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THE CORE MICROBIOTA IN A HEALTHY POPULATION

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Introduction

Over the last few decades, a growing awareness of the gut microbiome has largely reshaped our understanding of health and disease. This dynamic population of approximately 100 trillion microorganisms – including bacteria, fungi, viruses and protozoa – resides within the gastrointestinal (GI) tract, but its effects within the body are far reaching.[1,2] In fact, our gut microbiome is thought to interact with our bodies via numerous metabolic, immune, neural and endocrine pathways.[3] The bacteria lining our digestive tracts therefore play a pivotal role in preserving a healthy immune system and metabolism, and disruptions to this microbial community may lead to dysbiosis, inflammation and disease.

Research to understand the intricate interplay between the gut microbiota and overall health is ongoing, and increasingly sophisticated methods – such as the **GA-map® Dysbiosis Test** – are being developed to characterise this complex bacterial ecosystem (Figure 1). This white paper explores the composition and function of the gut microbiome, its effects on a systemic level, and how advances in microbial profiling are enhancing our understanding of health and disease.

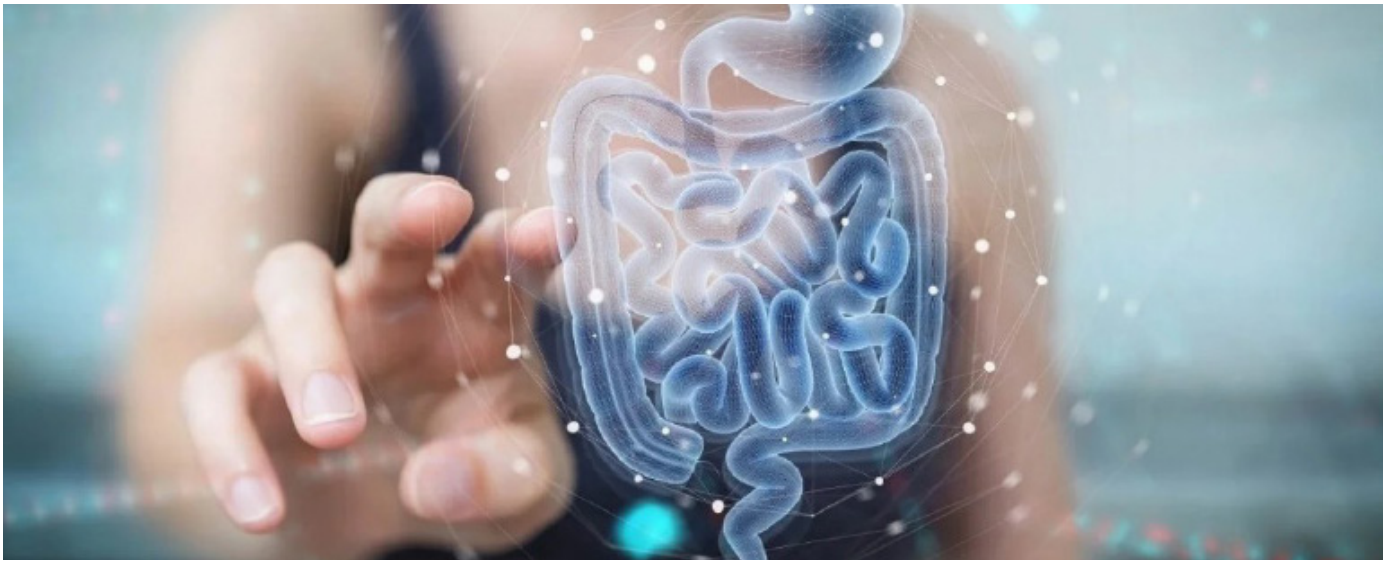

Figure 1: A growing body of research is dedicated to understanding the complex relationship between the gut microbiota and overall health.

Understanding the gut microbiome

Scientists have been interested in understanding the composition and function of the gut microbiome for many years but, until recently, research has been limited by difficulties in culturing some of these microorganisms.[4] Several methods are now available that allow researchers to identify and quantify the components of the gut microbiome without culturing, including next generation sequencing (NGS) approaches – which can be used to analyse either entire genomes or targeted regions of DNA or RNA in stool samples – and metabolomic profiling, to measure byproducts of the microbial metabolism in stool and serum.[2]

Over the last decade, the most common approach for studying the gut microbiome has been the amplification of the bacterial 16S ribosomal RNA (rRNA) gene, which contains nine hypervariable regions within its relatively short (~1,500 bp) structure.[5] These gene sequences can be exploited with polymerase chain reaction (PCR) and metagenomics sequencing to characterise the phylogenetic signatures of bacteria within the gut on different taxonomical levels. Genetic Analysis – a diagnostics company based in Oslo, Norway – has taken this approach to develop the GA-map® Dysbiosis Test, which uses a novel probe-based technique to recognise nucleotide differences in the bacterial 16S rRNA gene. The test is capable of identifying a highly specific panel of predetermined targets selected from almost 300 species of bacteria, and uses cutting-edge high throughput technology to provide a full overview of the microbial species present within the gut.

The composition and function of the core microbiota

Advances in our ability to analyse the microbial species in the gut has identified variations in both the bacterial profiles within an individual – in different parts of the GI tract, and at different stages of life – and between different people.[4] This variation is represented by the fact that the average healthy adult gut microbiome contains just over 200 different bacterial species, from a diverse range of over 5,000 species collectively found in the digestive tracts of individuals globally.[6] Host-specific differences in the gut microflora are shaped by a variety of factors, including genetics, method of birth, early life experiences, diet, lifestyle, and exposure to medications.[7] Despite this diversity, a consistent set of microbes – known as the core microbiota – exists in healthy individuals across populations.

The core microbiota can be described in two ways: in terms of the microbial species most commonly found within the human digestive tract, or according to the key physiological functions that these microbes perform. From a taxonomic perspective, 52 bacterial species were found in more than 70 per cent of samples making up the human microbial reference genome database, which represents a core community of healthy adult human gut microbiota.[6] However, healthy microbiotas often share some degree of functional redundancy, so the roles of the various bacterial strains found in the digestive tract can overlap.[8] Therefore, a healthy core microbiota is more often identified by its ability to strengthen the integrity of the intestinal epithelium, harvest energy from the nutrients we digest, protect the body against ingested pathogens, and regulate host immunity.[1]

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The key functions of the gut microbiome include:

Short chain fatty acid production

Bacteria within the large intestine express various enzymes that allow them to ferment complex carbohydrates, aiding digestion.[2] Several metabolites are generated as a byproduct of these processes, including short chain fatty acids (SCFAs) – such as propionate, butyrate and acetate – that are rapidly absorbed by the colonocytes lining the GI tract.[2,9] Butyrate is a particularly important energy source for these cells, and it is crucial for regulating functions such as gene expression, chemotaxis, differentiation, proliferation and apoptosis.[1] Butyrate has also been linked to the regulation of inflammatory and immunological responses within the gut, and it is known to play a role in the maintenance of intestinal barrier function.[9]

Vitamin synthesis

Probiotic bacteria within the gut are able to synthesise certain vitamins and amino acids, such as vitamin K and most of the water-soluble B vitamins.[10] While these compounds are important for bacterial metabolism, they also carry out key functions throughout the human body. For example, vitamin B12 plays a crucial role in DNA synthesis and epigenetic modifications, red blood cell formation, nervous system function, energy metabolism and brain health.[11] On the other hand, vitamin K2 is essential for activating the blood clotting process, maintaining bone, nervous system and cardiovascular health, and regulating cell growth.[12]

Serotonin production

It is estimated that over 90 per cent of serotonin production occurs in the gut, and research has demonstrated that microbes can influence the production and function of this neurotransmitter.[13,14] Serotonin plays an important role as an enteric signalling molecule, is important for regulating GI activities, and is also pivotal for activating immune cells and inflammatory processes within the digestive system. Furthermore, serotonin is often referred to as the 'happy hormone', and it is an important mediator in the bidirectional crosstalk that occurs between the central nervous system and the gut, known as the gut-brain axis.[15]

Maintaining gut integrity

The intestinal mucosa provides a selectively permeable barrier for nutrient absorption, while protecting the body from external factors, such as pathogenic organisms entering the body.[16] Part of this defensive barrier is a layer of mucus lining the GI tract, and mucosa-associated bacteria play a crucial role in creating and maintaining this protective environment.[16,17] Any disruptions to this mucosal layer can cause intestinal permeability, leading to 'leaky gut syndrome' and the translocation of bacteria and other components of the gut through the lumen.[16]

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A delicate balance between health and disease

Given the numerous functions that the gut microbiota performs in sustaining optimal metabolic function, immune responses and overall health, it is unsurprising that disruptions to this microbial community can result in adverse effects. Under normal conditions, the immune system and gut microbiota work together to prevent the infiltration and proliferation of pathogenic bacteria, maintaining the normal level of protective bacteria within the gut. However, a loss of diversity in the gut microbial population – resulting from either an increase in potentially harmful bacteria, and/or a decrease in commensal bacteria – can lead to a condition known as dysbiosis.

Since many of the microorganisms in the gut work cooperatively to maintain digestive and protective functions, even minor changes to the gut microbiome can have wide-reaching effects on the individual's health. Dysbiosis is known to contribute to the pathogenesis of many chronic diseases,[18] from inflammatory bowel disease (IBD) and type 2 diabetes (T2D) to autoimmune conditions and even neurological disorders (Figure 2).

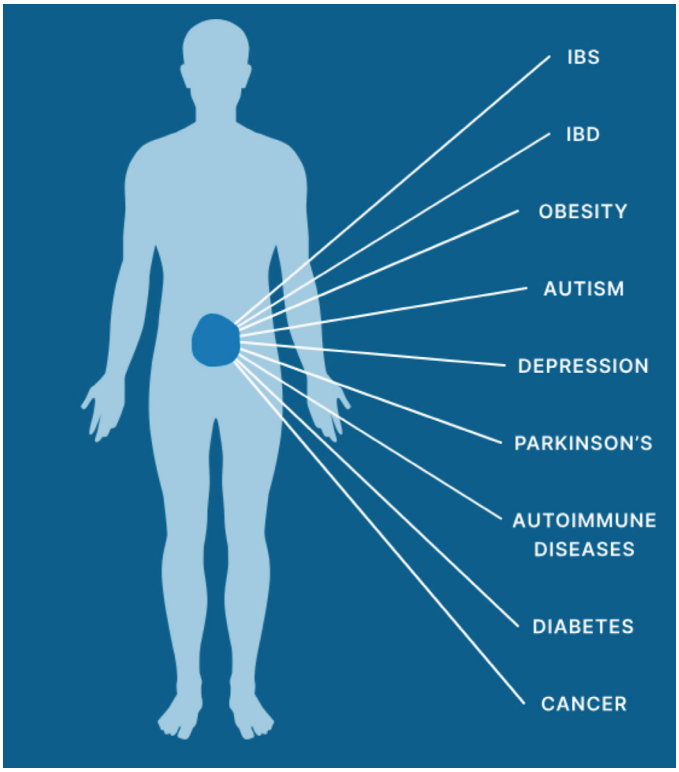

Figure 2: Dysbiosis is known to play a role in multiple inflammatory and systemic diseases.[18]

Dysbiosis in diabetic individuals[19]

An altered gut microbiota composition has been associated with detrimental metabolic outcomes in both human and animal models, including a raised body mass index (BMI), increased fat mass, reduced insulin sensitivity, dyslipidaemia and overall inflammation. A recent pilot study aimed to analyse and compare the gut microbiota of 24 pre-diabetic patients, 18 patients with established T2D and 52 healthy individuals, using GA-map® and LUMI-Seq® sequencing technology. Research revealed that 10 bacterial taxa were differentially abundant between pre-diabetic and healthy individuals, and nine taxa varied significantly between diabetic patients and healthy individuals. A notable difference in the microbial profiles included variations in the abundance of SCFA producers and typical opportunistic, pro-inflammatory bacteria.

Dysbiosis in systemic sclerosis[20]

Systemic sclerosis is a rheumatic disease that affects the skin and internal organs. A cross-sectional study examined the stool samples of 98 patients with systemic sclerosis using GA-map®, and both GI and systemic manifestations of the disease were studied using clinical, laboratory and radiological measures. Over 75 per cent of the sample group exhibited dysbiosis, and the extent of this imbalance was more severe in patients with oesophageal dysmotility. In comparison, only 24 patients received a normobiotic score, and only one normobiotic patient was at risk of malnutrition. The results demonstrate a clear correlation between a gut microbial imbalance and disease severity.

Disease-specific variations in the gut microbiota[21]

Ankylosing spondylosis (AS) is a chronic autoimmune condition that primarily affects the spine and joints. The disease is also often associated with additional inflammation presenting in the digestive tract, and therefore shares several similarities with conditions such as ulcerative colitis (UC) and Crohn's disease (CD). A study was carried out to compare the faecal microbiota composition of 150 patients with AS, 18 patients with UC, and 17 healthy individuals, and GA-map® results revealed that the three patient groups had distinct microbiota signatures. Dysbiosis was found in 87 per cent of AS patients, and 94 per cent of UC patients. In addition, patients with increased calprotectin – a marker of intestinal inflammation – had a lower abundance of anti-inflammatory bacteria compared to healthy individuals.

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Identifying normobiosis and dysbiosis in the gut

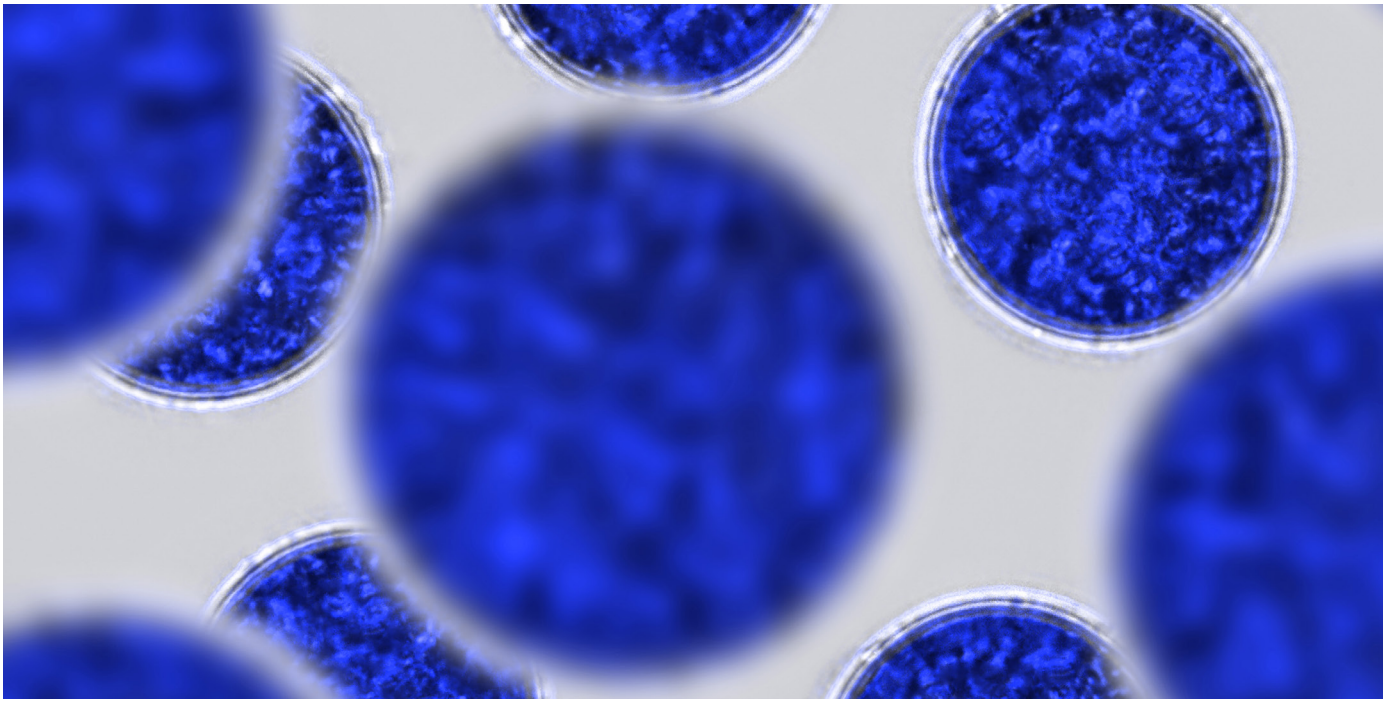
As the link between the gut microbiota and many intestinal and extra-intestinal diseases has become increasingly apparent, a greater number of individuals have begun to seek ways to understand precisely what is happening within their digestive system. This includes people living with chronic health conditions, fitness enthusiasts and the 'worried well', who wish to optimise their nutrition and performance in an evidence-based way. GA-map® (Figure 3) can provide a full overview of the gut microbiota, revealing any imbalances in the health-promoting or -inhibiting microbial species present within the gut, and helping to direct patient-specific therapies to restore an optimal bacterial profile.

Figure 3: GA-map® can aid in a diagnosis of dysbiosis by comparing a person's gut microbiota to a healthy reference profile.

Development and validation of GA-map®

GA-map® was initially created by analysing the gut microbiota of 165 healthy adults.[21] Stool samples from these individuals were screened for the presence and abundance of 48 pre-selected bacterial markers, detecting bacteria at different taxonomic levels and covering more than 300 different species. Results were used to establish a reference normobiotic bacterial profile, as well as a dysbiosis index score output.[22] The test can analyse a faecal sample by comparing it to this normobiotic reference, classifying any deviation from this normal composition as dysbiotic.

Following its initial development, GA-map® was validated in samples from 287 healthy volunteers, IBS patients and IBD patients, to determine its ability to detect dysbiosis.[22] The test identified dysbiosis in 73 per cent of IBS patients, 70 per cent of treatment-naïve IBD patients and 80 per cent of IBD patients in remission, compared to just 16 per cent of healthy individuals. This aligned with the outcomes from deep sequencing of the same samples, confirming the ability of the test to provide accurate insights into a patient's intestinal microbiota.[22]



How to use GA-map®

GA-map® is fully standardised, documented and CE marked, and is simple to perform in any molecular laboratory. To perform the test, a stool sample is collected from the patient and sent to a laboratory for analysis. Genomic DNA is extracted from the sample, and the 16S rRNA gene is amplified.[23] After quantifying and cleaning up the PCR product, the pre-selected probes are labelled, hybridised and detected (Figure 4). Using a clinically relevant probe allows the technology to analyse almost the entire length of the 16S gene.

Figure 4: GA-map® can be carried out in any molecular laboratory.[23]

The raw data is then processed through a validated software algorithm, and compared to a healthy reference population to obtain clinically meaningful results. The report generated from the test results includes a dysbiosis index (Figure 5), as well as a list of bacterial species that are over- or under-represented in the gut (Figure 7).

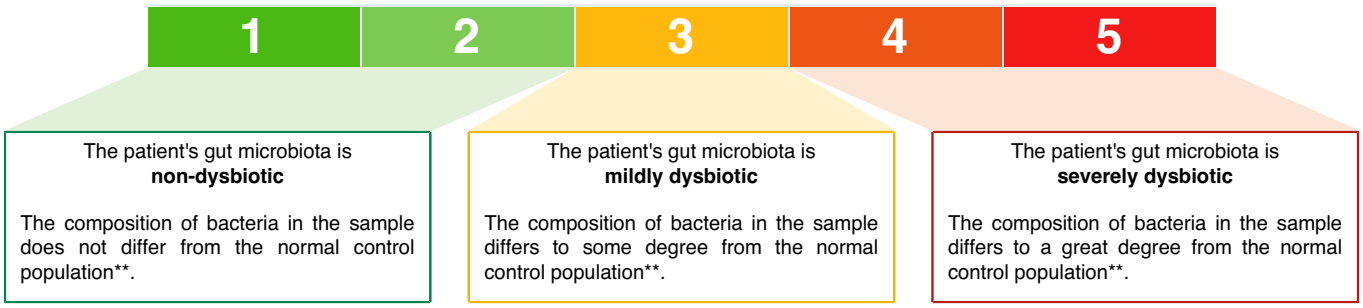


Figure 5: The dysbiosis index generated by GA-map® reports the degree of dysbiosis in a faecal sample on a scale from 1 (normobiotic) to 5 (severely dysbiotic).

FUNCTIONAL IMBALANCE – BACTERIA PROFILES*

	FUNCTIONAL PROFILES	TEST RESULTS	COMMENTS
A	Butyrate producing bacteria	!	Slightly deviating abundance
B	Gut mucosa protective bacteria	✗	Deviating abundance
C	Gut health marker	!	Slightly deviating abundance
D	Gut barrier protective bacteria and potentially harmful bacteria	!	Slightly deviating abundance
E	Pro-inflammatory bacteria	✓	Expected abundance
F	Diversity	✓	Expected diversity

Figure 6: An example of test results from GA-map®.

BACTERIA ABUNDANCE TABLE*

	Actinomycetota*	Reduced -3	-2	-1	Normal **	Elevated 1	2	3
100	Actinomycetota				●			
101	Actinomycetales				●			
103	*Bifidobacterium spp.*				●			

	Bacteroidota*							
201	*Alistipes*				●			
202	*Alistipes onderdonkii*					●		
203	*Bacteroides fragilis*				●			
204	*Bacteroides pectinophilus*				●			
205	*Bacteroides spp.*				●			
206	*Bacteroides spp. & Prevotella spp.*					●		
207	*Bacteroides stercoris*				●			
208	*Bacteroides zoogleoformans*							●
209	*Parabacteroides johnsonii*							●
210	*Parabacteroides spp.*							●

	Bacillota*							
300	Bacillota				●			
302	Bacilli				●			
304	*Catenibacterium mitsuokai*				●			
305	Clostridia				●			
306	*Clostridium methylpentosum*			●				
307	*Clostridium sp.*				●			
308	*Coprobacillus cateniformis*				●			
310	*Dialister invisus*				●			
311	*Dialister invisus & Megasphaera micronuciformis*				●			
312	*Dorea spp.*				●			
313	*Holdemanella biformis*				●			
314	*Anaerobutyricum hallii*			●				

	Bacillota* cont.	Reduced -3	-2	-1	Normal **	Elevated 1	2	3
315	*[Eubacterium] rectale*				●			
316	*Eubacterium siraeum*				●			
317	*Faecalibacterium prausnitzii*			●				
318	*Lachnospiraceae*				●			
319	*Lactobacillus ruminis & Pediococcus acidilactici*				●			
320	*Lactobacillus spp.*				●			
321	*Lactobacillus spp. 2*				●			
322	*Phascolarctobacterium sp.*				●			
323	*Ruminococcus albus & R. bromii*				●			
324	*Ruminococcus gnavus*					●		
325	*Streptococcus agalactiae & [Eubacterium] rectale*					●		
326	*Streptococcus salivarius ssp. thermophilus & S. sanguinis*				●			
327	*Streptococcus salivarius ssp. thermophilus*			●				
328	*Streptococcus spp.*				●			
329	*Streptococcus spp. 2*				●			
330	*Veillonella spp.*				●			
331	Bacillota (various)				●			

	Pseudomonadota*							
500	Pseudomonadota				●			
501	*Acinetobacter junii*				●			
502	*Enterobacteriaceae*				●			
504	*Shigella spp. & Escherichia spp.*				●			

	Mycoplasmatota*							
601	*Mycoplasma hominis*				●			

	Verrucomicrobiota*							
701	*Akkermansia muciniphila*			●				

* For a more detailed explanation of the results, please refer to pages 3-4, 'GA-map® Dysbiosis Test Lx - REPORT FORM SUPPLEMENT'.

** Reference population: an unselected group of nongastrointestinal-symptomatic individuals (age 18-70).

Figure 7: The test analyses 48 different bacterial markers according to their abundance to indicate any imbalances between commensal bacteria and potentially harmful species.

Using microbiota analysis to optimise health

Obtaining a gut microbiota profile is the first step in understanding and treating the variety of health conditions that have been linked to poor microbial diversity in the gut. Armed with detailed information about their patient's gut microbiome – including the abundance of the core bacteria that perform key physiological functions – clinicians can develop personalised treatment plans to help restore the gut microbial balance. A range of approaches targeting the microbiome are available, including dietary and lifestyle changes, the use of therapeutics[24] and supplementation with live beneficial bacteria.[25] These interventions may be useful as a complementary strategy for managing patients experiencing GI symptoms – such as bloating, constipation, diarrhoea and abdominal pain – as well as inflammatory conditions and systemic diseases. Repeatedly testing the gut microbiome using GA-map® at regular intervals before, during and after treatment – and mapping these profiles to a patient's symptoms – can help to track the progress of microbial changes within the GI tract, providing an overview of treatment outcomes. The most common interventions aimed at restoring a healthy gut microbiota are outlined on the next page.

Using GA-map® to monitor faecal microbiota transplant (FMT) outcomes[25]

A three-year **longitudinal study** was carried out to establish the long-term efficacy of FMT treatment in managing IBS. Of the 125 IBS patients included in the study, 38 patients received a placebo treatment, 42 patients received 30 g of donor faeces, and 45 patients received 60 g of donor faeces administered to the duodenum. Participants provided a faecal sample – which was analysed using GA-map® – and completed questionnaires at baseline, and at two and three years after FMT. Results demonstrated that patients in the treatment groups experienced significantly fewer IBS symptoms, reduced fatigue and a greater quality of life after treatment. This correlated with a decrease in the dysbiosis index of the treatment groups. In comparison, the placebo group experienced no improvements in symptoms or in their microbiota profile. **The study showcases the utility of GA-map® for monitoring treatment efficacy over time**.

Dietary and lifestyle changes

Nutritional strategies are often a first step in altering the composition and function of the gut microbiome, and a wide range of studies have investigated the response of bacterial species to specific dietary interventions.[26] For example, increases in dietary fibre and unsaturated fat intake have been shown to improve the abundance of butyrate-producing bacteria that can improve health outcomes. In addition, there is some evidence that lifestyle changes – such as stress reduction, regular exercise and improvements in sleep quality and quantity – can positively influence microbial diversity and balance in the gut.[27]

Pharmacological approaches

Clinical approaches to modifying gut bacteria typically focus on administering antibiotics or antifungal agents to deplete overabundant species in the GI tract.[24, 26] In addition, prebiotics and probiotics can be prescribed to encourage the growth of commensal bacteria.[28]

FMT

FMT may be considered as an appropriate treatment option in severe cases of dysbiosis or certain infections. This involves transferring faecal material from a healthy donor to the patient, in an attempt to restore a healthy microbial balance.[25, 26]

Conclusion

The evolution of technologies for microbiome analysis is generating novel insights into the health of patients looking to optimise their quality of life. Cutting-edge tools, such as the GA-map® Dysbiosis Test, have enhanced our understanding of what a healthy gut microbiome looks like, as well as how deviations in our gut microbial profile can contribute to a variety of gastric and systemic conditions. Although further research is needed to understand the precise mechanisms linking our gut microbiome and health status, as well as the benefits of treatments aimed at restoring our gut microbial balance, microbiota analysis holds significant potential for supporting a personalised approach to evaluating gut health and managing disease.

References

1. Thursby, E. and Juge, N. 2017. Introduction to the human gut microbiota. *Biochemical Journal*, 474(11):1823-1836. doi:10.1042/bcj20160510.
2. Valdes, A.M. et al. 2018. Role of the gut microbiota in nutrition and health. *BMJ*, 13(361):k2179. doi:10.1136/bmj.k2179.
3. Huang, Z. *et al.* 2022. The gut microbiome in human health and disease – where are we and where are we going? A bibliometric analysis. *Frontiers in Microbiology*, 13:1018594. doi:10.3389/fmicb.2022.1018594.
4. Rinninella, E. *et al.* 2019. What is the healthy gut microbiota composition? A changing ecosystem across age, environment, diet, and diseases. *Microorganisms*, 7(1):14. doi:10.3390/microorganisms7010014.
5. Johnson, J.S. *et al.* 2019. Evaluation of 16S rRNA gene sequencing for species and strain-level microbiome analysis. *Nature Communications*, 10(1). doi:10.1038/s41467-019-13036-1.
6. Hiseni, P. *et al.* 2021. Humgut: A comprehensive human gut prokaryotic genomes collection filtered by Metagenome Data. *Microbiome*, 9(1):165. doi:10.1186/s40168-021-01114-w.
7. Jandhyala, S.M. *et al.* 2015. Role of the normal gut microbiota. *World Journal of Gastroenterology*, 21(29):8787. doi:10.3748/wjg.v21.i29.8787.
8. Sharon, I. *et al.* 2022. The core human microbiome: Does it exist and how can we find it? A critical review of the concept. *Nutrients*, 14(14):2872. doi:10.3390/nu14142872.
9. Rowland, I. *et al.* 2017. Gut microbiota functions: Metabolism of nutrients and other food components. *European Journal of Nutrition*, 57(1):1-24. doi:10.1007/s00394-017-1445-8.
10. LeBlanc, J.G. *et al.* 2013. Bacteria as vitamin suppliers to their host: A gut microbiota perspective. *Current Opinion in Biotechnology*, 24(2):160-168. doi:10.1016/j.copbio.2012.08.005.
11. *Vitamin B12.* 2022. NIH Office of Dietary Supplements. Accessed: 7th November 2023. Available at: https://ods.od.nih.gov/factsheets/Vitaminb12-HealthProfessional/.
12. Beulens, J.W. *et al.* 2013. The role of menaquinones (vitamin K2) in human health. *British Journal of Nutrition*, 110(8):1357-1368. doi:10.1017/s0007114513001013.
13. Banskota, S., Ghia, J.E. and Khan, W.I. 2019. Serotonin in the gut: Blessing or a curse. *Biochimie*, 161:56-64. doi:10.1016/j.biochi.2018.06.008.
14. Stasi, C., Sadalla, S. and Milani, S. 2019. The relationship between the serotonin metabolism, gut-microbiota and the gut-brain axis. *Current Drug Metabolism*, 20(8):646-655. doi:10.2174/1389200220666190725115503.
15. Layunta, E. *et al.* 2021. Crosstalk between intestinal serotonergic system and pattern recognition receptors on the microbiota–gut–brain axis. *Frontiers in Endocrinology*, 12. doi:10.3389/fendo.2021.748254.
16. Di Tommaso, N., Gasbarrini, A. and Ponziani, F.R. 2021. Intestinal barrier in human health and disease. *International Journal of Environmental Research and Public Health*, 18(23):12836. doi:10.3390/ijerph182312836.
17. Takiishi, T., Fenero, C.I. and Câmara, N.O. 2017. Intestinal barrier and gut microbiota: Shaping our immune responses throughout life. *Tissue Barriers*, 5(4). doi:10.1080/21688370.2017.1373208.
18. *Accelerate your research with GA-Map®.* GA-Map®. Accessed: 7th November 2023. Available at: https://ga-map.com/researchers/.
19. Gravdal, K. *et al.* 2023. Exploring the gut microbiota in patients with pre-diabetes and treatment naïve diabetes type 2 - a pilot study. *BMC Endocrine Disorders*, 23(1):179. doi:10.1186/s12902-023-01432-0.
20. Andréasson, K. *et al.* 2016. Intestinal dysbiosis is common in systemic sclerosis and associated with gastrointestinal and extraintestinal features of disease. *Arthritis Research & Therapy*, 18(1). doi:10.1186/s13075-016-1182-z.
21. Klingberg, E. *et al.* 2019. A distinct gut microbiota composition in patients with ankylosing spondylitis is associated with increased levels of fecal calprotectin. *Arthritis Research & Therapy*, 21(1). doi:10.1186/s13075-019-2018-4.
22. Casén, C. *et al.* 2015. Deviations in human Gut Microbiota: A novel diagnostic test for determining dysbiosis in patients with IBS or IBD. *Alimentary Pharmacology & Therapeutics*, 42(1):71-83. doi:10.1111/apt.13236.
23. *Microbiome testing for labs.* GA-Map®. Accessed: 9th November 2023. Available at: https://ga-map.com/laboratories/.
24. Wang, X., Zhang, P. and Zhang, X. 2021. Probiotics regulate gut microbiota: An effective method to improve immunity. *Molecules*, 26(19):6076. doi:10.3390/molecules26196076.
25. El-Salhy, M. et al. 2022. Efficacy of fecal microbiota transplantation for patients with irritable bowel syndrome at 3 years after transplantation. *Gastroenterology*, 163(4). doi:10.1053/j.gastro.2022.06.020.
26. Vijay, A. and Valdes, A.M. 2021. Role of the gut microbiome in chronic diseases: A narrative review. *European Journal of Clinical Nutrition*, 76(4):489-501. doi:10.1038/s41430-021-00991-6.
27. Foster, J.A., Rinaman, L. and Cryan, J.F. 2017. Stress & the gut-brain axis: Regulation by the microbiome. *Neurobiology of Stress*, 7:124-136. doi:10.1016/j.ynstr.2017.03.001.
28. You, S. *et al.* 2022. The promotion mechanism of prebiotics for probiotics: A Review. *Frontiers in Nutrition*, 9: 1000517. doi:10.3389/fnut.2022.1000517.

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