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EXPLOITING THE MICROBIOME: MARKET DEVELOPMENTS AND INTELLECTUAL PROPERTY LANDSCAPE

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EXECUTIVE SUMMARY

The intention of this white paper is to provide an overview of the market developments across the microbiome commercial and patent landscapes. The information in this report does not constitute legal advice and should not be interpreted as such.

The academic, market and patent trends show that the microbiome industry is at an early stage but has been undergoing rapid growth over the last two years. In particular, therapeutics based on the human gut microbiome are a source of enormous commercial potential, as indicated by several licensing deals completed in 2016 which are worth hundreds of millions of dollars each. There are no marketed microbiome based drugs currently on the market, but the first drugs and diagnostics could launch by 2018.

For the purposes of this report, the market has been segmented into three areas: human health and wellbeing, animal health and plants and agriculture. Most activity is still in the academic space. Academic microbiome research is highly active across all three market segments, and this is supported by a large amount of governmental funding and national and international research programs in several developed countries. Human health is by far the largest industry sector. In this area, and in plants and agriculture, a handful of multinational healthcare companies are increasingly partnering with a range of smaller biotech companies, start-ups and/or best-in-class academic institutions to develop or license microbiome products. The key areas of interest are in drugs to tackle diseases like gastrointestinal disorders, cancer and diabetes. Venture capital (VC) firms in the U.S. and Europe have recently become active in microbiome technologies. VC firms have invested around $1 billion in various rounds of financing since 2014.

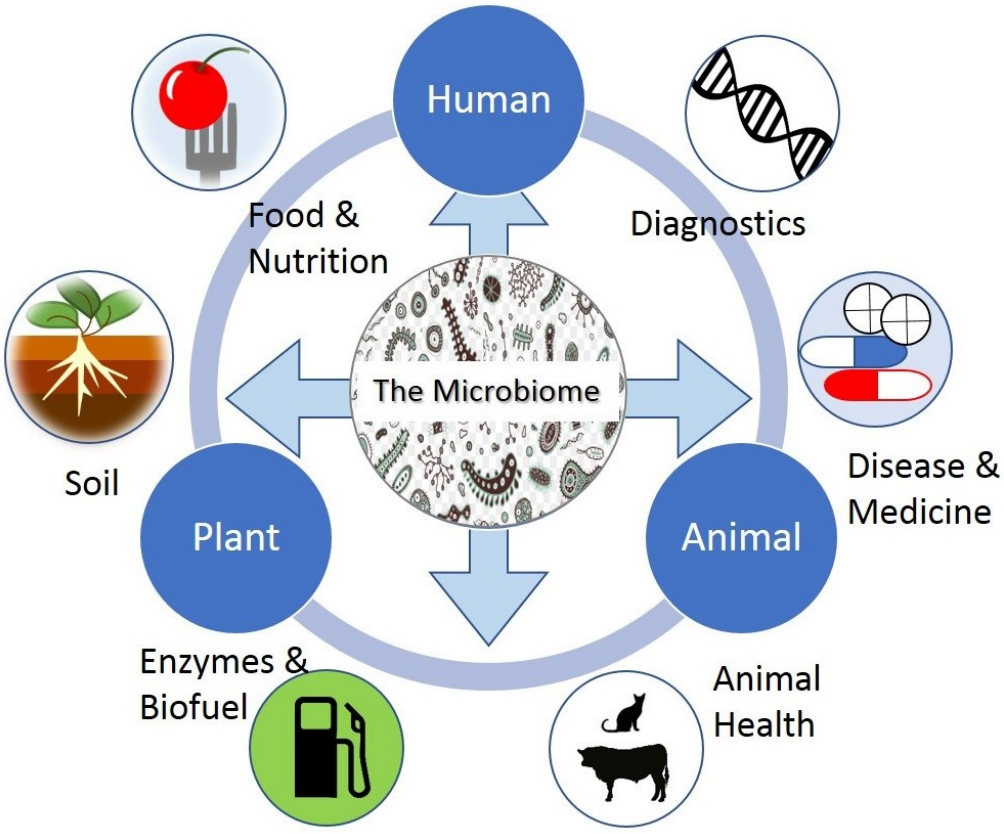
The animal microbiome industry is still at a very early stage, with little market activity compared to human health or agriculture. For all segments, standardised regulations around live bacterial drug formulations and international agricultural applications are still in the process of being developed by different countries and regional bodies. The outcome of these decisions, in particular around the safety of administering live bacteria or bacterial products in the human body, will affect the industry potential of some microbiome technologies (e.g. faecal microbiota transplantation).

Patenting of microbiome technology has also undergone rapid growth over the last two years. Many patents have been granted to leading companies in the sector, such as **Seres Therapeutics**'s patent titled "synergistic bacterial compositions and methods of production and uses thereof". However, there remains some scepticism from industry commentators of the patentability of subject matter based on naturally-occurring organisms, due to novelty, obviousness issues and patent law constraints. There has been little litigation in the industry, which may continue to be the case since this is currently a fairly collaborative industry and many companies appear to have found their niche. However, this could change in the future as a new generation of foundational microbiome patents are created.

Overall, there is great excitement at the possibilities afforded by microbiome-exploiting technologies. The industry is undergoing rapid expansion, with a strong focus on collaboration and innovation. However, key microbiome drug candidates are currently in Phase II clinical trials and the success or failure of a handful of such treatments may have a decisive impact on the future of the whole microbiome industry.

INTRODUCTION

This white paper by IP Pragmatics focuses on the microbiome industry, which has undergone huge expansion in recent years as a result of improved diagnostic capabilities and increased funding for large-scale characterisation initiatives. The main emphasis of this paper is on the human microbiome – specifically the human gut microbiome – since this is by far the largest area of research activity, though there is also an increasing amount of interest in animal, plant and soil microbiomes.



Acknowledged as one of the "biggest game-changers in healthcare"[1] and cited in 2015 by former Google Ventures president, Bill Maris, as having the potential to revolutionise life sciences[2], microbiome research has become increasingly prominent in academia and industry searching for fresh approaches to health management and disease treatment, such as novel antibiotics. It has also caught the imagination of the public through food marketing campaigns and large crowd-funded endeavours offering personal microbiome analysis.

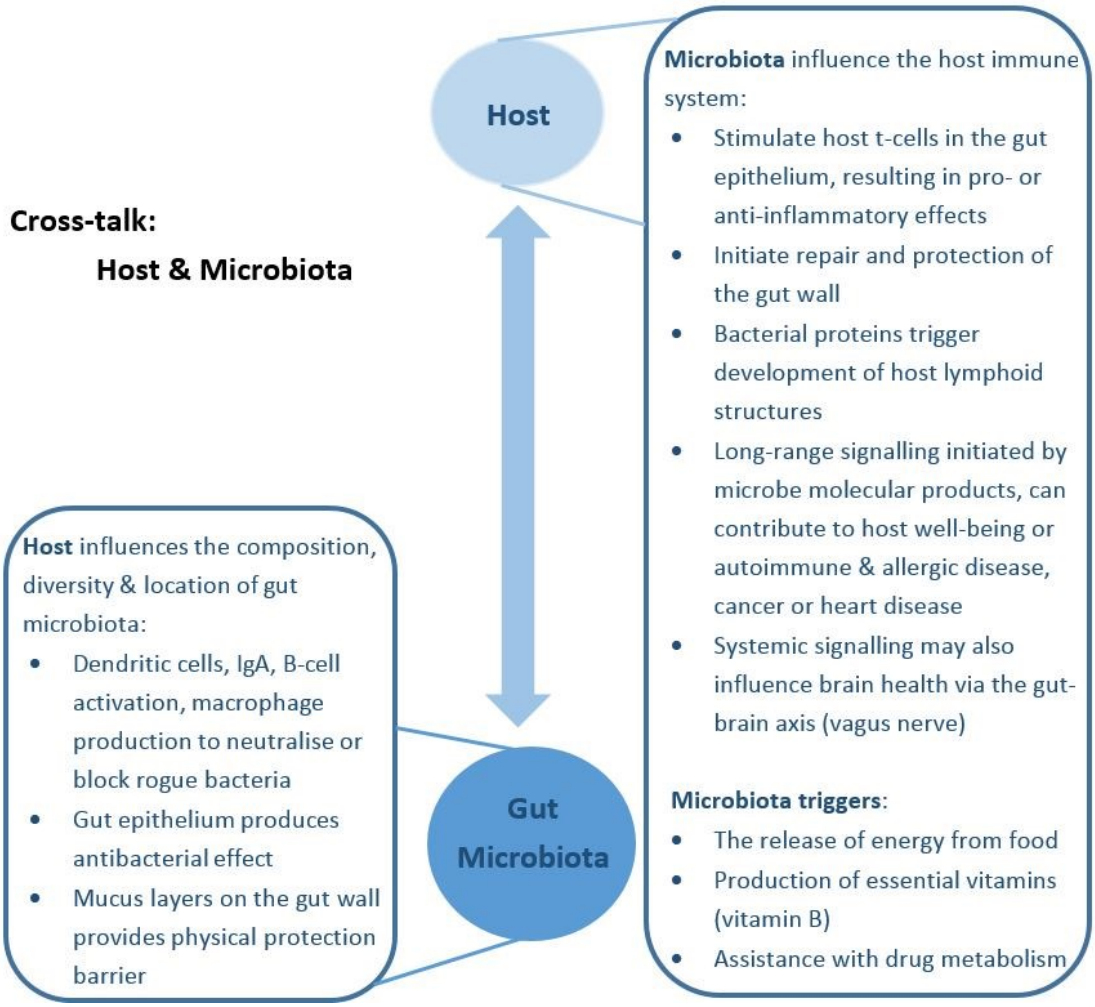
The term "microbiome" refers to the collective genomes of resident microorganisms. The human body is home to over 100 trillion microbes and over 2 million microbial genes, weighing around 2 kg. The human microbiome is therefore sometimes considered our "forgotten organ" or "second genome". Microbiota residing inside and on the human body play a significant role in the body's physiological functions – some beneficial and others harmful.

[1] Frost & Sullivan. (2016) *Key Technologies Impacting the Future of Healthcare Industry*

[2] https://library.gv.com/medicine-s-transistor-moment-fb6c88f4352f

The largest population of microbes in the human body is found in the gut, where it plays a multifaceted role in host biology and dysbiosis, as shown in the Figure below. Accordingly, the gut microbiome is the most active area of microbiome research and technology development. Other populations of interest in disease treatment include the skin, oral (mouth) and vaginal microbiomes.

Research has shown that imbalances in microbiota can induce inflammation, release toxic substances, trigger immune system disequilibrium and cause diseases both in their immediate and distant environment. There is now a multitude of diseases associated with such imbalances across the human body – gastrointestinal diseases, dental caries or bacterial vaginosis, for instance – that can potentially be treated with live bacteria in pre- or probiotic-containing microbiome therapeutics which disrupt this imbalance and restore a healthy microbial community.



Role and mechanisms of the human gut microbiome

Humans and animals suffer from some of the same diseases, including osteoarthritis, renal and cardiovascular diseases and immune-related diseases such as atopic dermatitis and certain cancers. Disease in animals is a key driver of the risk of pandemics in humans. This can be seen with resistant bacteria and emerging pathogens which continue to cause new epidemics in humans and animals. Plants and soil are also closely associated with microbes. Distinct microbial communities live inside roots, on leaves and within flowers, and can have

three to six orders of magnitude greater genetic diversity than their plant hosts. This second genome, much like the human microbiome, provides plants access to nutrients and helps to suppress disease. The same technological advances that allow the mapping of the human microbiome now enable the understanding, isolation, and reintroduction of microbial species into the soil to repair the damage and restore healthy microbial communities that sustain crops and provide nutritious food. As understanding of the interactions between plants, soil and microorganisms grows, scientists, growers and entrepreneurs alike regard the plant microbiome as the new frontier for soil and crop technology.

There is a host of other microbiome populations which may have potential industrial application, such as water, wood, oil and gas. However, industry is still a long way from realising potential technologies in these areas, which are therefore not discussed any further in this report.

Many developed countries have initiated ambitious governmental microbiome funding programs in the last five years. The USA, UK and Ireland, for example, have spent or announced $1.6 billion, £100 million and €50 million, respectively, for microbiome R & D programs. Knowledge and understanding of the microbiome and its role in a multitude of various diseases has grown exponentially since the completion in 2012 of the publicly-funded Human Microbiome Project (HMP) in the USA and the Metagenomics of the Human Intestinal Tract (MetaHIT) project in Europe. The HMP led to the identification of 60 million predicted genes, 600 microbial reference genomes, and 700 metagenomes sequenced. The initial 2010 MetaHIT study reported sequencing 3.3 million non-redundant faecal microbial genes. By 2012, the MetaHIT reference catalogue was thought to contain nearly a complete set of genes for most human gut bacteria.[3]

HMP and MetaHIT have been followed by a number of other public and private research programs[4] which are outlined in the table below to demonstrate the range and level of activity in microbiome research.

Initiative	Dates	Funding	Location	Description
Human Microbiome Project (HMP)	2007-2012	National Institute of Health (NIH)	USA	Five-year initiative aimed at cataloguing the vast array of microbial genes and species present in the various ecological niches of the body and at determining their role in health and disease.
Data Analysis and Coordination Center (DACC)	2008-2013	National Institute of Health (NIH)	USA	Central repository for all HMP data. The aim of the HMP is to characterize microbial communities found at multiple human body sites and to look for correlations between changes in the microbiome and human health.

[3] Shreiner et. al. (2015) The gut microbiome in health and in disease. *Current Opinion in Gastroenterology*, 31, 69-75

[4] http://www.human-microbiome.org/index.php?id=30

Initiative	Dates	Funding	Location	Description
MetaHIT	2008-2012	European Commission	EU	MetaHIT aimed to establish associations between the genes of the human intestinal microbiota and our health and disease. The scientists focused on two disorders - inflammatory bowel disease (IBD) and obesity
Canadian Microbiome Initiative	2009-present	Canadian Institutes of Health Research Institute of Infection and Immunity (CIHR-III)	Canada	Using a sequenced and analysed genomic reference database, it is hoped to be able to predict the genetic capabilities of unknown species on the basis of similarities with known genes and to assess the role of the human microflora in health and disease.
Human Oral Microbiome Database (HOMD)	2010-present	National Institute of Dental and Craniofacial Research	USA	Goal is to provide the scientific community with information on 700 prokaryote species present in human oral cavity. The project has been able to identify and name 54% of these microbes, 14% have been cultivated but not named and 32% are known as uncultivated phylotypes.
Earth Microbiome Project (EMP)	2010-present	Crowd funding	Worldwide	Aims to characterise the diversity, distribution, and structure of microbial ecosystems across the planet and has already gathered over 30,000 samples. Their focus is on diverse microbiome ecosystems, including terrestrial, marine, freshwater, sediment, air, and constructed environments
International Human Microbiome Standards (IHMS)	2011-2015	European Commission	Worldwide	Optimization of methods for the assessment of the effects of the gut microbiome on human health through the standardization of procedures and protocols.
RuminOmics	2012-2017	European Commission	EU	The project will use state-of-the-art technologies to understand how the ruminant microbiome is controlled by the host animal's genetics, its diet and how this impacts on methane production. The outputs will lead to new knowledge, tools and technologies to help the livestock industry reduce the environmental impact from methane and nitrogen emissions.
MetaGenoPolis (MGP)	2012-2019	Investissements d'Avenir	France	Has a strategic goal to demonstrate the impact of the human gut microbiota on health and disease, by making available cutting-edge metagenomics technology, quantitative and functional, to the medical, academic and industrial communities.

Initiative	Dates	Funding	Location	Description
Human Food Project	2012-present	Corporate sponsors	Worldwide	Aims to understand modern diseases within the context of our ancestral and microbial past.
Integrative Human Microbiome Project (iHMP)	2014-present	National Institute of Health (NIH)	USA	In this second phase of the HMP, the iHMP will create integrated longitudinal datasets of biological properties from both the microbiome and host from three different cohort studies of microbiome-associated conditions using multiple "omics" technologies.
American Gut	2015-present	Crowd funding	Worldwide	Stool donors get the results of their metagenome analysis at differing levels of detail (depending on the size of their financial contribution).
National Microbiome Initiative (NMI)	2016-present	Over 100 public and private institutions	USA	$400 million investment aiming to support interdisciplinary research to answer fundamental questions about microbiomes in diverse ecosystems, develop platform technologies that will generate insights and expand the microbiome workforce through citizen science, public engagement, and educational opportunities.
NIFA Early Concept Grants for Exploratory Research (EAGER)	2017-present	USDA's National Institute of Food and Agriculture (NIFA)	USA	11 grants worth a total $3 million for EAGER projects focused on plant and animal phenomics and microbiomes. NIFA expects that these studies will lead to a better understanding of how microbial communities interact with one another and with their plant and animal hosts.

The number of studies addressing the role of the microbiome on animal health is limited compared to human studies, though investments in livestock and companion animal microbiome are growing. Studies have so far largely focused on exploring the gut microbiota in representative animals including mice, rats, broilers, swine and cows. Although mice and rats are the most commonly studied animals, they are mainly used as animal models for the engineering of human microbiome. Microbiome studies are also expanding into insects and marine species of commercial interest, such as oysters and salmon. The microbes of soil invertebrates (e.g. earthworms, nematodes, etc.) are under investigation as gut microbes of soil animals can play an important role in the digestion of plant material and are a vital part of the global carbon cycle.

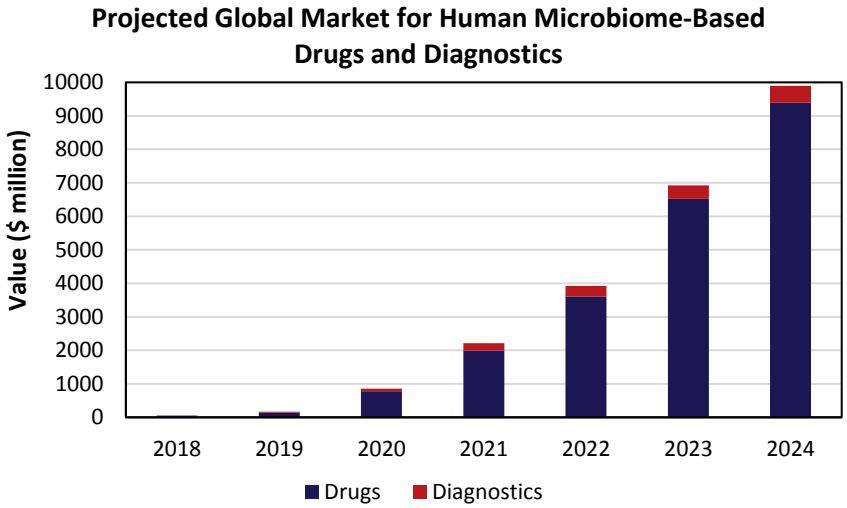
This white paper aims to give an overview of microbiome technologies through a combination of market research and patent landscaping, focusing on the current and future applications of microbiome technology in key industries. These key industries are also well-aligned with the areas of expertise of IP Pragmatics: Human Health, Animal Health, and Plants and Agriculture. The paper also incorporates details of key organisations, factors affecting the market, licensing, partnerships and collaborations.

MARKET OVERVIEW

HUMAN HEALTH AND WELLBEING

The microbiome industry is a nascent but rapidly developing field. There are no marketed microbiome based drugs currently on the market, but the first crop of drugs and diagnostics could launch by 2018. The human microbiome based drugs and diagnostics pipeline is strong, with over 25 companies active in this space and over 50 programs in clinical/preclinical development.[5] The huge growth potential but uncertainty surrounding the future of many leading innovations in the human health sector (e.g. depending on successful clinical trials for drug candidates) is reflected by the wildly different estimations of the global human microbiome market value.

Research by Markets and Markets and others[6,7] estimates that the overall human microbiome market is expected to reach $899.1 million by 2025 from $506.5 million in 2022, growing at a compound annual growth rate (CAGR) of 21.1%.[7] Various other estimates put the value at $1.1 billion by 2021[8] and $2.2 billion by 2025[9], while BCC Research forecasts a market size of nearly $9.9 billion in 2024 with a CAGR of almost 70%[5], as shown in the adapted Figure below.



[5] BCC Research. (2017) *Human Microbiome Based Drugs And Diagnostics Market*

[6] Occams Business Research & Consulting. (2017) *Global Human Microbiome Market Insights, Opportunity, Analysis, Market Shares And Forecast 2017 – 2023*

[7] Markets and Markets. (2017) *Human Microbiome Market by Disease (Diabetes, Obesity, Autoimmune, Cancer, Diarrhea, Mental Disorder), Application (Therapeutic, Diagnostic) & by Product (Probiotic, Prebiotic, Food, Medical Food, Supplement, Device, Drug) – Global Forecast to 2023.*

[8] Mordor Intelligence. (2016) *Global Human Microbiome Market - Growth, Trends and Forecasts (2016 - 2021)*

[9] Research and Markets. (2016) *Global $2.2 Billion Microbiome Therapeutics and Diagnostics Pipeline Analysis and Market Outlook 2016-2025*

Clearly, the growth potential of the human microbiome industry is not without risk and is still to be proven – pending successful clinical trials, regulatory approvals, and demonstrations of long-term efficacy and safety – and therefore care should be taken when citing market forecasts.

The human microbiome market can be broadly segmented by application into therapeutics (including therapeutic and medical foods) and diagnostics. The therapeutics segment is considered to be the leading segment of the two, with BCC Research estimating a 95% market share by 2024, as shown in the Figure above. This is due to the need for reliable, precise and quicker treatment of chronic lifestyle diseases and various other disorders.

Product segments are drugs, prebiotics, probiotics, foods, medical foods, other supplements and devices. Of course, prebiotics and probiotics (mostly containing lactobacillus) are already well-established within the food and nutraceuticals industries, worth hundreds of billions of dollars collectively.[10,11] The weight control market, for instance, is worth nearly $60 billion in the U.S. alone, and products containing probiotics contribute to more than half of that.[12] However, these generic products are preventative, rather than therapeutic, and are not sold based on microbiome analysis or understanding of individual microbiome imbalances. As understanding of the microbiome develops, there is a growing interest in the application of microbiome technologies in personalised medical foods which bridge the gap between a food and a pharmaceutical. The overall medical foods market was estimated to be worth $12.3 billion in 2015 and is expected to grow at a CAGR of 6.9% until 2025.[13] The larger market players have not overlooked this opportunity and have built and acquired innovation in this area, such as **Nestlé** who invested $1 billion in **Nestlé Health Science**, and **Danone**, whose Medical Nutrition division, **Nutricia**, reported over $1.2 billion sales in 2011.[14] Both are actively engaged in R & D to bring microbiome-based medical foods to market.

Microbiome research has been accelerated significantly by improved microbiome sequencing capabilities, allowing high-throughput sequencing and metagenomics to develop and provide insight into microbial communities, independent of laboratory culture methods. Most interest in high-throughput sequencing is in the human health space, particularly for microbiome screening and associated diagnosis of gastrointestinal tract disorders. The market for human microbiome-based diagnostics will now in turn be driven by the demands of the microbiome based drugs market. BCC Research estimates that the microbiome-based diagnostics market will reach $392 million in the U.S. and $152 million in rest of the world regions by 2024, over half of which is for diagnosing gastrointestinal disorders.[5] Though the market share of microbiome diagnostics is far smaller than the drugs sector, sequencing technologies are

[10] BCC Research. (2017) *Nutraceuticals: Global Markets*

[11] BCC Research. (2016) *The Probiotics Market: Ingredients, Supplements, Foods*

[12] Marketdata Enterprises Inc (2015) *The U.S. Weight Loss Market: 2015 Status Report & Forecast*

[13] Gran View Research. (2017) *Medical Foods Market Analysis By Route Of Administration, By Product Type, By Application Type, And Segment Forecasts, 2014 - 2025*

[14] Life Sciences Sector Team, Scottish Enterprise. (2013) *Emerging Opportunities: The Gut Microbiome*

applicable in other related markets. For instance, it is predicted that, overall, the global microbiology automation and technology market sector will grow from $3.7 billion in 2015 to approximately $4.9 billion in 2020 at a 6.1% CAGR.[15] High-throughput sequencing technologies in the global clinical sector are expected to grow at a CAGR of 31.3%, from $997.1 million in 2015 to nearly $3.9 billion by 2020.[16] The overall global market for high-throughput microbiology systems is expected to grow from $777 million in 2015 to $1.1 billion in 2020 at a 6.6% CAGR.[15]

As well as application and product segments, the global human microbiome market can also be segmented by disease, as outlined in the Table below, based on global market figures by BCC Research. The largest segments driving the market projections are diseases associated with dysfunction in the gastrointestinal tract (35.8% share), orphan diseases (28% share) and cancer (13% share). The growth of the market in years 2018-2020 will remain modest but will pick up significant momentum by 2021 with the launch of a number of microbiome-based drugs in 2021 and 2022. This analysis is an overview of the main disease areas which have established proof-of-concept, strong evidence and multiple companies and/or researchers working on various projects. It does not include the other numerous diseases for which the science is at an early concept stage, such as liver disease, kidney disease, hypertension, polycystic ovary syndrome, multiple sclerosis, autism spectrum disorder, depression, schizophrenia and Parkinson's disease.

Disease Area	Human Microbiome Drugs - Global Market Value ($ million)								CAGR %
	2017	2018	2019	2020	2021	2022	2023	2024	2021-2024
Cancer					262.6	530.9	772.1	1222.6	67.0
Obesity						146	208.9	301.5	
Type-2 diabetes		14.3	44.4	121.7	174.5	213.5	589.7	704.5	59.2
Ulcerative colitis				75.6	260.8	566.2	914.8	1179.7	65.4
Crohn's disease				76.4	153.5	481.2	657.3	814.7	74.4
C Difficile infection		42	76.1	225.1	388.4	517.8	739.1	979.1	36.1
Lactose intolerance				47.8	68.9	142	181.4	224.2	48.2
Dental caries			79.4	130.3	167	293.4	313.4	321.3	24.4
Recurrent bacterial vaginosis and UTI					42.1	86.7	159.6	197.3	67.3
Skin disorders			21.6	44.6	131.1	169	400.3	575.7	63.8
Hyperoxaluria					131.2	253.5	405.4	551.9	
Celiac disease							87	161.5	
Urea cycle disorder							65.3	134.5	
Phenylketonuria							261.2	639.1	
Non-alcoholic steatohepatitis					114.2	336.1	465.1	832.4	93.9
Hepatic encephalopathy							261.1	478.7	
Total		56.3	221.5	721.5	1894.3	3736.3	6481.7	9318.7	70.1

[15] BCC Research. (2016) *Global Markets for Microbiology Technology, Equipment and Consumables*

[16] BCC Research. (2015) *Next-Generation Sequencing: Emerging Clinical Applications and Global Markets*

In addition, research into the human microbiome is underpinned by a research tools market. By technology this is divided into cell culture technology, high-throughput technology, omics technology, and computational tools. Cell culture technology is still the most widely-used technique in microbiome research, which can be attributed to its usage in in vitro modelling to reproduce in vivo conditions and to study host-microbial community interactions.[7]

Geographical analysis indicates that the USA is expected to be the largest market for drugs and diagnostics due to earlier predicted drug approval dates over the next few years, before European and Rest of the World approval dates in the early- to mid-2020s.[5] However, Europe is expected to be the largest market for foods and drinks due to broader cultural acceptance of a variety of prebiotics and probiotics and other food supplements to maintain microbiome balance. This is followed by Asia-Pacific, then USA, which at present is regarded as a smaller market due to the lack of awareness among the population regarding the beneficial usage of prebiotics and probiotics.[7] Europe is also expected to be the largest growth market for diagnostic and service offerings, especially for metabolic diseases.

THERAPEUTICS

A number of organisations are developing therapeutic products across various disease areas in the human microbiome space. Generally, companies have developed their own proprietary technology platforms and innovative approaches to microbiome-based treatment.[1,17] Broadly speaking, product development strategies fall into seven main categories which are outlined in the Table below and highlighted with some selected examples of relevant companies and diseases studied (adapted from BCC Research[5]).

The use of natural, live bacteria either as a single agent or in a mixture form is the most common strategy deployed for a variety of products. Some companies are engineering bacteria, programming them to take over certain physiologic functions to tackle rare disorders. Faecal transplantation from healthy donors is being explored in gastrointestinal disorders. Bacterial products (*i.e*. proteins, spores) are also being used by some companies. Small molecules and biologics-based approaches are also being examined to remove the bacteria or bacterial toxins from the body. Some other companies are using proteins and or antibodies to remove the toxins from the body. Finally, natural products that help modulate the gut microbiome diversity are also under investigation.[5]

Strategy	Action	Disease	Company
Natural, live bacteria-based therapeutics	Use of live bacteria to modulate the immune system	Cancer	Evelo Biosciences
	Use of live bacteria to remove toxins in the body	Phenylketonuria	Synlogic
	Use of live bacteria from healthy donors	C.difficile infection	Rebiotix
	Use of bacterial mixtures that secrete therapeutic proteins	Crohn's disease	ViThera

[17] Frost & Sullivan. (2017) *Advancements in Microbiome and Genetics – Genetic Technology TechVision Opportunity Engine*

Strategy	Action	Disease	Company
	Use of commensal bacterial mixture to develop healthy microbiome	C.difficile infection	Seres Therapeutics
	Use of live topical bacteria to produce anti-inflammatory effect	Skin disorders	AOBiome
	Use of live food grade bacteria	Bacterial vaginosis	Osel
Engineered bacteria-based therapeutics	Engineering bacteria to perform certain physiological functions	Urea cycle disorder	Synlogic
	Engineering bacteria to correct enzyme deficiency	Phenylketonuria	
Bacterial transplantation-based therapeutics	Use of faecal microbiome from healthy donors	Obesity and C. difficile infection	Seres Therapeutics, Rebiotix
Bacterial proteins-based therapeutics	Bacterial proteins that target bacteria	Bacterial infections	AvidBiotics
	Bacterial spores for microbiome dysbiosis	Crohn's disease	Seres Therapeutics
Small molecule-based therapeutics	Small molecule inhibitor which uses a microbiome mechanism of action to target pain and inflammation	Inflammatory bowel disease	Second Genome
	Small molecules to remove bacterial toxins	Crohn's disease	Enterome
	Small molecules that inhibit bacterial enzyme responsible for adverse events	C.difficile infection	Enterome
Antibodies and proteins-based therapeutics	Use of therapeutic proteins to remove bacterial toxins	Oral mucositis	Immuron
	Antibodies with specificity for certain, harmful bacteria causing disease	Dental caries	C3J Therapeutics
Natural products-based therapeutics	Use of natural product or mixture to modulate the gut microbiome and stimulate the growth of certain bacteria	Lactose intolerance	Ritter Pharmaceuticals
	Use of food mixtures to expand microbial diversity in the gut	Type-2 diabetes	Microbiome Therapeutics

Of these platforms, one of the most promising is faecal microbiota transplantation (FMT) (or microbiota restoration therapy), which has shown overwhelmingly successful treatment of C. difficile infection in cases where antibiotics have proven ineffective. The non-profit stool bank **OpenBiome**, alongside some facilities in various US hospitals, have recently revived and reimagined this long-established technique, where a carefully screened stool sample is transplanted into a patient, and the donor's microbes then restore the recipient's gut bacteria to their normal density and diversity. The therapeutic potential of FMT in other non-gastroenterologic conditions is also being explored. However, the FDA announced in 2016 that it will regulate faecal transplants as drugs[18], which will hinder the growth of organisations such as **OpenBiome**. Though stool banks can still operate, the development of safer, more reproducible alternatives may phase them out.

[18] Food and Drug Administration. (2016) *Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat Clostridium difficile Infection Not Responsive to Standard Therapies*

To this end, a number of companies such as **Seres Therapeutics** and **Rebiotix** are developing drug-based approaches to FMT. Here, large amounts of microbiome data are curated to understand the biology of the microbes in disease states and computational approaches are used to understand the microbial communities and functioning networks. Microbial strains are then isolated from purified stool samples and delivered in a capsule for a more targeted approach to treatment.[19] **Seres Therapeutics**' "Ecobiotic®" drugs have shown great potential in early clinical trials, but the lead candidate, SER-109, failed in Stage II trials in 2016, causing the company's share prices to plummet. They have now been granted a do-over to repeat and modify the trial. As the most high-profile microbiome drug in development, SER-109 is in some respects an acid test for the microbiome drug industry and will be watched with interest by many industry observers.

As further associations between microbes and specific disease states are established, this could generate a suite of exciting new targets for drug developers or vaccine manufacturers. For example, microbiome research in cancer has resulted in a number of metagenomic and pre-clinical proof-of-concept studies that have established the link between microbial product, inflammation and carcinogenesis. The Table below shows a range of cancers and associated microbes that are known to play a role in cancer development and progression.[5]

Indication	Associated Microbiota
Colorectal cancer	Fusobacterium, Porphyromonas
Gastric cancer	H. Pylori
Esophageal cancer	H. Pylori
Skin cancer	Bifidobacterium
Head and Neck cancer	Human Pappiloma Virus
Cervical cancer	Human Pappiloma Virus
Lymphomas	Epstein-Barr Virus
Kaposi's sarcoma	Human immunodeficiency virus
Hepatocellular carcinoma	Hepatitis B Virus, Hepatitis C Virus
Adult T-cell leukemia and lymphoma	Human T-cell lymphotropic virus type-1
Pancreatic cancer	Neisseria elongata and Streptococcus mitis
Gall bladder cancer	Salmonella
Breast cancer	Gut bacteria implicated in oestrogen resorption
Graft-versus Host disease	Lactobacillus

Current drug development strategies for cancer treatment fall into four categories[5]:

- **Microbiome Based Drugs as Immune System Activators**

  Bacteria is used as an agent to activate the immune system in a defined way and kill tumour cells. **Evelo** and **4D Pharma** are two companies that are using this approach

- **Microbiome Based Drugs as an Add-on to Immuno-Oncology Drugs**

  Certain immuno-oncology drugs (e.g. Anti-CTLA-4 agents) are not very effective on their own as their anti-tumour activity is dependent upon gut microbes like B.

[19] Frost & Sullivan. (2017) *Microbiome Therapeutic and Diagnostic Innovations – Genetic Technology TechVision Opportunity Engine*

fragilis. Adding B. fragilis bacteria to Immuno-Oncology drugs like anti-CTLA-4 agents could improve their efficacy by providing immune-stimulatory effects and reduce the severe side effects like colitis that are associated with the anti-CTLA-4 agents

- **Microbiome Based Drugs as Probiotic Mixtures**

  Probiotic mixtures containing beneficial microbes when administered in certain cancer patients have shown to reduce the tumour size significantly. These bacteria produce their therapeutic effect by either metabolizing necessary nutrients to starve the tumour (e.g. asparginase from E.coli starving acute lymphoblastic leukaemia of amino acid asparagine), or modulating the cell growth

- **Microbiome Based Drugs as Chemotherapy Adjuncts**

  Some gut microbes reactivate the drug metabolites from chemotherapy treatments and cause toxicity. Microbiome-based drugs can work as a chemotherapy adjunct for reduction of dose limiting toxicity (**Symerix**).

Further industrial applications of the microbiome in the therapeutic space include novel antibiotics, using the rich source of novel actives and enzymes from microbes. In particular, the development of ultra-precise antibiotics may be one approach to fight infections such as C difficile and tackle antibiotic resistance. Current antibiotics have a profound effect on the composition of the microbiota, and their overuse is linked with an increase in antibiotic-resistant pathogens.[20] **Eligo Bioscience** have developed a CRISPR-based microbiome precision engineering technique which can use gene-edited bacteriophage capsids, taken with a probiotic, to discriminate between close bacterial strains and selectively eradicate harmful bacteria from the microbiome.

Though the role of the gut microbiota on local gastrointestinal conditions is well-researched and has great potential for treatment, there is also an array of systematic diseases affected by gut dysbiosis, including autoimmune and neurological disorders (e.g. multiple sclerosis, Parkinson's disease), cancer and respiratory ailments (e.g. asthma, COPD) for which research and development is less well-advanced. In particular, the brain-gut-microbiota axis represents a paradigm shift in neuroscience and provides a novel target for treating diseases like depression, autism and Parkinson's disease.[21] The actions of microbial metabolites on the central nervous system and brain, and the importance of immunological mediators, are crucial to understand for future therapeutic development, and for which more advanced diagnostics will play a key role in generating better targets.[22]

One factor which needs to be further addressed for industrial applications of the microbiome is the complex interactions of the human microbiome with the human metabolome and epigenome. In particular, knowledge is still lacking on the potential interplay between the human microbiome and the action of prescribed therapeutics. For example, the gut

[20] Clemente *et. al.* (2012) The Impact of the Gut Microbiota on Human Health: An Integrative View. *Cell*, 148, 1258-1270

[21] Dinan & Cryan. (2016) The Microbiome-Gut-Brain .Axis in Health and Disease. *Gastroenterology Clinics of North America*, 46, 77-89

[22] Zeus Capital. (2017) *The Gut Microbiome*

adsorption of certain orally administered drugs may be affected via their metabolism by gut microbiota and their interactions with bacterial metabolites, thereby contributing to individual variations in drug safety and efficacy. The gut microbiome in turn depends on individual diet, health status (including immune function), as well as individual genetic and epigenetic profiles.[23] With an increasing number of research articles and reviews on the topic, there is reason to believe that the gut microbiota is moving toward centre stage in drug safety studies. Biotransformations of drugs/drug metabolites performed by the gut microbiota are now understood for a range of compounds, but the extent of gut microbial metabolism is probably underestimated as this aspect of drug biotransformation is not routinely investigated.

Greater understanding of the human microbiome and drug metabolism, alongside microbiome-based drug discovery platforms in combination with new diagnostic capabilities, will play a major role in enabling a strategic shift in the healthcare industry towards an era of personalised medicine and nutrition.[16]

FOOD & NUTRITION

Links between diet, microbiome activity and population, and the nutrition value of food is well-established, though complicated by numerous genetic and environmental factors.[24] Probiotics are the most frequently used and well-known product segment of the human microbiome industry, as a result of "friendly bacteria" featured in numerous foods aimed at improving gut and digestive health. Food and drink comprises almost three quarters of the $35 billion probiotics market[11], overlapping heavily with the nutraceuticals industry.[10] Key food types include dairy products (yoghurt, cheese, milk), non-dairy beverages (probiotic fruit and vegetable drinks, wine, beer), infant formula, baked goods and other products (cereals, pickles, some meat products). Dietary supplements (e.g. capsules, tablets, powder, liquids) capture 17.8% of the probiotics market.

However, in the precision medicine era developments in the industry are moving towards personalised nutrition (through greater understanding of genetic and environmental interactions with food) and microbiome-based medical foods.[1] Probiotic foods and dietary supplements are non-specific products, mostly containing lactobacillus, intended to enhance wellness among healthy adults. Similarly, nutraceuticals are nutrients, foods, or parts of foods that provide health benefits and may combat disease. Medical foods, however, are formulated specifically to manage nutritional deficiencies that affect disease progression, are tested for effectiveness in clinical trials and are used under medical supervision.[25]

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[23] Gurwitz (2013) The Gut Microbiome: Insights for Personalized Medicine. *Drug Development Research,* 74, 341-343

[24] Turnbaugh *et. al*. (2009) The Effect of Diet on the Human Gut Microbiome: A Metagenomic Analysis in Humanized Gnotobiotic Mice. *Science Translational Medicine,* 1, 6-14

[25] Today's Dietician. (2012) *Medical Foods — Learn How They Manage Disease and Ways to Incorporate Them in Practice*

Personalised medical food programs are thought to be effective in helping manage Alzheimer's disease, heart disease, IBS, diabetes and depression, among others.[13] **Nestlé Health Science** is currently using microbiome analysis to develop personalised programs for conditions like epilepsy and intestinal disorders that are tailored to specific genetic profiles. A study from 2015 demonstrated that sequencing of the gut microbiome allowed the design of a personalised nutrition plan to predict which food items should be associated with healthy and unhealthy glycaemic responses for each individual, resulting in significantly improved glucose homeostasis.[26] Further studies of the gut microbiome have shown that different probiotic formulations have been successfully applied to help prevent or treat patients with a range of gastrointestinal diseases[27], in particular for young children, which, along with the elderly, is a key area of interest for interest for novel developments in medical foods.[1] For instance, recent immunotherapy studies[28] have demonstrated successful treatment of peanut allergies using a small dose of protein powder with a probiotic. **Second Genome** (USA), in partnership with **King's College London**, is one example of a company now conducting skin and gut microbiome profiling to investigate if the early introduction of allergenic foods into an infant's diet can prevent the development of food allergies in children.[29]

DIAGNOSTICS

There are four major applications for microbiome diagnostics[5]:

- 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

The development of microbiome diagnostics involves full sequencing and mapping for total bacterial gene content that characterizes the personal metagenome associated with a disease phenotype. Advancements in DNA sequencing technologies along with falling costs has given

[26] Zeevi *et al.* (2015). Personalized nutrition by prediction of glycemic responses. *Cell,* 163, 1079–1094

[27] Hsieh & Versalovic. (2008) The Human Microbiome And Probiotics: Implications For Pediatrics. *Current Problems in Pediatric and Adolescent Health Care,* 38, 309-327

[28] https://www.mcri.edu.au/news/peanut-allergy-cure-one-step-closer-after-8m-cash-boost-melbourne-treatment

[29] http://www.secondgenome.com/news/second-genome-partners-kings-college-london-evaluate-influence-microbiome-landmark-eat-study/

rise to enhanced capabilities for sequencing large data sets, which has had a transformative effect on microbiome research and metagenomics (the culture-independent study of the collective set of genomes of mixed microbial communities). High-throughput, massive parallel sequencing (or next-generation sequencing; NGS), adapted from the philosophy of shotgun sequencing, has demonstrated the capacity to sequence DNA at unprecedented speed, thereby enabling a host of novel biological applications.[30] Though most interest is in the human health space, patent searching and market research shows that metagenomics is beginning to find a wide variety of applications in a number of different fields, summarised in the Figure below.

There are currently five major next-generation platform families used as the basis for sequencing in diagnostic industrial applications, summarised in the Table below, adapted from Hodkinson & Grice (2015).[31]

Platform Family	Clonal Amplification	Chemistry	Highest Average Read Length
Roche/454	Emulsion PCR	Pyrosequencing (seq-by-synthesis)	700 bp (paired-end sequencing available)
Illumina	Bridge amplification	Reversible dye terminator (seq-by-synthesis)	300 bp (overlapping paired-end sequencing available)
SOLiD	Emulsion PCR	Oligonucleotide 8-mer chained ligation (seq-by-ligation)	75 bp (paired-end sequencing available)
Ion Torrent	Emulsion PCR	Proton detection (seq-by-synthesis)	400 bp (bidirectional sequencing available)
PacBio	N/A (single molecule)	Phospholinked fluorescent nucleotides (seq-by-synthesis)	8,500 bp

The massive amounts of data produced by NGS presents a significant challenge for data storage, analyses, and management solutions. Advanced digital and bioinformatic tools are essential for the successful application of NGS technology in microbiome diagnostics. Bioinformatics associated with next-generation sequencing can typically be divided into five main categories: sequence pre-processing, sequence assembly, community characterisation, hypothesis testing (within a statistical framework), and data visualization.[31] Some companies involved in therapeutics development also own proprietary diagnostic technology. **Second Genome**, for example, has developed a proprietary data analytics platform that enables identification of novel mechanisms in microbe-microbe and microbe-human interactions. Using these microbial data points, the company anticipates the issues of dysbiosis present due to the prevalence of metabolic and inflammatory diseases.[19]

[30] Zhang *et. al.*(2011) The impact of next-generation sequencing on genomics. *Journal of Genetics and Genomics,* 38, 95–109

[31] Hodkinson & Grice (2015) Next-Generation Sequencing: A Review of Technologies and Tools for Wound Microbiome Research. *Advances in Wound Care*, 4, 50-58

Overview of potential metagenomics applications

A gap in the market regarding metagenomics is the simultaneous detection of all microorganisms in a clinical sample without a priori knowledge of their identities. Metagenomic approaches have the potential to detect and quantify both known and unknown pathogens and are beginning to be used in the case of novel pathogen detection but are not used on a broad scale.[32]

The combination of big data, advanced diagnostic and processing capabilities and the falling costs of application has changed how genomic etiology of disease is used to diagnose and develop treatments for many diseases.[33] The emerging information is beginning to provide insight into mechanisms of disease and how to apply this to personalised medicine and companion diagnostics. This is particularly important for diseases currently without known mechanisms of their development.

Though metagenomics is a powerful tool for microbiome analysis, a broader multi-"omics" approach to microbiome diagnostics will become more common in future industrial applications. It has been argued that solely using metagenomics to study a microbiome is limited in value since the reference databases used to classify and label bacteria are limited to what has been catalogued.[34] Current methods typically either discard reads from undocumented microbes or label them based on the closest documented microbe from the database. A more comprehensive picture is obtained using additional omics approaches such as metatranscriptomics and metabolomics. Indeed, the launch of the Integrative Human Microbiome Project (iHMP) led to the creation of the first integrated dataset of biological properties from both the microbiome and the host using multi-omics technologies in 2015.

By focusing on what genes are expressed by an entire microbial community, metatranscriptomics sheds light on the active functional profile of a microbial community. The metatranscriptome provides a snapshot of the gene expression in a given sample at a given moment and under specific conditions by capturing the total mRNA, and allows the monitoring of gene expression patterns. Metabolomics is the comprehensive analysis by which all metabolites of a sample are identified and quantified. The metabolome is considered the most direct indicator of the health of an environment or of the alterations in homeostasis (i.e., dysbiosis). The metabolomic profile associated with the microbiome may reveal strong dependences on environmental factors (e.g., diet, exposure to xenobiotics, and environmental stressors), providing valuable information not just about the characteristics of the microbiome but also about the interactions of the microbial community with the host environment. Furthermore, the application of metabolomics to drug discovery represents a promising avenue for personalised medicine within the microbiome space.[35] The integration of multiple omic datasets is a problem that researchers are just beginning to tackle, and may

[32] Miller *et. al.* (2013) Metagenomics for pathogen detection in public health. *Genome Medicine*, 5, 81

[33] http://macrogenlab.com/2017/02/21/advances-in-microbiome-diagnostics/

[34] Aguiar-Pulido *et. al.* (2016) Metagenomics, Metatranscriptomics, and Metabolomics Approaches for Microbiome Analysis. *Evolutionary Bioinformatics*, 12, 5-16

[35] Beger *et. al.* (2016) Metabolomics enables precision medicine: ''A White Paper, Community Perspective''. *Metabolomics*, 12, 149

be one area of future industrial diagnostic application which could lead to predictive modelling.[34]

Companies such as **uBiome** (USA) and **EpiBiome** (USA), currently offer diagnostic DNA sequencing platforms to allow consumers to identify bacteria in their stool samples, for a fee. **Map My Gut** (UK) is a similar microbiome testing company offering their platform through accredited US healthcare practitioners, with test results explained by the clinician. **Map My Gut** also shares test results with researchers to improve research towards understanding how food and human microbes affect health.

Map My Gut and **uBiome** diagnostics are still undergoing beta testing, but analysis by Frost and Sullivan[19] notes that from a clinical standpoint, such tests will not be a disruptive technology as they do not promise any clarity in making medical decisions: the data is used only to get a better understanding of microbiome compositions and possibly relate that data to some minor day-to-day GI discomfort. However, the technology may be more effective for the development of personalised nutrition programs. Indeed, **DayTwo** (Israel) now offers a similar diagnostic which uses metagenomic sequencing to provide each consumer with a personalised nutrition plan. This technology is also in the beta testing phase.

There is a growing interest among researchers for instruments for the collection of biopsy-like samples from the bowel. This would allow the collection of the true mucosa-associated microbiome since optimal stool sample collection for analysis of genomic, transcriptomic or proteomic biomarkers can be hindered by variations in sample collection, handling and processing techniques. Novel diagnostic platforms in this space are also likely to have a good growth potential. **Origin Sciences** (UK) is one company developing sampling devices through its approved OriCol platform, which is also currently being tested for the validation of Calprotectin as a biomarker for the differential diagnosis of inflammatory bowel diseases.

Given the drive towards stratified (and ultimately personalised) medicine and companion diagnostics, the unique nature of the human gut microbiome offers an interesting new source of biomarkers to distinguish between patients and diseases. It may be possible to map microbial fingerprints and define microbial-derived biomarkers that identify individuals at risk of disease, better enable diagnosis of existing conditions and monitor efficacy of treatment.[14] The Paris-based stratified medicine company, **Enterome**, which was founded on research arising from the MetaHIT Project, is developing biomarker diagnostic tests for chronic conditions linked to changes in gut microbiota such as type-2 diabetes and irritable bowel disorders. These are expected to launch alongside microbiome-based drugs for ulcerative colitis and Crohn's disease. Gothenburg-based **MetaboGen** is a biomarker and personalised treatment company offering data-driven mapping of how the gut microbiota affects metabolism to help industry develop the next generation of pharmaceuticals and functional food.

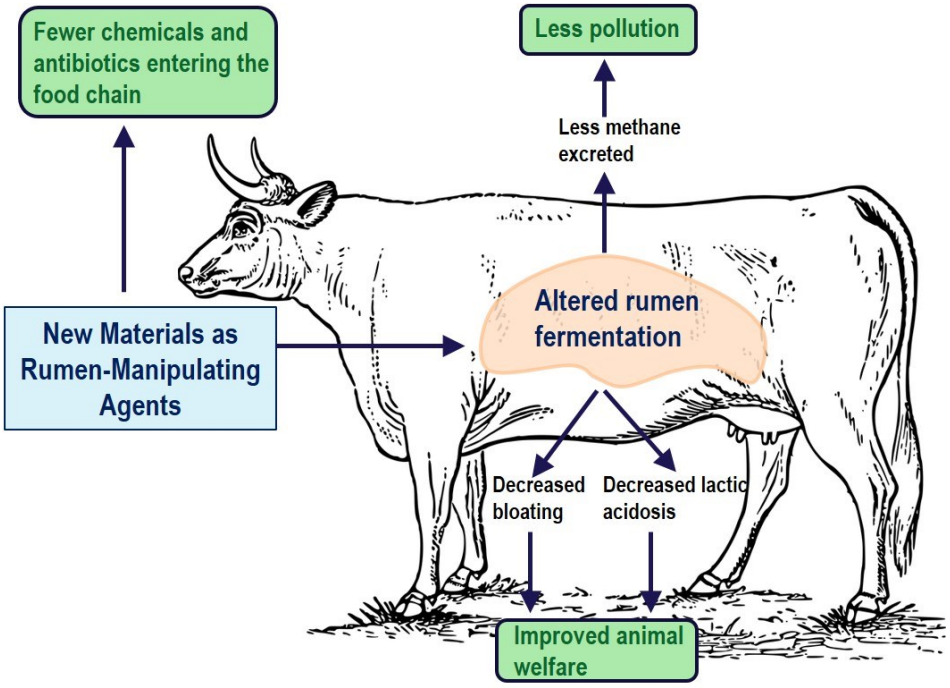
For other non-gut microbiome applications, important diagnostic areas are women's health and dental caries. The current microbiome diagnostics assays for women's health involve predicting early pre-term labour and prognostic tests for understanding the changes in the vaginal microbiome through the monthly menstrual cycle and through the reproductive life. **Whole Biome** (USA) is a leading company active in this space. It uses specialised analytics to integrate high-throughput and long read-length DNA sequencing data that generates microbiome profiles highlighting imbalance in the vaginal microbiome. **C3J Therapeutics**

(USA) is developing a collection kit and an analysis report that describes the microbiome composition in the dental caries sample, expected to be used in conjunction with microbiome drugs for the dental caries infection.

ANIMAL HEALTH

The animal microbiome field is currently very active at the early-stage and research level, but is still in its infancy industrially. 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. Poor health reduces productivity of farmed livestock and can lead to diseases entering the human food chain. Nutrition is fundamental to health and wellbeing in livestock and therefore knowledge gained through microbiome studies could open up attractive opportunities.

The ban on prophylactic antibiotic use in farming has triggered intense research into natural alternatives that can come in the form of feed additives. The overall global market for feed additives was $13.5 billion in 2016 and is forecast to grow to $14.5 billion by 2021 with a 1.3% CAGR.[36] Production animals hold the majority of the market share (82%) while companion animals hold 18% of the market. Fish feed is also an expanding market, worth in excess of £5 billion and with an annual growth of 10%, as aquaculture steps up to replace the shortfall between demand and supply from natural fisheries. The market for seafood feed additives is estimated at around £1 billion.[37] Feed additives could also lead to reduced methane production in ruminants, offering significant benefits to the environment, as summarised in the Figure below.



Overview of the benefits of microbiome-based feed additives for ruminant animals

[36] BCC Research. (2017) *Global Markets for Animal Therapeutics and Diagnostics*

[37] Markets And Markets. (2011) *Global Animal Feed Additives*

According to an industry report published by Research And Markets,[38] the global probiotics in animal feed market is poised to grow at a CAGR of 7.9% over the next decade, to reach approximately $6.37 billion by 2025. Demand extends beyond the livestock market to pets and the equine industry.

The pet health care market is a viable target group for prognostic/diagnostic tools that can spot pets at risk of diet and genetic predisposition to health problems. The market for animal diagnostics is expected to exceed $4.5 billion by 2021 growing at a CAGR of 8.4%.[36] Today's pets are prone to suffering health conditions not so dissimilar to that of their owners (obesity, arthritic conditions, depression, heart disease), with several specially formulated diets to address these. The pet food market was worth around $66 billion (2010) and is expected to reach $96 billion by the end of 2017.[39]

Overall spending in the pets market spending has remained robust, supported by the "humanisation" of pets, new product development and increased insurance coverage, suggesting this is a viable long-term market. Pet owners have demonstrated a willingness to buy products aimed at improving their pets' digestive health. Market researcher Packaged Facts reported that spending by Americans on pet supplements is expected to increase from $750 million a year in 2014 to $1 billion by the end of 2017, while an estimated 7% of pet products currently contain probiotics.

Microbiome research could also lead to new animal pharmaceuticals, which represent a lucrative and growing market. The global market for animal pharmaceuticals was valued at $17.2 billion in 2016 and is expected to exceed $21.5 billion by 2021 on a 4.5% CAGR.36 Companion animals and livestock represent 51% and 49% of the market respectively, providing a significant market opportunity for both subsectors. Geographically the US dominates (38% market share), followed closely by Europe (33% market share), although emerging markets represent an important growth driver for the market as a whole.

SUSTAINABLE FARMING

As the global demand for milk and meat continues to increase, with beef and dairy cattle contributing greatly in this regard, the environmental impacts of these industries are being highly scrutinised. Farming contributes significantly to global warming (through methane production and the use of fossil fuel for farming) and environmental pollutions and hence technologies that can improve efficiency are sought after.

The production of methane, which is the principal method by which ruminant livestock dispose of hydrogen, is the main cause of concern. Globally, ruminant livestock produce about 80 million metric tons of methane annually, accounting for about 28% of global methane emissions from human-related activities.[40]

[38] Research And Markets. (2017) *Global Probiotics in Animal Feed Market Analysis & Trends - Industry Forecast to 2025*

[39] Global Petfood Sales, Euromonitor International

[40] US Environmental Protection Agency website

Due to the increased meat consumption in rapidly developing emerging economies, meat production will have to double by 2050, which could result in substantial environmental impact.[41]

Researchers are now exploring novel approaches to manage livestock methane emissions. Because energy is lost through the production of methane, these strategies may not only reduce the carbon footprint of ruminant livestock production, but may increase production efficiency. Researchers suggest that studying the interaction between food and the gut microbiome, could offer a means to mitigate the negative consequences of the intensification of modern farming. Additionally, methanogens also are present in the human GI tract and have been associated with several disease states, including constipation, colorectal cancer, and inflammatory bowel diseases.

Europe is already focusing on this potential of animal microbiome studies under the EU FP7 Project RuminOmics. This €7.7 million, 4-year project is a collaboration of 11 European organisations and will use state-of-the-art technologies to understand how the ruminant microbiome is controlled by the host animal's genetics, its diet and how this impacts on methane production. The outputs are expected to lead to new knowledge, tools and technologies that will help the livestock industry reduce the environmental impact from methane and nitrogen emissions.

ANIMAL HEALTH AND WELFARE

As with humans the interactions between animals and microbes play an important role in animal health, susceptibility to infection and the response to a treatment. However, there is an underlying complexity of these interactions that is currently not fully understood. There is a lack of comprehensive studies in the veterinary literature with regards to the effect of microbial populations on the health, disease susceptibility and metabolic changes in animals. Examining host and microbial interactions in the different organ systems in animals can help understand the pathophysiology of diseases, how the microbiome interacts with the immune system and how it contributes to the initiation and/or aggravation of diseases. This could lead to the development of therapies aimed at modulating microbial communities and their produced metabolites.

Today's pet dogs and cats are afflicted by many of the same complex diseases present in humans, (e.g. obesity, diabetes, inflammatory bowel diseases), which may be influenced by diet and gastrointestinal microbiota. Research suggests that the animal microbiome impacts the nutritional supplementation, tolerance to environmental perturbations, and maintenance and development of the immune system. Given their proximity to humans, microbiome research in companion animals may not only lead to improved pet nutrition and veterinary care, but may improve understanding of host–microbe interactions, with regards to human metabolism, diseases and public health at large.

Prevention and/or early identification of disease or other indicators of health is key in farming. With the rise of new molecular platforms it is possible that microbial indicators of "wellness" could be used to monitor domestic animals and identify those at risk. Species-specific

[41] UN Food and Agriculture Organisation figures

therapeutics targeting gut microbes could offer tractable targets and solutions to treat animal disorders without potential human risk.

In addition to their use in human health applications, microbiome therapeutics can also be used to improve animal health. For example, the **Penn Vet Centre** for Host-Microbial Interactions (CHMI) is investigating the role of the microbiome on animal health and how viruses, parasites and bacteria influence animal health.

In animal health, beneficial microbes are reducing or replacing antibiotics. Unlike antibiotics (which have a bactericidal effect), direct-fed microbials act through alterations to the intestinal microbiome, enhancement of intestinal efficiency, and modulation of the host immune response. A recent review identified approximately 1,250 research papers on the use of direct-fed microbials for livestock across seven journals.[42] Some companies are already marketing such products. For example, **EpiBiome** offers phage therapy providing targeted deletion of specific strains within the microbiome. **EpiBiome**'s platform can produce phage cocktails to treat mastitis in cows.

Demand for probiotics in animal feed is being met by a few companies, such as the multinational **Alltech**, whose Bio-Mos product, which derives from a specific yeast strain, helps increase milk yields in dairy cattle and overall animal performance. In 2012, **Biomar** (UK) launched the first fish feed range (LARVIVA) containing probiotics for all aquaculture species to protect fish larvae and small fry against developing deformities. All LARVIVA diets contain Bactocell®, a probiotic approved by the EFSA that offers high growth, healthy and stable rotifer cultures.

More studies are being published regarding the relationship between an animal's diet and its microbiome, including by researchers at large industry players such as **Nestlé**'s Purina Petcare.[43] The provision of diagnostic DNA sequencing platforms to allow consumers to identify bacteria in their stool samples has also spread to the animal microbiome industry. The screening company **AnimalBiome** (USA), like **uBiome** and **EpiBiome** in the human health space, offers a service that allows pet owners to understand the state of their pet's gut bacteria and make corresponding diet and lifestyle choices.

ENZYME DISCOVERY

Microbes in the animal gut, as with microbes in other parts of the body, can serve as a good source of novel enzymes and active molecules with applications in multiple industrial markets. Microbes of the gut are of particular interest as they are known to assist with the degradation and digestion of a range of food and materials. For example, microbes capable of digesting particular plants could be of great value to the biofuel industry. Such projects are already underway worldwide.

[42] Buntyn *et al.* (2016). The Role of Direct-Fed Microbials in Conventional Livestock Production. *Annual Review of Animal Biosciences*, 4, 335-355.

[43] Lit *et al*. (2017). Effects of the Dietary Protein and Carbohydrate Ratio on Gut Microbiomes in Dogs of Different Body Conditions. *mBio*, 8, 1

Through a massive-scale DNA sequencing effort (of 270 billion pieces of genetic code), researchers at the **U.S. Department of Energy Joint Genome Institute**, with support from the **Energy Biosciences Institute**, have characterized the genes and genomes of plant-digesting microbes isolated from the cow rumen.[44] A significant faction of the 30,000 genes identified could offer novel enzymes for biofuel researchers.

Metagenomic approaches as well as sequencing of more animal genomes is expected to greatly assist in mining novel enzymes with industrial applications from animal gut microbiomes.

LIVESTOCK PRODUCTIVITY

Many of the challenges facing today's producers (particularly swine), such as minimising dysbiosis, maximising performance and feed efficiency, and maintaining human food safety, pertain to the gastrointestinal microbiota and their management. Pre- and pro-biotics along with direct-fed microbials could offer solutions but require significant investment in terms of microbiome research and could be met with stringent regulations in many countries around the world.

The resources required by livestock to protect the body from pathogenic bacteria and the toxins they may produce can be costly. The ban on antibiotic growth promoters has created a need for alternative approaches and an increased interest in feeds and feed supplements that can boost the innate health and growth potential of livestock. Engineering the microbiome of production animals could greatly assist in this field.

Feed enzymes, such as phytase, amylase, non-starch polysaccharide (NSP)-degrading enzymes, and proteases, have been used to promote gut health in swine and poultry by improving substrate digestion, increasing production of prebiotics from dietary NSPs and reducing anti-nutritive factors.[45] Thus far, feed enzymes have demonstrated positive effects in promoting animal growth.

Probiotics administration is also effective for engineering animal microbiomes. Besides treating infectious disease, their administration can be used to promote growth performance. For example, administration of *B. subtilis* CH16 increased daily weight gain and reduced food conversion rate in chickens.[46]

[44] Hess, M *et al.* (2011) Metagenomic discovery of biomass-degrading genes and genomes from cow rumen. *Science,* 28, 463

[45] Kiarie *et al.* (2013). The role of added feed enzymes in promoting gut health in swine and poultry. *Nutrition Research Reviews*, 26, 71–88.

[46] Nguyen *et al.* (2015). Isolation and characterization of Bacillus subtilis CH16 strain from chicken gastrointestinal tracts for use as a feed supplement to promote weight gain in broilers. *Letters in Applied Microbiology*, 60, 580– 588.

PLANTS AND AGRICULTURE

All indicators suggest that the use of and market for microbiome tools and microbial products in agriculture (including the whole microbial community as well as single species products) is growing rapidly and has great potential to create entirely new market opportunities and boost economic growth.

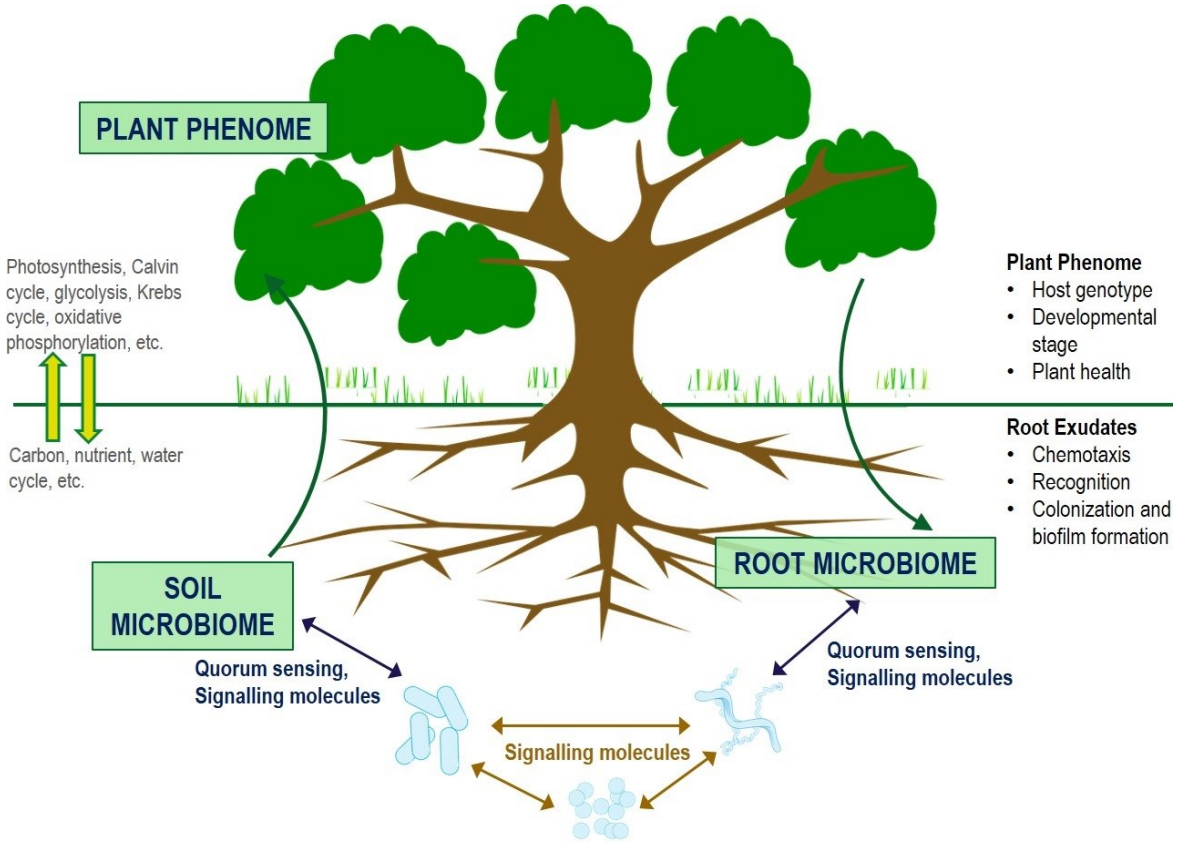
Research by **Monsanto** estimates a $2.9 billion market value for agricultural biologicals as a whole, citing approximately $1.8 billion to microbials. Additionally, within biopesticides, which account for over $2 billion annually, microbially-derived products account for more than 50% of the market.[47] Some market estimations estimate biological sales for agriculture in general could exceed $5 billion within the decade.[48]

FOOD PRODUCTION & FOOD SECURITY

A model of the phytobiome (the plant and soil microbiome) is shown in the Figure below. The manipulation of plant and environmental microbiomes is becoming an increasingly popular tool to sustainably increase farm productivity for food and nutrient security. In order to meet the continuously increasing demand for food, farm productivity must increase by 70% by 2050. To further exacerbate the issue, this significant increase in food production must come from shrinking arable lands. Continuous land degradation means that farm productivity targets need to be met from 8-20% less arable land. In addition, climate change, the high cost of fertilizers, and the decline in soil fertility means approaches to utilise available natural resources are highly sought after. Harnessing the plant and soil microbiome is increasingly being recognized as one such approach. Microbes could help to improve soil fertility, improve nutrient uptake, strengthen plant resistance to insect pests and diseases, and help plants to tolerate temperature fluctuations.

[47] Singh. (2017) Creating new business, economic growth and regional prosperity through microbiome-based products in the agriculture industry. *Microbial Biotechnology*, 10, 224-227

[48] Global Engage. (2016) *Exploring The Microbiome In The Agricultural Industry*



Overview of the plant and soil microbiomes

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. So the immediate key to success is choosing the right discovery and product development approach. Market penetration is dictated by access to existing distribution channels to end users (growers), and by ease of adoption for those end users. Most biological products focus on increasing yield by enhancing plant health and mitigating stress (both biotic and abiotic), however, in many cases the market opportunity lies in complementing traditional chemistries by reducing the need for agrochemical application.

Indigo Agriculture, a U.S.-based agbio company, is a characteristic example of a company active in this new field. **Indigo** exploits the knowledge they have obtained by sequencing over 40,000 microbes to create microbiome-engineered seed-coatings that promote plant growth and provide pest protection. The company has released data from its first commercial product, Indigo Cotton, which is designed to stimulate crop growth in low-water conditions by incorporating beneficial microbes to the plant through seed treatment. When the seed germinates, it takes the microbes up inside the plant, where they multiply. **Indigo** claims that their coated seeds yield 10 per cent more crop than uncoated seeds when grown under water stress.

The industry has had some successes with a number of microbial products in the market that provide measurable benefits to crop productivity. Some examples are:

- **Bayer Crop Science** markets Poncho/Votivo, a seed treatment that prevents early-season damage to seedlings and allows roots to develop before pests attack them.

The formulation incorporates a systemic insecticide and a *Baccilus thuringiensis* additive to protect corn, soybeans, and cotton against pest such as black cutworm, wireworm, and aphids.

- **FMC** and **Chr. Hansen** have co-developed Nemix C, a blend of *Bacillus subtilis* and *Bacillus licheniformis* for the treatment of sugarcane roots. Recently released in Brazil, Nemix C increases yields and helps plants resist attack from nematodes.
- **Novozymes**'s Met52, a bioinsecticide fungus containing spores of the pathogenic fungus *Metarhizium anisopliaem*, is already used on millions of acres.

However, there is a belief that with a better understanding of complex plant-microbe interactions and with recent technological advancements, microbiome research can deliver more effective biological agricultural solutions. Although it will be many more years before microbiome-based solutions become more efficient than traditional agrochemicals, increasing investment by both government agencies and industry giants, combined with a large number of specialist start-up companies suggest that microbiome products for agriculture will exponentially increase in the near future, propelled by sophisticated new technologies (e.g. next-generation sequencing) as well as by the increasing number of complete microbial genomes on public and private databases.

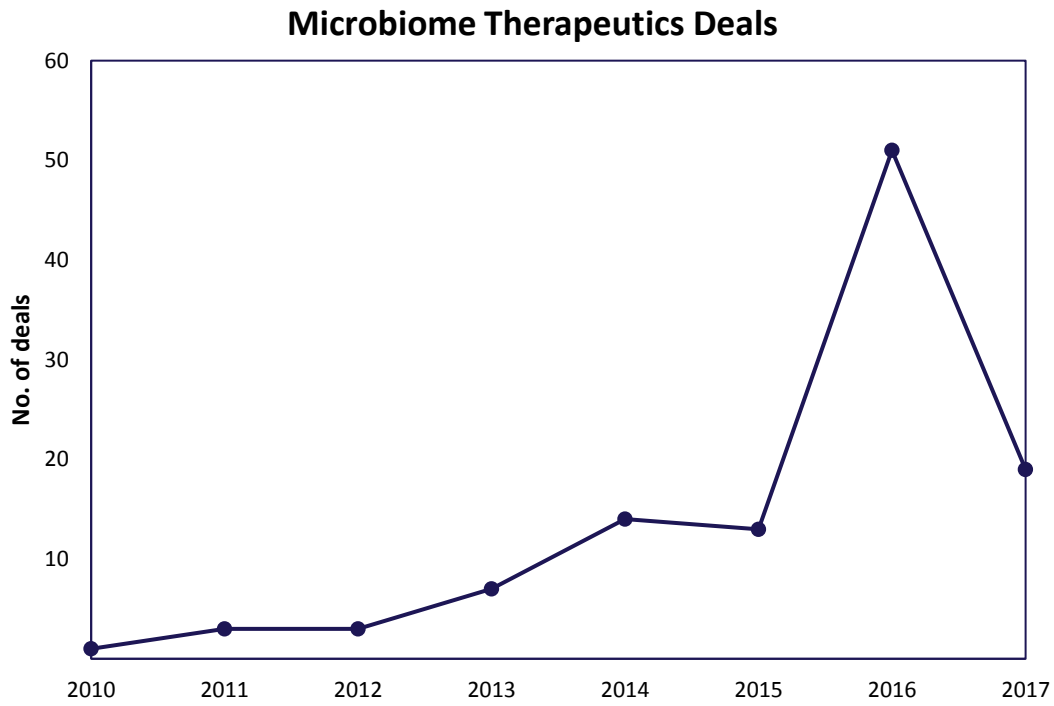
It is likely that the movement toward biologicals, biopesticides and plant biostimulants that harness the plant and soil microbiome will follow a similar trajectory to that of the pharmaceutical sector's cell and gene therapy markets, in what is a more 'personal' approach to treatment. Future industrial applications might see crop protection and growth enhancement that begins with sequencing the microbiome of a specific cropland and an accurate determination of the nutritional status of a field, followed by an individual approach to treatment. This could mean anything from a unique coating on the seeds that infuses crops with specific bacteria, fungi, or other microorganisms, all the way to the integration of microbial inoculants into farming practices. Such a model envisions that farmers optimise their yields by capitalising on microbial traits and, at the same time, reduce costly and unsustainable inputs of agrochemicals.

DEALS

A combination of internet-based searching and deal information from subscription databases was used to collate information on collaborations, licensing agreements, investments and acquisitions in the microbiome industry. There have been numerous deals completed, which have been further categorised by industry sector, technology area and year of completion in order to analyse the data. Details of the identified deals are listed in reverse chronological order in Appendix 1.

HUMAN HEALTH AND WELLBEING

By far the most common field for deal-making is therapeutics for the human gut microbiome, related to projects in the areas of gastrointestinal disorders, cancer, and metabolic disorders. The scope includes the discovery and development of biomarkers, new drug targets and development of therapeutics. The deal rate in the sector has rapidly increased over the last two years, as shown in the Figure below adapted from GlobalData (2017) (note that deals are only shown for the first quarter of 2017).



Multinational healthcare companies are increasingly partnering with smaller biotech companies and start-ups to develop microbiome therapies. These partnerships are the source of the most significant deals in the microbiome industry. For example, **Seres Therapeutics** (USA) entered into collaboration with **Nestlé Health Science** in January 2016 under the following terms:

- **Nestlé** obtained an exclusive, royalty-bearing license to develop and commercialise products for C. difficile infection and irritable bowel disorder.
- $120 million in upfront fees
- $295 million in milestone payments for development
- $365 million in regulatory payments
- $1.1 billion for commercial milestones

The total deal has the potential to generate up to $2 billion for **Seres Therapeutics**, which is one of the few microbiomics company to have gone public, with a $134 million IPO in 2015. **Nestlé Health Science**, like **Danone** and other key players in the "nutritional therapies" industry, has also been consolidating its position across the wider sector with a number of strategic acquisitions including **Prometheus Labs** (US; developing diagnostics for various gastric disorders) and **VitaFlo** (UK; innovative specialised clinical nutrition products for specific conditions such as kidney disease). **Nestlé** has also purchased a share in **Accera**, which makes a food supplement for the treatment of mild-to-moderate Alzheimer's disease.

The deal terms of two other significant licensing agreements are summarised below:

- **Allergan** entered into a licensing agreement with **Assembly Biosciences** (USA), a clinical stage biotech company
    - January 2017
    - **Allergan** obtained worldwide rights to preclinical microbiome compounds
    - Treatment of ulcerative colitis and Crohn's disease
    - $50 million upfront fee
    - Undisclosed milestone payments
- Boston start-up **Vedanta Biosciences** announced a licensing deal with **Janssen Pharmaceutical** (**Johnson and Johnson**)
    - January 2015
    - Development of a drug candidate (VE202) for inflammatory bowel disorders
    - Upfront and milestone payments of $241 million
    - Undisclosed potential royalty payments

Other significant microbiome industry collaborations include **Enterome**-**Bristol Myers Squibb**, **Enterome**-**Abbvie**, **Synlogic**-**AbbVie**, **Enterome**-**Takeda**, **Nubiyota**-**Takeda**, **Finch Therapeutics**-**Takeda**, **Second Genome**-**Janssen** and **Second Genome**-**Evotec**.

In the microbiome diagnostics industry there has been some industry collaboration, though contrary to the therapeutics industry, these are usually strategic partnerships between two smaller companies with a mutual interest in advancing their respective technologies. For example, in 2015 **uBiome** entered into an agreement with **PicnicHealth** (USA), a provider of medical records, to advance research on the role of the microbiome in inflammatory bowel disease, using validated clinical data. Diagnosed participants receive a complementary **PicnicHealth** account as well as a complementary **uBiome** research kit. **Genewiz, Inc**. (USA), a genomic contract services provider, formed a joint venture with **Hy Laboratories Ltd**. (Israel) for the development of novel diagnostic panels for the determination of the gut microbiome

in obesity and diabetes. They will target the most relevant microbiota in the gut system through stool sample collection expertise at **Genewiz** and medical metadata provided by **Hy**. Also in 2015, **Origin Sciences Ltd** entered into a distribution agreement with **Metabiomics Corporation** for **Origin Sciences**' products for research into gastrointestinal diseases in the USA. Under the agreement, **Metabiomics** will develop, test, and commercialize the novel OriCol gastrointestinal sampling technology for clinical research and diagnostic applications and the OriCol Microbiome Sampling Kit, which has been designed for use in gut microbiome research, in the US market.

Venture capital firms in the U.S. and Europe have recently become active in the human microbiome industry. VC firms have invested more than $800 million in various rounds of financing since 2014. The major areas of interest are in microbiome drugs to tackle diseases like gastrointestinal disorders, cancer and diabetes. **Seventure Partners** (France) are one of the top firms, with investments in **TargEDys** (France), **Vedanta Biosciences** (USA), **Eligo Bioscience** (USA) and **Enterome** (France). **Flagship Ventures** has also invested in **Evelo Therapeutics** (USA) and **Seres Therapeutics**. Other firms active in the microbiome space include **New Enterprise Associates** (NEA) (USA) and **Orbimed Ventures** (USA). The venture capital arms of pharmaceutical companies **Roche** and **Pfizer** have also invested in **Second Genome**.

A number of academic institutions are currently collaborating with key industrial players – both small biotech companies and multinationals – on microbiome therapeutics in key disease areas, with six major partnerships announced in the first quarter of 2017 alone. Most academic-industrial deal terms are of undisclosed value, though the most significant disclosed partnership of recent years is the four-year $5.23m deal in 2015 between **4D Pharma** (UK) and the APC Microbiome Institute (APC) at **University College Cork** to research the potential applications of live biotherapeutics in relation to Autism Spectrum Disorders. The **University of Manchester** has also licensed its skin health technology to **OptiBiotix Health Plc**, who in turn invested $0.37m into a joint venture, **SkinBiotix**, in 2016.

Mayo Clinic is a major institution for industrial collaboration on gut microbiome therapeutic research, with partners including **Evelo Biosciences**, **Seres Therapeutics**, **Second Genome** and **OxThera**. It is also engaged in the development of microbiome diagnostic tests for women's health and predictive nutritional response with **Whole Biome** and **Enterome**, respectively. Other significant academic-industrial collaborations include **Weizmann Institute-Janssen-DayTwo**, **University of Chicago-Takeda**, **Elysium Health-Harvard University**, **Massachusetts General Hospital-Seres Therapeutics**, **University of Pennsylvania-Seres Therapeutics**, **Stanford University-uBiome**, **King's College-Second Genome**, **Stanford University-Vedanta Biosciences and University of British Columbia-Ritter Pharmaceuticals**.

ANIMAL HEALTH

Deal-making for microbiome technologies in the animal health sector is at a much earlier stage than in human health with less deals taking place and even fewer being disclosed. The most significant activity is still in the academic research space. There are a handful of companies/academic institutions attracting VC or industry partnerships, though on a much smaller scale than in human health. **AnimalBiome** secured $0.2 million in venture funding in 2016, while in 2017 **Bactana Animal Health** secured an undisclosed sum from **Sustainable Income Capital Management** and **Connecticut Innovations** to begin preparing for the

commercialisation of their animal microbiome products aimed at reducing antibiotic use. Connecticut-based start-up **Bactana** has also exclusively licensed cattle microbiome technology from **Cornell University** in 2016 for an undisclosed fee.

A strategic partnership was announced in 2015 between genomics data provider **Diversigen** (previously Metanome; Texas) and **Companion PBx** (New York), a company developing microbiome-based nutritional products for cats and dogs. The two companies are working together to develop a sample collection kit and web-based survey, which will be used to build a microbiome database containing information on thousands of healthy and sick dogs. In one of the earliest partnerships in the field (2012), Paris-based **Da Volterra** entered into a development agreement with a leading animal health company (not disclosed) to take its novel microbiome product DAV133 from human use into veterinary applications. Under the agreement, **Da Volterra** is responsible for the product optimization and preclinical studies, and the animal health company handle regulatory, pre-marketing, and final-development steps.

PLANTS AND AGRICULTURE

The deal-making landscape for plant and soil microbiome technologies is smaller than that of human microbiome therapeutics, but the structure is similar. There are a number of start-ups developing a few key technologies, backed by significant VC investments and/or partnerships with key multinational players in the industry.

In the largest agtech investment to date, **Indigo Agriculture** (USA) raised $100 million in Series C funding in 2016 as it launched its first commercial product, a microbial seed coating promoting water efficiency in cotton. The round was led by the **Alaska Permanent Fund**, with participation from **Flagship Ventures**, who created the company in 2014 and who had previously invested $56 million in **Indigo** in 2016.

Other start-ups in the field include: California-based **BioConsortia**, which is developing microbial consortia for increasing agricultural yields and in 2016 raised a $15 million Series B round from **Khosla Ventures** and **Otter Capital**; **Biome Makers** (USA), an ag bioinformatics start-up for the wine industry which has raised $2.2 million in seed funding from global investment firm **Viking Global Investors** and genomics company **Illumina**'s accelerator in 2016; **NewLeaf Symbiotics** (USA), which is focused on the commercialisation of beneficial plant bacteria and in 2014 closed a $17 million Series B round of financing; and **Pivot Bio** (USA) which completed a $16 million Series A round in 2016 to map the dynamics of the plant microbiome and evolve beneficial traits .

In 2016, **AgBiome** (USA), which is using plant microbiomes to create innovative products for agriculture, was awarded a multi-year funding grant by the **Bill & Melinda Gates Foundation** to help African sweet potato farmers combat the sweet potato weevil. **AgBiome** also raised $34.5 million in 2015 from investors led by the **Gates Foundation** and, in an indication of multinational agbio company involvement in the microbiome field, the venture capital arms of **Syngenta**, **Monsanto** and **Novozymes**.

In 2016 **Monsanto** (USA) and **Novozymes** (Denmark) created the **BioAg Alliance**, a partnership focused on testing thousands of bacteria isolated from soil around the world to catalyse the development of new microbial solutions for agriculture. **Monsanto** also acquired selected assets of **Agradis**, a company that identifies microbes to enhance crop productivity, for an

undisclosed sum in 2013, and in 2016 entered into an undisclosed multi-year research agreement with **Second Genome** to develop microbiome-based insect control tools.

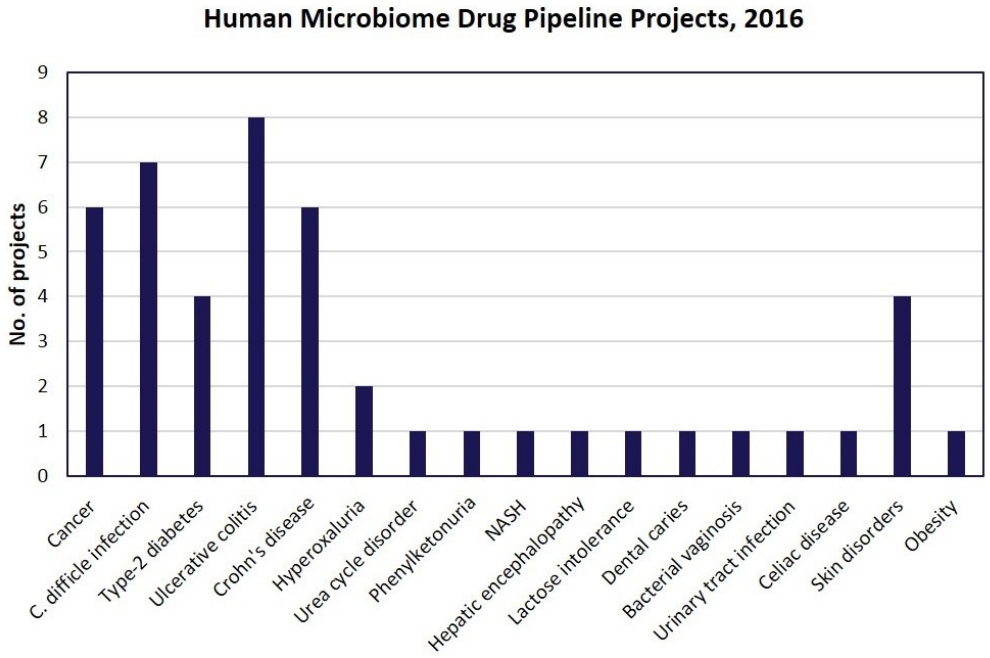
In 2015, **DuPont** acquired the California-based microbiome discovery company, **Taxon Biosciences** Inc, for an undisclosed sum. There are also signs that **Bayer Crop Science** will be more involved in the plant microbiome field in the future.[49] **Bayer** has demonstrated interest in the wider market sector by acquiring **AgroGreen**, a supplier of bionematicides and biofungicides, in 2009 as well as filamentous fungi expert, **Prophyta**, in 2013. **Bayer** has also acquired **Biagro Group**, an Argentina-based maker of inoculants and growth-promoting microorganisms and **AgraQuest**, a maker of bioinsecticides and plant-growth-enhancing soil treatments.

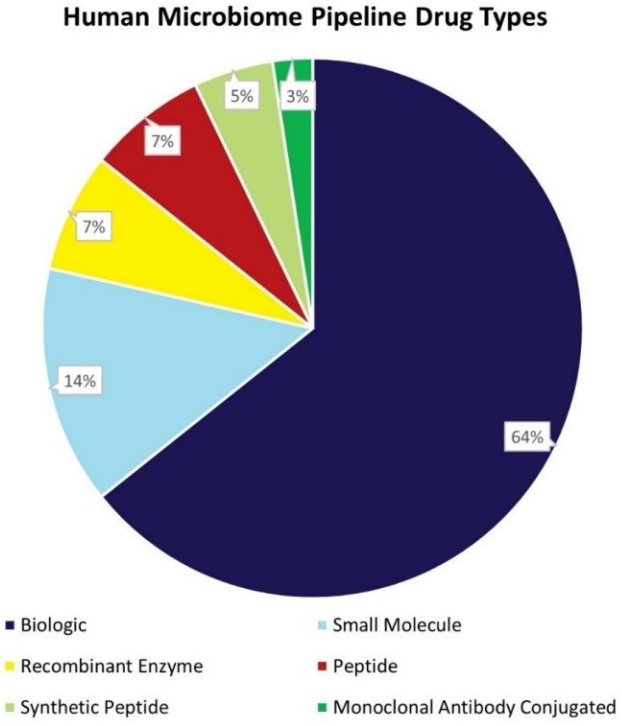
It is thought that over the last two years, big players like **Bayer**, **BASF**, **Chr**. **Hansen**, **Monsanto** and **Novozymes** have invested over $2 billion in their R & D programs in the plant and soil microbiome sector.

[49] https://agfundernews.com/bayer-grows-digital-farming-dept-with-ma-as-ceo-discusses-microbiome-research5510.html

PIPELINE

The vast majority of current pipeline products in the microbiome industry are for human therapeutics and diagnostics. These are listed in Appendix 2 and this features many of the key players in the industry. This information was compiled based on information from subscription databases and internet-based searching, and is categorised by drug/diagnostic, company, development stage and indication. A general overview of the clinical and pre-clinical drugs projects by disease area in 2016 is provided in the Figure below, adapted from research performed by BCC Research.[5] An overview of the type of drug products in development is shown in the second Figure below, based on data compiled by GlobalData (2017).





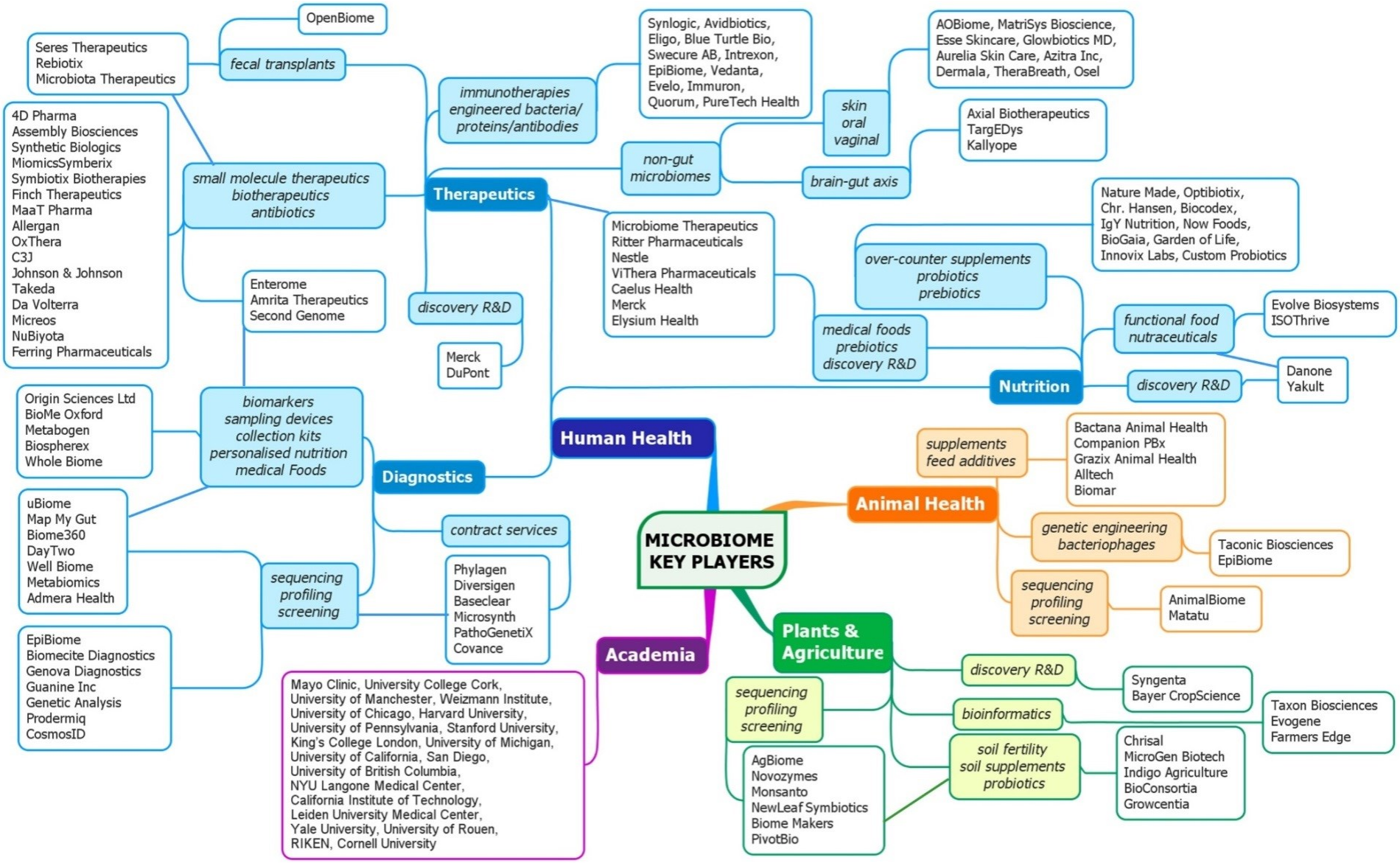
KEY PLAYERS

The key players in the microbiome industry were identified using information from subscription databases, press articles, internet-based searching and academic literature. The landscape is comprised predominately of companies working on the development of novel human microbiome therapeutics. In this sector, there is a broad mix of active organisations. There are many start-ups with a narrow focus and early-stage drug or medical food pipeline. There are also some small companies with a broader pipeline portfolio and potentially game-changing technology, backed by substantial funding from investors and/or large companies. There are also a handful of multinational companies with a wide remit of interests being developed through their specialised microbiome R & D divisions and in partnership with smaller companies.

In contrast to the human therapeutics sector, the diagnostics sector is far smaller and generally at an earlier stage. The field is dominated by a few independent, development-stage companies working on one or two novel technologies.

The animal health sector is not currently a crowded field, with only a few active small companies working on different technologies. Key players in the plants and agriculture sectors are mainly small companies, some backed by larger agritech investment, developing platform microbial products.

The key players are mapped according to sector and main technology areas in the Figure below. Those identified in the academic space in this Figure are based on industry deals and investments rather than academic literature, so this should not be considered an exhaustive list.



HUMAN HEALTH AND WELLBEING

The key players in novel human microbiome therapeutics are summarised in the Figure below, based on market research by BCC Research and others.[5] The Figure shows projected market shares of the top companies by disease area in the overall U.S. therapeutics market, estimated to reach $6.9 billion by 2024. It should be noted that a number of companies listed are also developing pipeline products in other disease areas not represented in their projected market share below, but the uncertainty of the effectiveness of numerous early-stage drugs means that potential market shares and disease areas are highly subject to change.

Projected 2024 U.S. Market Share for Microbiome-Based Drugs by Company and Disease

For the purposes of this white paper, we have provided more information on seven prominent companies in more detail below:

- 4D Pharma
- Enterome Bioscience
- Evelo Biosciences
- Second Genome
- Seres Therapeutics
- Synlogic
- Vedanta Biosciences

These companies have been compared using the following parameters, which provide an indication of their strengths and longer-term strategies:

- Number of products in their pipeline
- Number of disease areas they cover in their pipeline (e.g. gastrointestinal, oncology, etc.)
- Number of industry sectors they operate in
- Number of in-licenses
- Number of out-licenses
- Number of partnerships/collaborations
- Number of acquisitions or spin-outs
- Funding raised from venture financing

The scores are based on the number of deals, products or sectors and range from 0 to 10 for each of the factors. This information is displayed on radar charts for each company in the Sections below. To allow venture financing to be represented on each chart, this has been scored by the band of funding raised, as outlined in the Table below.

Score	Total Investment ($ million)
1	0 – 15
2	15 – 30
3	30 – 45
4	45 – 60
5	60 – 75
6	75 – 90
7	90 – 105
8	105 – 120
9	120 – 135
10	135 – 150

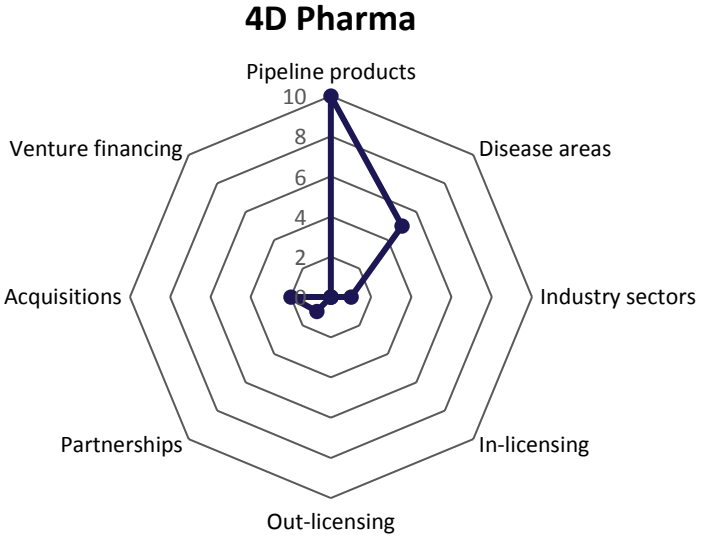
It should be noted that most pipeline products are in preclinical or Phase I development. The exceptions are **Seres Therapeutics** and **Second Genome**, which both have a product in Phase II. More details can be found in Appendix 2.

4D PHARMA

4D Pharma is a Leeds, UK-based company founded in 2014 which has identified and isolated over 4000 bacterial strains from healthy human samples. 4D's MicroRx technology platform is a proprietary tool that interrogates this library of bacteria for therapeutic potential in various diseases. After selecting the bacterial strain, the company prepares the biotherapeutic formulation which is delivered orally to the gut where it interacts with the patient and exerts therapeutic effects.

4D Pharma is one of three microbiome therapeutics companies to have gone public (as well as **Seres Therapeutics** and **Ritter Pharmaceuticals**), completing its initial public offering on AIM in February 2014, raising a total of £16.55 million before expenses, with a further placing in June 2014 raising a total £21.5 million. Further equity offerings worth £64.5 million were announced in 2015, and have been used to advance development of 4D Pharma's biotherapeutic drug candidates to Phase I clinical trials, expand its pipeline and invest in its manufacturing capability.

The company has made three acquisitions of microbiome therapeutics companies – **The Microbiota Company Ltd**. (2014), **GT Biologics** (2015) and **Tucana Health** (2016) – which have allowed **4D Pharma** to strengthen its research capabilities and product offering and broaden its disease area targets. They have also acquired production assets from Spanish CRO, **Insituto Biomar**, giving the company end-to-end development capability to progress its research programmes from the laboratory stage through to clinical development.

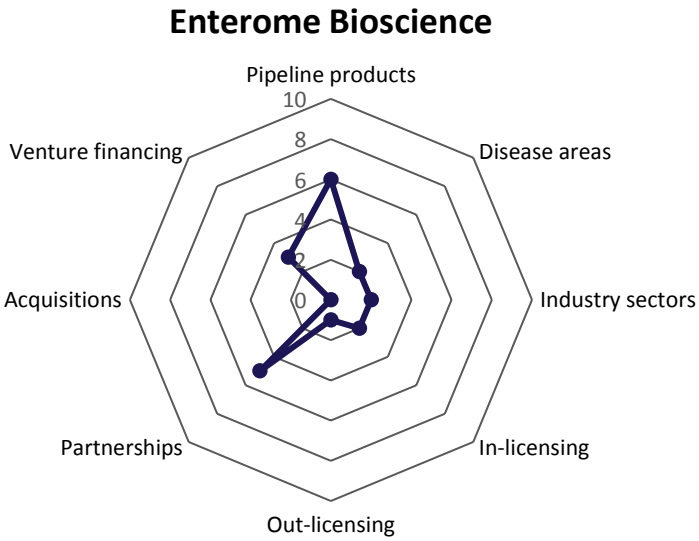


The chart above indicates that **4D Pharma** performs very well in its product pipeline offering, which covers a range of diseases. The company has not in- or out-licensed any of its technology and has been involved in one collaboration with the APC Microbiome Institute (APC) at **University College Cork**, where it invested €4.8 million, and from where its most recent acquisition, **Tucana Health**, was spun out.

ENTEROME BIOSCIENCE

Enterome Bioscience is a private company developing companion diagnostic products for the management of the human gut microbiome. It was formed in 2012 and is based in Paris and Cambridge (MA). **Enterome** uses its technology platforms to sequence the microbiome implicated in the disease and determine linkages of diseases such as cancer, obesity and gastrointestinal diseases, and pathways to identify novel drugs and targets

Enterome's quantitative metagenomics platform sequences and maps the total faecal bacterial gene content and characterises the personal metagenome associated with a disease phenotype. This helps in identification of biomarkers and bacteria linked with various diseases. The platform screens genomic or metagenomics libraries on cell based assays and specific pathways of interest, aiding in the discovery and development of new drugs and targets.



As the above chart shows, **Enterome** has entered into a number of partnerships. Three of these are major partnerships for undisclosed upfront payments with large pharmaceutical companies – **Abbvie** (2014), **Janssen Pharmaceutical** (2016) and **Takeda Pharmaceuticals** (2016). These collaborations are based around discovery of novel drug targets and development of bioactive molecules for gastrointestinal diseases which complement Enterome's diagnostic technology.

One of the small molecule drugs under development with Janssen is EB-8018, which **Enterome** has in-licensed from **Vertex Pharma**. In a licensing agreement with three French academic institutes in 2013, the company has also received worldwide rights on the 'Prognostic of diet impact on obesity-related co-morbidities' patent owned by INRA, UPMC and IRD.

Enterome has out-licensed some of its diagnostic technology to **Bristol**-**Myers Squibb** in 2016 for a $15 million upfront fee and undisclosed milestones, for the discovery and development of microbiome-derived biomarkers, drug targets and bioactive molecules to be developed as potential companion diagnostics and therapeutics for cancer. **Bristol**-**Myers Squibb** will be granted exclusive rights to intellectual property and therapies generated during the collaboration.

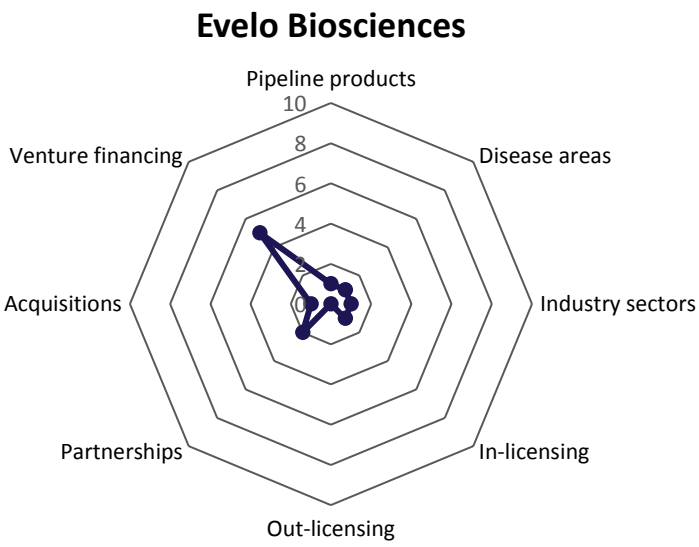
Enterome has also raised €32 million from investors who include **Nestlé Health Science** and **Seventure Partners**.

EVELO BIOSCIENCES

Evelo Biosciences (Cambridge, MA), formerly Evelo Therapeutics, is an immune microbiome company formed in 2015 by **Flagship Ventures** to develop microbiome immunotherapies for cancer, autoimmune and inflammatory diseases. The company focus is on the pharmacological interactions between the immune system and the microbiome.

It has identified specific bacteria that are able to modulate the immune system. **Evelo**'s "Oncobiotic" platform utilises the knowledge of biology of cancer associated bacteria and bacterial immune activators to develop oral drug candidates which leverage the ability of specific strains of microorganisms to potentially activate the immune system against tumours. It is noteworthy that David Perry, the CEO of **Indigo Agriculture**, the most significant player in the plants and agriculture microbiome industry, is also a board member of **Evelo Biosciences**.

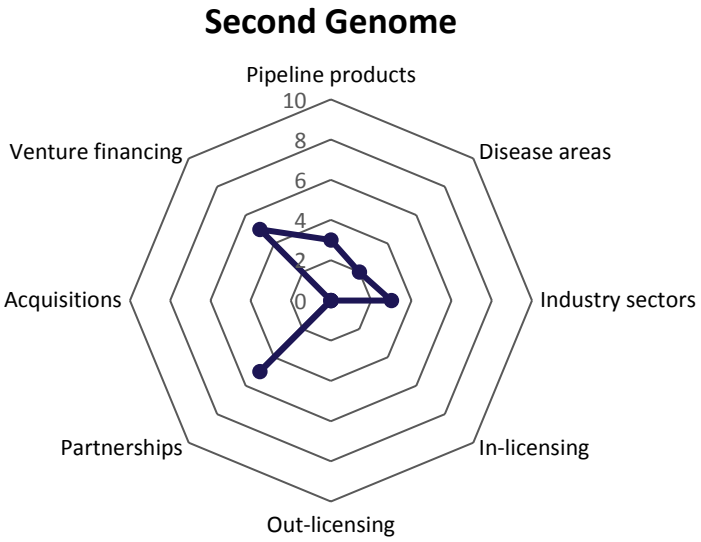
Evelo has received over $65 million in funding from investors including **Flagship Ventures**' Venture Labs innovation group since 2014. In April 2016, **Evelo Biosciences** was merged with **Epiva Biosciences**, an immunobiotic therapeutics developer, to establish the industry-leading immuno-microbiome therapeutics platform.



The company has established strategic collaborations with leading academic institutions like **Mayo Clinic** (2016), to isolate and characterize cancer-associated bacteria from patient stool samples and tumour biopsies, and the **University of Chicago** (2015). However, the company is still at an early stage, as indicated by the smaller pipeline and deal-making activity in the chart above.

SECOND GENOME

Second Genome is a clinical stage company founded in 2009 in San Francisco to develop drugs based on microbiome science. **Second Genome**'s proprietary microbiome modulating platform integrates microbiome and host biology to identify microbes and microbial biomarkers that influence gastrointestinal diseases and generate new drug molecules to target these microbes. With this platform, the company evaluates and develops a variety of small molecules, peptide biologics and bacterial strains that modulate microbe-microbe and microbe-human interactions.



Second Genome is not involved in any licensing activity but is engaged in several drug discovery collaborations including with **Janssen Biotech** (2013) for ulcerative colitis and **Mayo Clinic** (2014) for metabolic disorders and colorectal cancers. It has also established a partnership with **Evotec** (2015) to together screen microbiome-mediated targets of interest identified by the Second Genome microbiome discovery platform alongside **Evotec**'s integrated drug discovery technology platform, chemical libraries and other pre-clinical capabilities.

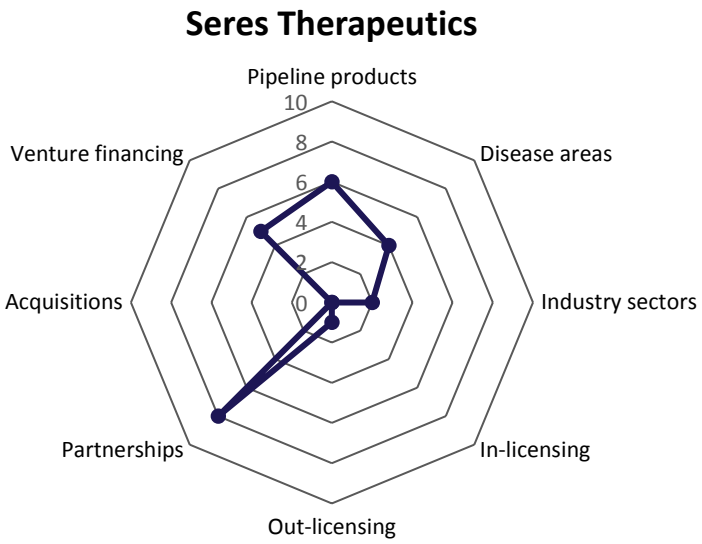
The company is involved in academic collaborations with **Kings College London** for microbiome profiling in skin disorders, and with Alimentary Pharmabiotic Centre (2015) at **University College Cork** for gastrointestinal disorders.

Second Genome has performed well in venture financing, attracting around $62.5 million from investors including **Advanced Technology Ventures**, **Morgentaler Ventures**, **Roche Venture Fund** and **Pfizer Venture Investments**. It is also one of the only human microbiome therapeutics companies to be working in the agriculture microbiome sector, having entered into an undisclosed multi-year research agreement with **Monsanto** in 2016 to develop microbiome-based insect control tools.

SERES THERAPEUTICS

Seres Therapeutics (Cambridge, MA), founded in 2010, is a publicly-traded company developing a range of ecobiotic drugs that deploy consortia of microbes designed to deliver targeted functions in various diseases including cancer and C. difficile infection. **Seres Therapeutics** uses a combination of understanding of systems biology, comparative genomics and its expertise in isolating and characterizing microbes to create microbiome drugs. The company's ecobiotics are compositions of commensal microbes that catalyse the transition to a healthy microbiome ecology.

The company has three clinical programs and a series of preclinical programs in its pipeline, though as discussed previously, the initial failure of its lead candidate, SER-109, in Phase II illustrates the degree of volatility in the microbiome industry. However, **Seres Therapeutics** is currently one of the most well-funded companies in the field, having attracted considerable investment via venture financing ($68.5 million) and raised around $220 million from equity offerings in 2015. As discussed above, its out-licensing deal with **Nestlé** in 2016 has the potential to generate over $2 billion for Seres.

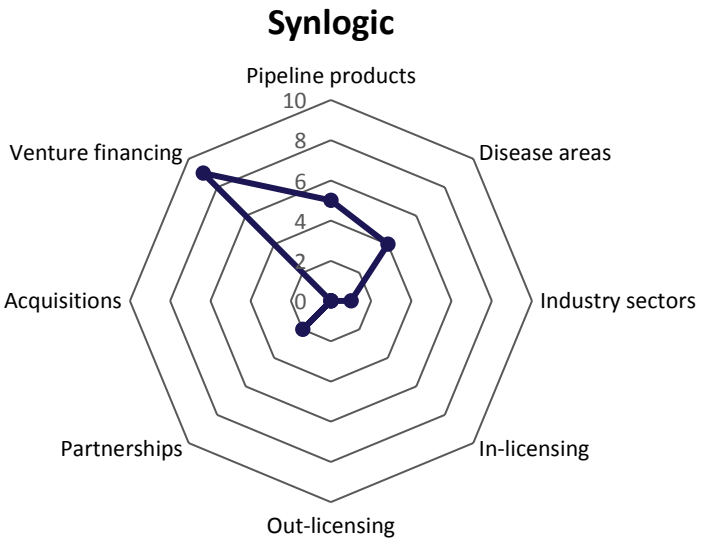


Seres Therapeutics is also one of the most collaborative companies in the microbiome industry, establishing eight strategic partnerships in 2016 to allow it to consolidate and broaden its offering. These are mostly medical partnerships (**Medical University of Graz**, **Massachusetts General Hospital**, **St. Joseph's Healthcare Hamilton**, **Memorial Sloan Kettering Cancer Center**) to perform clinical trials or obtain donor and patient samples from faecal microbiota transplantation (FMT). The company is also involved in academic partnerships (**Mayo Clinic**, **University of Pennsylvania**) to develop novel treatments for rare diseases, and an industry collaboration with **Emulate Inc**, to further advance **Emulate's** intestine-chip platform – a micro-engineered, living-tissue-based system that models the human intestine.

SYNLOGIC

Synlogic (Cambridge, MA), formerly TMC Therapeutics Inc, is a private microbiome-based therapeutics company developing a new class of drugs called "synthetic biotics" which are designed from natural probiotic bacteria and precision-programmed to correct disease-causing metabolic dysregulation. **Synlogic**'s technology platform is a fusion of microbial engineering, physiology, state-of-the-art metabolic gene circuitry, design of regulatory genetic switches and proprietary assays and disease models.

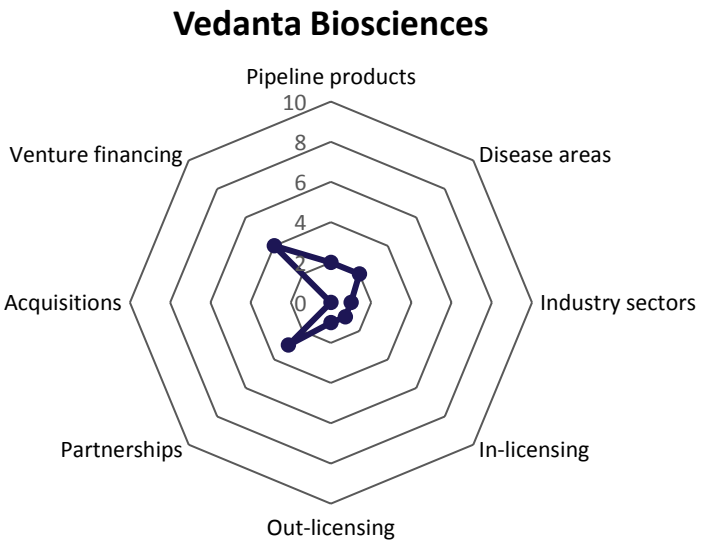
Synlogic has a number of products in its pipeline, with its urea cycle disorder drug candidate the most advanced, approaching Phase I trials. It is engaged in a multi-year global R&D collaboration with **Abbvie** to develop novel medicines for the treatment of inflammatory bowel disease (IBD). Under the terms of the agreement, **Synlogic** will discover, characterise and optimise synthetic biotics-based drug candidates through an R&D program covering a limited number of effectors modulating the IBD pathophysiology, with special emphasis on Crohn's disease and ulcerative colitis. The agreement will combine **AbbVie**'s expertise in metabolic and inflammatory diseases with **Synlogic**'s platform to generate and advance to the clinic a novel, oral probiotic therapeutic candidate.



As shown in the chart above, **Synlogic** is the top-performing company in attracting venture funding, having secured $133 million from prominent investors including the **Bill & Melinda Gates Foundation**.

VEDANTA BIOSCIENCES

Vedanta Biosciences (Cambridge, MA), founded in 2010 by **PureTech Health** (Boston), is developing microbiome-based drugs that use live commensal microbes to modulate interaction between the human microbiome and immune system. The company's proprietary technology platform is based on research by Dr. Kenya Honda that showed that compositions of bacterial strains belonging to clostridium clusters IV and/or XIVa could be used to treat a range of diseases including infectious, allergic and autoimmune diseases. The company has isolated a vast collection of human-associated bacterial strains, characterised how the immune system recognises and responds to these microbes. **Vedanta**'s pipeline is smaller and at an early stage than some of other key players, but it secured $50 million in venture financing in 2016 to progress its infectious and autoimmune disease programs to the clinic.



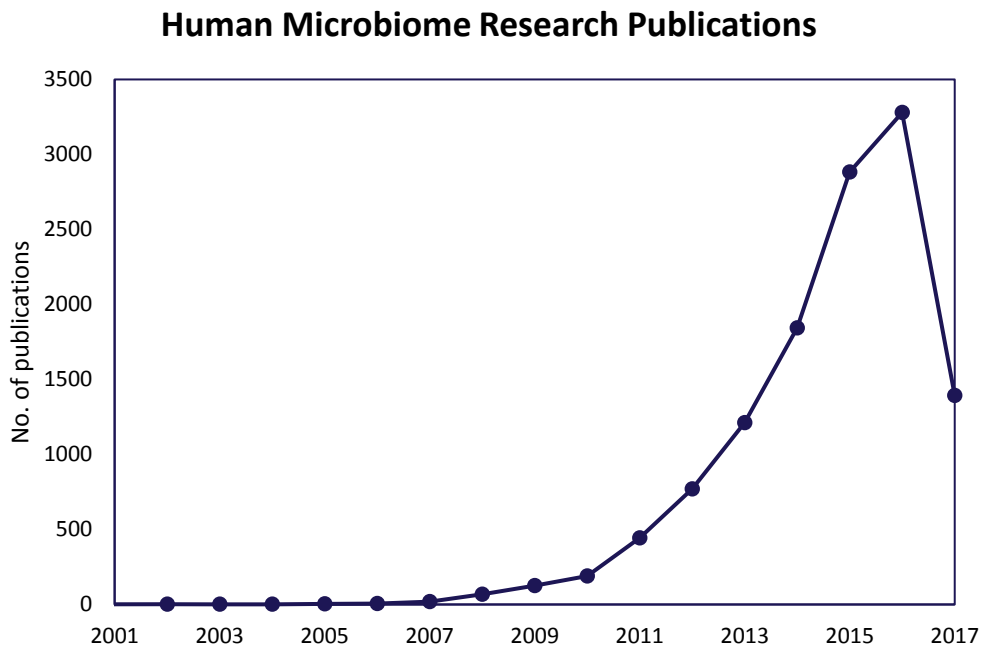
In 2015 the company entered into a major licensing agreement with **Janssen Biotech** to develop a drug candidate (VE202) for inflammatory bowel disorders. **Vedanta** received an up-front payment and is eligible to receive development and commercialisation milestone payments for an IBD indication up to a potential total of $241 million, plus possible additional consideration related to commercialisation.

Vedanta also entered into strategic academic partnerships with the medical schools of **NYU Lagone** (2016) and **Leiden University** (2017) to generate clinical data to support new microbiome therapeutics for cancer and C. difficile, respectively. It has also established a collaboration with **Stanford University** (2017) to analyse the potential connection between the gut microbiome and responses to oral immunotherapies in children with food allergies.

RESEARCH LANDSCAPE

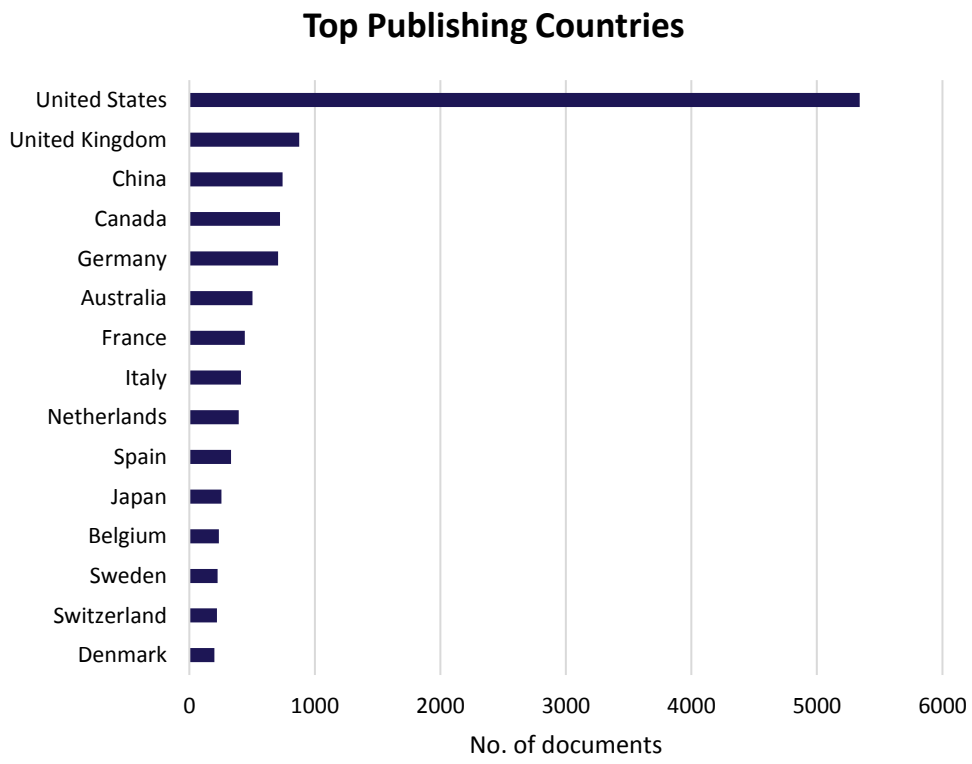
To give an indication of the academic institutions contributing to the field, a broad search of academic publications was carried out. A search of the abstract, title and keywords for "microbiome*" identified 9396 document results, including both peer-reviewed research articles and topic reviews, in the subject areas of medicine, nursing, biochemistry, genetics, molecular biology, immunology, microbiology, pharmacology, psychology, toxicology, pharmaceutics, neuroscience, chemistry and dentistry. The search term was kept deliberately broad since many human microbiome (or animal model) publications do not explicitly state the species of the subjects of the study, or the type of technology or techniques.

As shown in the graph below, the number of academic publications has undergone explosive growth over the last five years. The drop in publication numbers for 2017 is reflective of the time of the search (May 2017).



Sorting the dataset by affiliation gives a rough indication of the top publishing organisations. Unsurprisingly, given the deal-making landscape outlined above, the industry is dominated by US institutions as shown by the top 15 publishing organisations below. All are public sector academic and/or medical institutions and many are also key players for industry partnerships and licensing.

Given that top US-based institutions are some of the pioneers in the microbiome industry, it is unsurprising that the top publishing country by a large margin is the USA. The top 15 countries by publishing territory are summarised in the Figure below.



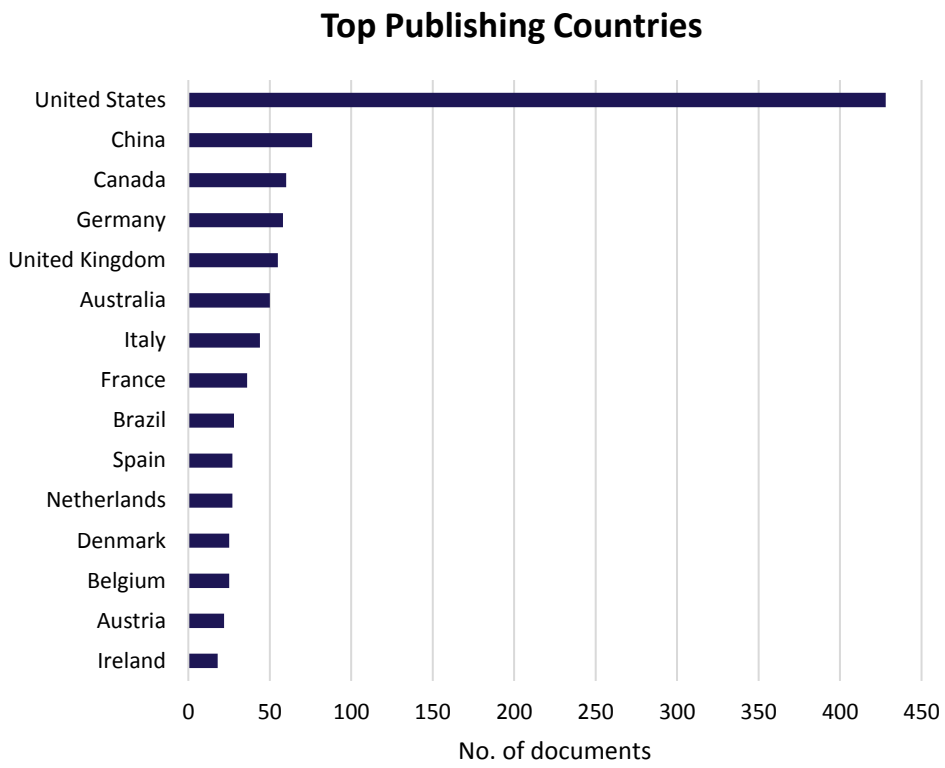
ANIMAL HEALTH

As discussed previously, the microbiome-based animal health sector is far smaller and at a much earlier stage than human health and wellbeing. Key industry players are identified in the previous overview map and in the above Deals Section. The most significant activity is still at the academic research stage, summarised below.

RESEARCH LANDSCAPE

Owing again to the overlap in studies, and in particular the academic literature keywords, of animal and human microbiomes, a broad search of academic publications was carried out using only the word "microbiome*" but publications were limited to veterinary and environmental subject areas. This identified 882 documents. Just over half are US institutions or research agencies. **Cornell University** is the most prolific publisher, which is unsurprising given its involvement in animal microbiome deal-making, as discussed previously. There are also European, Canadian, Australian and Brazilian institutions featured which have a strong background in animal health.

The top 15 countries by publishing territory are broadly similar in breakdown as observed for the human health sector:



PLANTS AND AGRICULTURE

Like animal health, the plant and agriculture microbiome sector is still fairly small. The key activities are described in the Deals Section above and three of the key industry players are described in more detail below.

INDIGO AGRICULTURE

Indigo Agriculture (Boston) is a private agbio company, created as Symbiota by **Flagship Ventures** in 2014 and rebranded in 2016. It is 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. Similar to companies in the human health space, Indigo uses a computational biology approach to focus on identifying beneficial microbes that live within the plants — endosymbionts or endophytes.

In 2016, the company released data from its first proprietary commercial product, Indigo Cotton, which is designed to stimulate crop growth by adding live microbes through a seed treatment. The yield of treated cotton planted over 50,000 acres in Texas during 2016 was 11% higher than untreated cotton in comparable fields. It is currently testing yield-boosting microbes in several different crops. Its next commercial product will be Indigo Wheat, which is designed to improve water use efficiency.

To overcome sceptical grower perception of using microbials, **Indigo** has adopted a unique pricing model whereby it plans to charge a minimum for its seeds in exchange for a 33 percent

share of any additional value that Indigo's crop creates for a grower. This means that Indigo will turn a profit only when their seeds perform well. This model allows farmers to purchase Indigo's novel products and attempt to increase their yield without taking on too much risk.

Indigo is a highly collaborative company, involved in research partnerships with 12 organisations[50] and in 2017 launched Indigo Partners, a program that enables **Indigo** and growers to test new technologies together and increase the turnaround time for new innovations. The company is one the most well-funded in the microbiome industry, having raised $156m in venture capital funding in 2016.

AGBIOME

AgBiome is a private company, formed in 2013, which occupies a state-of-the-art 30,000 square foot laboratory and greenhouse facility in North Carolina. Its proprietary technology platform has enabled a sequenced strain collection of over 40 000 isolated microbial strains and identification of hundreds that are active leads in its ongoing research pipeline. The company is using these leads to develop products aimed at helping farmers combat many of the most important unresolved problems in agriculture, such as plant diseases, insect pests, and parasitic nematodes. It anticipates the launch of its first commercial product, Howler, a fungicide, in 2017.

AgBiome has 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**, **Monsanto** and **Novozymes**.

The company is also engaged in R & D partnerships with **Geneactive** to create novel insect-resistant crops and with Syngenta to develop specific traits in various crops. It also has multiple undisclosed academic and industry partnerships. Most recently, **AgBiome** was awarded a multi-year funding grant by the **Gates Foundation** to help African sweet potato farmers combat the sweet potato weevil.

BIOAG ALLIANCE

In 2016 **Monsanto** (USA) and **Novozymes** (Denmark) 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. **Novozymes** is responsible for the discovery, production and supply of the microbial solutions, while **Monsanto** will lead field testing, registration and commercialization of all Alliance products. In terms of overall agricultural microbial products, the BioAg Alliance's products are currently used on 80m acres of farmland, mainly in North and South America, and it is aiming for more than 250m acres by 2025.

The key goal of the alliance is the development of microbiome-based solutions to increase crop yields and reduce fertiliser and pesticide use. The two companies, through their BioAg Alliance, have recently concluded the world's biggest field-test program of seeds coated with

[50] Financial Times. (2017) *Agriculture takes promising step towards boosting crop yields*

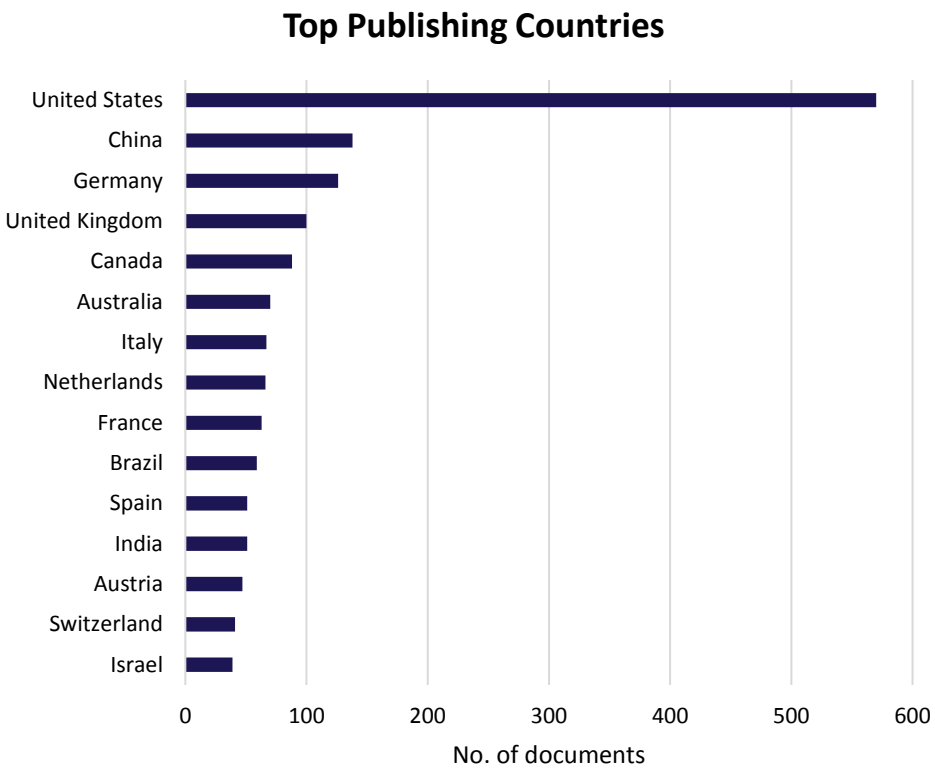
beneficial microbes. They tested a wide range of crops with more than 2,000 microbial strains across 500,000 field trial plots in more than 50 locations in the U.S. The companies said results showed that top microbes increased corn yields by an average of 4-5 bushels per acre and soy yields by an average of 1.5 bushels per acre.

The companies are currently seeking partnerships with academics, public institutions and other companies who are investigating the power of microbes. Regardless of the stage of development, the BioAg Alliance has technology validation capabilities to determine which microbes and enabling technologies may be able to play a role in the next innovation in agriculture. Though the BioAg Alliance is still at an early stage, the market reach and recent investments of its founder companies may in the coming years be an important factor in driving the plant and agriculture microbiome industry.

RESEARCH LANDSCAPE

The most relevant academic publication search results were obtained by searching abstract, title and keywords for “microbiome*” and “plant* OR agricultur* OR soil” across all subject areas. This returned 1370 articles or reviews. These are from a more geographically diverse mix of institutions and national research agencies than observed for human or animal health. The top 15 publishing institutions, which mostly have a strong agricultural focus, are shown below.

Overall, US-based organisations again dominate the publication landscape in the plants and agriculture microbiome sector, as shown by the top 15 publishing countries below.



MARKET DRIVERS AND TRENDS

Rapidly improving capabilities in sequencing and data analytics underpin the growth across all sectors of the microbiome industry. The speed and simplicity of next-generation sequencing is driving diagnostic applications across healthcare, food and drink, environmental and industrial contexts.

The proliferation of analytical platforms promotes the identification of a plethora of new targets that can then be developed into therapeutics. There are currently multiple proof-of-concept data from a wide-range of microbiome projects in a number of disease areas with substantial unmet needs which will help drive the therapeutics sector. Current use of data analytics to focus on the digitalisation of healthcare is relevant to microbiome technologies, where industry continues to seek ways to improve care management programs, veterinary diagnostics and digital farming.

Other market drivers for the microbiome industry as a whole are the increased level of collaboration activity between industry and academia to generate data and treatments for existing and new targets, continued investment by both private and public sector players, and the increased awareness and spending power of the middle classes for therapeutic, food and pet supplement products.

HUMAN HEALTH AND WELLBEING

Microbiome technologies are expected to play a crucial role in the development of new drug discovery platforms and companion diagnostics in the precision medicine era. More personalised approaches in both diagnostics and therapeutics can be reached with enhanced understanding of human microbiomes. The shift from acute care to care management programs due to rising global healthcare costs have led more healthcare professionals and individuals to focus on preventative care, self-diagnosis and self-medication.

The rising incidence of lifestyle diseases globally is a strong driver of the microbiome market, as therapeutics may provide an alternative route to tackle significant healthcare challenges such as obesity. The increasing occurrence of autoimmune disorders and antibiotic resistance are also important areas which are in great need of fresh treatment approaches, and for which microbiome therapies may have significant impact over the next few years.

With advancements in precision medicine, personalised nutrition is also playing a crucial role. Microbiome technologies strive for novel developments in the area. The ageing population, rise of chronic health problems (often lifestyle related), and increased awareness of the health benefits of “functional foods” have all driven growth in this market. The elderly population is increasingly adopting nutraceutical products to provide nutritional and health benefits for greater enjoyment of their lengthening lives. The rapid increase in consumption of dairy products in China will also fuel growth in dairy-based functional foods and drinks.

ANIMAL HEALTH

The demand for microbiome therapeutics in human health also extends to animals. The animal population is increasing amidst a booming demand for meat and animal products as the global population grows in number and affluence. New technology platforms for the prevention and early identification of disease and other indicators of health is a key driver for microbiome diagnostics in farming, while therapeutics targeting specific gut microbes – potentially unique to that species – may offer tractable targets (and solutions) to treat veterinary disorders without risk of detriment to humans. The companion animal market is driven by an ageing population and increasing insurance coverage. Pet owners are also prepared to spend more on the health and welfare of their animals, taking advantage of prognostic/diagnostic tools, treatments and supplements similar in principle to functional foods for humans. Demand for new approaches to therapeutics is also driven by society as a whole becoming increasingly conscious and empathetic to the needs of animals.

The practice of treating animals with Antibiotic Growth Promoters (AGPs) – antibiotics used prophylactically to kill specific bacteria in the gut to enhance growth and yield – is still common practice globally. In the EU, however, the practice was banned in 2006 following fears that overuse contributed to the rise in multi-drug resistant bacterial infections ("superbugs") in humans. There is now increasing pressure from consumers and regulators globally to minimise antibiotic use in farming, which is driving demand for alternative feeds and feed supplements that boost the innate health and growth potential of livestock.[14]

The animal microbiome industry will also be driven by urgent environmental concerns. Finding ways to reduce methane production, for example by studying the interaction between food and the gut microbiome, may offer a means to mitigate the negative consequences of the intensification of modern farming.

PLANTS AND AGRICULTURE

The key factors driving the microbiome market for plants and agriculture overlap extensively with drivers of the animal health industry. With the global population set to reach almost 10 billion by 2050, more efficient, high-yield farming practices are vitally important. This is reflected by the deal-making activity in the agriculture microbiome sector, which is based predominantly on improving crop efficiency or yields. New plant materials as agents to reduce methane emissions from ruminant animals also requires an understanding of plant microbiomes and their interaction with the gut microbiome.

The increasing interest of the industry in biological products as alternatives to existing pesticides and fertilizers is strongly promoted by national strategic plans to restrict chemical input in agriculture. Additional drivers for the initial interest in biologicals include heightened regulation of synthetics and public perception of environmental and health impacts of residues and GM traits.

From an economic perspective, investing in biological agricultural solutions is attractive because it is difficult and increasingly expensive to trial and register agrochemicals. Due to lower regulatory hurdles and fewer restrictions, timelines for microbial-based products to market are shorter, while research costs for microbials can be up to ten times less than that of synthetics or GM crops.

BARRIERS TO ENTRY

As the microbiome industry is mostly still at an early, developmental stage, the main barriers and challenges common to all sectors of the industry relate to the costs and regulatory hurdles of commercialising new technology and adoption into mainstream practice. There a number of issues outlined in the Table below.

Barrier	Description	Relevant Industry Sector		
		Human Health	Animal Health	Plants and Agriculture
Safety	Many of the advances in the development of microbiome therapeutics have been demonstrated in rodent models and their translation to humans, due to the fundamentally different nature of their respective microbiomes, has yet to be tested in a comprehensive fashion[51], which may affect the success of upcoming clinical trials.	✓		
	The spread of genetically modified DNA from recombinant organisms to endogenous members of the microbiota may a be a concern as natural horizontal gene transfer is prevalent in the human microbiome	✓	✓	✓
	The escape of engineered microbiomes into the environment that may lead to unintentional colonisation of others may be a concern, even though most genetically modified organisms developed in the lab seem to be less fit than wild-type	✓	✓	✓
	Long-term safety studies addressing the effect of engineered animal and plant microbiomes on human consumers and the environment may need to be performed	✓	✓	✓
	The ability of bacteria to stably colonize their target environments may enable greater therapeutic efficacy, but the pharmacology and control of such therapies is important to understand.[51]	✓	✓	✓
Regulation	No standard regulatory framework for microbiome based drugs and diagnostics exists today. The FDA and other regulatory agencies will need a solid proof regarding the safety of administering live bacteria or bacterial products in the human body.	✓		
	Despite the popularity of bioactive dairy products, it has been difficult to gain new health claims for functional ingredients since the European Food Standards Agency (EFSA) tightened labelling regulations around health claims on food products. Clinical evidence to support any health claims is essential but many food companies baulk	✓		

[51] Mimee *et. al.* (2016) Microbiome therapeutics — Advances and challenges. *Advanced Drug Delivery Reviews*, 105, 44-54

Barrier	Description	Relevant Industry Sector		
		Human Health	Animal Health	Plants and Agriculture
	at the associated cost, which may not be justifiable given the market for the final product.[14]			
	In Europe, animal feed additives come under similar scrutiny to that of human food additives, as there is obvious need to protect the human food chain. In addition, pre/probiotics will have to come supported by rigorous scientific evidence to support the benefits claimed. However, several have already been approved so precedent has been set for this product class.		✓	
	Regulations in the European Union with respect to the lack of quality restrictions concerning biofertilizers has left a situation where national or regional rules are applied; these are often variable and not consistent with one another.[52]			✓
	The regulatory processes for product registration of Biocontrol agents within EU is long, complicated and requires significant levels of expertise.			✓
	Further regulatory approvals for speciality crops treated by biopesticides			✓
Ethical issues	At first, participants in microbiome research and drug trials may simply be asked to accept the uncertainty inherent in conducting microbial research as a condition of participation. As human microbiome research advances, however, new risks and benefits will be discovered, necessitating changes to the consent process.[53]	✓		
	The inability to predict what research may be done in the future from the collection of human microbial DNA and the potential risks associated with that research raise the important question of whether participants should be permitted to give general consent for unspecified future research.	✓		
	There is also the issue around informing subjects of research-related results. The potential discovery of asymptomatic or subclinical infectious diseases or susceptibilities to them raises the question of whether researchers have an obligation to report such findings to participants, individuals they may infect, or public health authorities.	✓		
	Data sharing and privacy is a major concern for research participants, particularly in the area of genetic research. Researchers are once again	✓		

[52] Timmusk *et. al.* (2017) Perspectives and Challenges of Microbial Application for Crop Improvement. *Frontiers in Plant Science*, 8, 1-10

[53] McGuire *et. al.* (2008) Ethical, Legal and Social Considerations in Conducting the Human Microbiome Project. *Genome Research*, 1861-1864

Barrier	Description	Relevant Industry Sector		
		Human Health	Animal Health	Plants and Agriculture
	faced with the decision of whether to adopt data sharing policies that allow public access.			
	Since microbial populations can vary by age, ethnicity and location, and thus the safety/efficacy of microbiome-based treatments could be variable, the diversity of participants used in studies and trials is an important consideration	✓		
Efficacy	A significant barrier will be proving causal links between dysbiosis and disease as a means to justify the hundreds of millions of dollars it can cost to bring a new drug or product to market. The establishment of causative relationships is the only route to clinical potential. For a microbiome-based diagnostic, it will be crucial to provide conclusive evidence of the link between potentially multiple biomarkers and disease states.	✓	✓	✓
	Numerous microbial sequencing, metagenomics and disease correlation studies have proven the correlation of microbes with variety of diseases. However, in reality there is a significant inter-subject and intra-subject variability in microbiome compositions. This effectively presents a challenge for designing clinical trials as the lack of uniformity in microbiome in target patient pool may affect clinical trial outcomes and reproducibility	✓	✓	✓
	Current microbiome based drugs in development are being tested in placebo controlled clinical trials and lack the active control arm. These drugs will need to show the differential value versus existing therapeutic options.[5]	✓		
	One of the main factors limiting more widespread use of plant growth promoting bacteria is their selectivity. Conventional agrochemicals are as a rule broad-spectrum products that impact many different kind of organisms. PGPB/PGPR, on the other hand, tend to be highly targeted. This can result in variable quality and efficacy under field conditions i.e. in the complex field environment where various players act simultaneously.[52]			✓
	For the development of animal microbiome products, variable factors such as genetic background, how the animals are maintained, sterility of the environment, diet etc. may mean that a one-size-fits all approach is not possible.		✓	
	Despite the high potential microbial inoculants display in lab and greenhouse experiments, the efficacy and the consistency of desired effects of microorganisms under various field conditions still represent a major bottleneck for product			✓

Barrier	Description	Relevant Industry Sector		
		Human Health	Animal Health	Plants and Agriculture
	development. Microbial products will need to work in a variety of environmental and climatic conditions and achieve efficacy comparable, if not better, to agrochemicals. Demonstration of efficacy in long-term field trials is crucial.			
Knowledge gaps	The companies' active in this space will need to educate the physicians, patients, vets, farmers etc. regarding the use, efficacy and safety of this new class of products	✓	✓	✓
	There is a need to ensure that adequate expertise and infrastructure is in place to meet the challenge of collecting, storing and analysing the vast amount of data generated by omics technologies as well as a robust and reliable context or framework for interpreting the data.	✓	✓	✓
	Much of the funding for microbiomes is in human R & D, with comparatively little in animal or ag microbiome research		✓	✓
	The vast majority of intestinal microbes remain uncultivable. Can novel culture methods or creative strategies to selectively eliminate targeted agents be developed?	✓	✓	
	Screening thousands of microbes is basically a "fishing" process, with less understanding around the biological mechanisms, making targeted discovery more difficult	✓	✓	✓
Intellectual property	Though a number of microbiome companies have successfully developed significant patent portfolios, concerns regarding the patentability of microbiome products remain. Some patent experts indicate that some of the inventions in the microbiome field may not pass the patent law hurdles as bacteria are considered natural organisms/product so may come under scrutiny regarding "novelty", "obviousness" and "patentable subject matter".	✓	✓	✓
Manufacture	Companies will need food nutritional security and sustainability guarantees, and require the transformation of current production systems for live microbe products, which will also have to account for the heat-sensitivity of microbes.	✓	✓	✓
Existing players	The microbiome market, particularly in human therapeutics, is highly competitive and crowded with a number of large, well-funded companies. New companies may find it difficult to gain market share without backing from big pharma. There is also competition from non-healthcare related participants.	✓		
Future uncertainty	Market confidence in the whole microbiome industry currently seems to hinge on a handful of key human therapeutic technologies, which have not yet made it to Phase III trials.	✓	✓	✓

Barrier	Description	Relevant Industry Sector		
		Human Health	Animal Health	Plants and Agriculture
Price	Microbiome-based products will command a high price, which may not be a problem in human health applications such as nutraceuticals where consumers are willing to pay more. However, in other key sectors where price is a more important factor, such as healthcare and farming, microbiome-based solutions will need to be competitive.	✓	✓	✓
Consumer perception	Though there is awareness among the public of the "good bacteria" in yogurts etc., there is still relatively little awareness regarding microbiome therapeutics or the beneficial use of nutraceuticals and medical foods, compared to traditional pharmaceuticals.	✓	✓	✓
	Despite solid scientific data and enthusiasm from the general population, grower perception of microbials still poses a hurdle to the broad adoption of biologicals. Biologicals have a historic reputation of inconsistency while growers need reliable solutions. Growers remain sceptical and so far biological products have been used to a limited extent			✓

PATENT ANALYSIS

In order to understand the intellectual property landscape in the microbiome space, an assessment of the registered industrial patent rights was carried out. Thomson Innovation, a global comprehensive patent database, was used to undertake patent searches for patent applications published in the microbiome space over the last 10 years. A simple, broad search was conducted using the following keywords within the Title/Abstract/Claims of any patent (CTB):

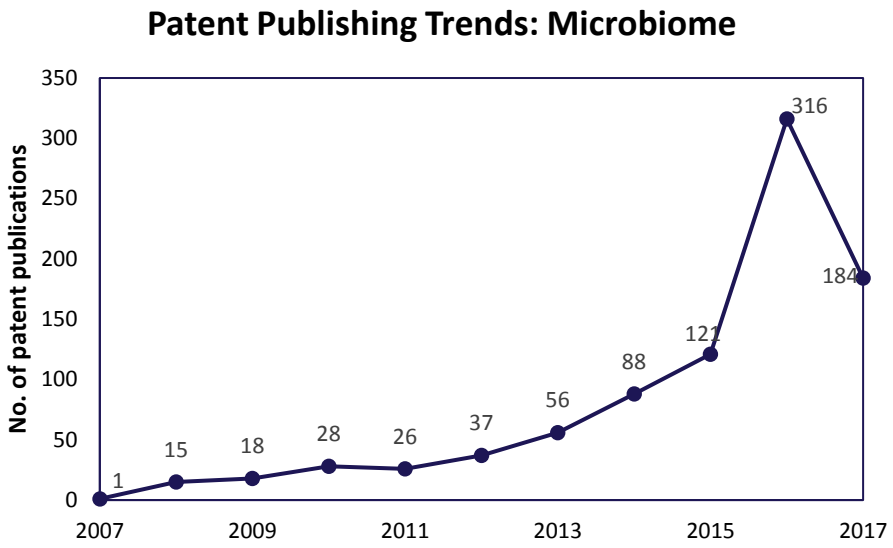
CTB=((microbiome) or (microbiomics) or (microbiota)) AND AD>=(20070503) AND AD<=(20170503);

The search pulls data from all available patent authority collections within the database, including the full patent text for: US Granted; Australian Innovation; Canadian Granted; German Granted; US Applications; Australian Granted; Canadian Applications; German Applications; European Granted; Australian Applications; French Granted; European Applications; UK Granted; French Applications; WIPO Applications; UK Applications; German Utility Models. In addition, the bibliographic data for: Japanese Applications; Korean Granted/Examined; Korean Applications; Other Authorities. In addition, the Thomson Innovation proprietary DWPI data fields were searched for these selected collections.

The resulting search identified 2,802 patent records filed in the 10 years from May 2007 to May 2017. These cases make up 888 INPADOC patent families with which we have conducted the patent analysis below.

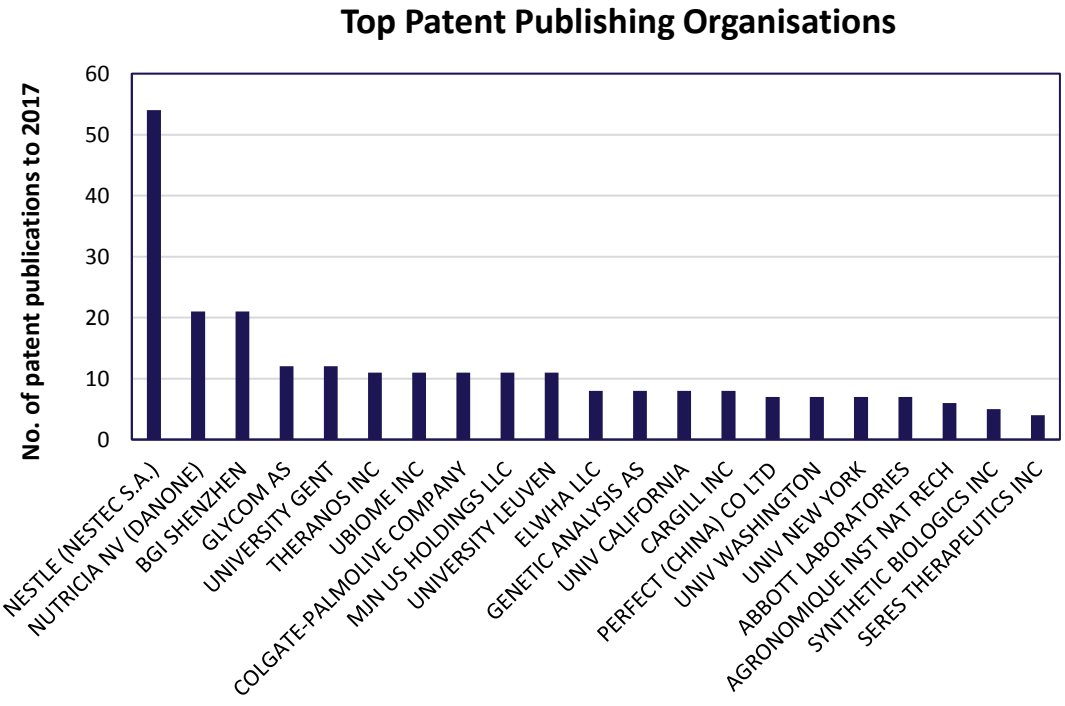
PATENT PUBLISHING TRENDS

Patent publishing trends offer a snapshot overview of the level of activity in the space over the given period. This filing data gives an indication of the number of new inventions published in the microbiome arena over the course of the past 10 years. Thomson Innovation uses the publication number to include both published application numbers and granted patent numbers. The dataset begins in 2007, and the graph shows that this is the same point at which patents in the microbiome space began to be published. There is steady increase from then until 2012, when filings become more frequent and start to rise more steeply. A step-wise increase can be seen from 2015 to 2016, and all indications suggest this is the start of an exponential growth phase. Note the drop in 2017 is reflective of the point at which the search was conducted (May 2017).



KEY ENTITIES

Focusing on the top organisations filing in the sector allows for identification of those organisations carrying out R&D in the area and the comparative level of activity in the space. The analysis is based on the number of patent publications assigned to them in the broad dataset. The data illustrate a fragmented market with a number of large companies, small biotech companies and academic institutions. The following chart summarises the top players by patenting activity: **Nestle** (via its R&D subsidiary, **Nestec** S.A) is by far the most prolific patent filing organisation, followed by **Nutricia** (part of the **Danone** group specialising in infant nutrition) and **BGI Shenzhen** (the Beijing Genomics Institute); **Glycom** & **University of Ghent**.



CLUSTER BY ENTITY TYPE: COMMERCIAL VS. ACADEMIC

The top patent publishing organisations were divided into commercial companies and academic research institutions. The table below summarises the top commercial organisations in order of patenting activity, and a corresponding industry sector. We can see that food & drink/nutrition companies occupy the top positions, perhaps because microbiome research has emerged in part from food and nutrition research over the last 20 years. Thus **Nestle**, **Danone** and **Glycom AS** are the top three entities. Lower down the list, but important still to the microbiome landscape, are diagnostics organisations with a focus on the microbiome specifically: **uBiome** Inc and **Genetic Analysis** AS. This is reflective of the growing focus in the healthcare industry on diagnostics for preventative medicine. These focus on genetic and biomarker tools to identify the balance of components within the microbiome, enabling appropriate solutions to be developed and offered.

Pharma and biotech companies are also listed with between three and five patent families in this dataset: **Abbott** from the big pharma space, and five smaller biotech organisations: **Synthetic Biologics Inc**, **Seres Therapeutics Inc**, **Ixcela Inc**, **Microbiome Therapeutics LLC** and **Salix Pharmaceuticals Inc**. Given that the technology area is still young, it is not surprising that biotech plays a greater role in the microbiome space than large pharma. At this point in the development of a novel technology space, pharma will likely be collaborating or investing in the biotech companies, but not necessarily undertaking in-house R&D, which has comparatively greater risk. Indeed this patent trend aligns with the growing importance of public-private partnerships and university spin-outs in progressing microbiome R&D.

Commercial Assignee/Applicant	No. of patent publications 2007-2017	Sector/Category
NESLTE (NESTEC S.A.)	54	Food & Drink
NUTRICIA NV (DANONE)	21	Nutrition
GLYCOM AS	12	Nutrition
THERANOS INC	11	Medical Devices
UBIOME INC	11	Diagnostics (Microbiome)
COLGATE-PALMOLIVE COMPANY	11	Consumer Products
MEAD JOHNSON NUTRITION (MJN US HOLDINGS LLC)	11	Nutrition
ELWHA LLC	8	
GENETIC ANALYSIS AS	8	Diagnostics (Microbiome)
CARGILL INC	8	Food & Drink
PERFECT (CHINA) CO LTD	7	Nutrition
ABBOTT LABORATORIES	7	Pharma/Biotech
SYNTHETIC BIOLOGICS INC	5	Pharma/Biotech (Microbiome)
SERES THERAPEUTICS INC	4	Pharma/Biotech (Microbiome)
CLASADO INC.	4	Nutrition (Microbiome)
10X Genomics, Inc.	4	Genetics
IXCELA INC	3	Pharma/Biotech (Microbiome)
REBIOTIX INC	3	Pharma/Biotech (Microbiome)
INTERNATIONAL DEHYDRATED FOODS INC	3	Nutrition

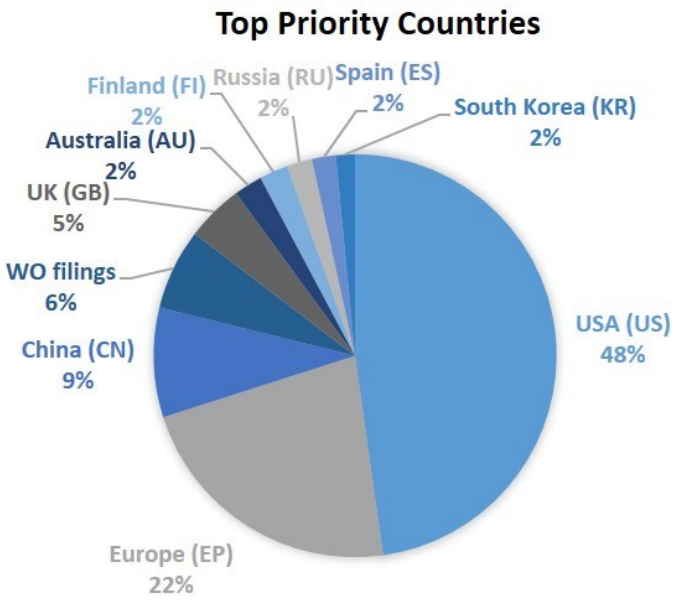
Commercial Assignee/Applicant	No. of patent publications 2007-2017	Sector/Category
MICROBIOME THERAPEUTICS LLC	3	Pharma/Biotech (Microbiome)
SALIX PHARMACEUTICALS INC	3	Pharma/Biotech (Microbiome)
JENNEWEIN BIOTECHNOLOGIE GMBH	3	Nutrition

The data also identified some of the key patenting research institutions. The table below summarises each of these in order of patent publishing activity, and the location in which that research institute or university is based. Clearly some of the top US-based universities are heavily active in the microbiome research space, with approximately 60% of the top 12 academic organisations. Two universities from Belgium are listed, along with one each from Israel and Germany. The top academic institution filing in the space however, is China's **BGI Shenzhen** (previously the Beijing Genomics Institute).

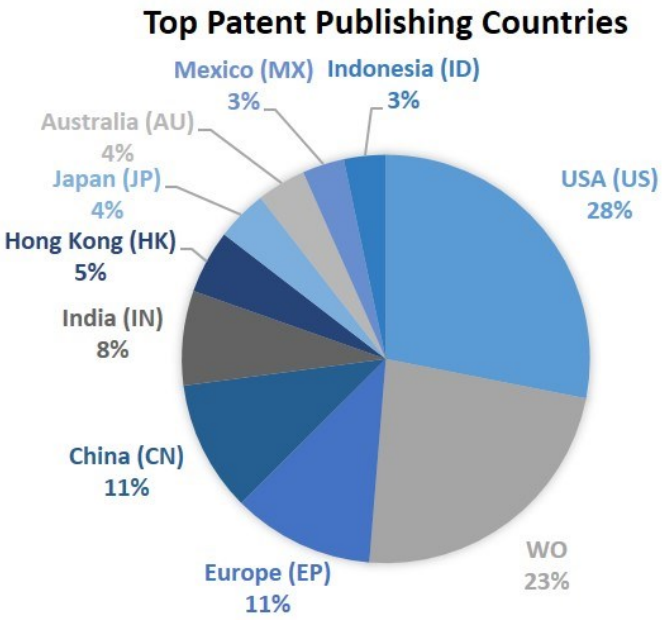
Research Institution Assignee/Applicant	Location	Number of patent publications 2007-2017
BGI SHENZHEN (Beijing Genomics Institute)	China	21
UNIVERSITY GHENT	Belgium	12
KATHOLIEKE UNIVERSITEIT LEUVEN	Belgium	11
UNIV CALIFORNIA	CA, USA	8
UNIV WASHINGTON	WA, USA	7
UNIV NEW YORK	NY, USA	7
UNIV JOHNS HOPKINS	MD, USA	5
YEDA RES & DEV	Israel	4
CONARIS RES INST AG	Germany	4
UNIV YALE	CT, USA	4
HARVARD COLLEGE	MA, USA	4
REGENTS OF THE UNIV OF MINNESOTA	MN, USA	3

GEOGRAPHICAL ANALYSIS

To identify the top countries for R&D and innovation in the microbiome space, we can look at the priority patent filings. This is the country in which the patent was first filed, and typically this will be the country in which the invention was discovered, although not always. Unsurprisingly US priority patent filings dominate the dataset with almost half of the priority filings (48%), followed by the European patent (EP) at 22% and China (CN) with 9%. This aligns with the key markets for both the pharmaceutical and nutrition industries. Other individual countries with research focus on the microbiome include the UK, Australia, Russia, Finland, Spain and South Korea.



The top countries for patent publication can also be analysed, this gives an indication of those countries considered to be important for commercialisation. Organisations will choose to publish the patent in those countries where the industry sector is likely to be most commercially viable, to secure patent exclusivity rights in those markets. The regions considered to be important in this regard largely align with the priority country filings for the top three (US with 28%, Europe and China). However, in addition to these, the Australasian markets of Hong Kong (5%), Japan (4%) and Australia (4%), as well as India (8%), are likely to be important markets for microbiome related technologies in future. In addition, PCT applications are the second most important "region" after the US (23%). This indicates a tendency of applicants to maintain a broad geographical scope of protection for microbiome patents. Further, it reflects the current early-stage situation of the market since patent applications are still at a relatively young stage of the patenting process, many of which are yet to progress to national phase.

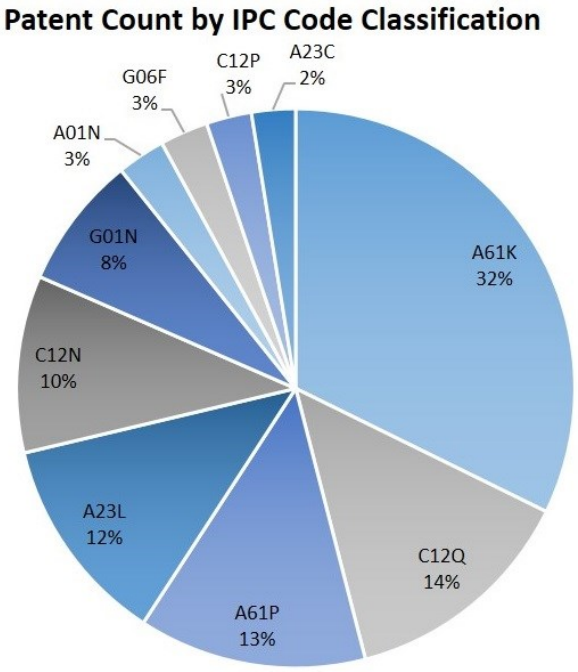


TECHNOLOGY AREAS

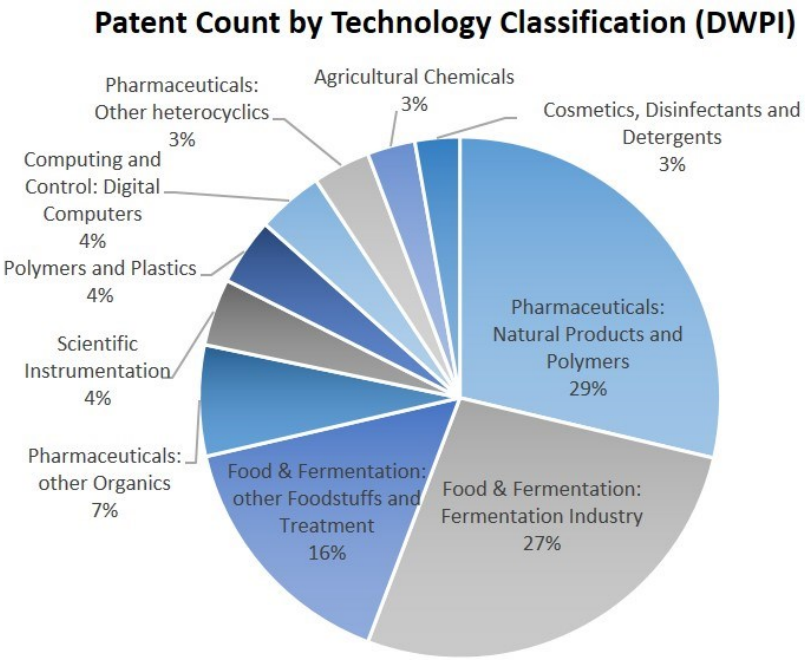
The patent dataset was analysed further to identify the top International Patent Classification (IPC) codes. The international classification system provides for a hierarchical system of language-independent symbols for the classification of patents and utility models according to the different areas of technology to which they pertain. Therefore, these give an indication of the most important specific technology sub-areas for the microbiome patent landscape. Some of this can be gleaned from the top assignees as described above, which operate in key sectors such as: Food & Drink, Nutrition, Pharma/Biotech (with a focus on microbiome) and Diagnostics. However, the IPC code is the formal structure in which technologies described within a patent are classified, and so provide additional information. Below is a table displaying the top 10 IPC codes in order of commonality, with the corresponding description.

IPC Code	Description
A61K	Medical Preparations: Preparations for medical, dental or toilet purposes
C12Q	Micro-organisms or enzymes: measuring or testing processes involving enzymes or micro-organisms; compositions or tests, processes of preparing such compounds, condition-responsive control in microbiological or enzymological processes
A61P	Medical Preparations: Specific therapeutic activity of chemical compounds or medicinal preparations
A23L	Food: Foods, Foodstuffs or non-alcoholic beverages; their preparation or treatment e.g. cooking, modification of nutritive qualities, physical treatment; preservation of foods or foodstuffs in general
C12N	Micro-organisms or enzymes: propagating, preserving or maintaining micro-organisms, mutation or genetic engineering, culture media
G01N	Measuring; Testing: Investigating or analysing materials by determining their chemical or physical properties
A01N	Agriculture: preservation of bodies of humans or animals or plants; biocides as disinfectants, pesticides, herbicides, pest repellents or attractants, plant growth regulators
G06F	Instruments: Electronic digital data processing
C12P	Chemistry: fermentation or enzyme using processes to synthesise a desired chemical compound or composition to separate optical isomers from a racemic mixture
A23C	Food: dairy products, e.g. milk, butter, cheese; or substitutes; and making of such foodstuffs

These top application areas based on the above IPC codes are described in the chart below. The Human Necessities (A) category is most common among the data, with the broad category for medical preparations given as top (32%). Similarly, other categories of medical preparation, specifically for therapeutic activity (A61P), and more broadly for human necessities in agriculture (A01N) are given. Micro-organisms, enzymes or fermentation is next common (C12) with propagating, genetic engineering or culture (C12N) as well as measuring or testing (C12Q) or for use in fermentation or enzyme based compound synthesis (C12P).



The parallel Thomson Innovation DWPI classification of the main technology areas are given below. We can see that pharmaceutical natural products & polymers is the most common category (29% of the dataset), followed closely by the food & fermentation industrial technology (27%); food & fermentation, other foodstuffs and treatment; and then pharmaceutical organic compounds (7%); scientific instrumentation (4%) and polymers and plastics (4%). The dominant focus for this microbiome patent data therefore is confirmed to be pharmaceutical natural products and polymers as well as nutritional food and foodstuff applications. These subcategories are described in detail in the table following.



DWPI Class-Main	Description	Document Count
B04	Pharmaceuticals: Natural products and polymers - including testing of body fluids (other than blood typing or cell counting), pharmaceuticals or veterinary compounds of unknown structure, testing of microorganisms for pathogenicity, testing of chemicals for mutagenicity or human toxicity and fermentative production of DNA or RNA, and general compositions	580
D16	Food & Fermentation: Fermentation industry – including fermentation equipment, brewing, yeast production, production of pharmaceuticals and other chemicals by fermentation, microbiology, production of vaccines and antibodies, cell and tissue culture and genetic engineering	546
D13	Food & Fermentation: Other foodstuffs and treatment – including preservation of food, milk, milk products, butter substitutes, edible oils and fats, non-alcoholic beverages, artificial sweeteners, food additives and animal feed (A23B-L)	316
B05	Pharmaceuticals: Other organics - aromatics, aliphatic, organo-metallics, compounds whose substituents vary such that they would be classified in several of B01 - B05	139
S03	Instrumentation, measuring and testing: Scientific Instrumentation (G01J, K, N, T-W): Photometry, calorimetry. Thermometers. Meteorology, geophysics, measurement of nuclear or X-radiation. Investigating chemical or physical properties.	84
A96	Polymers and Plastics: Applications Medical, dental, veterinary and cosmetic	84
T01	Computing and Control: Digital Computers (G06C-F, G06T) Input/output arrangements and interfaces, data conversion and handling, e.g. arithmetic functions. Program control and systems software e.g. program and instruction execution, operating systems, etc. Error detection and correction, computer system architecture and data transfer. Distributed computing and computer networks. Computer applications.	83
B03	Pharmaceuticals: Other heterocyclics (NOT fused ring heterocyclics)	72
C03	Agricultural Chemicals: Other organic compounds, inorganic compounds and multi-component mixtures, polymers and proteins	60
D21	Cosmetics, Disinfectants and Detergents: Preparations for dental or toilet purposes - including filling alloys, compositions for dentures or dental impressions, anti-caries chewing gum, plaque disclosing compositions, toothpastes, cosmetics, shampoos, topical anti-sunburn compositions and toilet soaps (A61K)	56

PATENT LANDSCAPING

The patent search was mapped using Thomson Innovation's proprietary ThemeScape mapping tool. ThemeScape uses term frequency and other algorithms to cluster documents based on shared language – in this case the English Title, Abstract and Claims from the patent filings together with the DWPI-enhanced Titles and Abstracts. It uses several algorithms to perform terminology based clustering. The text from one record is compared with the text from all other patent records within the search collection. The map then uses vectors to give each patent record a proximity score to all of its peers. The outcome of this analysis is a visualisation of the patent space with extra patent (dot) represented once in the map. Patents

in close proximity share more phraseology than those located apart. The patents are grouped into map "contours" to show areas of high and low patenting activity organised into common themes. The illustration shows these contour lines, with the "mountain peaks" representing a concentration of patents. Each peak is labelled with the key terminology concepts contained in the patents within the cluster.

Although the landscaping is not an entirely precise tool, it is possible to identify clusters of technology areas on the map which can be useful for analysing trends within the dataset. The resulting maps from these searches are shown in the following pages.

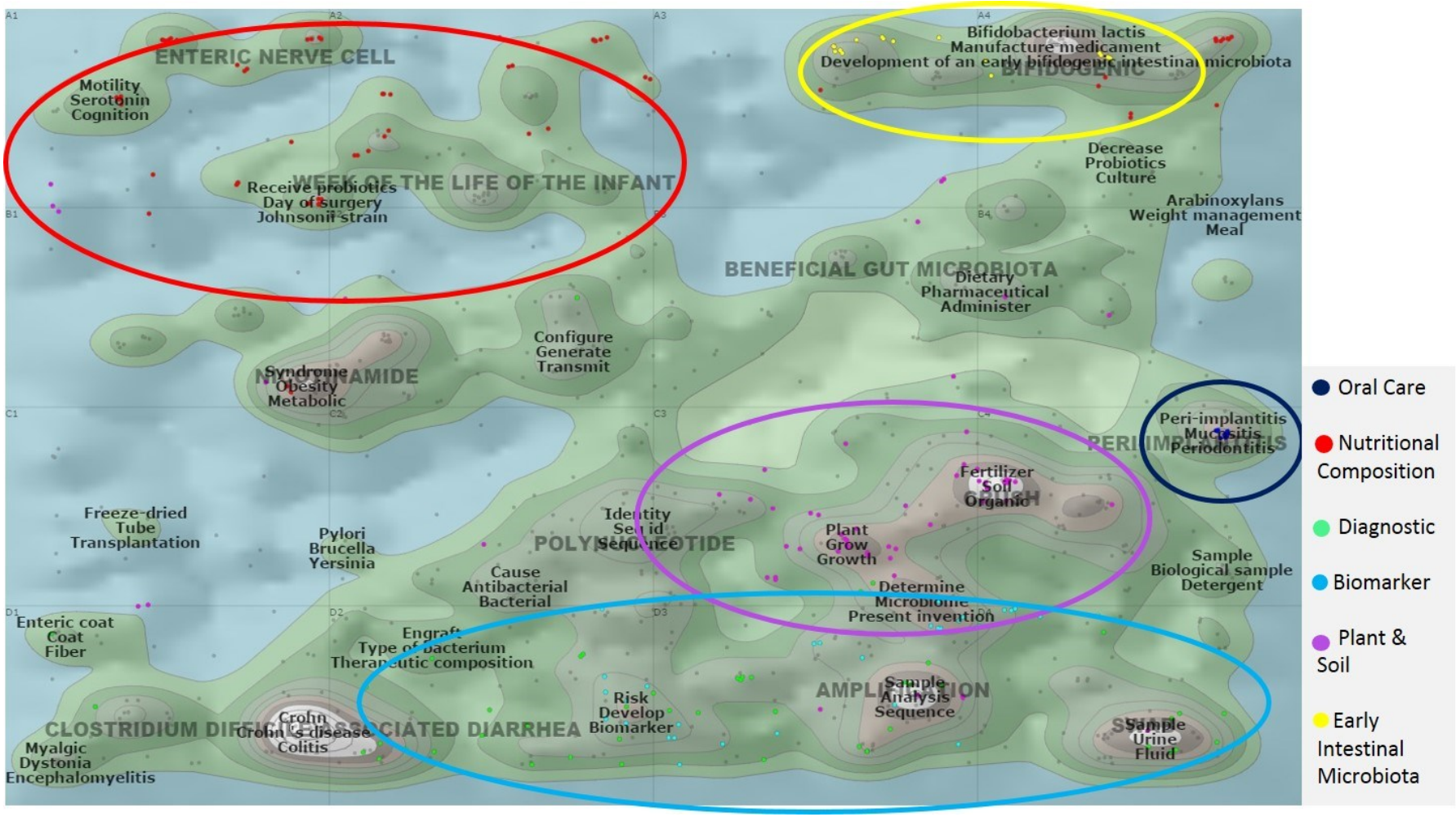
Literature reviewed during the research for this whitepaper has indicated that within the human necessities IPC category, A61K 35/74, for live biotherapeutic products, the therapeutic indications of focus can be broadly categorised as: infection, digestive disorders, metabolic disorders, inflammatory or immune disorders and other indications (including cancer, mental and neurological disorders, oral disease, skin disease, kidney disease, connective tissue disorders and cardiovascular diseases).[54] These trends were also apparent in our broader patent search across the IPC codes. Additional technology commentary indicates that across the broader microbiome patent space, some common themes which are emerging include: bacterial supplements; engineered bacteria; bacterial mixtures; restoration of gut bacteria; small molecules or biologics for promotion of growth of beneficial bacteria.[5]

The patent analysis given here reinforces these therapeutic areas of focus, but also builds a broader picture of the landscape. The technology areas of interest within the dataset (Landscape 1) show some of the key terms identified in various clusters include topical areas such as: Beneficial Gut Microbiota; Clostridium Difficile Associated Diarrhoea; Amplification (which is often associated with genetics and diagnostics). In addition, there were many key terms associated with early infant diseases and microbiota (such as *Bifidobacterium lactis*) identified in the top-right and top-mid of the map. This is a key area for one of the top players, Danone, which has a core focus on infant formula manufacture. The gut-brain-axis is another key theme for the microbiome, and can be seen in the top left of the map under the enteric nervous system (ENS) section. The ENS is a network of neurons that run through the GI-tract, through which the gut vagus nerve endings communicate with the brain and vice versa. Technologies relating to gut microbiota influencing the synthesis of neurochemicals fall under this theme. Other keywords are highlighted in colour on landscape 1, and include the top, broad, theme of Nutritional Compositions; as well as Plant and Soil-related patents as well as oral care. There are many additional technology areas within the landscape which may become increasingly important and more prevalent in future.

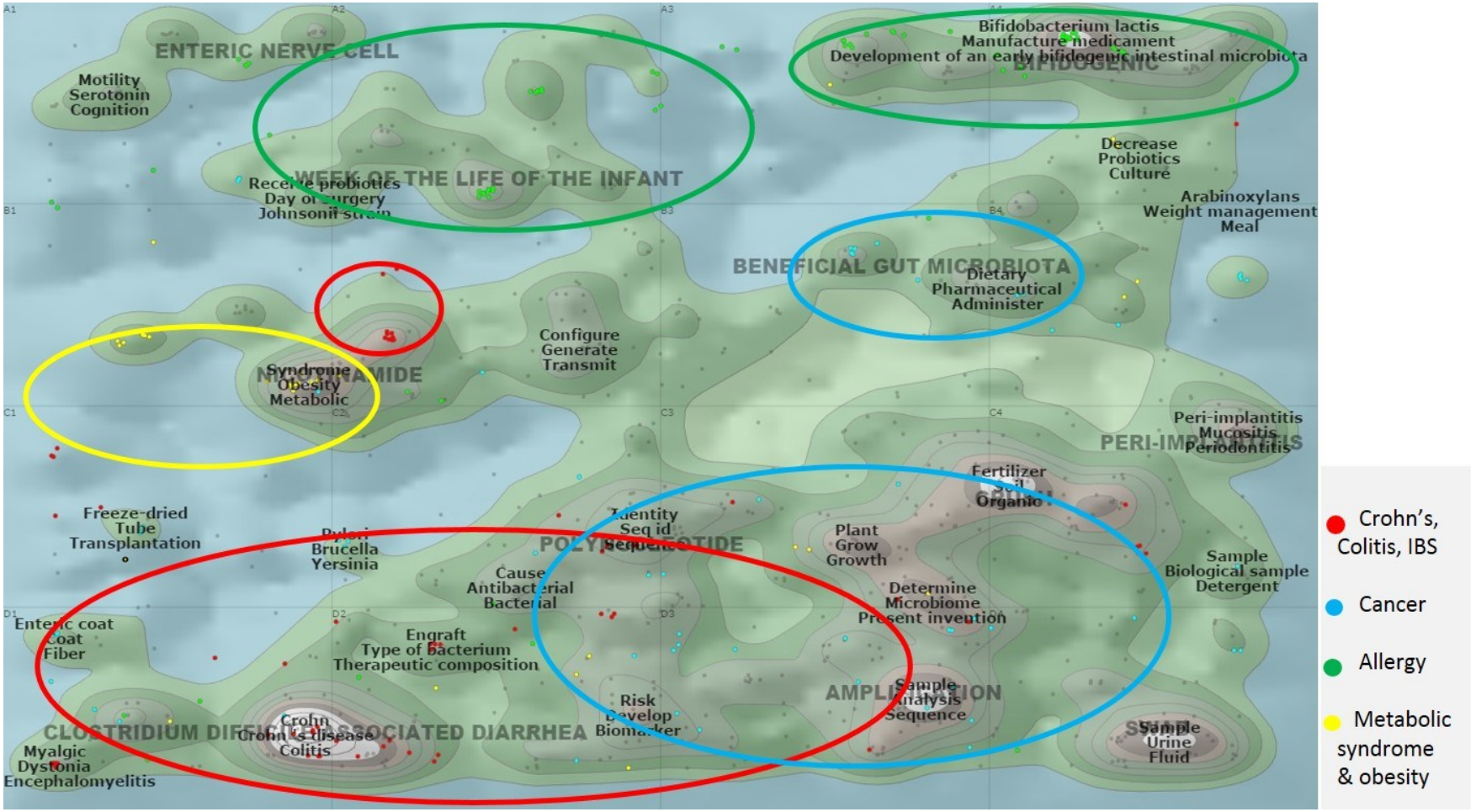
The second landscape map (Landscape 2) attempts to focus more on the therapeutic topics, where several of the top themes were identified. The commonly used terms of therapeutic focus included diseases such as Crohn's Disease, Ulcerative Colitis, Chronic Fatigue and Irritable Bowel Syndrome (IBS). These diseases unsurprisingly have a strong tendency to cluster together as diseases of the gut. Furthermore there was significant overlap with these patent cases and the Clostridium Difficile Associated Diarrhoea topic area in the bottom left

[54] Sun et al. (2016). Patent watch: Modulating the human microbiome with live biotherapeutic products: intellectual property landscape. *Nature Reviews Drug Discovery*, 15, 224-225.

of the map. Allergy was another common therapeutic topic of therapeutic focus within the landscape. This overlapped significantly with the early infant theme in the top right and top middle of the map. Cancer appeared as another disease area of interest within the dataset. Interestingly there was significant overlap with the diagnostic and genetics technology area of the map in the bottom right; with some overlap in the beneficial gut microbiota and dietary pharmaceutical theme area in the mid-right. This suggests that there is significant activity in the cancer diagnostics space in relation to the microbiome as well as the cancer therapeutics space. Metabolic syndrome (including type-2 diabetes) and obesity also occupied a peak on the map around the mid-left; also close to a small spin-off section of patent cases related to the Crohn's, Colitis and IBS cluster.



Landscape 1: The landscape aims to select some of the key technology themes from the broad microbiome patent search of 886 patent families. The coloured dots refer to patents with keywords shown in the legend. The circles indicate clusters of similar patents. Here some common themes include infant health, denoted by the early intestinal microbiota legend (yellow) as well as the key topic life of the infant. This overlaps with nutritional composition (red), other topics include diagnostics (blue/green) and oral care. Some patents relate to soil and plant growth.



Landscape 2: Notably missing from Landscape 1 was the therapy technology category. This is because this technology theme is fairly ubiquitously spread throughout the microbiome patent dataset. Therefore this Landscape 2 aims to give an overview of some of the key disease areas within the dataset. There is much overlap, suggesting that patents will mention or cover multiple disease areas – whether for therapy or diagnostic purposes. We can see above there is a prevalence of traditionally known gut disorders (Crohn's, Colitis, Irritable Bowel Disease (IBS), Chronic Fatigue Syndrome etc. (red dots and circles); similarly, Cancer is well spread throughout the landscape, with overlap for the diagnostic theme (bottom right) and Beneficial Gut Microbiota theme.

KEY PATENTS

A patent citation analysis identifies key patents and patent applications and their corresponding assignees, within a patent dataset. Citations link documents together based on the citing of one document in another. For patents this means the document has related content. In patent literature citations will either mean that the applicant has disclosed the former patent as prior-art, or the examiner from the patent office identified the former patent during the search.

A backward citation is the term used for a traditional citation, and refers to the document cited in a more recent publication. A forward citation is commonly used in patent analytics and refers to the citing documents. The number of forward citations refer to citations received by a particular patent by subsequent patents. The frequency may be an indicator of key inventions or patents with high value. Publications with higher numbers of recent backward citations on the other hand are more likely to be key strategic or defensive patents.[55]

FORWARD CITATION ANALYSIS

The table below summarises the top 10 patent publications with the highest number of forward citations. The DWPI summary for the novelty described in the patent abstract is included for each publication. The more recent the application date, the more likely it is that the given publication is a key invention in the microbiome space. There are several noteworthy patents in relation to gut microbiotics and diagnostics within the dataset.

1. US9028841B2 – **Seres Therapeutics** patent titled *synergistic bacterial compositions and methods of production and uses thereof*

2. US20120149584A1 – **PureTech Ventures** titled *Methods of diagnosing and treating microbiome-associated disease using interaction network parameters*

[55] Abrams *et al*. (2013). Patent Value and Citations: Creative Destruction or Strategic Disruption? *National Bureau of Economic Research*; NBER Working Paper No. 19647

	No. of citations	Publication Number	Assignee - DWPI	Application Date	Publication Date
1	14	US20130121968A1	ATOSSA GENETICS INC (Seattle, USA)	03/10/2011	16/05/2013
	Title: Methods of combining metagenome and the metatranscriptome in multiplex profiles				
	Abstract - DWPI Novelty: The method involves isolating and quantifying a portion of 16S ribosomal RNA of a sample from a patient to determine a metagenomic profile. A portion of messenger RNA of the sample is isolated and quantified to determine a metatranscriptome profile. A multiplex profile of the metatranscriptome profile and the metagenomic profile is compared with a multiplex profile of population of patients diagnosed with a medical condition using a general-purpose computer to determine the presence or absence of the medical condition.				
2	14	WO2011005756A1	PURETECH VENTURES	06/07/2010	13/01/2011
	Title: DELIVERY OF AGENTS TARGETED TO MICROBIOTA NICHES				
	Abstract - DWPI Novelty: Delivering (M1) a pharmaceutical formulation to a bacterial niche of an animal host involves selecting at least one feature that differentiates the bacterial constituents of the niche from the rest of bacterial residents that coexist in the same anatomical location; and providing a delivery system that exploits the feature to release a pharmaceutical formulation preferentially in the vicinity of the constituents of a bacterial niche.				
3	11	US20120149584A1	PURETECH VENTURES	20/02/2012	14/06/2012
	Title: METHODS OF DIAGNOSING AND TREATING MICROBIOME-ASSOCIATED DISEASE USING INTERACTION NETWORK PARAMETERS				
	Abstract - DWPI Novelty: The method involves analyzing a biological interaction network within a superorganism includes microbial derived component, such that a superorganism is an organism consisting of many organisms, and a microbial derived component is a microbe, or a gene, protein, transcript, carbohydrate, lipid, or metabolite derived from a microbe. A node or edge is selected in the network, such that a node is a terminal point or an intersection point of a graphical representation of a network and an edge is a link between two nodes. The modulators of the node or edge are provided.				
4	10	US20140179726A1	UNIV VIRGINIA COMMONWEALTH | US DEPT VETERANS AFFAIRS | UNIV MASON GEORGE	17/02/2014	26/06/2014
	Title: GUT MICROFLORA AS BIOMARKERS FOR THE PROGNOSIS OF CIRRHOSIS AND BRAIN DYSFUNCTION				
	Abstract - DWPI Novelty: Assessing presence or the risk of development of encephalopathy in patient with liver disease involves (a) analyzing gut microflora of the patient in order to determine gut microbiome signature for the patient, (b) comparing the gut microbiome signature of the patient to one or more gut microbiome reference signatures, (c) concluding patient having or is at risk of developing encephalopathy, and/or (d) concluding patient not having or is at risk of developing encephalopathy.				
5	9	WO2011096809A1	FRIESLAND BRANDS BV	04/02/2011	11/08/2011
	Title: USE OF SIALYL OLIGOSACCHARIDES TO MODULATE THE IMMUNE SYSTEM				

	No. of citations	Publication Number	Assignee - DWPI	Application Date	Publication Date
	Abstract - DWPI Novelty: In the manufacture of a dietetic, nutraceutical, nutritional or pharmaceutical composition for enhancing the maturation of the developing immune system a sialyl-oligosaccharide is used.				
6	8	US9028841B2	SERES THERAPEUTICS	20/03/2014	12/05/2015
	Title: Synergistic bacterial compositions and methods of production and use thereof				
	Abstract - DWPI Novelty: Treating or preventing an occurrence or a recurrence of a Clostridium difficile infection, comprises administering, to a human subject, a composition comprising a first purified bacterial population comprising bacteria comprising 16S ribosomal RNA (rRNA) sequence identical to a 16S rRNA sequence present in a reference Collinsella aerofaciens operational taxonomic unit (OTU), and a second purified bacterial population comprising bacteria comprising 16S rRNA sequence identical to a 16S rRNA sequence present in a reference bacterium e.g. Actinomyces europaeus.				
7	8	US20140363397A1	UNIV QUEENS KINGSTON | KINGSTON GEN HOSPITAL | UNIV GUELPH	20/08/2014	11/12/2014
	Title: METHOD FOR TREATMENT OF DISORDERS OF THE GASTROINTESTINAL SYSTEM				
	Abstract - DWPI Novelty: Synthetic stool preparation comprises a mixture of bacterial strains, where at least one of the bacterial strain is the strains as given in the table of specification, or from strains having all of the identifying characteristics of the strains as given in the table of specification, and the mixture comprises one or more isolated bacterial strain.				
8	7	US20150224152A1	UNIV CALIFORNIA | UNIV NEW YORK STATE	29/10/2014	13/08/2015
	Title: METHODS FOR MODULATING BACTERIAL INFECTION				
	Abstract - DWPI Novelty: Enhancing (m1) mucosal immunity in a subject involves administering a single species of T helper 17 (Th17) inducing bacteria or its component, to the subject.				
9	6	US20100048595A1	UNIV WASHINGTON IN ST LOUIS | UNIV WASHINGTON OFFICE TECHNOLOGY MANAGE | UNIV WASHINGTON ST LOUIS	28/09/2009	25/02/2010
	Title: USE OF ARCHAEA TO MODULATE THE NUTRIENT HARVESTING FUNCTIONS OF THE GASTROINTESTINAL MICROBIOTA				
	Abstract - DWPI Novelty: Modulating the carbohydrate degrading properties of the gastrointestinal microbiota, carbohydrate metabolism, or the transcriptome or the metabolome of at least one microbe comprising the gastrointestinal microbiota in a subject involves altering the presence of the archaeon population in the subject's gastrointestinal tract, is new.				
10	5	US9186278B2	ELWHA LLC	27/11/2013	17/11/2015
	Title: Systems and devices for sampling and profiling microbiota of skin				

	No. of citations	Publication Number	Assignee - DWPI	Application Date	Publication Date
	Abstract - DWPI Novelty: The system (100) has an analyser including sensor component whose circuitry detects signals emitted or reflected from microbe-capture region of elongated flexible strip (130) of microbe sampling unit and transforms detected signals into sensor output. A location information reader comprises circuitry to read information associated with location of regions of skin surface (110) of individual (120) from location information storage component of microbe sampling unit and to transform information into location output. The microbe-capture region comprises biomolecule-binding polymer.				

BACKWARD CITATION ANALYSIS

The table given below summarises the top 10 patent publications with the highest number of backward citations. As with the forward citation analysis, the DWPI Novelty has been included for each publication. Several patents are assigned to organisations identified as key in the sector throughout this report.

Seres Therapeutics is again listed, this time with US9585921B2 as the joint second top cited patent with *Compositions and methods for populating gastrointestinal tract of mammalian subject involves orally administering composition having purified population of spore-forming bacteria produced by providing faecal material, and subjecting material purification of bacteria.* In addition, the previously identified patent from the forward citation analysis is given; US9028841B2 *Synergistic bacterial compositions and methods of production and use thereof.*

The US **National Institutes of Health** (NIH) have the top backward cited patent with the patent filing US9649343B2 *Compositions and methods for transplantation of colon microbiota*. The patent has a priority filing date of 09/03/2011 and was granted in May 2017.

Two filings from **Elwha LLC** in relation to their systems and devices for profiling microbiota of the skin are included in this table of top cited patents, indicating an authoritative position within the skin microbiome technology applications. It seems **Elwha LLC** is a holding company of Intellectual Ventures, itself a patent holding company.

Rebiotix Inc, a US-based microbiota restoration therapy company, also have a patent filing of interest in this top 10. US9642880B2 *Microbiota restoration therapy (MRT), compositions and methods of manufacture* with a priority filing date in June 2013 may be central to the ulcerative colitis therapeutic applications of microbiome patents.

	No of citations	Publication Number	Assignee - DWPI	Application Date	Publication Date
1	128	US9649343B2	National Institutes of Health (NIH)	09/09/2016	16/05/2017
	Title: Compositions and methods for transplantation of colon microbiota				

	No of citations	Publication Number	Assignee - DWPI	Application Date	Publication Date
	Abstract - DWPI Novelty: The present invention provides compositions that include an extract of human faces, and methods for using such compositions, including methods for replacing or supplementing or modifying a subject's colon microbiota, and methods for treating a disease, pathological condition, and/or iatrogenic condition of the colon.				
2	110	US9642871B2	MARINE POLYMER TECHNOLOGIES INC	29/10/2015	09/05/2017
	Title: Anti-bacterial applications of poly-N-acetylglucosamine nanofibers				
	Abstract - DWPI Novelty: Treating a bacterial infection in a subject, comprises topically administering a composition comprising shortened fibers of poly-N-acetylglucosamine and/or their derivatives (sNAG nanofibers) to a subject diagnosed with the bacterial infection/displaying one or more symptoms of the bacterial infection, where more than 50% of the sNAG nanofiber is 1-15 µ m in length, the sNAG nanofibers do not have an effect on bacterial growth/survival of Staphylococcus aureus bacterial cultures in vitro and the sNAG nanofiber is non-reactive when tested in an intramuscular implantation test.				
3	110	US9585921B2	SERES THERAPEUTICS INC	15/10/2015	07/03/2017
	Title: Compositions and methods for populating gastrointestinal tract of mammalian subject involves orally administering composition having purified population of spore-forming bacteria produced by providing faecal material, and subjecting material purification of bacteria				
	Abstract - DWPI Novelty: Populating the gastrointestinal tract of a mammalian subject involves orally administering to the mammalian subject a therapeutic composition comprising a purified population of spore-forming bacteria produced by a) providing faecal material, and b) subjecting the material to treatment step resulting in purification of spore-forming bacteria, where purified population is present in an amount effective to engraft and/or augment in gastrointestinal tract in order to treat or prevent a dysbiosis in the mammalian subject.				
4	99	US9539269B2	ABBOTT LABORATORIES	22/12/2011	10/01/2017
	Title: Methods for decreasing the incidence of necrotizing enterocolitis in infants, toddlers, or children using human milk oligosaccharides				
	Abstract - DWPI Novelty: Reducing the incidence of necrotizing enterocolitis in an infant in need, toddler or child involves administering to the infant, toddler or child, a composition comprising human milk oligosaccharides.				
5	88	US9610037B2	ELWHA LLC	27/11/2013	04/04/2017
	Title: Systems and devices for profiling microbiota of skin				
	Abstract - DWPI Novelty: A microbe profiling system comprises replaceable microbe sampling unit, location information storage component configured to store information associated with location of one or more regions of skin surface (110) of individual (120), and analyser in which replaceable microbe sampling unit consists of substrate consisting of microbe-capture region, microbe-capture region is configured to capture ≥ 1 type of microbe from one or more regions of skin surface of an individual, and analyser consists of receiving region sized to accept replaceable microbe sampling unit and ≥ 1 sensor component.				
6	88	WO2017021961A1	YEDA RESEARCH AND DEVELOPMENT CO.	02/08/2016	09/02/2017
	Title: METHODS OF SCREENING FOR RIBOSWITCHES AND ATTENUATORS				

	No of citations	Publication Number	Assignee - DWPI	Application Date	Publication Date
	Abstract - DWPI Novelty: An isolated polynucleotide comprising a nucleic acid sequence of SEQ ID NOs: 1-44 operatively linked to a heterologous nucleic acid sequence is new.				
7	87	US9526450B2	ELWHA LLC	27/11/2013	27/12/2016
	Title: Devices and methods for profiling microbiota of skin				
	Abstract - DWPI Novelty: A microbe profiling device (100) comprises device head (130) comprising epidermis-engaging component (140) and ≥ 1 access window (150) and hand-held housing (160) in which device head is configured to dislodge ≥ 1 microbe from skin surface (110) of individual (120), hand-held housing is defined as opening aligned with access window, and hand-held housing comprises motor operably coupled to ≥ 1 motivatable component, substrate disposed in relation to motivatable component and configured to be operable communication with opening defined by hand-held housing, and location-capture component.				
8	82	US9642880B2	REBIOTIX INC	12/11/2015	09/05/2017
	Title: Microbiota restoration therapy (MRT), compositions and methods of manufacture				
	Abstract - DWPI Novelty: Treating ulcerative colitis, comprises administering a microbiota restoration therapy composition to a patient. The microbiota restoration therapy composition is pre-screened for bacterial diversity, where the pre-screened microbiota restoration therapy composition comprises bacteria from at least seven different families and has a Shannon diversity index of 0.4-2.5 when calculated at the family level and the microbiota restoration therapy composition comprises a mixture of faecal microbiota and polyethylene glycol.				
9	79	US9028841B2	SERES THERAPEUTICS	20/03/2014	12/05/2015
	Title: Synergistic bacterial compositions and methods of production and use thereof				
	Abstract - DWPI Novelty: Treating or preventing an occurrence or a recurrence of a Clostridium difficile infection, comprises administering, to a human subject, a composition comprising a first purified bacterial population comprising bacteria comprising 16S ribosomal RNA (rRNA) sequence identical to a 16S rRNA sequence present in a reference Collinsella aerofaciens operational taxonomic unit (OTU), and a second purified bacterial population comprising bacteria comprising 16S rRNA sequence identical to a 16S rRNA sequence present in a reference bacterium e.g. Actinomyces europaeus.				
10	49	US9215997B2	Shuck L. Zane (WV,USA)	28/06/2013	22/12/2015
	Title: In vivo technology system for human gut research, diagnostics and treatment				
	Abstract - DWPI Novelty: In vivo gut technology system provides new investigative and health care methods and processes, and three individual, stand-alone inventions, that when combined logistically, strategically, and applied in combinations, and comprises synergistic, multidisciplinary system with diversified applications for gut healthcare.				

COMMENTARY ON GRANTING OF PATENTS

Alongside the patent analysis given above, there is some interesting commentary from patent experts about key microbiome filings and new patent issues.

Market reports have suggested that although there are a number of companies building patent portfolios, there are also some concerns about patentability in the microbiome field. Microbiome-based therapies typically involve compositions of bacteria (e.g. probiotics). Many of the therapies will use desirable bacterial species to change the microbiome composition to

conditions which are favourable or less susceptible to disease. Some experts in patent prosecution have indicated that where bacterial consortia are a key element of the claims, there may be issues with regard to the validity of patentable subject matter as natural organisms or products are not patentable material in and of themselves.[5] However, it seems there are still key patents being granted, as the above backward cited patents list and patent publication trends chart indicates.

In August 2016 **Vedanta Biosciences** were successfully granted their US patent. **PureTech**, the founder of **Vedanta**, has been identified in our forward citation analysis given above. This filing broadly covers pharmaceutical compositions for microbiome therapeutics based on clostridium live bacterial strains. The USPTO issued US9,415,079 after the patent was also issued in Japan. The patent is exclusively licensed to **Vedanta** from the University of Tokyo, and it is subject to an inflammatory bowel disease collaboration agreement with **Janssen Biotech**. As such, the successful issue of the US patent triggered a $2 million milestone payment from Janssen. The patent coverage is likely to persist through to at least 2031, providing the companies with approximately 15 years' exclusivity on broad, fundamental claims on key compositions in the microbiome space. **Vedanta** believes that the case puts it in a position of IP leadership in the microbiome field.[56] Additional related patents in **Vedanta**'s portfolio have also been issued (US 9,421,230 and US 9,433,652).

At a similar time in 2016, **Synthetic Biologics** announced the granting of European and US composition of matter patents for Ribaxamase. The therapy is a phase II drug candidate for prevention of C. difficile infection (CDI), antibiotic-associated diarrhoea (AAD) and antibiotic-resistant organisms. Whilst it targets the microbiome, the drug itself is enzymatic in nature. **Symbiotix Biotherapies Inc**. was also issued their US patent for a novel class of molecular therapeutics, ZPS therapeutics, which are based on zwitterionic polysaccharides. The press release indicates that the microbiome-based therapy represents a novel approach to modulating the immune system. The patent was the first composition of matter patent issued by the USPTO for a molecule which emerged from the human microbiome.[57]

A central idea for harnessing the microbiome is in neurological medicine. The gut-brain-axis, beginning with the enteric nervous system, and gut microbes interacting with it, have been found to alter human brain function and mood. The promise of bacteria and treatment for mood disorders, or "psychobiotics", is now a promising area of therapy development. **NuBiome**, based in California have one of the first patents issued in the space (US8,927,242) for treatment of children suffering Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS), which can result in obsessive compulsive disorder.[58]

Evolve Biosystems, a biotech developing novel solutions for infant gut dysbiosis, recently faced patent opposition from **Danone**. **Evolve**, a spin-off from the Foods for Health Institute

[56] Financial Times (August, 2016). *PureTech's Vedanata Biosciences Granted US Patent*.

[57] Businesswire, (Feb, 2017). *Symbiotix Biotherapies Announces Issuance of First Composition of Matter Patent Covering a Microbiome-derived Therapeutic Molecule*.

[58] Dillworth IP (2015). *The Emergent Microbiome: A Revolution for the Life Sciences – Part II, 2015 Patent Trends.*

(FFHI) at the **University of California Davis** (USA), have significant overlap with **Danone** in their technology focus area given the latter's market penetration for infant nutrition. The EPO upheld **Evolve**'s EP2405918 in 2016, which has claims relating to prophylactic and therapeutic compositions of certain galactoooligosaccharides and key commensal species of bifidobacteria. The rights are applied to the prebiotic and bifidobacteria space in relation to infant nutrition.[59] The patent was originally licensed to **Evolve** from the Regents of the **University of California**, which has been identified in our list of top academic patenting institutions.

In the plant and agriculture field, **NewLeaf Symbiotics** secured European and Japanese patents for the technology which permits the rapid cost-effective production of large quantities of Pink-Pigmented Faculative Methylotrophs (PPFM), a naturally occurring beneficial bacteria which can improve yield and pest tolerance in treated crop[60].

[59] http://www.marketwired.com/press-release/evolve-biosystems-successfully-defends-european-patent-opposition-danone-maintaining-2184462.htm

[60] http://www.brdgpark.com/press_release/newleaf-symbiotics-secures-key-patents-in-europe-and-japan/

APPENDIX

APPENDIX 1: DEALS

Sector	Acquirer/Investors/ Licensee	Acquired /Licensor	Deal Type	Year	Financials	Details
Human Health Therapeutics	Spruce Capital Partners/MLS; Horizons Ventures; Tate & Lyle Ventures. Bow Capital; Acre Venture Partners	Evolve BioSystems, Inc	Venture Financing	2017	$20m	Evolve BioSystems, Inc. announced that it has completed a $20 million Series B financing to fund the commercialization of its initial products.
Human Health Therapeutics	AJU IB Investment Co., Ltd. ; Perceptive Advisors LLC ; Atlas Venture L.P. ; others	Synlogic Inc	Venture Financing	2017	$42m	Synlogic, Inc. has raised USD42 million in series C preferred stock financing. The company intends to use the proceeds to progress its two lead metabolic disease programs through patient proof-of-concept studies as well as advance the development of its earlier product candidates.
Human Health Therapeutics	Mirna Therapeutics, Inc	Synlogic Inc	Merger	2017		Synlogic, Inc. and Mirna Therapeutics, Inc., a developer of microRNA (miRNA) replacement therapies for cancer, have agreed to merge in a reverse merger transaction. The merger will enable Synlogic and Mirna to advance Synlogic's platform for the discovery and development of novel synthetic biotic medicines.
Human Health Therapeutics	Commense, Inc	University of British Columbia	Licensing Agreement	2017	undisclosed	PureTech Health plc is pleased to announce a licensing agreement between Commense, Inc, a subsidiary of PureTech Health, and UBC for a microbiome-based therapy directed toward the prevention of asthma and other allergic diseases that present in childhood.
Animal Health	Sustainable Income Capital Management, Connecticut Innovations	Bactana Animal Health	Venture Financing	2017	undisclosed	This Series A investment will allow Bactana to further validate previously published trial results, expand the product pipeline, and begin preparing for commercialization
Human Health Therapeutics	NCI Gestion, S.A.S; Pontifax Ltd.; Seventure Partners; Zaluvida Corporate Sdn. Bhd.	TargEDys SAS	Venture Financing	2017	$3.7m	TargEDys SAS has raised an additional EUR3.5 million (USD3.71 million) in series A financing. The finance was provided by new investor Zaluvida Corp. Sdn Bhd.
Human Health Therapeutics	Nubiyota LLC	Takeda Pharmaceutical Company Ltd	Partnership	2017		Takeda has entered into a agreement with NuBiyota LLC for the development of Microbial Ecosystem Therapeutic products for gastroenterology (GI) indications with a high unmet medical need.

Sector	Acquirer/Investors/ Licensee	Acquired /Licensor	Deal Type	Year	Financials	Details
Human Health Therapeutics	Takeda Pharmaceutical Company Ltd	Finch Therapeutics Inc	Licensing Agreement	2017	$10m upfront; undisclosed milestones	Takeda has entered into licensing agreement with Finch Therapeutics to jointly develop FIN-524, a synthetic microbiome therapy for IBD.
Human Health Therapeutics	Ferring International Center SA	VSL Pharmaceuticals Inc	Partnership	2017		Ferring Pharmaceuticals has entered into agreement with CD Investments (VSL Pharmaceuticals, Inc.) for CDI's VSL3 marketing rights in European markets. VSL3 is a food supplement, containing 450 billion live bacteria in eight different strains per sachet.
Human Health Therapeutics	Elysium Health Inc	Harvard University	Partnership	2017		Elysium Health has entered into a multi-year agreement with Harvard University to fund research projects focused on cellular function and other key modulators in the aging process. The project will focus on generating a fundamental understanding of the biological mechanisms by which the microbiome and dysbiosis affect systemic levels of NAD+
Human Health Therapeutics	Finch Therapeutics Inc	OpenBiome	Licensing Agreement	2017	undisclosed	Finch Therapeutics has entered into a licensing agreement with OpenBiome to develop FIN-403, an orally administered microbial therapy for recurrent C. difficile infections. Finch Therapeutics obtained license biomanufacturing quality system from OpenBiome. Finch Therapeutics will upgrade this manufacturing system, and provide microbiota preparations produced in this improved environment to OpenBiome.
Human Health Therapeutics	Stanford University School of Medicine	Vedanta Biosciences Inc	Partnership	2017		Vedanta Biosciences has entered into translational medicine collaboration with Stanford University School of Medicine to focus on food allergies in children and on patients with C. difficile infection or graft-versus-host disease. Vedanta Biosciences will analyze the potential connection between the gut microbiome and responses to oral immunotherapies in children with food allergies.
Human Health Therapeutics	Leiden University Medical Center	Vedanta Biosciences Inc	Partnership	2017		Vedanta has entered into translational medicine collaboration with Leiden University Medical Center to focus on food allergies in children and on patients with C. difficile infection or graft-versus-host disease. Vedanta will generate clinical data from interventional studies of faecal transplantation in C. difficile patients treated with donors from the Netherlands Donor Feces Bank
Human Health Therapeutics	Ritter Pharmaceuticals Inc	The University of British Columbia	Partnership	2017		Ritter Pharmaceuticals has entered into an agreement with Dr. B Brett Finlay, from the Michael Smith Laboratories at the University of British Columbia (UBC) to study the role of the microbiome and RP-G28 in environmental enteropathy.
Human Health Therapeutics	Malin Corporation Plc	Artizan Biosciences Inc	Acquisition	2017		Malin Corporation has acquired a 32% shareholding of Artizan Biosciences, Inc. Malin invested in a founding equity round along with the participation of Hatteras Venture Partners. Artizan Biosciences is focus on creating therapies that target the microbiome.
Human Health Therapeutics	DayTwo Ltd.; Weizmann Institute of Science	Janssen Research & Development LLC	Partnership	2017		Janssen Research & Development (Johnson & Johnson), through its Janssen Human Microbiome Institute (JHMI), has entered into an agreement with DayTwo Ltd and the Weizmann Institute of Science for treating metabolic disorders through microbiome-based solutions.

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Human Health Therapeutics	Weizmann Institute of Science	Janssen Research & Development LLC	Partnership	2017		Janssen Research & Development (Johnson & Johnson), through its Janssen Human Microbiome Institute (JHMI), has entered into a research agreement with the Weizmann Institute of Science for human microbiome datasets.
Human Health Therapeutics	Johnson & Johnson Innovation - JJDC Inc; Life Sciences Fund Amsterdam BV	Caelus Health	Venture Financing	2017	$2.68m	Caelus Health BV has raised USD 2.68 million in a series A financing round. The financing was led by Johnson & Johnson Innovation-JJDC, Inc. (JJDC), along with a participation of Life Sciences Fund Amsterdam B.V. (LSFA). The company intends to use the proceeds to advance its pipeline of microbiota-based products for early intervention in cardio-metabolic disease.
Human Health Therapeutics	Stanford University School of Medicine	uBiome Inc	Partnership	2017		Stanford University School of Medicine and uBiome, Inc. have entered into a research agreement to study individuals at risk of developing type 2 diabetes. uBiome will partner with Professor Michael Snyder of Stanford's School of Medicine to conduct a comprehensive research study that will investigate host-microbiome relationships during the onset of type 2 diabetes.
Human Health Therapeutics	Ritter Pharmaceuticals Inc	University of Nebraska	Partnership	2017		Ritter Pharmaceuticals has entered into an agreement with University of Nebraska to study the role of the microbiome and RP-G28 in metabolic syndrome. University of Nebraska plan to conduct research exploring the microbiome's role in metabolic syndrome.
Human Health Therapeutics	Ferring Pharmaceuticals Inc	Intralytix Inc	Partnership	2017		The partners will jointly investigate bacteriophage-based drugs to regulate the microbiome of the female reproductive tract, oral cavity, and skin, in addition to the gut.
Human Health Therapeutics	Allergan Plc	Assembly Biosciences Inc	Licensing Agreement	2017	$50m upfront; undisclosed milestones	The agreement provides Allergan with worldwide rights to preclinical compounds ABI-M201 and ABI-M301, targeting ulcerative colitis (UC) and Crohn's disease (CD).
Human Health Therapeutics	Finch Therapeutics Inc	Intract Pharma Ltd	Partnership	2017		Finch Therapeutics has agreed to use Intract Pharma's Phloral technology to develop a capsule for the targeted delivery of microbial communities into the colon.
Human Health Therapeutics	Undisclosed	Evelo Biosciences Inc	Venture Financing	2017	$30.5m	Evelo Biosciences, Inc. has raised USD30.5 million in a venture financing round. To raise this finance, the company issued equity securities to seven investors.
Human Health Therapeutics	Yale University	Artizan Biosciences Inc	Equity Offerings	2016		Artizan Biosciences has spun out from Yale University. Artizan Biosciences will focus on creating therapies that target the microbiome. In collaboration with Yale University, Artizan has developed a capability of distinguishing certain pathogenic bacteria from the remainder of the intestinal microbiota.
Human Health Therapeutics	Flight Partners Management LLC	Finch Therapeutics Inc	Venture Financing	2016	$5.6m	Finch Therapeutics Inc. has raised USD5.6 million in series A financing. The financing was led by Flight Partners Management LLC.

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Human Health Therapeutics	Undisclosed	Finch Therapeutics Inc	Venture Financing	2016	$3.73m	Finch Therapeutics Inc. has raised USD3.73 million of its planned USD3.75 million venture financing round. To raise this finance, the company issued series A preferred shares to 6 investors.
Human Health Diagnostics	8VC, Slow Ventures, Stanford-StartX	uBiome	Venture Financing	2016	$22m	uBiome, Inc. has raised USD22 million in series B financing round. The company intends to use the proceeds to launch of its testing
Human Health Therapeutics	Axial Biotherapeutics, Inc	California Institute of Technology	Licensing Agreement	2016	Undisclosed	Axial will focus to translate novel and proprietary CNS biotherapeutics into a unique class of microbial-targeted biotherapeutics that could become breakthrough therapies for a variety of neurological diseases and disorders
Agriculture	Khosla Ventures; Otter Capital; Square 1 Bank	BioConsortia	Venture Financing	2016	$12m	BioConsortia, Inc., announced that it has raised this year a total of $12 million for future growth. Last week, BioConsortia closed an $8 million equity round of investment financed by existing investors, Khosla Ventures and Otter Capital, and earlier in the year raised $4 million of venture debt from Square 1 Bank, a division of Pacific Western Bank.
Human Health Therapeutics	Life Sciences Partners BV, Ysios Capital Partners, Sunstone Capital A/S and Flerie Invest AB	OxThera AB	Venture Financing	2016	$34m	OxThera AB has raised EUR32 million (USD34 million) in a venture financing round. The company intends to use the proceeds to complete the Oxabact development program for treatment of primary hyperoxaluria.
Agriculture	Monsanto	Second Genome	Partnership	2016		Monsanto and Second Genome, Inc. have announced a research agreement to accelerate the discovery of new microbiome-based solutions to help farmers better manage environmental challenges on their farms. The collaboration will leverage Monsanto's extensive genomic databases with Second Genome's expertise in analyzing microbial function through big data metagenomics, protein discovery, machine learning, and predictive analytics.
Human Health Therapeutics	Longwood Fund, Domain Associates LLC	Axial Biotherapeutics, Inc	Venture Financing	2016	$19.5m	Axial Biotherapeutics has raised USD19.5 million in series A round of financing.
Human Health Therapeutics	Cambridge Innovation Capital Plc; IP Group Plc	Microbiotica Ltd; Wellcome Trust Sanger Institute	Equity Offerings	2016	$9.98m	Microbiotica Ltd has spun out from Wellcome Trust Sanger Institute. Microbiotica will develop and commercialize defined bacteriotherapies based on the human gut microbiome. Cambridge Innovation Capital plc (CIC) and IP Group plc have invested GBP4 million (USD4.99 million) each, totaling to GBP8 million (USD9.98 million) in Microbiotica.
Agriculture	Family Offices, Illumina Accelerator, Viking Global Investors	Biome Makers	Venture Financing	2016	$2.2m	Biome Makers, an ag bioinformatics startup for the wine industry, has raised $2.2 million in seed funding. The startup will use the funding to perform more testing and expand the database ahead of its commercial launch next year.
Human Health Therapeutics	Aisling Capital; Essex Woodlands Management, Inc.; Health Evolution Partners, LLC	Prolacta Bioscience Inc	Private Equity	2016	$35m	Prolacta Bioscience, Inc. has raised USD35 million in a mezzanine round of financing. The company intends to use proceeds to expand Prolacta's commercial presence in the European market and to support clinical trials for the company's human milk-based nutritional products.

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Human Health Therapeutics	Ferring Pharmaceuticals Inc	MetaboGen AB	Partnership	2016		MetaboGen has developed and patented a concept for how patterns of bacteria in the gut could affect ICP. Ferring Pharma will fund an exploratory study to demonstrate this concept and define differences in the microbiome of healthy women and women with a history of IPC.
Human Health Therapeutics	Bio-Rad Laboratories Inc	Genetic Analysis AS	Partnership	2016		Genetic Analysis AS has entered into agreement with Bio-Rad Laboratories in which Genetic Analysis will receive an equity investment from Bio-Rad in exchange for commercialization rights, in certain territories, for Genetic Analysis's GA-map technology to detect gut dysbiosis.
Human Health Therapeutics	Bristol-Myers Squibb Company	Enterome Bioscience SA	Licensing Agreement	2016	$15m upfront; undisclosed milestones	Bristol-Myers Squibb Company has entered into an agreement with Enterome Bioscience for the discovery and development of microbiome-derived biomarkers, drug targets and bioactive molecules to be developed as potential companion diagnostics and therapeutics for cancer. Bristol-Myers Squibb will be granted exclusive rights to intellectual property and therapies generated during the collaboration.
Human Health Therapeutics		Synthetic Biologics Inc	Equity Offerings	2016	$25m	Synthetic Biologics, Inc. has completed the underwritten public offering of 25,000,000 shares of its common stock and accompanying warrants to purchase 50,000,000 shares of its common stock at a price to the public of USD1 per share and accompanying warrants for USD25 million. The company will receive net proceeds of USD23.3 million.
Animal Health	SOSV LLC	AnimalBiome	Venture Financing	2016	$0.05m	AnimalBiome, engaged in advancing animal health through the latest research on the microbiome, has secured USD0.05 million in venture funding from SOSV LLC, a seed stage venture capital firm.
Human Health Therapeutics		Ritter Pharmaceuticals Inc	Equity Offerings	2016	$5m	Ritter Pharmaceuticals has completed the underwritten public offering of 2,127,660 shares of its common stock at a price of USD2.35 per share, for gross proceeds of USD5 million.
Human Health Therapeutics	Centers for Disease Control and Prevention	Synthetic Biologics Inc	Partnership	2016		Synthetic Biologics has entered into a research contract with the Centers for Disease Control and Prevention (CDC) for microbiome assessment and intervention to address antibiotic resistance.
Animal Health	SOSV LLC	AnimalBiome	Venture Financing	2016	$0.15m	AnimalBiome, engaged in advancing animal health through the latest research on the microbiome, has secured USD0.15 million in venture funding from SOSV LLC, a seed stage venture capital firm. Both companies involved in the transaction are based in the US.
Human Health Therapeutics	Johnson & Johnson Consumer Inc	Xycrobe Therapeutics Inc	Partnership	2016		The agreement, facilitated by Johnson & Johnson Innovation, to focus on further understanding applications of Xycrobe Therapeutics' platform technology developed for the treatment of inflammatory skin diseases.
Human Health Therapeutics	Vedanta Biosciences Inc	NYU Langone Medical Center	Partnership	2016		Vedanta Biosciences will collaborate with NYU Langone on clinical studies to support the identification of new microbiome immunotherapies for cancer. The studies will also explore mechanisms by which the gut microbiome influences the efficacy of checkpoint inhibitors in cancer patients.

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Human Health Therapeutics	Evelo Biosciences Inc	Mayo Clinic	Partnership	2016		Evelo Biosciences will work with Mayo Clinic to isolate and characterize cancer-associated bacteria from patient stool samples and tumor biopsies.
Human Health Therapeutics	Matrisys Bioscience Inc	University of California, San Diego	Licensing Agreement	2016	undisclosed	MatriSys Bioscience, Inc has entered into licensing agreement with University of California for a microbiome based therapy for skin disease.
Human Health Therapeutics	Digitalis Ventures; Pfizer Venture Investments; Roche Venture Fund; SR One Ltd	Second Genome Inc	Venture Financing	2016	$8.4m	Second Genome has raised USD8.4 million in extended series B financing, bringing the total proceeds to USD51 million. The company intends to use the proceeds to accelerate the translation of its microbiome discoveries into a pipeline of clinical opportunities.
Human Health Therapeutics	Seres Therapeutics Inc	Emulate Inc	Partnership	2016		Seres Therapeutics and Emulate will work to further advance Emulate's intestine-chip platform, a micro-engineered, living-tissue-based system that models the human intestine. Seres Therapeutics intends to use the technology to identify novel bacteria compositions with therapeutic potential.
Human Health Therapeutics	Evelo Biosciences Inc	Epiva Biosciences Inc (Inactive)	Merger	2016		Epiva Biosciences has merged with Evelo Biosciences, Inc, developing therapeutics for cancer, autoimmune and inflammatory diseases. The new entity will keep the name Evelo Biosciences
Human Health Therapeutics	Galmed Pharmaceuticals Ltd	Yeda Research and Development Company Ltd	Partnership	2016		Galmed Pharmaceuticals Ltd has entered into research and option agreement with Yeda Research and Development Company Ltd, a subsidiary of Weizmann Institute of Science, to assess the effects of Galmed Pharma's proprietary molecule, Aramchol, microbiome on the human gut.
Human Health Therapeutics	TargEDys SAS	Inserm Transfert SA; Rouen University Hospital; University of Rouen	Licensing Agreement	2016	undisclosed	TargEDys SAS has entered into an exclusive and international license agreement with Inserm Transfert SA, a technology transfer company, University of Rouen, and Rouen University Hospital, to acquire rights of a portfolio of four patents aimed at developing new approaches nutrition and therapeutics based on the microbiome.
Human Health Therapeutics	Bioxyne Ltd	Datapharm Australia Pty Ltd	Partnership	2016		Bioxyne Limited has entered into an agreement with Datapharm Australia Pty Ltd. to undertake a clinical trial to support its Australian launch and marketing of Progastrim and proTract.

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Human Health Therapeutics	Seres Therapeutics Inc	Massachusetts General Hospital	Partnership	2016		Seres Therapeutics will fund a placebo-controlled, proof-of-concept clinical study to evaluate the impact of faecal microbiota transplantation (FMT) derived from lean individuals on the body weight and glycemic control of adults suffering from clinically-significant obesity and metabolic disorders
Human Health Therapeutics	Seres Therapeutics Inc	Mayo Clinic Center for Individualized Medicine	Partnership	2016		Mayo Clinic will collaborate with Seres Therapeutics scientists on clinical and preclinical studies to identify novel microbiome therapeutic candidates for primary sclerosing cholangitis (PSC), an orphan indication characterized by bile duct inflammation and reduction in bile acid flow.
Human Health Therapeutics	Invesco Asset Management Ltd.; Puretech Health plc; Rock Springs Capital LP; Seventure Partners	Vedanta Biosciences Inc	Venture Financing	2016	$50m	Vedanta Biosciences has raised USD50 million in a venture financing round. The company intends to use the proceeds to accelerate infectious and autoimmune disease programs to the clinic and support scale up its technology platform.
Animal Health	Bactana Animal Health	Cornell University	Licensing Agreement	2016	undisclosed	Bactana is developing products using patented technology exclusively licensed from Cornell. The firm is working on its FPS-4 product platform, which is based on years of research at Cornell, and peer-reviewed research published in December 2015 relating to the company's novel bacteria isolates.
Human Health Therapeutics	Seres Therapeutics Inc	Memorial Sloan Kettering Cancer Center	Partnership	2016		Seres Therapeutics and MSKCC have agreed to collaborate in two diverse areas of focus related to the discovery and development of microbiome therapeutics which includes improving the morbidity and mortality outcomes of patients undergoing Hematopoietic Stem Cell Transplantation (HSCT) for treatment of cancer, by prevention of Transplant-Related Infections and Graft Versus Host Disease (GVHD)
Human Health Therapeutics	Seres Therapeutics Inc	University of Pennsylvania	Partnership	2016		Seres Therapeutics has entered into a multi-year agreement with microbiome clinical-scientists from the University of Pennsylvania to support the development of novel treatment approaches for certain rare genetic metabolic diseases including urea cycle disorders, and inflammatory bowel disease (IBD).
Human Health Therapeutics	Seres Therapeutics Inc	St. Joseph's Healthcare Hamilton	Partnership	2016		Seres Therapeutics has formed a partnership with Research Institute of St. Joseph's Hamilton to support Seres' ongoing development of the first potential microbiome therapeutics for inflammatory bowel disease (IBD). Seres has agreed to obtain donor and patient samples from completed and ongoing faecal microbiota transplantation (FMT) clinical studies and to perform metagenomic and other analyses on these clinical samples to better characterize the microbiome signatures associated with clinical response.
Human Health Therapeutics	Nestle Health Science SA ; Seventure Partners ; Lundbeckfond Ventures ; Undisclosed	Enterome Bioscience	Venture Financing	2016	$16.44m	Enterome Bioscience SA, a pharmaceutical company, has raised EUR14.5 million (USD16.44 million) in series C venture financing round. he company intends to use the proceeds to advance the development of its lead drug candidate EB8018 into first clinical studies during 2016 as a potential treatment for inflammatory bowel diseases

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Agriculture	Alaska Permanent Fund, Flagship Pioneering	Indigo Agriculture	Venture Financing	2016	$100m	Indigo Agriculutre raised $100 million in Series C funding as it launched its first commercial product, a microbial seed coating promoting water efficiency in cotton.
Human Health Therapeutics	Seres Therapeutics Inc	Medical University of Graz	Partnership	2016		Seres has agreed to obtain donor and patient samples from completed and ongoing faecal microbiota transplantation (FMT) clinical studies and to perform metagenomic and other analyses on these clinical samples to better characterize the microbiome signatures associated with clinical response.
Human Health Therapeutics	Galmed Pharmaceuticals Ltd	Icahn School of Medicine at Mount Sinai	Partnership	2016		Galmed Pharmaceuticals Ltd. has signed a clinical trial agreement with the Icahn School of Medicine at Mount Sinai, to evaluate a placebo-controlled single-blinded study of aramchol with supplemental vitamin D in patients with vitamin D deficiency and nonalcoholic fatty liver disease (NAFLD) and fibrosis.Tthe study will provide information about the impact of aramchol and vitamin D3 on the intestinal flora comprising the microbiome.
Human Health Therapeutics	Advanced Technology Ventures; Adveq Management AG; Digitalis Ventures; Lifeforce Ventures, LLC; Matthew Winkler; Mayo Clinic; MBL Venture Capital Co., Ltd.; Morgenthaler Ventures; Pfizer Venture Investments; Roche Venture Fund; Seraph Group	Second Genome Inc	Venture Financing	2016	$42.6m	Second Genome, Inc. has raised USD42.6 million in series B round of venture financing. The company intends to use the funds to expand its microbiome discovery platform in a range of indications associated with barrier function, insulin sensitivity, and immune regulation. In addition, proceeds from the financing will be used to advance the clinical investigation of SGM-1019, a small molecule inhibitor of a key microbiome-mediated target to address inflammation and pain in ulcerative colitis, through human proof-of-concept studies.
Human Health Therapeutics	Enterome Bioscience SA	Vertex Pharmaceuticals Inc	Licensing Agreement	2016	undisclosed	Enterome Bioscience obtained licenses to novel compounds from Vertex Pharma to treat microbiome-related IBD.
Human Health Therapeutics	Evelo Therapeutics Inc	University of Chicago	Licensing Agreement	2016	undisclosed	Evelo Biosciences has entered into a worldwide licensing agreement with University of Chicago (UOC) to develop and commercialize a microbiome-based cancer immunotherapy.
Human Health Therapeutics	4D Pharma PLC	Instituto Biomar S.A	Asset Transaction	2016	$6.83m	4D Pharma plc has acquired the production assets of Instituto Biomar S.A., a contract research organisation specialising in microbial fermentation. his transaction enables 4D Pharma to progress its research programmes from the laboratory stage through to clinical development.
Human Health Therapeutics	OptiBiotix Health Plc	Royal DSM NV	Partnership	2016		OptiBiotix Health plc has entered into a joint development agreement with Royal DSM N.V. to develop new products using OptiBiotix's OptiBiotic technology platform. If successful, the agreement allows both parties to agree commercial terms such that OptiBiotix grants an exclusive licence to DSM in the DSM field, and an option to license in other fields, in return for royalty payments on sales of future products.

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Human Health Therapeutics	Icahn School of Medicine at Mount Sinai; University of Chicago	Takeda Pharmaceuticals USA Inc	Partnership	2016		Takeda has entered into a multi-year research agreement with the University of Chicago and the Icahn School of Medicine at Mount Sinai, to inflammatory bowel disease (IBD) research and care.
Human Health Therapeutics	Vedanta Biosciences Inc	Azabu University; RIKEN; The University of Tokyo	Licensing Agreement	2016	undisclosed	Vedanta Biosciences has entered into licensing agreement with Riken, University of Tokyo and Azabu University, for new immune boosting microbiome technology. The technology has potential clinical applications in infectious disease, vaccine design and immuno-oncology.
Human Health Therapeutics	Undisclosed	AzurRx BioPharma Inc	Venture Financing	2016	$0.64m	AzurRx BioPharma has raised USD0.64 million out of its planned USD12 million in financing. The company intends to use the proceeds for working capital and general corporate purposes.
Human Health Therapeutics	OptiBiotix Health Plc	University of Manchester	Partnership	2016	$0.37m	OptiBiotix Health plc has acquired the exclusive rights to skin health intellectual property from The University of Manchester. Concurrently, OptiBiotix Health has formed a joint venture (JV) with The University of Manchester. The JV will be called SkinBiotix Limited. Under the terms of the agreement, OptiBiotix have invested GBP0.26 million (USD0.37 million) into the JV and will own 52% of SkinBiotix, with the remaining 48% owned by the University of Manchester and key researchers.
Human Health Therapeutics	AbbVie Inc	Synlogic Inc	Partnership	2016		Synlogic, Inc. has entered into multi-year global R&D agreement with AbbVie Inc. to develop novel medicines for the treatment of inflammatory bowel disease (IBD) using Synlogic's proprietary approach for a new class of synthetic biotic medicines that power the microbiome.
Human Health Therapeutics	4D Pharma PLC	Tucana Health Ltd	Acquisition	2016		4D pharma plc has acquired the entire issued share capital of Tucana Health Limited, a company focused on investigating the use of microbiome signatures to aid the diagnosis and treatment of diseases, from University College Cork (UCC)
Human Health Therapeutics	Alexandria Venture Investments; China Rock Capital Management Limited; Illumina, Inc.; Matrix Capital Management Company, LLC; SV Tech Ventures	EpiBiome, Inc.	Venture Financing	2016	$6m	EpiBiome, Inc. has raised USD6 million in series A financing round. The company intends to use the proceeds to develop alternatives to small-molecule antibiotics for use in agriculture, to invest in its microbiome engineering platform, and to file for additional patents on its technology.
Human Health Therapeutics	undisclosed	Immuron, Ltd	Venture Financing	2016	$1.7 million	Immuron has executed a funding agreement with a New York-based Investment Fund. The company said the financing will be used to fund the immediate start of the clinical phase for IMM-529 in Clostridium difficile.
Human Health Therapeutics	Seneca Partners Limited; Undisclosed	OptiBiotix Health Plc	Equity Offerings	2016	$1.46m	OptiBiotix Health plc has completed the private placement of 1,282,051 shares of its common stock at a price of GBP0.78 (USD1.14) per share, for gross proceeds of GBP1 million (USD1.46 million).

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Human Health Therapeutics	Ferring International Center SA	Karolinska Institutet	Partnership	2016		Ferring Pharmaceuticals has entered into a co-development agreement with Karolinska Institutet for the establishment of a research center exploiting the human microbiome. The programme will be fully funded by Ferring Pharma and governed by a joint steering committee.
Human Health Therapeutics	Caelus Health	Chr. Hansen Holding	Partnership	2016		Chr. Hansen Holding has entered into partnership with Caelus Health to develop a CP-001 product formulation that will allow for progression to a phase II clinical trial and a subsequent market introduction.
Human Health Therapeutics	Nestle Health Science SA	Seres Therapeutics Inc	Licensing Agreement	2016	$120m upfront; $660m develop. milestones; $30m clinical trial milestone; $1 125m sales-based milestones	Nestle Health Science has entered into a licensing agreement with Seres Therapeutics, Inc. for SER-109 and SER-262 for Clostridium difficile infection (CDI), and SER-287 and SER-301 for inflammatory bowel disease (IBD). Nestle Health Science obtained from Seres Therapeutics an exclusive, royalty-bearing license to develop and commercialize certain products based on Seres Therapeutics' microbiome technology.
Agriculture	Bill & Melinda Gates Foundation, Monsanto Growth Ventures (MGV), Data Collective	PivotBio	Venture Financing	2016	$16m	Pivot Bio has completed a $16 million Series A round
Agriculture	Flagship Pioneering	Indigo Agriculture	Venture Financing	2016	$48.5m	Indigo Agriculutre raised $48.5 million in Series B funding
Human Health Therapeutics	Janssen Biotech Inc	Enterome Bioscience SA	Partnership	2016	undisclosed upfront payment	Enterome Bioscience has entered into research agreement with Janssen Biotech and the French National Institute for Agriculture Research (INRA), to discover novel targets and bioactive molecules from the gut microbiome for the potential development of therapeutic solutions to crohn's disease.
Human Health Diagnostics	Hansjorg Wyss, NanoDimension AG,Cedars-Sinai Medical Center	Emulate Inc	Venture Financing	2016	$28m	Emulate Inc has raised USD28 million in series B financing round. The company intends to use the proceeds to accelerate its R&D effort, expedite the launch of its products and expand strategic relationships with industry and academic partners
Human Health Therapeutics	Johnson & Johnson Consumer Inc	ProdermIQ Inc	Partnership	2016		Johnson & Johnson Consumer, Inc. has entered into agreement with ProdermIQ, Inc. to explore the potential of ProdermIQ's proprietary SKINdex Skin Health Measurement platform.

Sector	Acquirer/Investors/ Licensee	Acquired /Licensor	Deal Type	Year	Financials	Details
Human Health Therapeutics	OrbiMed HealthCare, Atlas Venture, New Enterprise Associates (NEA), the Bill & Melinda Gates Foundation, Orbimed and Deerfield Management	Synlogic	Venture Financing	2016	$57m	Synlogic, Inc. has raised USD40 million in a series B venture financing round.
Human Health Therapeutics	Enterome Bioscience SA	Takeda Pharmaceutical Company Ltd	Partnership	2016	undisclosed upfront payment	Takeda has entered into a drug discovery agreement with Enterome Bioscience SA to research and develop potential new therapeutics directed at microbiome targets thought to play crucial roles in gastrointestinal disorders. Enterome Bioscience will use its proprietary metagenomic platform to support the discovery of potential novel agents. Takeda Pharma has an option to license selected agents on an exclusive global basis and will be responsible for their regulatory and clinical development as well as their commercialization.
Agriculture	Mitsui & Co, Kleiner Perkins Caufield & Byers, Osmington	Farmer's Edge Laboratories	Venture Financing	2016	$41m	Farmers Edge, the Canadian ag big data company, has raised C$58 million ($41 million) in equity funding from existing investors. Farmers Edge will use the new funding for global expansion into South America, Australia, and Eastern Europe.
Human Health Diagnostics	Origin Sciences	Metabiomics	Partnership	2015		Origin Sciences Ltd has entered into a distribution agreement with Metabiomics Corporation for Origin Sciences' products for research into gastrointestinal diseases in the US. Under the agreement, Metabiomics will develop, test, and commercialize the novel OriCol gastrointestinal sampling technology for clinical research and diagnostic applications and the OriCol Microbiome Sampling Kit, which has been designed for use in gut microbiome research, in the US market.
Human Health Therapeutics	Woodford Investment Management LLP ; Invesco Asset Management Ltd.	4D Pharma PLC	Equity Offerings	2015	$45.25m	4D pharma plc has announced a private placement of 3,797,469 shares at a price of GBP7.9 (USD11.91) per share, to raise gross proceeds of GBP30 million (USD45.25 million). The company intends to use the proceeds to accelerate the development of the second generation MicroRx live biotherapeutics into the clinic
Human Health Therapeutics	Adam Reynolds; David Evans; Jim Laird; Stephen Patrick O'Hara; Undisclosed	OptiBiotix Health Plc	Equity Offerings	2015	$2.27m	OptiBiotix Health plc has completed the private placement of 2,000,000 shares of its common stock at a price of GBP0.75 (USD1.13) per share, for gross proceeds of GBP1.5 million (USD2.27 million).
Human Health Therapeutics	Enterome Bioscience SA	Institut Gustave Roussy	Partnership	2015		Enterome Bioscience SA has entered into a co-development agreement with Gustave Roussy, an oncology center, for the development of a new generation of drugs and non-invasive monitoring tools of the gut microbiome in immuno-oncology.

Sector	Acquirer/Investors/ Licensee	Acquired /Licensor	Deal Type	Year	Financials	Details
Human Health Therapeutics	Evelo Therapeutics Inc	University of Chicago	Partnership	2015		Evelo Therapeutics Inc. has entered into partnership with University of Chicago (UOC) to advance an immunotherapy employing certain gut microbes to boost the immune system's attack on cancer cells and improve the effectiveness of anti-cancer drugs. UOC provides Evelo Therapeutics with the option to acquire worldwide rights to the microbiome-based immunotherapy.
Human Health Therapeutics	Evelo Therapeutics Inc	Flagship Ventures	Venture Financing	2015	$35m	Evelo Therapeutics Inc. has raised USD35 million in initial financing round. The financing was led by Flagship Ventures. The company intends to use the proceeds to develop novel therapies for cancer.
Human Health Therapeutics	Immuron Ltd	One Way Liver SL	Partnership	2015		Immuron Ltd has entered into agreement with One Way Liver Genomics, S.L.(OWL Metabolomics) to evaluate and validate the efficacy of non-invasive markers for the development of a non-alcoholic steatohepatitis (NASH) companion diagnostic to IMM-124E.
Human Health Therapeutics	Synlogic Inc	undisclosed	Partnership	2015		Synlogic has entered into a multi-year R&D agreement with a global pharmaceutical company, to focus on inflammatory bowel disease (IBD).
Agriculture	Monsanto Growth Ventures (MGV), Syngenta Ventures, Bill & Melinda Gates Foundation; 6 others	AgBiome	Venture Financing	2015	£34.5m	AgBiome has raised Series B $34.5 million from investors that it plans to plow into research and development and the anticipated launch of its first product.
Human Health Diagnostics	uBiome, Inc.	PicnicHealth	Partnership	2015		uBiome, Inc. has entered into an agreement with PicnicHealth, a provider of medical records, to advance research on role of the microbiome in inflammatory bowel disease (IBD), using validated clinical data. Participants diagnosed with IBD will receive a complementary PicnicHealth account as well as a complementary uBiome research kit. uBiome aims to research the IBD-associated microbiome using well-validated clinical data. This agreement enables uBiome and PicnicHealth to provide patients to access their medical records.
Human Health Therapeutics	Seventure Partners	Eligo Bioscience	Venture Financing	2015	$2.2m	Eligo Bioscience S.A.S. a developer of next generation ultraprecise antibiotics, has raised EUR2 million (USD2.2 million) in a seed financing round.
Human Health Diagnostics	Genewiz	Hy Laboratories Ltd.	Partnership	2015		Genewiz, Inc. has formed joint venture (JV) with Hy Laboratories Ltd. for the development of novel diagnostic panels for the determination of the gut microbiome in obesity and diabetes. Genewiz and Hy Labs will target the most relevant microbiota in the gut system through stool sample collection and medical metadata to detect and determine the relative abundance of bacterial and archaeal species in the 16S obediome.
Human Health Therapeutics		Seres Therapeutics, Inc	Equity Offerings	2015	$153.8m	Seres Therapeutics, Inc., has completed the initial public offering (IPO) of 8,545,138 shares of its common stock, at a price of USD18 per share, for gross proceeds of USD153.8 million, including exercise in full by the underwriters of their option to purchase 1,114,583 additional shares of common stock.

Sector	Acquirer/Investors/ Licensee	Acquired /Licensor	Deal Type	Year	Financials	Details
Human Health Diagnostics	Biocartis NV	Microbiome Ltd	License Agreement & Partnership	2015		Biocartis NV has entered into a worldwide license and collaboration agreement with Microbiome Ltd. for the development of an integrated multiplex real-time PCR assay for rapid detection of bloodstream infections. Biocartis will further develop the platform and plans to launch it for use in conjunction with the pathogen identification test licensed from Microbiome as a streamlined solution for the diagnosis of bloodstream infections.
Human Health Therapeutics	4D Pharma PLC	University College Cork	Partnership	2015	$5.23m	4d pharma plc has entered into a four-year partnership with the APC Microbiome Institute (APC) at University College Cork to research the potential applications of live biotherapeutics in relation to Autism Spectrum Disorders and associated CNS Disorders ('ASD'), for an investment of EUR4.8 million (USD5.23 million).
Human Health Therapeutics	Horizon Ventures, Tate and Lyle Ventures	Evolve Biosystems	Venture Financing	2015	$9m	Evolve Biosystems has raised USD9 million in series A venture financing round. The company will fund the pre-commercialization phase of its growth; support its ongoing clinical activities, operational expansion, and preparations for commercial launch of its novel probiotic and prebiotic products, which restore the balance of the infant microbiota.
Human Health Therapeutics		Synthetic Biologics Inc	Equity Offerings	2015	$45.9m	Synthetic Biologics, Inc. has completed the underwritten public offering of 15,300,000 shares of its common stock, at a price of USD3 per share, for gross proceeds of USD45.9 million, including full exercise of over-allotment option by the underwriters to purchase additional shares of 2,000,000 of its common stock.
Human Health Therapeutics	OptiBiotix Health Plc	Venture Life Group Plc	Partnership	2015		OptiBiotix Health plc has entered into strategic development and commercial agreement with Venture Life Group plc, a consumer healthcare company manufacturing, marketing and selling healthcare products. OptiBiotix and Venture Life bring together OptiBiotix's R&D expertise in developing microbiome modulators to improve health and Venture Life's formulation, manufacturing and international distribution capabilities.
Human Health Therapeutics	Second Genome Inc	Alimentary Pharmabiotic Centre	Partnership	2015		Second Genome, Inc. has entered an agreement with Microbiome Institute of the Alimentary Pharmabiotic Centre (APC), a part of University College Cork (UCC), a research institute for diet, medicine and the microbiome, to advance the development of therapies that prevent and treat inflammatory bowel disease (IBD)
Human Health Therapeutics	4D Pharma PLC	GT Biologics Ltd	Acquisition	2015		4d pharma plc has acquired the remaining minority stake in GT Biologics Limited. Currently, the company acquired approximately 16.5% of issued share capital of GT Biologics. Following the transaction, 4d pharma owns 100% stake in GT Biologics, which is now wholly owned and has been renamed 4D pharma Research Limited.
Agriculture	DuPont	Taxon Biosciences, Inc	Acquisition	2015		DuPont announced it has agreed to acquire Taxon Biosciences, Inc, which will build on DuPont's in-house capabilities and market access in both seed and crop protection to discover and commercialize biological solutions for agriculture customers globally.

Sector	Acquirer/Investors/ Licensee	Acquired /Licensor	Deal Type	Year	Financials	Details
Human Health Therapeutics	Evotec AG	Second Genome Inc	Partnership	2015	undisclosed upfront payment	Second Genome, Inc. has entered into an agreement with Evotec AG for microbiome discovery and development for the treatment of microbiome-mediated diseases. Second Genome and Evotec will work together to screen microbiome-mediated targets of interest identified by the Second Genome microbiome discovery platform with Evotec technology platform, chemical libraries and other pre-clinical capabilities.
Human Health Therapeutics	Crohn's & Colitis Foundation Inc; Perelman School of Medicine at the University of Pennsylvania	Nestle Health Science SA	Partnership	2015		Crohn's & Colitis Foundation of America (CCFA), a non-profit, volunteer-driven organization, has entered into a research agreement with Perelman School of Medicine at the University of Pennsylvania (known as Penn Med) and Nestle Health Science to study the effects of diet on gut bacteria.
Human Health Therapeutics	Janssen Biotech Inc	Vedanta Biosciences Inc	Licensing Agreement	2015	$241m upfront; undisclosed milestones	Vedanta Biosciences has entered into a licensing agreement with Janssen Biotech to develop Vedanta Biosciences's microbiome-based drug candidate (VE202) for inflammatory bowel disorders.
Human Health Therapeutics	undisclosed	4D Pharma PLC	Equity Offerings	2015	$52.55m	4D pharma plc has completed the private placement of 8,475,610 new ordinary shares at a price of GBP4.1 (USD6.2) per share, for gross proceeds of GBP34.75 million (USD52.55 million). The company intends to use the proceeds for clinical development of Blautix, Thetanix and Rosburix; scaling up the Micro Rx platform to expand its discovery and development capability, to expand its pipeline; and building in house development capability.
Agriculture	Symbiota	University of Saskatchewan	Partnership	2015		University of Saskatchewan have been awarded $1.9 million through Genome Canada's Genomic Applications Partnership Program. They will work with Cambridge, Mass. based plant microbiome company, Symbiota™, on a $16-million research project aimed at improving yield and stress resistance in food crops.
Human Health Therapeutics	Nestle Health Science SA	Seres Therapeutics Inc	Equity Offerings	2015	$65.19m	Seres Health has raised CHF65.6 million (USD65.2 million) in financing. The financing was led by Nestle Health Science S.A. As part of the financing, Seres Health issued series D preferred stock. The company intends to use the proceeds to fund the further development of its first-in-field, lead product candidate, SER-109, for preventing the recurrence of clostridium difficile infection, into Phase III clinical trials
Animal Health	Metanome	Companion PBx	Partnership	2015		The two companies will work together to develop a sample collection kit and web-based survey, which will be used to build a microbiome database containing information on thousands of healthy and sick dogs. Houston-based Metanome will analyze the samples, enabling Companion PBx to develop products addressing digestive health and to provide advice to dog owners and veterinarians

Sector	Acquirer/Investors/ Licensee	Acquired /Licensor	Deal Type	Year	Financials	Details
Human Health Therapeutics	Centers for Disease Control and Prevention	uBiome Inc	Partnership	2014		uBiome, Inc. has entered into research agreement with Centers for Disease Control and Prevention (CDC) to analyze the gut bacteria of patients before, during, and at the end of hospital stays, in order to better understand how intestinal microbes are affected during an admission to a health care facility.
Human Health Therapeutics	Undisclosed	Seres Therapeutics Inc	Venture Financing	2014	$48m	Seres Health, Inc. has raised USD48 million in series C venture financing round. The finance was provided by public healthcare investors. The company intends to use the proceeds to advance the development of its product candidate, SER-109
Human Health Therapeutics	Undisclosed	Rebiotix Inc	Venture Financing	2014	$25m	Rebiotix Inc., has raised USD25 million in series B venture financing round. The company intends to use the proceeds to support pivotal clinical research to advance lead product RBX2660
Agriculture	Innotech Advisers, Polaris Partners, Novozymes, Harris & Harris Group, ARCH Venture Partners, Monsanto Growth Ventures (MGV)	AgBiome	Venture Financing	2014	$17.5m	AgBiome disclosed the participation of Syngenta, Monsanto, and Novozymes alongside Polaris Partners, ARCH Venture Partners, Harris & Harris and Innotech Advisors in a $17.5M Series A which closed last year.
Human Health Therapeutics	Atlas Venture Inc ; New Enterprise Associates Inc; Bill & Melinda Gates Foundation	Synlogic Inc	Venture Financing	2014	$34.4m	Synlogic, Inc. has raised additional USD5 million in series A venture financing round, bringing total proceeds to USD34.4 million.
Agriculture	Flagship Ventures	Symbiota	Venture Financing	2014	$7.5m	Flagship VentureLabs announces Symbiota™, after two years of development in stealth mode and a $7.5 million Series A financing from Flagship Ventures
Human Health Therapeutics	AbbVie Inc	Enterome Bioscience SA	Partnership	2014		Enterome Bioscience SA has entered into an agreement with AbbVie Inc to develop molecular diagnostic tools to monitor the gut microbiome in patients with crohn's disease and other microbiome-related diseases.
Agriculture	Otter Capital, RockPort Capital, Open Prairie, Pangaea Ventures	NewLeaf Symbiotics	Venture Financing	2014	$17m	NewLEaf Symbiotcs has closed a $17 million Series B round of financing. The proceeds will be used to further accelerate its successful R&D program, ramp up production from pilot to commercial scale, and go to market with its first biological products.
Human Health Therapeutics	Second Genome Inc	Mayo Clinic Center for Individualized Medicine	Partnership	2014		Second Genome, Inc. has entered into an extensive partnership with Mayo Clinic Center for Individualized Medicine (Mayo Clinic) to develop microbiome therapeutic products for multiple disease indications, starting with inflammatory bowel disease, metabolic disorders, and colorectal cancer. Second Genome will identify up to eight clinical indications where the microbiome has a potential role in disease and will collaborate on microbiome research with Mayo Clinic investigators who specialize in each of the designated disease areas.
Agriculture	Flagship Pioneering	Indigo Agriculture	Venture Financing	2014	$7.5m	Indigo Agriculutre raised $7.5 million in Series A funding

Sector	Acquirer/Investors/ Licensee	Acquired /Licensor	Deal Type	Year	Financials	Details
Human Health Therapeutics	4D Pharma PLC	The Mcrobiota Company LTd	Acquisition	2014	$3.49m	4d pharma plc, has acquired Microbiota Company Limited, a developer of patented bacteria focused at treating irritable bowel syndrome and related symptoms, for a purchase consideration of approximately GBP2.04 million (USD3.49 million), including the assumption of GBP1.08 million (USD1.84 million) significant loan. This transaction compliment 4d pharma's unique platform technology and strengthens its portfolio of drug candidates in development; and enables to reshape the areas of medicine to focus on its position in the pharma market.
Human Health Therapeutics	Undisclosed	Assembly Biosciences Inc	Equity Offerings	2014	$15.75m	Assembly Biosciences has announced the private placement of 1,959,000 shares of its common stock at a price of USD8.04 per share, to raise gross proceeds of USD15.75 million. The company intends to use the proceeds to advance its two proprietary platform technologies.
Human Health Therapeutics	Dermala Inc	University of California	Licensing Agreement	2014		Dermala Inc has obtained an exclusive, world-wide licensing agreement with Regents of the University of California, an educational institute, for skin microbiome technology.
Human Health Therapeutics		4D Pharma PLC	Equity Offerings	2014	$36.5m	4d pharma plc has announced the private placement of shares, to raise the gross proceeds of GBP21.5 million (USD36.5 million). The company will issue 14.33 million shares at a price of GBP1.5 (USD2.54) per share. The company intends to use the proceeds to further develop Thetanix and Rosburix
Human Health Therapeutics	Enterome Bioscience SA	Mayo Clinic US	Partnership	2014		Enterome Bioscience SA has entered into an agreement with Mayo Clinic to develop and commercialize gut microbiome-based diagnostic tests for predicting response to medical nutritional intervention in obese or overweight patients.
Human Health Therapeutics	Alexandria Venture Investments; Enso Ventures Ltd; Flagship Pioneering Inc; Mayo Clinic US; Undisclosed	Seres Therapeutic s Inc	Venture Financing	2014	$10m	Seres Health, Inc. has raised USD10 million in series B venture financing round. Concurrently, SeresHealth has entered into a research agreement with Mayo Clinic Center for Individualized Medicine to define diseases for which a microbiome-based intervention may change the course of the illnesses. The company intends to use the proceeds to advance its rapidly growing pipeline of Ecobiotic therapeutics including its lead candidate, SER-109.
Human Health Therapeutics	Seres Therapeutics Inc	Mayo Clinic Center for Individualiz ed Medicine	Partnership	2014		Seres Health, Inc. has entered into a research agreement with Mayo Clinic Center for Individualized Medicine, a provider of medical care, research, and education services, to define diseases for which a microbiome-based intervention may change the course of the illnesses, as well as the discovery and development of key means to treat such conditions.
Human Health Therapeutics	4D Pharma PLC	GT Biologics Ltd	Acquisition	2014	$2.04m	4d pharma plc acquired an additional 37.5% stake in GT Biologics ltd for a purchase consideration of approximately GBP1.22 million (USD2.05 million). Following the transaction, 4d pharma increased its stake in GT Biologics to approximately 83.5% of the issued share capital.
Agriculture	Khosla Ventures; Otter Capital	BioConsorti a	Venture Financing	2014	$15m	Khosla Ventures and Otter Capital funded BioConsortia's $15 million Series B round, enabling the move from New Zealand to the US, and establishing operations and headquarters in Davis, California.

Sector	Acquirer/Investors/ Licensee	Acquired /Licensor	Deal Type	Year	Financials	Details
Human Health Therapeutics	Kurma Partners, including IdInvest Partners, Mayo Foundation	OxThera AB	Venture Financing	2014	$10.64m	OxThera AB has raised SEK70m (US$10.64m) in a venture financing round. The company intends to use the proceeds to develop a first-in-class therapy for patients suffering from this very severe genetic disease.
Human Health Therapeutics	Renaissance Holding Company, LLC (RHC), Delta Dental Plans Association	C3J Therapeutics	Venture Financing	2014		C3J raised US$60.5m in series D venture financing round. The company intends to use the proceeds to support continued clinical development of its lead product, C16G2 to reengineer the microbiota by selectively killing the targeted pathogen
Human Health Therapeutics	Lundbeckfond Ventures; Omnes Capital SAS; Seventure Partners	Enterome Bioscience SA	Venture Financing	2014	$13.83m	Enterome Bioscience raised €10m (US$13.83m) in the first tranche of a series B financing round. The financing round was led by its existing investors namely, Seventure Partners and Lundbeckfond Ventures, along with a participation of Omnes Capital. The company intends to use the funds to undertake R&D and business development activities needed to capitalize on its metagenotyping process.
Human Health Diagnostics	Whole Biome	Mayo Clinic	Partnership	2014		Mayo Clinic Center for Individualized Medicine, has entered into an agreement with Whole Biome, Inc. to develop microbiome-targeted diagnostics for early indication of preterm labor. Whole Biome utilizes sample preparation techniques and specialized analytics that integrate high throughput and long read-length DNA sequencing data to generate high-accuracy microbiome profiles that enable the identification of relevant changes.
Human Health Therapeutics	Debiopharm International SA	Affinium Pharmaceuticals, Inc (Inactive)	Asset Transactions	2014		Debiopharm Group acquired antibiotic clinical assets and technology platform of Affinium Pharmaceuticals, Inc., a pharmaceutical company.
Human Health Therapeutics	4D Pharma PLC	GT Biologics Ltd	Acquisition	2014	$0.82m	4d pharma plc has acquired 46% stake in GT Biologics Limited for purchase consideration of GBP0.5 million (USD0.81 million). Under the transaction, 4d pharma acquired 50,000 ordinary shares of GBP0.01 (USD0.016) in GT Biologics representing approximately 46% of the issued share capital of GT Biologics.
Human Health Therapeutics	BVM Capital LLC; Undisclosed	MicroBiome Therapeutics LLC	Venture Financing	2013	$1.3m	MicroBiome Therapeutics LLC raised US$1.3m in a bridge financing round. The financing was led by existing investor BVM Capital LLC, along with the other investors. The company intends to use the proceeds to support completion of two ongoing clinical studies and preparations for further clinical trials of NM504.
Human Health Therapeutics	Synthetic Biologics Inc	Cedars-Sinai Medical Center	Licensing Agreement	2013		Synthetic Biologics, Inc. entered into worldwide license and option agreements with Cedars-Sinai Medical Center to develop new treatment approaches to target non-bacterial intestinal microorganism life forms known as archaea to treat chronic diseases such as irritable bowel syndrome (IBS), obesity and type 2 diabetes, through its newly formed subsidiary, Synthetic Biomics, Inc. Synthetic Biologics licensed and optioned from Cedars-Sinai a portfolio of intellectual property comprised of several US and international patents and pending patent applications for various fields of use, including C-IBS, obesity and diabetes.

Sector	Acquirer/Investors/ Licensee	Acquired /Licensor	Deal Type	Year	Financials	Details
Human Health Therapeutics	Flagship Pioneering Inc; Undisclosed	Seres Therapeutics Inc	Venture Financing	2013	$10.5m	Seres Health raised US$10.5m in series A financing. The finance was provided by Flagship Ventures, along with other investors.
Human Health Therapeutics	Ascension Health Ventures, LLC; Excel Venture Management LLC; HealthCare Ventures LLC	Pathogenetix Inc	Venture Financing	2013	$10m	Pathogenetix, Inc. raised US$10m in series C financing round. The company intends to use the proceeds to commercialize its Genome Sequence Scanning (GSS) technology, a rapid bacterial identification technology for use in food safety testing and public health foodborne outbreak investigations.
Human Health Therapeutics	Enterome Bioscience SA	Institute for Development Research; National Institute of Agricultural Research; Pierre and Marie Curie University	Licensing Agreement	2013		Enterome Bioscience has entered into a licensing agreement with Institut National de la Recherche Agronomique (INRA, National Institute for Agronomic Research), Universite Pierre et Marie Curie (UPMC) and Institut de Recherche pour le Developpement (IRD, Institute of research for development). Under the agreement, Enterome received worldwide rights on 'Prognostic of diet impact on obesity-related co-morbidities' patent owned by INRA, UPMC and IRD.
Human Health Therapeutics	Johnson & Johnson Innovation - JJDC Inc	Vedanta Biosciences Inc	Venture Financing	2013		Vedanta Biosciences raised funds through a venture financing round. In conjunction with the transaction, Vedanta and Johnson & Johnson Innovation center entered into an agreement to advance a novel class of therapies that modulate pathways of interaction between the human microbiome and the human immune system.
Human Health Therapeutics	Janssen Biotech Inc	Second Genome Inc	Partnership	2013	undisclosed upfront payment	Second Genome entered into an agreement with Janssen Biotech, Inc. for microbiome drug discovery which is used in the treatment of the inflammatory bowel disease known as ulcerative colitis.
Human Health Therapeutics	Morgenthaler Ventures ; Advanced Technology Ventures ; Wavepoint Ventures, LLC ; Corey Goodman; Matt Winkler	Second Genome Inc	Venture Financing	2013	$6.5m	Second Genome, Inc. raised US$6.5m in extended series A financing round. The company intends to use the proceeds to advance treatments for metabolic disease, inflammation and infection.
Human Health Therapeutics	Harvard University	UCB SA	Partnership	2012	$4.5m	UCB, S.A., a biopharmaceutical company, entered into an agreement with Harvard University (HU) for the development of therapeutic applications for the treatment of immunology. This agreement enables UCB and HU to develop drugs for the treatment of unmet health care needs in immunology.
Human Health Therapeutics	HealthCap, Industrifonden, and Q-Med AB	OxThera AB	Venture Financing	2012	$5.93	OxThera AB raised SEK39m ($5.93m) in a venture financing round. The company intends to use the proceeds to complete a new clinical study to confirm the positive effects of treatment with Oxabact, used to treat primary hyperoxaluria.

Sector	Acquirer/Investors/ Licensee	Acquired /Licensor	Deal Type	Year	Financials	Details
Animal Health	Da Volterra	Animal Health Company	Partnership	2012		Da Volterra has entered into development agreement with Animal Health Company to develop its novel product DAV133 in veterinary applications. Under the agreement, Da Volterra is responsible for the product optimization and preclinical studies, and the Animal Health Company taking charge of the regulatory, pre-marketing, and final-development steps.
Human Health Therapeutics	Advent Venture Partners LLP; BVM Capital LLC; Undisclosed	MicroBiome Therapeutics LLC	Venture Financing	2012	$1.5m	Nume Health LLC raised additional $0.39m in series A financing round, bringing the total proceeds to $1.5m. The company intends to use the proceeds to advance NM504 towards commercialization, including developing the initial format for its first consumer product, completing the pilot clinical trial and preparing for an initial direct-to-consumer launch.
Human Health Therapeutics	Advanced Technology Ventures; Morgenthaler Ventures; Seraph Group; Undisclosed; Wavepoint Ventures, LLC	Second Genome Inc	Venture Financing	2011	$5m	Second Genome, Inc. secured $5m in its series A financing. The company intends to use the funds to further its development of microbiome-based personalized medicine solutions for gastrointestinal diseases and disorders.
Human Health Therapeutics	BVM Capital LLC	MicroBiome Therapeutics LLC	Venture Financing	2011	$0.67m	NuMe Health LLC secured $0.67m in its series A-1 financing round. The company intends to use the funds to accelerate the development and launch of its first prebiotic products.
Human Health Therapeutics	GQ Life Sciences Inc	Pathogenica Inc	Partnership	2011		GenomeQuest, Inc. entered into an agreement with Pathogenica, Inc. to offer discovery services in infectious disease research. Pathogenica's technology for detecting and sub-selecting pathogen genomes in human tissue, is combined with GenomeQuest's large-scale whole genome, exome, and microbiome analysis, to provide an important advancement for infectious disease research, including the interaction between the human microbiome and human genome.
Human Health Therapeutics	Mayo Clinic US	University of Illinois	Partnership	2010		Mayo Clinic entered into an agreement with University of Illinois (UIC) to promote a broad spectrum of collaborative research, development of new technologies and clinical tools, and design and implementation of novel education programs.

APPENDIX 2: PIPELINE

An overview of the product pipeline for therapeutics and diagnostics in the human health and wellbeing sector is given in the Tables below. Data has been compiled using the GlobalData pharma and medical databases (2017), internet-based searching and press articles, and grouped alphabetically by company.

Therapeutics

Drug	Company	Stage	Indication
Blautix	4D Pharma	Phase I	Irritable Bowel Syndrome
Thetanix	4D Pharma	Phase I	Crohn's Disease
Biologics for Anxiety and Depression	4D Pharma	Preclinical	Anxiety Disorders; Depression
Biologics for Autism	4D Pharma	Preclinical	Autism
Biologics for Autoimmune Disorders	4D Pharma	Preclinical	Autoimmune Disorders
MRx-0001	4D Pharma	Preclinical	Asthma
MRx-0002	4D Pharma	Preclinical	Multiple Sclerosis
MRx-0004	4D Pharma	Preclinical	Asthma
MRx-0006	4D Pharma	Preclinical	Rheumatoid Arthritis
MRx-518	4D Pharma	Preclinical	Cancer, Solid Tumour
Rosburix	4D Pharma	Preclinical	Ulcerative Colitis
ABIM-301	Allergan	Discovery	Crohn’s Disease
ABIM-201	Allergan	Discovery	Ulcerative Colitis
AT-01	Amrita Therapeutics	Preclinical	Cancer
B-244	AOBiome, Inc	Phase III	Acne
B-244	AOBiome, Inc	Preclinical	Atopic dermatitis, Rosacea
MB-102	Assembly Biosciences	Discovery	Gastrointestinal infections
ABIM-101	Assembly Biosciences	Preclinical	C. Difficile infection
MicAbodies	Avidbiotics	Preclinical	Cancer, Solid tumors
AVID Preclinical	Avidbiotics	Preclinical	C. Difficile infection
Biologic for Autism Spectrum Disorders and Parkinson's Disease	Axial Biotherapeutics Inc	Preclinical	Multiple Sclerosis, Parkinson's Disease
AZT-01	Azitra Inc	Preclinical	Atopic dermatitis
C16-G2	C3 Jian, Inc	Phase III	Dental Caries
CP-001	Caelus Health	Phase I	Type-2 diabetes
DAV-132	Da Volterra	Phase II	C. Difficile infection
Drug for Athlete's Foot	Dermala Inc	Discovery	Tinea pedis (Athlete Foot)
Drug for Candidiasis	Dermala Inc	Discovery	Candidiasis
Drug for Dandruff	Dermala Inc	Discovery	Pityriasis Simplex Capillitii (Dandruff)
Drug for Onychomycosis	Dermala Inc	Discovery	Onychomycosis (Tinea Unguium)
Drug for Psoriasis	Dermala Inc	Discovery	Psoriasis
Drug for Atopic Dermatitis	Dermala Inc	Preclinical	Atopic dermatitis

Drug	Company	Stage	Indication
Small Molecule for MRSA Skin Infection and Wound Healing	Dermala Inc	Preclinical	Wounds, skin infections
EB-120	Enterome	Phase I	Ulcerative Colitis
EB-8018 + EB-110	Enterome	Preclinical	Crohn's Disease
Oncobiotics	Evelo Biosciences	Preclinical	Cancer, Solid tumors
FIN-403	Finch Therapeutics	Phase I	C. Difficile infection
FIN-524	Finch Therapeutics	Preclinical	Ulcerative Colitis
IMM-124E	Immuron	Phase II	Non-Alcoholic Steatohepatitis
Bovine Colostrum product	Immuron	Preclinical	Type-2 diabetes
IMMU - Preclinical	Immuron	Preclinical	Crohn's Disease
IMMU- Preclinical	Immuron	Preclinical	Ulcerative Colitis
AG 013	Intrexon	Phase I	Oral mucositis
AG-014	Intrexon	Phase I	Crohn's Disease
AG-015	Intrexon	Phase I	Ulcerative Colitis
Actobiotics	Intrexon	Preclinical	Celiac Disease
MSB-03	Matrisys Bioscience Inc	Phase I	Psoriasis, Rosacea
MSB-01	Matrisys Bioscience Inc	Phase II	Atopic dermatitis
MSB-02	Matrisys Bioscience Inc	Preclinical	Bacterial Infections
NM-504	Microbiome Therapeutics	Phase II	Obesity, Obesity in Type-2 diabetes
NM-313	Microbiome Therapeutics	Preclinical	Obesity
Lactin-V	Osel, Inc	Phase II	Recurrent BV and urinary tract infections
CBM-588	Osel, Inc	Phase II	C. Difficile infection
Oxalbact	OxThera	Phase II	Primary Hyperoxaluria
Oxazyme	OxThera	Phase II	Primary and Secondary Hyperoxaluria
Qi-201	Quorum Innovations	Preclinical	Eosinophilic Esophagitis
Qi-301	Quorum Innovations	Preclinical	Sinusitis
Qi-401	Quorum Innovations	Preclinical	Keratoconjunctivitis sicca (Dry Eye)
Qi-402	Quorum Innovations	Preclinical	Blepharitis
RBX-8225	Rebiotix	Preclinical	Ulcerative Colitis
RBX-2660	Rebiotix	Phase II	C. Difficile infection
RBX-2477	Rebiotix	Preclinical	Hepatic encephalopathy
RPG-28	Ritter Pharmaceuticals	Phase III	Lactose intolerance
SGM-1019	Second Genome	Phase II	Crohn's Disease
SGM-1019	Second Genome	Phase II	Ulcerative Colitis
Second Genome Diabetes program	Second Genome	Preclinical	Type-2 diabetes

Drug	Company	Stage	Indication
Drugs for Clostridium Difficile Infections	Second Genome	Preclinical	C. Difficile infection
SER 155	Seres Therapeutics	Phase I	Cancer, Stem cell transplantation
Faecal microbial transplant therapy	Seres Therapeutics	Preclinical	Obesity
SER-287 / SER-301	Seres Therapeutics	Phase I / Preclinical	Ulcerative Colitis
Seres Diabetes program	Seres Therapeutics	Preclinical	Type-2 diabetes
SER- Preclinical	Seres Therapeutics	Preclinical	Crohn's Disease
SER-109 / SER-262	Seres Therapeutics	Phase II/I	C. Difficile infection
SWE-02	Swecure AB	Preclinical	Inflammatory Bowel Disease
SGM Compound	Symberix	Preclinical	Cancer, Chemotherapy induced toxicity
Biologic for Ulcerative Colitis and Crohn's Disease	Synlogic	Discovery	Ulcerative Colitis, Crohn's Disease
Biologic 1 + 2 for Orphan Disease	Synlogic	Discovery	Orphan diseases
Biologic for Metabolic Disorders	Synlogic	Discovery	Metabolic Disorders
SYNB-2010	Synlogic	Preclinical	Phenylketonuria
SYNB-1020	Synlogic	Preclinical	Phenylketonuria
SYN-020	Synthetic Biologics	Preclinical	Bacterial Infections
SYN-004 / SYN-007	Synthetic Biologics	Phase II / Preclinical	C. Difficile infection
VE-202	Vedanta Biosciences	Preclinical	Ulcerative Colitis
VE-203	Vedanta Biosciences	Preclinical	C. Difficile infection
VT-301	ViThera	Phase I	Crohn's Disease
VT-301	ViThera	Phase I	Ulcerative Colitis

Diagnostics

Diagnositc	Company	Stage	Indication
MicroDx	4D Pharma	Clinical	Irritable Bowel Syndrome
FloraCheck Microbiome Testing	Admera Health	Early development	Infectious Diseases
Ingestible Gut Sampling Device	BioMe Oxford	Early development	Gastrointestinal Disease
Gastriome Test	Biomecite Diagnostics	Clinical	Crohn's Disease, Inflammatory Bowel Disease, Ulcerative Colitis
Companion Diagnostic Assay - C16G2	C3J Therapeutics Inc	Early Development	Dental Caries
OMNIgene•GUT OM-200	DNA Genotek Inc	Clinical	Faecal Microbiota
IBD-110	Enterome	Clinical	Crohn's Disease
IBD-210	Enterome	Early Development	Ulcerative Colitis
Non-invasive Monitoring Tool	Enterome	Early development	Cancer

Diagnositc	Company	Stage	Indication
Diagnostic Panel - Gut Microbiomes	Genewiz Inc	Early development	Diabetes Mellitus, Obesity
Microbiome Biomarker Screening Test	Metabiomics	Clinical	Colon Polyps, Colorectal Cancer
Microbiome Biomarker Screening Test	Metabiomics	Early development	Crohn's Disease, Inflammatory Bowel Disease, Liver diseases
Oricol	Origin Sciences Ltd	Early Development	Colorectal Cancer