



Innovate
UK

Human Intestinal Microbiome Therapies and Diagnostics

The Science, Opportunities
and Challenges

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Welcome

In line with the goals we set ourselves at the end of 2019 with the launch of the Innovate UK KTN Microbiome Innovation Network, last year we published a Strategic Roadmap and delivered a Landscape Map aimed at raising the visibility of, access to and investment in microbiome science and innovation in the UK. Innovate UK KTN Microbiome Innovation Network has rallied to deliver this new report, which focuses on the science, opportunities and challenges of developing human intestinal microbiome therapies and diagnostics.

Given that the intestinal microbiome influences many aspects of human health and disease, this is an exciting field of a new medicine that holds the promise of addressing several key healthcare challenges from new treatments for intestinal diseases such as recurrent *C. difficile* and inflammatory bowel diseases (ulcerative colitis and Crohn's disease) to new therapies for the treatment of cancer and neurodegenerative diseases. Delivering on this, requires that we not only have some of the best microbiome science in the world but also have an infrastructure in the UK that attracts and supports companies to start, grow and invest here.

With learnings from the development of advanced therapy medicinal products, including cell and gene therapies, this report highlights the steps needed to create an outstanding environment in the UK for microbiome innovation to succeed. This ranges from establishing GMP-certified facilities for manufacturing development and scale-up of live biotherapeutic products to seizing opportunities that the UK is especially capable of delivering on such as microbiome biobanking and drug-microbiome interaction discovery and development.

We would like to express our sincere thanks to all of the report contributors, comprising twenty-eight leading industrial and academic scientists working in the field of the human microbiome. Writing a report of this scope, depth, and serious intent requires not only people who are highly knowledgeable within the field but also able to step up to the challenge, come together, give of their time and create a document with recommendations we can all stand behind.

We hope that the recommendations in this report will prompt action needed to make the UK the number one destination in Europe for microbiome therapeutics and diagnostics innovation, attracting scientists, industry, venture capital and private equity and entrepreneurs from across the world.

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Executive Summary

The human microbiome is a new frontier in health and wellbeing, poised to revolutionise the way we tackle disease [1]. The growing evidence of this has led to the rapid global growth of microbiome-focused drug development activities, and in 2020 more than 640 patents were granted and approximately 575 clinical trials based on microbiome science were launched, increasing the number of ongoing microbiome clinical trials to approximately 2,000 [2]. Some of the recent clinical trial successes such as Seres Therapeutics' and Rebiotix's positive Phase 3 data for their *Clostridioides difficile* treatments, are generating evidence of safety and efficacy for the potential of microbiome based-treatments and encouragement to the field.

The discovery and development of human microbiome therapies and diagnostics build on the UK's unique life sciences research strengths in clinical research, genomics and health data capabilities as identified in the Life Sciences Vision 2021 (LSV21)[3]. Moreover, this new field of human medicine has the potential to significantly impact many healthcare challenges, including cancer (immunotherapy in particular), autoimmune, gastrointestinal, neurodegenerative, infectious and cardiometabolic diseases, antimicrobial resistance, obesity, and mental health.

The UK is a world leader both in microbiome academic science, ranked third after the US and China, and in innovation, ranked fourth after the US, France and South Korea [4]. While tremendous progress has been made in microbiome science and innovation in the UK, both in the public and private sectors, by building on the UK's existing life science infrastructure and taking advantage of its unique clinical research, genomic and digital capabilities, there is an opportunity to accelerate translational microbiome research, start-up company formation and industry-academic partnerships to make the UK a key destination for microbiome innovation and investment.

This report's recommendations build on those from the Innovate UK KTN Microbiome Innovation Network Strategic Roadmap and closely align with those of the LSV21. It calls for investment in and further strengthening of the UK's unique life science infrastructure and capabilities to address the great healthcare challenges and create an outstanding environment for microbiome companies to start, grow and invest.

Drawing on the lessons learned from the development of cell and gene therapies, this report provides the background to the science, market, opportunities and challenges associated with the fast-developing new field of human intestinal microbiome science. It makes a number of key recommendations to address the science translation gap, including the creation of the following centres, networks, and programmes:

- **A Microbiome Bioprocess Innovation Centre (MBIC).** The new centre needs to have pharma GMP-certified facilities focused on manufacturing development and scale-up of live biotherapeutic products (LBPs) and other microbiome therapeutic modalities. MBIC could perhaps be a new arm of the High Value Manufacturing (HVM) Catapult.
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Inspired by the Cell and Gene Therapy (CGT) Catapult, consideration should be given to physically placing the MBIC alongside or as part of a proposed Microbiome Innovation Hub to create a one-stop-shop for microbiome entrepreneurs.

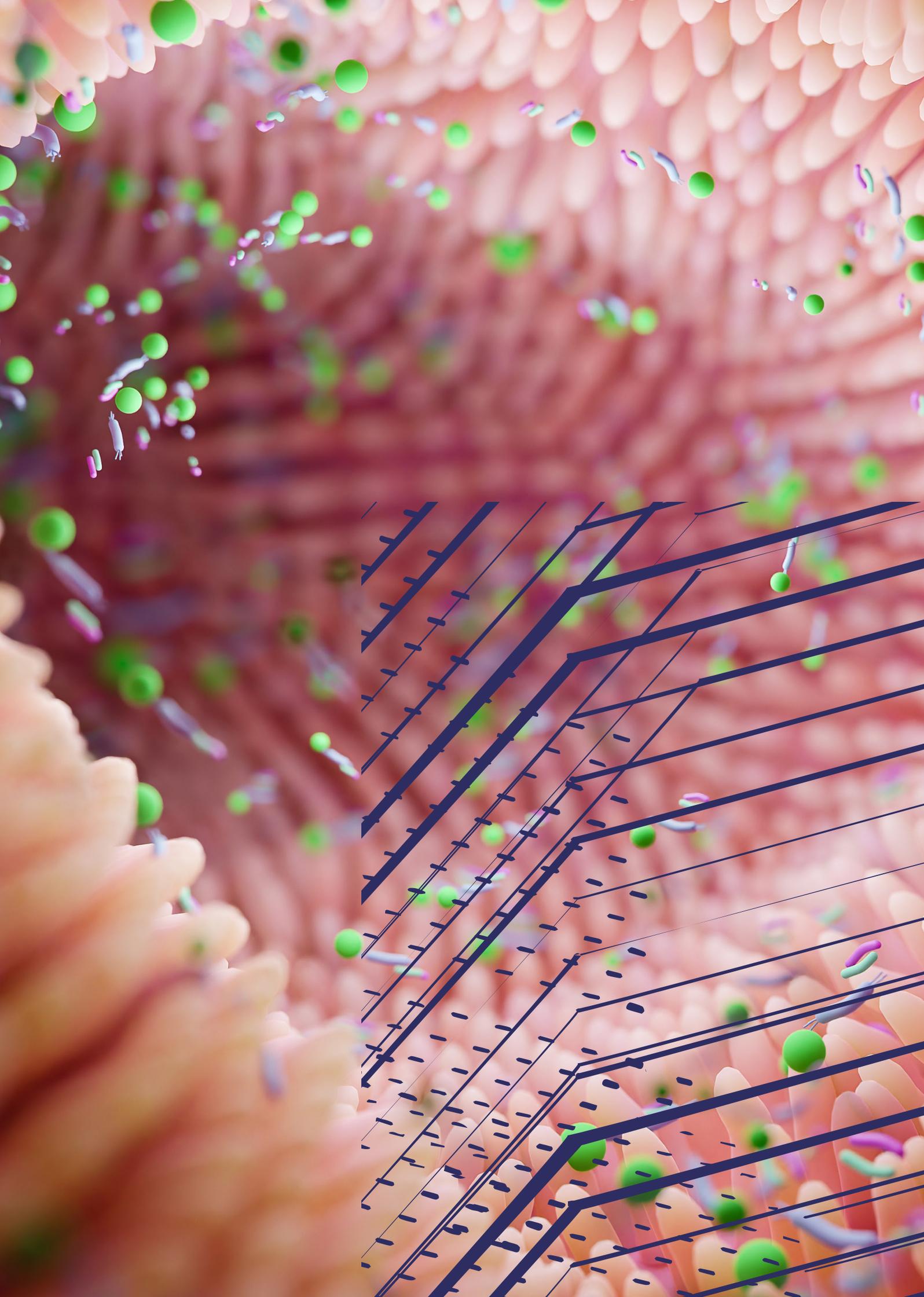
- **A Microbiome Innovation Hub (MIH)** for entrepreneurs to access end-to-end guidance and signposting for support in financing, regulatory, IP, preclinical studies, clinical trials and manufacturing. In addition, the MIH should be able to facilitate engagement between the microbiome science and innovation communities as well as individual enterprises and the regulatory and other government agencies to promote dialogue with the agencies in the early stage of the development of a new product. Specifically, through access to key stakeholders and regulatory and standards bodies, the MIH could play a key role in defining standards for microbiome therapeutics and diagnostics.
- **A microbiome skills and training network** platform, similar to the Advanced Therapies Skills and Training Network (ATSTN), to upskill, retrain and allow people to transfer from other sectors. An existing centre could deliver the platform, though integrating this activity into the proposed MIH, which would have the advantage of providing a fully integrated end-to-end microbiome innovation support structure.
- **A UK Microbiome Bank**, akin to the UK Biobank, for conserving and preserving the biodiversity of microbiomes, with the added role of setting standards for sampling, as well as for associated analyses and storage. It will be important to invest in the underpinning science – for example, ensuring sample integrity and the actual methodology for achieving stability. This endeavour would be a major asset for the research community and industry. It would cover human, animal, plant and environmental microbiomes as similar needs apply, leveraging technology across all of these domains. Note: The UK Biobank does not store microbiome samples, and this is a gap.
- **A drug-microbiome interaction centre** should be considered by the funding bodies as there is increasing evidence of the role played by the microbiome in the efficacy and side effects of major drug therapies. This is an exciting and emerging area that has the potential to translate into new precision medicines and associated diagnostic opportunities, including the development of new therapies combining intestinal microbiota transfer (IMT), LBPs or other microbiome therapeutic modalities as adjunct precision therapies for a range of existing and new drug classes.

In addition to establishing the necessary infrastructure, funding support is needed, directed towards:

- **Larger multidisciplinary programmes** through integration of the UK's best key opinion leaders (KOLs) in microbiome and KOLs in target disease areas. The UK has a number of outstanding microbiome research centres and groups. By funding larger, multidisciplinary and multicentre collaborations aimed at driving translation of the science into new microbiome therapies and diagnostics, the UK can leverage its existing ecosystems and resources, upscale its efforts and increase the impact of its investments and thereby enhance UK competitiveness in this field.
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- **Innovation support for spin-out ideas, start-ups, scale-ups and SMEs.** In addition to setting up a Microbiome Innovation Hub, existing funding programmes should be tailored to include microbiome innovation. For example:
 - MRC and Innovate UK Biomedical Catalyst Partnership.
 - Innovate UK's Investor Accelerator.
 - National Institute for Health Research (NIHR) i4i.
 - Innovation Scholars.
- **A clinical microbiome-based diagnostics funding competition** supported by, for example, Innovate UK or NIHR i4i programme. This should be business-led and challenge-based to build on the UK's strength in this area. This competition should focus on solving unmet clinical needs and bring together clinical expertise and various underpinning technologies and spearhead early-stage partnerships between academia, start-ups and larger companies.
- **Microbiome-focused doctoral and apprenticeship training courses.** Given that microbiome science transects human, animal, plant and environmental sectors, the Biotechnology and Biological Sciences Research Council (BBSRC) would most likely be the most relevant sponsor of these.
- An annual **microbiome research exchange conference** to showcase research excellence in the microbiome space to national and international industry representatives as well as to early-stage investors. This will be a forum to exchange ideas and encourage industry, academic and clinical collaborations.

All of the above is aimed at making the UK the number one destination in Europe for microbiome therapeutics and diagnostics innovation attracting scientists, industry, venture capital and private equity and entrepreneurs from across the world.



1. Therapies and Diagnostics

1.1. Faecal microbiota-derived treatments

Intestinal microbiota transfer (IMT), also referred to as faecal microbiota transplantation (FMT), has been demonstrated to be a successful treatment strategy for recurrent *Clostridioides difficile* infection (CDI) with significantly improved efficacy rates compared to antibiotic therapy [5] [6] [7].

A recent Phase 3 clinical trial has confirmed the benefits of faecal-derived-microbiota formulation for the treatment of recurrent CDI [8]. Since 2015, formulations for IMT have been defined as a medicinal product under the Human Medicines Regulations 2012 in the UK. In the US and Canada, IMT formulations are considered biologic drugs. Under the UK's Medicines and Healthcare products Regulatory Agency (MHRA) regulation, formulations for IMT must be produced in good manufacturing practice (GMP) compliant facilities, and such formulations can only be released for use when specified donor screening, production and storage criteria are satisfied [9].

Other examples of medicinal products derived and produced from donor samples include SER-109 from Seres Therapeutics. SER-109 is comprised of purified Firmicutes spores and was shown in a Phase 3 study to significantly reduce recurrence rates of CDI when administered orally following antibiotic treatment [10]. Others include Maat Pharma, a French microbiome-based medicinal products company, which has an advanced platform in faecal microbiota-derived products and recently announced a highly successful IPO [11].

The UK is well positioned to capitalise on the substantial and growing IMT opportunity based on an unparalleled IMT-enabling infrastructure that includes several MHRA-licensed GMP-compliant manufacturing facilities (e.g. EnteroBiotix, Guys and St Thomas' NHS Foundation Trust, University of Birmingham). EnteroBiotix, a fast-growing Scottish microbiome start-up focused on IMT, has recently announced the completion of a bespoke manufacturing facility focused on gut microbiome therapies.

Such infrastructure will enable further research of IMT as a treatment modality for other conditions such as inflammatory bowel disease (IBD), graft versus host disease, and other diseases associated with gastrointestinal dysbiosis. In addition, IMT has the potential to improve immunotherapy response in cancer patients [12] [13].

1.2. Live biotherapeutic products

Live biotherapeutic products (LBPs) are medicinal products for which the active substance is a living microorganism. The Food and Drug Administration (FDA) defines a LBP as ‘a biological product that contains live organisms, such as bacteria; is applicable to the prevention, treatment, or cure of a disease or condition of human beings; and is not a vaccine’. The European Pharmacopeia defines LBPs as ‘medicinal products containing live microorganisms (bacteria or yeasts) for human use’ [14] [15]. LBPs are being developed either as single bacterial or yeast strains or as multi-strain consortia.

LBP candidates (single strain or consortia) have been identified by applying several research approaches, including:

- Screening of bacterial isolates for functional properties, e.g. to promote short-chain fatty acid production, to attenuate inflammatory response or to elicit a certain immune response.
- Comparison of microbiome profiles of subjects with a certain disease/condition and healthy control subjects and identification of potentially ‘healthy’ microbes that are present in healthy subjects but missing in disease.
- In-depth analysis of microbiome signatures following IMT intervention which correlate with positive patient response.
- Modelling approaches to identify ecologies of microbes associated with health.

Many of the leading microbiome biotech companies have developed defined proprietary LBPs and obtained validation using industry-robust preclinical mouse models of disease. For example, in IBD, metabolic diseases such as type 2 diabetes, neurological diseases such as Parkinson’s and in oncology, and some have progressed to clinical trials.

There are specific challenges for LBPs both in relation to their safety assessment and mode of action which is often based on complex interaction with/modulation of the native microbiome and host immune system [16]. Early engagement with competent regulatory authorities is recommended in order to overcome some of the challenges and define a solid clinical development strategy [17] [18]. Two leading UK biotech companies focusing on LBPs are Microbiotica, with a focus on ulcerative colitis and immuno-oncology, and 4D Pharma with a pipeline targeted at immuno-oncology, neurology, respiratory health, autoimmune diseases and gastrointestinal diseases.

Overall, the field of LBPs is still at an early stage, particularly in terms of the translation of discovery research into clinically-proven treatments. Although the number of candidate microbiome-based therapies in the pipeline of biotech companies in the UK within the LBPs space is currently smaller than, for example, the US and France, there is ample opportunity to build on the strong fundamental research capabilities, including:

- New discovery approaches, including multi-omics, to identify LBPs with a high probability to be causally linked to disease [19].
 - Isolation, culturing and biobanking of novel bacterial species that can be used for screening and development.
 - New pre-clinical models to validate the efficacy of LBPs (e.g. organ-on-chip models using human cell lines or animal models that allow more meaningful study of microbiome–human host immune interactions).
 - Emerging therapeutic areas linked to dysbiosis such as autoimmune diseases, neurology and new infectious diseases such as Covid-19.
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- Moving beyond the gut microbiomes, e.g. lung microbiome for respiratory health, vaginal microbiome for women's health, tumour microbiome for oncology.
- Moving beyond bacteria, i.e. studying the role of the human gut virome and mycobiome.
- Design of fast-track clinical trials for early validation of causality.
- Anaerobic manufacturing capabilities (pharma GMP).
- Development of new and advanced manufacturing strategies for LBPs.

Engineered microbes/genetically engineered microbial medicines

Some companies are working on engineered microbes to deliver therapeutic payloads to target tissues including Synlogic in the US and Prokarium and CHAIN Biotechnology in the UK. Novome Biotechnologies in the US has reported a first-in-human study testing safety, tolerability and engraftment of a proprietary microbial strain genetically engineered to degrade oxalate with the goal to treat patients with enteric hyperoxaluria [20]. Others are targeting specific microbes in the gut or other organs with CRISPR-Cas technologies to either selectively kill target pathogens or to have target commensals produce therapeutics in situ, e.g. SNIPR Biome in Denmark and Eligo Bioscience in France; both companies are using engineered phage to target delivery of CRISPR-Cas payloads.

Phage therapy

Whereas the use of bacteriophage to target and kill specific pathogenic bacteria in the gut, was applied for many decades in Eastern Europe (most notably in Tbilisi, Georgia) and was adopted in the West over the past 25 years for food safety applications, it is now attracting considerable attention in the context of 'microbiome therapy' and to tackle an emerging global antimicrobial resistance (AMR) crisis.

One of the side-effects of antibiotics is dysbiosis and antibiotic-associated diarrhoea because traditional antibiotics typically kill a wide range of bacteria including beneficial bacteria residing in the gut. Phages, on the other hand, are highly specific, killing only selected bacterial species or strains. Hence the attraction and why phage therapy is now being considered in the context of microbiome-related therapeutics development.

Traditional antimicrobial therapy through antibiotic use has led to the emergence of drug-resistant pathogens. As a global AMR crisis looms, the need to develop safer and more targeted antimicrobial treatments is becoming increasingly urgent. Antimicrobials such as bacteriocins and bacteriophages are being investigated as potential alternatives to antibiotics. Conventional phage therapy uses naturally occurring phages to infect and lyse bacteria at the site of infection. Advances in biotechnology have expanded the toolbox of potential phage therapies to include novel strategies such as bioengineered phage and purified phage lytic proteins. As mentioned above, the specificity of bacteriophage towards a particular species or group of bacteria means that off-target effects on the rest of the microbiota are significantly minimised, helping to avoid the collateral damage often associated with antibiotic use. Research and development activities on phage therapies are gaining momentum, and a growing number of companies are now developing bacteriophage-based products to modulate the human microbiome for therapeutic purposes.

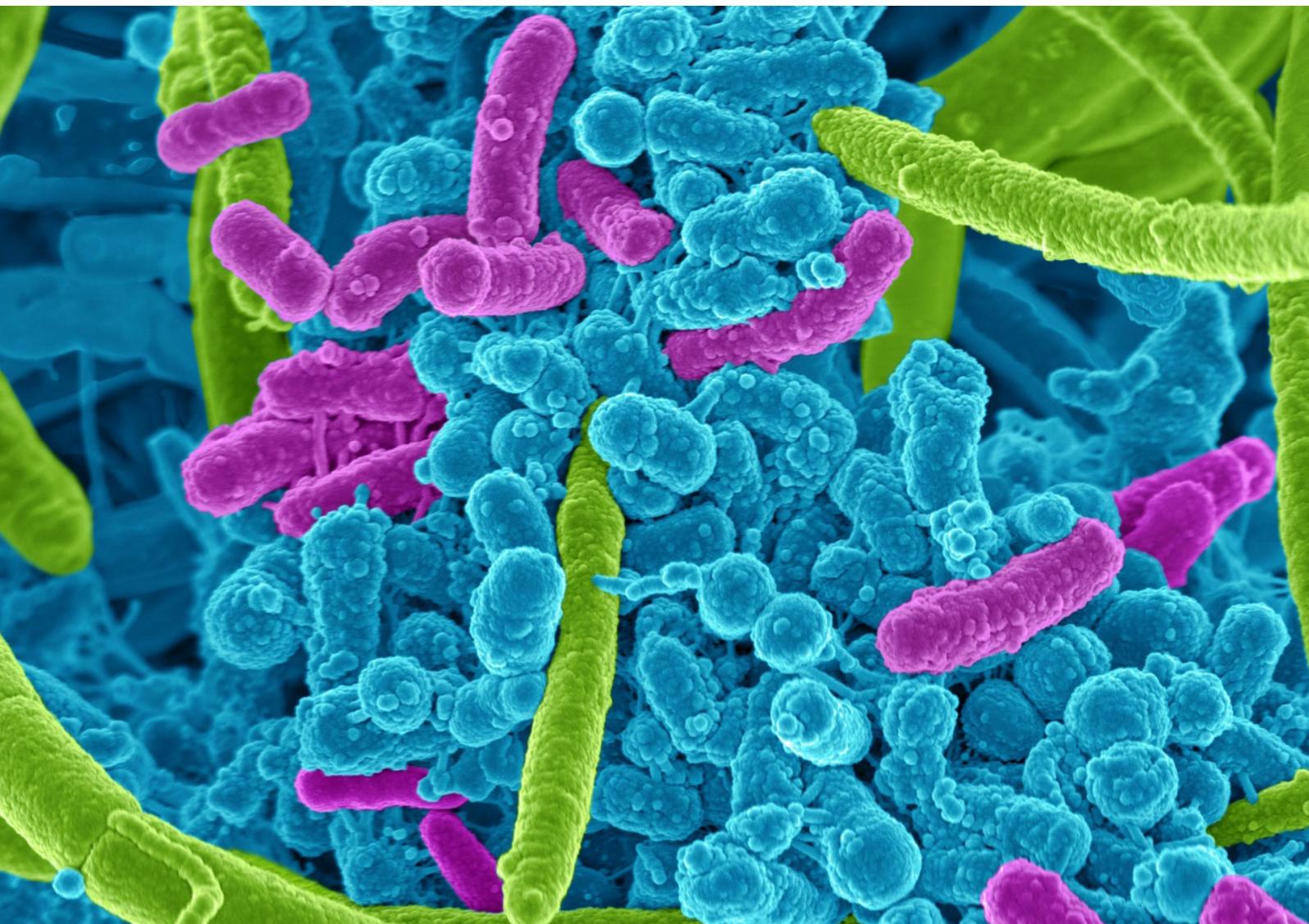
There are a growing number of bacteriophage therapies entering clinical trials. For example, investigation into the use of phage treatments for Covid-19 patients with bacterial co-infection (Adaptive Phage Therapeutics, US), cystic fibrosis patients with chronic *Pseudomonas aeruginosa* pulmonary infection (BiomX Inc, Israel), treatment for serious and life-threatening *Staphylococcus aureus* and *Pseudomonas aeruginosa* infections (Armata Pharmaceuticals, US), phage preparations for managing *Shigella* infection in humans to prevent or reduce the severity of illness (Intralix, US), and phage-based solutions to support the fight against AMR by targeting various

bacterial pathogens such as *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli*, *Staphylococcus aureus*, to support the fight against AMR (Phico Therapeutics, UK).

It is anticipated that the market for bacteriophage will grow, and in light of the current AMR crisis plus the rise in bacteriophage research centres, growth projections for the sector look positive [21]. Although promising, phage technology for therapeutic use is still in the development phase in the West, and challenges need to be overcome to accelerate clinical testing.

The development of efficient, scalable manufacturing processes for phage is a major hurdle, plus ensuring the quality, efficacy, purity, titre/dose and optimal product formulation to retain stability are factors critical to the success of phage therapy. A flexible microbiome bioprocessing facility that could accommodate phage process development and scale-up when required would help to support the development of new therapies and growth of the sector in the UK, as well as attract international clients working in this field.

Whilst bacterial and phage-based therapy research has attracted most attention, there is also interest in the role of the fungal microbiota or 'mycobiota' [22] in health and disease and how this might be translated into new treatments and diagnostics. Several groups in the UK are engaged in this field of research, including the MRC Centre for Medical Mycology at the University of Exeter [23].



1.3. Other ‘microbiome therapeutic’ modalities

The exploration of the gut microbiome as a source of new therapeutic drug candidates.

Drugs have been discovered and produced from microbes since the first half of the 20th century including antibiotics and anti-cancer drugs. The close association between human health and disease and the gut microbiome suggests that the microbiome could be a rich source of new drug candidates [19]. One example of this is the development of mimetic vaccines based on specific peptides derived from gut bacteria that closely mimic tumour peptides. Enterome, a leading French microbiome company, has a pipeline of new cancer drugs based on this technology. Bacteriocins (antimicrobial peptides or proteins produced by bacteria) are also gaining attention as potential clinical antimicrobial treatments [24].

Novel microbiome modulator platforms.

Live microbes represent one of the main strategies being followed in the development of microbiome therapeutics, but there are also various other strategies being explored. In particular, several molecules produced through synthetic chemistry that target the mitigation of pathophysiological dysbiosis or harmful microbial products such as ammonia are at an advanced stage of development. Examples include:

- The development by Enterome of an anti-adhesion therapy that blocks the attachment to the gut wall of a group of Enterobacteriaceae that are highly represented in Crohn’s patients [25].
- Axial Therapeutics, a US start-up focused on the microbiome and gut-brain axis diseases and disorders, is developing gut-targeted small molecule drugs that target microbial metabolites in the gastrointestinal tract [26].

1.4. The microbiome and drug efficacy

It is well-known that individual responses to different drugs can vary widely. For example, only a proportion of cancer patients respond to treatment with immune checkpoint inhibitors (ICIs), a class of monoclonal antibody therapy that has transformed the field of oncology over the past decade. What has emerged over recent years is that the gut microbiome is implicated in the variability of this response with very recent studies demonstrating that IMT has the potential to enhance the response to ICIs [27].

Moreover, the microbiome has been implicated in the efficacy or side effects of some widely used medications such as metformin for treatment of diabetes [28] and L-dopa for treatment of Parkinson’s disease [29].

This is an exciting and emerging area that has potential to translate into new precision medicine and associated diagnostic opportunities [30] [29] [31] including the development of new therapies combining IMT, LBPs or other microbiome therapeutic modalities as adjunct precision therapies for a range of existing and new drug classes.

Evidence of the strong industry interest in the burgeoning field of drug–microbiome interactions can be seen in the recent Pistoia Alliance-led project funded by alliance members: Bayer, BMS, Eagle Genomics, Pfizer, Roche, and Takeda. This will be a ‘pre-competitive microbiome and drug metabolism project’, which aims to gather all existing microbiome data to create a global standardised ‘atlas’ that scientists can refer to when choosing new drug candidates. This atlas will map out the bi-directional relationship between a drug and the microbiome, enabling researchers to identify patterns in drug behaviour. This collaborative work will speed up

the advancement of new, precision medicines and treatments.

Given the potential of this emerging area of microbiome science, it is recommended that the funding bodies add 'drug-microbiome interaction' to their key 'science areas' for funding and even consider setting up a dedicated centre for drug-microbiome interaction studies.

1.5. Microbiome-based diagnostics, biomarkers and related technologies

According to BCC Research, diagnostics represents 5% of the potential human microbiome market with the other 95% covering therapeutics. Although diagnostics represents a smaller potential market, the time to market is shorter than for therapeutics.

Microbiome-based diagnostics can be defined as 'tools that allow detection of, and/or making prognoses on, human disease using microbial signatures of different types' [32]. It usually requires sequencing the total metagenome found in a specific body site and associated with a particular disease. Microbiome-based diagnostics can be used for disease diagnosis, monitoring, and prognosis, as well as predictive tests allowing patient stratification and personalised treatment selection [32] [1]. All of these can bring significant benefits to patients and their families, reduce costs and save time for the NHS. Another application for microbiome diagnostics is in drug discovery and development, where microbiome-based companion diagnostics could be used to predict treatment outcomes based on microbiota biomarkers [26].

Underpinning technologies

Advances and reduced costs in next generation sequencing, bioinformatics, big data analysis, artificial intelligence (AI), machine learning, and processing capabilities have allowed the clinical metagenomics and multi-omics fields to thrive [26]. All of these are part of the UK's strategic key technology families [33].

Opportunity

The UK is in a solid position to capitalise on microbiome diagnostics, as it has excellent science and infrastructure in the underpinning technologies mentioned above. It also has a healthcare system with cutting-edge genomic testing technologies being delivered through NHS Genomic Medicine Service and the National Genomic Laboratory Network [34]. The UK's world-leading genomic sequencing capabilities were demonstrated during the Covid-19 pandemic, where it played a critical role in the surveillance and discovery of new variants of the SARS-CoV-2 [35]. It also has a world-class science, industry and infrastructure working on the microbiome, precision medicine and medicines manufacturing [36] [37] [38].

Although the microbiome diagnostics industry is still nascent, Table 1 includes a few examples of UK companies active in the sector.

Main technology	Company	City
Biomarkers	Microbiotica	Cambridge
Companion diagnostics	Alphabiomics	London
AI-augmented knowledge discovery platform	Eagle Genomics	Cambridge
Novel sampling devices	BioMe Oxford	Oxford
	Enteromics	London
	Origin Sciences	Cambridge
Rapid sequencing technologies	DNA Electronics	London
	Oxford Nanopore Technologies	Oxford
Rapid sequencing technologies home kits	Atlas Biomed	London
	Invivo Diagnostics ⁺	Bristol
	Ome health	London
Microbiome analysis for personalised nutrition	ZOE	London
	Biomesight	London

Table 1 shows examples of UK companies active in microbiome diagnostics and related sectors.

⁺Registered as Invivo healthcare Ltd.

An up-to-date list of microbiome solutions companies can be found on the Innovate UK KTN Microbiome Innovation Network Landscape Map [36].

The principal inherent challenges in the microbiome diagnostic space are:

- Difficulty in establishing a clear connection between disease and microbiome signatures.
- Analysing complex microbiota samples (viruses, bacteria, fungi and protists) paired with their genetic diversity and plasticity [39].
- Large datasets of patients are required to validate biomarkers and drug targets [32]. Once more, the UK has the National Institute for Health Data Science that supports innovation at scale by uniting healthcare data from across the UK. The Gut Reaction – Hub for Inflammatory Bowel Disease is particularly relevant for this report [40].

- Standardisation of microbiome practices including sample collection, nucleic acid extraction, data analysis and result reporting [1] [39].
- Defining quality control and regulatory standards [39].

Developing microbiome-based diagnostic systems requires the collaboration of several underpinning technologies combined with clinical insight. Therefore, to build on the UK's strength in this area, consideration should be given to designing a business-led and challenge-based funding competition to support microbiome-based diagnostics.

This competition should focus on solving unmet clinical needs and bring together clinical expertise and various underpinning technologies. Innovate UK could take advantage of the accelerator programme and provide grant funding and early venture capital investment by partnering with larger companies such as Illumina, Oxford Nanopore, IBM, Microsoft, and large pharmaceutical companies. This could support early-stage partnerships not only providing financial resources, but also commercial, technical and scientific expertise.

1.6. Nutritional interventions as a component of prevention and treatment

The gut microbiome composition and/or function has been identified as a significant variable in defining human health including the importance of establishing a healthy infant microbiome for health status later in life [41]. Microbiome-modulating diets and food ingredients can make significant contributions to the health and wellbeing of consumers and to healthcare cost savings. The recently published Personalised Responses to Dietary Composition Trial (PREDICT 1) study based on data from more than 1,000 UK individuals identified associations between microbes, cardiometabolic biomarkers and specific nutrients, foods, food groups and general dietary indices characteristic for a healthy diet [42]. In addition, probiotics, prebiotics, fibres and plant-derived polyphenols have been shown to modulate the gut microbiome and contribute to health and wellbeing. Probiotics, for example, have been demonstrated to significantly reduce the impact of upper respiratory tract infections [43] [44].

The UK is well positioned to benefit from the numerous world-leading academic institutions (such as Imperial College London, The Quadram Institute, King's College London, The Rowett Institute) actively researching microbiome-modulating nutritional interventions for human health and wellbeing as well as for disease prevention and treatment. This research will enable UK food and consumer healthcare manufacturers to translate the findings into health and nutrition innovations and marketing science-backed products.

With more research highlighting the link between a healthy diet, a healthy microbiome based on a high diversity of microbes and human digestive, immune, metabolic and cognitive health, there are multiple opportunities for further research and development of nutritional microbiome-modulating solutions. Key areas are:

- Immunomodulation
 - Infant immune system development (including prevention of atopic conditions).
 - Infection prevention throughout the life cycle (including viral upper respiratory tract infection such as cold and flu and Covid-19).
 - Inflammaging and immunosenescence.
 - Immuno-oncology.
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- Digestive health
 - Functional constipation.
 - Irritable bowel syndrome.
 - Prevention of antibiotic side effects (e.g. antibiotic associated diarrhoea).
 - Infant colic.
 - Food intolerances.
- Emerging areas
 - Cognitive health (gut-brain axis).
 - Neurodegenerative diseases.
 - Support management of symptoms associated with autism spectrum disorders.
 - Metabolic health.
 - Women's health.
 - Skin health (gut-skin axis).

Personalised nutrition

Personalised nutrition is one of the most promising emerging areas of interest in the nutrition-microbiome space. Building on the UK's world-leading capabilities in sequencing and multi-omics technologies, the UK should aim to become a world leader in this field by combining these fundamental capabilities with the ability to conduct human clinical studies and apply machine learning technologies.

An example of a successful international collaboration between Massachusetts General Hospital, King's College London, Stanford Medicine, and Harvard T.H. Chan School of Public Health is the London-based company ZOE which has raised a total investment of £42 million [45]. Its offer is based on large-scale nutritional intervention studies that combine standardised nutrition challenge tests, microbiome sequencing, and AI to provide personalised nutrition recommendations with an at-home test kit [46] [42].

One significant challenge for further innovation in the field of nutritional microbiome modulating solutions, lies in the regulatory environment in the UK and EU. This limits the communication of published research findings to consumers and further investment in the substantiation of health benefits by well-designed human interventions studies.

2. Market Opportunity and Sector Development

2.1. An overview of the market opportunity for human intestinal microbiome therapeutics

The human microbiome market is often segmented into therapeutics (including therapeutic and medical foods) and diagnostics. The therapeutics segment is where, to date, most of the investment has been made.

As evidenced by the levels of investment in this field (see below), the expectations are very high for the long-term global market opportunity for microbiome therapeutics and diagnostics. It is, however, a challenging process to bring IMT-based and LBP-based products to the market and to patients. Therefore, it will likely take several more years before we see significant launches of new LBP-based therapies. The global market size is estimated to reach \$1.3 billion by 2026 [47]. Gastrointestinal diseases and infections dominate the landscape currently, though metabolic, inflammatory (cancer in particular) - and neurological diseases are expected to emerge as key market segments over the coming years [48].

Following innovations in next generation sequencing and scaled manufacturing, research, and development infrastructure, the past two years have seen significant investment in microbiome-focused pharma biotech companies. Between 2019 and 2021, over 133 investors contributed \$1.6 billion in invested capital across 64 companies globally [49]. By 2021 there were 118 microbiome-focused research and development (R&D) companies and 458 drug candidates in development worldwide [4].

There has additionally been significant growth in investment in contract manufacturing organisations (CMOs) and contract development and manufacturing organisations (CDMOs) producing live biotherapeutic products [50].

Large pharmaceutical and nutrition and health companies have been actively partnering with and/or investing in microbiome start-ups including AstraZeneca, Bristol Myers-Squib, Danone (Nutricia), Roche/Genentech, GSK, J&J, IFF, Merck & Co, Nestlé and Takeda.

Despite growing interest in microbiome-based therapeutics by large public and private entities, it is especially start-ups in this space that continue to drive research and development of therapeutics for novel indications [49]. The numerous diseases for which the science is at an early concept stage include liver disease, kidney disease, hypertension, polycystic ovary syndrome, multiple sclerosis, autism spectrum disorder, depression, schizophrenia, and Parkinson's disease. Continued investment in research efforts such as the 'annotation of hundreds of as yet unknown chemical compounds in the metabolomes and peptidomes of various body fluids as well as approaches to decipher compounds of solely host, microbial and dietary origin, or of combined origin' is essential and will further contribute to market growth [19].

2.2. How the UK compares to other countries in terms of microbiome innovation

The UK has world-leading microbiome science, driving significant impact in research with the ethos of public money to enable public benefit. There is a diversity of research, including the NHS work on gastrointestinal tract conditions as well as the government's investigation of the role of the microbiome in measuring and maintaining public health, including obesity.

The top three UK institutions publishing microbiome-related work are Imperial College London, King's College London and the University of Oxford [1]. Outside the public sector, the UK similarly hosts a robust research community and has a growing start-up ecosystem and established pharmaceutical players invested in driving microbiome innovation across diverse therapeutic indications.

The UK is well-known for its life sciences capability and, in terms of private capital raised, the UK continues to be the leading life sciences biotech country in Europe followed by Switzerland and then Germany [51]. Regarding microbiome innovation, the UK ranks fourth after the US, South Korea and France for microbiome drug candidate development [4]. If the UK wants to continue to be one of the leading players in Europe in the field of the microbiome, it will need to recognise the microbiome as a disruptive technology and invest further resources to bring microbiome-based technologies to market as some other countries are doing. For example, France has recently announced that it will invest Euro 449.5 million over the next five years dedicated to developing solutions for a sustainable and healthy diet, much of which is expected to come from research into the microbiome [52]. Whilst this investment targets largely nutritional microbiome science-based solutions and not therapeutics, it is a strong indication of the interest and commitment of the French government in continuing to maintain France's European leadership position in microbiome innovation.

In 2021, the South Korean government announced a 10-year programme and close to \$1 billion investment to support the development of their emerging microbiome industry. Building a world-leading microbiome biobank is one of the key thrusts of the programme [53].

While individual countries are increasingly establishing public organisations dedicated to enabling disruptive microbiome innovation, true progress will come from further international ecosystem development for collaboration on disruptive technologies.

In the UK, there has been considerable public investment in infrastructure and research related to the microbiome (see Section 3), and there are a handful of notable microbiome innovators that have forged ahead and attracted considerable private investment, namely 4D Pharma, Microbiotica, Prokarium, EnteroBiotix and Eagle Genomics. 4D Pharma, a publicly-listed biotherapeutics firm, has 13 biotherapeutics in development [54]. 4D Pharma's clinical trial candidates span immuno-oncology, central nervous system, respiratory, autoimmune and gastrointestinal and are generated using a proprietary platform known as MicroRx. Microbiotica provides leading microbiome profiling capabilities in addition to immuno-oncology and ulcerative-colitis programmes entering Phase Ib clinical trials in 2022 [55] and in March 2022 announced that it has raised £50 million to advance its pipeline; this represents the largest financing of a microbiome company in Europe so far.

These companies are just a sample of the innovation landscape developing across the country. A growing list of UK intestinal microbiome therapeutic and associated manufacturing or formulation companies is provided below. The list only includes organisations where microbiome therapeutics is a key part of what they do, not the larger multinational companies also participating in this field, as mentioned above. An up-to-date and more comprehensive list of microbiome solutions companies can be found on the Innovate UK KTN Microbiome Innovation Network Landscape Map [36].

- 4D Pharma
- Neobe Pharma
- CHAIN Biotechnology
- CPI
- Eagle Genomics
- Enterobiotix
- Ferryx
- Fixed Phage
- Microbiotica
- Quay Pharma
- Prokarium
- Vemico.

Whilst tremendous progress has been made in microbiome science and innovation both in the public and private sectors, significant opportunity space and headroom for innovation exist to accelerate translational microbiome research, start-up company formation and industry-academic partnerships.

Historically notable private investments into UK-based microbiome firms include those made by Seventure Partners, IP Group plc, Oxford Finance LLC, and Cambridge Innovation Capital, amongst others [56].

2.3. Lessons learned from the development of other advanced therapies

The UK is a world leader in advanced therapy medicinal products (ATMPs), including cell and gene therapies. According to the UK's CGT Catapult Annual Review 2020, over 12% of global gene and cell therapy clinical trials occur in the UK, creating 3,000 jobs in around 90 UK organisations and £300 million turnover. The industry could be worth around £10 billion, including 18,000 jobs by 2035 [57] [58].

This achievement resulted from the UK recognising the opportunity and taking an early lead in the sector. Thus, creating an environment for these technologies to flourish by investing in research, development, scale-up, manufacturing, and skills. In addition, it has put in place the mechanisms to support regulation, commercialisation, and adoption.

For this reason, ATMPs industry represents a valuable model for other emerging sectors such as the microbiome to follow.

Supporting basic research to help support downstream translation

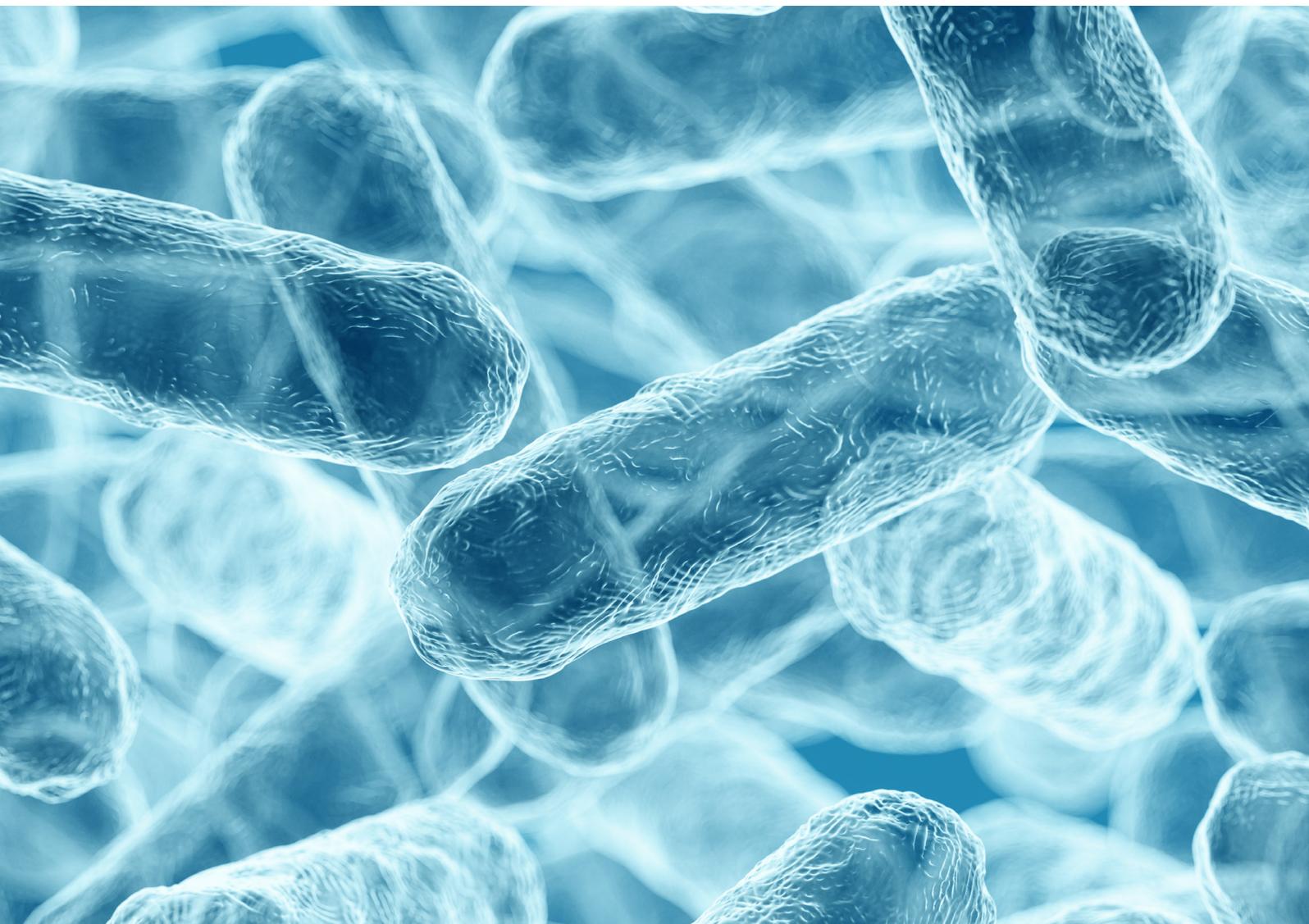
Translating basic research into consistent and accurate preclinical models for cell and gene therapies has been and remains a challenge. Improved understanding of the pathological causes of disease and the mode of action of therapies is essential, including more accurate and relevant modelling. Such needs can be equally applied to microbiome therapeutics, although many of these might have broader applicability to a range of diseases [59] [60].

Therefore, funding to support understanding pathological causes of disease and mode of action of potential therapies and how this translates from in vitro to non-human in vivo preclinical models is key. To that end, the UK Microbiome Bank, similar to the UK Biobank, dedicated to conserving and preserving the biodiversity of microbiomes, would provide a unique resource for both the research community and industry.

Taking therapies from research and development to successful scale-up and manufacturing

Currently, there is a manufacturing bottleneck for small-scale research-led IMT studies. The need for specialised culture and manufacturing equipment, and the expertise to support development and scale-up at the suitable regulatory standard (GMP, ISO), have proved to be a challenge.

In the UK, support for the translation and scale-up manufacturing capacity for advanced therapies has been in part addressed by the CGT Catapult's manufacturing innovation centre and large-scale GMP manufacturing centre in Stevenage. The CGT Catapult Annual Review 2020 [57] indicates that 77% of UK ATMP trials are



sponsored by commercial organisations, mainly non-UK-based companies, compared to 25% in 2013. Such facts demonstrate the benefits of the UK ecosystem on the global stage, having established both expertise and the standards and regulation required to get such therapies closer to being a clinical reality. The UK has also been focused on capturing investment by providing competitive loan and/or grant funding such as the Government's Advanced Manufacturing Supply Chain Initiative and continues to invest via existing mechanisms such as Innovate UK, which have helped ensure that the UK stays at the forefront of cutting-edge technologies in this space [61].

Leaders in the microbiome-based therapeutics field are starting to establish internal capabilities to support their development programmes and have control over the supply chain..

Thus, considerations around future scale-up requirements need to be incorporated earlier on in development, including monitoring and testing, the application of modelling approaches and automation. Ensuring the supply chain is also prepared and readily able to scale and align patient care with fast manufacturing for products with shorter shelf-lives, for example, certain IMT approaches. Such an approach has the potential to foster UK-based companies and draw interest from non-UK companies to benefit from the country's world-class expertise in microbiome therapeutics.

In the future, drug development enterprises focused on whole-community microbiome therapeutics could face a 'buy or build' scenario. This decision could be guided by the availability of high-quality contract development and manufacturing capacity and capability, which currently does not exist globally. There is an opportunity for the UK government and established industry players to invest in this area so that the UK can become the global leader in this domain. Such endeavours could also include establishing a Microbiome Bioprocess Innovation Centre (MBIC), which could become a new arm of the HVM Catapult. Consideration should be given to physically placing the MBIC alongside or as part of the proposed Microbiome Innovation Hub to create a one-stop shop.

Regulatory and standardisation challenges

Developing regulations and approval of advanced therapies in the UK has taken a coordinated effort between the government, regulatory bodies such as the MHRA and medical and scientific experts.

In 2015, the UK government published its 'Advanced therapy medicinal products: regulation and licensing' guidance [62], which outlined information on classification. It established a 'one-stop shop' approach to queries via the MHRA Innovation Office, providing scientific advice, guidance on conducting clinical trials, applying for market authorisation and manufacturing licenses. The guidance also outlines ways unlicensed ATMPs can be made available in the UK.

The CGT Catapult has continued promoting innovation and developing technology transfer expertise for cell and gene therapy manufacture. It has been critical to have scalable production systems to make high-quality, traceable products, map out various product classes, and put platforms in place. This includes more automated, predictable and testable production. It has also helped establish and promote therapeutic standards, including analytical innovation for improved product characterisation, reference standards to ensure global consistency, manufacturing, packaging and transportation considerations and standardising the complex and diverse processes within the hospitals. Achieving the correct regulation around the sector has also been important, working proactively with the companies and regulators to ensure that the right mechanisms have been put into place.

It is vital to establish efficient clinical trials by keeping close communications with regulatory bodies such as MHRA and FDA and having a 'one-stop shop' government support model similar to the one for ATMPs. Intellectual property (IP) and commercialisation requirements are also necessary, including other factors that might require patenting other than the treatment itself, including patents and know-how around the biological starting materials and cell-derived from them, and delivery of treatments within a surgical/clinical procedure. Publication and sharing of non-IP sensitive know-how through mechanisms similar to the CGT Catapult can also help accelerate the development and consistency of microbiome-based therapeutics.

The MIH could facilitate the engagement between the microbiome science and innovation communities, enterprises, and regulatory agencies to promote dialogue during the early development of new products. While MIH could play a key role in defining microbiome therapeutics and diagnostics standards, the UK Microbiome Biobank could set standards for sampling and the associated analyses and storage of microbiome samples.

Reimbursement and access to treatments

To ensure that advanced therapies are adopted into routine clinical practice, the UK Bioindustry Association has called for the UK government to address several points relating to reimbursement processes for cell and gene therapies that balance affordability and risk. These challenges are also relevant to microbiome therapeutics. Therefore, it is necessary to understand and start establishing as early as possible mechanisms for reimbursement of microbiome therapeutics by working with developers, manufacturers, and regulatory and other government groups to accelerate the adoption of microbiome-based therapeutics into routine clinical practice.



3. Infrastructure and Innovation Support

3.1. Science infrastructure

The research and development of therapeutic products targeting the human gut microbiome, such as LBPs and other modalities offers tremendous and transformative healthcare benefits and commercial opportunities; however, it does demand multiple areas of expertise across discovery, preclinical and clinical testing, manufacturing, IP and regulatory.

The UK has leading microbiome science highly dispersed within many universities and institutes, as comprehensively listed in Innovate UK KTN Microbiome Innovation Network Landscape Map [36]. The highly dispersed nature of microbiome research in the UK does bring some advantages, as it can enable close integration with specialists working in a range of different fields covering different biological processes that can potentially be impacted by the intestinal microbiome. There are, in addition, some notable centres with critical mass in key areas of microbiome research:

- National Biologics Manufacturing Centre, CPI, Darlington
- Industrial Biotechnology Facility, CPI, Wilton
- Earlham Institute, Norwich
- European Bioinformatics Institute (EMBL-EBI), Hinxton
- Hartree National Centre for Digital Innovation, Daresbury
- Imperial College London's Microbiome Network including the National Phenome Centre
- King's College London
- Mary Lyon Centre at MRC Harwell
- Oxford Centre for Microbiome Studies
- Quadram Institute Biosciences, Norwich
- Rowett Institute, University of Aberdeen
- Cardiff University, Microbiomes, Microbes and Informatics Research Unit
- University of Liverpool Microbiome Innovation Centre
- University of Manchester
- University of Reading
- Wellcome Sanger Institute.

Key capabilities include: in vitro models, ex vivo models, rodent models, omics analytical platforms, computational science and bioinformatics, bioprocessing technology including manufacturing process development and scale-up, and clinical trials infrastructure. The Innovate UK KTN Microbiome Innovation Network Advisory Board has assessed these capabilities as ranging from good to excellent.

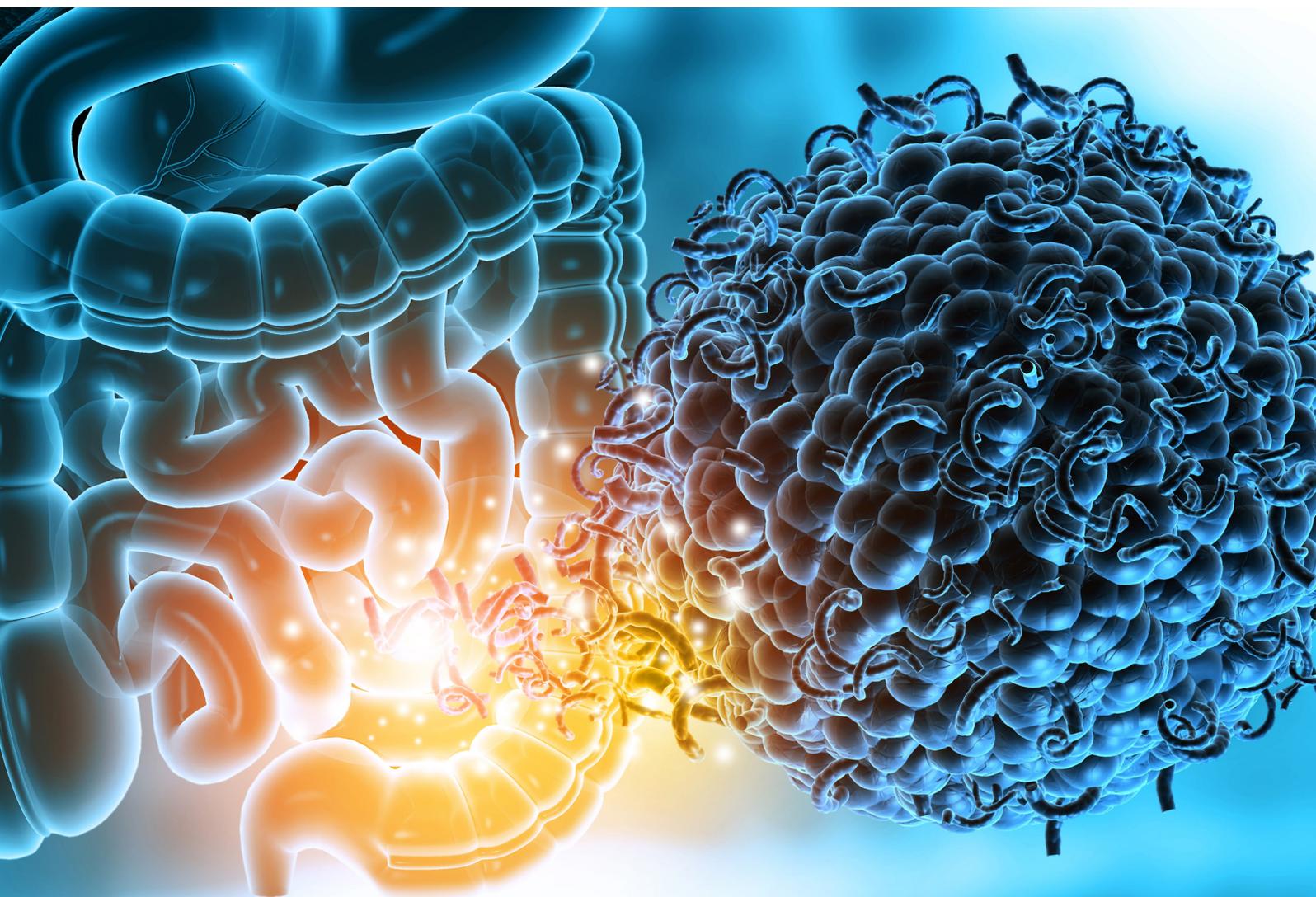
A number of these centres provide services to industry and others. The challenge for academic centres, where much of the UK's microbiome expertise naturally resides, is to provide professional and timely services that do not undermine or compete with academic priorities. Having said that, the UK university sector infrastructure is extensive and able to support early-stage microbiome innovation. The UK infrastructure for clinical trials is also world-leading with an extensive network of university and/or NHS CTUs (see UK Clinical Trials Research Collaboration) or CROs and is a critical component for any new therapeutic development.

Even with these strengths, universities and UKRI institutes are not so easy to access for conducting professional and timely research service work. This is where catapult-like or innovation hub-type organisations can come into their own. This model is very well developed in other Europe countries, for example, the Netherlands with TNO and Finland with VTT. Another academic+service hybrid model exists in Belgium with VIB, the Alimentary Pharmabiotic Centre in Ireland and French National Research Institute for Agriculture, Food and the Environment in France. These centres provide leading-edge microbiome services that compete with those in the UK, meaning that UK-based start-ups will often choose to conduct aspects of their microbiome research abroad.

The biggest infrastructure gaps for microbiome innovation in the UK are:

- Manufacturing and formulation of microbiome therapeutics especially LBPs.
- Microbiome innovation knowledge support – offering guidance and support in all aspects of microbiome innovation from discovery through manufacturing to commercialisation.

These gaps and recommendations on how to address them are covered over page.



The UK's human intestinal microbiome science infrastructure

	Short description
In vitro models	<ul style="list-style-type: none"> Batch culture and continuous culture fermenter systems are regularly used at the Rowett Institute, University of Reading and Quadram Institute Bioscience (QIB).
Ex vivo models	<ul style="list-style-type: none"> Organoid models used at the Rowett Institute, QIB and Earlham Institute. Gut-on-a-chip systems (QIB). Access to primate tissue/samples (MRC Centre for Macaques).
Rodent models	<ul style="list-style-type: none"> Germ-free mouse facilities at QIB: <ul style="list-style-type: none"> Both in germ-free and in SPF animals, it is possible to modulate the microbiome via different approaches, including IMT and the use of antibiotics, prebiotics, probiotics and synbiotics as well as dietary interventions. QIB also has expertise in a wide range of preclinical mouse models for diseases associated with changes in the microbiome that can be used on gnotobiotic and SPF mice. Oxford Centre for Microbiome Studies: <ul style="list-style-type: none"> Access to experimental support and gnotobiotic and SPF models. This includes germ-free, axenic, and synthetic microbiomes. Able to provide germ-free rederivation of strains as service. University of Manchester Axenic and Gnotobiotic Mouse Facility: <ul style="list-style-type: none"> Expertise in germ-free and gnotobiotic mouse models and can provide support in the generation and long-term maintenance of mono-colonised and minimally diverse microbiota gnotobiotic mice. Within a germ-free environment, can provide experimental and technical support for the use of infectious agents (including single and multicellular pathogens). Multiple isolator platforms (Teknoplant Isocages and small isolators) available for use. Mary Lyon Centre at MRC Harwell: <ul style="list-style-type: none"> Expertise in the generation of genetically-altered mouse models and rederiving mouse strains into germ-free conditions. Currently establishing germ-free mouse models for supplying UK academic and industrial researchers.
Omics analytical platforms	<ul style="list-style-type: none"> Imperial College London's National Phenome Centre (https://phenomecentre.org/platform/). University of Liverpool Centre for Genomic Research (https://www.liverpool.ac.uk/genomic-research/) and Centre for Metabolomic Research (https://www.liverpool.ac.uk/health-and-life-sciences/research/liverpool-shared-research-facilities/multi-omics/cmr/).

Computational science and bioinformatics	<ul style="list-style-type: none"> · MRC-funded CLIMB-BIG-DATA (https://climb.ac.uk) provides cloud computing facilities for the UK microbiology community, with containerised pipelines in development for microbiome research. · European Bioinformatics Institute resources: <ul style="list-style-type: none"> · MGnify (https://www.ebi.ac.uk/metagenomics/) provides access to thousands of metagenomic, metatranscriptomic and metabarcoding datasets. Also establishing catalogues of prokaryotes. Provides services for the assembly and analysis of results. Pipelines and associated containers are available for further development. · MetabLights collects and annotates metabolomic data from microbiomes · PRIDE - Proteomics resources, that allow collection. · Hartree National Centre for Digital Innovation, which supports organisations in the use and adoption of digital technologies like supercomputing, data analytics, AI and quantum computing. Growing expertise in microbiome applications. (https://www.hartree.stfc.ac.uk/Pages/Hartree-National-Centre-for-Digital-Innovation-%28HNCDI%29.aspx).
Clinical trials infrastructure	<ul style="list-style-type: none"> · QIB has a clinical trials unit, which includes specialised applications devoted to microbiome work (e.g. IMT). · CTUs with similar activities going on elsewhere in UK.
Microbiome science centres of expertise	<ul style="list-style-type: none"> · On the Norwich Research Park, Quadram Institute Bioscience (https://quadram.ac.uk) and the Earlham Institute (https://earlham.ac.uk) have a lively programme of human microbiome research (https://quadram.ac.uk/targets/understanding-the-microbiome/) with a strong infrastructure that includes a biobank, endoscopy suite and world-class sequencing and bioinformatics support. · The Rowett Institute in Aberdeen (https://www.abdn.ac.uk/rowett/) has longstanding expertise in gut microbiome research, and most particularly in the cultivation of anaerobic gut bacteria in the laboratory. The Institute has a suite of anaerobic microbiology facilities, as well as core sequencing and metabolomics capabilities, and a dedicated human nutrition unit for dietary intervention studies. · Wellcome Genome Campus - Finn (EMBL-EBI) and Lawley (Sanger Institute) teams - provides experience in wet/dry lab techniques for microbiome research, especially with respect to human associated microbiomes. · Oxford Centre for Microbiome Studies (https://www.kennedy.ox.ac.uk/ocms) is capable of supporting microbiome research for academic and industry partners. It draws on expertise in immunity and inflammation available from within the Kennedy Institute of Rheumatology. · Imperial College London Microbiome Network (https://www.imperial.ac.uk/microbiome-network) spans microbiome expertise in life and environmental sciences as well as human health and disease. Considerable expertise in metabolomics. · Liverpool Microbiome Innovation Centre (https://www.liverpool.ac.uk/microbiome-innovation-centre/). · King's College London Centre for Host-Microbiome Interactions with a focus on oral microbiome.

Table 2 lists the UK's human intestinal microbiome science infrastructure.

Investment into microbiome research in the UK is predominantly through the Biotechnology and Biological Sciences Research Council (BBSRC), Medical Research Council (MRC), Innovate UK, and the Natural Environment Research Council (NERC). Collectively, these organisations have contributed in excess of £107 million to ca. 300 microbiome research projects.

The UK's world-leading research centres should continue to fuel new start-up creation and collaborations with industry to further accelerate the growing innovation space in microbiome therapeutics and diagnostics.

3.2. Manufacturing infrastructure

Manufacturing infrastructure including fermentation process development, scale-up and finished dose formulation.

Whilst there is tremendous potential for microbiome-based therapies, there is, however, a lack of manufacturing capacity to enable the translation of these treatments into the clinic. The lack of capacity can be felt at a global scale, but it is particularly acute in the UK, and, as a result, the UK risks falling behind the US and the rest of Europe in terms of commercialisation of microbiome research unless this situation is rectified. Constraints are especially acute for companies developing intestinal microbiome LBPs strains as they require anaerobic/low-oxygen culture conditions and may produce spores, requiring specialist handling facilities. Microbiome therapeutics face unique scaling challenges compared to other biotherapeutics, and the diversity of microbiome-based medicines (bacterial products, virus/phage therapies, microbially-derived postbiotics and small molecules) requires a broad range of expertise, operational flexibility and handling requirements.

The manufacturing infrastructure needed to support the supply chain for microbiome therapeutics includes:

- Process development, scale-up, and small batch manufacture to provide academics and start-ups with material for pre-clinical and clinical development, coupled with commercial manufacture to support the pipeline of products entering later-stage clinical trials.
- The analytical facilities and tools for the characterisation of microbiome therapeutics to ensure safety, efficacy and develop a greater understanding of what the critical quality attributes are and how they affect performance. Potency assays are especially complex with microbiome products, presenting challenges with predicting how a candidate product may work in the complex environment of a patient's own microbiota.
- Development of manufacturing processes and analytical tools with increased standardisation to help reduce variability across the industry, plus the development of reference standards to help benchmark manufacturing and testing.

It has been reported by a number of companies that fermentation process development and scale-up in the UK is proving difficult for start-ups and SMEs in the field [63]. This is clearly a significant gap that has to be addressed.

An obvious solution to this problem is for Innovate UK to build on the facilities and expertise at CPI's bioprocess development, scale-up innovation facilities in the North East of England and establish a new MBIC under CPI and perhaps as a new arm of the HVM Catapult. The new centre needs to have pharma GMP-certified facilities focused on manufacturing development and scale-up of microbiome therapeutics and spanning the full range of microbiome therapeutic modalities. CPI already has capabilities spanning the production of live microbes, small molecules and recombinant proteins and, more recently, has added an RNA Centre of Excellence and Training Academy to address RNA therapies and vaccines. However, it lacks GMP facilities with strict anaerobe and spore production capabilities and the capacity to address the needs of the fledgling microbiome industry in the UK. The proposed new centre could also provide an integrator function, i.e. a Microbiome Innovation Hub providing end-to-end discovery to commercialisation microbiome innovation knowledge support and training as part of the new centre offering.

This would still leave commercial-scale microbiome therapeutics production as a gap in the UK compared

to elsewhere in Europe, e.g. Biose Industrie in France and Bacthera in Denmark and Switzerland. In the US, Arrantabio is establishing itself as a CDMO focused on advanced therapies (LBPs and mRNA) and has announced a \$150 million investment plan to build out its facilities in Massachusetts [64]. Having said that, the timing for investing in large-scale commercial production of microbiome therapeutics in the UK will likely depend on the outcomes of clinical trials. This needs to be monitored carefully so that the capacity is there when needed. Regarding dose formulation, this is known to be one of the major challenges in manufacturing microbiome therapeutics. Therefore facilities and expertise are needed for developing and optimising the formulation and lyophilisation conditions for LBPs to ensure stability. Unlike many other biopharmaceuticals, LBPs are living organisms, so viability must be maintained whilst also considering stability and shelf life. Quay Pharma is one of the leading CDMOs in live biotherapeutics formulation here in the UK.

3.3. Innovation support, including research and development funding, networking, partnering and other support

Advancing the translation of microbiome science through industry-academic collaborations

The key to a thriving knowledge-based economy is a solid and continued translation of science [65]. The UK is one of the best globally in science and research in the academic and clinical sectors [3]. To reap the benefits presented by the microbiome field, it is necessary to further enhance industry-academic collaborations.

A challenge for many universities and other academic research centres is to understand the scientific, technical and commercial problems that UK companies face. For industry, the challenge is to be aware of the range of projects that are taking place in research centres across the country.

To facilitate industry-academic collaborations, a yearly 'microbiome research exchange' conference should be considered, where UK microbiome research excellence could be showcased to national and international industry representatives and investors (venture capitalists, angel, and corporate investors). This event will be a forum for exchanging ideas and finding collaborative solutions and could be a key component of a thriving informal network underpinning microbiome research.

The Innovate UK KTN Microbiome Innovation Network aims to continue to play a key role in driving support for microbiome translational research and innovation and facilitating industry-academic collaborations

Funding for innovation

The UK has well-established funding mechanisms to support health and life sciences innovation. These funding mechanisms are managed by various public sector organisations such as research councils, Innovate UK, and NIHR, among others [66]. Funding varies in nature depending on the stage of development, but most of them are non-thematic such as SMART Award, the Biomedical Catalyst and the iCure programme.

To encourage and support collaborative R&D in the microbiome space, some existing funding programmes

could be tailored towards microbiome innovation, for example by:

- Including the microbiome as one of the specific themes in the Biomedical Catalyst funding competition.
- Encouraging and supporting early private investment for early-stage projects through a microbiome-specific investor accelerator.
- Encouraging industry, academic and clinical collaboration by setting up a challenge-based funding programme to address key unmet clinical needs. In particular, for microbiome diagnostics, which could be done in partnership with NIHR i4i programme. Continue supporting programmes that allow industry-academic collaborations such as Innovation Scholars, Knowledge Transfer Partnerships, apprenticeships and CASE PhD studentships.

3.4. Skills and expertise

To ensure the UK is ideally positioned as a leading destination for microbiome innovation, it is necessary to create a workforce with the right mix of technical, scientific and entrepreneurial skills.

There is a significant shortage of expertise in dealing with the GMP development path of exotic microorganisms (anything which is not *E coli*, certain *Pseudomonas sp* and organisms used for the manufacture of 'conventional protein-based biopharmaceuticals'). This shortage in several critical skill areas includes the microbiology, physiology, handling, formulation of and analytics for microbiome products. Investment in skill development is needed at graduate, postgraduate and postdoctoral levels. Some microbiome products are likely to be developed as complex consortia of relevant organisms. The skills to understand, develop, manufacture and deliver such systems need to be significantly strengthened.

In 2020 BBSRC ran a workshop to understand the current and future capabilities needed for microbiome research. It identified gaps in quantitative skills, big data, machine learning, single-cell work and experimental design. It positioned them as opportunities for improving doctoral training and upskilled early-career scientists. It also noted the need for closer links between academia and industry to assist in the translation of research. However, companies found navigating the fragmented microbiome communities challenging [67], which was one of the reasons that the Innovate UK KTN Microbiome Innovation Network developed its Microbiome Landscape Map.

It is almost impossible for a single organisation to afford all the expertise and infrastructure required in the microbiome field. Therefore, collaborations across the entire supply chain and a range of training models that provide diversity and a breadth of opportunities are essential. In line with 'Pillar 2 – People' of the UK Innovation Strategy, these models should allow people to continue further education, retrain, move from another sector, return to work, and come from abroad [33].

The UK has already developed a successful skills and training model for advanced therapies, namely the Advanced Therapies Skills and Training Network (ATSTN). This initiative was funded by BEIS and Innovate UK to address the skill gap in the sector. It offers:

- On-site training courses through their National Training Centres, including the National Horizons Centre, RoslinCT and the University of Birmingham.
- Online training platform that provides remote and flexible industry-standard training programmes delivered by various academic and research institutions.

This training platform is designed to support people to upskill, retrain, and join from different sectors by assessing transferable skills and matching them with suitable roles. It also suggests the training needed for the matching jobs. Finally, the network has several industry partners that post their employment opportunities on the ATSTN online platform [68].

The microbiome sector could implement a similar training initiative, the 'microbiome skills and training network', which could take advantage of some of the existing infrastructures such as the National Horizons Centre (NHC), CPI's National Biologics Centre (NBC) and the National Biofilms Innovation Centre (NBIC) as well as expertise from research institutions, commercial and public organisations.

Therefore, consideration should be given to the following:

- The creation of an all-in-one platform, 'Microbiome skills and training network', similar to the ATSTN to upskill, retrain and allow people to transfer from other sectors. An existing centre such as NHC, NBC and NBIC could deliver the platform, though integrating this activity into a Microbiome Innovation Hub as described elsewhere in this report would have the advantage of providing a fully integrated end-to-end microbiome innovation support role.
 - Online training should cover technical, scientific skills and microbiome-specific commercial, IP and regulatory courses delivered through the microbiome skills and training network.
 - BBSRC could look at funding microbiome-focused doctoral training courses delivered by microbiome research and innovation collaboration networks/virtual microbiome institutes.
-



4. Regulatory, Standards and Biobanking Support

4.1. The emerging regulatory framework and how the challenges can be addressed

In the UK, a well-established legal system and regulatory frameworks exist for multiple sectors, the quality of which has been given the highest overall country score by the OECD[69].

The following key points are extracts from the Innovate UK KTN Microbiome Innovation Network Strategic Roadmap [1], which provides a very good overview of the regulatory challenges and opportunities for microbiome science-based product development.

- Determination of the appropriate regulatory pathways is difficult even for those with considerable regulatory experience. Lack of standards and regulatory definitions hamper developments, as does the lack of specific regulatory guidance to aid developers to interpret and apply existing regulations [16] [70]. Concerns have also been expressed about the complexity of rules and diverse requirements that impact biobanking and research, such as the Nagoya Protocol and General Data Protection Regulation. Also, too few opportunities exist to engage experts, regulators, and other stakeholders in open, pre-competitive discussions.
- Several approaches could help support microbiome advances in the regulatory domain, most importantly:
 - The provision of single points of access for early and close dialogue between developers and regulators
 - Development of regulatory guidance that outlines and clarifies specific requirements developers must meet for products [16] [71] [72].

Microbiome innovation and technologies can be fostered and incentivised by the government and regulators to help secure the economic and societal benefits of world-class microbiome research across the UK. Ideally appropriate regulations would be rapidly evolved (within appropriate constraints of human safety). This would pay dividends by reducing the time and cost to launch innovative products. The current UK government has stated its intention to foster such an agile approach [73].

4.2. Standards in microbiome research and development

The International Standards Organisation (ISO) characterises its ‘microbiology’ standards under TC 34/SC 9 [74]. The scope of this category of standards includes ‘horizontal methods in the field of microbiological analysis of the food chain from primary production stage to food and animal feed products, including the environment of food production and handling’ [74]. Fourteen global regulatory agencies act as liaisons for the standards category. EDMQ is a key European-related standards body that has adopted standards for LBPs [15]. The Food and Drug Administration has issued guidelines to the industry for conducting early clinical trials with LBPs [14]. Other relevant agencies include the World Health Organization, the European Commission and the National Microbiome Data Collective (NMDC) in the United States [75]. Scientific and business organisations also contribute to the elaboration of standards, such as the American Oil Chemists Society and the International Dairy Federation [74].

4.3. Data standards

The rapid expansion of the microbiome field has led to the exponential development of new methods, algorithms and computational tools for functional annotations and analyses of microbial species and associated metabolic pathways. However, a lack of standardisation across methodologies has led to significant variation in reproducibility and interpretability of the results when using different protocols to analyse the same samples [76]. In addition to technical inconsistencies (storage and collection of the sample, DNA extraction, next generation sequencing platforms and approaches used for sequencing, differences between the 16S rRNA region amplified), the complexity of the underlying biological data, the lack of proper metadata information and the scarcity of standard data formats as well as computational resources for high-volume data, is creating a significant computational analysis challenge. Effective standardisation of methodologies and data is essential to the entire microbiome community to produce efficient and scalable solutions, enable high-throughput strategies, reduce the biases introduced by computational protocols and increase the precision, specificity, and accuracy of data-driven findings. The introduction of in-silico research also adds an additional layer of complexity to microbiome data standardisation and analysis.

Data standards and FAIR (Findable, Accessible, Interoperable and Reusable) principles are key components to ensure data longevity. Initiatives to standardise computational protocols and tools, ontologies as well

Name	Description
Elixir [77] [78]	The European life-sciences Infrastructure for biological Information.
IMMSA [79]	The International Microbiome and Multi-Omics Standards Alliance.
NMDC [80]	National Microbiome Data Collaborative.
NIBSC [81]	The National Institute for Biological Standards and Control.
PRI [82]	Pharmabiotic Research Institute.
PA [83]	Pistoia alliance.
MTIG [84]	The Microbiome Therapeutics Innovation Group.
GA4GH [85]	The Global Alliance for Genomics and Health.
IMI [86]	Innovative Medicines Initiative.
GSC	The Genomic Standards Consortium.

Table 3 shows active organisations involved in data standardisation.

as promoting FAIR data stewardship are slowly emerging with organisations (Table 3). The initiatives and collaboration across these organisations, along with industrial and academic committees could potentially enable advancement in the microbiome field if funding is available.

4.4. Biobanks and culture collections

Biobanks and culture collections are integral to research and medicine. They are repositories of archival tissue, preservers of genetic diversity, providers of microbes for biomanufacturing and probiotics, and sources of life-saving therapeutics. The biobanking requirements for research in the gut/intestinal microbiome are interchangeable with the needs of other sectors.

The storage and distribution of microbiome samples presents new challenges. Biobanks store a temporal snapshot of samples. Culture collections propagate and store isolated organisms. In the UK, medical and veterinary organisms are publicly available and are curated by Public Health England, while smaller collections of microbes are held in veterinary and medical institutes across the country, although not all are publicly available. Some private companies also hold both culturable collections of microbes and samples of intestinal flora. Expertise in both is highly specialised around their biological holdings. Biobanks need to adapt to multi-omic profiling, capturing large amounts of data and disseminating detailed and accurate metadata. They must ensure that metadata and provenance information is linked with the sample and sequence information stored in digital archives. Biobanks must work closely with each other and with standards organisations to develop and agree on both experimental, such as extraction, characterisation, description, storage of microbiomes, their associated data and computational standards, such as metadata analysis and ontology.

Established UK culture collections are represented by the UK Biological Resources Centre Network, but microbiome biobanks and academic and privately held collections are not represented. Integrating and sharing expertise across taxonomic silos in the UK community is critical to preserving, distributing, and understanding microbiome samples. In the agri-food domain, a UK Microbiome Cryobank microbiome project has been established, a collaboration between five UK research Institutes (CABI, Rothamsted Research, Scotland's Rural College, John Innes Centre, James Hutton Institute) [87]. Extending links between biobanks will be essential to create a UK 'network of excellence' for addressing the challenges of microbiome storage, encouraging cross-disciplinary technology transfer, and addressing key scientific research questions.

Recent advancements in high-throughput sequencing, automated liquid handling, machine learning, single-cell analysis and microfluidics provide 'research at scale'. The search for microbiome-derived, functional strains to deliver targeted effects requires the ability to culture them on an industrial scale and provides benefits to multiple industry sectors. Leveraging existing investment in UK high-throughput infrastructure and understanding the requirements of the microbiome community to advance biobanking technology will offer a significant return to the UK's bioeconomy through the isolation and characterisation of products, as well as, bringing benefits to patients and consumers.

Summary of considerations

- The approach for the development of biobanking infrastructure should be cross-sectoral. Biobanks and culture collections should rapidly engage with stakeholders across the microbiome community to understand their requirements.
 - Biobanks and culture collections must provide integrated, cross-disciplinary expertise to meet the needs of the UK microbiome community to:
 - Facilitate UK industry in developing microbiome-derived products.
 - Underpin UK research activity into microbiomes.
 - Support industry in complying with regulatory processes and support intellectual property protection.
 - New methods are required; it is important to invest in the underpinning science such as core cryobiology expertise and preservation protocol research and development. This includes the need to ensure that storage approaches do not compromise the functional potential of LBPs/microbial consortia and these elements should be incorporated in broader funding call arrangements.
 - There must be an investment to bridge existing scientific infrastructure with the biobanking community to grow expertise and develop next-generation biobanking capabilities.
 - There should be a data standard to enable biobanks to communicate about the samples they hold, facilitate the formation of an integrated national network of biobanks and facilitate the possibility of a national portal for researchers to find suitable samples for research. The Innovate UK KTN Microbiome Innovation Network has launched an initiative to develop a cross-sector UK Microbiome Bank proposal. It should be supported in its efforts to create the world's leading microbiome bank, a significant asset for research and innovation.
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5. Intellectual Property

5.1. IPR challenges and opportunities

The rapidly growing understanding of the importance of the human gut microbiome on human health has triggered a dramatic rise in innovation in this area in recent years, with an expansive range of research and numerous clinical trials being carried out to evaluate the effect of gut bacteria on various diseases.

It is clear that this is a hugely competitive market, and it is no coincidence that this increase in R&D has resulted in a significant rise in the number of patent applications being filed for microbiome-related inventions, as innovators protect their innovations. As shown in Figure 1, the number of published patent applications with the word 'microbiome' in the title, abstract or claims has risen almost exponentially between 2010 and 2020.

**Number of PatBase patent family publications with
"microbiome" in the title, abstract or claims**

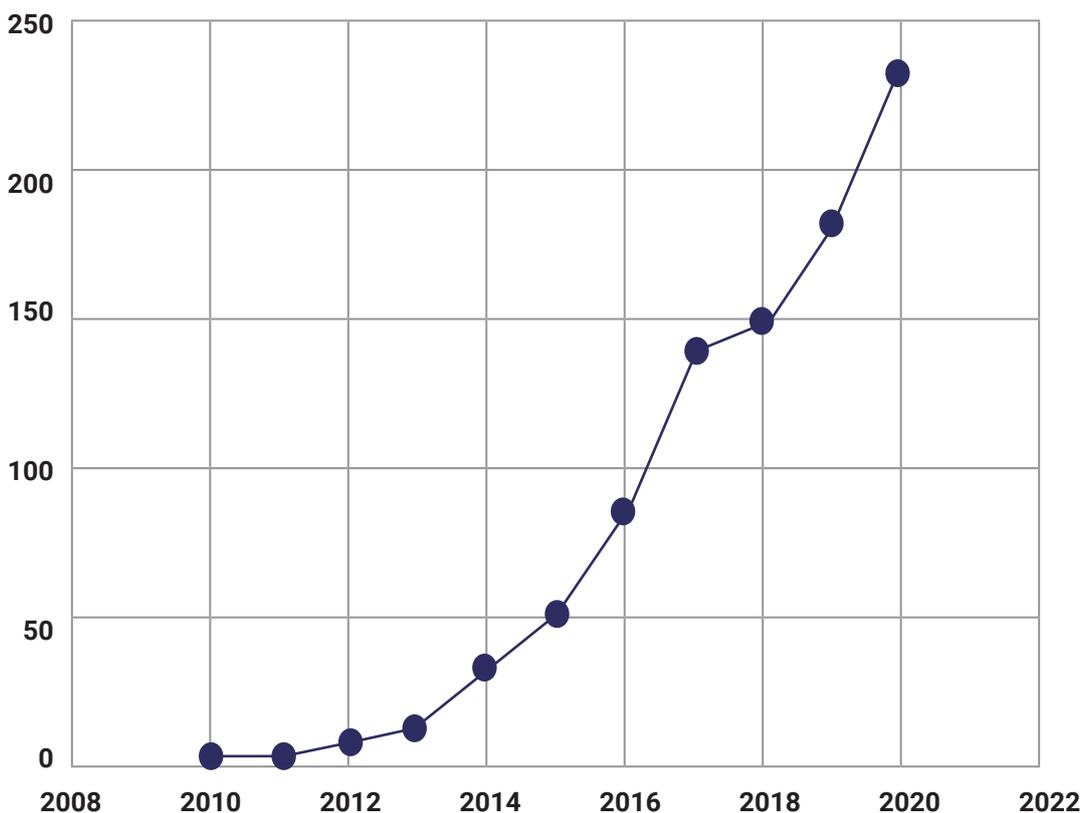


Figure 1 shows the number of published microbiome-related PatBase patent families having an EP, WO or US member. Courtesy of Venner Shipley LLP.

Patent applications cover a wide range of aspects associated with the human gut microbiome, including various therapeutic, diagnostic, and agricultural applications. In addition, applications of the human microbiome in the cosmetic and nutraceutical fields are also being patent-protected, and recent advances in AI and machine learning have seen them being harnessed in sophisticated bioinformatics analyses on the microbiome both in terms of microorganism species and sequence (DNA, RNA, protein etc.). Table 4 summarises the key Cooperative Patent Classification (CPC) codes most commonly used for microbiome-related inventions.

CPC group	Definition
C12Q1	Testing processes involving nucleic acids/bacteria/enzymes.
A61K35	Medicinal preparations according to active agents of unknown constitution; this heading includes bacteria compositions.
A61K31	Medicinal preparations according to organic active ingredients.
G16H50	Bioinformatics for medical diagnosis.
A61K9	Medicinal preparations according to physical form/site of use.
C12Q2600	Oligonucleotides according to use (indexing heading).
G01N33	Analysing materials by chemical means.
Y02A90	Indirect adaptation of technology to combat climate change.
G16B40	Bioinformatics for biostatistics.
A61K45	Medicinal preparations not indexed elsewhere.
A61P1	Treatment of alimentary/digestive system.

Table 4. CPC groups for microbiome-based inventions.

At present, the UK Intellectual Property Office and European Patent Office (EPO) are particularly 'patent friendly' when it comes to assessing the patentability of human gut microbiome inventions, where the following aspects of the microbiome are patentable per se:

- A new microorganism per se - either previously unidentified and isolated from its natural environment, or modified in some way, e.g. genetically.
- A previously unidentified extract from a microorganism.
- A novel consortium of known and/or unknown microorganisms.
- A novel composition of matter including known microorganisms/extracts and/or any of the above. For example, cosmetic, food or therapeutic formulations for administration of microorganisms or extracts.
- A novel therapeutic use of microorganisms/extracts, e.g. a new use in treating a new disease, or patient group, or new dosing regimen.
- A novel method of using a known microorganism/extract defined by novel steps, or a novel order of known steps.

- A novel method of culturing a microorganism or generating a microbial extract.
- A diagnostic method based on analysis of the presence/absence/proportion of microbial populations.

Many of the above microbiome-related inventions are also patentable in the United States. However, patenting certain microbiome-related inventions in the US is not without its own specific challenges following the two landmark US Supreme Court decisions [88] [89]. In these decisions, the Court held that naturally occurring phenomena are not, in the main, regarded as being 'patent-eligible', meaning naturally occurring microorganisms are not patentable subject matter per se in the US unless they have been modified in some way, for example by genetic engineering, such that they can no longer be described as being 'naturally occurring'. Accordingly, for unmodified microorganisms to achieve valid patent protection in the US, it is important to focus patent claims on novel applications or uses of the naturally occurring microorganisms, or to include claims and examples defining novel formulations comprising the microorganisms to render them patent-eligible per se. Unmodified, naturally occurring microorganisms are, however, patentable per se in Europe and the UK provided they are previously unidentified and are claimed in an isolated form (from their natural environment).

In view of the above, it is clear that numerous types of microbiome-based inventions can be patented. Different patent offices take different standpoints regarding their patentability and how they can be validly claimed in a patent. Therefore, it is crucial for innovators in the microbiome field to think globally about their IP strategy and ensure that their patent specifications are drafted in a way that maximum protection can be obtained in each territory of commercial importance. The sector will likely see the nearly exponential growth in the number of patent applications to continue for the foreseeable future, especially given the increasing value in microbiome innovations. With such an explosion of patent applications and granted patents, it is critical that entrepreneurs can also access support in developing their patent strategies to navigate such a complex landscape.

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Appendix 1 – Abbreviations

AI	Artificial Intelligence
AMR	Antimicrobial Resistance
ATMPs	Advanced Therapy Medicinal Products
ATSTN	Advanced Therapies Skills and Training Network
BBSRC	The UK's Biotechnology and Biological Sciences Research Council
CABI	Centre for Agriculture and Bioscience International
CAS	CRISPR associated protein
CDI	Clostridioides difficile Infection
CDMOs	Contract Development and Manufacturing Organisation
CGT	Cell and Gene Therapy
CMOs	Contract Manufacturing Organisation
CPC	Cooperative Patent Classification
CPI	Centre for Process Innovation
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
CROs	Contract Research Organisations
DNA	Deoxyribonucleic Acid
EDMQ	European Directorate for the Quality of Medicines & HealthCare
EMBL-EBI	European Molecular Biology Laboratory's European Bioinformatics Institute
EPO	European Patent Office
FAIR	Findable, Accessible, Interoperable and Reusable
FDA	US Food and Drug Administration
FMT	Faecal Microbiota Transplantation (also referred as IMT)
GMP	Good Manufacturing Practice
HVM	High Value Manufacturing
i4i	Invention for innovation
IBD	Inflammatory Bowel Disease
ICIs	Immune Checkpoint Inhibitors
IMT	Intestinal Microbiota Transfer (also referred as FMT)

Innovate UK KTN	Innovate UK - Knowledge Transfer Network
IP	Intellectual Property
IPO	Intellectual Property Office
ISO	International Organization for Standardization
KOLs	Key Opinion Leaders
LBP	Live Biotherapeutic Products
LSV21	Life Sciences Vision 2021
MBIC	Microbiome Bioprocess Innovation Centre
MHRA	UK's Medicines and Healthcare products Regulatory Agency
MIH	Microbiome Innovation Hub
mRNA	Messenger Ribonucleic Acid
MRC	The UK's Medical Research Council
NBC	National Biologics Centre
NBIC	National Biofilms Innovation Centre
NERC	The UK's Natural Environment Research Council
NHC	National Horizons Centre
NHS	The UK's National Health Service
NIHR	National Institute for Health Research
NMDC	National Microbiome Data Collective
OECD	Organisation for Economic Co-operation and Development
QIB	Quadram Institute Bioscience
R&D	Research and Development
RNA	Ribonucleic Acid
SMEs	Small and Medium-sized Enterprises
SPF	Specific Pathogen Free
TNO Netherlands	Netherlands Organisation for Applied Scientific Research
UKRI	UK Research and Innovation
VIB Belgium	Flemish Institute for Biotechnology
VTT Finland	Finnish Technical Research Centre

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