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Review

Microbiome One Health model for a healthy ecosystem

Antonietta Tomasulo [a,*], Barbara Simionati [b], Sonia Facchin [c]

[a] Master NUESA Department Biomedical Science, University of Padova, Italy
[b] Eubiome Srl, Italy
[c] University of Padova, Department of Surgery, Oncology and Gastroenterology DISCOG, Padova, Italy

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ABSTRACT

The attention on microbiome research and its translation to application deployment is escalating along with diffused hype. There is real excitement in this new science, leveraging the growing potential of advances in molecular biology and sequencing techniques. Yet, despite the substantial efforts provided by the scientific communities, the true significance of research achievements requires coordinated and constructive actions across interdisciplinary fields. Individual researchers, universities, small and large companies, venture capitalists, and governments play a fundamental role in fostering collaboration and promoting knowledge that will benefit each other and sustain global prosperity. Making meaningful connections across different fields and getting a new perspective on how technological developments interrelate are the main drivers for creativity and progress.

To help the broader innovation community focus on potentially new cross-sectorial developments, the One Health-microbiome-centric approach, defined here as "*Microbiome One Health*", is considered as the efficient, holistic approach to product and service exploitations meant to preserve human well-being within a healthy ecosystem. The model opposes the biomedical system and generalizes the "One World-One Health ™" concept. The focus will be given to Nutrition as a driver of health and the food system for its commercial exploitation microbiome-centric, specifically at the interface of human/animal/agricultural. Remarkably, at the interface of humans/animals, the interaction with pets, specifically dogs, has been recognized as a driving force of novel microbiome exploitation.

1. Introduction

The word "microbiome" combines microbe and biome and describes the microbial ecosystem. The microbiome refers to both the community of microorganisms (microbiota) of trillions of microorganisms inhabiting their host and the whole spectrum of molecules produced by these microorganisms, including nucleic acids, proteins, lipids, polysaccharides, metabolites, and others made by coexisting hosts and modulated by the surrounding environmental conditions [1]. The microbial world has lived with us all these millennia and evolved in extreme complexity. Yet, only recently, through an advanced understanding of biology and the adoption of novel technologies, we are beginning to unravel its applicability, enabling significant discoveries.

The new approaches in molecular biology are not just the start but the catalyst of a revolution that will change everything. What was considered primarily inert or of marginal importance is now regarded as essential to life and a driver of health [2]. The process took time since the most important milestones had been achieved over almost four centuries. However, the interest in microbiome science has picked up in the last decade, with unprecedented knowledge sharing and funding opportunities, and it will become the driving force behind personalized health [3]. In retrospect, the idea that the micro-organisms surrounding and living within us must be essential for our survival is obvious. Still, it differed from the mainstream medical science's view so far.

Today, medical science is adopting solutions based on microbiome research results, including prebiotics, probiotics, fecal microbiota transplantation, and phages [4–6]. Moreover, there is growing interest in multi-omic analysis, including viromics, metabolomics, proteomics, and host-specific properties such as genetic, epigenomic, antibody, and other study-specific features [7].

Evidence shows that the microbiome affects many activities involving health, disease, and aging [8]. The composition of the microbiome and its output are applied in most if not all, of the biological processes as we proceed through our life cycle [9]. Each person is also unique regarding microbiome acquisition and its variation throughout life [10]. As the Pulitzer Prize Ed Yong brilliantly wrote: "*Every one of us is a zoo in our own*

* Corresponding author.
E-mail address: antoniettat@gmail.com (A. Tomasulo).

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right, a colony enclosed within a single body. A multi-species collective. An entire world" [11].

Similarly, animals are influenced by the presence and composition of resident microbial communities, too, and so are the entire life entities of the planet [12].

Researchers are just beginning to unravel the importance of the microbiome and how it affects humans and the environment. The microbiome is a perfect example of a large and complex domain connecting all living organisms, including those yet to be discovered.

The Microbiome One Health Model is a holistic approach that emphasizes the critical role of microorganisms in the health of the entire ecosystem, recognizing their interconnection and interdependence. The objective is to advance transdisciplinary research and innovation leveraging the economic interests driving the microbiome-based products and services and more active collaboration of the public and private sector organizations in health and environmental management.

2. Before and after a microbiome research revolution: evolution in models of health

Acknowledging the importance of focusing on the microbiome leads to a "before" and "after" in health research and innovation. Microbiome research shows no definite separation of organisms from their environments; therefore, human health relates to the ecology of microbial communities living in and out of our bodies [13]. Health itself evolves into an "ecological" perspective involving the interaction between living entities and the environment. Moreover, with the technological advancements in microbiome research, not only health but also healthcare models are expected to evolve.

By rethinking health focused on microbiome science, the evolution from a biomedical approach to an ecosystemic "One Health" approach [14] is unavoidable. Switching to an ecosystemic model, microbiome-focused, would enhance results, create new competencies, and maximize innovation.

2.1. Before: biomedical approach

Fig. 1 provides a visualization of how healthcare technologies are siloed in a model based on the biomedical approach. No interdisciplinary procedure is envisioned between human, animal, or environmental fields. Diseases or deviations from what is believed to be biological "health" status are approached as independent issues. This approach is still present in modern Western societies despite its criticisms over four decades and attempts to improve the interaction of biological, psychological, and social factors [15]. The basic principle is built around health, defined as the absence of illness and disease resulting from biological failings. The focus on the cure, instead of preventing disease and treating symptoms rather than the cause, and the complexity of including social and psychological factors as determinants of health, called a bio-psychosocial approach [16], reduces the quality of care and misses the holistic view.

The same biomedical approach is used for treating animal and environmental health, where "health" is considered the absence of physical disease. As a result, curing a disease is exclusively a task for "health" professionals adopting specific technologies, with the apparent lack of vision on the interdependence of different factors and the redundancy of resources. This approach focuses mainly on humans, discarding the anthropogenic impact on animals and the environment. Animals are used as model systems to explore human diseases, test drugs, or understand physiological processes. Environmental factors are merely considered modulators of health (pollution/weather).

2.2. After: Microbiome One Health approach

Fig. 2 provides the visual representation of the "Microbiome One Health" approach, enhanced on microbiome science and the possible new fields of opportunities raised by microbiome research.

The original inception of "One World-One Health" was promoted by the World Organization for Animal Health in 2009 and earlier derived from the "one medicine" concept of Calvin Schwabe [17]. It is "*an integrated, unifying approach that aims to sustainably balance and optimize the health of people, animals, and ecosystems*". It recognizes the health of humans, domestic and wild animals, plants, and the wider environment, closely linked and inter-dependent" [18]. This concept is now integral to the World Health Organization initiatives [19], whose importance has been highly evident due to increased planetary threats, such as the rapid deterioration in biodiversity, the extreme consequences brought by climate change, and the plagues created by resource depletion, to name a few. If anything, the COVID-19

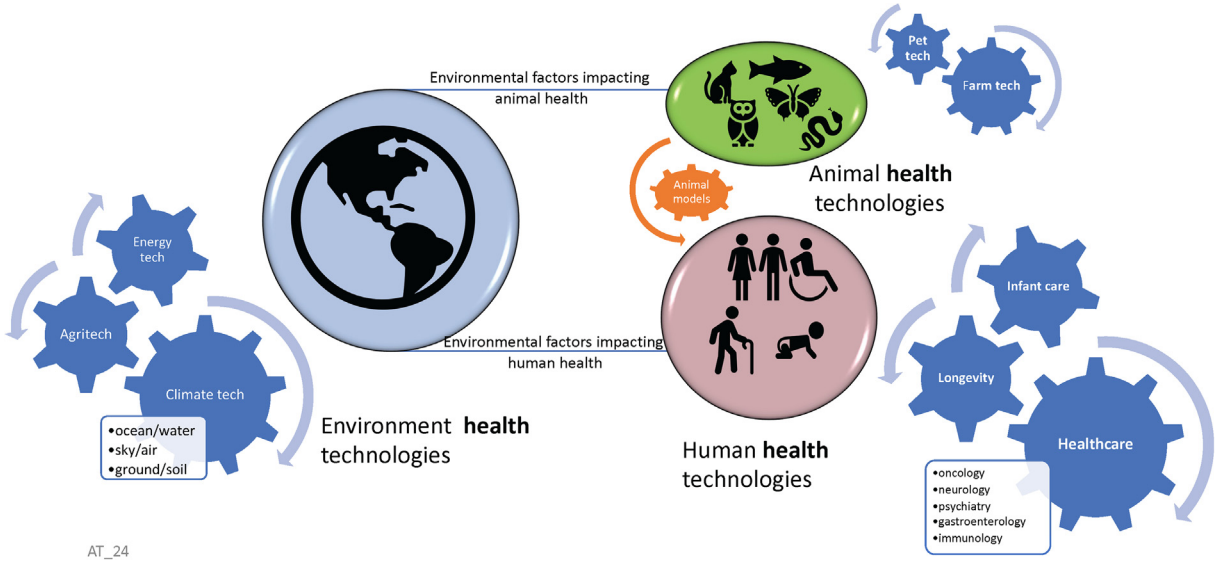

Fig. 1. Biomedical approach: A model of understanding health as the absence of disease. The model is based on curing the disease to restore the individual's health (individual being humans/animals/environment). Technologies are siloed and deployed on specific issues. The cure is considered without interdisciplinarity biological/psychosocial factors and discarding the anthropogenic impact on animals and the environment. In this extreme simplification, this figure shows the limitation of approaches based merely on promoting or maintaining health. Once a problem is characterized as a biomedical problem, one will naturally start searching for a biomedical solution. However, the problems are not only physical, and a more holistic approach is needed.

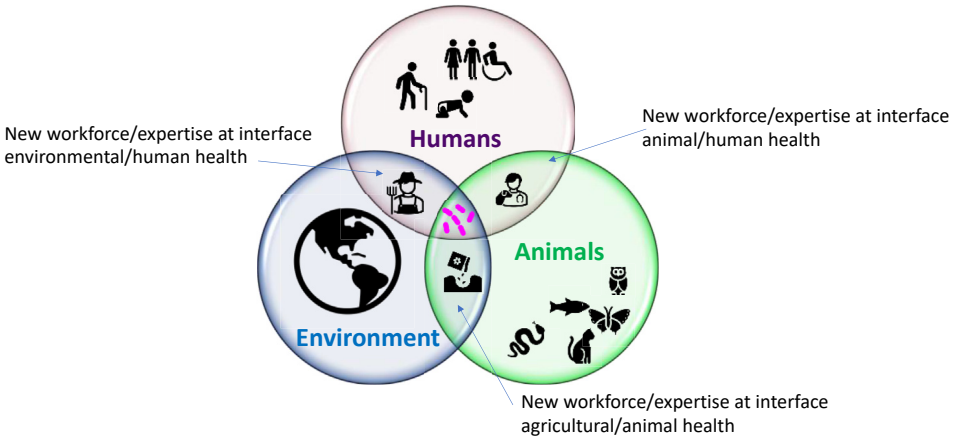

Fig. 2. Microbiome One Health concept with a focus on microbiome science. Highlighted the opening for possible new expertise at the various interfaces.

pandemic should have taught us that maintaining individual and public health requires an interdisciplinary approach with contributions from a wide range of professionals such as ecologists, immunologists, epidemiologists, neurologists, veterinaries, engineers, social scientists, psychologists, economists, anthropologists, behavioral scientists, as well as the stakeholder communities and their representatives. A "business as usual" approach has been unsustainable, considering animal, human, and environmental health separately and not integrating a broader social and economic structure [20].

Notably, the philosophical One Health approach is particularly rooted in China, where the Confucian concept of harmonious coexistence of humans and nature is the foundation of more holistic health and, lately brought to the establishment of the Chinese Consortium for One Health [21].

However, the One Health approach has been primarily applied to research, policy, and development activities focused on addressing the emergence and spread of zoonotic diseases and antimicrobial resistance [22]. Because using the multi-disciplinary research required is challenging, health and development activities tend to be siloed within a specific topic or sector to meet narrow objectives and concrete deliverables, missing its evolving context [23].

Finally, the microbic relationships between biodiversity can connect the scientific evidence for animal and human health and overall planet well-being, which is fundamental to understanding how humans and other life forms contribute to the ecosystem [24]. The symbiotic relationship between the host and microbiota and their continuous exchange is the basis of maintaining health.

Microbiome research has stimulated a more nuanced view of microbes, acknowledging the importance of biotic and non-biotic interactions on host health. The new model of health must recognize the interconnection of the microbiome with the biotic environment, e.g., humans, animals, and plants. The outcome of this new model is that the health and well-being of animals and humans are related through microbes. Still, at the same time, the non-biotic environment, e.g., water, air, and land, influences the microbes, and it is influenced by them. Because the health conditions of all organisms in an ecosystem are interconnected, the microbiomes of different macroorganisms and the environment in which they live are connected [25].

The potential to adopt the Microbiome One Health approach to use microbiome science to protect and improve human and animal health while reducing the impact of human-related activities on the biosphere is clear. We need to understand better the role of interconnected microbiomes in promoting and maintaining plant and animal health and possible ways to stimulate a healthy, diverse microbiome throughout human-dominated ecosystems.

2.3. New competencies for a new model

The new paradigm proposed here is not the "holobiont-hologenome", indicating hosts and their microbiomes evolving as "superorganisms" [26]. Hosts and microbes work in symbiosis but still are different organisms. Therefore, ecology, genetics, and evolutionary biology are the most appropriate intellectual frameworks for applications within host-microbiome communities.

In this model, health solutions require new forms of cross-sectorial collaboration. In addition, new educational programs should be implemented to drive the change process. The output should create the foundation for interdisciplinary research activities rather than sectorized medicine as a reaction to diseases [27]. Furthermore, this integrated approach requires open communication and novel forms of knowledge sharing to encourage participation.

3. Microbiome One Health applications

The next decade will probably see substantial growth in microbiome-based solutions: the goal should be to integrate ecology into the innovation pipeline from conception to commercialization [28]. An open innovation governance needs a continuous cross–stakeholder interaction to maximize knowledge exchange between disciplines and move from discovery to innovation more efficiently [29].

3.1. Current microbiome-centric research and development

Microbes support many industrial activities, from the traditional fermentation of bread, cheese, beer, and wine to the production of chemicals, energy sources, enzymes, pharmaceuticals, waste treatment, and pollution control, including fossil oils and plastics. The application of microbes helps find sustainable solutions to most of the critical problems that face our health [30]. Microbial diversity is essential to maintaining the functions that support life on the earth; therefore, monitoring and preserving that diversity is critical [31].

In a sign of the continued commercial potential and strategic national importance of microbiome research, in 2018, a group of 23 US government agencies, including the National Science Foundation (NSF), collaborated to produce a five-year Interagency Strategic Plan for Microbiome Research, which outlines the objectives, structure, and principles for coordinated microbiome research [32]. In January 2021, the UK's Knowledge Transfer Network launched its Microbiome Strategic Roadmap, which reviewed the landscape of microbiome science and laid out critical recommendations on advancing science translation and business creation across the human, animal, and plant microbiome sectors [33]. Action plans, like implementing the Italian microbiome initiative, have been proposed in different countries

[34]. Establishing multidisciplinary research centers to foster collaborations and develop standards, like the Penn State One Health Microbiome Center, funded recently, May 2023 [35], is foreseeably going to increase worldwide. KPMG's report in 2022 on 35 internationally successful microbiome hub initiatives highlighted the recommendation of installing shared Ph.D. programs and research infrastructures [36].

Most initiatives investigated so far had the human microbiome as their key focus area, indicating that research at the human/animal/environment interface still needs to catch up. Shifting from research microbiome-centric to innovation ecology-focused approaches will require long-term vision, continuous investment in training and education, and sustained policy support. Each country or research entity needs help to tackle the individual field satisfactorily and efficiently. Economic drivers are enormous, and an entrepreneurial ecosystem is critical for this to happen. Moreover, traditional economic models must be readapted in a novel "ecosystem economic" form [37].

3.2. *Microbiome-One Health model driver of transdisciplinary innovation*

Choi and Pak [38] defined the effectiveness of multiple disciplines in health research, suggesting that *multidisciplinarity* draws on knowledge from different disciplines but stays within their boundaries; *interdisciplinarity* analyzes, synthesizes, and harmonizes links between disciplines into a coordinated and coherent whole, *transdisciplinarity* integrate the natural, social, and health sciences in a humanitarian context and transcends their traditional boundaries. Transdisciplinary, community-based, interactive, and participatory research approaches are therefore indicated as appropriate means to meet both the requirements posed by real-world problems as well as the goals of sustainability.

The One Health concept has been associated with a transdisciplinary approach comprising a holistic framework for decision-making, yet with substantial implementation complexities [39]. Building bridges among human health, domestic animal health, wildlife health, and environmental disciplines requires funding for joint research and full-time professionals with expertise in transdisciplinary development. Despite international organizations and governments recognizing the importance of the One Health concept, the One Health workforce still needs to be qualified [40]. With the current fragmented approach to environmental and health sciences, the transdisciplinary knowledge and interdisciplinary interactions needed for action-oriented, future-focused, participatory, holistic, and systemic efforts are still in the early stages [41].

The Microbiome One Health Model expands on the traditional One Health approach by explicitly incorporating the critical role of microbiomes across the different domains of health, humans, animals, and the environment. Like the One Health approach, this model transcends individual disciplinary boundaries to create a holistic framework integrating knowledge, methods, and perspectives from various fields to address complex health challenges. The forward-thinking goal is to harness the power of complex interactions within microbial communities to foster a comprehensive understanding and management of health. Moreover, the growing awareness of the microbiome's critical role in human, animal, and environmental health has positioned microbiome science as a vital driver of investment, increasingly attracting sizeable private sector in formulating new products and services, creating new job opportunities, and alternative practices that can help overcome the multiple challenges that One Health faces [42]. Therefore, focusing on microbiome science can speed up the advances in scientific understanding and bridge knowledge gaps through investment in trans and interdisciplinary research innovation and international cooperation.

Fig. 3 shows a conceptual model for Microbiome One Health innovation solutions, where microbiome science drives environmental integrity and health, considering input by the social system (including culture,

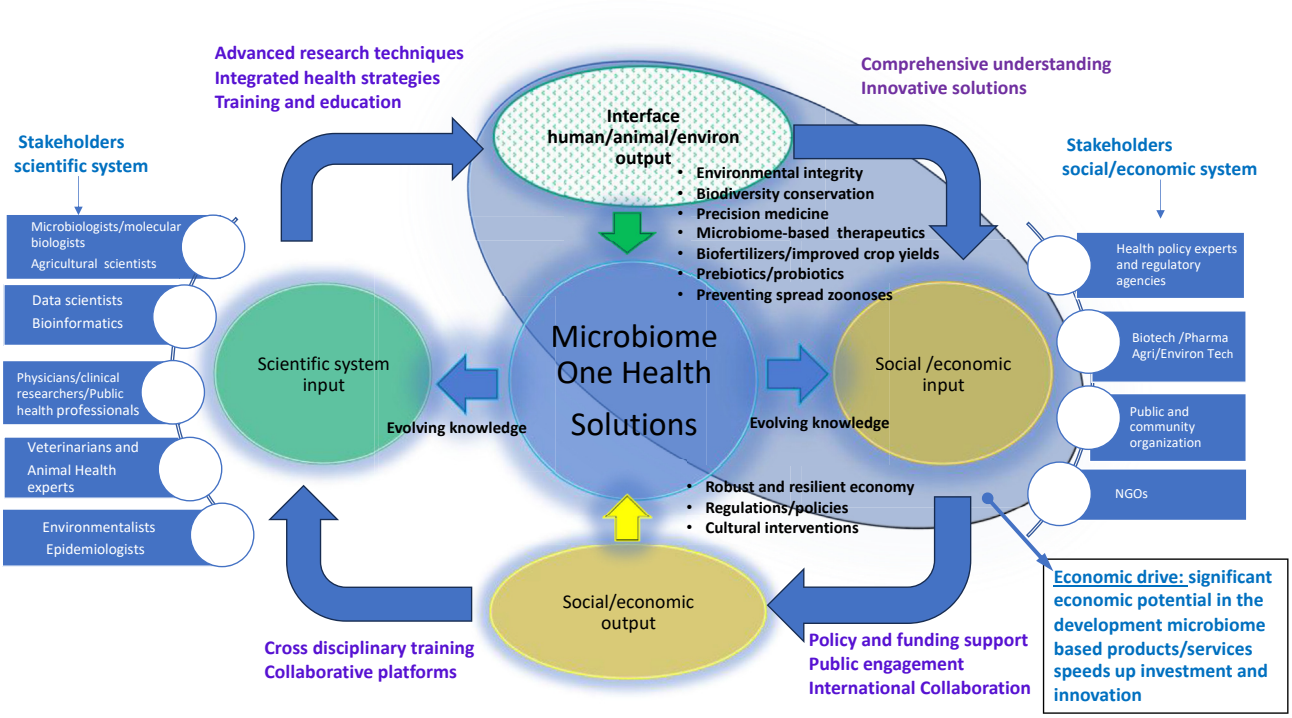

Fig. 3. The concept model is promoting innovation beyond a research-centered to a societal-industry centered perspective involving active collaboration with public and private sectors, research organizations, governments, and communities. The integration of technologies, knowledge and research is provided by cross disciplinary training, collaborative platforms, policy and funding support, public engagement, and international collaboration. The successful implementation leads to integrated health strategies bringing to innovative solutions that will advance scientific understanding but also promote practical applications that benefit ecosystems. While challenges exist, it is envisioned that the economic interests in microbiome health solutions may speed up the potential for research and commercialization leading to more effective strategies for promoting One Health and preventing diseases.

economy, and institutions) and the scientific systems (comprising health, biological, and information technology sciences). Based on interdisciplinarity and transdisciplinary concepts inspired by design principles in sustainability research [43], each system delivers output to the other system. The social system, including elements such as economics, affects the natural system directly and indirectly. The scientific system provides an evolving understanding of human/animal/environment interface and advanced research techniques with related goods and services to society. In this transdisciplinary model, integrated solutions, modulated by microbiome understanding, contribute to the socioeconomic equilibrium between human–animal–environment interactions, acknowledging the importance of biodiversity.

Implementing the Microbiome One Health model requires coordinating and collaborating with diverse stakeholders, each with specific roles. On the scientific front, microbiologists, agricultural scientists, data scientists and bioinformatics, environmental scientists, physicians, and clinical researchers, veterinarians and animal health experts, public health professionals, and epidemiologists understand the dynamics of microbiomes in different environments, optimizing sustainable farming practices supporting crop productivity, applying computational tools, and developing and implementing strategies to incorporate microbiome health into broader public health initiatives, including disease prevention and health promotion programs and managing antibiotic use to reduce resistance and understanding of zoonotic transmission. On the social/economic front, health policy experts, regulatory agencies, biotech, pharmaceutical companies, and agricultural and environmental companies, together with public and community organizations and NGOs, integrate microbiome science into healthcare, agriculture, and environmental policies, to develop new therapies, diagnostics, and interventions based on microbiome research, including personalized medicine approaches, and to advocate for policies and practices through public education campaigns and lobbying efforts.

This model relies primarily on an evolutive understanding of human–animal–environment interactions, viewing health as a continuum that spans across species and environments, influenced by the dynamics of microbiomes. For example, implementing control and prevention measures associated with zoonotic pathogens can only be addressed by understanding interactions between viral, bacterial, and other pathogens, including antibiotic resistance and the host microbiome [44]. At the same time, microbiome associations go beyond just pathogens. Microbial ecosystems in soil play a critical role in maintaining ecological balance, acting as a reservoir of microorganisms that determine the plants, animals, and human microbiomes [45,46].

Like the One Health approach, implementing the Microbiome One Health model presents a range of potential limitations that span technical, economic, and social barriers, like standardization, data management and integration, cultural and institutional barriers, and political constraints [47], even more challenged in low-middle income countries [48]. However, the advantages of focusing on the microbiomes could lead to improved disease prevention and management strategies. For example, it addresses the novel "One Allergy" concept indicating that all allergic diseases, irrespective of their manifestation, share a common exposure pathway, known as the skin–gut–lung axis [49,50], which suggests that the host genome and the microbiota mutually influence each other, creating an intricate relationship that can significantly impact health and disease.

Focusing on microbiome science opens new avenues for research and innovation and may ease the collective efforts for transitioning to a healthier ecosystem [51]. We encourage and invite further explorations of the principles presented here, hoping to engage organizations to change the approach rapidly and fundamentally to promote health and ecology.

3.3. *Microbiome-One Health model for health solutions*

The Microbiome One Health approach is at the forefront of developing innovative solutions and promises to revolutionize health care and environmental management. Fig. 4 shows a holistic representation of microbiome-centric envisioned developments rather than focusing on specific health issues. Nutrition, Therapeutics, and Drugs are intended for humans and animals, embedded into the environment where they share microbes and fate. As microbes impact most, if not all, complex ecological systems, exploitation of biological know-how is expected to offer

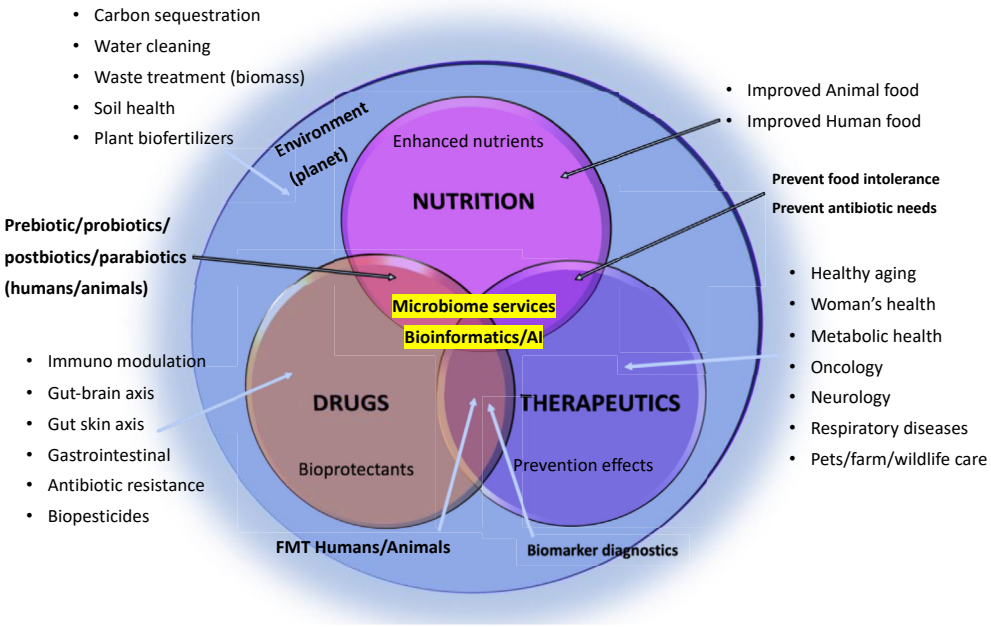

Fig. 4. Holistic view of health solutions microbiome centric: Nutrition, Drugs and Therapeutics are related to humans/animals, embedded into a living environmental system.

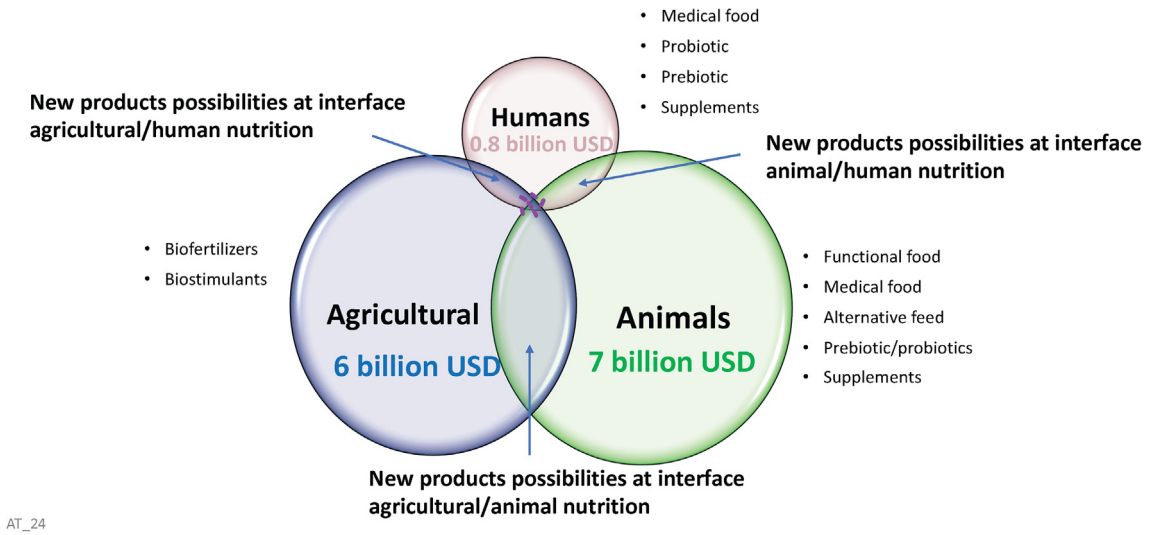

Fig. 5. Estimated market size food microbiome-centric by 2030: Humans (www.precedenceresearch.com); Animals (www.insightaceanalytics.com); Agricultural (www.marketsandmarkets.com). Estimations do not include digital applications exploitation on personalized nutrition.

innovation options in a broad range of biotechnology fields and be at the core of new markets and business models. At the heart, together with the traditional synthetic biology, biomaterials engineering, and microbiology services, unique bioinformatics and artificial intelligence expertise is foreseen to support these new classes of products.

On the digital application front, there are enormous opportunities for channeling microbiome-based health solutions into state-run healthcare systems to harness the benefits on a wide scale. For example, expanding on the concept of the innovative DIGA system developed in Germany in 2019, allowing digital health applications to be prescribed by doctors to patients with various diagnoses [52,53].

3.4. Microbiome One Health exploitation: food supply chain example

Developing a Microbiome One Health food system has enormous potential to widen our understanding of the whole food supply chain from nutrition to climate to circularity, safety, and security and how we produce, obtain, prepare, consume, and manage our resources. Agricultural microbiome-based products could be essential for holistically improving plant health and enhancing crop productivity while controlling animal disease outbreaks and refining the nutrient process for humans. Work on microbiome-based applications will help fight malnutrition and gut dysbiosis of the increasingly displaced population because of climate change [54]. However, the successful transformation of food systems requires individuals who profoundly understand the complex interactions and interdependencies within the system. To guide transformative actions, these professionals should be skilled in applying a holistic approach, considering social, economic, environmental, and cultural factors. It will be a challenging journey but necessary [55].

Diet is one of the most important and effective means of modifying the microbiome, improving health, and reducing healthcare costs. This is why investments in gut microbiome solutions are still by far the largest sector of the microbiome industry [56]. Many companies offer prebiotic and probiotic supplements to keep a healthy microbiome. The EU has already funded over 500 projects under the Seventh Framework Programme (2007–2013) and Horizon 2020 (2014–2023), with a total budget of 1.4 billion euros to accelerate microbiome science and provide a way forward for the European Food 2030 strategy [57].

Fig. 5 shows the estimated food market by 2030, with data referring to a current exploitation vision on microbiome-based development and related fields, as indicated in the figure. Estimations reported here need to include data from personalized nutrition based on individual microbiome profiles, which is very promising but still limited by technological advances in computational fields. As the current predictions show, the potentiality of animal and agricultural fields is tenfold compared to the human market.

Microbiomes, considered nutraceuticals, could reach a market size of up to USD 420 billion with a projected growth rate of 7% by 2024 [58]. Advances in microbiome science have broadened the scope for developing next-generation probiotics and Live Biotherapeutic Products (LBPs), including donor-derived fecal microbiota for transplantation (FMT). BIOMICTRA, registered by the Australian Register of Therapeutic Goods [59] and the FDA approval in April 2023 of the first orally administered fecal microbiota product for preventing the recurrence of Clostridium Difficile infection, Vowst [60], further opens the nutraceuticals market. FMT may act as a chronic therapy, a new line of biotherapeutic products that can be identified and generated in a highly controllable, scalable, and reproducible way [61].

4. Untapped potential in the household: pets as modulators of human health

The enormous potential of microbiome-inspired product applications at the interface of human/animal/agricultural systems seems clear. Variation in the human microbiome also stems from differences in environmental microbial exposure, particularly from interactions at human–animal interfaces [62]. Still, these effects have received much less attention than other factors. Taking full benefit of microbiome functions and incorporating the ecological model from the microbiome–host relationship may increase predictive capability towards sustainable and resilient systems. Microbial transmission at human–animal interfaces has often been viewed as a threat. Still, a better understanding of its effects on the microbiome can also be an opportunity. This could include, for example, assessing and modifying the microbiome environment to enhance the health of humans and animals in the household. Domesticated animals can be leading players in future efforts to mitigate the health effects of altered microbial diversity in industrial human settings.

Understanding the need to build upon the interaction of humans and pets as a larger animal model to assess treatments to improve human and animal well-being, Hill's Pet Nutrition and Harvard T.H Chan School of Public Health created in August 2023 the One Health Microbiome Resource (OHMR) [63]. The center is the first of its kind, promising to be the largest and most comprehensive human and companion animal microbiome database and a valuable resource made available to the scientific community.

Given the similarity between human and dog guts [64], there is an opening for optimizing microbiome exchange between humans, dogs,

and the households they use. Pet dogs share their owner's space, hence the same "lifestyle," their well-being is closely intertwined with their human counterparts [65], so they may be utilized in translational sciences to identify therapies and maximize clinical benefits [66]. Novel veterinary research should leverage human experience, benefitting both species. To the best of current knowledge, only one Italian startup is translating the fecal microbiome transplant experience from humans to dogs [67]. However, this is only the beginning.

Identifying what factors drive microbial variation and its resulting health impacts will provide essential scientific knowledge, direct the design of useful microbiome-targeted manipulations, and lead human behavioral changes, ultimately affecting national and international policies.

Following a holistic One Health approach is fundamental for our survival. Microbiome research and its related innovation deployments should lead the way.

5. Conclusions

The next decade will foreseeably be the "decade of the microbiome business", with new and improved bioproducts and consumers perceiving the benefits of using microbes to replace traditional offerings.

For this exploitation to be sustainable and meaningful for the planet's health, a new approach that includes many stakeholders and involves interdisciplinary effort is required. Novel medical research happens at the human/animal/environment interface, requiring cross-discipline trained talents and different animal model deployments. Some implementation actions are already in place, and intergovernmental agencies are fostering research. Siloed communications and fragmented implementations, however, hinder speed.

A new health model, called Microbiome One Health, would drive translational research and business development. Educational and training programs must be crafted with a holistic "One Health-One Microbiome" framework perspective, encompassing the entire ecosystem, from conception to market to successful end users' behaviors. This approach guarantees that research outcomes can be translated into long-term solutions.

Author contributions

Conceptualization, A.T., S.F., and B.S.; writing-original draft preparation A.T.; writing-editing A.T., writing-review A.T., S.F., and B.S.; supervision S.F. and B.S. All authors have read and agreed to the published version of the manuscript.

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Data availability statement

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Conflicts of interest

The authors declare no conflict of interest.

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