Proposal to Launch the "International Chinese Ethnicity Health Microbiome Research Initiative" Postprint

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Abstract

The human body constitutes a highly complex ecosystem. The microbial cells inhabiting both the interior and exterior of the human body number in the hundreds of trillions, with the genes they encode reaching up to 100 times the number of human genes, collectively termed the human microbiome (Human-Microbiome). Notably, over 90% of symbiotic microorganisms reside within the human digestive tract, constituting the "gut microbiota," which plays an indispensable role in human health. Dysbiosis of its structure is intimately associated with the initiation and progression of numerous chronic diseases. Consequently, investigation into the relationship between the human microbiome—exemplified by the gut microbiota—and health and disease has emerged as a major scientific question at the forefront of international academia. The Chinese nation represents one of the most historically documented civilizations and constitutes the most populous and widely distributed ethnic group on Earth. With economic development and societal transformation, the disease spectrum among Chinese populations both domestically and overseas is undergoing dramatic shifts, with chronic diseases such as diabetes and cancer posing the greatest threats to public health. The "International Chinese Microbiome Research Project" seeks to systematically study the relationship between structural alterations in the gut microbiome and health among global Chinese populations, thereby achieving a deeper understanding of the role and significance of microbiota structural changes within the context of shifting disease patterns when genetic backgrounds remain relatively stable while dietary structures and lifestyles undergo rapid transformation. This will facilitate the elucidation of novel pathogenic mechanisms underlying chronic diseases. Furthermore, by harnessing Traditional Chinese Medicine and traditional Chinese health preservation wisdom, the project aims to develop novel pharmaceuticals, functional foods, and health products targeting the gut microbiota. Through initial adoption by overseas Chinese communities and subsequent gradual promotion worldwide, this initiative may

provide a unique opportunity for the modernization and globalization of China' s traditional medicine industry, and could potentially enable the Chinese nation to make substantial contributions to global human health.

Full Text

Preamble

China Microbiome Initiatives
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"International Healthy Chinese Microbiome Research Plan"

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Abstract

The human body is an exceedingly complex ecosystem. The microorganisms living inside and on the human body number in the hundreds of trillions of cells, encoding genes that can reach 100 times the number of human genes. Collectively, these are known as the human microbiome. Over 90% of symbiotic microorganisms reside in the human digestive tract, forming the "gut microbiota," which plays an indispensable role in human health. Dysbiosis of this microbial community is closely associated with the onset and progression of numerous chronic diseases. Consequently, research on the relationship between the human microbiome—represented by the gut microbiota—and health and disease has become a major scientific frontier in international academia.

The Chinese nation is one of the oldest ethnic groups with written historical records and the most populous and widely distributed ethnic group on Earth. With economic development and social transformation, the disease spectrum among Chinese populations worldwide is undergoing rapid changes, with chronic diseases such as diabetes and cancer becoming the greatest threats to public health. The "International Healthy Chinese Microbiome Project"aims to systematically investigate the relationship between gut microbiome structural changes and health among Chinese populations worldwide. By deeply understanding how microbiome alterations contribute to shifting disease patterns against a relatively stable genetic background but rapidly changing dietary structures and lifestyles, this project will help reveal novel mechanisms underlying chronic disease pathogenesis. Moreover, by leveraging traditional Chinese medicine and health preservation wisdom, developing new medicines, foods, and health products targeting the gut microbiota, and promoting their use through overseas Chinese communities, this initiative could become a rare opportunity for China' s traditional medicine industry to modernize and go global, while potentially enabling the Chinese nation to make significant contributions to global human health.

Keywords: Chinese populations, microbiome, international cooperation,

health
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1. Research Progress on the Microbiome-Human Health Relationship

The Chinese nation is one of the oldest ethnic groups with written historical records and the only ancient human civilization that has continued to thrive in its place of origin to this day. It is also the most populous and widely distributed ethnic group on Earth. Throughout its long history, the Chinese people have accumulated vast experience in disease control and health promotion, preserved in various forms of traditional medicine including Traditional Chinese Medicine (TCM), Tibetan medicine, Mongolian medicine, and Miao medicine, which continue to play a significant role in national healthcare and disease prevention. However, with China' s continuous economic development and social progress, the Chinese disease spectrum has undergone dramatic changes, shifting from infectious diseases to a combination of infectious and chronic diseases, with chronic diseases becoming the primary health threat in developed regions. Chinese descendants living worldwide who have immigrated to developed countries and adopted local lifestyles and dietary structures also exhibit chronic disease patterns similar to local populations. Preventing and treating chronic diseases to safeguard public health has become a major scientific and technological challenge that urgently needs to be addressed.

A significant research breakthrough in international biomedicine over the past decade has presented a major opportunity for the Chinese nation to improve health standards across the entire population while making outstanding contributions to global human health: research on the health effects of human symbiotic microorganisms. In 2000, Nobel laureate Lederberg pointed out that the human body is a "superorganism" composed of human cells and all symbiotic microbial cells, representing a highly complex ecosystem [1]. The number of microbial cells living inside and on the human body can reach ten times the number of human cells, totaling in the hundreds of trillions. Over 90% of symbiotic microorganisms reside in the human digestive tract, forming the "gut microbiota," but all body sites that contact the environment—including the skin, respiratory tract, and reproductive tract—harbor their own microbial communities. The genes encoded by microbiomes across the body exceed the number of genes in the human genome by 100-fold and are collectively termed the human microbiome [2-7].

In modern medical history, 1908 Nobel laureate Metchnikoff was the first to explicitly propose that toxins produced by the gut microbiota are important causes of human aging and disease, and that regulating and optimizing the gut microbiota could achieve disease prevention and anti-aging effects [8]. He was also among the first scientists to suggest that the longevity and health of Bulgarian peasants might be related to their consumption of yogurt. This marked the first time scientists recognized that human-associated bacteria were

not merely "hitchhikers" —some were beneficial to human health while others were harmful. However, the human gut microbiota comprises over a thousand microbial species, including not only bacteria but also archaea, viruses, fungi, and protozoa. Which are beneficial? Which are harmful? Which are neutral and could become harmful if not properly controlled? These questions could not be resolved using traditional isolation and culture methods. On one hand, suitable culture methods could not be found for many gut bacteria; on the other hand, identification and enumeration using culture-based methods were extremely tedious, slow, and inaccurate.

Due to these technological limitations, the view that "human symbiotic microorganisms, represented by the gut microbiota, make important contributions to health and disease" did not gain mainstream medical attention or recognition for nearly a century after Metchnikoff's proposal. This situation only began to change in 2004 with the publication of a landmark paper titled "The gut microbiota as an environmental factor that regulates fat storage" in *Proceedings of the National Academy of Sciences* [9]. This milestone paper came from the Gordon laboratory at Washington University in St. Louis. Their series of studies found that germ-free animals do not become obese even when fed high-calorie diets; when the microbiota from obese mice was transplanted into germ-free mice, the recipient mice accumulated significantly more fat than those receiving microbiota from healthy lean mice. In other words, without a microbiota, animals cannot become obese, while obesity symptoms can be transferred between individuals along with the microbiota [10,11]. Using gene knockout and sequencing technologies, they also discovered that the gut microbiota can turn off genes required for fat burning in the intestine and activate genes required for fat synthesis in the liver, thereby transforming the animal into an efficient fat-accumulating machine [9].

This important discovery benefited from several key technological advances: (1) germ-free animal and microbiota transplantation techniques; (2) DNA sequencing technology for determining gut microbiota composition; and (3) gene chip technology for identifying which mouse genes were regulated by the gut microbiota. With these methods enabling large-scale determination of gut microbiota composition changes and animal gene expression changes, researchers could investigate the "molecular dialogue" between thousands of gut bacteria and tens of thousands of animal genes. With germ-free animals and microbiota transplantation techniques, researchers could purposefully inoculate specific bacteria into animals to identify which are harmful, which are beneficial, which are "neutral" or "opportunistic," and under what conditions they might "defect and turn against" human health. The publication of this paper marked the entry of microbiome research into mainstream medical vision.

In October 2005, scientists from 13 countries convened in Paris under the organization of Professor Hervé Bercovici of the French National Institute for Agricultural Research (INRA) for a roundtable meeting on the Human Microbiome Project. Representatives from Shanghai Jiao Tong University and BGI attended

the meeting. After vigorous discussions, consensus was reached that, similar to the Human Genome Project, global efforts should be organized to launch the "Human Microbiome Project" to sequence the genomes of all human symbiotic microorganisms and thereby advance microbiota-health research. The meeting established the International Human Microbiome Consortium and issued the Paris Declaration on promoting human microbiome research, marking the beginning of a new era of international collaboration using modern biotechnology to study the health effects of human symbiotic microorganisms.

Subsequently, scientists from various countries actively sought support from their governments. Ultimately, the EU allocated €12 million under its Seventh Framework Programme to support gut microbiota research, launching the renowned MetaHIT project. The United States later launched the Human Microbiome Project (HMP) with an investment of $130 million. In 2006, during President Jacques Chirac' s visit to China, the second of 14 agreements signed was the Sino-French Declaration on Gut Metagenomics Cooperation, which jointly launched the MetaGUT project with obesity as a common research focus.

Since 2004, over a hundred research papers on the relationship between gut microbiota and disease/health have been published in top-tier journals such as *Nature*, *Science*, *Cell*, and *PNAS*, with thousands more appearing in other biomedical journals. Evidence indicates that over 50 diseases—including obesity, diabetes, cancer, and autism—are associated with gut microbiota dysbiosis. Reports on preventing and alleviating diseases through microbiota modulation using formulated nutrition, probiotics, prebiotics, and drugs have emerged in large numbers. Fecal microbiota transplantation for treating refractory diarrhea was listed among the top ten scientific breakthroughs of 2013.

2. China' s Foundation, Characteristics, and Advantages in Human Microbiome Research

Chinese scientists have been among the pioneers in this surging international research wave. In 2005, Professor Liping Zhao became a member of the inaugural governing board of the International Human Microbiome Consortium, participating in the organization of all major international academic activities. From 2014 to 2016, Academician Lanjuan Li served as the rotating chair of the consortium. In 2008, Shanghai Jiao Tong University organized multidisciplinary Sino-British collaboration, publishing in *PNAS* a method for studying the potential functions of gut bacteria through correlation analysis of urine metabolites and gut microbiota, which became one of the most highly cited papers in the human microbiome field [12]. In 2010, BGI Shenzhen collaborated with European scientists to publish the first human gut microbial gene catalog in *Nature* [3]. In 2012, BGI published a large-scale sequencing study comparing gut microbiota differences between diabetic patients and healthy individuals in *Nature* [13]. At the end of 2012, Shanghai Jiao Tong University published a paper in *The ISME Journal* reporting that a conditional pathogen isolated from an obese patient' s gut could induce obesity in germ-free animals, receiving widespread

international attention and media coverage, with over 35,000 downloads within just two weeks of publication [14]. In 2014, Zhejiang University collaborated with French scientists to publish in *Nature* the gut microbiota structural characteristics of liver cirrhosis patients, laying a solid foundation for disease diagnosis and preventive treatment [15]. In the same year, Guang' anmen Hospital and Shanghai Jiao Tong University collaborated to publish in *The ISME Journal* a paper that not only confirmed the significant therapeutic effect of the classical Han Dynasty formula "Gegen Qinlian Decoction" on diabetes through randomized, double-blind, placebo-controlled clinical trials, but also provided molecular evidence that this traditional Chinese medicine formula may exert its efficacy by modulating the microbiota [16].

Many drugs and therapies in traditional Chinese medicine may exert disease prevention and treatment effects by modulating the microbiota. First, many components of traditional Chinese medicines are poorly absorbed into the bloodstream, making their clinical efficacy unexplainable by Western pharmacology and thus unrecognized by Western medicine. However, the targets of these non-absorbable drugs may not be human cells but the gut microbiota. For example, research from Shanghai Jiao Tong University found that berberine (the active component of Coptis chinensis) can dramatically alter gut microbiota structure, particularly by reducing harmful bacteria and increasing beneficial butyrate-producing bacteria, which may be an important mechanism for the clinically effective treatment of diabetes by berberine despite its poor absorption [17]. In 2015, a multidisciplinary team led by Shanghai Jiao Tong University published in *EBioMedicine* (a journal jointly supported by *Cell* and *The Lancet*) a clinical study on nutritional intervention using medicinal food ingredients from traditional Chinese medicine to successfully improve genetic obesity in children through microbiota modulation, highlighting the enormous potential of TCM medicinal foods to alter microbiota and prevent disease [18].

"Fecal medicine" has a history of over a thousand years in traditional Chinese medicine and was long considered ignorant and superstitious, leading to its abandonment and prohibition. However, a 2012 paper in the *New England Journal of Medicine* on fecal transplantation for treating *Clostridium difficile* infection-induced refractory diarrhea brought fecal medicine back to the international academic forefront [19]. Although TCM does not have the concept of "microbiota," its use of fecal medicine involved not only strict donor selection but also rigorous long-term anaerobic processing of feces to ensure efficacy and safety. Current Western medical practice of using fresh feces directly as transplant material is, in some ways, less advanced than traditional Chinese medicine. In addition to fecal medicine experience and microbiota-modulating drugs, the TCM concept of "medicine and food sharing the same origin" and extensive dietary therapy experience likely exert effects through microbiota modulation.

China is home to 56 ethnic groups, each with its own genetic background, dietary habits, and traditional medicine/health preservation experience. Currently, with economic development, lifestyle and dietary patterns are changing,

and each group faces the severe challenge of chronic disease epidemics. Outside China, millions of descendants of the Chinese nation live abroad. Some maintain Chinese dietary habits and lifestyles, while others have fully integrated into local lifestyles, though their genetic backgrounds remain unchanged. Evidence suggests that overseas Chinese who adopt local dietary patterns develop disease spectra similar to local populations. Therefore, these overseas Chinese populations provide invaluable sample resources for studying the relationships among genetics, diet, microbiota, and disease.

Through systematic research on gut microbiota structural changes and health among Chinese populations worldwide, we can deeply understand the role of microbiota alterations in disease spectrum changes when genetic backgrounds remain relatively stable while dietary structures and lifestyle environmental factors undergo rapid transformation, thereby elucidating novel mechanisms of chronic disease pathogenesis. Simultaneously, by leveraging traditional Chinese health preservation experience to develop new medicines, foods, and health products targeting the gut microbiota, and promoting their use through overseas Chinese communities with gradual global expansion, this initiative could become an opportunity for the Chinese nation to make significant contributions to global human health and a rare chance for China' s traditional medicine industry to modernize and enter the world market.

On October 29, 2015, Professor Liping Zhao from Shanghai Jiao Tong University, together with American and German scientists, published a commentary in *Nature* calling for the implementation of an "International Microbiome Project" to organize multidisciplinary research forces from multiple countries. By establishing unified technical protocols and standards to achieve data integration and sharing, this global initiative would deeply investigate microbiome functions at a global scale, providing novel research ideas and technical means to fundamentally address major challenges plaguing humanity, including chronic disease epidemics, environmental pollution, and energy shortages [20]. For instance, fundamental breakthroughs in the pathogenesis and prevention of major diseases such as type 2 diabetes, cancer, and Alzheimer' s may lie in identifying bacteria that produce inflammatory toxins, carcinogens, and neurotoxins from among thousands of gut bacterial species and elucidating their pathogenic mechanisms. Therefore, "the human microbiome field alone may nurture multiple Nobel Prize-level theoretical achievements" and become a powerful technological innovation engine driving the formation and development of new high-tech industry paradigms.

Thus, at this critical moment when a new medical revolution centered on the gut microbiota-human health relationship is imminent, and given that we possess such rich resources while Chinese scientists' research is not lagging behind, the time has come to move beyond scientists' spontaneous, dispersed "guerrilla warfare" and organize large-scale "decisive battles." We propose that the Chinese government innovate organizational forms and management mechanisms, fully mobilize domestic and international resources, and strongly launch the "Inter-

national Healthy Chinese Microbiome Project" (IHCMP), striving to make this project a pilot initiative for the "International Microbiome Project" and thereby guide and lead the organization and implementation of this new international scientific endeavor.

3. Content and Implementation of the International Healthy Chinese Microbiome Project

3.1 Basic Research

3.1.1 International Healthy Chinese Microbiome Standard Reference Sequence Database

Focusing primarily on Chinese populations and their descendants, while also including other ethnic groups, we will collect respiratory, reproductive, digestive, and skin samples, as well as blood, urine, and fecal specimens from healthy individuals of different geographic locations, genders, age groups, and lifestyles both within China and worldwide. By completing nutritional epidemiology and lifestyle questionnaires, we will establish a Chinese microbiome metagenomic sequence dataset with complete clinical examination, dietary structure, and urine metabolome phenotypic data to serve as a reference standard for healthy microbiomes.

3.1.2 Reference Genome Sequence Database of Representative Chinese Microbiome Strains

From representative healthy Chinese individuals' gut, reproductive tract, respiratory tract, and other sites, we will isolate symbiotic bacterial strains of different taxonomic and functional statuses. Through high-quality whole-genome sequencing and annotation, we will establish a reference genome sequence database for mining human metagenomic sequences.

3.1.3 Metagenomic Sequence Database for Major Chinese Chronic Diseases

Collecting blood, urine, and fecal samples, as well as skin, oral, respiratory, and reproductive tract microbiota or lesion tissue samples from patients with major chronic diseases including obesity, diabetes, cancer, inflammatory bowel disease, neurological and psychiatric disorders, and chronic respiratory diseases, we will establish a metagenomic sequence dataset for major Chinese chronic diseases with complete clinical disease phenotypes, disease-related gene expression profiles, and urine metabolome data to serve as a reference standard for disease diagnosis.

3.1.4 Reference Metagenomic Sequence Database for Major Chinese Infectious Diseases

Collecting blood, urine, and fecal samples, as well as skin, oral, respiratory, and reproductive tract microbiota or lesion tissue samples from patients with major infectious diseases such as hepatitis, influenza, and AIDS, we will establish a metagenomic sequence dataset for major Chinese infectious diseases with com-

plete clinical disease phenotypes, disease-related gene expression profiles, and urine metabolome data to serve as a reference standard for disease diagnosis.

3.1.5 Clinical Efficacy and Mechanism Studies of Traditional Medicine and Health Foods on Human Microbiome Modulation

Following randomized, double-blind, placebo-controlled principles or evidence-based medical case study methods, we will dynamically monitor changes in patients' immunity, metabolism, and microbiota before and after using traditional Chinese medicines and health foods. Through correlation and mining of multi-omics data including blood immunomics, urine metabolomics, fecal metagenomics, and clinical phenomics, we will study their effects and mechanisms in improving health and preventing disease by modulating the human gut microbiome.

3.2 Frontier Technologies

3.2.1 High-Throughput Microbiome Sequencing and Analysis Technology

Applying next-generation sequencing equipment and technologies to human microbiome sequencing, we will optimize sequencing workflows and establish technology platforms suitable for hospital use, achieving at least 1,000 samples per day for 16S rRNA gene sequencing and 100 fecal samples for metagenomics (10 G data per sample). Algorithmic breakthroughs are needed in optimizing memory utilization, improving computational speed, and accuracy for high-throughput metagenomic data analysis. New methods for association analysis, cluster analysis, and functional bacterial species mining suitable for microbiome data characteristics must be developed.

3.2.2 Health Assessment and Measurement Based on Microbiome-Human Interactions

Selecting physical examination populations, we will regularly collect breath, blood, urine, and fecal samples to analyze correlations between physical examination index changes and breath composition, urine metabolomics, and dynamic changes in gut metagenomics. This will enable discovery of new disease biomarkers and establishment of health assessment and measurement technologies that can predict disease development trends.

3.2.3 Multi-Omics Data Integration and Modeling for the "Superorganism"

We will establish new algorithms, software, and technologies for integrating and modeling dynamically collected omics data from the same population, including immunomics, breathomics, metabolomics, and metagenomics. This will lay the foundation for establishing "digital human" technology that includes the human microbiome.

3.2.4 Novel Technologies for Isolation, Culture, and Genome Acquisition of Important Symbiotic Microorganisms

Guided by metagenomic sequence information, we will isolate and culture im-

portant functional bacterial species, establishing new technologies and methods for large-scale, high-throughput isolation of various functional bacterial strains. For difficult-to-culture or uncultivated important human symbiotic functional bacteria, we will establish micro-manipulation techniques to isolate single cells and achieve genome sequencing through single-cell whole-genome amplification.

3.2.5 Human Microbiome Reconstruction Technology Based on Restoration Ecology Principles

From restoration ecology principles, we will achieve recovery of severely dysbiotic gut microbiota through microbiota transplantation and nutritional support to reconstruct healthy microbiomes. We will establish safety evaluation methods and quality control standards for microbiota transplants, develop dietary nutrition technology systems that can stably support reconstructed healthy microbiome structures and functions, and establish microbiome-based methods and standards for evaluating transplantation and nutritional support effects.

3.2.6 Germ-Free Animal-Based Model Animal Technology

We will establish germ-free mouse strains and technical systems for developing various genetic model mice into germ-free strains. We will also establish human microbiota-associated pig models to provide model animals for verifying causal relationships and investigating mechanisms of gut microbiota functions.

3.3 Capacity Building

3.3.1 Construction of National Database and Clinical Standard System for Healthy Chinese Microbiome

Integrating the healthy Chinese microbiome reference sequence set, major chronic disease microbiome reference sequence set, and major infectious disease microbiome reference sequence set, we will establish a national microbiome database. Relying on medical examination and clinical cohort datasets, we will establish a clinical standard system for healthy Chinese microbiomes as an important reference standard for health assessment, disease diagnosis, and efficacy evaluation to guide drug research and development, personalized precision disease prevention and treatment, and personalized health preservation, providing infrastructure for promoting national health.

3.3.2 Construction of Chronic Disease Management System Centered on Chinese Human Microbiome Structure and Function Clinical Detection Technology

Targeting microbiome structure and functional molecular-level dynamic changes, we will establish a new health monitoring technology system. Focusing on developing portable, home-based, or wearable intelligent devices for rapid, real-time, online monitoring of microbiome changes from breath, blood, urine, and feces, we will achieve digital dynamic monitoring and real-time intelligent assessment and regulation of national health status.

3.3.3 Construction of National Sample Bank for Healthy Chinese Mi-

crobiome
Microbiome samples from healthy individuals contain large amounts of beneficial bacterial communities—precious genetic resources that have co-evolved with Chinese genetic characteristics over millions of years. However, due to the overuse of cesarean sections, antibiotics, and bottle feeding, these beneficial bacterial communities transmitted through maternal-infant channels face the danger of disruption and extinction, urgently requiring systematic research and long-term storage. These microbiome repositories can become transplant inocula for rescuing and reconstructing severely dysbiotic microbiota in critically ill patients, "pioneer microbiota" for establishing intestinal microecosystems in infants born through non-natural delivery methods, and "seed microbiota" for restoring elderly microbiome structures and reducing geriatric diseases. This has both immediate clinical value and represents a major strategic initiative for Chinese national health.

3.4 Important Products

3.4.1 Monitoring Instruments and Equipment
We will develop new instruments and equipment for monitoring microbiome-targeted preventive healthcare.

3.4.2 Development of Novel Nutritional Foods for Microbiome Modulation and Optimization
Relying on microbiome-centered health measurement and assessment technologies, we will develop new nutritional foods, particularly staple food products, that can modulate and optimize microbiome structure and function. Their active components must have clear chemical characteristics and evidence-based medical proof for altering microbiome structure and function and improving health indicators for disease prevention.

3.4.3 Artificial Community Products for Microbiome Modulation and Optimization
Relying on microbiome-centered health assessment and measurement technologies, we will select "keystone species" and "foundation species" with clear functions in the human microecosystem as bacterial strains to develop artificial community products that can restore, modulate, and optimize human microbiome structure and function, along with nutritional products supporting their growth. The genome sequences and mechanisms of action must be clear, nutritional requirements well-defined, and evidence-based medical proof must demonstrate significant effects on altering microbiome structure and function and improving clinical health indicators.

3.4.4 Drugs for Microbiome Modulation and Optimization
Relying on microbiome-centered health assessment and measurement technologies, we will screen drugs that can modulate and optimize human microbiome structure and function, particularly from traditional Chinese medicines with unique advantages. Their chemical structures and mechanisms of action must

be clear, indications well-defined, and evidence-based medical proof must demonstrate significant effects on altering microbiome structure and function and improving clinical indicators.

4. Conclusion

We should leverage the advantages of the wide global distribution of Chinese populations and diverse health preservation experience, combine large-scale sample resources with modern omics and big data technologies, establish standard databases and strain banks for healthy microbiomes of typical Chinese populations, develop new health monitoring technologies centered on microbiome structure and function dynamics, and create new technologies and products that can improve or reconstruct healthy microbiomes. This will make unique contributions to disease prevention, public health maintenance, and the upgrading and globalization of the traditional medicine industry.

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Note: Figure translations are in progress. See original paper for figures.