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Perspective

The microbiome for clinicians

Serena Porcari,[1,2,3] Siew C. Ng,[4,5,6] Laurence Zitvogel,[7,8] Harry Sokol,[9,10,11] Rinse K. Weersma,[12] Eran Elinav,[13,14] Antonio Gasbarrini,[1,2,3] Giovanni Cammarota,[1,2,3] Herbert Tilg,[15] and Gianluca Ianiro[1,2,3,*]

[1]Department of Translational Medicine and Surgery, Università Cattolica del Sacro Cuore Facoltà di Medicina e Chirurgia, Roma, Italy
[2]Department of Medical and Surgical Sciences, UOC Gastroenterologia, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Roma, Italy
[3]Department of Medical and Surgical Sciences, UOC CEMAD Centro Malattie dell'Apparato Digerente, Medicina Interna e Gastroenterologia, Fondazione Policlinico Universitario Gemelli IRCCS, Roma, Italy
[4]Microbiota I-Center (MagIC), Hong Kong, China
[5]Department of Medicine and Therapeutics, Centre for Gut Microbiota Research, The Chinese University of Hong Kong, Hong Kong, China
[6]New Cornerstone Science Laboratory, The Chinese University of Hong Kong, Hong Kong, China
[7]ClinicoBiome, Gustave Roussy, Villejuif, France
[8]University Paris Saclay, Kremlin Bicêtre Medical School, Kremlin Bicêtre, France
[9]French Fecal Transplant Group (GFTF), France
[10]Sorbonne University, INSERM, Centre de Recherche Saint-Antoine, CRSA, AP-HP, Saint Antoine Hospital, Gastroenterology Department, Paris, France
[11]Paris Centre for Microbiome Medicine FHU, Paris, France
[12]Department of Gastroenterology and Hepatology, University of Groningen and University Medical Center Groningen, Groningen, the Netherlands
[13]Department of Systems Immunology, Weizmann Institute of Science, Rehovot, Israel
[14]Microbiome & Cancer Division, German Cancer Research Center (DKFZ), Heidelberg, Germany
[15]Department of Internal Medicine I, Gastroenterology, Hepatology, Endocrinology & Metabolism, Medical University Innsbruck, Innsbruck, Austria
*Correspondence: gianluca.ianiro@unicatt.it
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SUMMARY

Despite promising evidence in diagnostics and therapeutics, microbiome research is not yet implemented into clinical medicine. Several initiatives, including the standardization of microbiome research, the refinement of microbiome clinical trial design, and the development of communication between microbiome researchers and clinicians, are crucial to move microbiome science toward clinical practice.

GUT MICROBIOTA IN CLINICAL PRACTICE: LOST IN TRANSLATION

Recent advances in sequencing technologies and bioinformatic tools have enabled a comprehensive mapping of the gut microbiota composition and functional potential and associated microbiome disruption with several human disorders. Alongside these analogic connections, mechanistic studies unveiled a key role of the gut microbiome in human health and disease.

This progression has raised interest toward investigating the potential of the gut microbiome for improving human health. However, microbiome science is still far from being implemented into clinical practice. For example, fecal microbiota transplantation (FMT) is approved for clinical use in recurrent *Clostridioides difficile* infection (rCDI)[1] but, despite extensive investigations, has not gone beyond the research setting for other indications. Also, although probiotics are one of the key drivers of healthcare expenditure, their use is often not supported by strong levels of evidence[2] and their real role on human health is under debate.

Several reasons, including biological, methodological, logistical, and clinical limits, lie behind this loss in translation between research and clinical application in the microbiome field (Box 1).

First, the heterogeneity and complexity of the human microbiome may prevent establishing clear causal relationships between the gut microbiome and specific diseases or outcomes, complicating the translation of preclinical findings into human studies, which frequently yield inconsistent or suboptimal results, particularly in the field of noncommunicable chronic disorders (NCDs).

From a methodological point of view, the effects of diet, the environment, concomitant medications, and other factors influencing microbiome composition also need to be considered. Additionally, the poor diffusion of standardized protocols for microbiome analysis and intervention hinders the generation of reproducible findings across human studies and, consequently, of practical implementation.

Also, although the inter-individual variability and the plasticity of the gut microbiome support a personalized microbiome modulation over a one-size-fits-all therapy, it is prevented by challenges associated with the implementation of microbiome profiling and patient-tailored treatment approaches in clinical practice. Notably, most evidence in the microbiome field was generated predominantly from academic centers, which do not have the strength of industry to develop large and well-organized

Box 1. Challenges that prevent the application of microbiome research in clinical practice

Type of challenge	Details
Biological	The identification of causal links between the gut microbiome and human conditions is difficult due to the heterogeneity and complexity of the gut microbiome.
Methodological	Consideration of diet, environments, concomitant medications, and other environmental influences in the design of microbiome studies; the lack of standardized protocols for microbiome analysis and intervention prevents the release of reproducible findings (and subsequently their implementation).
Logistical	A personalized approach for the microbiome is prevented by challenges associated with the practical implementation of microbiome profiling and patient-tailored microbiome-based interventions; most evidence in the microbiome field comes from academia, often resulting in modest-sample-size single-center studies that may hamper the generalizability of results and the advancement of microbiome-based therapies or biomarkers from research to clinical application.
Cultural	The limited confidence of most clinicians in dealing with microbiome science prevents the clinical application of research data.

clinical trials. This often resulted in modest-sample-size single-center studies that may hamper the generalizability of results and the advancement of microbiome-based therapies or biomarkers from research to clinical application

Finally, although biological evidence may support the application of the microbiome in medicine, direct evidence is not yet sufficiently established to make its implementation ready for prime time in several clinical indications. For example, promising data support the use of the microbiome as a diagnostic or therapeutic tool in several disorders, e.g., cancer, as detailed later. However, current findings still need to be validated in larger cohorts, confirmed after assessment of confounders, and/or corroborated by mechanistic proofs. Generally, this absence of consolidated evidence prevents most clinicians from embedding the microbiome in their clinical practice. Also, most of them are not sufficiently confident in dealing with the nuances and complexity of microbiome science. These additional critical factors prevent the application of research data to clinical practice.

MOVING THE MICROBIOME INTO CLINICAL PRACTICE: POTENTIAL, CURRENT LANDSCAPE, AND CHALLENGES

Although gut microbiome research is far from being widely implemented in clinical practice, in recent years, several lines of evidence concerning the use of the microbiome both as a diagnostic and as a therapeutic tool have started filling the gap between science and clinical medicine in this field, as summarized in Figure 1.

The microbiome as a diagnostic tool

The human microbiome offers potential for different applications as a diagnostic tool in clinical medicine, including the diagnosis or risk assessment of specific diseases or the prognostication of their natural history, the prediction of response to therapies, and the fine-tuning of therapeutic microbiome modulators, e.g., FMT, and their monitoring efficacy. Current developments in bioinformatics, e.g., machine learning, are progressively enabling the transformation of complex microbiome data in manageable metrics and decision support tools for clinicians.

In the immediate past, several lines of research have generated direct or indirect evidence for implementing microbiome diagnostics in these clinical settings.

Microbiome diagnostics for the prediction/early diagnosis of diseases

Colorectal cancer (CRC) has attracted a considerable number of research efforts in the diagnostic microbiome field so far. First, two metagenomic analyses of geographically different datasets identified microbial signatures reproducibly associated with CRC that were able to increase the diagnostic accuracy of fecal occult blood test.[3,4] More recently, CRC precursors, specifically tubular adenomas and sessile serrated adenomas, were associated with two distinct microbiome signatures in a large cohort of nearly 1,000 patients undergoing colonoscopy,[5] supporting the investigation of the gut microbiome as a screening tool for CRC. However, several key pieces of clinical information, including the cost-effectiveness and/or the clinical impact of this approach (e.g., its gain in number-needed-to-diagnose), have yet to be addressed before considering its use in daily routine.

Similarly, a recent metagenomic analysis of nearly 6,000 samples has identified global cross-cohort bacterial clusters for the diagnosis of inflammatory bowel disease (IBD), with distinct profiles for ulcerative colitis and Crohn's disease, respectively, and achieved areas under the curve >90% in separating patients from controls; this has been transformed into a multiplex droplet digital polymerase chain reaction test for clinical use.[6]

Microbiome diagnostics to predict the response to therapies

The gut microbiome has also raised the interest of the scientific and medical community for its potential to predict the response to specific therapies. Most available data concern the use of immune checkpoint blockade (ICB) in patients with epithelial cancers. This line of evidence has progressively become more consolidated, starting from the clinical observation of negative correlation between antibiotics and ICB response,[7] moving to

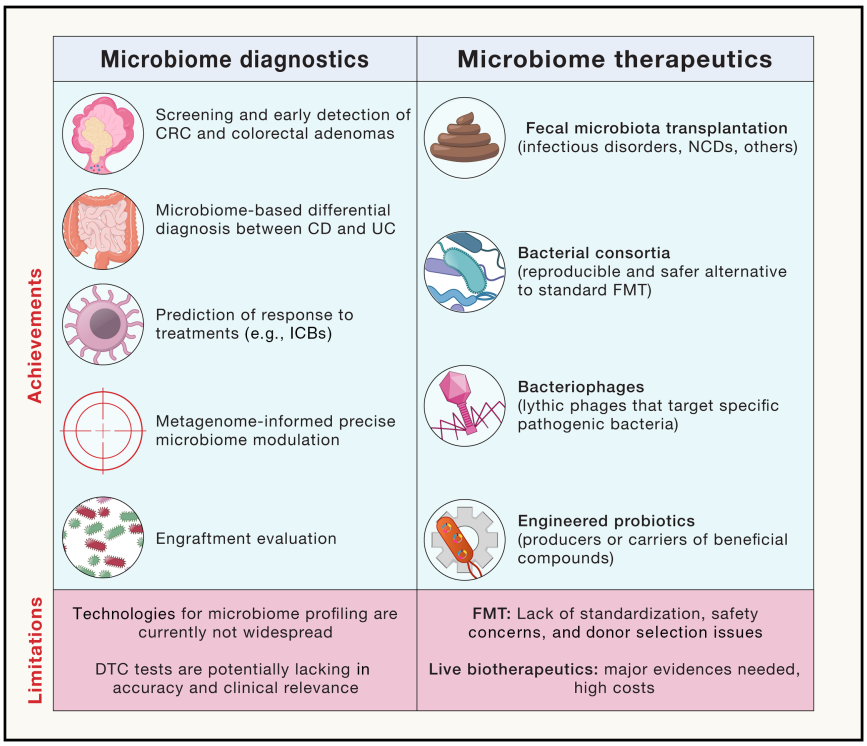

Figure 1. Scientific achievements, with related limits, that support the use of the microbiome for diagnostics and therapeutics

the metagenomic identification of baseline and longitudinal microbial signatures associated with clinical outcomes of cancer after ICB,[8] and finally to a validated microbial test to find reproducible bacterial clusters in different cancer types.[9]

Another emerging example refers to the role of the microbiome in predicting drug response in IBD, including salicylates,[10] immunodulators, or biological drugs,[11] although these data are still conflicting and not yet conclusive.[12]

Microbiome diagnostics to inform therapeutic microbial modulation

Finally, increasing evidence supports the application of microbiome diagnostics to therapeutic microbiota modulation. Microbiome profiling might be useful to target microbial therapies, e.g., to improve FMT outcomes by selecting specific donors,[13] donor-recipient matching, or to monitor the microbial engraftment with the aim of predicting clinical response to FMT.[14]

Open challenges to implement microbiome diagnostics

Despite the promising potential, several open issues prevent a full exploitation of the gut microbiome as a diagnostic tool in medicine. First, state-of-the-art technologies for microbiome profiling, i.e., shotgun metagenomics, which enable strain-level resolution analysis of gut microbiota composition as well as inference of functional microbial potential, are not yet widely utilized, despite the progressive decrease in equipment and consumables costs.

The availability of such tools might appear as a research luxury but may be relevant, at least in some cases, to inform clinical decisions, i.e., disease risk stratification and management/monitoring. For example, *Fusobacterium nucleatum* is known to be enriched in CRC, being also correlated with advanced disease and poor prognosis, but recent evidence suggests that its specific clade, Fna C2, is mostly responsible for this association.[15] Also, colibactin-producing/*pks*+ *E. coli* strains have a known procarcinogenic potential for the development of CRC compared with other *E. coli* representatives.[16] Finally, specific clades of *Klebsiella pneumoniae* may be associated with IBD[17] and some others may enable endogenous production of alcohol in the gut,[18] thus supporting a microbial-dependent pathogenic pathway for metabolic-associated fatty liver disease (MASLD).

The evaluation of the tissue/mucosal microbiome also has a considerable potential, but our understanding of its role is still preliminary compared with what we know on the microbial communities of the gut. For example, in the cancer field, the immunomodulatory role of the intratumoral microbiome is emerging, but it is still controversial. Specifically, available studies do not unravel causal relationships between intratumoral microorganisms and cancer immune control. Moreover, it is unclear to what extent tissue microbes represent infection of established tumors or simply reflect incidental bacteremia supported by the systemic immunosuppression of the host. However, innovative diagnostic tools, e.g., culturomics of fresh tumor tissues and other emerging pipelines, are proving to be effective in accurately capturing microbial signals in human clinical tissues in order to properly evaluate host-microbiome interactions at single-cell resolution.[19]

Beyond the microbiome, other omics approaches able to provide a direct evaluation of microbial functions (e.g., metaproteomics or metabolomics) may overcome limitations of pure metagenomics, e.g., the inability to identify metabolically active vs. dormant commensals or actual functions rather than DNA-based functional potential. For instance, metagenome-informed metaproteomics enables a unified functional characterization of diet-host-microbiome interactions and has yielded new trans-kingdom protein-based biomarkers for multiple features of IBD.[20] However, the translation from metagenomics to functional omics is highly complex due to the variety of products that a single microbe can release.

Beyond technicalities, the field of microbiome diagnostics is facing more critical issues. In recent years, direct-to-consumer (DTC) microbiome testing has rapidly become popular worldwide for their claim to provide personalized health checks. This trend has raised several concerns related to standardization, quality control, regulatory oversight, and clinical usefulness.

These tests indeed display significant variability in methodologies and analytical rigor.

Along with this gap, health risk assessments and dietary recommendations provided by some DTC services frequently lack robust scientific substantiation, creating risks of misinterpretation and unnecessary concern among both consumers and healthcare providers. These issues have prompted experts to call for regulatory frameworks to limit the distribution of potentially misleading or clinically irrelevant information.

Generally, microbiome testing is currently set as a vague tool to satisfy the curiosity of the general population rather than being conceived as a diagnostic tool for patients with specific indications. This perception is shared in respect of several human genetic DTC tests, which are now losing their hype after years of popularity.[21] However, human DNA diagnostics is also well established in clinical practice as a key tool for precision medicine, e.g., in oncology.[22]

A comprehensive breakthrough in the current structure and landscape of microbiome testing, including its standardization and the development of direct supporting evidence for its use, is needed to move these tests from being simply marketable to becoming reliable diagnostics for clinical practice and, consequently, avoiding their rapid disappearance.

The microbiome as a therapeutic target or tool

Microbiome therapeutics: The example of FMT and associated issues

In the last decade, the field of microbiome therapeutics has experienced a tremendous advancement in scientific evidence, quality of research, and expansion in approaches to modulate the microbiome. For several reasons, a prime example of this rise can be found in FMT. First, a continuously growing body of evidence has supported the rapid transition of FMT from being a research approach to becoming an accepted treatment in clinical practice for the management of rCDI.[23] Moreover, this procedure has become regulated by international guidelines, e.g., with comprehensive recommendations for donor screening and manufacturing to strengthen its safety.[24] FMT has also shown preliminary potential for effectiveness in other disorders beyond rCDI, such as IBS (irritable bowel syndrome) and IBD, or as a modulator of response to ICB. Additionally, FMT trials have progressively included state-of-the-art technologies of microbiome investigation, such as whole-genome sequencing or metabolomics, or innovative delivery routes, e.g., lyophilized oral FMT. Interestingly, FMT has also been exploited as a model to disentangle the interactions between two different microbial ecosystems, understand the ecological dynamics of FMT success,[14] and generate a biological background for the amelioration of FMT protocols and, likely, clinical outcomes.

Altogether, these steps provide considerable potential for the advancement of the FMT field. However, it is still encumbered by a number of challenges that prevent not only its widespread application in clinical practice but also its expansion toward other diseases beyond rCDI.

First, biological mechanisms of FMT are not yet fully disentangled, although their understanding, e.g., the importance of microbial engraftment and of its persistence in the recipient gut, is needed to increase FMT effectiveness.[14] Also, regulatory frameworks of FMT differ substantially among countries and range between the categorization as a drug, a tissue transplant, a medicinal product, or a practice of medicine, complicating efforts toward standardization and dissemination. Moreover, despite the high quality standards of current screening procedures, safety concerns, mainly related to the transmission of infectious agents, have been raised.

Finally, several issues are related to donor selection. First, the highly rigorous process for selection and maintenance of FMT donors makes them unlikely to have widespread uptake in the long term. Moreover, although a healthy microbial mass, regardless of its composition, appears to be effective anyway for rCDI, the clinical success of FMT in NCDs might be influenced by the characteristics of the donor microbiome, recipient microbiome, and by some kind of "compatibility" between them. Although FMT might remain an established therapy for rCDI, these features make it unlikely to be released on a large scale if a stable donor biomass must be used in the long run for chronic disorders. Therefore, scalable approaches for microbiome modulation, named artificial microbiome therapeutics, have been recently envisioned and investigated.

Artificial microbiome therapeutics and related limitations

In recent years an innovative line of therapeutic agents, referred to as artificial microbial consortia or, more widely, live biotherapeutic products, have emerged to overcome these challenges. Being safe, reproducible, and scalable, these products are therefore proposed as an alternative to standard FMT.

Initial evidence comes from donor-derived microbiome consortia that, after being investigated in randomized trials (e.g., RBX2660 or SER-109), have been recently approved by the U. S. Food and Drug Administration (FDA) for the prevention of rCDI.[25] These products, despite being available on a large scale, still share some limitations of standard FMT, including traceability and reproducibility. Subsequently, defined bacterial consortia have been developed and successfully investigated in rCDI.[26]

Due to their ability not only to guarantee the reproducibility of the microbial biomass but also to allow its fine-tuning, bacterial consortia enable a microbiome-based precision medicine approach and are currently being investigated in several NCDs.[25] Finally, available studies are also disentangling the mechanisms of their effectiveness,[17] with considerable potential for advancing the field in the near future. The identification of defined consortia that combine ease of manufacturing and clinical effectiveness is still a challenge for the expansion of these products.

Other artificial microbiome therapeutics are expanding the possibilities of gut microbiome modulation even more. Single-strain live biotherapeutics (also called "next-generation probiotics"), such as *Akkermansia muciniphila*, *Akkermansia massiliensis*, or *Faecalibacterium prausnitzii*, differ from most standard probiotics as they are autochthonous members of the human gut microbiome and have been successfully investigated in several NCDs. Engineered probiotics are genetically modified organisms enabled to perform specific functions within the gut environment, such as producing therapeutic compounds or acting as vectors (i.e., for vaccines).

Finally, bacteriophages can suppress specific taxa due to their lytic action on the bacterial genome, with potential for targeting not only multi-drug-resistant bacteria but also those known for contributing to NCDs.[26] This growing toolbox of opportunities also faces several challenges. First, established evidence is needed before supporting artificial microbiome therapeutics for the management of NCDs. Moreover, high quality standards are required for their clinical use, as already claimed for probiotics or FMT. Notably, microbiome therapeutics should also be affordable and equitable, but market costs are currently high and minorities are underrepresented in pertinent clinical trials.

Therefore, beyond the advancement in evidence and technologies, a wider set of actions is needed to move the gut microbiome into clinical practice.

ACTIONS TO ACCELERATE THE POSITIONING OF THE MICROBIOME IN CLINICAL PRACTICE

The integration of microbiome science into clinical practice represents one of the most exciting challenges of modern medicine, supported by recent advancements both in microbiome diagnostics and therapeutics, as discussed above. To fully realize this potential and accelerate the positioning of microbiome research in healthcare settings, a multifaceted strategy involving different actions and related stakeholders is required, as described below and in Figure 2.

Standardization of microbiome research to improve translatability of findings

The intrinsic complexity of the gut microbiome makes the design and the reporting of clinical trials challenging, and this obstacle may prevent the translatability of research into clinical practice.

In recent years, several initiatives have attempted to standardize different aspects of microbiome research. For example, the recently released STORMS ("Strengthening The Organization and Reporting of Microbiome Studies") checklist provides a set of recommendations for the reporting of human microbiome studies, from study design to sample collection, sequencing methods, and computational and statistical analyses, with the aim of facilitating the synthesis of findings across studies.[27] Another example is represented by the Human Microbiome Action,[28] a collective initiative aimed at harmonizing European microbiome research, with the ultimate purpose of making healthcare systems take it into account. This consortium has already dealt with different aspects of the gut microbiome, from the identification and relevance of microbial biomarkers to the challenges that concern the definition of a "healthy microbiome." Other initiatives dealt with more technical aspects of microbiome research. The International Human Microbiome Standards (IHMS) project aimed to develop standard operating procedures for sample collection, storage, and processing, whereas the Microbiome Quality Control (MBQC) project was built to improve the reproducibility of microbiome analyses across different laboratories. Another international consensus action has recently released recommendations to standardize the methodological framework for the provision of microbiome testing, to mitigate the use of inappropriate tests and to lay the methodological groundwork for the use of microbiome diagnostics in clinical practice.[29]

Finally, ongoing efforts in harmonizing the regulatory frameworks of the microbiome, e.g., the recent classification of microbiota as a substance of human origin (SoHO) and its assimilation to other transplantable tissues by the European Union,[30] are expected to add a further dimension of standardization and ease both research and clinical practice in this field.

Improving the design and implementation of microbiome clinical trials to generate actionable results

The promising insights in diagnostic and therapeutic microbiome research prompt the evolution and strengthening of microbiome clinical trials, with the aim of generating outputs that are translatable in clinical practice. This process, propped up by initiatives for the standardization of microbiome research described above, involves a series of actions, most of which are already ongoing. First, statistics of clinical studies should be applied to microbiome trials in their different aspects. For example, as already advocated and facilitated by specific tools,[31] a proper sample size estimation is crucial for both diagnostic and therapeutic microbiome studies to increase their reliability and generalizability. Sample size of microbiome studies may be influenced by different factors—including the specific research question (i.e., evaluating differences among groups in one taxon/cluster or in the whole microbial community) or the definition of type I and type II errors—and effect size, based on the study design.[31]

Metagenomic meta-analyses should also follow the systematic approach usually required for clinical meta-analyses, e.g., the application of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist, to guarantee the reliability of results.[14] Another issue relates to the selection of trial outcomes. Often, microbiome trials include non-clinical primary endpoints, although the choice of clinical primary outcomes enables a smoother translation of trial results into practice. Also, study populations should be identified to answer clinically relevant needs. For example, several studies that associated CRC with microbiome signatures focused on patients with advanced stages of disease.[3] Although these efforts built sufficient evidence to support the further pursuit of this research line, healthcare systems would benefit from the investigation of screening populations or patients with premalignant lesions rather than patients already at advanced cancer stages. Initiatives aimed at filling this gap have been recently released[5] or are ongoing.[32] Also, defined subgroups of patients or specific disease stages that could benefit more than others from therapeutic microbiome modulation should be identified, and this step might be actionable by the application of microbiome diagnostics to microbiome interventional studies. The search for specific patient-based or disease-based targets is also justified by the potential of microbiome-based therapies to be extremely precise.

So far, microbiome therapeutics have been investigated as an alternative to conventional, host-directed treatments (e.g., biotechnological therapies in IBD), although the combination of these two treatment options is still unexplored. This innovative strategy might be biologically interesting as it would involve the targeting of both host and microbiome features of the patient, with increased chances of success.

However, the implementation of these actions might be challenging, for different reasons, if confined to academic settings.

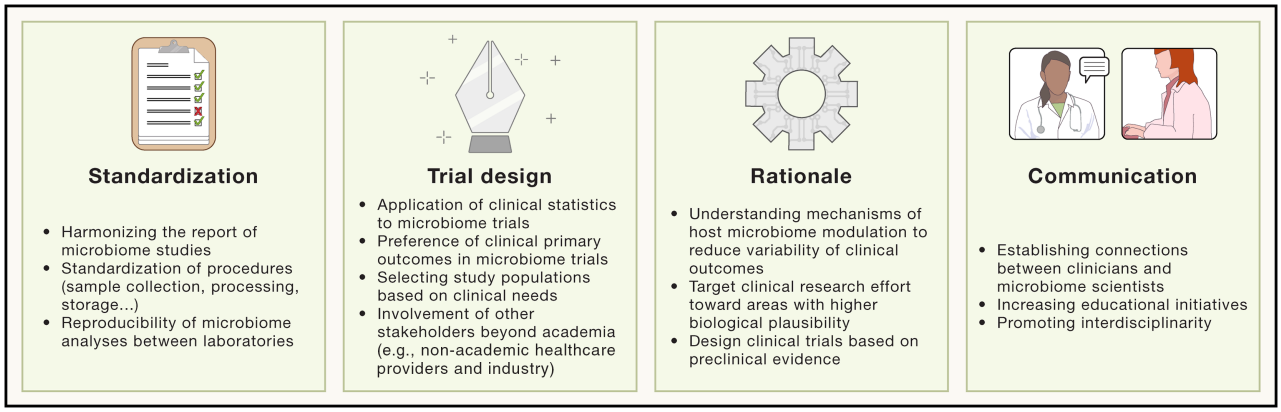

Figure 2. Necessary actions to move the microbiome from research to clinical practice

First, academia does not have the same capacity and pace of industry in carrying out applied research, e.g., the development and investigation of artificial microbiome therapeutics and/or the conduction of large multi-center interventional trials under rigorous methodological frameworks (i.e., following quality standards such as Good Clinical Practice [GCP]). Additionally, academic centers are a small minority compared with the whole healthcare network (e.g., non-academic hospitals and community healthcare), which have, then, a much higher recruiting potential. This issue might be particularly critical for the development of large associative studies, aimed at discovering microbial biomarkers. Therefore, the involvement of other stakeholders beyond academia, including non-academic healthcare providers and industry, is essential to move the microbiome field toward diagnostic and therapeutic clinical practice. Notably, the engagement of companies in this process may be challenging, as researchers and investors naturally have different objectives and endpoints. So, the risk for marketing motivations to overcome research trajectories must be considered and prevented by a healthy and fair partnership between academia and industry.

Disentangling the mechanisms of microbiome modulation to enhance the success of human studies

Beyond the actions proposed so far, the most complex step to be taken is probably represented by a closer connection between preclinical findings and the design of clinical or translational studies.

On one hand, a comprehensive understanding of the bioactive mechanisms of host-microbiome modulation is essential to overcome inter-individual variability in clinical outcomes. Therefore, increased efforts in unraveling them may enable an easier translation into the clinic.

On the other hand, target diseases in clinical microbiome research might be those whereby biological plausibility and mechanistic evidence are more consolidated, to increase, at least in theory, the chances of success.

Details of microbiome trials should be designed with the support of findings from basic and translational research, as supported by several proofs. For example, the use of antibiotic pre-conditioning in FMT trials is supported by several lines of evidence, including the improved FMT outcomes in recipients with lower microbial α-diversity[33] but also the higher microbial engraftment in patients pre-treated with antibiotics before FMT.[14] Also, the evidence that the donor microbiome is unlikely to stably engraft the host intestine after one single FMT,[34] and that microbiome engraftment props up the clinical response,[14] supports sustained microbiome modulation in NCDs.

Furthermore, as already proven by elegant evidence,[17,35] the building or refinement of microbiome therapeutics, e.g., bacterial consortia or bacteriophages, should rely on mechanistic preclinical findings, as experienced for anticancer drugs or biotechnological therapies used in NCDs.

Lastly, microbiome modulation and therapeutics should be tested in different populations and geography with variable ethnicity and dietary patterns to ensure universal and consistent efficacy.

Interdisciplinary communication and educational strategies for healthcare professionals to enhance the clinical integration of microbiome science

Beyond limits in the standardization of research methodology and in the robustness of evidence, the unpreparedness of the medical community in this field and its insufficient communication with microbiome scientists represent another critical barrier against the translation of microbiome research in clinical practice. This drawback, in turn, encumbers further advancements, as it not only jeopardizes the clinical implementation and adoption of innovations in microbiome diagnostics and therapeutics but also prevents the improvement of microbiome clinical trials that might generate from the collaboration and mutual learning between these two areas.

Potential actions to bridge this gap rely both on establishing robust communication channels between microbiome scientists and clinicians and on developing targeted educational initiatives involving different stakeholders. For example, scientific societies should invest efforts in building multidisciplinary symposia and workshops, Also, the launch of cross-field calls from funding agencies and the promotion of translational research outputs by scientific journals would allow a reciprocal exchange of knowledge between basic scientists and physician scientists.

Furthermore, educational initiatives may be proposed by different stakeholders—from universities to train future generations of clinicians to scientific societies for postgraduate education offers.

These programs should focus on elucidating microbiome science from its basics and glossary, also explicating its relevance to various medical conditions and introducing the concept of "functional" pathways. By delineating how microbiome compositions and interactions influence physiological processes and disease states, clinicians can acquire a more nuanced understanding of the role of the microbiome in health and disease. Such educational endeavors may encompass workshops, seminars, and online modules that provide practical frameworks for interpreting microbiome data in clinical contexts. As a key element, these initiatives should have a transdisciplinary approach, as the communication between different specialties would be of utmost importance to understand the real, unmet clinical needs in different microbiome-associated disorders. Moreover, they should include not only physicians but also other healthcare professionals, e.g., dieticians, due to the tremendous opportunities for modulating the microbiome given by dietary interventions. On the other hand, the development of simple microbial biomarkers, easily interpretable by clinicians, and, more generally, the streamlining of microbiome diagnostic and interventional approaches, is needed to make them "clinician-friendly."

These actions are collectively expected to equip healthcare providers with the requisite knowledge and confidence to incorporate microbiome-based approaches into their diagnostic and therapeutic strategies, building the cross-field figure of "microbiome clinicians."

CONCLUSIONS

Microbiome research continues to release exciting and highly reliable discoveries, with far-reaching implications. Microbiome diagnostics are mostly investigated either for disease risk assessment, prediction of response to therapies, or refinement of microbiome modulation. Although nascent, these approaches are giving reliable findings that might be easily validated and reproduced in different clinical settings. Therapeutic microbial manipulation has evolved tremendously in the last decade, moving from anecdotal or methodologically weak experiences to more tailored and reproducible microbiome therapeutics that have already entered the healthcare market in some cases.

However, despite these promising insights, microbiome science is still far from being integrated into clinical medicine. Several initiatives, including the standardization of microbiome research to improve the translatability of findings, the refinement of clinical microbiome trials' design (also driven by fundamental discoveries) to allow the clinical application of results, and the development of communication between microbiome researchers and clinicians, also by educational activities, are crucial to move the microbiome field into clinical practice in the near future.

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AUTHOR CONTRIBUTIONS

G.I. conceived and designed this article. S.P. and G.I. wrote the initial draft of the manuscript. All panel members revised and edited the manuscript for important intellectual content and approved the final manuscript.

DECLARATION OF INTERESTS

S.P. has served as speaker for WellMicro. S.C.N. is a founder, member, and shareholder of GenieBiome Ltd. and has served as an advisory board member for Pfizer, Ferring, Janssen, and Abbvie. L.Z. is the founder of everImmune and its scientific advisory board president; has received a research contract from Kaleido, 9 meters/Innovate Pharma; and is sponsored by Pileje. H.S. reports lecture fees, board membership, or consultancy from Amgen, Fresenius, IPSEN, Actial, Astellas, Danone, THAC, Biose, BiomX, Eligo, Immusmol, Adare, Nestle, Ferring, MSD, Bledina, Pfizer, Biocodex, BMS, Bromatech, Gilead, Janssen, Mayoli, Roche, Sanofi, Servier, Takeda, and Abbvie; has stocks from Enterome bioscience; and is a co-founder of Exeliom Biosciences. R.K.W. received unrestricted research grants from Takeda, Johnson & Johnson, Tramedico, and Ferring; received speaker's fees from MSD, Abbvie, and Janssen Pharmaceuticals; and acted as consultant for Takeda Pharmaceuticals. E.E. is a scientific co-founder of DayTwo and BiomX and is an advisor to Purposebio, Aposense, Zoe, and MyGutly. A.G. reports personal fees for consultancy for Eisai S.r.l., 3PSolutions, Real Time Meeting, Fondazione Istituto Danone, Sinergie S.r.l. Board MRGE, and SanofiS.p.A; personal fees for acting as a speaker for Takeda S.p.A, AbbVie, and Sandoz S.p.A; and personal fees for acting on advisory boards for VSL3 and Eisai. G.C. has received personal fees for acting as advisor for Ferring Therapeutics. G.I. has received personal fees for acting as speaker for Biocodex, Danone, Sofar, Malesci, Metagenics, Illumina, and Tillotts Pharma and for acting as consultant/advisor for Ferring Therapeutics, Giuliani, Metagenics, and Tillotts Pharma.

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