendix 13: Apportionment of Microbiome Research Funding by Theme

Total funding for microbiome research by theme in each year and as a proportion of the total. All microbiome research in this Data Call was captured as a proportion of basic, applied, or development of tools. Each project was, therefore, not forced into one category but was apportioned among the three. Apportionment was weighted by funding to yield the percentages.



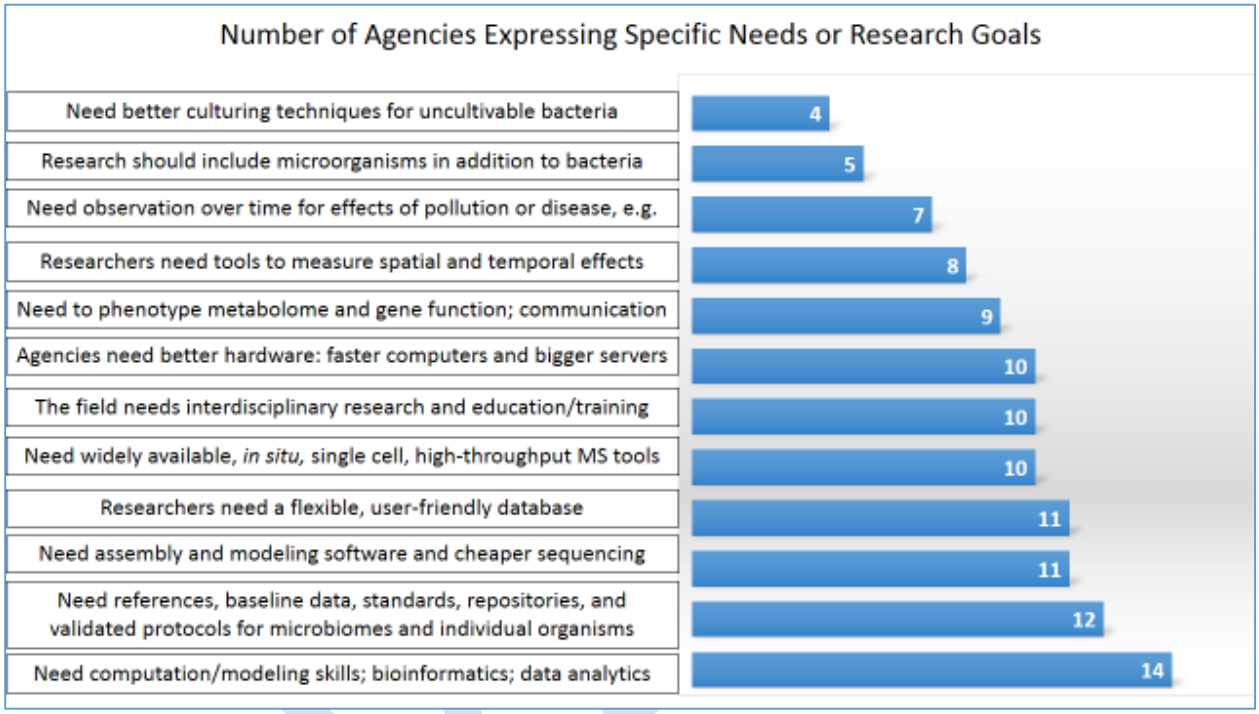
Appendix 14: Apportionment of Microbiome Research by Microbial Category

Total funding (left) or number of projects (right) for research by microbial category across FY12-14.



Appendix 15: Number of Agencies Expressing Specific Needs or Research Goals

Needs and research goals identified by at least four and up to all 14 departments independent agencies in the answers to a series of questions on the nature of their current support of microbiome research, technology and training needs, and future outlook.



Abbreviations

NSTC	National Science and Technology Council
OSTP	Office of Science and Technology Policy
R&D	research and development
STEM	Science, Technology, Engineering, and Mathematics

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