



CLINICAL GUIDE

Polyphenols

Discover the plant power of polyphenols
and their interaction with health and disease.

- + ANTHOCYANINS
- + CURCUMIN
- + ELLAGIC ACID
- + EPIGALLOCATECHIN GALLATE (EGCG)
- + FLAVONOIDS
- + ISOFLAVONES
- + RESVERATROL

What are polyphenols?

Polyphenols are plant phytochemicals (bioactive compounds produced by plants) and are grouped based on their structural characteristics.¹ More than 8,000 different types of polyphenol compounds have been identified; however, they can be broken down into four main structural groups:

- Flavonoids
- Phenolic acids
- Lignans
- Stilbenes

There are currently no daily targets for polyphenol intake, however a diet rich in polyphenols, such as the Mediterranean diet, is considered beneficial for supporting a resilient gut microbiome and for maintaining general health.

Polyphenols are predominantly found in fruits, vegetables, tea, coffee, chocolate, whole grains, nuts, seeds, and spices.



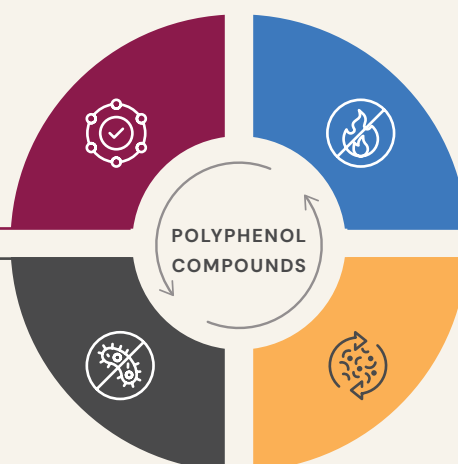
Polyphenol mechanisms

Antioxidant

The antioxidant action of polyphenols has been studied in humans via measuring total antioxidant capacity, superoxide dismutase and Malondialdehyde.⁴⁻¹¹

Antimicrobial

From in vitro studies we see most polyphenols are able to inhibit the growth of a wide range of pathogens and pathobionts.²⁰⁻⁴⁰



Anti-inflammatory

It is hypothesised that polyphenols suppress inflammation by blocking the Nf-kB inflammatory pathway.¹²⁻¹⁹

Prebiotic

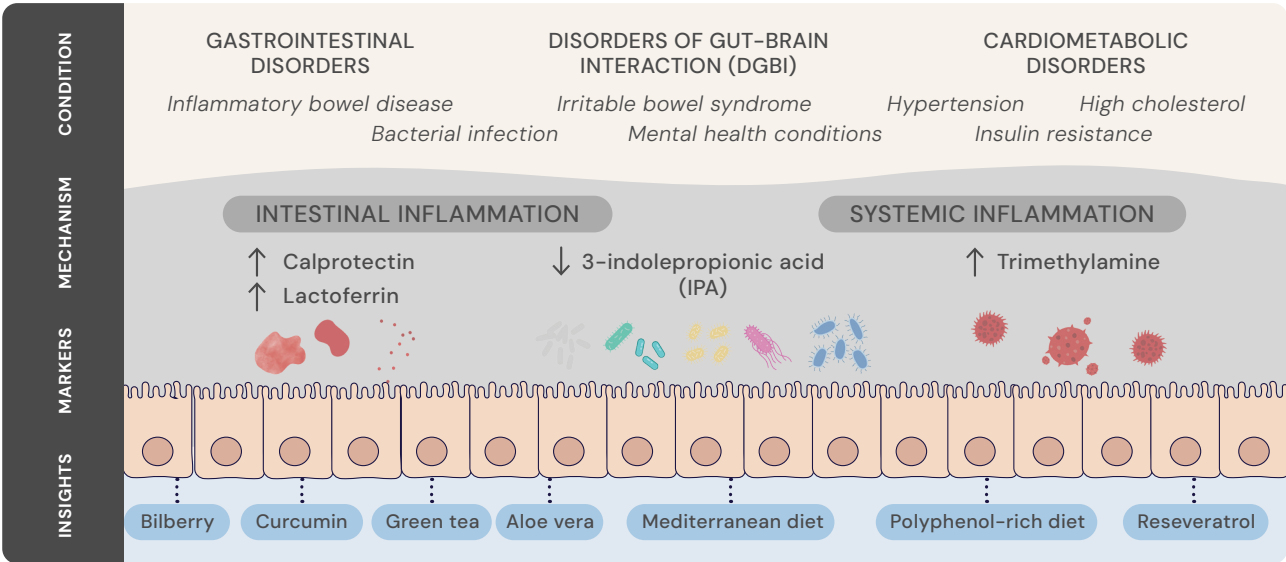
An estimated 90–95% of dietary polyphenols reach the lower gut. Therefore, a significant proportion of polyphenols interact with gut microbiota.²⁻³

Are polyphenols prebiotics?

In 2017, the International Scientific Association for Probiotics and Prebiotics (ISAPP) decided that polyphenols should be considered prebiotics.² With 90–95% of polyphenols reaching the lower gut, their limited bioavailability may correlate with greater prebiotic effects.³

Polyphenols for gastrointestinal health and gut microbiome modulation

Polyphenol compounds interact with the gut microbiome and gastrointestinal environment in a variety of different ways, including exerting an influence on select gastrointestinal health markers, as well as some microbial markers. Some common presentations for polyphenol evaluation may include intestinal and systemic inflammation.



| | | Microbiome Explorer Essentials | Microbiome Explorer Extended | Microbiome Explorer Comprehensive |
|-------------------------|------------------------------|--------------------------------|------------------------------|-----------------------------------|
| Intestinal Inflammation | Calprotectin | ✗ | ✓ | ✓ |
| | Lactoferrin | ✗ | ✓ | ✓ |
| | 3-indolepropionic acid (IPA) | ✓ | ✓ | ✓ |
| Systemic Inflammation | Trimethylamine (TMA) | ✓ | ✓ | ✓ |

Testing for invaluable insights

Testing the gut microbiome can provide insights into the potential for your patient’s gut microbiome to impact their health. Equipped with this information, you can make informed clinical decisions and provide your patient with personalised polyphenol recommendations to better support their health.

Dietary interventions to enhance polyphenol intake

• dominant polyphenol in food item

| | FLAVONOIDS | | | | | | | | NON-FLAVONOIDS | | | | |
|----------------------------------|-------------|-------------|-----------|-------|-----------|-------|------------|----------|----------------|-------|-------------|---------|-------|
| | Isoflavones | Anthocyanin | Flavanols | | Flavonols | | Flavanones | Flavones | Phenolic acids | | Resveratrol | Lignans | Other |
| | | | EGCG | Other | Quercetin | Other | | | Ellagic | Other | | | |
| Fruits | | | | | | | | | | | | | |
| Apple, 1 cup | | | | • | | | | | | | | | |
| Apricot, 1 cup | | | | | | | | | | | | • | |
| Black elderberry, 1 cup | | • | | | | | | | | | | | |
| Blackberry, 1 cup | | • | | | | | | | | | | | |
| Blackcurrant, 1 cup | | • | | | | | | | | | | | |
| Blueberry, 1 cup | | • | | | | | | | | • | | | |
| Grape, black, 1 cup | | • | | • | | | | | | | | | |
| Grape, green, 1 cup | | | | • | | | | | | | | | |
| Kakadu plum, freeze dried, 1 tsp | | | | | | | | | • | | | | |
| Nectarine, 1 cup | | | | • | | | | | | | | | |
| Grapefruit, 1 cup | | | | | | | • | | | | | | |
| Orange, 1 cup | | | | | | | • | | | | | | |
| Peach, 1 cup | | | | | | | | | | • | | | |
| Pear, 1 cup | | | | | | | | | | • | | • | |
| Plum, 1 cup | | • | | • | | | | | | • | | | |
| Pomegranate, arils, 1/3 cup | | | | | | | | | • | | | | |
| Prune, 1/2 cup | | | | | | | | | | • | | | |
| Quince, 1/2 cup | | | | | | | | | | • | | | |
| Red raspberry, 1 cup | | • | | | | | | | • | • | | | |
| Redcurrant, 1 cup | | • | | | | | | | | | | | |
| Strawberry, 1 cup | | • | | • | | | | | | | | | |
| Sweet cherry, 1 cup | | • | | | | | | | | • | | | |
| Vegetables and legumes | | | | | | | | | | | | | |
| Globe artichoke head, 1/2 cup | | | | | | | | • | | • | | | |
| Asparagus, 1/2 cup | | | | | • | | | | | • | | | |
| Broccoli, 1/2 cup | | | | | | • | | | | | | • | |
| Capers, 1/4 cup | | | | | • | | | | | | | | |
| Celery, leaves, 1/2 cup | | | | | | | | • | | | | | |
| Chicory, green, 1/2 cup | | | | | | | | | | • | | | |
| Chicory, red, 1/2 cup | | | | | | | | | | • | | | |
| Kale, 1/2 cup | | | | | | • | | | | | | | |
| Olive oil, extra virgin, 1 tbsp | | | | | | | | | | | | | • |
| Olive, black, 1/2 cup | | | | | | | | | | • | | | • |
| Olive, green, 1/2 cup | | | | | | | | | | • | | | • |
| Onion, red, 1/4 cup | | | | | • | | | | | | | | |
| Onion, yellow, 1/4 cup | | | | | • | | | | | | | | |
| Parsley, 1/4 cup | | | | | | | | • | | | | | |
| Shallot, 1 bulb | | | | | • | | | | | | | | |
| Soy products, 1/2 cup | • | | | | | | | | | | | | |
| Spinach, 1/2 cup | | | | | | • | | | | | | | |
| Nuts & seeds | | | | | | | | | | | | | |
| Almonds and Hazelnuts | | | | • | | | | | | | | | |
| Chestnut, 30g | | | | | | | | | • | | | | |
| Flaxseed meal, 30g | | | | | | | | | | • | | • | |
| Pecan, 30g | | | | • | | | | | • | | | | |
| Walnut, 30g | | | | | | | | | • | | | | • |
| Grains (flours) | | | | | | | | | | | | | |
| Oat, whole grain, 1/2 cup | | | | | | | | | | • | | | |
| Rye, whole grain, 1/2 cup | | | | | | | | | | | | | • |
| Wheat, whole grain, 1/2 cup | | | | | | | | • | | • | | | |
| Cocoa | | | | | | | | | | | | | |
| Cocoa powder, 30g | | | | • | | | | | | | | | |
| Dark chocolate, 30g | | | | • | | | | | | | | | |
| Non-alcoholic beverages | | | | | | | | | | | | | |
| Black tea, 1 cup | | | | • | | | | | | | | | |
| Coffee, filter, 1 cup | | | | | | | | | | • | | | |
| Green tea, 1 cup | | | • | • | | | | | | | | | |
| Alcoholic beverages | | | | | | | | | | | | | |
| Red wine, 150mL | | • | | • | | | | | | | | | |
| Seasonings (dried) | | | | | | | | | | | | | |
| Cloves | | | | | | | | | | | | | • |
| Rosemary | | | | | | | | | | • | | | |
| Sage, common | | | | | | | | | | • | | | |
| Thyme, common | | | | | | | | | | • | | | |
| Turmeric | | | | | | | | | | | | | • |

Supplement dosage table

Specific polyphenols can be used to manage intestinal and systemic inflammation, as highlighted through Microbiome Explorer's gastrointestinal and gut microbiome markers; calprotectin*, lactoferrin*, 3-indolepropionic acid (IPA) and trimethylamine.

| Polyphenol | Health effect | Dosage | Duration | Reference |
|--|--|--|--|-----------|
| Aloe vera <u>No established safe dose.</u> Avoid if hydroxyanthracene derivatives are present (whole leaf extract or aloe latex) as evidence of genotoxicity. ⁴³ | May reduce intestinal inflammation (Microbiome Explorer Extended and Microbiome Explorer Comprehensive measures intestinal inflammation via gastrointestinal health markers calprotectin and lactoferrin) | 2 x 100mL/day (aloe gel) | 4 weeks | 44 |
| | May reduce IBS symptoms | 500mg/day (freeze-dried gel) | 4 weeks | 45-46 |
| Bilberry <u>Max dose:</u> 160g considered tolerable limit Very high doses should be avoided in patients with haemorrhagic (bleeding) disorders. ⁴⁷ | May reduce intestinal inflammation (Microbiome Explorer Extended and Microbiome Explorer Comprehensive measures intestinal inflammation via gastrointestinal health markers calprotectin and lactoferrin) | 160g/day bilberry preparation equal to 95g dry weight (600g fresh fruit, equivalent to 840mg/day anthocyanins) | 6 weeks | 47 |
| Curcumin <u>No established safe dose</u> (based on 2023 TGA report on potential hepatic effects). ⁴⁸ | May reduce intestinal inflammation (Microbiome Explorer Extended and Microbiome Explorer Comprehensive measures intestinal inflammation via gastrointestinal health markers calprotectin and lactoferrin) | 2 x 50mg/day (bio-enhanced); 2 x 1.5g/day; 1g/day | 6 weeks; 1 month; 6 months | 49-51 |
| | Reduces CRP | ≤700mg/day; Not dose-dependent (most studies ~500mg) | >7 weeks; Greatest effect seen at ~13 weeks | 12-13 |
| | Reduces IL-6 | Not dose-dependent | Not duration-dependent | 12-13 |
| | Reduces self-reported gastrointestinal complaints | 500mg/day | 4 weeks | 52 |
| Epigallocatechin gallate (EGCG) <u>Max dose:</u> 300mg/day (risk of hepatic and gastrointestinal adverse effects if exceeded). ⁵³⁻⁵⁴ | May reduce intestinal inflammation (Microbiome Explorer Extended and Microbiome Explorer Comprehensive measures intestinal inflammation via gastrointestinal health markers calprotectin and lactoferrin) | May require >300mg/day. Need more studies to confirm if necessary. | 28 weeks; 56 weeks | 55-56 |
| | May reduce fasting blood glucose | May require >300mg/day | >12 weeks | 57-59 |
| | May reduce TC and LDL-C | ~200mg/day EGCG | 3 months | 60-62 |

| Polyphenol | Health effect | Dosage | Duration | Reference |
|---|--|---|----------------------------------|-----------|
| Ellagic acid <u>Max dose:</u> 2 x 500mg/day (limited number of studies. 2 x 500mg/day has been used safely for 12 weeks with no adverse effects). ⁶⁴ | May reduce LDL-C | ≥180mg/day | Not duration-dependent | 63 |
| | May reduce total triglycerides | ≥180mg/day | ≥8 weeks | 63 |
| | May reduce fasting blood glucose | ≥180mg/day | ≥8 weeks | 63 |
| | May reduce insulin | Not dose-dependent | ≥8 weeks | 63 |
| | May reduce HOMA-IR | Not dose-dependent | Not duration-dependent | 63 |
| | May reduce CRP | 180mg/day; 200mg/day; 2 x 450mg/day | 60 days; 8 weeks; 8 weeks | 14-16 |
| | May reduce TNF-α | 180mg/day; 200mg/day | 60 days; 8 weeks | 14-15 |
| Isoflavones <u>Max dose:</u> No adverse effects at 300mg/day for 2 years or 120mg/day for 3 years. ⁷⁰⁻⁷¹ | Isoflavone supplementation may improve symptoms of menopause (frequency of hot flashes) | 30 to 80mg/day Supplements providing >18.8mg genistein for at least 12 weeks were more than twice as effective | 6 weeks to 12 months | 65-66 |
| | Isoflavone supplementation may improve symptoms of menopause (severity of hot flashes) | 30 to 135mg/day | 12 weeks to 12 months | 65-66 |
| | Dietary soy intake may improve symptoms of menopause | 115.9g/day soy intake; 86g cooked soybeans | N/A; 12 weeks | 67-69 |
| Resveratrol <u>Max dose:</u> 150 – 450mg/day (recommended by EFSA, though no treatment-related effects observed for <1g/day in studies up to 3 months). ⁷⁶⁻⁷⁷ | May reduce plasma trimethylamine (TMA)/ trimethylamine N-oxide (TMAO) (Microbiome Explorer Extended and Microbiome Explorer Comprehensive measures systemic inflammation via microbial marker trimethylamine (TMA)) | 2 x 300mg | 28 days to 8 weeks | 72-73 |
| | May reduce CRP and TNF-α | Not dose-dependent | Not duration-dependent | 17 |
| | May reduce blood pressure | 300mg/day; 600-1000 mg/day | At least 3 months; 2-3 months | 74 |
| | May reduce LDL-C | ≥500mg/day | ≥12 weeks | 75 |
| | May reduce total cholesterol | Not dose-dependent | Not duration-dependent | 75 |

CRP: C-reactive protein
 IL-6: Interleukin-6
 TC: Total cholesterol
 LDL-C: Low-density lipoprotein-cholesterol

HOMA-IR: Insulin resistance
 TNF-α: Tumour necrosis factor alpha
 TMA: Trimethylamine
 TMAO: Trimethylamine N-oxide

Clinical considerations for polyphenol prescription

Nutrient and drug interactions

Diet and nutrients

| | |
|----------------|---|
| Iron | Polyphenols have iron-chelating effects by forming complexes with iron, inhibiting absorption. Polyphenol supplementation may have an inhibitory effect on serum iron concentration and transferrin saturation. ⁷⁸ 300 mg of EGCG has been shown to significantly reduce iron absorption. ⁷⁹ |
| Folic acid | 300 mg of green tea extract has been shown to potentially reduce absorption of folic acid supplementation. ⁸⁰ |
| High fat foods | Compared to a standard breakfast, a high-fat breakfast delays the absorption and reduces the exposure to resveratrol. ⁸¹ On the other hand, dietary fat has been shown to increase quercetin bioavailability. ⁸² |

Drugs

| Polyphenol | Drug | Exposure | Proposed mechanism | Reference |
|--------------|---|-----------|----------------------------|-----------|
| Curcumin | Sulfasalazine | Increased | Inhibited BCRP | 83 |
| | Talinolol | Decreased | Induced P-gp | 84 |
| | Caffeine, theophylline, clozapine, and acetaminophen (not yet assessed) | Increased | Inhibited CYP1A2 | 85 |
| | Caffeine, nicotine and cotinine (not yet assessed) | Decreased | Induced CYP2A6 | 85 |
| Resveratrol | Warfarin | Increased | Inhibited BCRP* and CYP2C9 | 86 |
| | Losartan | Increased | Inhibited CYP2C9 | 87 |
| | Buspirone | Increased | Inhibited CYP3A4 | 87 |
| | Dextromethorphan | Increased | Inhibited CYP2D6 | 87 |
| | Caffeine | Decreased | Induced CYP1A2 | 87 |
| Isoflavones | Theophylline | Increased | Inhibited CYP1A2 | 88 |
| | Midazolam | Decreased | Induced CYP3A4 | 88 |
| | Celecoxib* | Increased | Inhibited CYP2C9 | 88 |
| | Paclitaxel* | Increased | Inhibited CYP3A4 and P-gp | 88 |
| | Repaglinide* and omeprazole* | Increased | Inhibited P-gp | 88 |
| | Imatinib* and carbamazepine* | Decreased | Induced CYP3A4 | 88 |
| Ellagic acid | Metoprolol* | Increased | Inhibited CYP2D6 | 89 |
| | Diltiazem* | Increased | Inhibited CYP3 and P-gp | 90 |

| Polyphenol | Drug | Exposure | Proposed mechanism | Reference |
|------------|----------------------------|-----------|------------------------------|-----------|
| Green tea | Simvastatin and tacrolimus | Increased | Inhibited CYP3A4 and P-gp | 91 |
| | Sildenafil | Increased | Inhibited CYP3A4 | 91 |
| | Buspirone | Increased | Inhibited CYP3A4 | 92 |
| | Rosuvastatin and nadolol | Decreased | Inhibited OATP1A2 or OATP2B1 | 91 |
| | Digoxin | Decreased | Induced P-gp | 93 |
| Quercetin | Cyclosporine | Increased | Inhibited CYP3A4 | 94 |
| | Pravastatin | Increased | Inhibited OATP1B1 | 95 |
| | Fexofenadine | Increased | Inhibited P-gp | 96 |
| | Talinolol | Decreased | Induced P-gp | 97 |
| | Midazolam | Decreased | Induced CYP3A | 98 |
| | Paracetamol* | Increased | Inhibited P-gp | 99 |

NB: this is not an exhaustive list of potential drug–polyphenol interactions.

*Preclinical evidence in animals: clinical experiments are needed to assess these drugs when concomitantly administered with this polyphenol

Polyphenol safety considerations

| Polyphenol | Max dose | Adverse events | References |
|--------------|--|--|------------|
| Resveratrol | 150 – 450mg/day | Generally well-tolerated but GI symptoms, especially diarrhoea, are common (mild up to 1.5g/day, most common when of at least 2.5g/day). EFSA Panel suggests 150mg/day. resVida® is a trans-resveratrol supplement with GRAS status at 450mg/day. Caution when taking with warfarin as may increase anticoagulant effects. | 76–77 |
| Ellagic acid | 2 x 500mg/day | Limited number of studies. 2 x 500mg/day has been used safely for 12 weeks with no adverse effects. | 64 |
| Curcumin | No established safe dose | 2023 TGA report on potential hepatic effects determined there is no established safe dose. There are new TGA label requirements for curcumin products. Liver injury is idiosyncratic; therefore, dose cannot predict it. | 48 |
| Aloe vera | No established safe dose | Avoid if hydroxyanthracene derivatives are present (whole leaf extract or aloe latex) as evidence of genotoxicity. | 43 |
| EGCG | 300mg/day | Mild-moderate GI symptoms observed in 400 to 4000mg/day. Liver injury can occur when consumed in supplement form but does not appear to occur from green tea beverage consumption. Highest incidence from Polyphenon E supplement. | 53–54 |
| Isoflavones | No adverse effects at 300mg/day for 2 years or 120mg/day for 3 years | In 2015, the European Food Safety Authority declared soy isoflavones do not adversely affect the breast, thyroid, or uterus of postmenopausal women and is in support of their safety. However, more research is required on utero isoflavone exposure and the effects of isoflavone on thyroid in cases of iodine deficiency. | 70–71 |

EFSA: European Food Safety Authority

Framework for personalised polyphenol prescription in clinical practice

| | | |
|---|--|---|
| STEP 1 Clinical presentations | Intestinal inflammation (inflammatory bowel disease, irritable bowel syndrome, pathogenic infection, ischaemic colitis, food allergy) | ○ |
| | Systemic inflammation (autoimmune disease, cardiovascular disease, metabolic disease, mental health conditions) | ○ |
| STEP 2 Initial consultation | Patient assessment and gastrointestinal and gut microbiome testing | |
| | Evaluate patients' dietary habits, MEDAS score, health conditions and medication use | ○ |
| | Referral for Microbiome Explorer Essentials, Microbiome Explorer Extended or Microbiome Explorer Comprehensive report | ○ |
| | Mediterranean diet with polyphenol rich foods | |
| | Encourage patients to follow a Mediterranean style diet that includes a variety of polyphenol-rich foods | ○ |
| | Provide practical dietary advice and recipes to help patients integrate these foods into their daily meals | ○ |
| STEP 3 Follow-up consultation | Review of gut microbiome and gastrointestinal results | |
| | Review Microbiome Explorer Essentials, Microbiome Explorer Extended or Microbiome Explorer Comprehensive report for: <ul style="list-style-type: none"> • Calprotectin • Lactoferrin • 3-indolepropionic acid (IPA) • Trimethylamine (TMA) | ○ |
| | Polyphenol dietary and supplement prescription, if required | |
| | Manage out of range markers with SPECIFIC polyphenol dietary or supplement interventions if required | ○ |
| | Consider nutrient and drug interactions, and polyphenol safety before polyphenol supplement prescription | ○ |
| STEP 4 Subsequent follow-up consultations | Monitor and adjust as needed | |
| | Monitor the response and tolerability to the intervention | ○ |
| | Assess patients' symptom/condition improvement | ○ |
| | Amend the dose or change the intervention, if needed | ○ |
| STEP 5 Re-test | Re-test between 3–6 months to understand effectiveness of polyphenol intervention | ○ |

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This guide has been developed for healthcare professionals. The Microbiome Explorer™ range is only available for purchase through a healthcare professional. *The faecal occult blood, reverse transcriptase polymerase chain reaction (RT-PCR) and enzyme-linked immunosorbent assays (ELISA) used in the Microbiome Explorer™ range are diagnostic and are approved for clinical use. The faeces pH assay used in the Microbiome Explorer™ range is for research use only and not to be used as a basis for diagnosis. The metagenomic assays used in the Microbiome Explorer™ range are to determine the microbiome populations and associated functional pathways in a faecal sample. The application is for research use only and is 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 microba.com. The Microbiome Explorer™ testing range has been developed for adults 18 years or older and the microbiome results will be compared to a cohort of healthy adults. The clinical and research insights within the report are based on the assessment of the scientific literature in adults over 18 years of age.