White Paper

Bigger on the Inside: The Expanding World of Microbiome Therapeutics

The emergence of an exciting new area of medicines with the potential for novel treatments across a wide range of diseases and conditions

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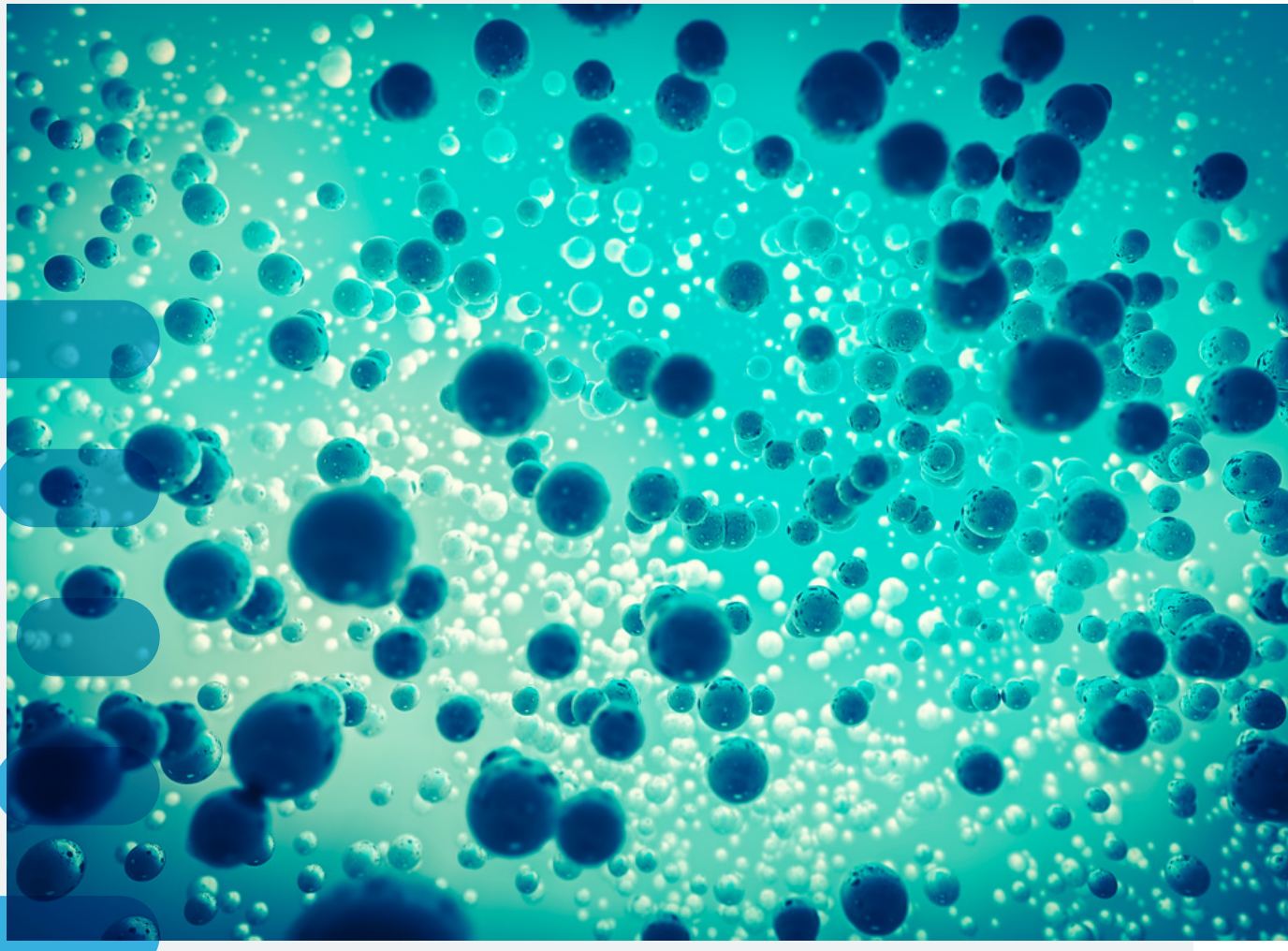

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Abstract

The approval of the first microbiome therapy with Ferring's REBOTYA by the FDA for patients suffering from recurring *C.diff.* infections represents a milestone achievement that sends waves of enthusiasm throughout the industry. It likely won't be the last. Seres Therapeutics expect the FDA's seal of approval for its SER-109 in the same indication in April 2023. There are many other disease areas with significant unmet medical need that are linked to the state of an individual's microbiome. Going forward, we expect to see more products gain market authorisation and this first breakthrough to mark the start of a new era of microbiome therapeutics.

Introduction

'What makes us human?' might sound like a philosophical question. Neuroscientists will point to our brain and associated self-awareness that distinguishes us from any other living organism whereas biologists might have a more reductionist answer saying that cells make up the human body. Intriguingly, our 30 trillion human cells are outnumbered by approximately 39 trillion microbial cells.[1] These passengers colonise us starting from the day of our birth and influence our physiology and behaviour in ways that we are only starting to comprehend. To understand the complexity of the human body and how it interacts with its environment in health and disease, we must look beyond our own cellular composition and explore the multitude of microorganisms living out- and inside us. The Microbiome.

According to the scientific literature, the microbiome is the complex collection of microorganisms, their genes, and their metabolites, colonising the human and animal mucosal surfaces, digestive tract, and skin.[2] The term 'microbiome' has been around since the 1960s but got more widely used only after a landmark paper got published by Lederberg and McCray in 2001.[3,4]

When talking about the human microbiome, we most often refer to the gut microbiome which has been the subject of extensive research and is thus better understood. However, other areas of the body, such as the skin, oral and urogenital microbiomes must also be included (Figure 1).

In 2007, the human microbiome project was launched to improve our understanding of the microbiome in health and disease.[5] In the following two decades, our understanding of what constitutes the microbiome and how it links to human health and disease has expanded rapidly with an avalanche of published studies. The cost decrease for next-generation

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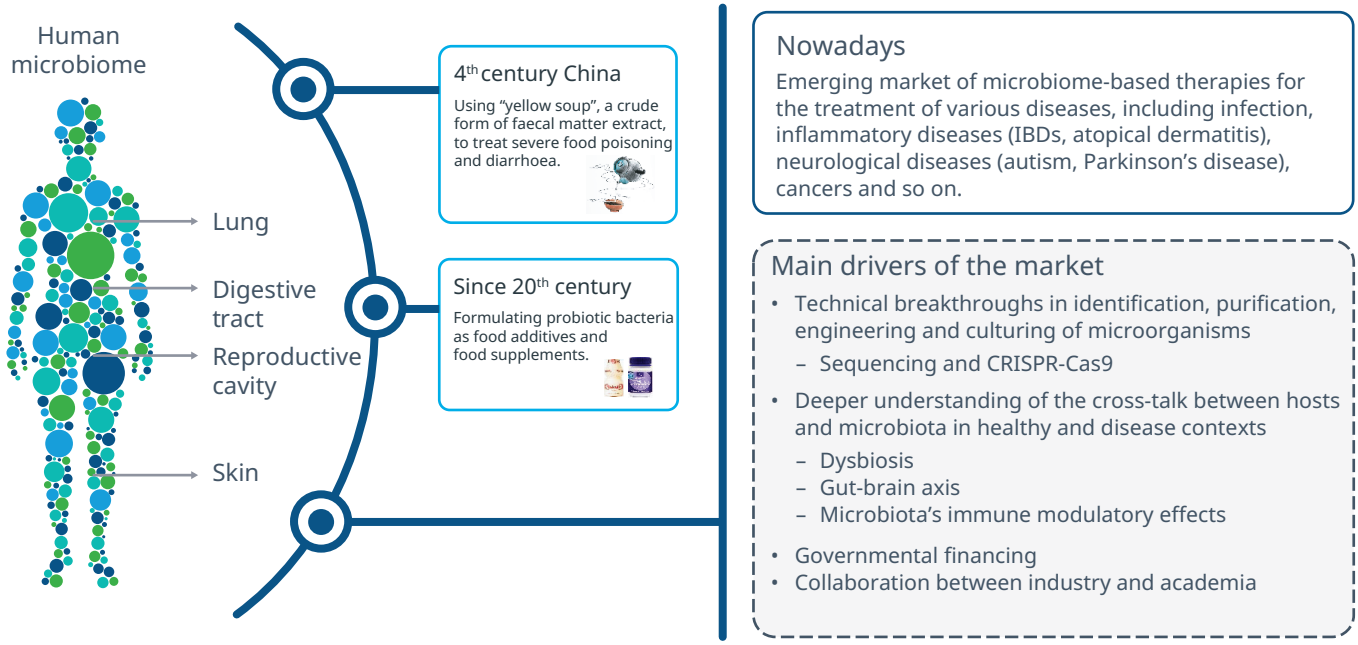
Figure 1: The human body is home to trillions of microorganisms



Source: IQVIA EMEA Thought Leadership

sequencing (NGS) from $100 million for the human genome project to $500 and increased financing from the public sector were two driving factors (Figure 2).[6] MetaHIT (METAgenomics of the Human Intestinal Tract) is a collaborative effort gathering expertise from 15 institutes across 8 European countries to leverage NGS to better understand the role of human microbial companions. The consortium started its work in 2021 and since then was able to define a broad catalogue of bacterial genes in the gut and the definition of 'enterotypes' — a way to classify the bacteriological composition of an individual's gut.[7]

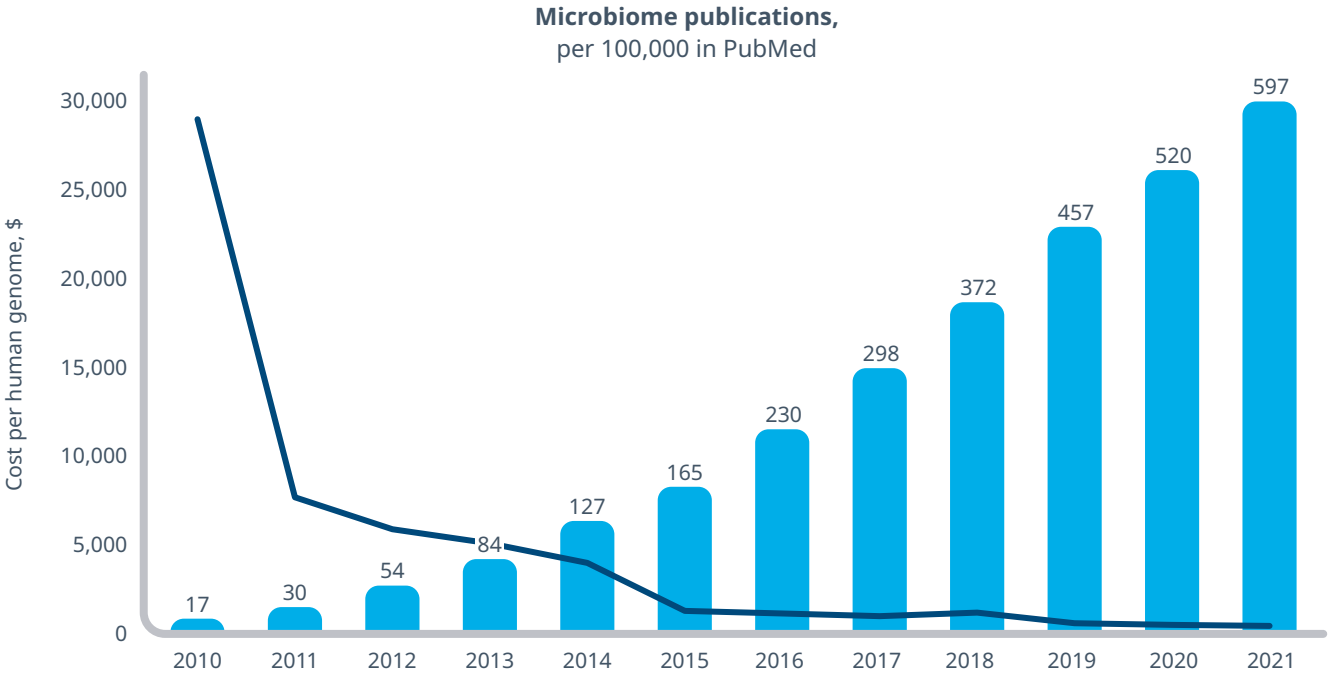
Today, there is scientific consensus that the microbiome is a dynamic living system affected hierarchically by our diet, antibiotic usage followed by partners, roommates, pets and daily fluctuations. We live in symbiosis with our microbiome under normal physiological conditions. In our gut for example, microorganisms aid digestion and provide nutrients. Moreover, there is growing evidence suggesting an important role in the training and development of our immune system.[8] Inversely, the microbiome was linked to various diseases if this symbiotic relationship is broken. There is mounting evidence of microbiome impact in autoimmune diseases, neurodegenerative diseases and also cancer.

GROWING MICROBIOME MOMENTUM IN CONSUMER HEALTH, DIAGNOSTICS AND RX

Microbiome-based products are already a viable business as food supplements or OTC products in the consumer health space. In recent years, more people have become interested in taking control of their own health and wellness and this trend has been driven by several factors, including an increase in access to information about health and wellness, the rise of social media, and a growing interest in natural and holistic approaches to healthcare. Despite controversies around efficacy and clinical health benefits in certain indications, both HCP and consumers demonstrated increased interest. Probiotics that positively affect the gut microbiome outperformed the total consumer health market

The microbiome was linked to various diseases if this symbiotic relationship is broken. There is mounting evidence of microbiome impact in autoimmune diseases, neurodegenerative diseases and also cancer.

Figure 2: Number of microbiome publications and costs per full human genome



Sources: IQVIA EMEA Thought Leadership; PubMed "Microbiome" in Title/Abstract normalized per 100k publications and NIH for full human genome sequencing costs

long-term and saw double-digit growth rates during the COVID-19 pandemic between 2020-2021. Moreover, skin related microbiome products are emerging.[9]

Consumers are also interested in knowing more about their individual microbiota and purchase self-testing kits online. The global gut microbiome testing market was valued at $637.5 million in 2018 and was expected to grow at double-digit rates.[10] After sample collection and next-generation sequencing, consumers receive a report on their microbiome profile and sometimes also advice on lifestyle or diet. Some big diagnostics players are still flush with cash from the COVID-19 gains. We thus expect to see more deal activity in the future. Today, diagnostics make up only 2% of overall healthcare expenditure but are involved in 66% of clinical decision making.[11] Identifying patients that are eligible and will benefit most will be crucial for development and successful commercialisation of future microbiome prescription therapeutics as well.

When it comes to therapeutics, pharmaceutical companies have failed multiple times to develop therapies to modulate patients' microbiomes but recently the tides are turning. Ferring's REBYOTA received a positive opinion from the Vaccines and Related Biological Products Advisory Committee (VRBPAC) in the US followed by the FDA approval on 30 November 2022.[12] BiomeBank got a market authorisation for BIOMICTRA in Australia.[13] By the end of April 2023, the FDA is expected to decide on Seres therapeutics' SER-109 product. If approved, it will be the first oral microbiome drug on the market.[14] All three products are for the treatment of recurrent *C. difficile* infections.

Setbacks during clinical trials are inevitable, and for microbiome-based candidates even more so, as we lack mechanistic understanding in many disease areas. Hence, the translation into therapeutics will be a challenge and opportunity at the same time. The CEO of PharmaBiome made the bold claim that every healthcare company should have a microbiome strategy.[15] In this paper, we provide a perspective on

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the current state of play of microbiome therapeutics, and examine the challenges companies must address to build a broad and viable commercial market.

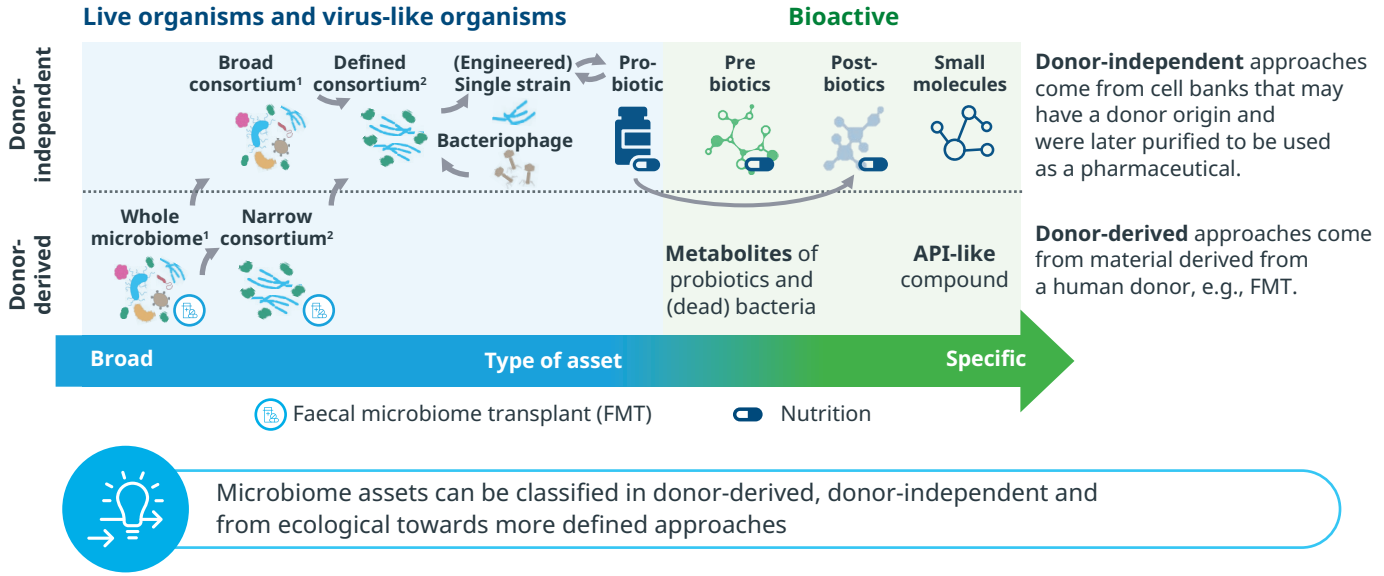
The spectrum of microbiome therapeutics

Techniques to manipulate the microbiome to improve human health and to treat diseases have evolved over time and vary greatly by mechanism specificity and type of the asset (Figure 3). As the field is still evolving, there is no full consensus yet on the formal classification of microbiome therapeutics. Starting at the bottom-left corner: Faecal matter transplant (FMT)-based products transfer the whole gut microbiome ecosystem form a donor to a patient. In such whole microbiomes, a donor's microbiome with undefined composition, is isolated and then transferred. In a broad consortium the microbiome community is isolated from cell banks instead. Narrow and defined consortia are more engineered approaches where different strains are mixed that act on a patient's microbiome. Narrow consortia rely on sample donors whereas defined consortia are donor independent — rely on cell banks. A single strain of bacteria might be sufficient and efficacious in certain conditions.

Such native single strain products can be further genetically modified for improved mode of action and are called engineered single strains. Bacteriophages are bacteria-infecting viruses that can kill specific strains, for example, disease-causing ones from the microbiome. Furthermore, phage therapy might also prove very potent in fighting antimicrobial resistant "superbugs". Such lytic — bacteria killing — phages cannot spread either virulence or resistance.[16] Probiotics are mostly nutritional products that contain living microorganisms intended to improve gut health and are considered a subgroup within the single strain application.

All of these approaches are microbiome-modifying living organisms. Bioactives in contrast, aim to confer health benefits by modulating the microbiome directly. Prebiotics promote the growth of beneficial bacteria in the gut whilst postbiotics are metabolic products deriving from prebiotics and probiotics. This can be certain vitamins, amino acids, and peptides which have antibiotic properties or simple short-chain fatty acids such as butyric acid which can contribute to a healthy microbiome. Small molecules — in the top right — can directly modify the microbiome are the most defined approach but also require detailed understanding of their mechanism of action.

Figure 3: Spectrum of microbiome therapeutics



Sources: IQVIA EMEA Thought Leadership Expertise, IQVIA Consulting Team Expertise, NHS FMT Overview

The consumer health origins of microbiotics

Usage of living microorganisms for human health is not a novel concept. Elie Metchnikoff, Ukranian-Russian scientist and Nobel laureate hypothesised a link between the consumption of fermented yogurt and the enhanced longevity of rural Bulgarian people in the early 1900s. Metchnikoff further devised the probiotic (meaning "for life") concept that harmful intestinal microbes could be replaced by beneficial ones. More than a hundred years later, in 2002, consensus has been reached that probiotics are living microorganisms which when administered in adequate amounts confer a health benefit on the host.[17]

Digestive health is big business as health maintenance has gained importance over treating symptoms for an increasingly health-conscious and mindful consumer base. Today, digestives with 15% market share are the 4th largest OTC market at $18 billion globally and probiotics show potential for growth and innovation. IQVIA expects the global digestives market to outperform the total consumer health market with 7% CAGR from 2022-2025.[18]

Global digestive health market

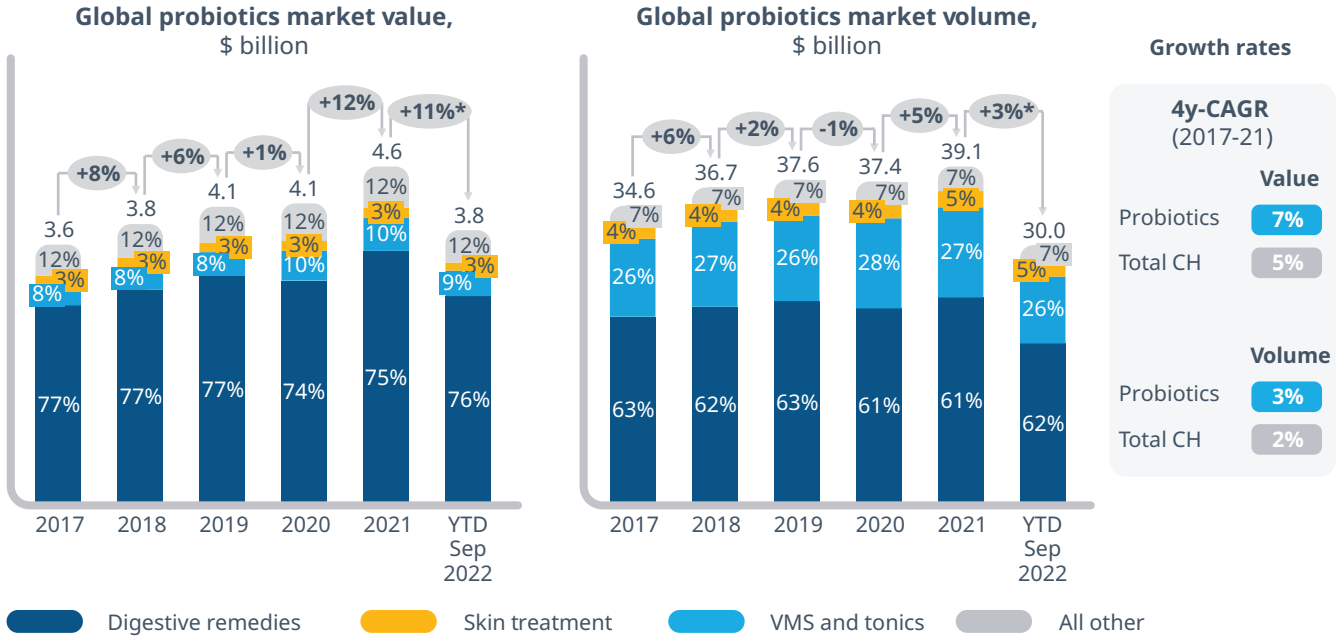
4th largest
OTC market

15%
OTC market share

7% CAGR (2022-25)
Forecast growth

IQVIA defines the probiotics market as OTC products that contain live microorganism either alone or in combination with other ingredients. Globally, probiotics reached $4.6 billion in value and — as expected — digestive remedies at 75% account for most sales followed by vitamins (10%) and skin treatments (3%). Long-term market growth is positive with 7% CAGR (2017-21) and recovered after a dip during the first year of the COVID-19 pandemic with 12% year-over-year (YoY) growth in 2021. Similar picture from a volume perspective — slight decline at -1% in 2020 followed by a 5% recovery in 2021. We expect the growth trend to continue. Comparing the first three quarters of 2022 to the previous period shows an 11% value and 3% volume increase (Figure 4).

Figure 4: Probiotics market development



*Year-over-year growth compared to previous period
Source: IQVIA Consumer Health; IQVIA OTC Audits

Probiotic products in the consumer health space are mostly marketed as food supplements or food products. Given the long experience developing and marketing these products, it is worthwhile looking at some learnings that will also apply to microbiome innovators wanting to successfully commercialise their future prescription-bound assets (Figure 5).

REGULATION

The use of the word "probiotics" for advertising and on food supplement packaging is not allowed in most EU countries due to EU health regulations categorizing it as an unauthorised health claim without relevant scientific evidence. No health claims for probiotics have been granted by the European Commission (EC) after evaluation by the European Food and Safety Agency (EFSA). France recently allowed label claims around "probiotics" for food supplements that meet specific conditions. Exemplifying the lack of harmonization on this topic in the EU as France and other countries are moving away from EU guidance. Like probiotics, prebiotic products are also important in the food supplement area and are generally accepted to have a positive impact on health, but only few health claims have been granted. The claim "Inulin contributes to the growth of bifidobacteria in the gut" for example was allowed by the EC after review of the scientific evidence by EFSA.

The dietary supplement category itself has a challenging claims situation, leading some companies to adopt different regulatory strategies. The German brand "Kijimea" categorises itself as a substance-based medical device due to its heat-deactivated Bifidum bacterium strain, which has physical properties that provide benefits for bloating, pain and diarrhoea. Its efficacy is backed by clinical studies published in peer-reviewed journals.[19]

The consumer health microbiome market will be characterised by a balancing act between innovation and regulation. New approaches to microbiotic products meet a growing consumer interest in and demand for therapies; claims about benefits must be tempered with scientific evidence.

EVIDENCE

The gut microbiome has been implicated in a number of health problems, including digestive health, obesity, diabetes, and various diseases. While advances have been made in analysing the composition of the microbiome, the abundance of data generated from comparing healthy and diseased individuals can lead to misleading claims about the link between bacteria and disease. Other factors, such as diet, drug treatments, and stool consistency, also play a role. Currently, most clinical evidence of the health benefits of probiotics and prebiotics is limited, often conducted by manufacturers to promote their products. The quality of studies is often low, with small sample sizes and limited understanding of individual differences in microbiome and immune response, making it difficult to draw firm conclusions.[20] Numerous companies promote their products by combining probiotics with vitamins and minerals to make health claims that align

Figure 5: Key learnings from the probiotics market

Source: IQVIA EMEA Thought Leadership

with the authorised claims for vitamins and minerals, such as boosting immune health.

Although this complies with regulatory guidelines, it would be preferable to increase efforts in generating evidence to establish direct health claims for probiotics. Consumers might perceive such a strategy as misleading. Ultimately resulting in distrust of future microbiome-based medicines in general. Instead, the consumer health industry could consider running hybrid studies and leverage RWE for marketing and regulatory purposes. Pharmaceutical companies will need to fill this evidence gap by running large-scale clinical trials and tackle the inherent variability amongst patients when running those studies.

DIAGNOSTICS

Consumer behaviour is evolving, and more people want to actively manage their (gut) health. Cara Care for example, is a prescription smartphone app approved for the management of irritable bowel disease (IBD) patients in Germany.[21] Moreover, consumers are interested in better understanding their gut microbiome. Diagnostics — based on metagenomic sequencing — can determine the individual microbiome composition and can provide comprehensive personalised insights on e.g., diet optimisation or food supplements. Test results must be interpreted with caution. Sequencing depth is typically low, a person's microbiome varies throughout the day and is heavily influenced by diet, stress or environmental factors. Despite these drawbacks, the diagnostics are bought and paid for by consumers and ideally must be carried out repeatedly for continuous gut health monitoring. The existing testing infrastructure, expertise and public awareness will also benefit future microbiome therapeutics as they will support in identifying patients that will most benefit from a given medicine.

Faecal matter transplants — the start of the microbiome era

Treatment-resistant *C.diff.* infections (CDI) can cause debilitating and sometimes even life-threatening diarrhoea and after multiple rounds of antibiotics — patients eventually run out of options. The global burden of disease of CDI is high and will likely increase as more people develop antimicrobial resistance (AMR). The CDC estimates over 223,000 hospitalised patients, 12,800 deaths and over $1 billion attributable healthcare costs in the US in 2017.[22] Both the US and European treatment guidelines recommend FMT as a treatment for second or further CDI recurrence.[23] The lack of standardisation, safety and clinical trial data left patients and physicians often sceptical about the procedure.

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Decades of research and clinical development of microbiome-based therapeutics culminated in the FDA's positive nod for Ferring's REBYOTA microbiome therapeutic to treat patients suffering from recurring CDI in November 2022.[24] This is clearly exciting news and sent waves of enthusiasm throughout the field.

Ferring is expected to launch in the first half of 2023 in the US, but there will be challenges to address. REBYOTA is administered as an enema, relies on stool donors and thus scaling has challenges.
In addition, issues around FMT's safety raised serious doubts in the pasts and the FDA is aware and issued a statement on the risk of pathogen transmission in 2020.[25] REBYOTA uses Ferring's proprietary Microbiota Restoration Platform that, according to the company, reduces the risk of infection and its safety profile convinced the FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) in September 2022.[26] Moreover, good manufacturing practice (GMP) and proper quality metrics for consistency will ensure a

REBYOTA is a first-in-class treatment in an area with significant unmet medical need and can help to reduce the high associated costs from repeated hospitalisations to healthcare systems.

standardised product that both HCPs and patients will feel comfortable with.

REBYOTA is a first-in-class treatment in an area with significant unmet medical need and can help to reduce the high associated costs from repeated hospitalisations to healthcare systems. rCDI disease burden is also significant outside the US but regulatory approval by the EMA is not expected soon. According to a 2019 survey, around 1000 FMTs are performed per 12,000 recurrent CDI patients in Europe — indicating a clear unmet potential.[27]

Ferring's REBYOTA has shown that regulatory approval is possible, but does that mean that the entire microbiome field is now likely to take off?

The microbiome future

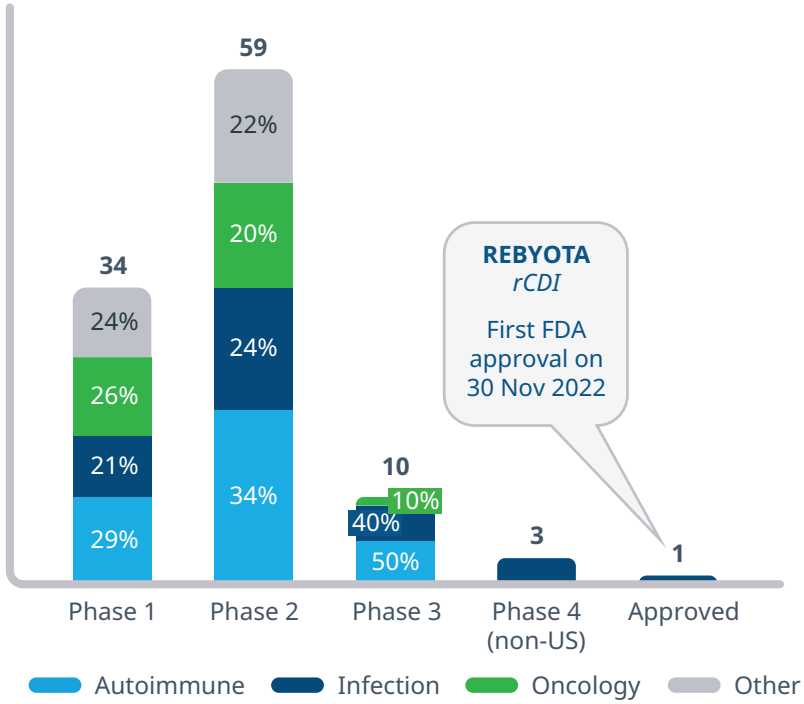
Faeces-based transplants are only the first generation of microbiome therapeutics. The evidence for the microbiome's role in disease pathology increased and is reflected in the research and development pipeline.

Autoimmune diseases that affect the gut are the most common indication and accounts for 35% of the total microbiome pipeline. Specifically, inflammatory bowel disease (IBD) which includes Ulcerative Colitis (UC) and Crohn's Disease (CD) is the leading targeted disease. Studies have shown that the gut microbiome differs in patients suffering from e.g., IBD compared to healthy subjects and identified presumed inflammatory bacteria.[28] Microbiome-based therapeutics aim to reset the balance and depending on the approach, can be a full replacement via an FMT or providing a defined selection of beneficial strains. In a condition where dysbiosis is caused by single bacterial species, a targeted phage therapy could be a viable option as well.

Recurrent CDI (rCDI) has been a focus area for microbiome research and with 12%, is the largest single disease area in microbiome clinical development. The FDA approval of Ferring's REBYOTA is only the first win for the field. Seres Therapeutics awaits the FDA's positive nod for its oral rCDI treatment SER-109 in the first half of 2023. In addition to its oral formulation, SER-109 also has better efficacy data than its enema-based competition.[29] Ferring is aware of the route of administration drawback and has with RBX7455 its own oral contender in development.[30]

Oncology is an important area for future microbiome therapeutics and represents 20% of the total pipeline (Figure 6). Immune checkpoint inhibitors (ICI) have proven transformative across many cancer indications. However, not all patients respond to the treatment and

Figure 6: Microbiome pipeline



35%

Autoimmune diseases

Mostly Inflammatory bowel disease (IBD) incl. Ulcerative Colitis (UC) & Crohn's Disease (CD)

20%

Oncology

Early phase products in both solid and blood cancers

12%

Clostridium difficile infections

Largest targeted single disease area within microbiome therapeutic incl. the first approval

rCDI — recurrent *Clostridium difficile* infection;
Source: IQVIA Pipeline Link and secondary research

there is growing evidence that the gut microbiome influences ICI efficacy.[31] Antibiotics also attenuate the efficacy of immunotherapy and there is growing evidence for a role of the microbiome in CAR-T immunotherapies.[32] Products in the pipeline are in early clinical phase and tested mostly in combination with ICI. Recently there were setbacks. Seres discontinued their SER-401 study and Vedanta had to stop its VE800 immuno-oncology trial as the response rate was too low.[33,34]

Bacterial lysates are known to stimulate the immune system and have been used for decades in both children and adults to stop respiratory tract infections.[35] OM-Pharma is testing their already marketed products in two phase 4 studies to prevent viral infections in children suffering from wheezing episodes. Preclinical R&D activity is moreover focused on understanding the detailed mechanism of action to develop products in other areas such as atopic dermatitis.[36]

The microbiota-gut-brain axis is a bidirectional communication pathway through which bacterial

We are only at the beginning to fully comprehend the role of the microbiome across therapeutic areas. Although, the scientific basis ranges from proven clinical efficacy to loose correlation. More translational research is needed to fill the evidence gap for future microbiome therapeutics in oncology, autoimmune or CNS conditions.

metabolites can enter the brain, influence neurodevelopment and are proposed to be linked to neurodegenerative disease including Alzheimer's Disease (AD), Parkinson's Disease (PD) or Multiple Sclerosis (MS).[37] GI symptoms have been long-known to be linked to PD — even years before the actual

Next-generation live biotherapeutic products outside of rCDI aim to modulate the microbiome and thus must be seen in the context of the patient's gut. Things get even more complicated for non-gastrointestinal indications where most studies are associative and correlate a disease state to the microbiome. For a clinical product, a causal link must be identified first.

diagnosis. Probiotics have already been shown to have a positive effect on patients' GI symptoms.[38] Neurodegenerative diseases are themselves inherently complex and the underlying disease causes not well understood. The microbiome is adding another layer of complexity and thus it will remain to be seen whether microbiome modulation will be a viable therapeutic option in PD or others.

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CHALLENGE OF MICROBIOME TRANSLATION

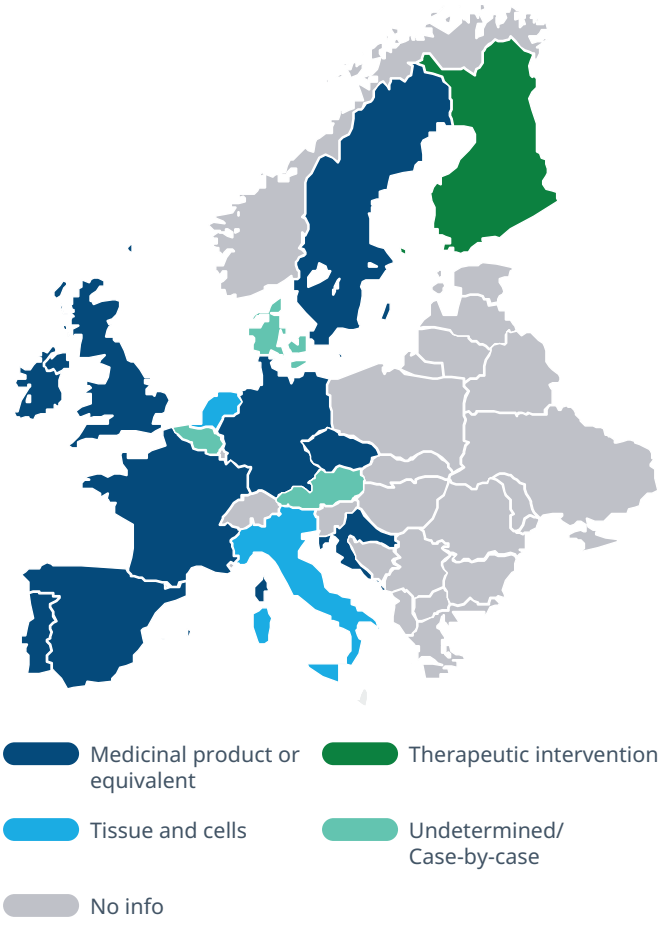
The clinical results of faeces-based microbiota replacement approach in rCDI are more robust whilst in other indications, the complex microbiome-disease interaction remains elusive despite the availability of better diagnostics and high R&D investment. Even in rCDI, success is not guaranteed. Finch Therapeutics announced — despite meeting primary endpoints in a phase 2 study — to discontinue the phase 3 trial of its investigative oral rCDI asset CP101.[39] Next-generation live biotherapeutic products outside of rCDI aim to modulate the microbiome and thus must be seen in the context of the patient's gut. Things get even more complicated for non-gastrointestinal indications where most studies are associative and correlate a disease state to the microbiome. For a clinical product, a causal link must be identified first. In the future, mechanistic models leveraging AI/ML advanced analytics and different omics data sources may help to better understand microbiome-host interactions.[40] The underlying data for such approaches — in both the pre- and clinical setting — must be collected in a standardised way before the full power of such advanced analytics approaches can unfold.

REGULATORY ENVIRONMENT

The approvals of Ferring in the US and BiomeBank in Australia by the FDA and TGA respectively are indicative of the authorities' high maturity of dealing with microbiome therapeutics. However, the regulatory environment varies across regions and sometimes even countries. The successful US and Australia approvals may not be as straightforward to replicate in other regions including Europe. In China, evidence for FMT usage goes back to the 4th century and today, the country's largest treatment centre alone has carried out over 60,000 procedures since 2012.[41] The Chinese Medical Association formulated an expert consensus on stool donor management, procedure quality control, adverse event reduction and promotion of standardisation.[42] In contrast, there is no clear regulation on FMTs or microbiome therapeutics in general in Europe by the EMA — leaving the individual member states to decide (Figure 7).[43]

To ensure that FMT and future microbiome therapeutics reach patients, regional and national regulatory bodies must push towards a harmonised framework. The EMA's network strategy to 2025 states that the development of appropriate regulatory pathways for, e.g., customised use and use of phage libraries or development of microbiome products may be required. Moreover, the recent substance of human origin (SoHO) regulation aims towards harmonisation at the EU level.[44]

Figure 7: Regulation of FMT in selected countries



Source: Faecal microbiota transplantation EU-IN horizon scanning report

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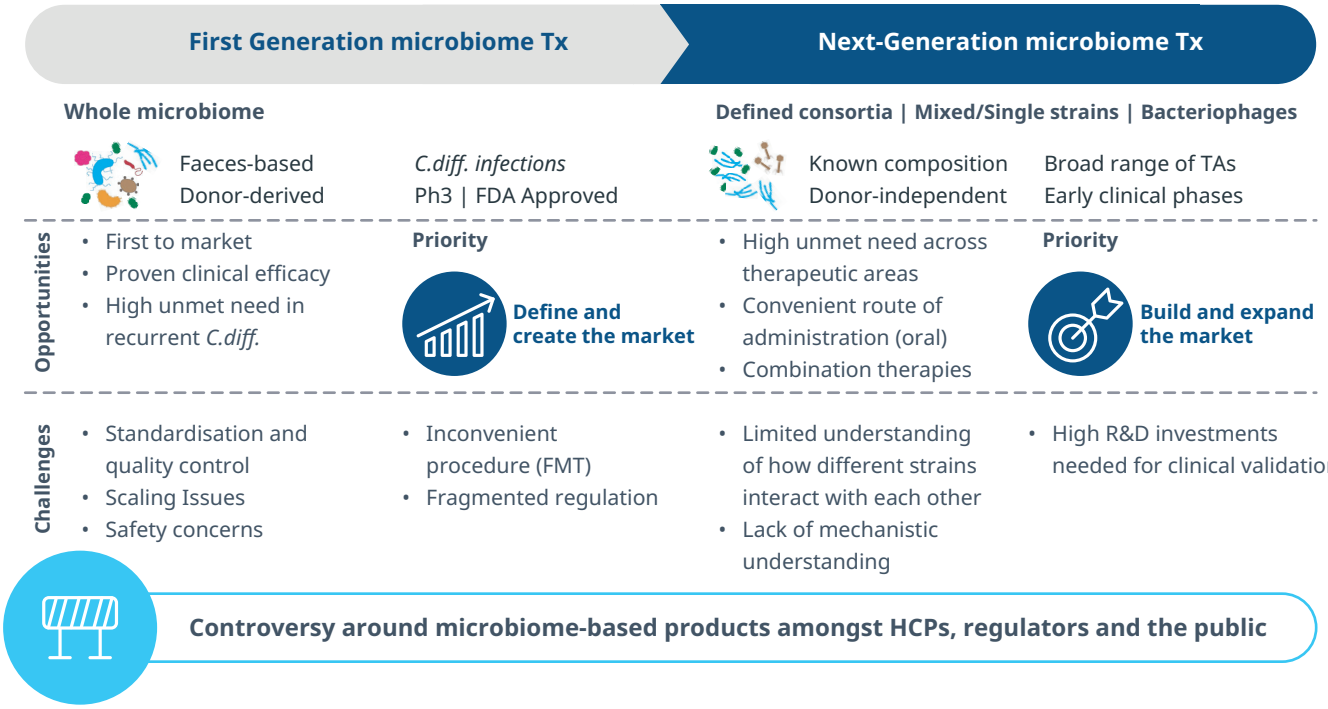
FUTURE PRIORITIES

Microbiome innovators must navigate a nascent and evolving market. The launch of first-generation microbiome therapeutics will enter a relatively small rCDI market with a clearly defined patient population. Getting this first-to-market opportunity right is paramount to establish that prescription-bound microbiome therapeutics have a superior safety profile compared to home-brew FMT and perform under real-world conditions. Thus, convincing stakeholders in the healthcare system and laying the foundation to create a new market that next-generation microbiome therapeutics can build on (Figure 8).

Figure 8: Microbiome future priorities



Source: IQVIA EMEA Thought Leadership

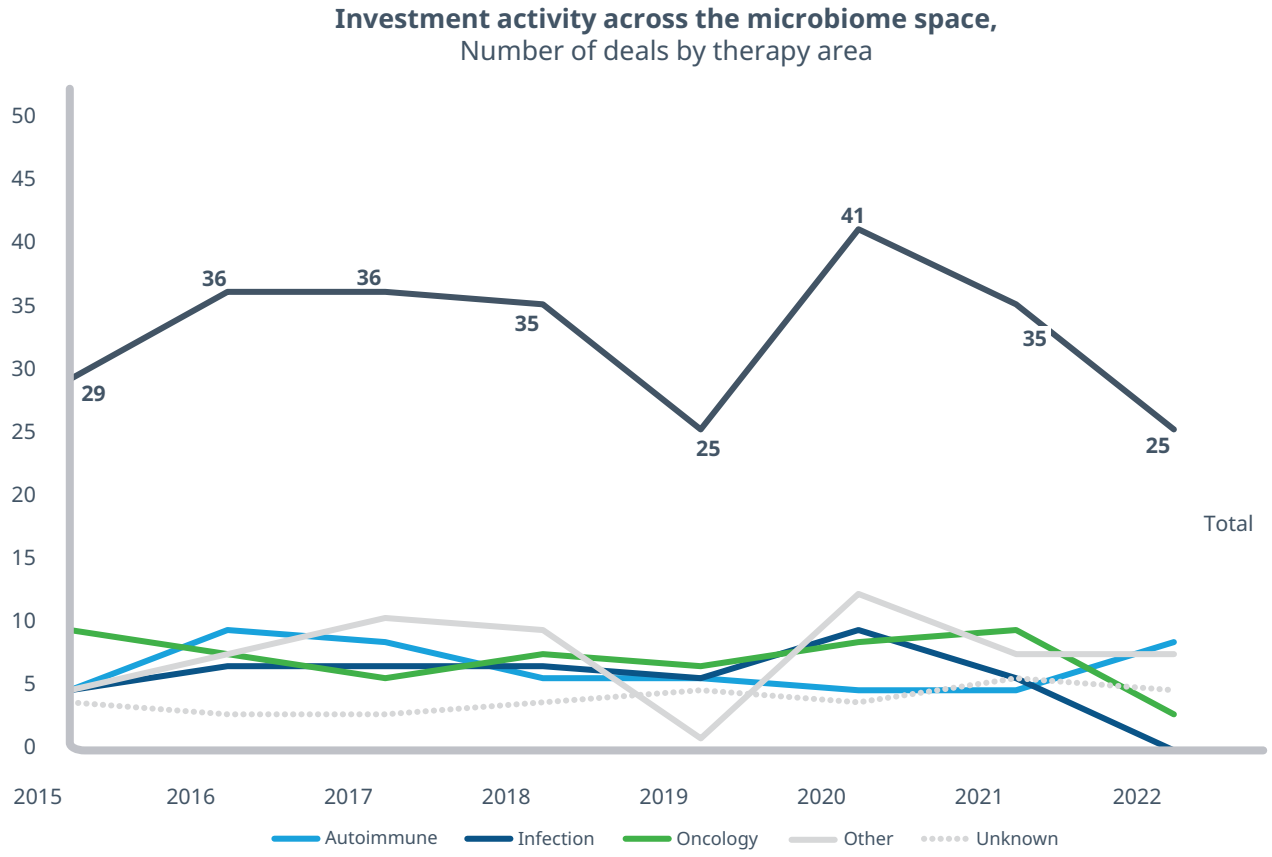
The microbiome investment case

Pharmaceutical investment activity did not stop during the COVID-19 pandemic. On the contrary, 2020 and 2021 saw more deal activity and the microbiome space was no exception.[45] The total number of investment deals pre-pandemic has remained stable, followed by a dip in 2019 — probably because not all deals have been disclosed — and in 2021 saw a record high of 41 published deals. Gastrointestinal (GI) autoimmune disease including IBD/UC leads the total number of deals followed by infectious diseases and oncology (Figure 9 top panel). Start-Up/Emerging Biopharma (EBPs) companies are with 56% the majority of originators. Interestingly, they partner with mid-sized pharma (46%) or other Start-Ups/EBPs (24%) over large pharma at just 16% (Figure 9 bottom panel). This trend is not the same across therapy areas. IBD/UC asset deals were predominantly by pharma players and large pharmaceutical has invested more. Compared to other areas, IBD/UC is more evolved and thus risk-averse large pharma is more active.[46]

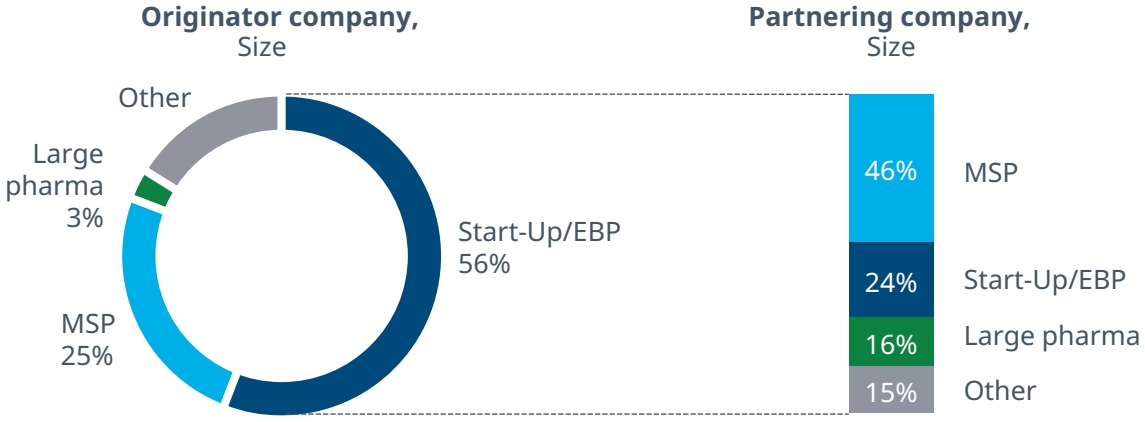
Getting this first-to-market opportunity right is paramount to establish that prescription-bound microbiome therapeutics have a superior safety profile compared to home-brew FMT and perform under real-world conditions.

Notably in 2016, Nestlé — a traditionally agriculture and alimentary food company — entered in a collaboration with Seres Therapeutics with a potential total deal value of over $1.9 billion.[47] Moreover, Nestlé also gained access to Enterome's drug discovery platform to develop and commercialise immunotherapies for food allergies and in IBD.[48] Large pharmaceutical companies tend to invest in the microbiome field depending on the strategic fit with their existing portfolio or to broaden their pipeline. Janssen, Takeda and Pfizer have all entered licensing agreements to expand their GI autoimmune franchise.

Figure 9: Microbiome investment activity



Investment rational	Asset type	Company types	
Expand existing portfolio	Rx, OTC	Large Pharma MSP & EBP	
Enter and **diversify** portfolio	Rx, OTC	Large Pharma MSP & EBP	Agro - alimentary players
Gain R&D capabilities	Biomarker, Genomics, Assays, Diagnostics	Large Pharma MSP & EBP	Agro - alimentary players



EBP – Emerging Bio Pharma; MSP – Mid-Sized Pharma

Source: IQVIA EMEA Thought Leadership; IQVIA Consulting; IQVIA PharmaDeals; Informa

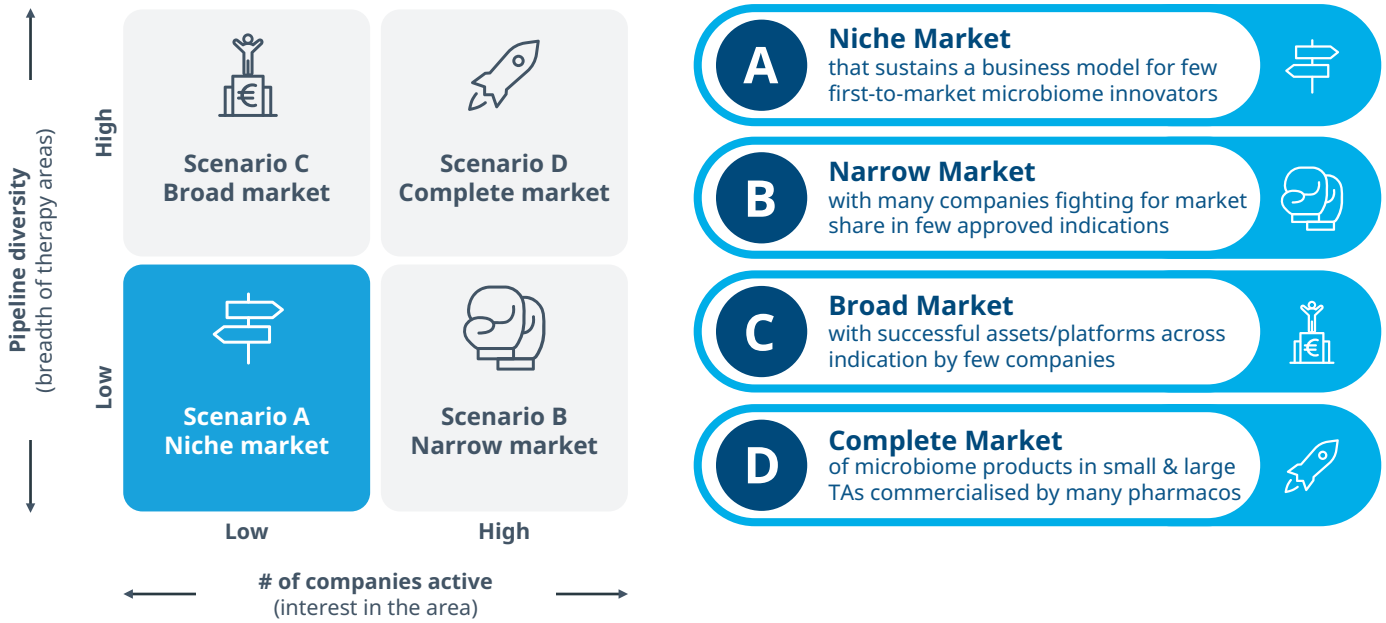
It is not just pharmaceutical companies that are actively investing in microbiome therapeutics or microbiome-based technology. Agro alimentary players also made big bets.

Janssen first invested in Vedanta's lead IBD candidate VE202 in 2015. The deal ended and the company is no longer an active investor but retains commercialisation royalties. Later in 2021, Pfizer invested $25 million in VE202 and secured an option on first negotiation for the asset.[49] Genentech currently does not have a microbiome program. Nonetheless, they entered in a collaboration for a precision microbiome platform to identify microbiome biomarker signatures of drug responses to gain R&D capabilities and potentially enter the microbiome area in the future.[50] Pharma tends to invest in early-stage assets and R&D collaborations to gain access to promising technology whilst asset acquisition is rare. China-based Xbiome bought Assembly Biosciences M201 asset to expand its geographic reach and microbiome footprint. A notable although not a recent event example for merger and acquisition (M&A) activity in the microbiome filed was Ferring's acquisition of Rebiotix back in April 2018.[51] The now FDA-approved REBYOTA originated from this deal.

It is not just pharmaceutical companies that are actively investing in microbiome therapeutics or microbiome-based technology (Figure 9 middle panel). Agro-alimentary players made big bets and aim to leverage the assets and technology in their line of business e.g., reduce the need for fertilisers in agriculture or minimise antibiotics usage in livestock

Large pharmaceutical companies tend to invest in the microbiome field depending on the strategic fit with their existing portfolio or to broaden their pipeline.

Figure 10: Future scenarios for the microbiome market



Source: IQVIA EMEA Thought Leadership

breeding. Microbiome research is considered risky given the limited proof outside of recurrent *C.diff.* infections. As a result, R&D collaboration are favoured to de-risk the exploratory nature of microbiome assets outside the infectious disease therapeutic area.

Multiple paths to success

2022 saw the first microbiome therapeutic approvals and 2023 will see the launch of REBYOTA in rCDI in the US. There are good reasons to believe this market will evolve and mature. Pharmaceutical and ex-pharmaceutical companies have made strategic investments in specific assets or platforms. The basic science offers compelling evidence that the microbiome is linked to and influential on human health and disease in many ways, and the pipeline is filled with innovative products in a broad range of indications (Figure 6). Drawing analogies from the broad spectrum of microbiome therapeutic approaches, we envision four future scenarios depending on the pipeline diversity and number of companies active (Figure 10).

At present and in the near-term future, microbiome therapeutics will be a niche market (Scenario A) with approved products against specific infectious diseases. As development in other indications proves challenging, more companies enter and could, unless more market segments open up result in competitive narrow market (Scenario B). If regulation does not harmonise across countries, the market would also be more local than global, which would limit development. Technological and regulatory barriers can be overcome. When this happens, we expect to see first few companies to commercialise assets for a wide range of indications with their technology platforms and potentially evolving portfolio of technology platforms within microbiomes. This envisages that certain pioneer companies with the most successful technologies and/or entry into the indications which are most attractive for microbiome therapeutics come to be amongst a small number of winners in this field. (Scenario C). This may not, however happen – if multiple microbiotic approaches are successful from multiple players, then follow-on companies will subsequently enter to reach a complete market with multiple players active and products approved across a broad range of therapy areas (Scenario D).

The next five years will see more approvals of microbiome therapeutics to treat rCDI. Moreover, our microbiome understanding, and regulation will continue to evolve. The EMA is aiming for harmonisation across member states and the recent approvals should give the agency the necessary confidence. Although the timeline for these advances is uncertain, there are some key areas for microbiome companies to focus on to succeed:

1. **Diversifying their business portfolio:** Having both prescription and non-prescription products can help companies spread their risk and reach a wider range of patients
2. **Working with regulators:** Collaborating with regulatory bodies to clarify and improve regulation will help companies navigate the regulatory landscape and bring new therapies to market more efficiently
3. **Preparing the market:** Investing in medical education and engagement with HCPs and payers is critical to increasing awareness and understanding of microbiome-based therapies. HCPs may not be familiar with these therapies, and payers are likely to demand real-world evidence (RWE) before covering these treatments

The next five years will see more approvals of microbiome therapeutics to treat rCDI. Moreover, our microbiome understanding, and regulation will continue to evolve.

4. **Generating RWE:** Companies should be prepared to generate high-quality RWE to demonstrate the effectiveness of their therapies and support their reimbursement. RWE is especially important for microbiome-based therapies, as the microbiome varies greatly between individuals and can impact treatment efficacy

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