



The All-Party Parliamentary Group on the Human Microbiome

Chair: Julie Elliott MP; Vice Chairs: Jessica Morden MP and Baroness Walmsley;
Secretary: Robert Goodwill MP; Treasurer: Siobhain McDonagh MP

We are seeking written submissions to inform our APPG Inquiry into:

The most promising health interventions arising through altering the gut microbiome that could be incorporated into healthcare programmes (including as prophylactics) soonest.

Purpose of the Inquiry

The aim of this Inquiry is to publish a report, giving regard to improving specific health outcomes and/or potential for financial savings, with the following recommendations:

- i. Specific illnesses and conditions where gut microbiome science supports the integration of the knowledge into healthcare programmes (including as prophylactics) immediately.
- ii. The specific illnesses and conditions where microbiome science is likely to become ready over the next 12-36 months for the knowledge to be integrated into mainstream healthcare.
- iii. The most promising illnesses and conditions that microbiome science currently suggests might have significantly improved health outcomes and/or potentially result in large financial savings but where the application is currently a long way off and where investment would expand the evidence base and speed up their availability for NHS use.

How to make a Written Submission

The APPG welcomes evidence in writing from individuals, academics, scientists, health practitioners, companies and organisations with an interest in the links between diet (including supplements), the human gut microbiome and improving human health.

It would help us if you used the questions below to inform your submission so we can compare and collate responses more easily around themes, but we will be pleased to accept submissions in any format. You can answer as many or as few of the questions as you believe are appropriate to provide your submission; and there is a final question for anything extra not covered by our specific questions that you think is relevant.

Please write in a way to explain to non-experts in your field. While there is no need for detailed scientific explanation and justification within your submission, please include references to support the science behind your submission as far as possible.

Please consider benefits in terms of both health outcomes and financial savings; and please consider interventions in terms of both treatment and prophylaxis.

Please include an email and telephone (preferably mobile) so we can contact you if we have questions or have further questions. And please indicate if you would be willing to give evidence in person to an APPG Panel at a future date.

Written submissions to the inquiry should be sent to Alan Barnard by email at barnarda@parliament.uk by 5pm on Thursday 16th June 2022. Alan is also available if you have any questions about the Inquiry or about the APPG more generally.

Questions around which to structure your submission

Q1. In the field of the gut microbiome, health and disease, which areas of gut microbiota research have the strongest evidence for benefits?

Microbiome research and clinical translation is still in the early stage of research and development. There are two key areas where microbiome science can have impact; (i) as a biomarker of disease, health, treatment response etc.; and (ii) as a therapeutic to influence health, disease, and treatment response.

The Microbiome as a Biomarker

The microbiome makes a particular effective biomarker of disease and treatment response because it is so complex. The microbiome is a diverse consortium of individual bacterial, archaeal, viral and fungal species often including some micro-eukaryotic species. With ~200-800 species of microorganisms in the intestine, and with each of these organisms maintaining 3000-8000 genes on average, our approaches to characterize the community composition and genetic potential create high dimensional datasets. A high dimensional dataset is one that has a lot of information on a lot of different categories, for example the human genome has high dimensionality, with lots of genes that do lots of different things; whereas blood pressure or height are very low dimensional, in that there is only one measurement.

In addition, the microbiome is a dynamic living community that rapidly grows, dies, and replicates. Unlike human genetics, it is continuously interacting with both host (patient) and environmental factors.¹ As a result, the microbiome can be seen as a canary in a coal mine, likely to respond rapidly to changes in health and to medication. In this way, the microbiome is highly dynamic, much like blood pressure or heart rate that changes frequently, unlike genetics, height and weight, which tend to be quite static in the short term.

¹ Schupack Daniel A., Mars Ruben A. T., Voelker Dayne H., Abeykoon Jithma P., Kashyap Purna C. The promise of the gut microbiome as part of individualized treatment strategies. *Nature Review: Gastroenterology and Hepatology* 2022; 19, 7-25

The microbiome is one of the ONLY measurements of human health that is both highly dimensional and highly dynamic. This means that it is very effective as a biomarker, as there are lots of potential biomarkers in the high dimensional data, and they are very responsive to changes in health or therapy, meaning that they can be used to detect those changes, and even predict future changes.

The Microbiome as a Therapeutic

The microbiome also contains a cornucopia of potential biopharmaceuticals, many of which we are only just now starting to understand. In this way the microbiome can act as a live biological therapeutic, with individual organisms used to deliver a therapeutic benefit as a probiotic (usually either by stimulating the immune system or by releasing a chemical that has therapeutic potential). Additionally, nutrients that stimulate beneficial microbial activity in the gut can also be delivered through our diet as a pre-biotic. We also know that the microbiome can change drug activity, and many drugs are designed with this in mind. So called ProDrugs are designed to be modified by microbial metabolism in the gut to make an active form.

While many probiotics and prebiotics exist on the market, in the form of direct-to-consumer products, and while they are often recommended by doctors for treatment, only ProDrugs are currently registered as approved medical by federal agencies. However, there is one currently approved form of microbial live therapeutic treatment, that is the faecal microbiota transplant, whereby live microbial communities from a healthy person are transplanted into the intestine of an unhealthy person. In the US this treatment is currently only approved (FDA approval) for treatment of re-current *Clostridioides difficile* infection (C.diff or CDI). However, many other treatment modalities are being explored through new drug licenses. Since gut microbiota play such a significant role in the efficacy and toxicity of pharmacological drugs, further research on the role of the gut microbiome in drug efficacy and ProDrugs is worth pursuing given the relatively low production and administration costs around orally ingested drugs.²

With these two modalities (biomarkers and live therapeutics) in mind, the strongest evidence for the effect on human health and disease outcomes can be divided in to 5 different areas, each with thousands of studies in humans and animals that demonstrate some level of efficacy. These five themes: infectious, immune, endocrine, metabolic and neurological disease, all have been associated with disturbance of the microbiome (so called dysbiosis). Moreover, they all have evidence of biomarkers associated with disease or treatment response and all have evidence of live-biological therapeutic efficacy. Some examples are included below in response to Q2.

Q2. Do you know of any examples where gut microbiome research is currently informing mainstream health practice?

² Wilson ID, Nicholson JK. Gut microbiome interactions with drug metabolism, efficacy, and toxicity. *Transl Res.* 2017 Jan;179, 204-222

(Please explain them and comment on how widespread use is, if the interventions are considered to be successful (promising) and how you think these practices might be further improved.)

Faecal Microbiota Transplant (FMT), which is used to treat recurrent *Clostridioides difficile* (C. diff or CDI) infections, is the mostly widely used and widely adopted example. FMT has proven significantly effective in treating recurrent C.diff infections regardless of the route of administration, level of engraftment, or specific features of the donor gut microbiome.³ This is approved and widely used in the United States and Europe and is routinely used in most countries. FMT has also shown promise with other disorders, including obesity, depression, autism, colorectal cancer, and GI disease (e.g., inflammatory bowel disease (IBD)) - although many of these are at different levels of development, and none are widely approved internationally.⁴

Other diseases where the microbiome has been shown to have potential include treating eczema with skin microbial therapies, predicting asthma risk and type with the lung microbiome, and detecting cancer stage and treatment response with blood-associated microbiome analysis. However, most developed and deployed strategies with actual promise are in the gut microbiome. For example, companies like Day Two Inc, are using the gut microbiome functional genetic traits to predict (along with other anthropometric data) dietary responses that influence insulin sensitivity. Currently this company provides this service to large businesses to improve the wellness of their staff by predicting unique diets that can reduce obesity and metabolic diseases such as diabetes. The clinical trial data is rigorous and ongoing studies demonstrate great success and potential for widespread benefit.

There is compelling evidence that changes in the in gut microbial activity, especially for immune activation (increasing or decreasing inflammation) and neurotransmitter production (the gut microbiome produces the majority of GABA and Serotonin precursors in the body), can influence brain chemistry and behaviour. This has led to numerous companies exploring commercializing anti-depressant probiotics, e.g., Holidome Inc, whose products aim to reduce neuroinflammation and increase systematic GABA levels to alleviate depression symptoms.

The use of probiotics, bioactive foods (yogurts), and live-fermented foods to influence gastrointestinal inflammation is also widespread. These all work through immune activation (as well as provision of microbial metabolites through fermentation) to alleviate conditions that are associated with inflammation, e.g., obesity, cardiometabolic disease, diabetes, asthma, etc.⁵ Many of these therapies are provided as holistic treatments, and none have regulatory approval for treatment. However, compelling evidence indicates they can have a pronounced impact on health. This has led the NIH to spend \$800M+ in the last few years to explore the

³ Schupack Daniel A., Mars Ruben A. T., Voelker Dayne H., Abeykoon Jithma P., Kashyap Purna C. The promise of the gut microbiome as part of individualized treatment strategies. *Nature Review: Gastroenterology and Hepatology* 2022; 19, 7-25

⁴ Gupta Akshita, Saha Srishti, Khanna Sahil. Therapies to modulate gut microbiota: Past, present and future. *World Journal of Gastroenterology* 2020; 26(8), 777-788

⁵ Fong Winnie, Li Qing, Yu Jun. Gut microbiota modulation: a novel strategy for prevention and treatment of colorectal cancer. *Oncogene* 2020; 39, 4925-4943

benefit of these treatments, and to form the National Center for Complementary and Integrative Health to create more robust investigations for these treatments.

Q3. Giving reasons for your answer, are there illnesses and conditions where gut microbiome science supports the integration of knowledge into healthcare programmes and treatments now?

One of the key examples of this is in cancer diagnosis. There is substantial evidence that variation in the gut and blood-associated microbiome signatures can be used to predict cancer type and stage with a high degree of accuracy and specificity.⁶ While not yet approved these approaches could be rapidly integrated into the diagnosis tool kit to ensure that patients are provided the timeliest diagnosis as well as giving clinicians the opportunity to make more precise therapeutic decisions. One company in the US, Micronoma, is attempting to bring these diagnoses to market. Data is available online that can be browsed to identify cancer-microbiome associations with evidence (e.g., <https://www.madet.info/> and <http://cancermicrobiome.ucsd.edu>).

Another example is in improving early life development. There have been a substantial number of clinical trials testing the efficacy of the probiotic *Bifidobacterium longum infantis* as a means to improve infant development. This probiotic is a natural gut-associated bacterium that appears to be missing in many infant guts, it is safe to use, and when introduced can help to digest breast milk and formula. It has also been shown to reduce systemic inflammation and improve atopy outcomes in at risk children. There is no reason why this probiotic could not be integrated into clinical practice today.

Q4. What are the specific illnesses and conditions for which microbiome science is likely to become sufficient over the next 12-36 months to support incorporation of this knowledge into mainstream healthcare?

Treatment of depression and anxiety will be a key one. A growing body of evidence supports the use of probiotic or FMT therapies to reduce systemic inflammation and improve gut-neurotransmitter production, which in the next 1-3 years should lead to sound clinical trial results showing real world efficacy and safety data.

Additionally, there have been extensive inroads into the use of vaginal microbiome transplants to improve vaginal health and wellbeing, reducing vaginosis and improving reproductive health and success. There is no reason why this approach could not be developed to point of application within 3 years. Clinical trials have already been proving efficacy. Many other conditions also exist, including treating atopic dermatitis, eczema, oral and dental health problems, lung fibrosis problems, osteoporosis, cardiovascular disease, etc. It is a complex and ever evolving field and the next 3 years could provide an extraordinary bounty of new information.

⁶ Poore Gregory D., Kopylova Evguenia, Zhu Qiyun, Carpenter Carolina, Fraraccio Serena, Wandro Stephen et al. Microbiome analyses of blood and tissues suggest cancer diagnostic approach. *Nature* 2020; 579, 567–574

Q5. What do you believe to be the most promising illnesses and conditions that microbiome science currently suggests might improve health outcomes significantly and/or potentially result in large financial savings, but which is still some way off and needs investment to expand the evidence base before it is ready for health care use?

Treating cardiometabolic diseases, especially improving diet recommendations for individuals, will have profound financial impacts with reasonable investment. Companies like DAYTWO Inc are already doing this. Reducing the burden of cardiometabolic diseases (heart and vascular disease, obesity, diabetes, etc.) on the health system would induce large cost savings. The NIH just invested \$170M in identifying how people respond to different diets, with the microbiome at the core of determining why different people react differently to the same diet. Yet more investment is needed to see what recommendations can actually be made. Regional investment is required as lifestyle and diet varies dramatically country to country.

The microbiome also plays a significant role in antimicrobial resistance (AMR). Some microbiome therapies have the potential to reduce the risk of AMR but require further investigation.⁷

Q6. How might microbiome science help to tackle health inequalities in the UK?

A special collection of papers detailing how microbiome plays in to social equity issues has recently been started at the journal mSystems - <https://journals.asm.org/topic/sss-taxonomy/special-series-semrdme> - the articles here, and especially this paper - <https://journals.asm.org/doi/10.1128/msystems.01240-21> - can be used as a solid foundation to guide UK science along valuable trajectories, tailored to the needs of the UK population. The broad themes of direct relevance to the UK include: (i) sociocultural interactions; (ii) humans, urban ecosystems, and environmental processes; (iii) human psychology and mental health; (iv) microbiomes and infectious diseases; (v) human health and food security; and (vi) microbiome-related planning, policy, and outreach. Focusing UK Microbiome Sciences through targeted funding in these areas could have profound impacts on inequalities.

Q7. Is there anything else that you wish to include that will be helpful to this Inquiry?

As evidenced above, microbiome research, is a promising field with much still to be discovered. However, it is important to note that there are still some challenges that need to be addressed before we can translate this research into clinical measures for patients, particularly for research outside the gut microbiome.

Currently, microbiome-based therapies lack regulatory and quality guidelines as

⁷ Relman David A, Lipsitch Marc. Microbiome as a tool and a target in the effort to address antimicrobial resistance. *Proceedings of the National Academy of Sciences* 2018; 115, 12902-12910

well as international harmonisations guidelines.⁸ Regulation enables researchers and developers to develop clinical studies that assess the benefits and risks through approved safety and quality checks. While some therapies, like FMT for C.diff, are widely used internationally, the FDA, EMA, and MHRA in the UK have not yet been formally regulated/approved. Moreover, despite over 50,000 research articles evidencing the potential of gut microbiome since 2000, there is still no common standardisation in the methods used for processing and analysing microbiome data.⁹ Without standardised approaches, such as sample collection, it is difficult to compare data across studies which limits their validity and usefulness. A standard product would facilitate more rigorous application and pave the way for regulation.

⁸ Paquet Jeanne-Céleste, Claus Sandrine P., Cordaillat-Simmons Magali, Mazier Wilfrid, Rawadi Georges, et al. Entering First-in-Human Clinical Study With a Single-Strain Live Biotherapeutic Product: Input and Feedback Gained From the EMA and the FDA

⁹ Quadram Institute. *Quadram Institute Best Practice in Microbiome Research*. <https://quadram.ac.uk/best-practice-in-microbiome-research/> [accessed 14 June 2022]