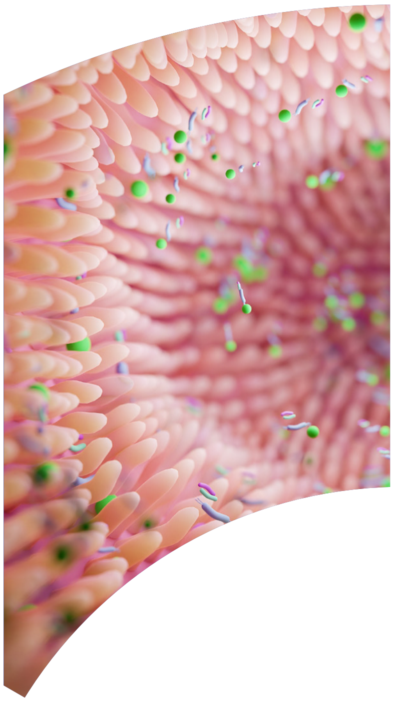


Interpretation guide

Learn how to interpret MetaXplore GI Plus
to support clinical decsiion-making.

MetaXplore™
Powered by MiCROBA


MetaXplore™ GI Plus
Functional Gut Microbiome Profile
Gastrointestinal Health Markers
qPCR Targeted Pathogen & Parasite Panel
STOOL SAMPLE COLLECTION KIT
REF MTXC-2403
invivo®
Unlock health from within

Contents

MetaXplore GI Plus

MetaXplore™ GI Plus is a comprehensive gut test. It provides a metagenomic driven functional gut microbiome profile, gastrointestinal health markers, plus targeted pathogen panels for the detection of pathogenic bacteria and protist parasites, along with science-backed clinical insights to assist clinical decision-making and interventions.

Report inclusions		
	Comprehensive report with easy-to-interpret findings	✓
	Personalised clinical[1] and research[2] insights providing scientifically graded statements on the evidence for diet and lifestyle interventions as well as probiotic, prebiotic, nutrient and polyphenol supplementation	✓[1,2]
Whole microbiome community insights		
	Metagenomic identification of >28,000 microbial species* including bacteria, archaea and eukaryotes (fungi and protist parasites)^[2]	✓
	Microbiome diversity, microbial richness count and relative abundance of the microbial community[2]	✓
	Gut microbiome impact on health categories Intestinal inflammation, intestinal barrier, detox/retox, systemic inflammation, intestinal motility and digestive secretions[2]	✓
	Production of microbial markers Butyrate, acetate, propionate, 3-indolepropionic acid (IPA), hexa-acylated lipopolysaccharide (hexa-LPS), trimethylamine (TMA), hydrogen sulphide, branched-chain amino acids (BCAA), *B.fragilis* toxin, methane, beta-glucuronidase[2]	✓
	Microbial consumption of Mucin, oxalate[2]	✓
	Emerging markers Histamine, ammonia (urease), gamma-aminobutyric acid (GABA) production, GABA consumption, vitamin K, lactate, human DNA[2]	✓
Whole microbiome community profiling & comprehensive pathogen detection		
Bacteria	**Presence and relative abundance of bacterial species within the following genera** *Agathobacter, Akkermansia, Bifidobacterium, Bilophila, Citrobacter, Desulfovibrio, Eggerthella, Enterobacter, Escherichia, Faecalibacterium, Klebsiella, Lactobacillus, Oxalobacter, Porphyromonas, Prevotella, Roseburia, Ruminococcus, Streptococcus* and more[2]	✓
	Diagnostic identification of pathogenic bacteria *E.coli* pathotypes, *C. difficile* pathotypes, *Campylobacter* spp., *Yersinia enterocolitica, Vibrio* spp., *Aeromonas* spp., *Salmonella* spp.[1]	✓
Parasites	**Whole microbiome profiling of parasites** Parasite detection of *Blastocystis* subtypes 1-9 and other protist parasites[2]	✓
	Diagnostic identification of protist parasites *Giardia lamblia, Entamoeba histolytica, Cryptosporidium spp., Cyclospora cayetanensis, Dientamoeba fragilis* (unconfirmed pathogen)[1]	✓
Fungi	**Whole microbiome profiling of fungi species** *Candida* genus, *Saccharomyces* genus and more[2]	✓
Gastrointestinal health markers		
	Diagnostic gastrointestinal health markers Calprotectin, faecal occult blood, lactoferrin, pancreatic elastase, secretory IgA, zonulin[1]	✓
	Investigative gastrointestinal health marker Faecal pH[2]	✓

* Can report on over 28,000 microbial species although a typical healthy sample will contain between 110 – 244 species.

^ Shotgun metagenomics can report on all species with a relative abundance above 0.01% including non-diagnostic eukaryotes (fungi and protist parasites).

[1] The faecal occult blood, Targeted Pathogen Panel and enzyme-linked immunosorbent assays (ELISA) used in the MetaXplore™ range are diagnostic and are approved for clinical use.

[2] The faeces pH assay used in the MetaXplore™ range is for research use only and not to be used as a basis for diagnosis. The metagenomic assays used in the MetaXplore™ range are to determine the microbiome populations and associated functional pathways in a faecal sample. The application is for research use only and not to be used as a basis for diagnosis. Learn more about the journey we are on to validate this gold-standard technology for clinical diagnosis and application at co-biome.com.

The technology

Whole genome metagenomics

MetaXplore's gut microbiome analysis is powered by Microba's proprietary analysis platform. This powerful platform uses whole-genome metagenomics to provide you with a high-resolution picture of the gut microbiome.

Metagenomics (also known as shotgun metagenomics) is the most comprehensive DNA sequencing method that:

- captures all microbes in a sample which allows you to see not just bacteria, but also fungi, parasites, and archaea
- identifies all microbes at the species level providing a precise understanding of which microbes are present in your client's microbiome
- measures microbes with the capacity to consume or create compounds resulting in a complete picture of microbiome function.

Gastrointestinal health markers

Calprotectin, lactoferrin, secretory IgA, pancreatic elastase and zonulin are assessed using ELISA assay kits from the ImmunoDiagnostik product range. Faecal occult blood is detected using the ulti med FOB Test. The test uses a double antibody sandwich assay to selectively detect faecal occult blood at 40 ng/ml or higher, or 4.8 µg/g faeces. Unlike guaiac assays, the accuracy of the test is not affected by the client's diet. The pH values of faecal samples are measured using a pH strip with confirmatory and increased resolution of measurement using electronic pH meter for accuracy and precision.

Diagnostic targeted pathogen panels

The MetaXplore GI Plus test uses targeted pathogen panels for pathogenic bacteria and parasite detection. The targeted pathogen panels use a highly sensitive method for the detection of specific regions of DNA which typically indicate the presence of the pathogen, species or genus reported. It will detect the listed microbes even if present at very low levels but will not provide any other information about the microbiome.

Whole genome metagenomics provides a complete picture of the whole microbiome, while the targeted pathogen panels use a highly sensitive method for the detection of the presence of the listed pathogen, species or genus.

Evidence-based client-focused holistic care

Our mission is to collaborate with clinicians to improve client health. MetaXplore offers the latest technology and science to support clinicians in practising evidence-based care.

Accurate and reliable results

MetaXplore provides accurate assessment of the client's microbiome, gut function and environment. The following terms are used when describing the test results as well as the mechanisms linking them to health:

Microbial markers:
The microbial markers assess the number of microbial cells within the microbiome that have the functional potential to either produce microbial metabolites or consume compounds. In addition, microbial diversity is considered a microbial marker as well as being included in the microbiome health section.

Gastrointestinal health markers:
The gastrointestinal health markers include six diagnostic markers plus faecal pH which provide an assessment of gut function and environment.

Health categories:
The health categories represent different aspects of gut function and health, as well as mechanisms by which the microbiome influences systemic health. Each health category groups associated microbial markers and gastrointestinal health markers to support mechanism driven assessment of gut and systemic health.

Comprehensive science review

Research into the microbiome is a rapidly evolving and expanding field of science which would be impossible for any clinician to keep up with. We have tackled this challenge by creating a dream team of clinicians and scientists who undertook an extensive review of the body of scientific evidence. We identified clinically-relevant research to help clinicians put client's results in context and determine evidence-based intervention options.

This results in the following three types of research statements:

Graded statements:
Summarise the evidence for how microbial markers and gastrointestinal markers are associated with the health categories.

Research insights:
Scientifically graded statements on the evidence for methods to modify markers. They are shown in the report if a microbial marker is different from the healthy cohort, or if faecal pH is outside of the literature derived reference range.

Clinical insights:
Scientifically graded practice recommendations. They are shown in the report if a diagnostic gastrointestinal health marker is outside of the reference range.

Applying results in clinical practice

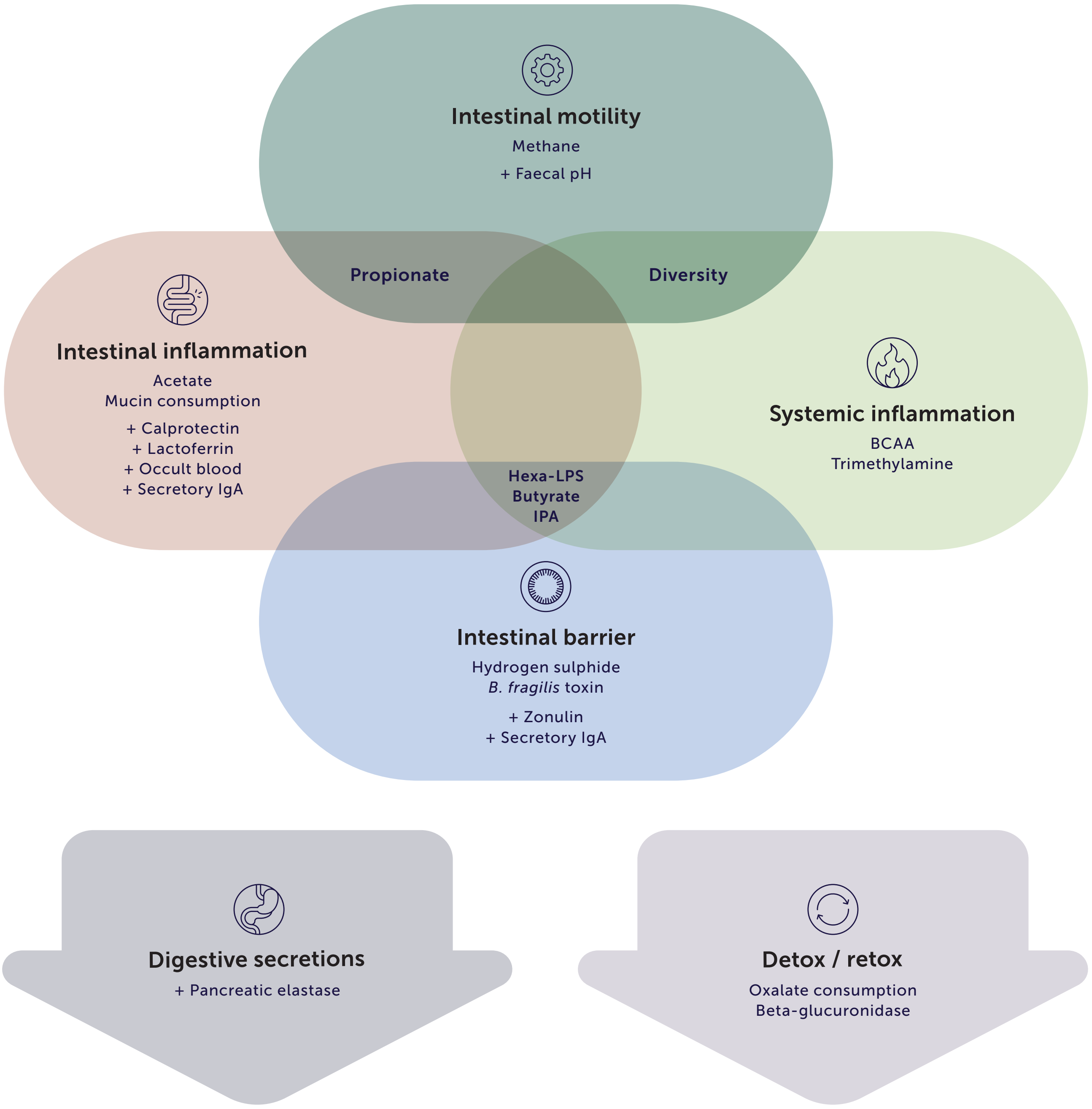
MetaXplore only provides part of the clinical picture and working in collaboration with healthcare professionals is essential to ensure the results are placed within the clinical context for holistic client care.

Accurate measurement	Mechanisms explained	Personalised insights
Microbiome Richness and diversity Microbial species Microbial markers **Gut function and environment** Gastrointestinal health markers	**Health categories** are mechanisms associated with gut and systemic health. **Graded statements** summarise research for how markers are associated with health categories.	**Research insights** review research for interventions for research use only markers. **Clinical insights** provide treatment recommendations for diagnostic markers.
Clinical assessment	**Client**	**Medical history**
Clinical presentation Signs and symptoms Bowel habits Current diet and lifestyle	Goals Values Motivation Preferences	Medical conditions Family history Mental health Sensitivities or allergies

Evidence-based client-centred holistic treatment plan

Health categories

There are six health categories which represent different aspects of gut function and health, as well as mechanisms by which the microbiome influences systemic health. The health categories include: intestinal motility, intestinal inflammation, intestinal barrier, systemic inflammation, digestive secretions and detox/retox.



Graded statement summarise the evidence for the link between health categories and markers. Graded statements on the clinical interpretation of markers can be found from page 24.

Intestinal motility

Intestinal motility is defined as the movement of contents through the gastrointestinal tract. The microbial markers can be used to assess the relationship between the microbiome and gut transit time. The gastrointestinal health marker (pH) can be utilised to evaluate gut transit time.

Intestinal inflammation

Intestinal inflammation refers to immune activation occurring within the gastrointestinal system. The microbial markers can be utilised to assess the potential for the microbiome to prevent or exacerbate intestinal inflammation. The gastrointestinal health markers provide a measure of the level of active intestinal inflammation.

Intestinal barrier

The intestinal barrier separates the contents of the intestinal lumen from the rest of the body. The microbial markers can be used to assess the potential for the microbiome to protect or impair intestinal barrier integrity. The gastrointestinal health markers provide a measure of intestinal barrier integrity within the small intestine.

Systemic inflammation

Systemic inflammation can be detected via elevated markers of immune activation within the blood. The microbial markers can be utilised to assess the potential for the microbiome to prevent or exacerbate systemic inflammation.

Detox/retox

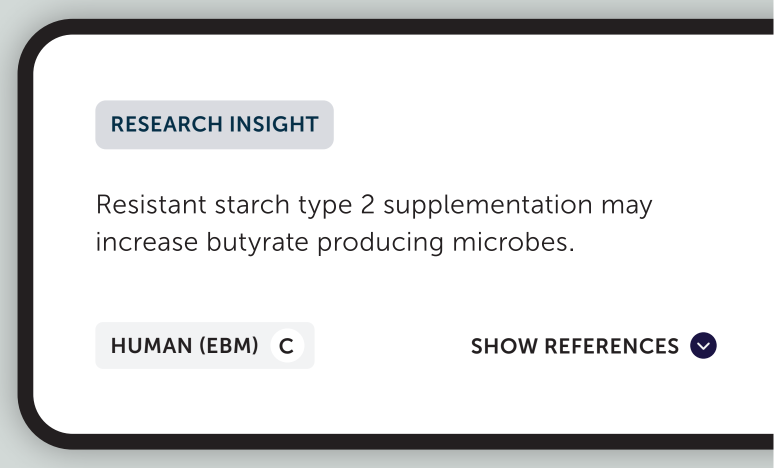
Detox represents the role of the microbiome in detoxification and elimination of compounds from the body. The microbial markers can be used to assess the potential for the microbiome to influence oxalate, drug and hormone excretion.

Digestive secretions

Digestive secretions reflect the role of exocrine functions in determining environmental conditions within the gastrointestinal tract.

Insights

The Microba science review process involved an extensive review of the body of scientific evidence to provide accessible research statements to help clinicians identify evidence-based intervention options for their client.



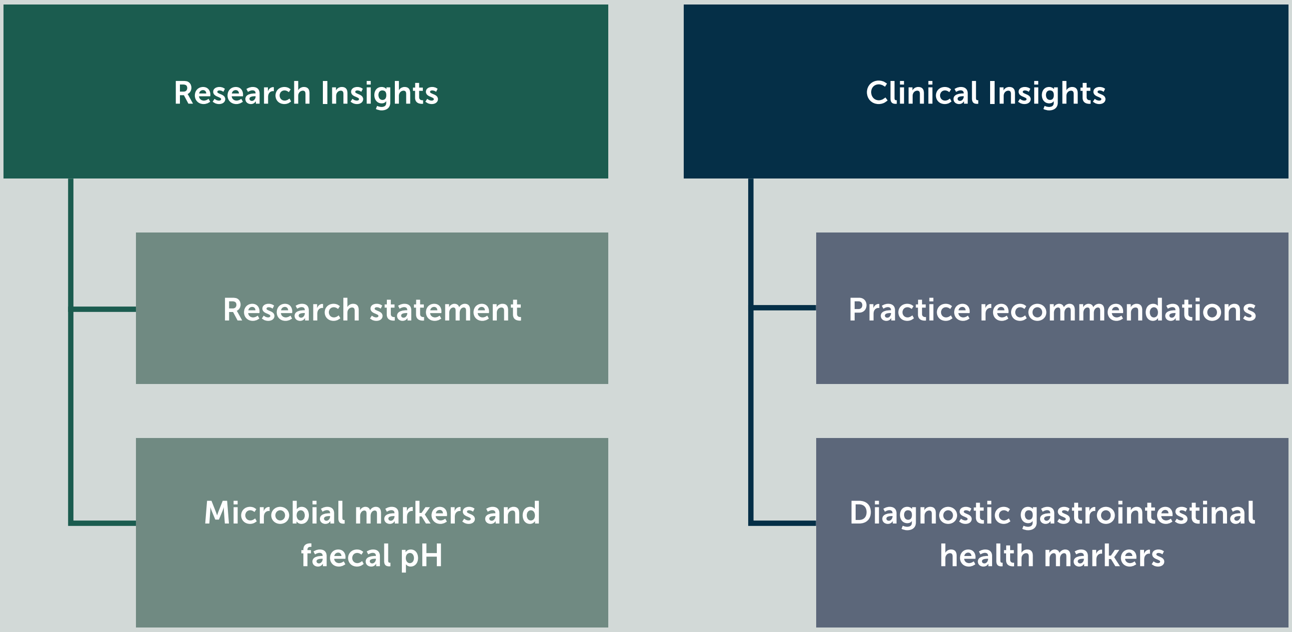
RESEARCH INSIGHT

Resistant starch type 2 supplementation may increase butyrate producing microbes.

Personalised to your client's results

Clinical insights are scientifically graded practice recommendations which are shown in the report if a diagnostic gastrointestinal health marker is outside of the reference range.

Research insights are scientifically graded statements which are shown in the report if a microbial marker is different from the healthy cohort, or if faecal pH is outside of the literature derived reference range.



- Research Insights
  - Research statement
  - Microbial markers and faecal pH
- Clinical Insights
  - Practice recommendations
  - Diagnostic gastrointestinal health markers

Filters to help clinicians explore all insights
You can explore all of your client's personalised insights by visiting the Insights page in the MetaXplore report. Insights can be filtered by marker, recommendation type, evidence type (human, in vitro) and evidence grade.

Diverse intervention options
Insights include diet and lifestyle interventions as well as probiotic, prebiotic, nutrient and polyphenol supplementation.

Evidence grade to rate quality and consistency of research
The grades provide clinicians with a simple method to understand the research and how much they can apply the results in clinical practice. The evidence grading below is based on the NHMRC guidelines.

Grades / Codes	Description
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation, but care should be taken in its application
D	Body of evidence is weak, and recommendation must be applied with caution
PP, H	Body of evidence is observational only and must be applied with caution
PP, IV	Body of evidence is in vitro and must be applied with a high degree of caution

Gastrointestinal health markers

The gastrointestinal health markers include six diagnostic markers which provide an assessment of intestinal inflammation, intestinal barrier and digestive secretions. In addition, faecal pH is provided as an investigative gastrointestinal marker.

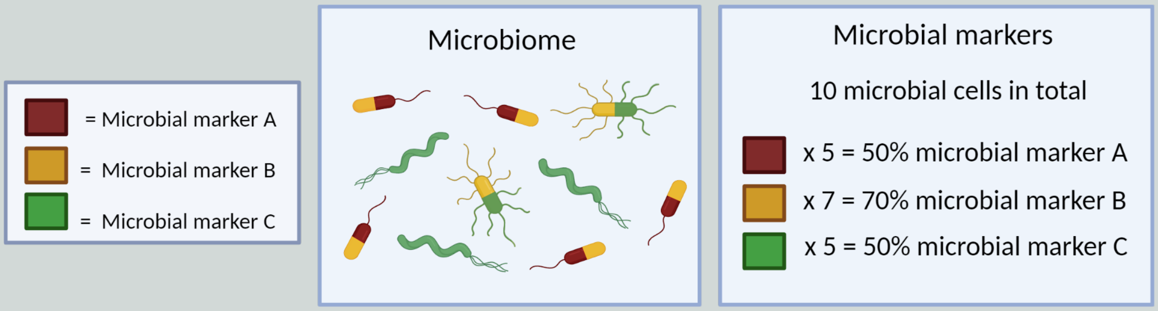
Graded statements on clinical interpretation of gastrointestinal health markers can be found from page 40.

Microbial markers

The microbial markers include the microbial consumption of two compounds and the production of 11 microbial metabolites. In addition, microbial richness and diversity are considered microbial markers as well as being included in the microbiome health section.

Understanding microbial markers

Metagenomics measures the relative abundance of microbial cells with the genetic capacity to produce or consume metabolites.



It is important to remember that the information provided by metagenomics is the genetic potential of the microbiome to produce metabolites, but which metabolites are actually made depends on the provision of fuel sources from the diet and environmental conditions in the gut. For example, you may have lots of genes for making butyrate but unless those cells are exposed to fibre, they will not actually be able to make the butyrate.

The amount of metabolites produced by the microbiome reflects:

- the number of microbial genes
- availability of fuel sources
- environmental conditions in the gut

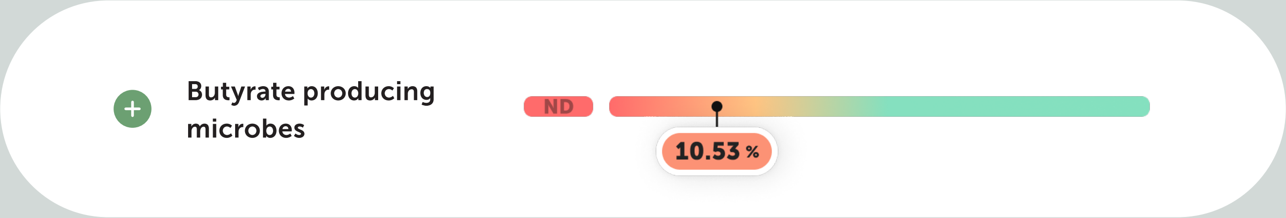
Graded statements on the clinical interpretation of microbial markers can be found from page 24.

Comparing microbial markers to the healthy cohort

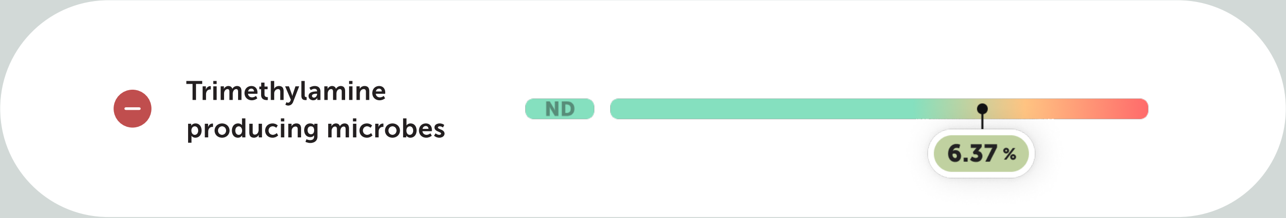
The relative abundance of microbial markers is compared to the healthy cohort.

A green, orange and red coloured reference bar is used to aid interpretation of a result compared to the healthy cohort. Green indicates a beneficial level and red indicates an undesirable level.

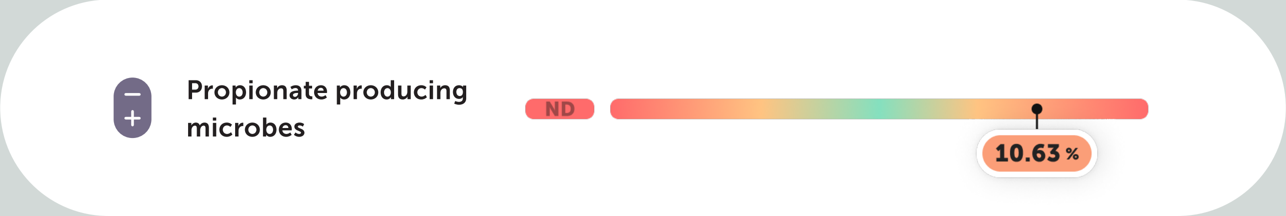
Beneficial microbial metabolites



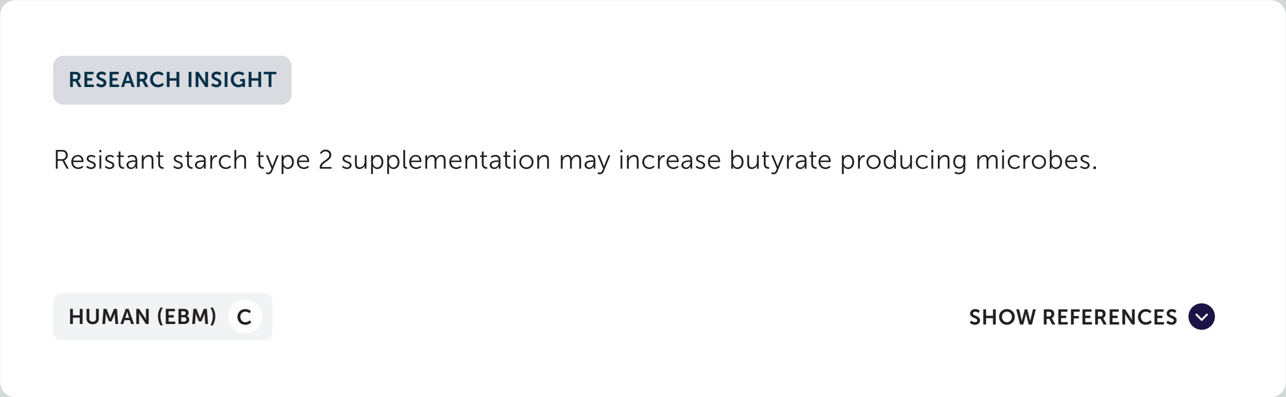
Detrimental microbial metabolites



Two sided microbial metabolites



Research insights are displayed when a microbial marker is identified to be different to the healthy cohort (yellow or red result).



RESEARCH INSIGHT

Resistant starch type 2 supplementation may increase butyrate producing microbes.

HUMAN (EBM) C

SHOW REFERENCES

Diversity

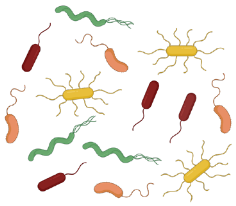
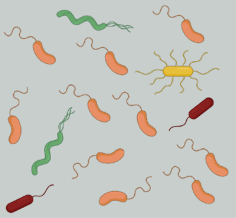
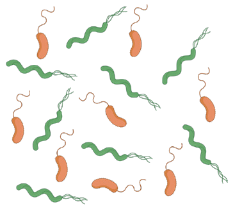
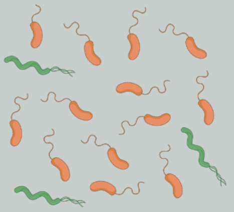
Diversity is a broad assessment of the number and spread of species within a sample. MetaXplore reports on both richness and diversity.

Microbial richness measures the number of species in a sample. A typical healthy sample will contain between 110 – 244 species.

Microbial diversity is a measure that accounts for the number of different species (richness) and their relative abundance (evenness). This is assessed using the Shannon Index, a measure widely used by the scientific community. Low microbial diversity could reflect low numbers of species (low richness) or that certain species dominate the microbiome (low evenness).

Interpreting diversity results

Considering both richness and diversity results together reveals whether a microbiome has a low number of species (low richness) or whether any species dominate the microbiome (low evenness).

Richness	Diversity	Interpretation	
🟩	🟩	Client has a high number of species, and no species dominate the microbiome.	
🟩	🟥	Client has high number of species but some species dominate the microbiome. Review the species explorer to identify the most abundant species in your client's microbiome.	
🟥	🟩	Client has a low number of species but no species dominate the microbiome.	
🟥	🟥	Client has low number of species and there may be species which dominate the microbiome. Review the species explorer to identify the most abundant species in your client's microbiome.	

Species Explorer

Each person's microbiome is made up of different combinations of microbial species. The species explorer lists all species detected in the sample at a relative abundance of over 0.01%.

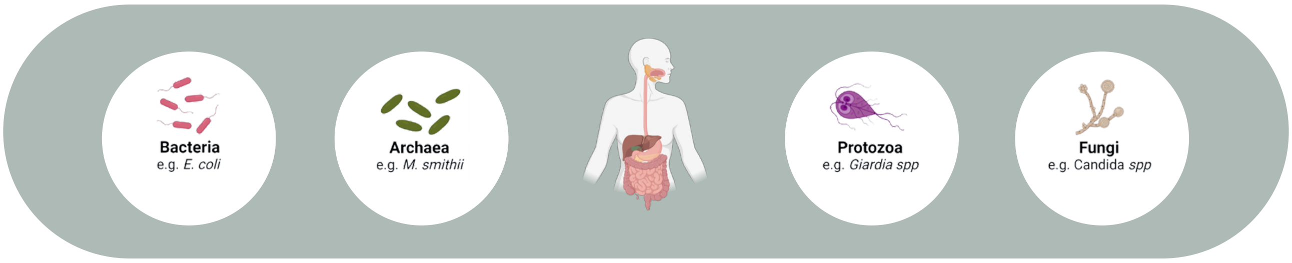
The species explorer provides information on:

- the species name
- how prevalent that species is in the healthy cohort
- the relative abundance of that species in your client's microbiome
- the distance from average which compares the relative abundance of that species to the healthy cohort

Species are the basic unit of taxonomy that identifies organisms which are genetically similar

Identifying parasites, fungi and archaea

Filters in the species explorer can be used to identify if archeae, fungi or protist/parasites were identified in your client's microbiome.



Archaea

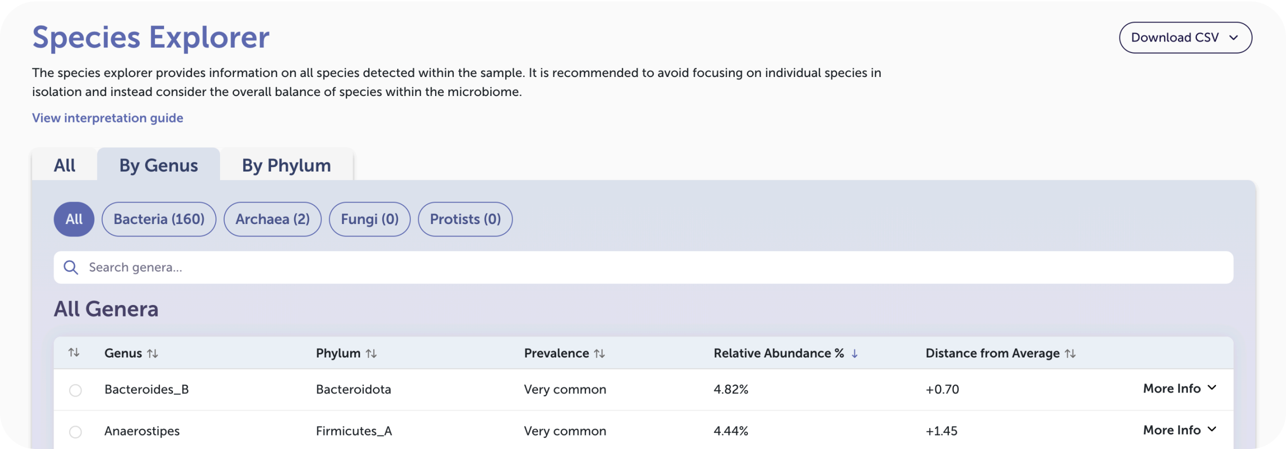
Archaea are a domain of life consisting of single celled organisms that are distinct from bacteria. In humans, archaea are detected in approximately one-third of gut microbiome samples.

Protist/parasites

Protists are a diverse group of organisms within the eukaryotic Domain of life. Some protists are parasitic and can cause infections. Metagenomics can provide high-resolution identification of some protists, such as *Blastocystis* subtypes.

Fungi

Fungi are a kingdom of organisms which includes single-celled yeasts. Fungi are a component of the gut microbiome, although the proportion (when compared to all other organisms in the gut microbiome) is typically less than 0.01% (Evidence Grade: D). As a result of the low overall proportion of fungi in the gut microbiome, they are only detected in approximately 2% of samples.



Species Explorer

The species explorer provides information on all species detected within the sample. It is recommended to avoid focusing on individual species in isolation and instead consider the overall balance of species within the microbiome.

View interpretation guide

All Genera

⇅	Genus ⇅	Phylum ⇅	Prevalence ⇅	Relative Abundance % ↓	Distance from Average ⇅	
○	Bacteroides_B	Bacteroidota	Very common	4.82%	+0.70	More Info ⌄
○	Anaerostipes	Firmicutes_A	Very common	4.44%	+1.45	More Info ⌄

Understanding species names

The species list will contain Latin scientific species names as well as species identified by alpha-numeric and MIC numbers. The type of name which a species has does not reflect the importance of that species in your client's microbiome.

Latin name:	Cultured species are given Latin scientific names which consist of the genus followed by species name.	*Escherichia* ↓ genus *coli* ↓ species
Alpha-numeric identifier:	Uncultured microbes are identified via an alphanumeric identifier e.g. CAG-302 sp001916775.	
MIC number:	Microba uses its world leading database to mine new genomes which are identified using a MIC number. These MIC species names are only found in Microba supported products.	

Understanding prevalence

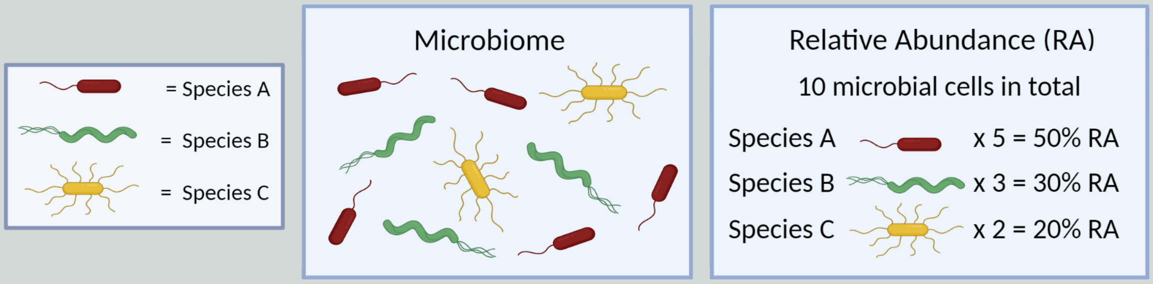
Prevalence provides information on how commonly a particular species is found in the healthy cohort.

There are no species which all microbiomes must contain however, more common species are more likely to have appeared in scientific studies and are therefore generally more well understood by the scientific community.

	Prevalence in healthy cohort	Number of samples in healthy cohort with species detected
Very common	≥ 90%	≥ 435
Common	30% - 90%	145 - 435
Less common	5 – 30%	24 - 145
Rare	< 5%	< 24

Understanding relative abundance

The relative abundance of each species reports the proportion of each species within the total microbial cells. For example, if the most common species in your client's microbiome has a relative abundance of 20% this means that one in five microbial cells are classified as this species.

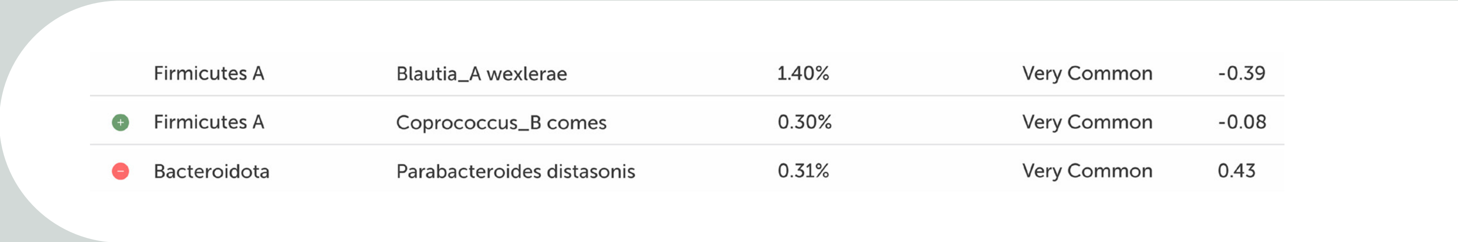


Understanding the distance from average

The distance from average in the species explorer can be used to compare the relative abundance of each species within your client's microbiome to the healthy cohort. The distance from average provides information on whether the species in your client's microbiome accounts for a higher or lower proportion of the microbiome than is seen in healthy microbiomes that contain that species. To ensure clinically relevant comparison, each species is compared only to members of the healthy cohort who are colonised with that species.

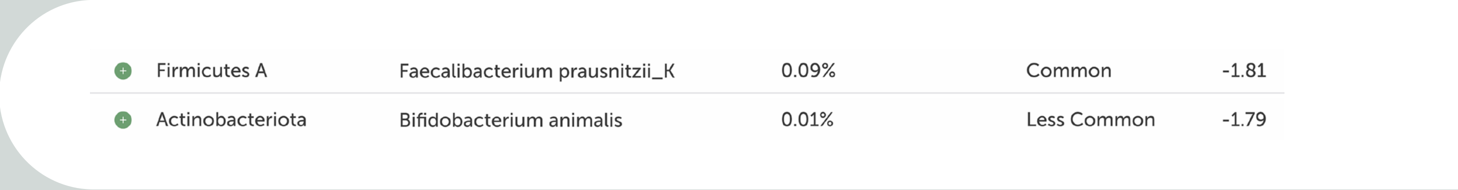
Interpreting the distance from average

A score equal to or near 0 means the abundance of that species is similar to the healthy cohort.



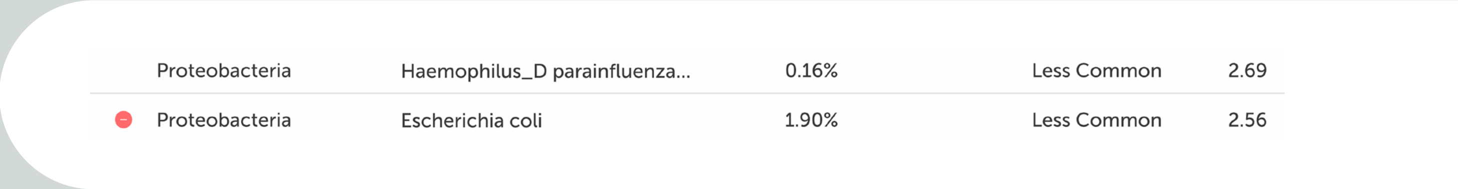
	Firmicutes A	Blautia_A wexlerae	1.40%	Very Common	-0.39
⊕	Firmicutes A	Coprococcus_B comes	0.30%	Very Common	-0.08
⊖	Bacteroidota	Parabacteroides distasonis	0.31%	Very Common	0.43

A negative score means that species is under-abundant compared to the healthy cohort. The lower the number the more reduced the relative abundance of that species compared to the healthy cohort.



⊕	Firmicutes A	Faecalibacterium prausnitzii_K	0.09%	Common	-1.81
⊕	Actinobacteriota	Bifidobacterium animalis	0.01%	Less Common	-1.79

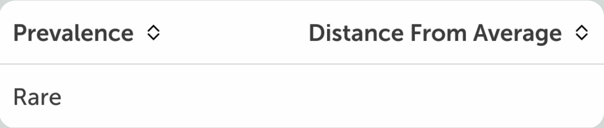
A positive score means that species is over-abundant compared to the healthy cohort. The higher the number the more increased the relative abundance of that species compared to the healthy cohort.



	Proteobacteria	Haemophilus_D parainfluenza...	0.16%	Less Common	2.69
⊖	Proteobacteria	Escherichia coli	1.90%	Less Common	2.56

No distance from average is provided for rare species

As rare species are found in less than 5% of the healthy cohort insufficient data is available to provide a reliable score.



Prevalence ◇	Distance From Average ◇
Rare	

Clinical interpretation

The distance from average can be used to identify health-associated species which are under-abundant in your client's microbiome. Providing a fuel source in the form of prebiotic fibre may feed these species.

Understanding the role of a species in your client's microbiome

Species descriptions

More Info ⌄

The species descriptions provide information to help inform the clinical assessment of the role of that species in your client's microbiome.

Species which have been associated with health outcomes in the scientific literature contain a summary of this research in their description.

Metagenomics can measure the functional capacity of all species providing information on the potential role of every species within your client's microbiome

For all species, the predicted functional capacity to produce microbial metabolites and consume compounds is provided. This information can be used to assess the role of each microbe, including newly discovered species within your client's microbiome. This information can be used to guide your understanding on the microbe's contribution to overall microbiome function, as well as provide insight into the fuel sources it utilises to thrive.

Symbols

Symbols are provided to highlight species which have been associated with health or disease in the scientific literature. This is often based on cross-sectional studies which show that a species is increased or decreased in a particular disease which does not imply causation.

Symbol	Description
⊕	The plus symbol indicates health-associated species that have been shown to be reduced in the microbiomes of people with a certain disease compared to healthy controls.
⊖	The minus symbol indicates disease-associated species that have been shown to be increased in the microbiomes of people with a certain disease compared to healthy controls.
∓	The plus/minus symbol indicates species that have been shown to be increased in the microbiomes of people with some diseases while reduced in the microbiomes of people with other diseases compared to healthy controls.

Search

The species explorer has a search function which will search the species name and description.

Search species

Search terms	Clinical use
Species name	Use the search function to identify the presence of a species of clinical interest. No genera or species must be present to ensure microbiome health.
Disease	Use the search function to identify species found to be associated, in the scientific literature, with a disease of clinical interest. This will select any species which have associations with that disease listed in the species description.
Microbial marker	The search function can be used to search the species description for a microbial marker of clinical interest. This will highlight any species which are contributing to the microbial marker result. For example, by searching 'butyrate' you will identify all the species capable of producing butyrate in your client's microbiome.

Sort

The species explorer can be sorted by each column. The most common columns used to sort the species explorer are the 'abundance' and 'distance from average' columns. Sorting by 'abundance' will identify the species which are most abundant (take up the largest proportion of the microbiome) while sorting by the 'distance from average' will identify the species which are most over-abundant (positive score) or under-abundant (negative score) compared to the healthy cohort.

⬍	Genus ⬍	Phylum ⬍	Species ⬍	Abundance ⬍	Prevalence ⬍	Distance from average ⬍
Sorting by the 'symbol' column will bring species which have been associated with health and disease in the scientific literature to the top of the species explorer.	Sorting by the 'genus' column will group the species by genus.	Sorting by the 'phylum' column will group the species by phylum.	Sorting by the 'species' column will sort the species names alphabetically.	Sorting by the 'abundance' column will bring the most abundant species (largest proportion of the microbiome) to the top of the species explorer.	Sorting by the 'prevalence' column will group the species by prevalence in the healthy cohort.	Sorting by the 'distance from average' column will identify the most over-abundant (positive score) or under-abundant (negative score) species compared to the healthy cohort.

Emerging markers

These are markers which have historically been of clinical interest. These markers have an emerging evidence base leading to uncertainty around their role in human health.

Human DNA	Most of the DNA in stool (>99%) is from microbes and only a small amount should be human. Sources of human DNA in stool can include mucus, shedding of epithelial cells, blood, or sample contamination from other body areas. **MetaXplore Evidence Statement:** High human DNA levels in the stool may be associated with several intestinal diseases including active ulcerative colitis, colorectal cancer, and *C. difficile* infection (Evidence Grade: D).
Ammonia (urease) producing microbes	The microbial enzyme urease breaks down the compound urea, (a nitrogen waste product created by the body), into ammonia. The role of gut bacteria that produce the enzyme urease is currently not well understood.
GABA producing microbes	GABA (gamma-aminobutyric acid) plays an important role in regulating mental state by calming the nervous system. Low levels of GABA have been associated with poor mental health. Most GABA is produced in the brain however, your gut microbiome may contribute to your GABA levels as some bacteria can also produce and/or consume GABA. The role of gut bacteria that produce GABA in mental health is currently not well understood. If you are concerned about your mental health, it is important to seek professional help.
GABA consuming microbes	GABA (gamma-aminobutyric acid) plays an important role in regulating mental state by calming the nervous system. Low levels of GABA have been associated with poor mental health. Most GABA is produced in the brain however, your gut microbiome may contribute to your GABA levels as some bacteria can produce and/or consume GABA. The role of gut bacteria that consume GABA in mental health is currently not well understood. If you are concerned about your mental health, it is important to seek professional help.

Histamine producing microbes	Histamine is a biogenic amine which plays an important role in immunoregulation and intestinal function. Histamine is produced by human cells as well as some microbes. Human colonocytes have the capacity to degrade and transport histamine, suggesting that human genetic variations will affect the capacity of the microbiome to contribute to systemic histamine levels. Variations in histamine receptor types will alter the impact of histamine within different body systems. In vitro studies suggest that histamine-2 receptor stimulation has an immunomodulatory impact resulting in an anti-inflammatory effect. **MetaXplore Evidence Statement:** Human studies have suggested that clients with IBD may have increased microbes that produce histamine, and histamine shows a reduced anti-inflammatory capacity potentially due to reduced expression of histamine-2 receptors on immune cells (Evidence Grade: D). Human studies in clients with IBS have shown that histamine-1 receptor antagonists reduce visceral hypersensitivity and abdominal pain (Evidence Grade: B).
Vitamin K producing microbes	K vitamins are a family of fat-soluble vitamins which play an important role in blood clotting. Vitamin K cannot be produced by human cells and must be obtained through diet or the microbiome. Vitamin K1 (phylloquinone) is found in plants, such as dark leafy vegetables, and is the principal form of dietary vitamin K used by the body. Bacterially derived vitamin K (menaquinones) are produced by our gut bacteria and are found in fermented foods, dairy products and meat. The amount of bacterially derived vitamin K (menaquinones) that can be absorbed by the large intestine is unknown.
Lactate producing microbes	Lactate is an organic compound produced through the microbial fermentation of carbohydrates.

Bacterial pathogens

Pathogens are microbes that can cause illness. The targeted pathogen panel detects bacterial pathogens at the genus, species, and pathotype level.

Detection of *E. coli* pathotypes

Escherichia coli naturally colonises the gastrointestinal tract and encompasses a wide number of strains. Most *E. coli* strains are harmless but some are foodbourne pathogens and can cause gastroenteritis.

Enterotoxigenic *E. coli* (ETEC)	Enterotoxigenic *E. coli* (ETEC) strains are the main cause of travellers' diarrhoea and cholera-like disease in areas with poor sanitation. Traveller's diarrhoea is usually self-limiting. Mild cases require symptomatic treatment only. Rehydration is the mainstay of therapy and anti-diarrhoeal drugs can be considered but should not be used in children. Antibiotics are effective for moderate to severe traveller's diarrhoea.
Enteroaggregative *E. coli* (EAEC)	Enteroaggregative *E. coli* (EAEC) strains are associated with travellers' diarrhoea and/or persistent diarrhoea. Traveller's diarrhoea is usually self-limiting. Mild cases require symptomatic treatment only. Rehydration is the mainstay of therapy and antidiarrhoeal drugs can be considered but should not be used in children. Antibiotics are effective for moderate to severe traveller's diarrhoea.
***E. coli* O157**	*E. coli* O157 can cause acute diarrhoea, bloody diarrhoea (haemorrhagic colitis), and haemolytic uremic syndrome (HUS). Medical treatment is recommended for symptomatic clients. If faecal occult blood is also positive or haemorrhagic colitis or HUS is suspected, urgent further investigation and specialist consultation is recommended.
Shiga toxin	Shiga toxin-producing *E. coli* (STEC) can cause acute diarrhoea, bloody diarrhoea (haemorrhagic colitis), and haemolytic uremic syndrome (HUS). Medical treatment is recommended for symptomatic clients. If faecal occult blood is also positive or haemorrhagic colitis or HUS is suspected, urgent further investigation and specialist consultation is recommended.
***Shigella* spp./EIEC**	*Shigella* spp. and enteroinvasive *E. coli* (EIEC) can cause diarrhoea with fever, and in some cases the diarrhoea is bloody. Medical treatment is recommended for symptomatic clients. If faecal occult blood is also positive or haemorrhagic colitis is suspected, urgent further investigation and specialist consultation is recommended.
Enteropathogenic *E. coli* (EPEC)	Enteropathogenic *E. coli* (EPEC) is a major cause of infantile diarrhoea in the developing world. Medical treatment is recommended for symptomatic clients.

Identification of specific pathogenic species

Yersinia enterocolitica	*Yersinia enterocolitica* is a foodbourne pathogen that can cause invasive gastroenteritis and is often associated with bloody diarrhoea. Colonisation with non-toxigenic strains is possible. Most cases are self-limiting. Medical treatment is likely only required for immunocompromised clients and those with severe or persistent symptoms; however, consideration of the client's clinical presentation is recommended. If faecal occult blood is also positive or haemorrhagic colitis is suspected, urgent further investigation and specialist consultation is recommended.

Detection of *Clostridium difficile* pathotypes

***Clostridium difficile* toxin B**	*C. difficile* is one of the major causes of healthcare-associated infections and *C. difficile* toxin B plays an important role in its pathogenicity. Risk factors include antibiotic use, proton pump inhibitor use, old age, immunosuppression and inflammatory bowel disease. Infections can cause severe gastroenteritis. Medical treatment is recommended for symptomatic clients. If faecal occult blood is also positive or haemorrhagic colitis is suspected, urgent further investigation and specialist consultation is recommended.
Hypervirulent *Clostridium difficile*	*C. difficile* is one of the major causes of healthcare-associated infections and hypervirulent *C. difficile* strains are suggested to produce more of the toxins A and B that are important for their pathogenicity. Risk factors include antibiotic use, proton pump inhibitor use, old age, immunosuppression and inflammatory bowel disease. Infections can cause severe gastroenteritis. Medical treatment is recommended for symptomatic clients. If faecal occult blood is also positive or haemorrhagic colitis is suspected, urgent further investigation and specialist consultation is recommended.

Identification of groups of species at the genus level

***Aeromonas* spp.**	*Aeromonas* spp. are food and waterbourne pathogens that are common in fresh and brackish water. Clinical presentations include asymptomatic carriage and traveller's diarrhoea. Most cases are self-limiting. Medical treatment is likely only required for immunocompromised clients and those with severe or persistent symptoms; however, consideration of the client's clinical presentation is recommended.
***Campylobacter* spp.**	*Campylobacter jejuni* and *coli* are foodbourne pathogens that can cause gastroenteritis. Most cases are self-limiting. Medical treatment is likely only required for immunocompromised clients and those with severe or persistent symptoms; however, consideration of the client's clinical presentation is recommended. If faecal occult blood is also positive or haemorrhagic colitis is suspected, urgent further investigation and specialist consultation is recommended.
***Salmonella* spp.**	*Salmonella* spp. are foodbourne pathogens that can cause gastroenteritis and sometimes bloody diarrhoea. Most cases are self-limiting. Medical treatment is likely only required for immunocompromised clients and those with severe or persistent symptoms; however, consideration of the client's clinical presentation is recommended. If faecal occult blood is also positive or haemorrhagic colitis is suspected, urgent further investigation and specialist consultation is recommended.
***Vibrio* spp.**	*Vibrio* species (*V. cholerae*, *V. parahaemolyticus* and *V. vulnificus*) are waterbourne pathogens that usually cause watery diarrhoea and fever, and sometimes bloody diarrhoea. Colonisation with non-toxigenic strains is possible. Most cases are self-limiting. Medical treatment is likely only required for immunocompromised clients and those with severe or persistent symptoms; however, consideration of the client's clinical presentation is recommended. If faecal occult blood is also positive or haemorrhagic colitis is suspected, urgent further investigation and specialist consultation is recommended.

Targeted Pathogen Panel

The targeted pathogen panel uses RT-PCR (real-time polymerase chain reaction) which is a highly sensitive method for the detection of specific regions of DNA which typically indicates the presence of the pathogen, species or genus reported. It will detect the listed microbes even if present at very low levels but will not provide any other information about the microbiome.

Protozoan parasites

Protozoan parasites are microscopic organisms that live within a host.

***Cryptosporidium* spp.**	*Cryptosporidium* are waterbourne parasites that can cause gastroenteritis. In humans, the majority of cryptosporidiosis cases are caused by *C.hominis* or *C.parvum*. Most cases are self-limiting. Medical treatment is likely only required for immunocompromised clients and those with severe or persistent symptoms; however, consideration of the client's clinical presentation is recommended. Specialist medical advice is recommended for treatment.
Cyclospora cayetanensis	*Cyclospora cayetanensis* is a waterbourne parasite that can cause gastroenteritis. Most cases are self-limiting. Medical treatment is likely only required for immunocompromised clients and those with severe or persistent symptoms; however, consideration of the client's clinical presentation is recommended.
Dientamoeba fragilis	The pathogenic role of *Dientamoeba fragilis* has not been established. Most cases do not require antimicrobial treatment and this will often not clear the protozoa but may disrupt the normal gut microbiome. If symptomatic, other causes should be excluded (e.g. other infections, irritable bowel syndrome, food intolerances). Screening for clearance of the organism or testing of family members is not recommended.
Entamoeba histolytica	*Entamoeba histolytica* is a food and waterbourne parasite that can cause amoebic dysentery. The clinical presentation can range from asymptomatic carriage to invasive gastroenteritis. Medical treatment is recommended even in asymptomatic clients to prevent the spread of disease. If faecal occult blood is also positive or haemorrhagic colitis is suspected, urgent further investigation and specialist consultation is recommended.
Giardia lamblia	*Giardia lamblia* (syn. *G.duodenalis* and *G.intestinalis*) is a waterbourne parasite that can cause gastroenteritis. The clinical presentation ranges from asymptomatic carriage to acute and chronic gastrointestinal infections. Medical treatment is recommended for symptomatic clients.

The pathogenic role of *Dientamoeba fragilis* has not been established.

Understanding targeted pathogen panel results

Detected	DNA target has been detected. The targeted pathogen panel is so sensitive that it can detect clinically insignificant levels of microbes. Results must be considered within the context of the client's clinical presentation.
Indeterminant	Testing has produced discrepant results that cannot be resolved as either a negative or positive. If indicated by the client's clinical presentation repeat sample collection for further testing is recommended.
Not detected	DNA target has not been detected which indicates the associated microbes are not present in the sample. There may be other pathogens present which are not covered by the targeted pathogen panel.

Microbial marker interpretation

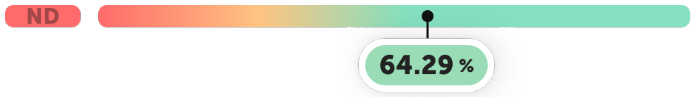
ACETATE PRODUCING MICROBES

Overview

Acetate is the most abundant short-chain fatty acid produced by our gut microbiome and can be converted by some species to butyrate, thus contributing to overall butyrate production.

Interpretation

+



Low levels of acetate may be associated with intestinal inflammation.

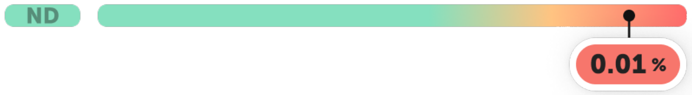
Health Category	Evidence Grade	Evidence Statement
Intestinal inflammation	PP,IV	Studies in human cell lines and animals suggest acetate can modulate intestinal inflammation. It will reduce inflammation when the immune system is in its normal state, but will enhance the immune response when the immune system is activated. Acetate does this by influencing the differentiation of T cells, activating the GPR43 receptor, and promoting gene transcription by histone acetylation.

Literature

Xu et al., 2019, Park et al., 2015

B. FRAGILIS TOXIN PRODUCING MICROBES

Overview	*Bacteroides fragilis* is a normal inhabitant of the human gut. A small proportion of *B. fragilis* strains have the ability to secrete a toxin called fragilysin.

Interpretation	−  High *B. fragilis* toxin may be associated with impaired intestinal barrier integrity.

Health Category	Evidence Grade	Evidence Statement
Intestinal barrier	PP,IV	In vitro and animal studies suggest *B. fragilis* toxin impairs intestinal barrier integrity. It does this by binding to colonic cells and promoting the cleavage of the adhesion protein E-cadherin, resulting in the disruption of tight junctions in the cell barrier.

Literature	Wu et al., 1998, Wu et al., 2007, Sears, 2009, Weikel et al., 1992, Kim et al., 2005

BETA-GLUCURONIDASE PRODUCING MICROBES

Overview

Beta-glucuronidase is a bacterial enzyme that can re-activate a wide variety of drugs and hormones.

Interpretation

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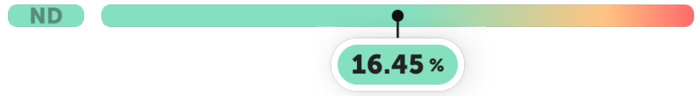


In vitro and animal studies suggest microbial beta-glucuronidases can re-activate a wide variety of drugs and hormones. High levels of beta-glucuronidase may affect drug response and toxicity.

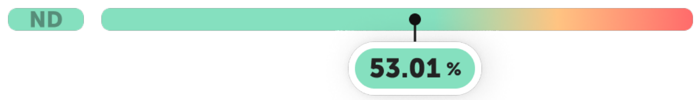
Health Category	Evidence Grade	Evidence Statement
Detox/retox	PP,IV	In vitro and animal studies suggest microbial beta-glucuronidases can re-activate a wide variety of drugs and hormones. High levels of beta-glucuronidase may affect drug response and toxicity.

Literature

Pollet et al., 2017, Ervin et al., 2019, Chamseddine et al., 2019

BCAA PRODUCING MICROBES

Overview	Branched-chain amino acids (BCAAs), which include valine, leucine and isoleucine, are essential amino acids. Although BCAAs are derived from the diet, they are also produced by the gut microbiome which can contribute to elevated levels of plasma BCAAs.

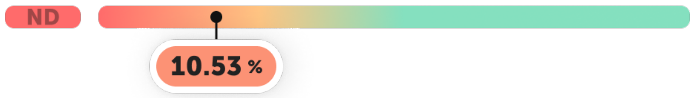
Interpretation	⊖	
	High levels of plasma BCAAs may be associated with systemic inflammation.	

Health Category	**Evidence Grade**	**Evidence Statement**
Systemic inflammation	D	High levels of plasma BCAAs may be associated with systemic inflammation in women.

Literature	Hamaya et al., 2021

BUTYRATE PRODUCING MICROBES

Overview	Butyrate is a beneficial short-chain fatty acid that is important for gut health.

Interpretation	+	
	Low levels of butyrate may be associated with intestinal and systemic inflammation and impaired intestinal barrier integrity.	

Health Category	Evidence Grade	Evidence Statement
Systemic inflammation	D	Lower levels of plasma butyrate may be associated with systemic inflammation in pregnant women.
Intestinal inflammation	PP,IV	Studies in human cell lines and animals suggest butyrate reduces intestinal inflammation. It does this through multiple mechanisms, including promoting the development of anti-inflammatory T regulatory cells, inhibiting activation of the NF-KB inflammatory pathway, and reducing production of pro-inflammatory molecules.
Intestinal barrier	PP,IV	In vitro and animal studies suggest butyrate enhances the intestinal barrier by serving as the main energy source for colon cells through beta-oxidation, and regulating the assembly of tight junction proteins and transcription factor HIF that coordinates barrier protection.

Literature	Arpaia et al., 2013a, Gomez-Arango et al., 2016, Kelly et al., 2015, Peng et al., 2009, Roediger, 1980, Rosser et al., 2020, Singh et al., 2014, Wang et al., 2020

HEXA-LPS PRODUCING MICROBES

Overview	Hexa-acylated lipopolysaccharides (hexa-LPS) are bacterial cell wall components of bacteria within the Gammaproteobacteria class.

Interpretation

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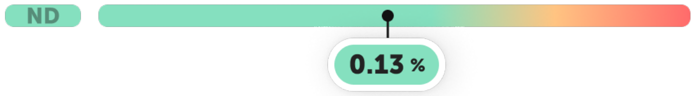


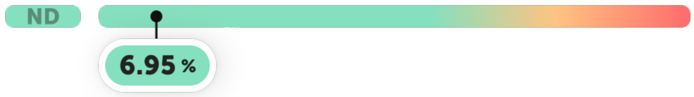
High hexa-LPS may be associated with intestinal and systemic inflammation and impaired intestinal barrier integrity.

Health Category	Evidence Grade	Evidence Statement
Intestinal inflammation	PP,IV	Studies in human cell lines and animals suggest that hexa-LPS promotes intestinal inflammation through the activation of the immune receptor TLR4.
Systemic inflammation	PP,IV	In vitro and animal studies suggest that hexa-LPS promotes inflammation through activation of the immune receptor TLR4. If hexa-LPS is able to leave the gut (e.g. poor intestinal barrier integrity), it may trigger an inflammatory response in immune cells within the peripheral circulation, contributing to low-grade systemic inflammation.
Intestinal barrier	PP,IV	In vitro and animal studies suggest that hexa-LPS can increase intestinal epithelial tight junction permeability through the activation of the immune receptor TLR4.

Literature	Schromm et al., 2000, Chang et al., 2021, Zamyatina & Heine, 2020, Nighot et al., 2017, Anhê et al., 2021, Matsuura, 2013

HYDROGEN SULPHIDE PRODUCING MICROBES

Overview	The gas hydrogen sulphide is produced by gut microbes when they break down sulphur-containing compounds. This gas is responsible for the rotten egg smell of flatulence.

Interpretation	±	
		Optimal hydrogen sulphide levels may be associated with intestinal barrier integrity.

Health Category	Evidence Grade	Evidence Statement
Intestinal barrier	PP,IV	In vitro and animal studies suggest high levels of hydrogen sulphide can compromise intestinal barrier integrity by splitting mucin disulfide bonds and inhibiting the uptake of butyrate by colon cells. In contrast, average to low levels of hydrogen sulphide can be protective of mucin barrier integrity.

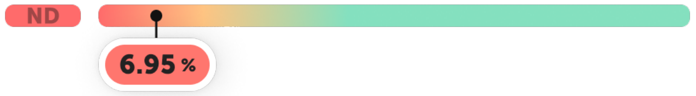
Literature	Ijssennagger et al., 2015, Blachier et al., 2021, Babidge et al., 1998

IPA PRODUCING MICROBES

Overview	3-indolepropionic acid (IPA) is a beneficial substance produced by some gut bacteria when they break down the amino acid tryptophan.

Interpretation

+



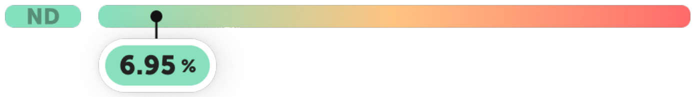
Low levels of IPA may be associated with intestinal and systemic inflammation and impaired intestinal barrier integrity.

Health Category	Evidence Grade	Evidence Statement
Systemic Inflammation	D	Higher levels of plasma IPA are associated with lower systemic inflammation.
Intestinal inflammation	PP,IV	Studies in human cell lines and animals suggest IPA reduces intestinal inflammation. It does this by inhibiting the activation of the immune receptor TLR4, promoting the development of anti-inflammatory T regulatory cells, and by helping to maintain a balance of pro- and anti-inflammatory molecules.
Intestinal barrier	PP,IV	In vitro and animal studies suggest that IPA can improve the intestinal barrier by reducing pro-inflammatory molecules, increasing production of tight junction proteins and increasing the secretion of mucin.

Literature	Alexeev et al., 2018, de Mello et al., 2017, J. Li et al., 2021, Yisireyili et al., 2017, Peron et al., 2022, Tuomainen et al., 2018, Venkatesh et al., 2014, Zhao et al., 2019

METHANE PRODUCING MICROBES

Overview	Methane is an odourless gas produced by Archaeal species which can also be called methanogens. Only around 1/3 of microbiomes contain methanogens.

Interpretation	⊖	
	High levels of methane may be associated with reduced intestinal motility.	

Health Category	Evidence Grade	Evidence Statement
Intestinal motility	C	A slower gut transit time and/or constipation may be associated with higher methane production.

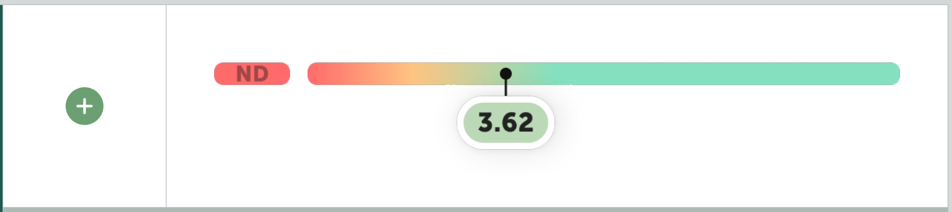
Literature	Asnicar, Leeming, et al., 2021a, Roager et al., 2016, Attaluri et al., 2010

MICROBIAL DIVERSITY

Overview

Microbial diversity is a measure that accounts for the number of different species (richness) and their relative abundance (evenness). This is assessed using the Shannon Index, a measure widely used by the scientific community. Low microbial diversity could reflect low numbers of species (low richness) or that certain species dominate the microbiome (low evenness).

Interpretation



Low microbial diversity may be associated microbiome instability, systemic inflammation and faster gut transit time.

Health Category	Evidence Grade	Evidence Statement
Other	B	Higher diversity is associated with stability of the microbiome over time.
Systemic inflammation	D	Low diversity may be associated with increased systemic inflammation.
Intestinal motility	D	A slower gut transit time may be associated with higher diversity.

Literature

Asnicar, Leeming, et al., 2021b, Mokkala et al., 2020a, Byrd et al., 2021, Zhernakova et al., 2016a, Mehta et al., 2018, Chen et al., 2021

MICROBIAL RICHNESS

Overview	Microbial richness is a measure of the number of different species in a sample.

Interpretation	+	
	Low microbial richness may be associated with systemic inflammation and faster gut transit time.	

Health Category	**Evidence Grade**	**Evidence Statement**
Systemic inflammation	D	Low richness may be associated with increased systemic inflammation.
Intestinal motility	D	A slower gut transit time may be associated with higher richness

Literature	Asnicar, Leeming, et al., 2021c, Mokkala et al., 2020b, Asnicar, Berry, et al., 2021

MUCIN CONSUMING MICROBES

Overview	Mucin is a component of the mucus layer that lines and protects the epithelial gut barrier.

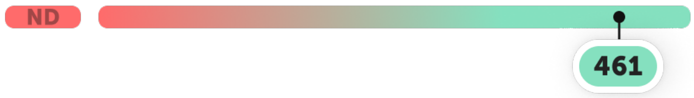
Interpretation	−	
	High levels of mucin consuming microbes may be associated with intestinal inflammation.	

Health Category	Evidence Grade	Evidence Statement
Intestinal inflammation	D	High mucin consuming microbes may be associated with intestinal inflammation.
Intestinal inflammation	D	Colorectal cancer may be associated with increased mucin consuming microbes.
Intestinal inflammation	D	Ulcerative colitis may be associated with reduced mucin consuming microbes.

Literature	Dubinsky et al., 2021, Wirbel et al., 2019, Zhernakova et al., 2016b

OXALATE CONSUMING MICROBES

Overview	Oxalate is a key component of calcium oxalate kidney stones.

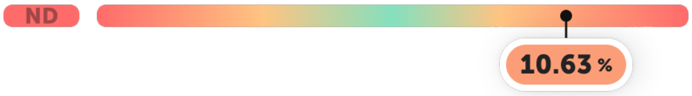
Interpretation	+	
	Low microbial oxalate consumption may be associated with increased urinary oxalate excretion.	

Health Category	Evidence Grade	Evidence Statement
Detox/retox	C	Decreased oxalate consuming microbes may be associated with increased urinary oxalate excretion and may be reduced in clients with recurrent kidney stones.

Literature	Siener et al., 2013, Ticinesi et al., 2018

PROPIONATE PRODUCING MICROBES

Overview	Propionate is a short-chain fatty acid produced by the gut microbiome.

Interpretation	+ −	
	Optimal propionate production may be associated with normal gut transit time and immune balance within the gastrointestinal tract.	

Health Category	**Evidence Grade**	**Evidence Statement**
Intestinal motility	D	Slower gut transit time may be associated with a higher proportion of propionate producing microbes.
Intestinal inflammation	PP, IV	Studies in human cell lines and animals indicate propionate can influence intestinal inflammation. It can reduce inflammation when the immune system is in its normal state, but can enhance the immune response when the immune system is activated. Propionate does this by promoting the development of anti-inflammatory regulatory T cells and by influencing the balance of pro- and anti-inflammatory immune molecules through activation of G-protein coupled receptors.

Literature	Asnicar, Leeming, et al., 2021d, Arpaia et al., 2013b, Jin et al., 2017, Smith et al., 2013

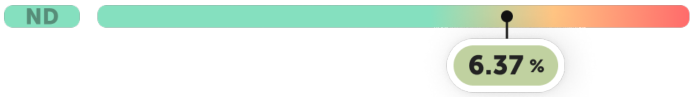
TRIMETHYLAMINE PRODUCING MICROBES

Overview

Trimethylamine is produced by gut microbes from the breakdown of choline and carnitine. It is transported to the liver where it is converted to the compound trimethylamine-n-oxide (TMAO).

Interpretation

⊖



High levels of TMAO may be associated with systemic inflammation.

Health Category	Evidence Grade	Evidence Statement
Systemic inflammation	B	Higher levels of plasma TMAO are associated with systemic inflammation, especially in clients with type 2 diabetes and cardiovascular disease.

Literature

Gencer et al., 2020, Senthong et al., 2016, Farhangi & Vajdi, 2020

Gastrointestinal health marker interpretation

CALPROTECTIN

Overview	Calprotectin is a marker for acute intestinal inflammation and can estimate the degree of inflammation. It is commonly used to distinguish active inflammatory bowel disease (IBD) from irritable bowel syndrome (IBS) and monitoring disease activity and relapse prediction in organic intestinal diseases, such as IBD and colorectal cancer.

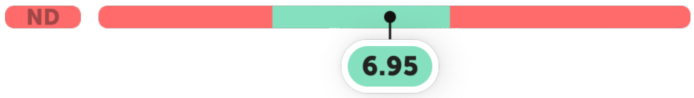
Interpretation	⊖	
	High calprotectin is seen in clients with IBD, bacterial diarrhoea, *C. difficile* toxin and NSAID use. High calprotectin should warrant further investigation if the cause is unknown.	

Health Category	Evidence Grade	Evidence Statement
Intestinal inflammation	A	Faecal calprotectin has a high sensitivity and lower specificity in identifying inflammation in IBD. Faecal calprotectin performs better in ulcerative colitis than in Crohn's disease
Intestinal inflammation	C	High faecal calprotectin may be considered to indicate bacterial causes for acute diarrhoea, as opposed to viral or non-infectious causes.
Intestinal inflammation	C	High faecal calprotectin may be associated with the presence of faecal *C. difficile* toxin.

Literature	Mosli et al., 2015a, Weh et al., 2013a, Barbut et al., 2017, Rokkas et al., 2018, J.-F. Lin et al., 2014, Shastri et al., 2008

FAECAL PH

Overview	Faecal pH is a marker of gut transit time.

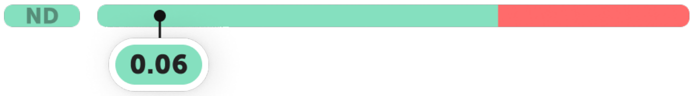
Interpretation	 Low faecal pH may be indicative of rapid transit time while elevated pH may indicate longer transit time. It can also be utilised to estimate absorption of short-chain fatty acids (SCFAs). As SCFAs are absorbed via passive diffusion, longer gut transit time is associated with increased absorption and therefore lower levels of faecal SCFAs. Low faecal pH may be seen in clients consuming lactulose at sufficient doses to cause osmotic diarrhoea or clients with lactose intolerance who are consuming lactose.

Health Category	Evidence Grade	Evidence Statement
Intestinal motility	C	Faecal pH is correlated with gut transit time with high pH suggesting longer gut transit time while low pH is associated with faster gut transit time.
Intestinal motility	B	Faecal pH is inversely related to faecal SCFA levels (pH range 5.7 to 8).
Intestinal motility	D	Methane production may be associated with increased faecal pH.
Intestinal motility	C	Lactulose at sufficient doses to cause osmotic diarrhoea reduces faecal pH.
Intestinal motility	D	Excess lactose consumption in clients with lactose intolerance may be associated with reduced faecal pH.

Literature	McOrist et al., 2008, Holma et al., 2013, Holma et al., 2012, Clausen et al., 1998, Lewis & Heaton, 1997, Abdel-Hafez et al., 1993, Atterbury et al., 1978, El Oufir et al., 1996, Stephen et al., 1986, Mortensen, 1992

LACTOFERRIN

Overview	Lactoferrin is a marker of intestinal inflammatory activity. It is commonly used to monitor disease activity, treatment response and relapse prediction in inflammatory bowel disease (IBD).

Interpretation	⊖	
		High lactoferrin is seen in clients with active IBD, bacterial diarrhoea and *C. difficile* toxin. High lactoferrin should warrant further investigation if the cause is unknown.

Health Category	Evidence Grade	Evidence Statement
Intestinal inflammation	C	High faecal lactoferrin may be associated with inflammation in Crohn's disease.
Intestinal inflammation	C	Faecal lactoferrin may assist in distinguishing bacterial from non-infectious and viral acute diarrhoea. High faecal lactoferrin may indicate bacterial infection while low faecal lactoferrin may be used to exclude bacterial gut infection.
Intestinal inflammation	C	High faecal lactoferrin may be associated with presence of faecal *C. difficile* toxin.

Literature	Mosli et al., 2015b, H. M. Lee et al., 2015, Weh et al., 2013b, Boone et al., 2013, Vernia et al., 2021

OCCULT BLOOD

Overview	Faecal occult blood is a marker of intestinal bleeding. Early diagnosis of faecal occult blood has been shown to significantly reduce the risk of a serious colorectal disease. In addition, the accuracy of the test is not affected by interfering substances, and dietary restriction is not necessary.

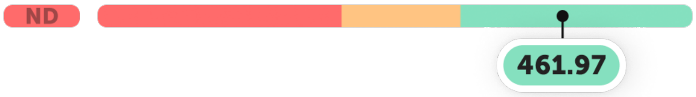
Interpretation	⊖	**DETECTED**
	A positive faecal occult blood is seen in clients with colorectal cancer and inflammatory bowel disease (IBD). A positive faecal occult blood should warrant further investigated if the cause is unknown.	

Health Category	Evidence Grade	Evidence Statement
Intestinal inflammation	A	A positive occult blood is predictive of an increased risk of a colorectal cancer diagnosis.
Intestinal inflammation	B	A positive occult blood is predictive of an increased risk of an IBD diagnosis.
Intestinal inflammation	A	A negative occult blood in clients with ulcerative colitis is a marker for mucosal healing.

Literature	J. K. Lee et al., 2014, He et al., 2019, Fu et al., 2017, Zhong et al., 2020, Digby et al., 2020, Dai et al., 2018, State et al., 2021, Lué et al., 2020

PANCREATIC ELASTASE

Overview	Pancreatic elastase is a marker of pancreatic exocrine function. It is commonly used for diagnosis or exclusion of exocrine pancreatic insufficiency and the monitoring of exocrine pancreatic function in cystic fibrosis, diabetes mellitus, or chronic pancreatitis.

Interpretation	⊖	
	A low pancreatic elastase concentration (< 100 μg/ml) indicates severe exocrine pancreatic insufficiency and should warrant further investigation if cause is unknown. Liquid stools may lead to false pancreatic elastase results. In such cases, it is recommended to also consider clinical symptoms and other diagnostic tests for the final diagnosis.	

Health Category	Evidence Grade	Evidence Statement
Digestive secretions	C	Pancreatic elastase testing may be a valid method for detecting severe pancreatic insufficiency. Elastase-1 may be an inaccurate marker for ruling out mild-moderate pancreatic insufficiency.

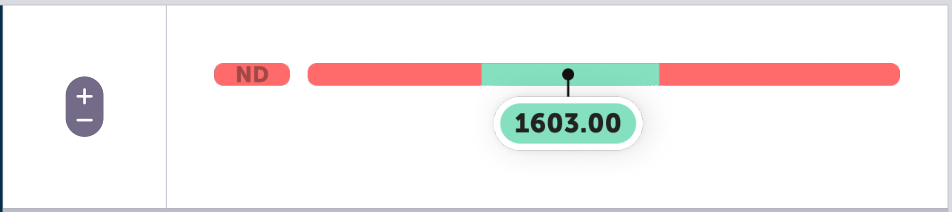
Literature	Leodolter et al., 2000, Vanga et al., 2018, Gullo et al., 1999

SECRETORY IgA

Overview

Secretory IgA (sIgA) is a marker of intestinal inflammation and increased intestinal permeability. It plays a major role in preventing adherence of microbes to mucosal sites, in activation of the alternative complement pathway and in activating inflammatory reactions.

Interpretation



Elevated sIgA is seen in clients with intestinal inflammation, intestinal permeability, IBS-D and autoimmune conditions. Low levels are seen in clients with increased fasting blood glucose.

Health Category	Evidence Grade	Evidence Statement
Intestinal inflammation	D	High faecal sIgA may be considered as a marker of intestinal inflammation and strongly associated with elevated faecal calprotectin.
Intestinal barrier	D	Faecal sIgA may be positively associated with faecal zonulin (a marker of intestinal permeability).
Intestinal barrier	PP,IV	Studies in human cell lines suggest sIgA reduces *C. difficile* toxin A induced intestinal permeability.
Other	D	Faecal sIgA may be considered to be elevated in IBS-D.
Other	D	Faecal sIgA may be considered to be elevated in systemic lupus erythematosus.
Other	D	Reduced faecal sIgA may be associated with increased fasting blood glucose in obese clients.

Literature

R. Lin et al., 2018, Chen et al., 2020, Olson et al., 2013, Gudi et al., 2022, Liu et al., 2020, Azzouz et al., 2019, Istomin et al., 2022

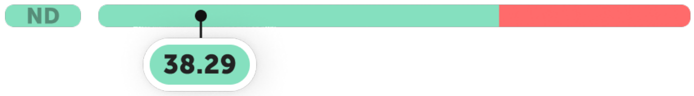
ZONULIN

Overview

Zonulin is a marker of increased intestinal permeability. Zonulin binds to a specific receptor on the surface of intestinal epithelia and triggers a cascade of biochemical events which induces tight junction disassembly and a subsequent increase in permeability across the intestinal epithelium. This allows substances from the gut lumen to pass across the epithelium and activate immune reactions.

Interpretation

⊖



Elevated zonulin is seen in clients with active coeliac disease, type 1 diabetes mellitus, metabolic syndrome, obesity, autoimmune disease, inflammatory diseases, neoplastic diseases, high faecal histamine, following high intensity exercise, and acute psychological stress.

Health Category	Evidence Grade	Evidence Statement
Intestinal barrier	PP,IV	In vitro and animal studies indicate that the release of zonulin family peptides stimulates the disassembly of intercellular tight junctions.
Intestinal barrier	C	High faecal zonulin may be associated with high faecal histamine.
Intestinal barrier	C	High intensity exercise may be associated with increased intestinal permeability.
Intestinal barrier	D	Acute psychological stress may be considered to increase intestinal permeability.

Literature

Drago et al., 2006, Tripathi et al., 2009, Schink et al., 2018, Vanuytsel et al., 2014, Marchbank et al., 2011, Axelrod et al., 2019, Davison et al., 2016, C. Li et al., 2016

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