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THE MICROBIOME MARKET 2021:
Recent developments, challenges and future directions

An update to IP Pragmatics' 2017 white paper, Exploiting the Microbiome: Market Developments and Intellectual Property Landscape

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1 INTRODUCTION

This white paper by IP Pragmatics focuses on technological and market developments in the microbiome industry over the last four years, serving as an update to our more in-depth 2017 white paper on the same topic. The information in this report does not constitute legal advice and should not be interpreted as such.

The term "microbiome" refers to the collective genomes of resident microorganisms in various environments. In our 2017 report, the academic, commercial and patenting trends reflected a microbiome industry which was at an early stage but had been undergoing rapid growth since 2015. In particular, **therapeutics targeting the human gut microbiome** were a source of huge commercial potential and investment. Human microbiome **diagnostics** were a nascent but active market. Other microbiomes – namely **animal and plant** – were generating much academic research interest while the commercial landscape for each was consolidated by only a handful of companies leading each market sector.

These general observations remain mostly valid in 2021. However, since 2017 there has been vertical and horizontal growth in the microbiome market, evolving technological capabilities and an increasingly diverse landscape of start-up formation, partnerships and deal-making.

The market for human gut microbiome therapeutics is still by far the largest sector of the microbiome industry. Despite ambitious projections by some industry observers in 2017 that the first crop of drugs could launch by 2018, there are still no microbiome-based drugs currently on the market. However, 2020 was a landmark year for microbiome therapeutics development, in particular for the treatment of *C. difficile infection* (CDI). Leading companies **Seres Therapeutics** and **Rebiotix** reported positive results from pivotal Phase III studies of their flagship pipeline candidates for recurrent CDI. 2021 is set to be another critical year as these companies and others advance their therapeutic candidates through the final stages of clinical development and regulatory submission.

To get to this point has been a remarkable turnaround for Seres, after its candidate SER-109 failed in a mid-stage clinical trial in 2016. This setback to some extent cooled big pharma's interest in the microbiome, but well-resourced, multinational drug developers have come back around, with **Roche**, **Merck**, **Takeda**, **AstraZeneca**, **Gilead Sciences** and others all teaming up with small, specialised biotech companies over the past few years to do microbiome research. There also continues to be vast amounts of money invested by venture capitalists and leading pharmaceutical investors in gut microbiome research and development.

One of the main challenges facing gut microbiome therapeutic developers now is real pressure to 'justify the hype' and successfully deliver efficacious drugs to market.

Human microbiome diagnostics is arguably the sector undergoing the fastest diversification in terms of technology development and commercialisation. In 2017 most of our analysis centred on the well-reported rise of sequencing and metagenomics capabilities, which continues to underpin much diagnostic technology. However, the last four years have seen these capabilities and the resultant data leveraged more effectively to support various complementary partnerships spanning biomarker identification, companion diagnostics, digital health, artificial intelligence and novel sampling devices. Big pharma companies are partnering with small innovators, while companies from outside the metagenomics and diagnostics sphere are strategically expanding their services or pivoting towards microbiome applications.

The three other market sectors discussed in this report are the human skin, animal health and agricultural microbiomes. Each has undergone rapid development and growth over the last four years.

The skin is the most accessible human organ, and therefore, a natural target for treatment and diagnostic sampling. Spurred by a growing body of research showing that commensal bacteria, probiotics and/or prebiotics can prove efficacious in the treatment of skin disorders, many cosmetics and consumer product companies, microbiome-focused pharmaceutical companies and biotechnology companies have begun targeting the skin microbiome market by developing cosmetic and therapeutic over-the-counter agents that alter or in some way maintain, benefit or balance the skin microbiome. Of particular note is the activity amongst an increasing number of multinational health/skincare and consumer product companies to invest in and partner with the leading early innovators.

In our 2017 white paper we observed that the animal microbiome field was currently very active at the early-stage and research level, but still in its infancy industrially. Since then, both the research and commercial landscapes have continued to grow and evolve.

Some of the emerging research themes we observed in 2017 included:

- microbiome-optimised feed additives (in particular for the reduction of methane emissions from ruminants)
- more advanced, targeted interventional probiotics and prebiotics
- diagnostic monitoring of microbial indicators for animal wellness
- enzyme discovery, e.g. animal gut microbes capable of digesting particular plants could be of value to the biofuel industry
- breeding for microbiome composition and function for performance, environmental and other benefits
- faecal microbiota transplantation, for instance for pets with digestive conditions or to allow animals to eat a wider range of food and possibly survive habitat loss

While these research areas remain active and promising, however, there are two animal microbiome themes in particular which have informed the activities of recent commercial players in this market: 1) potential to reduce antibiotic use and 2) gastrointestinal inflammation treatment.

When we published our previous white paper, the agricultural microbiome market was composed of just a handful of new and established players. Major companies are continuing to grow their presence in this market, and early innovators are expanding. However, of particular note is that since 2017 the start-up landscape has continued to grow and diversify, with companies focused on developing microbiome-targeting biofertilisers, biofungicides, biostimulants, biopesticides, crop probiotics, 'biological optimisers' or yield-optimising bacteria, for example.

There are several other emerging frontiers of microbiome research and commercialisation, such as the oral (e.g. for dental health treatments), vaginal (e.g. for bacterial vaginosis), lung (e.g. for airway infections) and 'built' (e.g. for building and cleaning material) microbiomes. However, discussion of these markets is beyond the scope of this report.

In our 2017 white paper we analysed and discussed the landscape for academic microbiome research, which has seen explosive growth in research publications since 2012. There are a large number of leading research institutes which have founded dedicated microbiome research centres and/or spun out some of the industry's pioneering companies including **4D Pharma** (from APC

Microbiome Institute, University College Cork), **Microbiotica** (Wellcome Sanger Institute), **Artizan Biosciences** (Yale University), **Evolve Biosystems** (University of California, Davis), **Matrisys Bioscience** (University of California, San Diego), **YUN Probiotherapy** (University of Antwerp), or produced the scientific teams which have gone on to found many other leading companies.

The academic landscape is not analysed in further depth in this report. However, it is worth briefly touching on the enormous list of publicly-funded microbiome research occurring over the last few years. In 2016, the National Microbiome Initiative (NMI) was launched in the US with $121 million of funding to advance understanding of microbiome behaviour and enable treatment of human diseases that may result from dysbiosis. Several organisations participated in this initiative with the provision of additional funding support in 2017, including the Department of Energy ($10 million), NASA ($12.5 million), the National Institutes of Health ($20 million), the National Science Foundation ($16 million) and the U.S. Department of Agriculture ($15.9 million). Support to NMI was provided by hundreds of other organisations.[1] In the year between June 2020 and June 2021, the US **National Institutes of Health** (NIH) funded around 1400 microbiome-focused research projects, mostly in the region of $100k - $800k each.[2]

A similar funding environment has been developing in the EU. The EU has already funded 216 projects under the Seventh Framework Programme (2007-2013) and Horizon 2020 (2014-2020) to accelerate metagenomics and advance knowledge of microbes. This support started with the MetaHIT project, which includes the advanced multidisciplinary SYSCID (systems medicine approach to chronic inflammatory diseases) research project. This looked at the role of the microbiome in chronic inflammatory diseases (inflammatory bowel disease, systemic lupus erythematosus and rheumatoid arthritis) as well as mechanisms of microbiome resilience and disruption. Together, these projects involve an investment of more than €498 million.[1]

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.[3] Similarly, in January 2021, the UK's Knowledge Transfer Network launched its Microbiome Strategic Roadmap[4] which reviewed the landscape of microbiome science and innovation and laid out key recommendations on how to advance science translation and business creation across the human, animal and plant microbiome sectors.

[1] BCC Research (2020) *Microbiome Therapeutics: Global Markets*
[2] GlobalData (2021)
[3] Microbiome Interagency Working Group (2018) *Interagency Strategic Plan for Microbiome Research FY 2018-2022*
[4] https://ktn-uk.org/news/ktns-microbiome-innovation-network-launches-the-microbiome-strategy-roadmap/

2 GUT MICROBIOME THERAPEUTICS

2.1 RECENT DEVELOPMENTS

2020 was a landmark year for live biotherapeutic product (LBP) development, in particular for treatment of *C. difficile infection* (CDI). CDI affects approximately 170,000 people annually in the USA – 30,000 fatally – but currently has very limited treatment options.

In August 2020, **Seres Therapeutics** (USA) reported positive results from the pivotal Phase III ECOSPOR III study evaluating its investigational stool-derived, oral microbiome therapeutic SER-109 for recurrent CDI. The study showed that SER-109 administration resulted in a highly statistically significant absolute decrease of 30.2% in the proportion of patients who experienced a recurrence in CDI within eight weeks of administration versus placebo.[5]

To get to this point has been a remarkable turnaround for Seres. In July 2016, it announced that SER-109 had failed in a mid-stage clinical trial. A reanalysis of the data found that some of the patients in the study did not actually have CDI.[6] In 2017, the FDA granted the company permission to conduct another clinical trial enrolling patients whose infection was confirmed with a diagnostic test. The study was also designed to test a higher dose over three days rather than two.

In September 2020, Seres announced that it has obtained correspondence from the Office of Vaccines Research and Review of the FDA regarding the company's plans to submit a Biologics License Application (BLA) to support product approval of SER-109 for CDI,[7] and anticipates that a regulatory filing will come this year.[8]

Though SER-109 stands to become the first FDA-approved microbiome therapy, several other live biotherapeutic microbial products are close behind. In May 2020, **Rebiotix** (USA) and **Ferring Pharmaceuticals** (Switzerland) announced positive preliminary findings from their ongoing Phase III trial of the investigational microbiome-based CDI treatment, RBX2660,[9] and then in May 2021 presented results showing that RBX2660 provided a relative reduction of recurrence of 29.4% compared to placebo.[10]

In June 2020, **Finch Therapeutics** (USA) also reported success from a Phase II study of a microbiome-targeting drug, CP101, for CDI.[11] Eight weeks in, the study showed a 62% cure rate for patients treated with just standard-of-care antibiotics, but a 75% cure rate for those who received antibiotics as well as CP101. The company expects to run a second trial to confirm the results before submitting its therapy to the FDA.

[5] https://www.businesswire.com/news/home/20200810005194/en/Seres-Therapeutics-Announces-Positive-Topline-Results-SER-109

[6] https://xconomy.com/boston/2017/01/31/seres-dissects-failed-microbiome-drug-trial-suggests-changes-to-fda/

[7] https://www.businesswire.com/news/home/20200911005082/en/Seres-Therapeutics-Announces-U.S.-Food-and-Drug-Administration-Correspondence-Following-Positive-SER-109-Phase-3-Study-Results

[8] https://www.biopharmadive.com/news/seres-microbiome-drug-data-fda/583217/

[9] https://www.rebiotix.com/news-media/press-releases/rebiotix-announces-worlds-first-positive-pivotal-phase-3-data-investigational-microbiome-based-therapy-rbx2660/

[10] https://www.microbiometimes.com/ferring-and-rebiotix-present-landmark-phase-3-data-demonstrating-superior-efficacy-of-investigational-rbx2660-versus-placebo-to-reduce-recurrence-of-c-difficile-infection/

[11] https://www.biopharmadive.com/news/finch-microbiome-c-difficile-study-results/580126/

Though CDI-targeting microbiome treatments are the most advanced in the field, there is a broad range of indications being targeted by microbiome therapeutics companies. For example, in November 2020, Seres announced that it has dosed the first patient in its Phase Ib trial evaluating SER-301 for the treatment of active mild-to-moderate ulcerative colitis.[12] Finch Therapeutics, meanwhile, is using a recent $90 million fundraising partly to move into ulcerative colitis and Crohn's disease (in collaboration with **Takeda**), hepatitis B, and in children with autism, of which at least 30% struggle with chronic constipation due to their unique microbiome.[13]

Some other examples of recent developments include:

- Infectious diseases
    - In November 2018, **Synthetic Biologics** (USA) reported results of its End-of-Phase 2 meeting with the FDA that discussed the development of SYN-004 (ribaxamase) for the prevention of antibiotic-mediated CDI. An outcome of the meeting was the proposition of criteria for Phase III clinical efficacy and safety which, if achieved, may support submission for marketing approval of ribaxamase on the basis of a single Phase III clinical trial. SYN-004 is an enzyme that works by degrading certain intravenous betalactam antibiotics within the GIT to prevent microbiome damage, CDI, overgrowth of pathogenic organisms and the emergence of antimicrobial resistance (AMR).
    - In July 2020, **Kaleido Biosciences** (USA) initiated a controlled clinical study with Massachusetts General Hospital, evaluating the microbiome metabolic therapy candidate KB109 added to supportive self-care for outpatients with mild-to-moderate COVID-19.
- Gastrointestinal (GIT) Diseases
    - In June 2020, **Vedanta Biosciences** (USA) announced positive topline data from two Phase I studies in healthy volunteers of VE202, an investigational LBP product for the treatment of IBD. The studies showed that the drug administered at different doses was found to be safe and demonstrated durable and dose-dependent colonisation.
    - In October 2019, **Biomica** (Israel; a subsidiary of Evogene Ltd.) initiated preclinical studies for BMC321 and BMC322, two rationally designed microbial consortia aimed at reducing inflammation for the treatment of IBD. The candidates were discovered using PRISM, a proprietary high-resolution computational microbiome analysis platform.
- Metabolic Diseases
    - In June 2020, **Kintai Therapeutics** (USA) was able to push its anti-obesity microbiome drugs KTX-0200 into IND-enabling studies. The results from animal studies for this drug showed positive results. In diet-induced obesity rodent models, KTX-0200 induced sustained weight loss of 14%, improved blood sugar tolerance as 12% improvement in glucose clearance, and increased insulin sensitivity with a 14.5% improvement based on a glucose clearance test. The drug is also being investigated for the treatment of non-alcoholic steatohepatitis.

[12] https://www.businesswire.com/news/home/20201106005080/en/Seres-Therapeutics-Announces-Initiation-of-Phase-1b-Trial-of-SER-301-for-the-Treatment-of-Ulcerative-Colitis

[13] https://www.fiercebiotech.com/biotech/finch-nets-90m-to-push-c-diff-microbiome-med-toward-fda-filing-move-into-hep-b-autism

- In December 2019, **Synlogic** (USA) reported data from the company's bridging study in healthy volunteers of a solid formulation of the LBP SYNB1618 for the treatment of phenylketonuria. The results allowed the company to select a maximum tolerated dose of the solid, oral formulation of SYNB1618 to move into a Phase II clinical trial.

- Cancer
  - In June 2020, **Assembly Biosciences** (USA) reported preclinical data from its immuno-oncology microbiome program. Animal studies and cell-based assay results have allowed Assembly to define single bacterial strains and consortia with reproducible anti-tumour activity and significant enhancement of checkpoint antibody efficacy.
  - In July 2020, **Synthetic Biologics** received a study-may-proceed letter from the FDA for the first clinical study of SYN-020, an oral formulation of recombinant intestinal alkaline phosphatase. The intended study is a Phase I single ascending dose study in healthy volunteers, designed to evaluate SYN020 for safety, tolerability and pharmacokinetic parameters. The Phase I clinical program, expected to start during the first quarter of 2021, will support the clinical development of SYN-020 in multiple indications, including the treatment of radiation enteropathy secondary to pelvic cancer therapy.

- Gut-Brain Axis Diseases
  - In April 2019, the FDA granted Fast Track designation to **Finch Therapeutics**' Full-Spectrum Microbiota (FSM) therapy for the treatment of children with ASD. In an open-label study investigating the role of FSM in 18 children with ASD, it was observed that the treatment was well tolerated and led to a 77% reduction of GI symptoms and a 24% reduction of core ASD symptoms at eight weeks posttreatment.
  - In October 2019, **Axial Biotherapeutics** (USA) shared preclinical data highlighting a strong association between bacteria-derived metabolites and ASD. Axial Biotherapeutics is currently investigating AB-2004, a novel therapeutic that removes metabolites in the GIT, in a Phase I/2a safety and tolerability study.

Seres' 2016 setback to some extent cooled big pharma's interest in the microbiome, but well-resourced, multinational drug developers have come back around, with **Roche**, **Takeda**, **AstraZeneca** and **Gilead Sciences** all teaming up with small, specialised biotechs over the past few years to do microbiome research.[11]

If successful, their work would fill big gaps in therapeutic options. Currently, the main treatment for an imbalanced gut microbiome is faecal microbiota transplantation (FMT; also known as gut microbiome transfer or intestinal microbiome transfer), an effective procedure but an invasive one that has triggered safety concerns at the FDA after two immunocompromised adult patients developed invasive infections by ESBL-producing *E. coli*.[14] Drugs such as those being developed by Seres and Rebiotix are essentially drug-based approaches to FMT.

The FDA has currently not approved any FMTs. It is actively involved in supporting product development and has issued guidance stating that it intends to exercise enforcement discretion,

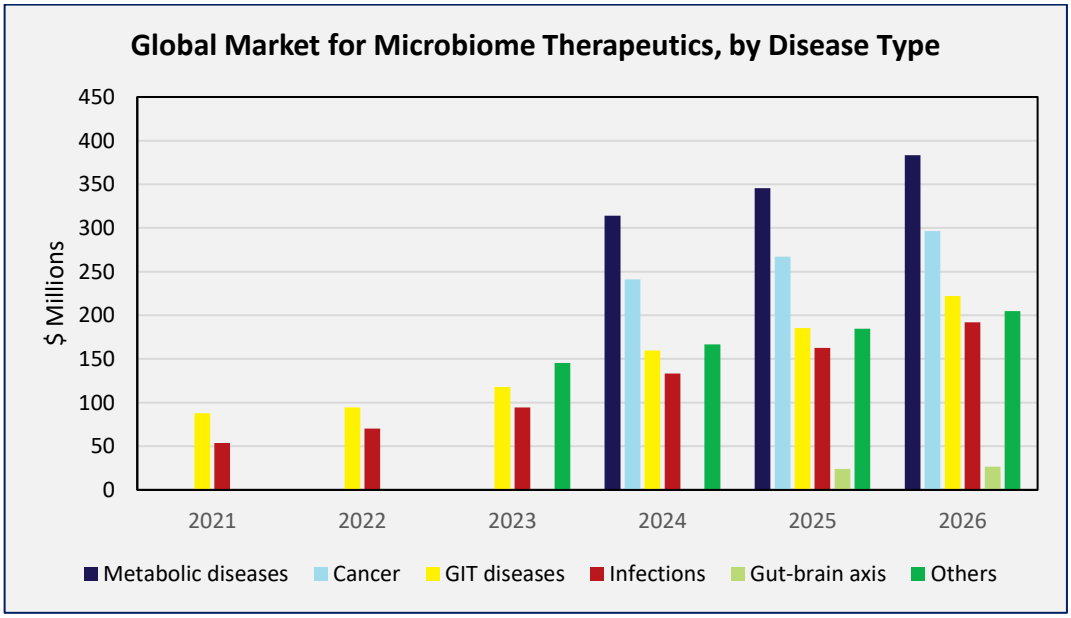
[14] https://www.reactgroup.org/news-and-views/news-and-opinions/year-2019/safety-concerns-of-fecal-microbiota-transplants

under limited conditions, regarding the investigational new drug requirements for FMT used to treat CDI. In Europe, The European Tissue and Cells Directive and affiliated technical guide provide extensive safety and quality standards which may readily be adopted in an FMT service to provide patients with this life-saving treatment embedded in a public blood centre.[15]

2.2 MARKET OVERVIEW

The human microbiome market is still nascent but is expected to grow rapidly, pending approval of key pipeline candidates in the near future. In our 2017 white paper we noted the wildly different projections of the size of the therapeutics market, with various market research sources forecasting global 2024 market values ranging from $800 million to $9.9 billion.

The projected market size remains uncertain, and subject to re-evaluation as pivotal drug candidates proceed through pipeline development. BCC Research projects the market for microbiome therapeutics to be worth $141.7 million in 2021, rising at a massive compound annual growth rate (CAGR) of 56.4% through 2026, to be valued at $1.3 billion.[16] Gastrointestinal diseases and infections dominate the landscape currently, though metabolic diseases and cancer are expected to emerge as key market segments by indication over the coming years, as shown in the figure below.



Adapted from: BCC Research (2020) *Microbiome Therapeutics: Global Markets*.[16]

It is noteworthy that this market value projection is a significant downgrade from previous BCC estimations in 2017, when microbiome drugs for cancer and various metabolic disorders were expected by some industry observers to launch as early as 2018 – an estimate that has proven to be overly optimistic. Indeed, one industry view is that "*there has been a lot of hype about microbiome-based drugs and the industry is under a lot of pressure. Many press releases have promised a lot and not many results have been delivered. Thus, there has been a difficult situation developing for microbiome companies, and it is getting harder for them to attract investors and get*

[15] https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30180-2/fulltext
[16] BCC Research (2020) *Microbiome Therapeutics: Global Markets*

capital. It is therefore important to prove that microbiome therapeutics can deliver what is promised. This industry is at an inflection point and the microbiome companies have to live up to the hype and prove statistically that the technology works."[17]

It is true that there have been some disappointing clinical trial results and that investment in microbiome therapeutics is down across all therapy areas.[18] Besides the Seres result, another high-profile study failure was **Ritter Pharmaceuticals** (now **Qualigen Therapeutics** (USA)), whose RP-G28 failed to beat placebo in reducing lactose intolerance symptoms in a Phase III trial in 2019.[19]

However, there remains high levels of investment and new, innovative therapeutics companies emerging, as well as an expansive patent portfolio and a large number of active clinical trials, as discussed in the sections below.

2.3 MARKET DRIVERS

- Potential of microbiome therapeutics to serve unmet medical needs which have not been solved by conventional treatments like small molecule therapeutics or biologics.
- Growing body of evidence of the influence of the gut microbiome on a huge range of diseases and disorders, from inflammatory bowel disease (IBD) to autism to depression.
- Continued investment by venture capitalists and pharma companies.
- Active support from the FDA.
- Increased feasibility in technology for microbiome testing. With the decreased cost of genetic sequencing and the increased computational power for analysis, experimental processes move much more quickly.
- Increased consumer awareness of the relationship between the microbiome and general health and wellness. The curiosity of the public in learning about regulating their own microbiome has led to customer engagement programs. Consumer education mixed with this new wave of microbiome-friendly wellness options has run alongside drug development and has further motivated the medical field to propel the microbiome therapeutics field forward.[17]
- The growing number of partnerships between clinical-stage microbiome companies with big pharmaceutical giants, combined with progress in technologies and growing understanding of the microbiome, will provide opportunities for further growth.

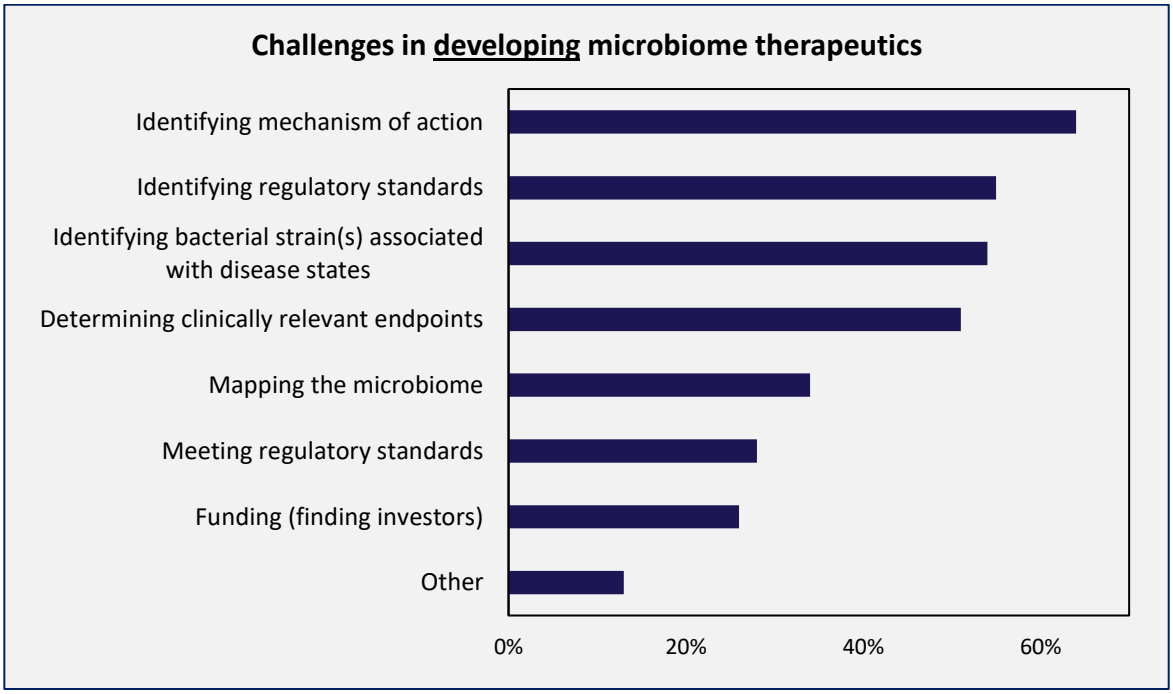
2.4 CHALLENGES

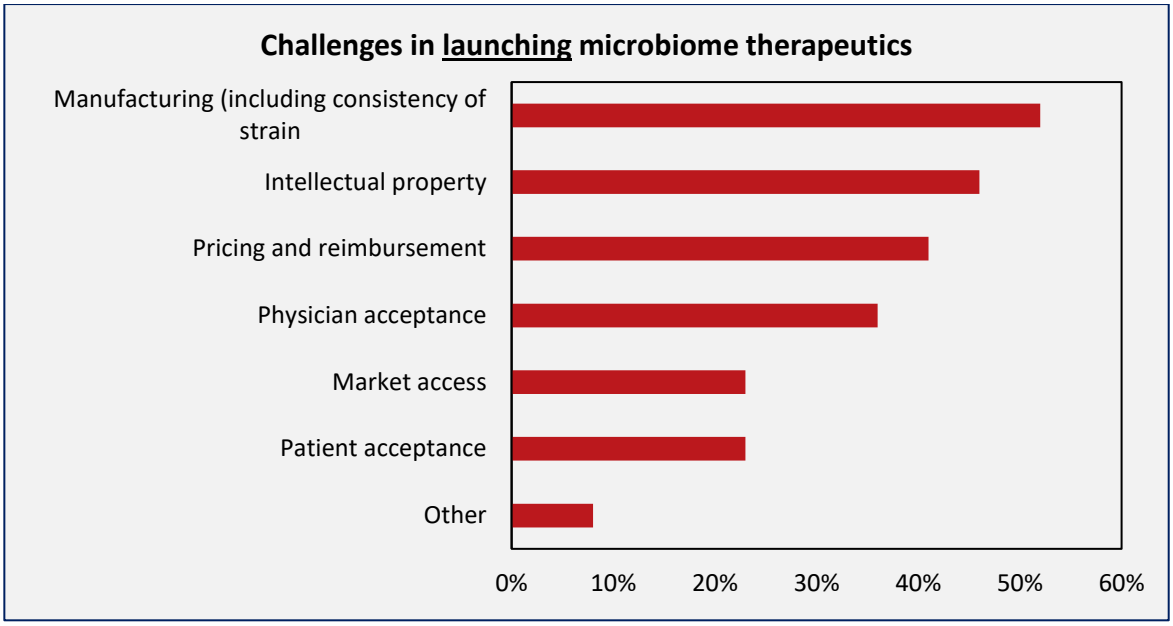
- The absence of a regulatory framework has created an uncertain situation for many developers in this novel market. Regulatory agencies will likely require drug developers to demonstrate the mechanisms of action of microbiome therapeutics (viewed as the biggest technical challenge facing microbiome companies) in order to gain regulatory approval.
- The complexity of the human microbiome and variations among different individuals add to the difficulties in the design of clinical trials.

[17] BCC Research (2020) *The Future of: Microbiome Therapeutics - A BCC White Paper*
[18] GlobalData (2019) *The State of the Microbiome*
[19] https://endpts.com/ritter-bombs-final-phiii-for-sole-lactose-intolerance-drug-shares-plummet/

- There may be hurdles in the manufacturing and scale-up of these novel therapeutic compounds, in addition to issues in preclinical and safety studies. In producing these compounds at scale, two issues arise: 1) The heterogeneity of the treatment and 2) The heterogeneity of the recipient's microbiome. Those producing live bacteria have even more challenges due to the additional complexity of biological fermentations and process development. Any small change in the bioprocess can drastically affect the product quality and yield.

- In 2019, GlobalData undertook a survey of 158 key opinion leaders involved in microbiome therapeutics development around the world. The main challenges associated with developing and manufacturing microbiome therapeutics are summarised in the figures below.[18] Identifying the mechanism of action is considered the biggest challenge. GlobalData anticipates regulatory bodies may require drug developers to demonstrate the mechanisms of action of microbiome therapeutics in order to gain regulatory approval. In addition, microbiome therapeutics may experience slow uptake upon launch if drug developers cannot explain how they work to physicians.





Survey responses (N=158) of perceived challenges facing microbiome therapeutics companies in developing and launching therapeutics. Adapted from: GlobalData (2019) *The State of the Microbiome*.[18]

- For the microbiome therapeutics market to grow, a strong collaborative effort is needed from all stakeholders, including the regulatory agencies. Statistically relevant results and proof-of-concept studies driven by technological advances in biomarkers, functional assays, and computational biology are required that will eventually pave the way for product approvals.
- The COVID-19 pandemic has significantly impacted the global economy. Supply chains have been disrupted, and shortages in essential supplies and effects on human resources have added to the problems. This has resulted in delays in clinical trials due to pauses in enrolment. Many microbiome companies have reported delayed results and are now expecting clinical studies to extend into 2021-2022.
- One challenge is to protect the IP and the investment. It is very easy for generics to enter the drug market. So, right now the goal is to bring a product to market that is safer, effective and less expensive and has protected intellectual property.[17]

2.5 PIPELINE

There are well over 200 companies working on different approaches to microbiome modulation, with a goal to target disrupted microbiota and offer treatment options in the form of microbiome-based drugs. Although FMTs have been in practice for some time, the use of LBPs in the form of single strains or microbial consortia is becoming a widely popular strategy due to targeted mechanisms and controlled production processes. The development of small molecule drugs (postbiotics) and use of phages are also being actively explored.

BCC Research found that there are at least 242 clinical trials registered in this area, targeting several different therapeutic indications.[16] In terms of the human gut, GIT diseases (at least 58 clinical trials) and infectious diseases (at least 48 clinical trials) are the most common areas. Cancer, metabolic diseases and neurological diseases are also gaining traction, and the interest of leading pharmaceutical companies.

Based on data compiled by GlobalData (2021), there are currently around 250 pipeline microbiome drugs in active development across all disease segments, including GIT, metabolic diseases, cancer, infections, gut-brain diseases and others. This is an increase of over 100% compared to our 2017 report.

Among the top companies with leading pipelines are **4D Pharma** (UK)**, Rebiotix** (USA)**, Evelo Biosciences** (USA)**, AOBiome** (USA)**, Synthetic Biologics** (USA) and **Enterome** (France), all of which have more than ten candidates in preclinical investigations.

A **non-exhaustive** overview of some of the leading companies and more advanced clinical pipeline drugs is provided in the table below.

Drug	Company	Strategy	Indication	Phase
Infections				
RBX-2660	Rebiotix	Modulatory	CDI	III
SER-109	Seres Therapeutics	FMT drug	CDI	III
CP-101	Finch Therapeutics	LBP	CDI	II
MRx4DP0004	4D Pharma	LBP	COVID-19	II
Lactin-V	Osel	LBP	UTI	II
SYN-004	Synthetic Biologics	Postbiotics	CDI	II
VE303	Vedanta Biosciences	LBP	CDI	II
EDP1815	Evelo Biosciences	LBP	COVID-19	II
Gastrointestinal (GIT) Diseases				
IBP-9414	Infant Bacterial Therapeutics	LBP	Necrotizing enterocolitis	III
MRx1234	4D Pharma	LBP	IBS	II
FMT	MaaT Pharma	FMT	Gastro-intestinal Acute GVHD	II
SER-287	Seres Therapeutics	FMT drug	UC	II
SYN-010	Synthetic Biologics	Postbiotics	IBS	II
HOST-G904	Host Therabiomics	Postbiotics	IBS	II
Profermin	Nordisk Rebalance	LBP	UC	I/II
Metabolic diseases				
KB195	Kaleido Biosciences	Postbiotics	Urea cycle Disorders	II
MET-3	NuBiyota	LBP	Obesity	I
SYNB1618	Synlogic	LBP	PKU	I
Cancer				
Pembrolizumab and EDP1503	Evelo Biosciences	Combination/LBP	Advanced melanoma	II
FMT + Pembrolizumab	Merck Sharpe & Dohme	Combination/FMT	Prostate cancer	II

Drug	Company	Strategy	Indication	Phase
EO2401	Enterome	Postbiotics	Metastatic adrenocortical carcinoma, or malignant pheochromocytoma	I/II
MRx0518 and Pembrolizumab	4D Pharma	Combination/LBP	Solid tumours	I/II
SYNB1891	Synlogic	LBP	Lymphoma	I
Gut-Brain Axis Diseases				
Microbiota restoration therapy	Rebiotix	Modulatory	Hepatic encephalopathy (HE)	II
Microbial transfer therapy + Vancomycin	Finch Therapeutics	Combination	Autism spectrum disorder (ASD)	II
AB-2004	Axial Biotherapeutics	Postbiotics	ASD	I/II

2.6 KEY PLAYERS

There are well over 200 companies working in this field and over 700 active research projects aimed at the development of microbiome-based therapeutics.[16] In our 2017 white paper we identified and mapped the leading players in this market according to sector and main technology areas. Many of these companies maintain leading positions in the industry in 2021. Examples include **Seres Therapeutics, Enterome Biosciences, Ferring Pharmaceutics, Evelo Biosciences, Finch Therapeutics, Quorum Innovations** (USA)**, Second Genome** (USA) and **Vedanta Biosciences**.

Other leading companies previously identified have since undergone rebranding or mergers to more effectively pivot into new areas and applications, such as Intrexon (now **Precigen** (USA)), C3J Therapeutics (now **Armata Pharmaceuticals** (USA)), Ritter Pharmaceuticals (now **Qualigen Therapeutics** (USA)) and LNC Therapeutics (now **YSOPIA Bioscience** (France)).

Many new companies have subsequently emerged with different approaches, technologies and targets, for instance:

- **Senda Biosciences** (founded 2020, USA), founded by venture capital company **Flagship Pioneering**, has raised $143 million in the nine months since its launch. Senda's platform enables the deployment of proteins or genetic material throughout the body, tunable modulation of the immune system, and precise intervention at the point of interaction between human and non-human species. By developing a new approach it calls intersystems biology, the company aims to develop novel medicines with unprecedented safety, efficacy, and precision.[20]

- **SFA Therapeutics** (founded 2016, USA) is a development-stage startup focused on a new advancement in the treatment of chronic inflammatory disease – the use of microbiome-derived metabolites (postbiotics) as drugs.

[20] https://www.prnewswire.com/news-releases/senda-biosciences-announces-closing-of-98-million-series-b-financing-301308492.html

- **Federation Bio** (founded 2019, USA) has a microbial therapy in development which leverages naturally occurring or engineered bacteria along with a diverse community of supportive bacteria to drive engraftment and durable therapeutic responses.
- **Solarea Bio** (founded 2017, USA) specialises in the research and development of therapeutics that are derived from natural sources. Using computational approaches, Solarea generates synergistic combinations of bacteria, fungi, and prebiotic fibers with powerful anti-inflammatory capabilities.
- **Scioto Biosciences** (founded 2017, USA) is a developer of an Activated Bacterial Therapeutics (ABT) platform intended to deliver live bacteria to the gut.
- **Noster Inc** (founded 2020, Japan) has built a unique library of gut microbes and their metabolites (postbiotics). It is using this library to develop innovative therapeutic treatments targeting the gut microbiome.
- **ImmunoBiome** (founded 2018, South Korea) is developing microbiome-mediated biologic therapies targeting autoimmunity, transplant rejection, and neurological diseases.
- **Bloom Science** (founded 2018, USA) is a platform biotechnology company discovering and developing genetically optimised microbes targeting pharmacoresistant or non-addressed diseases.
- **Bened Biomedical** (founded 2016, China) is the first psychobiotic brand to be developed in Asia

Broadly speaking, there are four generations of microbiome companies:[17] those that started with GI transplantation (FMTs) (1st generation); probiotics (2nd generation); LBPs (3rd generation); and companies that work with small molecules or postbiotics from the microbiome (4th generation). There are companies who are working with products from all four categories.

Cooperation continues to be vital for companies across an industry which is still an exploratory, emerging market and which is characterised mostly by small biotech companies. For example, **SFA Therapeutics** has stated that it is "*not designed to be an integrated company and will rely on a partner or technology transfer to bring a molecule successfully to market*."[17] However, it also notes that "*though this strategy may work for small-molecule based companies, it may not work for bacteria-based or FMT-based companies. The manufacturing and scale-up aspects may not allow them to be easy targets for partnerships*."

Companies are collaborating to find the best methods for clinical studies, strategies for product development, and production methods. Collaborations between these innovator companies, big pharma and academic institutes are aimed at bringing improvements to the technology, fostering innovation and finding treatments for many systemic and chronic diseases. Some examples of recent partnerships are summarised in the table below. This list is not exhaustive.

Date	Company	Company/ Institute	Details
Apr 2021	Kaleido Biosciences	University of Texas MD Anderson Cancer Center	To explore the potential of Kaleido's novel Microbiome Metabolic Therapies (MMT) in preventing febrile neutropenia—a serious complication associated with hematopoietic stem cell transplantations (HSCT). Within the collaboration, selected MMTs will be evaluated in disease animal models developed by Dr. Jenq, to further explore the molecular mechanisms by which MMTs act on the microbiome and gut barrier function and support the identification of a lead compound from Kaleido's compound library.
Mar 2021	Microba Life Sciences	Unilever	To allow Unilever to explore associations between the gut microbiome and sleep, with the aim to improve sleep for people across the globe.
Mar 2021	Genome & Co.	Merck, Pfizer	Clinical trial collaboration and supply agreement (CTCSA) with the aim of developing an immuno-oncology microbiome therapeutic.
Nov 2020	Galmed Pharma	MyBiotics Pharma	To identify and optimise the selected microbiome repertoire associated with the response to Aramchol. The research will also focus on development of a standalone microbiome-based treatment for non-alcoholic steatohepatitis (NASH) and fibrosis.
Jul 2020	DuPont Nutrition & Biosciences	Rutgers University	The two-year research partnership will focus on improving the benefit/risk ratio of chemotherapy by decreasing gut inflammation caused by chemotherapy to potentially improve response rates through modulation of the microbiome.
Jun 2020	Psomagen	Cell Biotech Co Ltd	Psomagen and Cell Biotech will research microbial organisms that will show clinical efficacy in health care, as well as develop new probiotics products. Using Psomagen's big data analysis technology, they will identify potential novel drug materials and develop probiotics products specifically targeting regional, racial characteristics.
Jun 2020	Microbiotica	Cancer Research UK, CUH	The collaboration with Cambridge University Hospitals NHS Foundation Trust (CUH) will identify specific gut bacterial signatures correlated with drug efficacy and side effects in patients under treatment for melanoma, non-small cell lung cancer and renal cancer. From these signatures, Microbiotica will progress live bacterial products as co-therapies and microbiome biomarkers predictive of immunotherapy response and toxicity into the clinic.
Apr 2020	Second Genome	Gilead Sciences	The companies entered into a four-year collaboration to identify biomarkers associated with clinical response to Gilead's investigational candidates. Second Genome will employ its proprietary Microbiome Analytics Platform to identify the biomarkers, in addition to seeking new targets and drug candidates relevant to inflammatory bowel disease (IBD).
Feb 2020	Enterome	BIOASTER	They will leverage their respective expertise in pursuing insights into Enterobiome's investigational microbiome therapeutics. BIOASTER's proprietary gnotobiotic mouse model, GNOTOMICE model, as well as a state-of-the-art immunological platform will be employed to further develop the oncomimetics by Enterome.

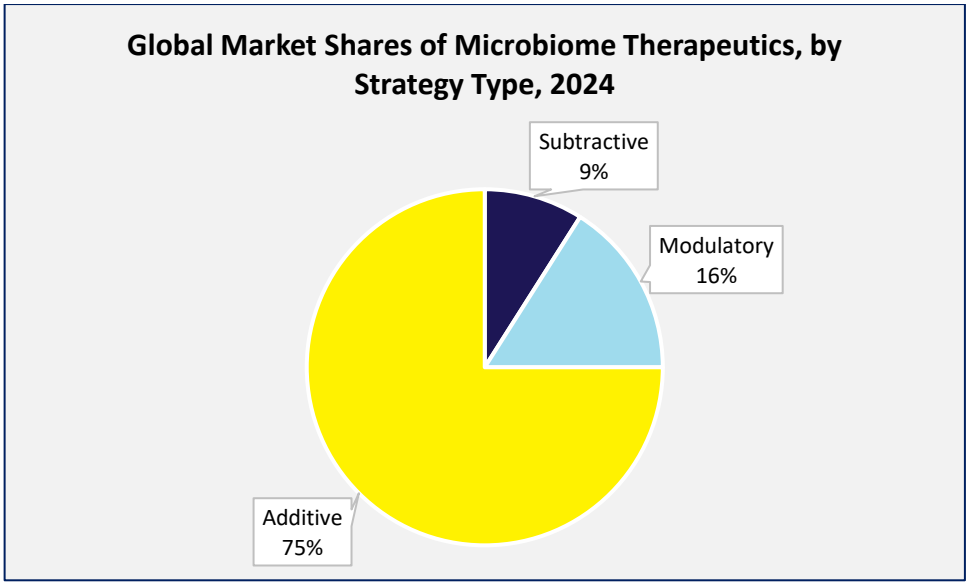
Date	Company	Company/ Institute	Details
Jan 2020	Genome and Co.	Merck & Co., Pfizer	To jointly develop a new drug through the combination treatment of the immune anticancer drug avelumab (Bavencia) owned by Merck and Pfizer and the immune anticancer drug (GEN-001) being developed by Genome and Co.
Dec 2019	LNC Therapeutics	Micalis Institute	The partnership is aimed at the identification of new therapeutic targets for the development of Christensenella single strain LBPs in inflammatory diseases.
Oct 2019	Biomica	Weizmann Institute of Science	To develop microbiome-based therapies against antibiotic resistant strains of Staphylococcus aureus infection.
Jun 2019	Synlogic	Ginkgo Bioworks	Platform collaboration to accelerate expansion and development of Synlogic's pipeline of synthetic biotic medicines using Ginkgo's cell programming platform.
Mar 2019	Seres Therapeutics	AstraZeneca	Seres Therapeutics entered into a three-year collaboration with AstraZeneca to evaluate microbiome-based approaches (SER-401) in combination with AstraZeneca compounds for targeting cancers. The insights into microbiome will be used as a predictor for finding the best patients for certain cancer immunotherapies.
Dec 2018	Vedanta Biosciences	Bristol-Myers Squibb	A clinical trial collaboration, to evaluate BMS's PD-1 immune checkpoint inhibitor Opdivo (nivolumab) in combination with Vedanta Biosciences' VE800, in patients with advanced or metastatic cancers.
Dec 2017	DuPont Nutrition & Biosciences	APC Microbiome Institute	The Microbiome Venture will engage in strategic partnerships with other microbiome science leaders in academia and industry to accelerate product development. The Microbiome Venture is a focused entrepreneurial team with a strong connection to the larger DuPont organisation. The Microbiome Venture investment will complement DuPont's existing product portfolio, especially in the areas of probiotics and prebiotics, including human milk oligosaccharides. The first major partnership of the Microbiome Venture is with the APC Microbiome Institute in Cork, Ireland.

Microbiome therapeutics companies can be segmented based on the type of therapeutic being developed:[16]

- Additive microbiome therapeutics includes oral therapies based on FMTs or LBPs that may be single strains or mixed consortia. The LBPs may be native strains or genetically modified to possess enhance properties. Some LBPs being developed by microbiome therapeutic companies are:
    - **Rationally selected LBP consortia**: based on bacterial strains isolated from carefully screened healthy human subjects. These therapeutics rely on the functional engagement of consortium microbes with the gut microbe-host environment.
    - **Monoclonal microbials**: single strains of microbes selected for defined pharmacological properties. Monoclonal microbials are naturally evolved strains that are not genetically modified.
    - **Engineered bacteria**: targeted modification of bacterial strains has enabled the development of therapeutic candidates with improved specificities and better performance characteristics.

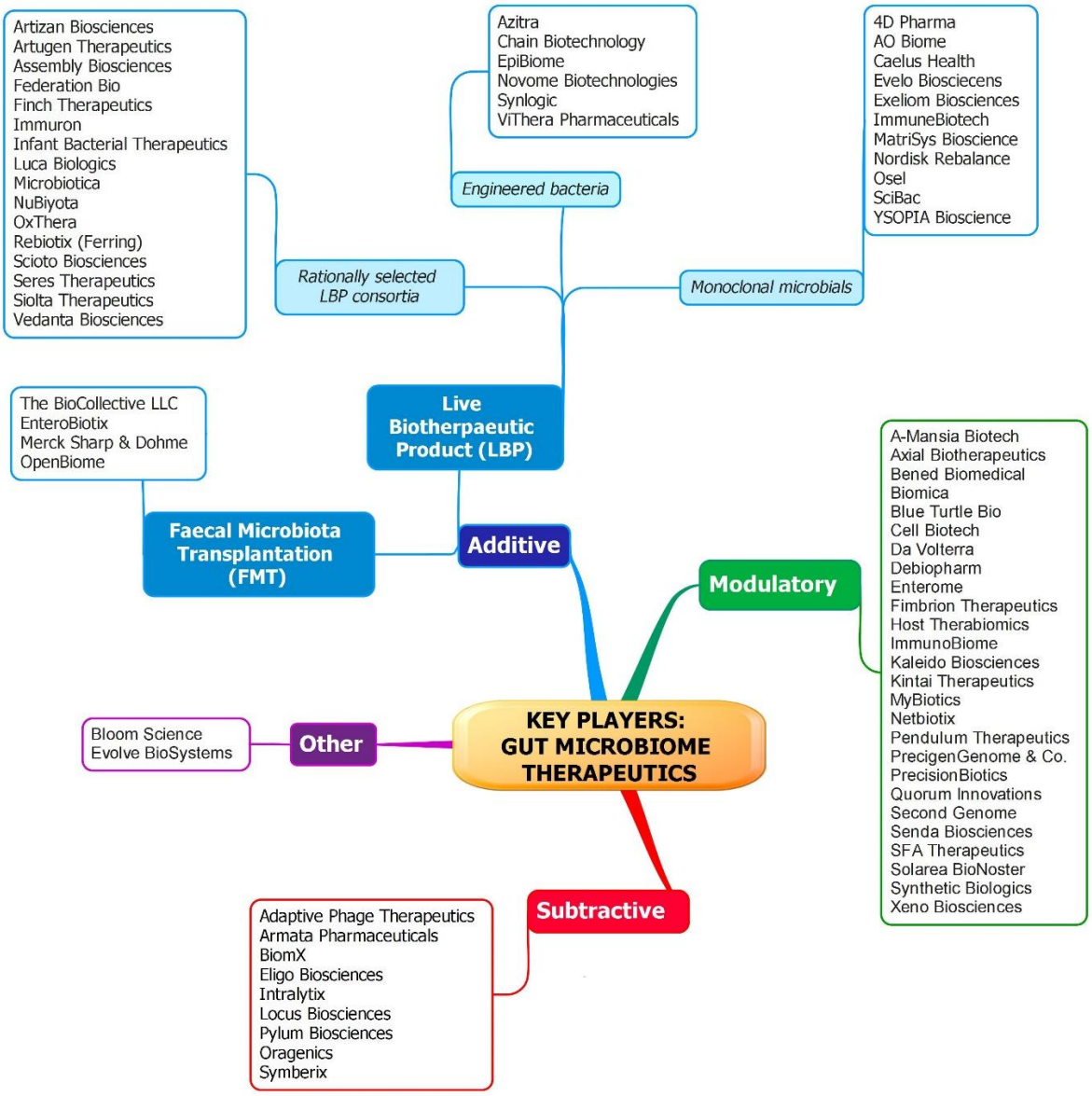
- Modulatory microbiome therapeutics consist of small molecule drugs and metabolites that can be used to alter the microbiome or its interactions with host tissues. These drugs are differentiated into postbiotics and prebiotic drugs and are essentially protein products expressed from the bacterial genes of the microbiome. Prebiotic drugs are mainly composed of poorly digestible carbohydrates and polyphenols, among others. Prebiotics tailored as microbiome therapeutics are distinct from prebiotics being marketed as dietary and food supplements, due to the extensive clinical development and safety and efficacy studies the prebiotic drugs undergo before they are approved for therapeutic purposes.
- Subtractive microbiome therapeutics refer to the specific elimination of bacterial pathogens or harmful bacteria without affecting either the host or beneficial bacteria within the microbiota. Also referred to as precision antimicrobials, the popularity of subtractive microbiome therapeutics is on the rise due to the growing concerns of increased antibiotic use.

BCC Research estimates that additive microbiome companies currently account for around 75% of the microbiome therapeutics market, as shown below:



Adapted from: BCC Research (2020) *Microbiome Therapeutics: Global Markets*.[16]

These product categorisations have been used to update our key players mind map from 2017 in the figure below and reflect changes and new players in the industry, and incorporate information on the strategy and technology type. Some companies have interests in more than one category, so they have been categorised by what we consider to be their core focus.



2.7 DEAL-MAKING

Deal-making in human gut microbiome therapeutics has been essential for the growth of the market. There have been many high-profile collaborations, partnerships, mergers and acquisitions between innovator companies, big pharma and academic institutes, and this has continued through the COVID-19 pandemic. Some recent examples of such partnerships are listed in Section 2.6, above.

As we discussed in our previous 2017 white paper, there has also been vast amounts of money invested by venture capitalists and leading pharmaceutical investors in gut microbiome research and development. Leading investors in this field include **Seventure Partners** (France)**, Flagship Pioneering** (USA)**, OrbiMed Advisors** (USA)**, Alexandria** (USA)**, Illumina Accelerator** (USA)**, Johnson & Johnson Innovation** (USA) among many others. While some observers believe that it is becoming more difficult for companies to attract funding[17], there is still plenty of investment taking place. In particular over the last year, there have been several large investments in established microbiome therapeutics companies. An extensive list of deals is provided in our earlier white paper. Some recent examples of venture funding and other deals in gut microbiome therapeutics companies are summarised in the table below. This list is not exhaustive.

Date	Investor/Licensee/Acquirer	Investee/Licensor /Acquired	Deal Type	Value	Details
June 2021	Flagship Pioneering, Longevity Vision Fund, Terra Magnum Capital Partners, Mayo Clinic, Partners Investment, Mint Venture Partners, Alexandria Venture Investments	Senda Biosciences	Venture Financing	$98M	Less than eight months after it emerged from stealth, Flagship Pioneering startup Senda Bioscience has raised another $98 million, and it's planning on advancing its three lead programs into clinical trials by the end of 2022.
May 2021	Undisclosed	eureKARE	Venture Financing	$60M	Technology commercialisation specialist Eurekare SA has launched after raising a $60 million series A, with which it plans to seed fund the formation of microbiome and synthetic biology startups.
Jan 2021	Novozymes	Microbiome Labs	Acquisition	$125M	Acquiring Microbiome Labs is a key step in building Novozymes' Human Health platform, adding a broad range of proprietary solutions to its existing activities and access to the company's network of health practitioners.
Nov 2020	OpenBiome	Finch Therapeutics	Licensing Agreement	Undisclosed	Finch Therapeutics granted OpenBiome a non-exclusive royalty-bearing license, with the right to grant sublicenses, under certain patents, patent applications, and know-how for the exploitation of products manufactured directly from stool from a stool donor source without the use of culturing or replication. Finch are entitled to receive tiered royalties on net sales of certain products.
Sep 2020	Baupost Group, Humboldt Fund, MSD Capital, MSD Partners, Octave Group, and OMX Ventures, Avenir Growth Capital, others	Finch Therapeutics	Venture Financing	$90M	Finch will use the proceeds from the financing to advance CP101 through the final stages of clinical development and regulatory submission in recurrent C. difficile infection (CDI), and to advance its platform and pipeline, including the initiation of Phase 1b studies evaluating FIN-211 for autism spectrum disorder (ASD) and CP101 for chronic hepatitis B (HBV).
Jul 2020	CARB-X	Eligo Bioscience	Grant	$1.82M upfront; $7.05M in milestones	For the development of a new generation of highly-specific antimicrobials to prevent multi-drug-resistant bacterial infections in organ transplant patients. Eligo's bacteriophage- and CRISPR-based therapeutics are designed to selectively eliminate extended-spectrum beta-lactamase-producing (ESBL) and Carbapenem-resistant E. coli and K. Pneumoniae (CRE) from the microbiome of transplant patients before their procedure.
Jun 2020	SymBiosis, LLC, Takeda Pharmaceutical Company Limited, Seventure, Health for Life Capital, Principia, Omnes Capital, Nestlé Health Science	Enterome	Venture Financing	$52.5M	To progress the clinical development of Enterome's therapeutic pipeline, including the first clinical trials of EO2401, a novel 'OncoMimic' cancer immunotherapy.

Date	Investor/Licensee/Acquirer	Investee/Licensor /Acquired	Deal Type	Value	Details
Apr 2020	Gilead Sciences	Second Genome	Licensing Agreement	$38M upfront: $300M in milestones	Under the terms of the agreement, Second Genome will utilise its proprietary Microbiome Analytics Platform to identify novel biomarkers associated with clinical response to Gilead's investigational medicines.
Feb 2020	SymBiosis, LLC, Seventure Partners, Crédit Mutuel Innovation, Biocodex	MaaT Pharma	Venture Financing	$21.2M	Additional proceeds will be used primarily to accelerate the development of a proprietary fermentation process to design targeted, full-ecosystem, large-scale, microbiome-based products.
Jan 2020	DCVC Bio, 5AM Ventures, Alta Partners, Alexandria Venture Investments, Mayo Clinic	Novome Biotechnologies	Venture Financing	$33M	To advance the company's lead hyperoxaluria program through Phase 1 clinical proof-of-concept work, as well as to expand its Genetically Engineered Microbial Medicines (GEMMs) platform to address additional indications.
Oct 2019	Merck	4D Pharma	Licensing Agreement	$347.5M	Research collaboration and option to license agreement with Merck (MSD) to discover and develop LBPs for vaccines.
Oct 2019	Aion Investment Management Co. Ltd., Tyel Asset Management Co. Ltd., CKD Venture Capital Corp, others	Genome & Co	Venture Financing	$25.2M	Series C investment with an IPO and global clinical trial plans for 2020.
Feb 2019	Seventure Partners	Microbiotica	Equity Investment	$15.7M	Microbiotica has made rapid progress in developing a unique capability to culture, characterise and phenotype the majority of a patient's gut bacteria, enabling the precise association of bacteria to function at clinical trial scale
Feb 2019	OrbiMed, Johnson & Johnson Innovation – JJDC Inc., Takeda Ventures Inc., 8VC, MiraeAsset, Seventure Partners' Health for Life Capital I, others	BiomX	Venture Financing	$32M	To continue preclinical development of its customized phage cocktail therapies aimed at eradicating the bacteria behind acne and inflammatory bowel disease.
Oct 2018	Takeda	Enterome	Licensing Agreement	$50M upfront; $640M in milestones	A global licensing, co-development and co-promotion agreement which covers Enterome's lead investigational drug candidate EB8018 in patients with Crohn's disease, with the potential to expand to other gastrointestinal (GI) disorders and liver diseases.
Apr 2018	Seventure Partners, Cambridge Innovation Capital, IP Group	A-Mansia Biotech	Venture Financing	$15.3M	To reach A-Mansia's goals of marketing a dietary supplement product, and testing its lead drug candidate in the clinic

3 MICROBIOME DIAGNOSTICS

3.1 RECENT DEVELOPMENTS

In our 2017 white paper, we outlined the four major applications for microbiome diagnostics:

- Diagnosis or prognosis: Use of microbiome markers to identify the disease and prognosis of the disease
- Treatment selection: Understanding of the patient's microbiome associated with the disease could lead to selection of right treatment
- Disease monitoring: Analysis of microbiota to predict the outcomes of the microbiome-based drugs and also normalization of the microbial flora using microbiome time-series analysis
- Microbiome research to develop targeted precision medicine using microbiota cocktails to target the affected microflora

In particular, we discussed the advancement of metagenomics, which involves sequencing and mapping of total bacterial gene content that characterises the personal metagenome associated with a disease phenotype. Metagenomics is used broadly across various microbiome R&D areas, such as drug discovery, medical fields etc, but is discussed here because multi-omics capabilities have in particular continued to underpin the advancement of microbiome diagnostics over recent years. While a more detailed overview of this technology field and market can be found in our previous white paper, there are some noteworthy trends emerging since 2017, including:

- Continued improvement in microbiome diagnostics capabilities. Analysis techniques have enabled faster and more accurate clinical diagnostics. Examples of using the gut microbiome as a possible diagnosis tool include progression of diabetes[21] and irritable bowel syndrome.[22] One recent paper reported the prediction of liver cirrhosis in two independent cohorts residing in China and Italy using the gut microbiome signature derived from patients residing in California.[23] Statistical methods to build such prognostic tools include random forests and penalised regression analysis that can take into account the compositional nature of the microbiome data. Moreover, pattern-matching techniques further expand the diagnostic potential of the microbiome to fields as diverse as forensics, where the microbial signature of a sample may provide insight into the source (individual, geolocation, etc.) of the sample. Similar techniques are evolving in ecology and environmental sciences to detect microbial species, hosts and health ecosystem states.
- Complementary partnerships to leverage data analysis, for instance:
    - A partnership between **Ardigen** (Poland) and **The BioCollective** (USA) will pair Ardigen's microbiome AI platform with The BioCollective's metagenomic and

[21] https://doi.org/10.1155/2018/5205126
[22] https://doi.org/10.1016/j.jmoldx.2019.01.006
[23] https://doi.org/10.1016/j.cmet.2020.06.005

patient metadata, aimed at the development of the world's first microbiome-based biomarker candidates for Parkinson's Disease.[24]

- **Vivante Health** (USA), a company focused on digital medicine for gut health and disease, is collaborating with **Janssen Biotech** (USA) to develop digital predictive biomarkers for chronic diseases.[25]
- Janssen is also collaborating with **BiomX** (Israel), a phage therapy company, to use BiomX's XMarker platform to discover microbiome-based biomarkers for inflammatory bowel disease.[26]

- Emergence of artificial intelligence and machine learning-based microbiome research for biomarker identification, disease prediction, and therapeutics.[27,28] **Xbiome**, China's first AI-based company that specialises in the development of the gut microbiome, recently raised around $10 million, for example.[29]
- *Companion* diagnostics emerging as one of the most relevant applications of microbiome biomarker discovery.[30]
  - Some companies are applying their microbiome-mining platforms to identify signatures in the microbiota to predict efficacy of established drugs, many of them in close collaboration with major pharmaceutical companies, whereas others are trialling their microbiome therapeutics as adjuvant therapies with medications, mainly for autoimmune diseases.[31] For instance, **Second Genome** (USA) and **Gilead** signed an agreement in 2020 by which Second Genome's Microbiome Analytics Platform™ will be employed to identify biomarkers associated with clinical response to Gilead's investigational medicines in IBD.
  - In the field of oncology, **Persephone Biosciences** (USA) are engaged in an observational trial to identify microbial biomarkers in blood, urine, and stool predictive of the efficacy of pembrolizumab (**Merck**) in lung and colorectal cancers. Persephone recently announced the initiation of an additional observational study for the development of companion diagnostics in lung, breast, colorectal and pancreatic cancers being treated with immunotherapy.
  - **New Biotic** (USA), which has developed a microbiome-based therapy for Amyotrophic Lateral Sclerosis, are simultaneously working on a companion diagnostic to predict therapeutic efficacy and disease progression, based on the

[24] https://ardigen.com/news/ardigen-and-biocollective-partner-to-detect-early-signs-of-parkinsons-disease-for-better-diagnosis-and-treatment/
[25] https://vivantehealth.com/2020/03/17/vivante-health-announces-collaboration-with-janssen-for-predictive-disease-modeling/
[26] clinicalomics.com/topics/precision-medicine-topic/companies/janssen-biomx-to-partner-on-discovering-microbiome-based-ibd-biomarkers/
[27] https://doi.org/10.3389/fmicb.2021.634511
[28] https://doi.org/10.1007/s12553-020-00486-7
[29] https://karmaimpact.com/chinese-gut-bacteria-developer-xbiome-has-raised-10-million-for-clinical-trials/
[30] Sandwalk Bioventures & Microbiome Times (2020) *Microbiome-based diagnostics and biomarkers: Changing the paradigm in microbiology and medicine*
[31] https://bmcmicrobiol.biomedcentral.com/articles/10.1186/s12866-020-01724-8

detection of serum glutamate levels and glutamine synthetase activity in the intestine.[30]

- Companies entering the microbiome diagnostics field from other sectors, such as:
    - Existing bioinformatics and sequencing companies which have expanded their services or pivoted towards metagenomics and microbiome applications, such as **Eagle Genomics** (UK), **Fios Genomics**[32] (UK), **Edinburgh Genomics**[33] (UK), **Novogene** (China) and others.
    - Microbiome therapeutics and probiotics companies moving into diagnostics applications, such as **Nestlé Health Science** (Switzerland) and **Enterome** creating **Microbiome Diagnostics Partners (MDP)**, which aims to lead the development and commercialisation of innovative microbiome-based qPCR diagnostics,[34] and BiomX collaborating with **Boehringer Ingelheim** (Germany) with the goal of discovering microbiome-based biomarkers for inflammatory bowel disease.[35]
    - Innovative fast-response diagnostic companies are now developing microbiome diagnostics, for example: **Oxford Nanopore Technologies** (UK), which has pioneered a rapid, low-cost, pocket-sized sequencing device called MinION, is testing the device in microbiome diagnostic applications; **DNA Electronics** (UK), which is developing LiDia-SEQ, a direct-from-specimen platform that performs DNA sequencing on a microchip; and **IS Diagnostics** (Netherlands) which has launched a microbiome diagnostics kit for inflammatory bowel disease targeting a specific location of the bacterial DNA called the IS region, which has a specific length for each species (rather than a distinct sequence), and is easier to detect and reduces the time to make a diagnosis down to 4-5 hours.[36]
- Development of novel microbiome sampling devices, in particular smart ingestible capsules by young companies like **Atmo Biosciences** (Australia) and **BioMe Oxford** (UK). The latter recently announced a partnership with **DuPont** (USA) and the **University of Sheffield**'s Advanced Manufacturing Research Centre to further the development of its BioCapture capsule.
    - Other novel sampling techniques focus on rectal sampling, such as the **Origin Sciences** (UK) OriCol rectal mucous sampling device which can be performed without the need for any type of bowel preparation or anaesthesia.
- Growing interest in infant microbiomes since the gut microbiome plays an important role in early life, protecting newborns from enteric pathogens, promoting immune system development and providing key functions to the infant host.[37] For example, microbiome analysis company **Floragraph** (USA) is developing an Infant Microbiome Monitoring Device designed to provide quantitative measure of a baby's developing microbiome by

[32] https://www.fiosgenomics.com/wp-content/uploads/2019/10/White-paper-microbiome-web.pdf
[33] https://genomics.ed.ac.uk/news-events/news/exploring-and-exploiting-microbiome
[34] https://www.nestlehealthscience.com/newsroom/press-releases/Nestle-Health-Science-enters-the-microbiome-diagnostics-field-through-a-partnership-with-Enterome
[35] https://ir.biomx.com/news-events/press-releases/detail/8/biomx-enters-collaboration-with-boehringer-ingelheim-with
[36] https://www.labiotech.eu/in-depth/microbiome-diagnostics-test-technology/
[37] https://doi.org/10.1038/s41598-020-80583-9

performing microarray-based analysis on a patient's stool sample. In February 2021, **Evolve BioSystems** (USA) raised $55 million from investors including **Cargill** (USA)**, Horizons Ventures Ltd** (Hong Kong), and **Johnson & Johnson Innovation** to continue commercialising a next generation of probiotic capable of addressing a widespread deficiency in the infant gut microbiome.

3.2 KEY PLAYERS

In our 2017 white paper, we noted that the diagnostics sector was far smaller than the gut therapeutics sector and was at an earlier stage. The field was dominated by a few independent, development-stage companies working on a few novel technologies. While diagnostics remains the smaller market, it has undergone rapid expansion and diversification over the last few years, driven by the factors discussed in the previous section and with many new players emerging or moving into or acquiring microbiome diagnostics from other fields.

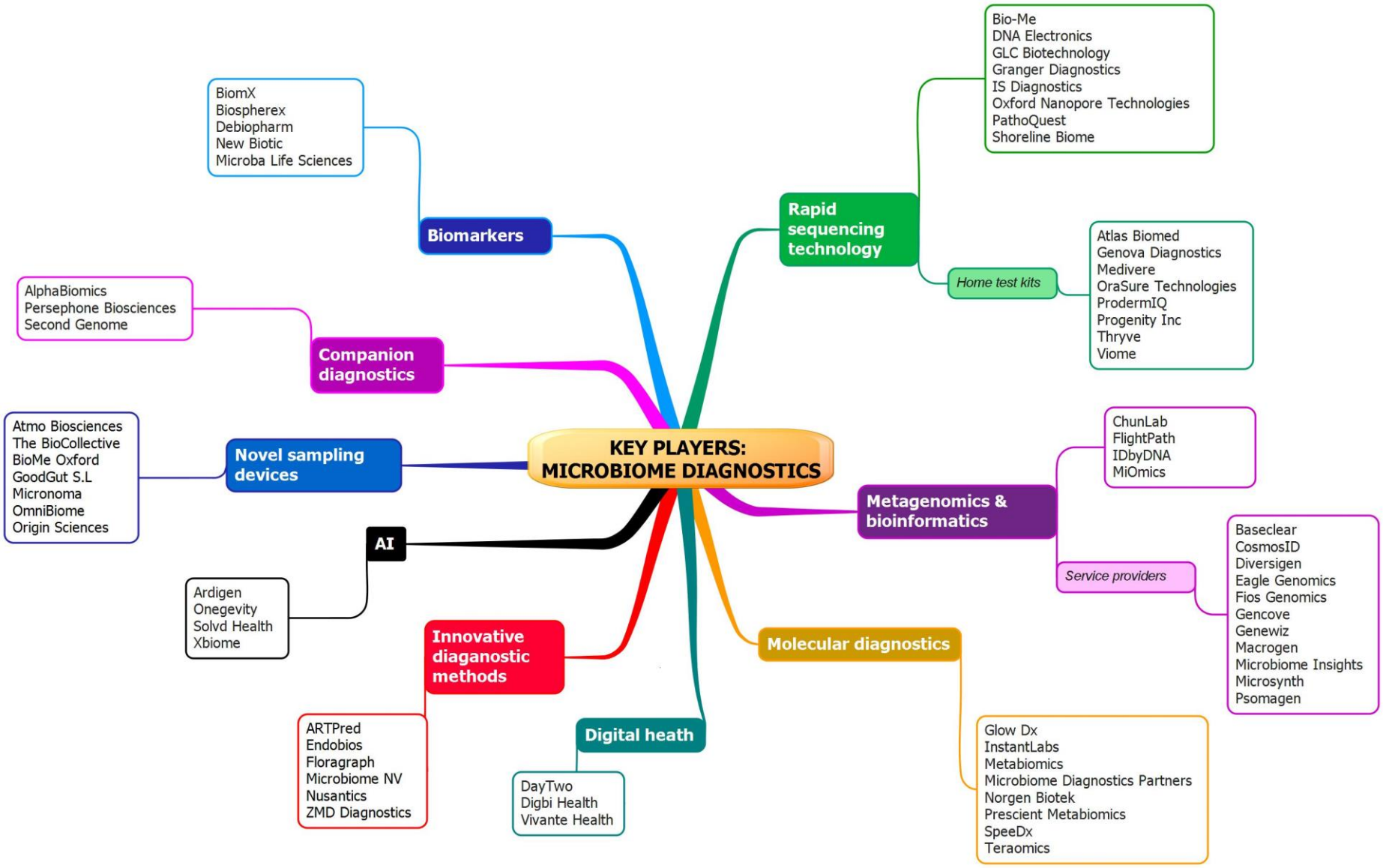
In particular, the expansion of sequencing technologies, faster diagnostic kits, at-home test kits and AI techniques feature strongly.

As observed in the therapeutics market, some of the leading players have since undergone rebranding, mergers or acquisitions, such as **EpiBiome**, a microbiome precision engineering company with high-throughput discovery and NGS technologies, which was acquired by pharmaceutical company **Locus Biosciences** (USA) in 2018. In 2019, **Whole Biome** (USA) announced a corporate name change to **Pendulum Therapeutics** (USA) to reflect the company's broader commitment to developing solutions that impact human health through microbiome interventions. Pendulum introduced its first product, a medical probiotic called Pendulum Glucose Control, in January 2020. It is the only probiotic clinically shown to lower blood sugar spikes and A1C levels in people with type 2 diabetes, even on top of metformin. In 2021, the company raised $54 million from **Meritech Capital** (USA) and others to expand its product line and meet customer demand.[38]

The most high-profile dissolution was **uBiome** (USA) – the leading "citizen science" microbiome company which offered diagnostic DNA sequencing platforms to allow consumers to identify bacteria in their stool samples – which shut down in 2019 following an investigation into possible insurance fraud.[39] uBiome's patents and data assets were acquired by sequencing companies **Psomagen** (USA) and **Macrogen** (South Korea) for $7 million (1% of uBiome's estimated corporate value).[40]

The key players mind map from our 2017 white paper has been updated in the figure below to reflect the changes and numerous new players entering the market, and incorporate information on their main technology or offering. As outlined above, there are a large number of companies operating across the diagnostics market so our summary should not be considered exhaustive.

[38] https://www.prnewswire.com/news-releases/pendulum-therapeutics-raises-54-million-to-meet-surging-customer-demand-301264187.html
[39] https://www.cnbc.com/2019/05/02/ubiome-what-really-happened-at-health-start-up-raided-by-fbi.html
[40] https://www.businesswire.com/news/home/20200102005156/en/Psomagen-Macrogen-Consortium-Acquires-All-Patents-and-Data-From-US-Company-uBiome



3.3 DEALS

Deal-making in microbiome diagnostics is increasing. This is due to the increasing maturity of the sector and increasing recognition of the clinical and commercial benefits sector, as well as the continued capability improvements and expansion of the market discussed in Section 3.1, above.

In our 2017 white paper we noted that deals in the microbiome diagnostics industry are commonly strategic partnerships between two smaller companies with a mutual interest in advancing their respective technologies (rather than the large and numerous venture financing deals observed in the therapeutics industry). This remains the case in 2021, although it is clear that there is also an increasing number of partnerships occurring between large companies and small, pioneering innovators. Some of these partnerships have already been discussed above in the context of market trends and key players. Other examples of diagnostics partnerships in the last few years are provided in the non-exhaustive summary table below.

There have also been several venture financing and licensing deals completed in the diagnostics industry since 2017, though these are far less frequent and far lower in value than in the therapeutics field. Some examples are also included in the table below.

Date	Investor/Licensee/Acquirer/Partner	Investee/Licensor/Acquired/Partner	Deal Type	Value	Details
May 2021	Microba Life Sciences	Illumina	Partnership		The partnership will bring together Microba's high-quality proprietary gut microbiome analysis platform with Illumina's revolutionising Next Generation Sequencing tools to generate the accurate metagenomic data researchers require to make new discoveries.
Mar 2021	Accel, Wisdom LLP Ocean Azul Partners, Seraph Venture	Digbi Health LLC	Venture Financing	$5.4M	Digbi Health, a precision digital therapeutics company intends to use the fund to forge additional payer, employer and third-party administrator (TPA) partnerships, along with expanding the company's product offering, engineering, gut microbiome and data science teams in the US and India. In particular, the company will develop its Software as a Medical Device (SaMD) - Functional Bowel Disorder mobile app, health monitoring tool, and prescription-grade digital therapeutic platform.
Mar 2021	Novozymes	Biota Technology	Asset Transaction		Novozymes has acquired the microbiome R&D team and data science platform of Biota Technologies Inc, a provider of genomic monitoring solutions. Pursuant to the transaction, Biota will retain a commercial license to apply the data science platform for genomic diagnostics.
Feb 2021	Illumina Accelerator	Flightpath Biosciences	Venture Financing		Flightpath Biosciences, Inc., a biotechnology company advancing microbiome-targeted therapeutics and diagnostics for the treatment of rare infectious diseases, has raised funds through seed financing.
Jul 2020	SOSV Investments, John Tuohy	GlowDx	Venture Financing	$1.29M	GlowDx is a company that aims to deliver diagnostic accessibility through bio-molecular innovation. The company intends to use the proceeds to expand its operations in Europe in the coming months with a number of R&D projects in the microbiome space underway.
Jun 2020	Diversigen	Alimentiv	Partnership		Collaboration agreement for a research study on patients with Acute Severe Ulcerative Colitis (ASUC). The study is designed to provide new insights into the molecular determinants of response to infliximab in patients with ASUC.
Jan 2020	ARTIS Ventures, Genesys Capital Partners	IdbyDNA Inc	Venture Financing	$20M	IDbyDNA, Inc., a metagenomics technology company intends to use the proceeds to fuel growth of its Explify Software Platform into the worldwide infectious disease and microbiome testing market and to support the opening of a CLIA-approved commercial laboratory at IDbyDNA's Salt Lake City facility.
Dec 2019	Metabiomics Corp	CoreBiome Inc	Partnership		Prescient Metabiomics, a subsidiary of Prescient Medicine Holdings, Inc., and CoreBiome, a wholly owned subsidiary of OraSure Technologies, Inc., announced a collaboration to develop a new test called LifeKit Prevent, which may represent a microbiome-driven paradigm shift in colon cancer screening.
Jun 2019	Macrogen	Microba Life Sciences	Strategic Investment	$4.1M	The microbiome service that both companies will co-develop targets the whole genome (shotgun) of all microorganisms in the gut, instead of targeting specific region (16S rRNA) of bacteria. Through this, it is expected that both companies will contribute to the development of new diagnostic methods and treatments as they can produce data, which will enable novel microorganism discoveries and metabolite analysis.
July 2017	Nestlé Health Science	Enterome	Partnership		Nestlé Health Science and Enterome are jointly creating Microbiome Diagnostics Partners (MDP), which aims to lead the development and commercialization of innovative microbiome-based diagnostics.

4 BEYOND THE HUMAN GUT

4.1 SKIN MICROBIOME

While many microbiome therapeutics and diagnostics have been made for the human gut, the skin is the most accessible human organ, and therefore, a natural target for treatment and diagnostic sampling.[41]

As understanding of the skin microbiome and its role in the maintenance of healthy skin has become better understood, the skin microbiome has emerged as a market brimming with potential in recent years. Indeed, according to data compiled by BCC Research in 2020, there are at least 60 clinical trials in progress for skin microbiome treatments – a greater number than for GIT diseases in human gut studies.[16]

The global skin microbiome modulators market was valued at $541.1 million in 2019 and is anticipated to grow to almost £3 billion by 2030.[42] This has been aided primarily by the high growth in the probiotics and prebiotics skincare market and the tremendous impact of 'natural' ingredient-based products on cosmetics. However, there are many different threads to the skin microbiome research field, including novel skin microbiome diagnostics, swabbing and application technologies, devices for real-time skin microbiome monitoring, and novel treatment devices such as microbiome-optimised bandages and wound dressings that also function as diagnostic in nature.[41]

Commercially, the market is at relatively early stage, with cosmetic formulators taking the initial steps toward developing their own microbiome product ranges informed by the scientific research output of recent years, including from initiatives such as the Human Microbiome Project.

Spurred by a growing body of research showing that commensal bacteria, probiotics and/or prebiotics can prove efficacious in the treatment of skin disorders, many cosmetics and consumer product companies, microbiome-focused pharmaceutical companies and biotechnology companies have begun targeting the skin microbiome market by developing cosmetic and therapeutic over-the-counter agents that alter or in some way maintain, benefit or balance the skin microbiome.

One of the key factors driving the skin microbiome market specifically is a perceived aversion to 'chemicals' by target consumers, who often have sensitive or problematic skin, and are increasingly aware that the skin is subject to a variety of assaults from sun radiation, urban pollution and chemicals in the environment. There are several prominent small companies driving innovation in this field, some of examples of which are provided below. This list is not exhaustive:

- **S-Biomedic**'s (Belgium) patented technology combines a unique pathogenicity biomarker with targeted modulation of bacterial compositions directly sourced from healthy human skin. S-Biomedic was founded by three pioneers in the microbiome research field – Veronika Oudova, Bernard Paetzold and Marc Guell – who filed a patent for a targeted microbiome modulation technology enabling them to transplant beneficial bacteria on the skin back in 2015.

[41] https://www.frontiersin.org/articles/10.3389/fmicb.2020.00136/full#h6

[42] Research and Markets (2020) *Global Skin Microbiome Modulators Market: Focus on Products, Applications, Distribution Channels, Country Data (14 Countries), and Competitive Landscape - Analysis and Forecast, 2019-2030*

- **Mother Dirt**'s (USA) "biome-friendly" skincare products either contain live ammonia-oxidizing bacteria (AOB) or are formulated to clean and moisturize while preserving the skin's "good" bacteria.

- **YUN Probiotherapy** (Belgium) uses live bacteria contained in patented-microcapsules in some of their creams to reduce acne and live bacteria in their foot spray to combat athlete's foot. The rest of YUN Probiotherapy's skincare line is created to balance, and not disrupt, the skin's microbiome.[43]

- **MatriSys Bioscience** (USA) is developing a novel class of safe and effective microbiome-targeting pharmaceuticals to transform the treatment of inflammatory skin diseases.

- **Azitra** (USA) is a clinical stage medical dermatology company that leverages proteomics, genetic engineering and the skin microbiome to create and develop novel products for the treatment of skin conditions and diseases.

- **Dermala** (USA) is a consumer dermatology company developing novel, personalised, microbiome-based solutions using a platform that combines microbiome-based topical and oral products with a proprietary data analytics app that enables personalisation and continuous optimisation of product formulations based on individual outcomes.

- **Dermbiont** (USA) is a 'precision' dermatology company developing targeted topical microbiome therapeutics that address the root cause of skin disease.

- **Gallinée** (UK) is a supplier of skincare products containing probiotics (*Lactobacillus*) with prebiotics (fibres and sugars).

An increasingly common trend in deal-making in this market is the emerging interests of multinational health/skincare and consumer product companies through investments in and partnerships with small early innovators. **Johnson & Johnson**, for instance, has announced multiple collaborations in skin microbiome research and product development over the last few years, including with **S-Biomedic** to develop a bacterial treatment for both therapeutic and cosmetic applications. Moreover, in 2018 multinational personal-care company **Beiersdorf** (Germany) took an equity investment in S-Biomedic in the single digit million Euro range.[44] In 2020, S-Biomedic then announced a commercial agreement with **DSM** (Netherlands) to develop and commercialise a skin care active that uses probiotic technology to treat acne.[45]

Other notable deals involving corporations and large consumer product/healthcare companies over the last four years include:

- **Amway** (USA) announced a new strategic partnership for research and development with a global leader in microbiome testing, **Microbiome Insights** (Canada).

- **Kaneka Americas Holding Inc.**, a subsidiary of **Kaneka Corp** (Japan), a chemical manufacturing company, entered into licensing agreement with **AB-Biotics**, a Spanish biotechnology company specialising in clinical probiotics

[43] https://resources.wellcertified.com/articles/the-new-frontiers-of-microbiome-research/
[44] https://www.beiersdorf.com/newsroom/press-releases/all-press-releases/2018/07/18-beiersdorf-takes-investment-into-s-biomedic
[45] https://www.dsm.com/personal-care/en_US/events-and-news/press-releases/2020/04-02-dsm-signs-a-collaboration-and-commercialization-agreement-with-s-biomedic.html

- **Counter Brands LLC** (USA), parent company of **Beautycounter**, a leader in safer skincare and cosmetics, acquired the worldwide assets of **NUDE Skincare, Inc** and **NUDE Brands, Ltd** (USA/UK).
- **LEO Pharma** (Denmark) invested $500k in microbiome-based skin therapeutics company **Naked Biome** (USA) to focus on clinical trial plans and formulation development.
- **Eligo Bioscience** (France), a biotherapeutic company, entered into a research and option agreement with **GSK** (UK), aimed at advancing Eligobiotics for the treatment or prevention of acne vulgaris with a pioneering CRISPR-based therapeutic for strain-specific microbiome modulation.
- **Bayer** (Germany) and **Azitra** partnered to harness the human skin microbiome as a source for new natural skin care products for sensitive and eczema-prone skin.
- **Genome and Co**. (South Korea) and **Donggu Biopharmaceutical** (South Korea) signed a collaboration agreement for the development of new skin microbiome drugs.

4.2 ANIMAL HEALTH

Understanding how the microbiome affects the health and welfare of domestic livestock, and the sustainability of modern farming is expected to generate significant market opportunities. Current research indicates that animal microbiome modulation could greatly improve pet health and increase the meat industry's productivity, while ensuring that it meets its sustainability targets.

By some estimates, the total global market for the commercialisation of animal microbiome research will grow to almost $10 billion by 2028 due to demand for innovation from the growing meat and pet-healthcare industries, provided the industry can navigate through tough legal and regulatory obstacles smartly.[46]

In our 2017 white paper we noted that the animal microbiome field was at the time very active at the early-stage and research level, but still in its infancy industrially. Since then, both the research and commercial landscapes have continued to grow and evolve. In a reflection of the growing importance of the research field, there was a new dedicated Springer research journal, Animal Microbiome, launched in 2021. Similarly, a prominent conference, Animal Microbiome Congress, launched in 2017.

Some of the emerging research themes we observed in 2017 included:

- microbiome-optimised feed additives (in particular for the reduction of methane emissions from ruminants)
- more advanced, targeted interventional probiotics and prebiotics
- diagnostic monitoring of microbial indicators for animal wellness
- enzyme discovery, e.g. animal gut microbes capable of digesting particular plants could be of value to the biofuel industry
- breeding for microbiome composition and function for performance, environmental and other benefits

[46] https://www.animalmicrobiomecongress.com/events/animal-microbiome-congress-2021

- FMT, for instance for pets with digestive conditions,[47] and more recently to allow koalas to eat a wider range of eucalypts and possibly survive habitat loss[48]

While these research areas remain active and promising, however, there are two main themes which appear to have informed the activities of recent commercial players in this market: 1) reduction of antibiotic use and 2) gastrointestinal inflammation treatment.

Resilient Biotics (founded 2016, USA) is a leading company developing microbiome-derived, live biotherapeutics for animal health. The company uses a discovery platform that combines proprietary bioinformatics and laboratory validation assays for therapeutic discovery. It is actively testing precision microbial therapeutics to prevent infectious diseases with the primary goal of decreasing or replacing antibiotics in the animal health industry.

Other animal microbiome-focused companies aiming to provide solutions which reduce antibiotic use include **Cytophage** (Canada), which is developing bacteriophages which aim to reduce and ultimately replace the use of antibiotics for illness prevention and growth enhancement in livestock, starting with poultry. **Midori** (USA) is developing what it calls a new category of non-drug products that harness the functional potential of the animal microbiome. Midori's platform transforms natural food sugars into tailored carbohydrates that activate the gut microbiome to support animal health and nutrition. These complex carbohydrates are not digested by the animal's upper digestive system, and reach the gut microflora where they have their effect.

Ferryx (founded 2019, UK) is developing lead product FX856, a live strain of a strain *of Streptococcus thermophilus* which can be used for the prevention or treatment of gastrointestinal inflammation in humans or animals, reducing symptoms and consequences of disease progression. The company is aiming to use FX956 to treat active disease or prolong remission in dogs and cattle with inflammatory gastrointestinal disease. **Gnubiotics** (Switzerland) is a biotech company specialised in producing glycans to 'naturally' modulate the microbiome of humans and animals. Its platform of Glycan Microbiome Modulators nurtures, maintains and restores microbiome diversity to support gut health including inflammation reduction.

Beyond the animal biotherapeutic development space, many of the animal feed companies identified in our 2017 white paper are still active. Large companies offering microbial-based supplements and additives (e.g. probiotics and postbiotics) such as **Bactana Animal Health** (USA)**, Alltech** (Ireland) and **BioMar** (UK) have been joined by **Phibro** (USA; which has a new direct fed microbial product that helps to optimise the gut microbiome for improved health in poultry[49]), **Tharos** (UK; horse feed derived from enzyme rich malt extract, which has been shown to improve the health and performance of racehorses suffering from common digestive problems), and **Teef** (USA; prebiotic balances the canine oral microbiome for a healthier mouth) among others.

There are a growing number of service-based companies offering various types of animal microbiome testing and sequencing, such as **AnimalBiome** (USA), **Matatu** (USA), **BaseClear** (Netherlands) and **Klifovet** (Germany). Another type of service model is also exemplified by 2018 startup **Anizome** (USA; sister company to human health service company **Diversigen**), which offers not just metagenomic sequencing services but a wider microbiome discovery platform that bridges the gap between research and commercial solutions. The platform "*consolidates state-of-the-art technologies inside a*

[47] https://www.animalbiome.com/blog/healing-your-dog-or-cat-with-fecal-transplant
[48] https://www.microbiometimes.com/poo-transplants-to-help-save-koalas/
[49] https://www.pahc.com/introducing_proviaprime/

single, structured research and development process focused on generating commercial solutions".[50] Through partnerships, joint ventures and licensing arrangements the company intends to develop a range of novel diagnostic and therapeutic solutions capable of optimising performance and preventing disease in animals.

4.3 PLANT HEALTH

A plant's microbiome refers not only to the microorganism community present in the plant but also to all the functions performed by that community, such as absorption of nutrients, protection from pathogens and drought resistance, among many other factors.[51]

The manipulation of plant and environmental microbiomes is becoming an increasingly popular tool to sustainably increase farm productivity for food and nutrient security. Like the animal microbiome field, there is a rapidly expanding research landscape for the study of the agriculture microbiome and new global conferences being established which are dedicated to it.[52,53]

Most agricultural companies are working on biologicals which aim to exploit the plant microbiome to increase crop yields. Companies are searching for efficient methods to screen thousands of microbes for hundreds of effects in varied agronomic environments. In many cases the market opportunity lies in complementing traditional chemistries by reducing the need for agrochemical application.

In our 2017 white paper we discussed the rapid growth of the market for microbiome tools and microbial products in agriculture (including the whole microbial community as well as single species products). Research by **Monsanto** (USA) estimated a $2.9 billion market value for agricultural biologicals as a whole, citing approximately $1.8 billion to microbials. Additionally, within biopesticides, which account for over $2 billion annually, microbially-derived products account for more than 50% of the market.[54] Some market estimations project that biological sales for agriculture in general could exceed $5 billion within the decade.[55] Some other more recent sources project that the market for microbiome-based agricultural products will be worth more than $10 billion by 2025 in the United States alone.[51]

When we published our previous white paper, the agricultural microbiome market was composed mainly of just a handful of new and established major players, for example:

- **Indigo Agriculture** (USA) was and is an industry leader developing microbiome-based products and a digital and data-focused software analytics platform to strengthen crops against disease and drought to increase crop yield for farmers, and is attempting to reintroduce microbes to plants that have been lost due to modern agriculture.
- **AgBiome** (USA) had, by 2017, raised $71.5 million in venture funding from investors which include the **Bill & Melinda Gates Foundation** and the venture capital arms of major agbio companies, **Syngenta** (Switzerland), **Monsanto** and **Novozymes** (Denmark). It develops products aimed at helping farmers combat many of the most important unresolved problems

[50] https://www.anizome.com/
[51] https://agencia.fapesp.br/microbiome-based-technologies-drive-multibillion-dollar-market/34195/
[52] http://www.global-engage.com/event/microbiome-for-agriculture-congress/
[53] https://www.global-engage.com/event/microbiome-agriculture-asia/
[54] Singh (2017) Creating new business, economic growth and regional prosperity through microbiome-based products in the agriculture industry. *Microbial Biotechnology*, 10, 224-227
[55] Global Engage (2016) *Exploring The Microbiome In The Agricultural Industry*

in agriculture, such as plant diseases, insect pests, and parasitic nematodes. It launched its first commercial product, Howler, a fungicide, in 2017.[56]

- In 2014 **Monsanto** and **Novozymes** created the BioAg Alliance, a unique partnership focused on testing thousands of bacteria isolated from soil around the world to catalyse the development of new microbial solutions for agriculture. However, Novozymes ended the alliance in 2019 after Monsanto was acquired by **Bayer**.[57]

Major companies are continuing to grow their presence in this market, and early innovators are expanding rapidly, such as:

- In 2017, **Bayer** and **Ginkgo Bioworks** (USA) launched a new company, **Joyn Bio**, that will manufacture microbial products using synthetic biology, to reduce the amount of chemical fertiliser that farmers need to apply to crops. This $100 million partnership uses Bayer's know-how combined with Ginkgo's manufacturing capabilities, which will purportedly allow the company to produce biologicals at 50- to 100-times the strength of products currently available on the market.[58]

- **Pivot Bio** (USA), a Californian company with $186.7 million in investor funding is engineering natural nitrogen-fixing bacteria that live on the roots of corn plants that can boost yields while reducing the need for synthetic fertilizers.[59]

- **BioConsortia** (USA) is a start-up developing microbial consortia for increasing agricultural yields, and has now raised around $37 million.[60] It has an expanding patent portfolio of novel metabolites, natural and gene-editing microbes for biopesticides and nitrogen fixation and in December 2020 announced a deal to develop and commercialise nitrogen fixing microbes for non-legume crops with the $9 billion revenue fertiliser company, **Mosaicb** (USA).[61]

- **Concentric Agriculture** (Canada) develops sustainable "biological optimisers" designed to target the phyto-microbiome of crops. The company's optimisers employs live microbes to actively improve the health of the entire phyto-microbiome and combine multi-strains of bacteria and yeasts into the soil and shorten growing periods. It has raised around $73 million in recent years.[62]

However, the most notable trend in the agricultural microbiome market since 2017 is the growth of the start-up landscape[63], for instance:

- **Intrinsyx Bio** (USA) is focused on delivering sustainable agriculture through the use of natural, biological fertilisers by developing the range of endophytes isolated by Professor Sharon Doty at the **University of Washington**.

[56] https://www.agbiome.com/howler/
[57] https://cen.acs.org/business/agriculture/Novozymes-Bayer-end-BioAg-microbe/97/i15
[58] https://agfundernews.com/joyn-bio-bayer-ginkgo-bioworks-joint-venture.html
[59] https://www.prnewswire.com/news-releases/could-unlocking-the-plant-microbiome-lead-to-the-next-green-revolution-asks-idtechex-301148864.html
[60] https://www.crunchbase.com/organization/bioconsortia
[61] https://bioconsortia.com/2020/12/09/mosaic-and-bioconsortia-to-collaborate-on-new-nitrogen-fixing-microbial-products/
[62] https://www.crunchbase.com/organization/inocucor/company_financials
[63] https://www.idtechex.com/en/research-article/could-unlocking-the-plant-microbiome-lead-to-a-new-green-revolution/21890

- **Boost Biomes** (USA) recently completed a $5 million Series A funding led by global crop nutrition company **Yara International** (Norway). The funding will go towards helping the startup continue commercialising its flagship biofungicide while also developing a broader product pipeline.[64]

- **NewLeaf Symbiotics** (USA) is an agriculture technology company that discovers, develops, produces and commercializes a new class of safe, sustainable and effective ag biologicals. Its products are based exclusively on a new class of ag biologicals called M-trophs (Pink Pigmented Facultative Methylotrophs) — one of the most abundant types of beneficial native microbes in the world.

- **Growcentia** (USA) creates microbial probiotics, focusing on soil microbiology, that enable growers to maximise plant growth, quality and health. Growcentia was founded by a team of three **Colorado State University** soil microbiologists and use a proprietary discovery method that creates consortia of bacteria that have synergistic qualities for specific functions.

Despite the progress in research and commercialisation, the industry is still young and faces challenges with product efficacy and consistency. Although microbes have major potential to boost crop yields if used properly, products can be difficult to develop. Understanding how a new microbe will impact the extremely complex microbial ecosystem around a plant is challenging, as is predicting how a microbe will respond to a specific soil environment. Formulating products and keeping the microbes alive for a long period of time can also be difficult.[59]

Regulations are still evolving and both product categories struggle from the lack of a formal definition and clear regulatory pathways. For biostimulants, this means they must either fit into unsuitable regulatory categories that do not adequately ensure efficacy or performance, or they escape regulation altogether, leading to a crowded market with little guarantee of product quality. Biopesticides face the opposite challenge - they often need to go through the same registration process as synthetic chemical pesticides, or a process mostly derived from it. This can be very difficult as requirements are often poorly suited to biological products, e.g. purity requirements, making it unnecessarily hard to bring a biopesticide to market.[65]

Compared with the wider agrochemicals industry, which is highly consolidated, the agricultural biologicals market is fragmented. Although this means there are lower barriers to market entry and the industry is fast-moving and innovative, it creates an environment where it is difficult for developers to differentiate themselves and for farmers to navigate, potentially harming the credibility of the industry and hampering growth. Additionally, the large number of companies with limited product ranges means there are several disparate products on the market that may interfere with each other.[65]

[64] https://agfundernews.com/breaking-exclusive-boost-biomes-nabs-5m-series-a-to-tap-into-ecology-of-microbes.html

[65] https://www.idtechex.com/en/research-report/biostimulants-and-biopesticides-2021-2031-technologies-markets-and-forecasts/773

5 PATENT LANDSCAPE

A fairly thorough analysis of the microbiome patent landscape is included in our 2017 white paper. It is beyond the scope of this 2021 report to perform updated analysis on the filing trends, statistics, key player portfolios, etc. However, it is worth briefly discussing here the challenges which inventors face in patenting new microbiome technologies, particularly in the therapeutics space and particularly in the USA, the largest market and home to the majority of leading companies across the microbiome industry.

Generally speaking, in the UK, Europe and most other patent jurisdictions (with the notable exception of the US, discussed further below), various classes of invention may be protectable by patent rights, for example:[66]

- A new microorganism; either previously unidentified and in a form isolated from its natural environment, or modified (e.g. genetically).
- A previously unidentified extract from a microorganism.
- A new consortium of known and/or unknown microorganisms.
- A new composition of matter including known microorganisms/extracts and/or any of the above.
- A new method of culturing or using (including a new therapeutic use) of known microorganisms/extracts.
- A diagnostic method based on analysis of the presence/absence/proportion of microorganism populations

Increasing numbers of patent applications directed to bacteria are being filed and granted as the microbiome field rapidly develops. However, drafting and prosecuting applications claiming bacteria is challenging due to the complexity of the technology and the products, inexperienced patent examiners and limited guiding case law. The scientific complexity of patenting microbiome-related inventions and claiming bacteria has recently been discussed in a now on-demand webinar by patent attorney firm **J A Kemp** (USA)[67], examples of which include:

- The fact that "a widely accepted, biologically meaningful definition of 'strain' in microbiomes remains elusive".[68]
- Regulatory context is also important to the *value* of patent claims for a deposited strain (e.g. what strain is approved for use, nature of the competition).
- Morphological characteristics and sequencing data may be considered by patent examiners and courts. In a recent case (Shanghai Finc v. Tianjin Lvshengpengyuan and Hongbinhesheng, Beijing IP Court) the whole genome sequencing data was held to lack the required certainty, with no consensus in the field on threshold similarity.

[66] https://ktn-uk.org/news/ktns-microbiome-innovation-network-launches-the-microbiome-strategy-roadmap/
[67] https://jakemp.com/en/events/j-a-kemp-webinar-the-microbiome-and-claiming-bacteria
[68] https://www.nature.com/articles/s41579-020-0368-1

- Under the doctrine of equivalents, claims can cover variants that achieve substantially the same result in substantially the same way, even if outside the literal meaning of the claims.
- Two strains of the same virus can be held to be different active agents, since they may have different efficacies.
- For claims to a species, there can be huge phenotypic variation in strains from a single species. Some strains within a species may be ineffective, while identifying effective strains may be an excessive burden.

The European Patent Office (EPO) granted 106 patents claiming naturally-occurring bacteria in 2019 and 2020: 45% were limited to specific deposited strains; 4% claim a specific deposit with some extra claim breadth; 30% claim a species; and 21% claim a genus or broader.[69]

Conversely, in the USA, obtaining patent protection for microbiome therapeutics has been affected profoundly by two US Supreme Court decisions in *Myriad* (2013) and *Mayo* (2012), which redefined the scope of which natural phenomena, including microbiome therapeutics, are patent eligible.[70] The only form of new microorganism that is patentable in the US is one that has been genetically modified. For this reason, for unmodified microorganisms, strategies focusing on formulations or use-restricted claims are important.

The only consortia that are patentable in the US are those that demonstrate synergy from the combination or a mixture of microbes that are not found in nature. Furthermore, for FMT-based therapeutics, the developers must also show that there is novelty in the product that is "non-obvious" and it can be sufficiently described. These additional points for patent eligibility can be particularly challenging as FMT is received from a donor and is a heterogeneous complex in nature. Nonetheless, broad patent designations have been granted to microbiome therapeutics companies (which is typical during the drug development phase) and will likely not be enforced until the drugs are on the market and are challenged through litigation.[17]

Obtaining commercially important broad patent claims for almost all forms of microbiome diagnostics in the US has become challenging, and a constantly evolving target. To optimise likelihood of success, one should take a proactive approach; starting up a dialogue with the US examiner in charge of the case is normally essential. [66]

[69] Ian MacLeod, JA Kemp (2020) *The Microbiome and Claiming Bacteria: Challenges and Recent Guidance*
[70] https://www.nature.com/articles/s41587-020-0579-z

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