The ZOE Microbiome Health Ranking: A Novel Tool for the Diet-Microbiome-Health Axis

Journal:	*The Innovation Medicine*
Manuscript ID	TIME-2026-0033.R3
Manuscript Type:	News & Buzz
Keywords:	Gut microbiome, Health markers, Dietary interventions

Pre-proof

SCHOLARONE
MANUSCRIPTS

The ZOE microbiome health ranking: A novel tool for the diet-microbiome-health axis

Kailin Liu[1], Yuhao Wang[1,2,3,*], Meng Wang[1,*]

1 Zhejiang Provincial Key Laboratory of Pancreatic Disease of The First Affiliated Hospital, Institute of Translational Medicine, Zhejiang University School of Medicine, Hangzhou, Zhejiang 310029, China

2 Cancer Center, Zhejiang University, Hangzhou, Zhejiang 310029, China

3 Institute of Fundamental and Transdisciplinary Research, Zhejiang University, Hangzhou, Zhejiang 310029, China

***Correspondence:** yuhaowang@zju.edu.cn (Y.W); mengwang21@zju.edu.cn (M.W.)

Pre-Proof For Review Only

In a recent publication in *Nature,* Asnicar et al.[1] conducted a large-scale integrative analysis of gut metagenomes, dietary patterns, and cardiometabolic health markers across over 34,000 individuals. Their work established the "ZOE Microbiome Health Ranking 2025", a robust framework that identifies key microbial species associated with host health. This research provides a transformative reference for defining healthy microbial communities and advances the implementation of precision nutrition in managing metabolic diseases.

The escalating burden of cardiometabolic diseases (CMDs) poses a major public health challenge.[2] While habitual dietary patterns are well established as key environmental determinants of CMD risk,[3,4] the mechanisms through which nutritional signals are translated into host physiological responses remain incompletely elucidated. Growing evidence positions the human gut microbiome as a critical "bioreactor" mediating diet–host interactions.[5] However, high inter-individual variability has hindered the identification of reproducible microbial signatures associated with health.

Over the past decade, a precise definition of a "healthy" gut microbiota has remained elusive, largely because conventional approaches have largely depended on broad ecological measures such as species diversity indices or taxonomic summaries at the phylum or class level. These low-resolution approaches lack the granularity required to identify functionally relevant taxa or to uncover the causal pathways governing host-microbiome interactions and impede the translation of microbiome discoveries into clinical diagnostics and targeted therapeutic strategies.

In a recent study published in *Nature*, Asnicar et al. addressed this challenge through large-scale, high-resolution multi-omics integration. Beyond establishing the most comprehensive microbiota-health association framework to date, the study introduced a quantifiable, modifiable, and clinically verifiable "microbiome health scoring system". This work exemplifies the field's transition from descriptive ecological observations toward a more mechanistic and actionable paradigm for precision nutrition and microbiota-targeted interventions.

In this groundbreaking research, Asnicar et al. conducted a multi-omic integrative analysis across a large meta-cohort of 34,694 participants from the United Kingdom (UK) and the United States (US). By combining high-resolution shotgun metagenomic sequencing with

For Review Only
Pre-proof

granular dietary records and comprehensive cardiometabolic profiling, the authors constructed one of the most statistically powered microbiome-health repositories to date. The methodological cornerstone of this research is the derivation of the "ZOE Microbiome Health Ranking 2025" and the "ZOE Microbiome Diet Ranking 2025", which transform high-dimensional metagenomic data into a quantifiable scoring system based on the robust correlations between 661 prevalent species-level genome bins (SGBs) and 37 distinct clinical biomarkers. This ranking identified a clear dichotomy between "favorable" SGBs, such as *Faecalibacterium prausnitzii*, which consistently aligned with cardioprotective markers, and "unfavorable" SGBs, including *Ruminococcus gnavus* and *Flavonifractor plautii*, which exhibited potent associations with elevated BMI, dyslipidemia, and systemic inflammation (Figure 1).

By systematically exploring the "dark matter" of microbiota, the authors further revealed that 44% of the top-ranked health-associated species represent uncultivated or previously uncharacterized taxa, whereas traditional probiotics, such as various *Lactobacillus* species, did not demonstrate competitive advantages in the health-centric ranking. To ensure the universal applicability of this framework, the authors validated the rankings across a heterogeneous external dataset of 5,348 samples from 27 global cohorts. Across these populations, depletion of favorable SGBs and enrichment of unfavorable SGBs emerged as consistent hallmarks of obesity and metabolic syndrome. Thus, this study establishes a robust data foundation for defining internationally applicable, species-level biomarkers of intestinal health, enabling the assessment of gut microbiome status to achieve a clinical reference value comparable to interpreting serological diagnostics in inflammatory bowel disease (IBD) or nutritional indices like the Subjective Global Assessment (SGA).

Furthermore, by analyzing microbial changes in clinical trials, the authors found that personalized dietary changes and targeted prebiotic supplementation significantly increased the abundance of beneficial microbes such as *Bifidobacterium adolescentis* and *Roseburia hominis*, whereas conventional probiotic supplements alone showed limited effects on overall microbial community structure. The study also revealed a critical geographical distinction: while the Health Ranking remained remarkably stable across the US and UK cohorts, the Diet Ranking varied considerably with local food environments. This underscores that effective microbiome-

For Review Only Pre-proof

targeted nutrition strategies must account for region-specific dietary patterns to maximize their health impact.

The methodological paradigm established by this study is transformative, moving beyond mere observation to create a functional blueprint of the gut ecosystem. Earlier large-scale initiatives were often constrained by genus-level taxonomic bins or single ecological indices such as alpha diversity, which can obscure strain-specific functional contributions. In contrast, this study leverages granular species-level resolution to delineate actionable health associations. Its innovation is twofold. First, by employing SGBs as its fundamental unit of analysis, it achieves an unprecedented resolution that transcends the limitations of genus- or phylum-level profiling. This granularity enables the precise mapping of microbial taxa to specific host cardiometabolic phenotypes, transforming the microbiome from a nebulous community into a collection of discrete, functionally attributable units.

Second, and perhaps more consequential, is its systematic illumination of the "microbial dark matter". The finding that nearly half of the top health-associated SGBs are uncultivated or poorly characterized taxa represents a conceptual shift for the field. It challenges the prevailing paradigm of probiotic development, which has been limited to a narrow, historically contingent set of culturable strains. This finding redefines the search space for next-generation live biotherapeutics, redirecting focus toward these prevalent yet elusive commensals that have evolved *in situ* ecological fitness. It posits that the most effective therapeutic agents may not be found in culture collections but must be discovered and understood within their native human habitat through metagenomic-guided discovery. Consequently, this work reshapes the broader research paradigm from one of descriptive cataloging toward a prescriptive, ecologically informed engineering of the gut ecosystem, wherein therapeutic strategies are designed not by what is merely culturable, but by what is functionally indispensable, as evidenced by high-resolution metagenomic data.

This refined framework directly informs the development of novel clinical tools. At the diagnostic level, it paves the way for a "microbiome vital sign". Rather than intervening only upon the manifestation of insulin resistance or dyslipidemia, clinicians could leverage panels quantifying key SGBs, analogous to a lipid profile, to assess dysbiosis-associated risk earlier in the disease trajectory. Integrated with predictive algorithms, such panels could generate

For Review Only
Pre-proof

personalized risk scores, enabling preemptive, microbiome-informed health strategies.

At the therapeutic level, it advocates for a transition from generic to precision microbiota modulation. The clear functional ranking of SGBs provides a rational template for designing targeted interventions. This could range from precision nutrition plans formulated to nourish specific high-ranking taxa to the future development of a "Microbiome Vault"—a repository of well-characterized, health-associated commensals for targeted bacteriotherapy or refined fecal microbiota transplantation. Such approaches move beyond empirical microbial transfer toward engineered consortia tailored to correct rank-identified deficiencies.

While the SGB-phenotype association network established in this study offers significant clinical promise, its practical implementation faces key technical bottlenecks. The current high cost of deep metagenomic sequencing limits broad clinical adoption, necessitating the development of more affordable, targeted diagnostic panels. Furthermore, the considerable inter-individual variability in response to microbiota-directed interventions requires the integration of host genomic data, detailed dietary records, and other multivariate factors to build more generalizable predictive models. Addressing these challenges will require interdisciplinary collaboration across microbiome science, clinical medicine, and artificial intelligence to develop comprehensive closed-loop systems, such as ingestible biosensors enabling real-time monitoring of microbial activity to guide personalized, adaptive interventions.

In summary, this landmark *Nature* study redefines the gut microbiome as a measurable and modifiable health determinant. By translating complex microbial ecosystems into phenotype-linked metrics, it establishes a framework for precision medicine integration. The work challenges existing probiotic paradigms by highlighting the health-relevant "microbial dark matter" and demonstrating the feasibility of personalized nutritional modulation. Ultimately, it provides a validated roadmap for microbiome-informed preventive strategies.

To translate this ranking system into clinical utility, we propose a tiered diagnostic framework. The initial tier would use a cost-effective, targeted qPCR or shallow-shotgun panel to quantify the top decile of health- and disease-associated SGBs identified in this study, serving as a rapid "microbiome vital sign". Should this screen indicate dysbiosis, the second tier would escalate to comprehensive metagenomic sequencing coupled with AI-driven integration of host

For Review Only Pre-proof

dietary logs and clinical biomarkers, as demonstrated by the ZOE framework. This tiered model not only addresses the current cost barrier to deep sequencing but also establishes a testable roadmap for evaluating the cost-effectiveness of microbiome-informed interventions in large-scale clinical trials.

REFERENCES

1. Asnicar F., Manghi P., Fackelmann G., et al. (2025). Gut micro-organisms associated with health, nutrition and dietary interventions. *Nature* DOI:10.1038/s41586-025-09854-7
2. Micha R., Peñalvo J.L., Cudhea F., et al. (2017). Association between dietary factors and mortality from heart disease, stroke, and type 2 diabetes in the United States. *JAMA* **317**:912-924. DOI:10.1001/jama.2017.0947
3. Asnicar F., Berry S.E., Valdes A.M., et al. (2021). Microbiome connections with host metabolism and habitual diet from 1,098 deeply phenotyped individuals. *Nat. Med.* **27**:321-332. DOI:10.1038/s41591-020-01183-8
4. Dicken S.J., Jassil F.C., Brown A., et al. (2025). Ultraprocessed or minimally processed diets following healthy dietary guidelines on weight and cardiometabolic health: A randomized, crossover trial. *Nat. Med.* **31**:3297-3308. DOI:10.1038/s41591-025-03842-0
5. Schroeder B.O. and Bäckhed F. (2016). Signals from the gut microbiota to distant organs in physiology and disease. *Nat. Med.* **22**:1079-1089. DOI:10.1038/nm.4185

For Review Only
Pre-proof

FUNDING AND ACKNOWLEDGMENTS

This work was supported by grant BX20250133 from the China National Postdoctoral Program for Innovative Talents (M.W.); grant 2025M782767 from the China Postdoctoral Science Foundation (M.W.); grant R26C110002 from Zhejiang Provincial Natural Science Foundation (Y.W.); grant 2025C02128 from the Department of Science and Technology of Zhejiang Province (Y.W.); grant 32471189 from the National Natural Science Foundation of China (Y.W.). The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

FIGURE LEGENDS

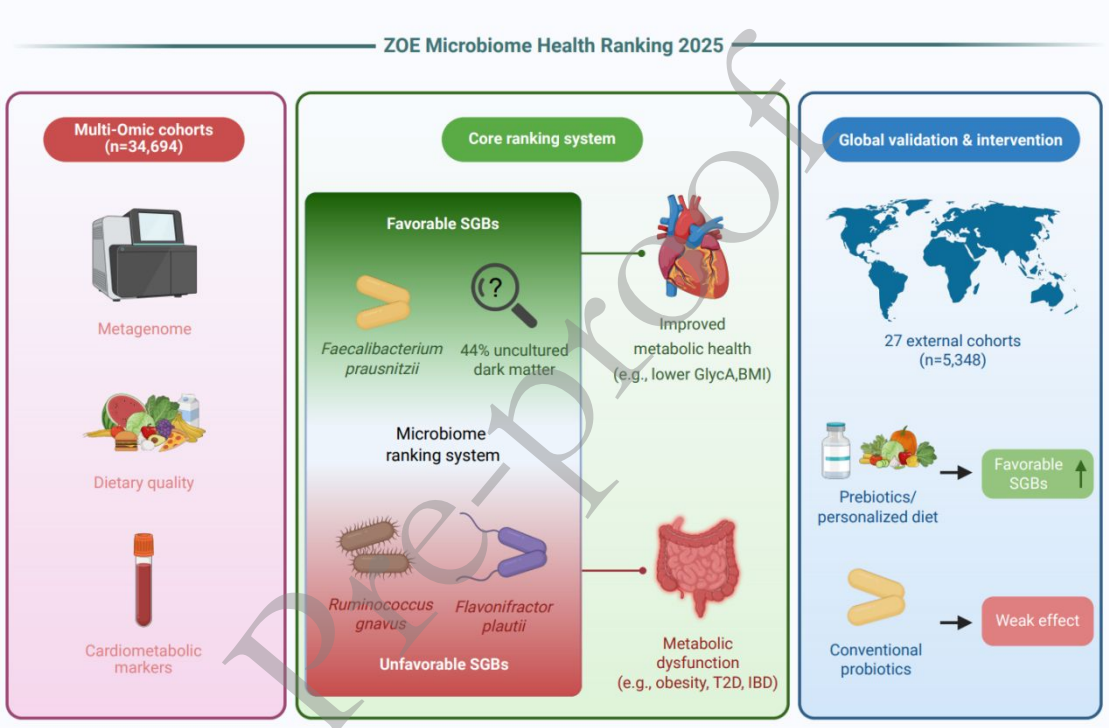
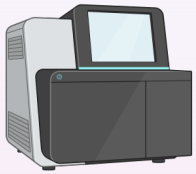


Figure 1. Derivation and validation of the "ZOE Microbiome Health Ranking 2025". Rankings were derived from metagenomic and clinical data of 34,694 participants and validated across 27 global cohorts. The ranking distinguishes health-associated (44% uncultured) from disease-associated microbial species. Personalized dietary interventions more effectively promoted beneficial taxa than probiotic supplementation.

Pre-proof

ZQ Microbiome Health Ranking 2025

Multi-Omic cohorts (n=34,694)



Metagenome

Dietary quality

Cardiometabolic markers

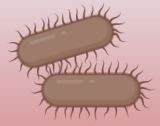
Core ranking system

Favorable SGBs

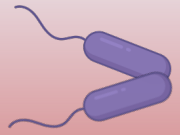
Faecalibacterium prausnitzii

44% uncultured dark matter

Microbiome ranking system

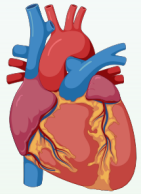


Ruminococcus gnavus

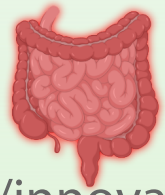


Flavonifractor plautii

Unfavorable SGBs



Improved metabolic health (e.g., lower GlycA,BMI)



Metabolic dysfunction (e.g., obesity, T2D, IBD)

Global validation & intervention

27 external cohorts (n=5,348)

Prebiotics/ personalized diet

Favorable SGBs

Conventional probiotics

Weak effect

https://mc03.manuscriptcentral.com/innovation-medicine