



SUPPORT GUIDE



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INTRODUCTION

Advances in research, combined with clinical insight, confirm the essential role of the gut in determining overall health and wellness. Genova’s stool profiles offer a comprehensive evaluation of GI function paired with the broadest clinical utility available. It is important that clinicians possess these tools since they provide the most accurate and comprehensive assessment of gastrointestinal health.

Genova’s line of stool testing provides immediate actionable clinical information for gastrointestinal health management. Utilizing both advanced technologies and premier biomarkers, the GI Effects Stool Profiles offer valuable insight into digestive function, intestinal inflammation, as well as the gastrointestinal microbiota. Our tests are designed to identify potential root causes of symptoms. They assist clinicians by providing targeted therapeutics that improve symptoms and overall gut health.

In addition to providing a comprehensive set of GI functional biomarkers, our stool profiles incorporate the most sophisticated tools in evaluating the microbial community of the GI tract, known as the microbiota. Genova uses multiple methodologies to provide the most clinically accurate assessment of bacteria, yeast, and parasites currently available on the market. The GI Effects Profiles include quantitative assessment of commensal bacteria to determine healthy bacterial balance based on research and analysis of hundreds of thousands of patient results. This data-driven, evidence-based analysis establishes a firm foundation from which to base clinical decisions and treatment. Furthermore, Genova is excited to incorporate Whole Genome Sequencing with the addition of our Microbiomix microbiome analysis as an add-on to the GI Effects Comprehensive profile.

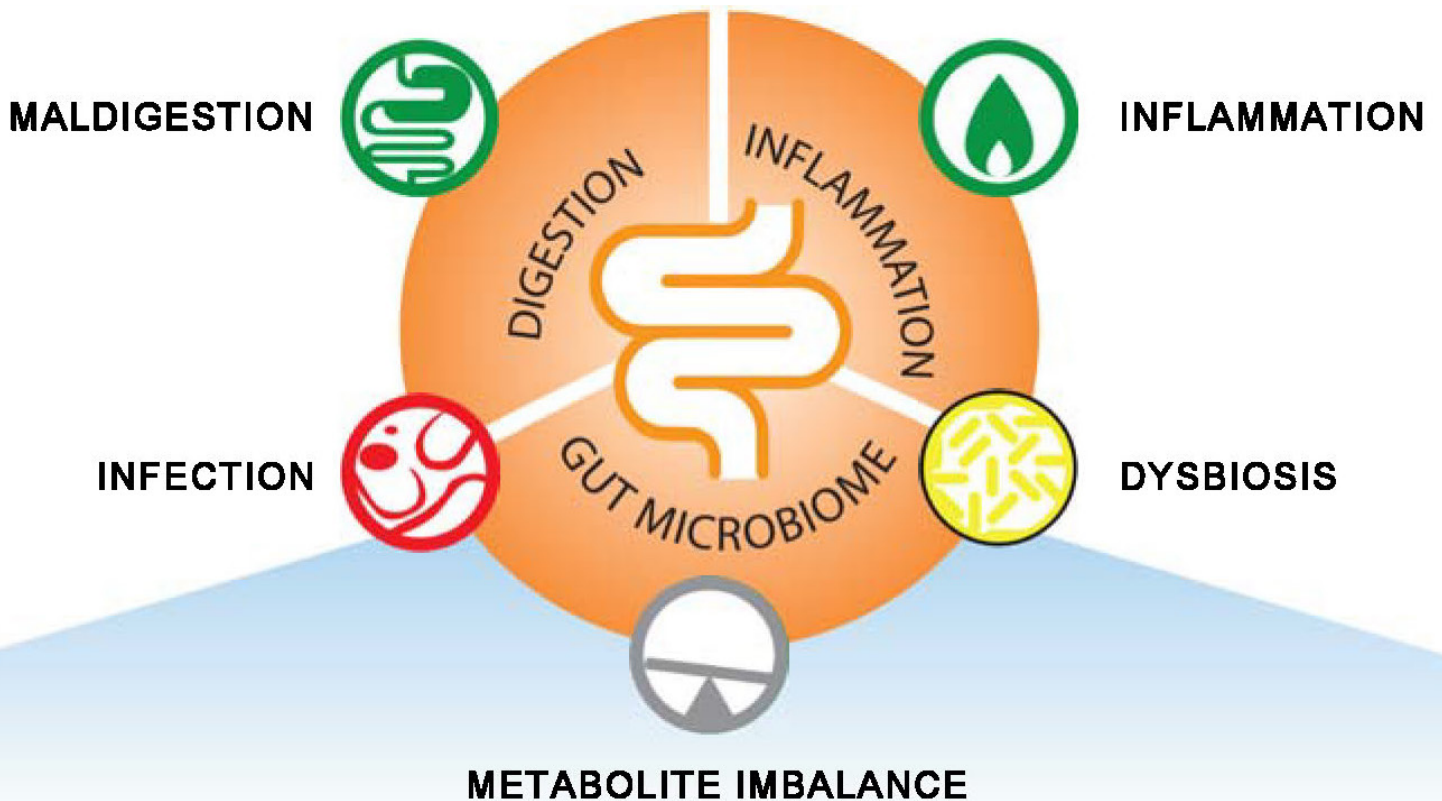
Lastly, the GI Effects utilizes an innovative scoring system that synthesizes the biomarker findings and groups them into 5 key areas relating to GI function: maldigestion, inflammation, dysbiosis, metabolite imbalance, and infection. This allows for clearer visualization of patterns among biomarkers. Protocol design and management of abnormal GI function through dietary, lifestyle, nutraceutical, and other relevant interventions are thus enhanced.

GI FUNCTION MARKERS	2200	2205	2207	2209
Digestion and Absorption				
Pancreatic Elastase 1	•			•
Products of Protein Breakdown (Total) (Valerate, Isobutyrate, Isovalerate)	•			•
Fecal Fat (Total)	•			•
Triglycerides	•			•
Long-Chain Fatty Acids	•			•
Cholesterol	•			•
Phospholipids	•			•
Inflammation and Immunology				
Calprotectin	•			•
Eosinophil Protein X (EPX)	•			•
Fecal secretory IgA	•			+
Gut Microbiome Metabolites				
Short-Chain Fatty Acids (SCFA) (Total) (Acetate, n-Butyrate, Propionate)	•			•
n-Butyrate Concentration	•			•
n-Butyrate %	•			•
Acetate %	•			•
Propionate %	•			•
Beta-glucuronidase	•			•
Gastrointestinal Microbiome (PCR)				

GI FUNCTION MARKERS	2200	2205	2207	2209
Gastrointestinal Microbiome (PCR)				
Commensal Bacteria (qPCR)				
Bacteroidetes Phylum				
<i>Bacteroides uniformis</i>	.	.		
<i>Phocaeicola vulgatus</i>	.	.		
<i>Barnesiella</i> spp.	.	.		
<i>Odoribacter</i> spp	.	.		
<i>Prevotella</i> spp.	.	.		
Firmicutes Phylum				
<i>Anaerotruncus colihominis /massiliensis</i>	.	.		
<i>Butyrivibrio crossotus</i>	.	.		
<i>Clostridium</i> spp.	.	.		
<i>Coprococcus eutactus</i>	.	.		
<i>Faecalibacterium prausnitzii</i>	.	.		
<i>Lactobacillus</i> spp.	.	.		
<i>Pseudoflavonifractor</i> spp	.	.		
<i>Roseburia</i> spp.	.	.		
<i>Ruminococcus bromii</i>	.	.		
<i>Veillonella</i> spp.	.	.		
Actinobacteria Phylum				
<i>Bifidobacterium</i> spp.	.	.		
<i>Bifidobacterium longum</i>	.	.		
<i>Collinsella aerofaciens</i>	.	.		
Proteobacteria Phylum				
<i>Desulfovibrio piger</i>	.	.		
<i>Escherichia coli</i>	.	.		
<i>Oxalobacter formigenes</i>	.	.		
Euryarchaeota Phylum				
<i>Methanobrevibacter smithii</i>	.	.		
Fusobacteria Phylum				
<i>Fusobacterium</i> spp.	.	.		
Verrucomicrobia Phylum				
<i>Akkermansia muciniphila</i>	.	.		
Gastrointestinal Microbiome (Culture)				
Bacteriology (Culture)
Mycology (Yeast/Fungi)
Bacterial Sensitivities (pharmaceutical & botanical)
Mycology Sensitivities (pharmaceutical & botanical)
Parasitology				
Microscopic Exam Results	.	.	.	+
qPCR Parasitology - Protozoa	.	.	.	+
Additional Findings				
Fecal Occult Blood	.	.		.
Color	.	.		.
Consistency	.	.		.
Add-on Testing				
<i>Campylobacter</i> EIA #2323	+	+	+	+
<i>Clostridium difficile</i> EIA #2325	+	+	+	+
<i>Helicobacter pylori</i> Stool Antigen EIA #2330	+	+	+	+
Fecal Lactoferrin #2206	+	+		
KOH Preparation for Yeast #2338	+	+	.	+
Macroscopic/Direct Examination for Parasites	+	+	.	+
Shiga-like Toxin <i>Escherichia coli</i> EIA	+	+	+	+
Zonulin Family Peptide, Stool	+	+		+
Microbiomix™	+			






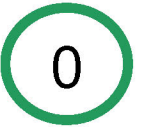



GI EFFECTS RESULTS OVERVIEW

The **GI Effects Stool Profile report** is organized to provide a quick overview and synthesis of results at the beginning of the report. The results overview graphic reflects the status of the 3 key functions of gut health arranged in the “**DIG**” format: **digestion, inflammation, and the gut microbiome**. The gut microbiome section is further broken down into three components: infection, metabolite imbalance, and dysbiosis. These individual gut microbiome sections allow the practitioner to differentiate between interventions that are antimicrobial versus supportive of the microbiome. The color-coded circles reflect the need for support in each area and help the practitioner prioritize therapeutic strategies. Green represents low need for support, gray (optional), yellow (moderate), and red (high need).



Functional Imbalance Scores

The functional imbalance scores are generated using weighted algorithms that incorporate biomarkers belonging to each functional category. The biomarkers that are represented in the algorithm are listed below the score in each functional column. A qualitative indicator of whether the biomarker is normal (green circle ●) or abnormal (yellow ▲ or red arrow ▲) is located adjacent to the biomarker name. The level of need for support in a functional area is reflected both by the color and score in the circle. Green represents a low need for support and corresponds with scores less than 2, grey represents an optional need for support and corresponds with a score of 2 or 3, yellow indicates moderate need with scores of 4-6, and red indicates high need with scores of 7-10.

Functional Imbalance Scores				
Key  : Low Need for Support  : Optional Need for Support  : Moderate Need for Support  : High Need for Support				
Need for Digestive Support	Need for Inflammation Modulation	Need for Microbiome Support	Need for Prebiotic Support	Need for Antimicrobial Support
MALDIGESTION 	INFLAMMATION 	DYSBIOSIS 	METABOLIC IMBALANCE 	INFECTION 
Biomarkers				
<ul style="list-style-type: none"> Products of Protein Breakdown ▼ Fecal Fats ▼ Pancreatic Elastase ● 	<ul style="list-style-type: none"> Secretory IgA ▲ Calprotectin ● Eosinophil Protein X ● Occult Blood ● 	<ul style="list-style-type: none"> PP Bacteria/Yeast ▲ IAD/Methane Score ● Reference Variance ● Total Abundance ● 	<ul style="list-style-type: none"> Total SCFA's ▼ n-Butyrate Conc. ▼ SCFA (%) ● Beta-glucuronidase ● 	<ul style="list-style-type: none"> PP Bacteria/Yeast ▲ Parasitic Infection ▲ Pathogenic Bacteria ● Total Abundance ●

Therapeutic Support Options

Therapeutic support options are listed at the bottom of each column. Therapeutic support options are static on every report to serve as potential treatment ideas. Clinician discretion is advised when selecting appropriate therapeutics for individual patients. More information on therapeutic support options is discussed throughout this guide as they relate to each biomarker.

Therapeutic Support Options	<ul style="list-style-type: none"> • Digestive Enzymes • Betaine HCl • Bile Salts • Apple Cider Vinegar • Mindful Eating Habits • Digestive Bitters 	<ul style="list-style-type: none"> • Elimination Diet/ Food Sensitivity Testing • Mucosa Support: Slippery Elm, Althea, Aloe, DGL, etc. • Zinc Carnosine • L-Glutamine • Quercetin • Turmeric • Omega-3's • GI Referral (If Calpro is Elevated) 	<ul style="list-style-type: none"> • Pre-/Probiotics • Increase Dietary Fiber Intake • Consider SIBO Testing • Increase Resistant Starches • Increase Fermented Foods • Meal Timing 	<ul style="list-style-type: none"> • Pre-/Probiotics • Increased Dietary Fiber Intake • Increase Resistant Starches • Increase Fermented Foods • Calcium D-Glucarate (for high beta-glucuronidase) 	<ul style="list-style-type: none"> • Antibiotics (if warranted) • Antimicrobial Herbal Therapy • Antiparasitic Herbal Therapy (if warranted) • <i>Saccharomyces boulardii</i>
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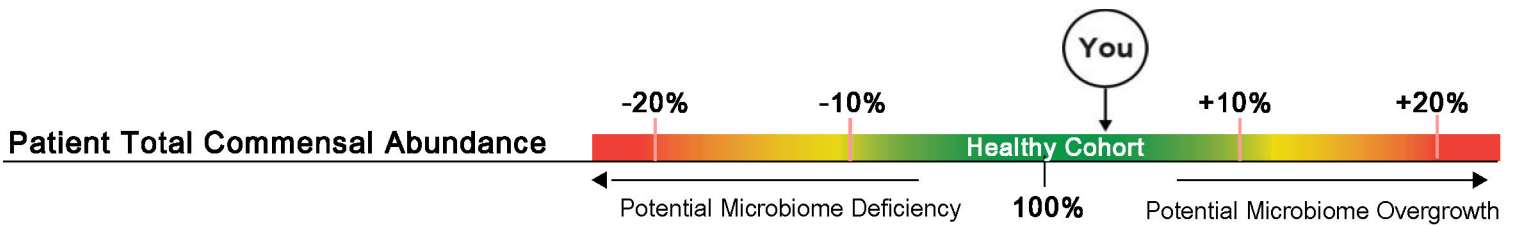
GI EFFECTS COMMENSAL MICROBIOME ANALYSIS

The GI Effects features a synthesis of the patient’s microbiome data. In addition to listing amounts of the 24 commensal bacteria, Genova has developed unique algorithms that account for the levels of bacteria and translate the patient’s microbiome data into clinically actionable information. The commensal microbiome analysis focuses on the areas of abundance, dysbiosis, and balance.

Commensal Abundance

Total Commensal Abundance

The total commensal abundance is a sum-total of the reported commensal bacteria compared to a healthy cohort. Results are denoted with a circle (You) and reported as a percent variance from healthy cohort levels. Low levels of commensal bacteria are often observed after antimicrobial therapy, or in diets lacking fiber and/or prebiotic-rich foods and may indicate the need for microbiome support. Conversely, higher total commensal abundance may indicate potential bacterial overgrowth or probiotic supplementation.



Relative Commensal Abundance

The relative abundance compares the quantity of each of 7 major bacterial phyla to a healthy cohort. Phyla are represented by various colors and each is reported as a percent variance from healthy cohort levels. This can indicate broader variances in the patient’s gut microbiome profile. Certain interventions may promote or limit individual phyla when clinically appropriate. Within a healthy cohort, there are a percentage of people who do not have specific bacteria within that phylum. “NR” means that bacteria was below detectable limits, but the bar graph reflects that this is in line with the healthy cohort.

Relative Commensal Abundance

	-50%	-25%	Healthy Cohort	+25%	
Bacteroidetes Phylum	[Bar from -50% to -25%]				Increase in <i>Bacteroides</i> spp. and <i>Odoribacter</i> spp. seen in animal-based diets; <i>Prevotella</i> increased with plant-based diet
Firmicutes Phylum	[Bar from -50% to +25%]				Contains many butyrate-producers; most species responsive to plant-based diets; <i>Faecalibacterium</i> spp. is anti-inflammatory
Actinobacteria Phylum	[Bar from -50% to -25%]				<i>Bifidobacterium</i> is increased with plant-based diets; <i>Collinsella</i> may be proinflammatory, and is elevated with a Western-diet
Proteobacteria Phylum	[Bar from -50% to -25%]				Some species may be proinflammatory; <i>E. coli</i> consumes simple sugars and is lower in individuals on plant-based diets
Euryarchaeota Phylum ***	NR				<i>Methanobrevibacter smithii</i> is associated with methane production and with diets high in carbohydrates
Fusobacteria Phylum ***	NR				Certain <i>Fusobacterium</i> spp. may be proinflammatory and increased on low fiber, high fat diets
Verrucomicrobia Phylum	[Bar from -50% to -25%]				<i>Akkermansia</i> spp. is involved in gut membrane integrity and may be increased with polyphenols and prebiotics

Commensal Dysbiosis Patterns

Genova's data analysis has led to the development of unique dysbiosis patterns, related to key physiologic disruptions, such as immunosuppression and inflammation. These patterns are based on the commensal bacteria and may represent dysbiotic changes that could pose clinical significance.

Inflammation-Associated Dysbiosis (IAD) Score

The Inflammation-Associated Dysbiosis score was developed from a pattern-based algorithm. When grouping patients according to their IAD scores, the group mean IAD score was negatively associated with commensal abundance and positively associated with fecal calprotectin, EPX, and slgA. The score was validated in clinical studies including Genova's database of IBD patients, and an independent UCLA study with a cohort of IBD patients.¹ More information about the IAD score can be found in the publication: <https://link.springer.com/article/10.1007/s10620-019-05828-8>

It is unknown whether inflammation-associated dysbiosis is a cause and/or an effect of inflammation. A low IAD score with elevated inflammatory markers indicates the gut microbiome may not play a role in the inflammatory condition and other etiologies should be investigated (see zone 1 pattern description below). Longitudinal studies are needed to determine the significance of a high IAD score with normal inflammatory markers. It is possible that an inflammatory microbiome pattern may precede the rise of inflammatory markers.



Methane Dysbiosis Score (Immune Suppression)

The Methane Dysbiosis score was derived from an analysis of breath methane test results that correlated with certain markers on the GI Effects stool profile. Genova's unpublished data found a unique correlation with markers indicating immune suppression (low fecal slgA and EPX) and the presence of methanogens, potentially pathogenic bacteria, bacterial overgrowth, and certain parasitic organisms. (See zones 2 and 3 below for more information.) This dysbiosis pattern is associated with immune suppression and is distinct from the IAD pattern.

It is unknown whether methane/methanogenic organisms are a cause and/or an effect of immune suppression. An elevated methane dysbiosis score may warrant treating potentially pathogenic organisms depending on the clinical picture. Additionally, intestinal barrier therapies may be helpful in supporting intestinal immune function.



Dysbiosis Pattern Zones

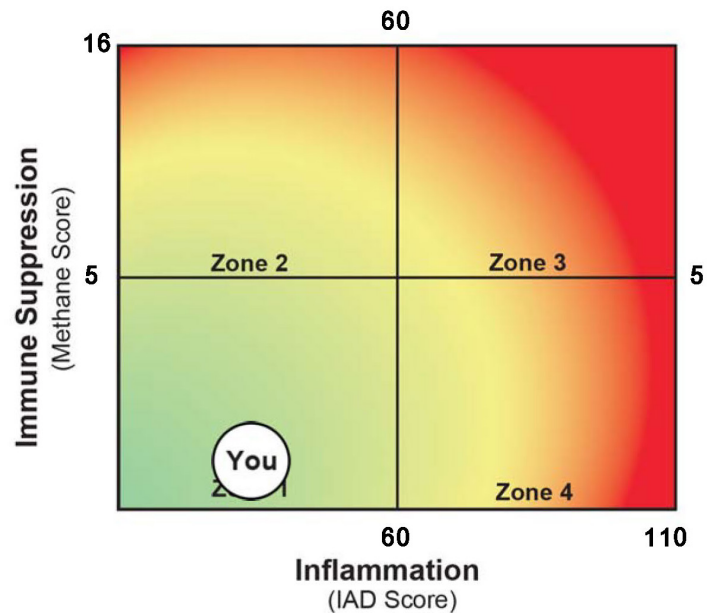
The IAD and methane scores are placed on the x- and y-axis, respectively, and certain cut points create 4 distinct zones. Each zone is associated with different clinical associations and treatment considerations.

Zone 1: The commensal profile in this zone does not align with profiles associated with intestinal inflammation or immunosuppression. Clinically, if a patient in this zone has elevated inflammatory biomarkers, other causes of intestinal inflammation other than dysbiosis need to be excluded. Other causes include infectious pathogens, food allergies and sensitivities, or more serious pathologies.

Zone 2: Profiles that demonstrate this pattern of bacteria are associated with a suppressed innate immune system (low fecal sIgA and EPX) and potentially impaired intestinal barrier function. Patients in this zone statistically have higher rates of opportunistic infections (e.g., *Blastocystis* spp. & *Dientamoeba fragilis*) as well as fecal fat malabsorption. In general, commensal abundance is high in this group suggesting potential bacterial overgrowth. Treating potentially pathogenic organisms and microbiome modulation is suggested to reduce methanogens and improve gut-barrier function.

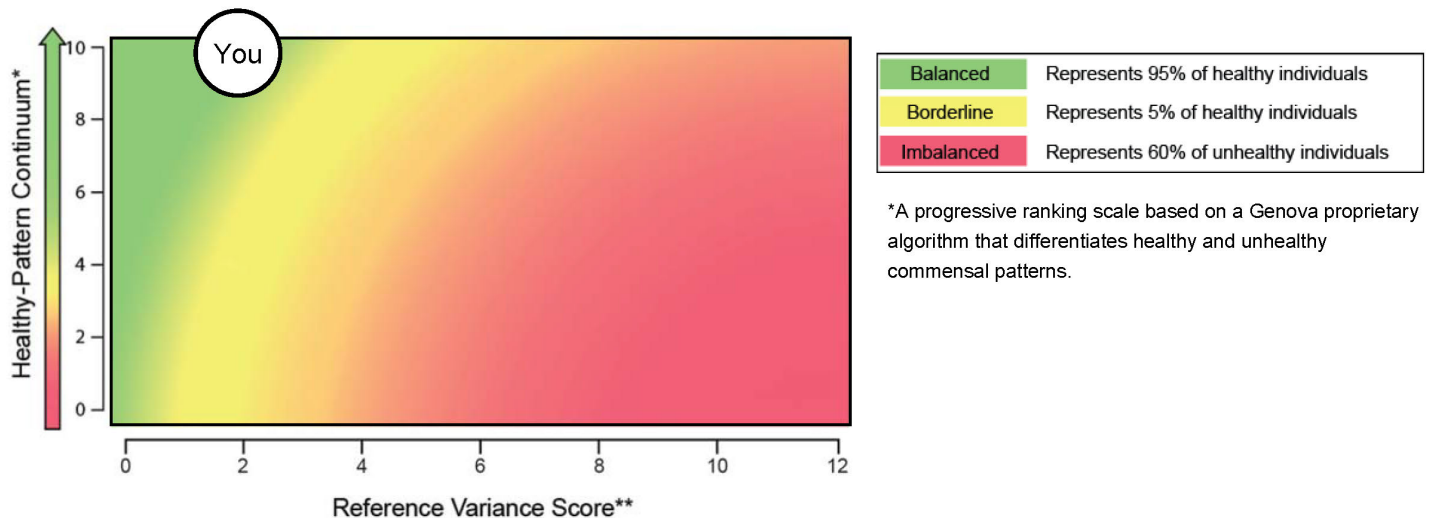
Zone 3: A small fraction of patients are found with this pattern of commensal bacteria. Patients in this zone may have more inflammation compared to those in zone 4. However, commensal abundance is usually higher making use of antimicrobial therapy relatively safer. Patients in this zone may have higher rates of pathogenic infections.

Zone 4: The commensal profile in this zone is associated with increased intestinal inflammation. Patients with IBD are more frequently found with this pattern of bacteria compared to non-IBD patients, and patients are more likely to present with diarrhea. Commensal abundance is lower in this zone and is associated with higher inflammatory biomarkers. Due to the decreased total abundance commonly seen in this group, antibiotic use for GI potential pathogens should be used with caution. In addition to standard treatment for intestinal inflammation, modulation of the commensal gut profile is encouraged.



Commensal Balance

The patient's result on the Commensal Balance infographic is denoted by a circle (You) against a color-coded gradient (green, yellow, and red). The position of the patient's result against this background provides an At-a-Glance comparison of the patient's current commensal findings against those seen in healthy and diseased cohorts. Green suggests a balanced commensal health profile, yellow suggests borderline, and red suggests an imbalance.



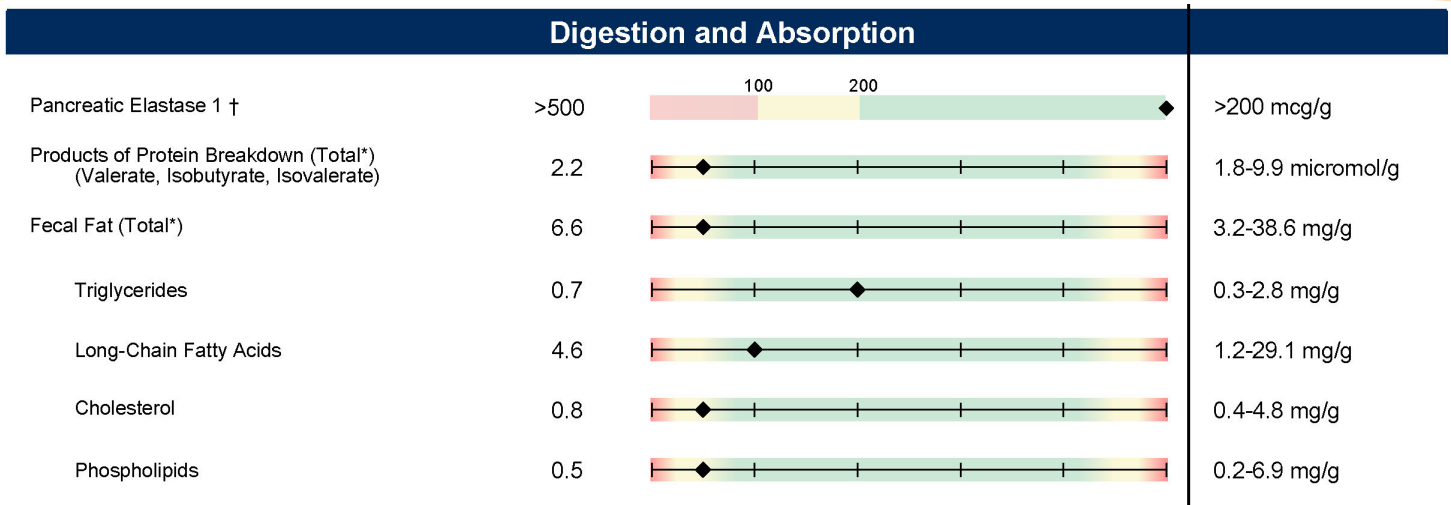
Healthy-Pattern Continuum

The Healthy-Pattern Continuum is a progressive ranking scale based on a Genova proprietary algorithm which differentiates healthy and unhealthy commensal patterns. This algorithm is applied to an individual patient's GI Effects commensal bacteria (PCR) findings and produces a numeric result ranging from 0 to 10 denoted by the 'y' axis of the Commensal Balance infographic.

Reference Variance Score

The Reference Variance Score reflects the total number of an individual patient's commensal bacteria (PCR) results that are out of reference range. This number ranges from zero to 12 and is denoted by the 'x' axis of the Commensal Balance infographic.

DIGESTION AND ABSORPTION



Pancreatic Elastase 1 (PE-1)

Pancreatic elastase 1 is a digestive enzyme secreted exclusively by the pancreas. PE-1 measurement in the stool provides insight into pancreatic exocrine function.

Biomarker Key Points

PE-1 is highly stable and is not degraded during passage through the gastrointestinal tract.² Fecal PE-1 levels are a good reflection of the pancreatic output of elastase, as well as other pancreatic enzymes, such as amylase, lipase, and trypsin.

PE-1 is not affected by transit time, though profuse watery stool samples may result in a falsely low PE-1 due to dilution.

PE-1 is not affected by pancreatic enzyme replacement therapy (PERT); therefore, it is a true reflection of pancreatic exocrine function.³ Genova utilizes the Schebo ELISA method using a monoclonal antibody which is highly specific for human PE-1. The monoclonal antibodies used in the test do not cross react with elastases of animal origin, which are contained in enzyme substitution preparations. Therefore, PE-1 should not be used to monitor PERT.

PE-1 correlates with the gold-standard test for pancreatic insufficiency, the secretin-erulean test. Additionally, low PE-1 levels correlate with gold-standard morphological tests for chronic pancreatitis, including endoscopic retrograde pancreatography (ERCP) and magnetic resonance cholangiopancreatography (MRCP).

Reference values are adopted from an FDA-cleared kit and are based on correlation with the gold-standard testing for exocrine pancreatic insufficiency (EPI) as described in the literature. Since the reference range for PE-1 was evaluated using patients with severe EPI, the fecal PE-1 test does not have a high sensitivity for mild and moderate EPI. An optimal range of PE-1 may be higher than 200µg/g. Although the sensitivity and specificity of fecal PE-1 in EPI varied among studies, in several healthy cohorts, most individuals had average values $\geq 500\mu\text{g/g}$.⁴⁻⁷

Fecal PE-1 (mcg/g)	Interpretation
>200	Normal exocrine pancreatic function
100 to 199	Mild-to-moderate exocrine pancreatic insufficiency (EPI)
<100	Severe pancreatic insufficiency

Symptoms

Exocrine pancreatic insufficiency (EPI) is a reduction of pancreatic digestive enzymes or enzyme activity leading to maldigestion and malabsorption. Clinical symptoms may not manifest until approximately 90% of pancreatic exocrine function has been lost.⁸ Some patients can have mild to moderate EPI, which may not be associated with maldigestion and/or malabsorption signs and symptoms.⁸ Signs and symptoms of EPI include:

- diarrhea
- steatorrhea
- foul-smelling stools
- bloating
- excess flatulence
- abdominal discomfort
- weight loss⁹⁻¹¹

Causes of EPI

Exocrine pancreatic insufficiency may be due to:

- Cystic Fibrosis¹²
- Chronic pancreatitis (CP)¹³
- Pancreatic resection¹⁴
- Autoimmune pancreatitis¹⁵
- Gallstones¹⁶
- Pancreatic tumor/cancer¹⁷
- GI surgery (i.e., gastric bypass, pancreatic resection)¹⁸

Other clinical factors associated with EPI through unknown mechanisms include

- Celiac disease¹⁹⁻²³
- Inflammatory Bowel Disease (IBD)²⁴
- Zollinger-Ellison syndrome^{25,26}
- Aging^{8,27}
- Excessive alcohol consumption²⁸
- Small Intestinal Bacterial Overgrowth (SIBO)^{8,29-32}
- Smoking²⁸
- Obesity³³
- Vegan/vegetarian diets³⁴
- Diabetes^{35,36}
- Infectious enteritis³⁷

Although exact mechanisms are unknown, it is thought that any condition that damages small intestine mucosa or causes villous atrophy may be associated with EPI. A damaged mucosa results in reduced enteric cholecystokinin (CCK) secretion.^{19,22,37} CCK is responsible for stimulating the exocrine pancreas as well as postprandial gallbladder

emptying.³⁸ Low pancreatic elastase levels may reflect damaged small intestine mucosa with levels normalizing when the mucosa is repaired. For example, in celiac disease, avoidance of gluten results in restoration of the mucosa and reverses pancreatic impairment.^{19,37}

Therapeutic considerations

1. Further investigation to determine the underlying cause of dysfunction (see above lists)
2. Support patients with pancreatic enzyme replacement therapy (PERT) with meals at doses appropriate for the size of the meal/snack^{10,11 39,40}
3. Consider small, frequent meals, smoking cessation, and reduced alcohol consumption^{10,11}
4. Consider SIBO testing if there is an elevated Total Abundance of commensal bacteria, high products of protein breakdown, high fecal fats, high short chain fatty acids, or high levels of *Methanobrevibacter smithii* via qPCR.

Products of Protein Breakdown

Dietary protein that is not digested or absorbed in the small intestine may be fermented by colonic bacteria to produce **products of protein breakdown**, also called putrefactive short chain fatty acids, or branched-chain fatty acids. Genova's products of protein breakdown (PPB) biomarker assesses total concentration of three short chain fatty acids (SCFAs) – valerate, isobutyrate, and isovalerate – which are bacterial fermentation protein products.

Biomarker Key Points

Human studies on the exact physiologic and pathophysiologic roles these SCFAs play are rare. Increased protein fermentation is associated with malodorous flatus, IBS, ulcerative colitis, and colorectal cancer, as shown in studies on other protein fermentation products including ammonia, phenols, and hydrogen sulfide.⁴¹ Most of our evidence-based knowledge regarding products of protein breakdown come from Genova's internal data analysis. Products of protein breakdown results should be considered in conjunction with patient lifestyle, other fecal biomarkers, as well as commensal bacteria profiles.

Bacteria ferment protein to produce putrefactive short chain fatty acids. They also ferment fiber to produce other short chain fatty acids (e.g., butyrate, acetate, and propionate). Dysbiosis can result in imbalanced levels of the short chain fatty acids.

In the literature, short chain fatty acid imbalances (from both protein and fiber fermentation) are associated with multiple conditions, including:

- Colorectal cancer⁴²⁻⁴⁴
- Depression⁴⁵
- Small Intestinal Bacterial Overgrowth (SIBO)⁴⁶
- Antibiotics⁴⁷
- Increased protein consumption⁴⁸
- Diverticulosis⁴⁹
- Celiac disease⁵⁰
- Autism⁵¹
- GI bleeding⁵²
- Chronic pancreatitis, steatorrhea⁵³
- Bariatric surgery⁵⁴

Causes of high fecal products of protein breakdown

- Exocrine pancreatic insufficiency⁵⁵
- High protein diet
- Small intestinal bacterial overgrowth (SIBO)⁵⁶
- Low gastric HCL (hypochlorhydria, acid-blocking medications)⁵⁷
- Certain types of dysbiosis
- GI bleeding and/or endogenous protein exudates associated with inflammatory and/or ulcerative conditions of the bowel^{41,52}
- Rapid transit time⁴¹

Causes of low fecal products of protein breakdown

- Very low protein diet
- Antibiotic use
- Low commensal bacteria abundance
- Intestinal inflammation

Therapeutic considerations for elevated PPB

1. Evaluate dietary protein intake

- Studies indicate that high-protein, low complex carbohydrate diets result in higher concentrations of PPB; dietary supplementation with complex carbohydrates results in a decrease in levels of PPB⁵⁸

2. Assess for, and treat, root causes of insufficient protein digestion:

- Hypochlorhydria
 - » Assess/reduce use of acid-blocking medications (as clinically indicated)
 - » Consider betaine HCl challenge (as clinically indicated)
- Exocrine pancreatic insufficiency
 - » Evaluate fecal PE1. If lower than 200 mcg/g, support with PERT as clinically indicated

3. Assess for small intestinal bacterial overgrowth and consider SIBO breath testing if any of these apply:

- Total abundance of commensal bacteria is high
- Fecal fats are elevated
- SCFAs are elevated
- *Methanobrevibacter smithii* is high via qPCR

4. Review, assess, and treat any abnormal inflammatory biomarkers or infection.

Therapeutic considerations for low PPB

1. Evaluate dietary protein intake
2. Evaluate total abundance of commensal bacteria
 - » Consider prebiotics, probiotics, and fermented foods
3. Assess inflammatory biomarkers (calprotectin, EPX, fecal sIgA) and treat causes of inflammation

Fecal Fats

Genova's fecal fat analysis evaluates multiple lipid analytes including **triglycerides (TG), long chain fatty acids (LCFAs), phospholipids, cholesterol, and total fecal fat**. Stool fecal fats are used clinically as surrogate markers for fat maldigestion and malabsorption. The total fecal fat is derived from a sum of the lipid analytes. The total fecal fat is usually dominated by the long chain fatty acid component, which has the greatest concentration among the four fats.

Because stool fat concentrations were measured without controls of fat ingestion, all test results need to be considered with a patient's diet.

Biomarker Key Points

Triglycerides (TGs) and cholesterol make up most, if not all, of our dietary fat intake. TG are broken down to form LCFAs. The fate of dietary fatty acids depends on their size. Smaller fatty acids passively diffuse through the enterocyte wall and are absorbed. LCFA absorption needs to be mediated by a transporter.

- **Triglycerides:** Increased fecal TG signifies maldigestion.^{59,60}
- **LCFAs:** Increased fecal LCFAs are often indicators of malabsorption.^{59,60}
- **Cholesterol:** Fecal cholesterol can come from different sources: diet, bile, and intestinal secretion.⁶¹ Our daily fecal cholesterol excretion may exceed cholesterol intake.⁶¹ With this, fecal cholesterol should not be used in isolation to determine maldigestion or malabsorption.
- **Phospholipids:** Fecal phospholipids can be derived from the diet, bile, shed epithelial cells, and bacterial cells. The diet is unlikely to contribute a dominant fraction to the fecal phospholipid pool. Dietary phosphatidylcholine

(PC) is generally hydrolyzed and absorbed by the small intestine. On the other hand, PC is the major phospholipid in bile, and accounts for 90% of intestinal mucus.⁶² Elevations in fecal phospholipids can be due to mucosal cell turnover, malabsorption, or bile.

Causes of fat maldigestion

1. Exocrine pancreatic insufficiency (EPI)⁶³
2. Bile salt insufficiency⁶³
3. PPI usage and hypochlorhydria⁶⁴
 - » PPI's increase the secretion of most pancreatic enzymes, but reduce the secretion of colipase.⁶⁵ Pancreatic colipase is secreted as a pro-protein and needs proteolytic enzyme activation. A deficiency in colipase production or activation can cause fat maldigestion, even when pancreatic lipase is normal or increased.
4. Small intestinal bacterial overgrowth due to:
 - » Acidic small-intestinal pH (impairment of small intestinal digestive enzymes)⁶⁴
 - » Bile acid deconjugation^{56,66}
5. Use of medications designed to impair intestinal lipase activity (Orlistat, Xenical, Alli), or use of synthetic fat-like products, indigestible by normal lipase (Olestra)⁶⁷

Causes of fat malabsorption

1. Intestinal dysbiosis and SIBO⁶⁸
2. Intestinal parasites⁶⁹
3. Gastric bypass, ileal resection, or other surgeries that limit absorptive surface area⁷⁰
4. Irritable bowel syndrome (often as a symptom of pancreatic exocrine insufficiency or bile acid malabsorption)^{63,71} – more likely with the diarrhea subtype
5. Inflammatory bowel disease⁷²
6. Celiac disease⁷³

Therapeutic considerations for elevated fecal fats

Target evaluation and treatment for common etiologies of fat maldigestion

- Pancreatic exocrine insufficiency
 - » If PE-1 is less than 200 mcg/g, consider PERT
- Small Intestinal Bacterial Overgrowth (SIBO)
 - » Consider SIBO breath testing if any of these apply:
 - › Total abundance of commensal bacteria is high
 - › Products of Protein Breakdown are elevated
 - › SCFAs are elevated
 - › *Methanobrevibacter smithii* is high via qPCR
- Hypochlorhydria
 - » Assess for acid blocking medication (PPIs) and reduce/remove if clinically indicated
 - » Consider betaine HCl challenge then treat as indicated
- Bile Salt Insufficiency
 - » Assess for causes, including liver damage and/or impaired gall bladder function
 - » Consider addition of bile salts and/or cholagogues

Target evaluation and treatment for common etiologies of fat malabsorption

- Assess and treat for infection
- Celiac Disease
 - » Consider Celiac Panel
- IBD
 - » Review calprotectin, if greater than 100 µg/g, GI referral

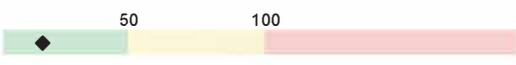


Further Evaluation

- Fat malabsorption or digestion may be associated with deficiencies in fat or fat-soluble nutrients
- Consider nutritional assessment of essential fatty acids and fat-soluble vitamins

Therapeutic considerations for low fecal fats (<3.2 mg/g)

Low fecal fats can be seen in low-fat diets. Genova's data analysis found specific associations between low fecal fats and inflammation markers. By evaluating inflammatory biomarkers (calprotectin and EPX), one may draw a distinction between lifestyle choice versus low-fat diet selection due to intestinal inflammation-related symptoms.

INFLAMMATION AND IMMUNOLOGY

Inflammation and Immunology			
Calprotectin †	<16		<=50 mcg/g
Eosinophil Protein X (EPX)†	<DL		<=2.7 mcg/g
Fecal secretory IgA	683		<=2,040 mcg/mL

Calprotectin

Calprotectin is a calcium-binding protein with antimicrobial properties.⁷⁴ It accounts for 60% of neutrophil cytosolic content and is also found in monocytes and macrophages.⁷⁵ Calprotectin is released from the intestinal mucosa into the stool in intestinal inflammation.

Biomarker Key Points

- Calprotectin is not subject to proteolytic degradation in feces.⁷⁶
- The Genova fecal calprotectin test is measured by an FDA approved ELISA assay.
- The normal range for fecal calprotectin is considered <50 mcg/g of feces.
- Dietary substances have not been found to interfere with the assay.
- Fecal calprotectin is useful in differentiating IBD from IBS and monitoring IBD treatment.⁷⁷

According to the literature, calprotectin levels can vary with age. It is higher in children younger than 5 years old due to increased intestinal mucosal permeability and differences in intestinal flora. In one study, fecal calprotectin for children between 2 to 9 years is considered normal if <166 mcg/g, in individuals between 10 and 59 years if <51 mcg/g, and after 60 years if <112 mcg/g.⁷⁸ Multiple studies have observed a normal elevation of calprotectin in pediatric individuals, however, standardized, age-stratified pediatric cut points are lacking.⁷⁹⁻⁸¹

Causes of elevated calprotectin

- Age (children younger than 5 years old, and patients greater than 60)⁸²
- IBD, not in remission⁸³
- Colorectal cancer and polyps⁸³
- Infection (bacteria and some parasitic organisms)⁸³

- Non-steroidal anti-inflammatory medication use (NSAIDs) and NSAID enteropathy⁸⁴
- Diverticular disease^{85,86}
- IBS patients may also have increased fecal calprotectin (at a much lower rate and level compared to IBD), indicating an inflammatory component to IBS (especially the diarrhea subtype). It is important to exclude IBD in patients with IBS-like symptoms when fecal calprotectin is high.^{83,87}
- Proton pump inhibitor (PPI) use is associated with elevated fecal calprotectin levels, although the cause-effect relationship is not clear.⁸⁸
- Bariatric surgery such as Roux-en-Y gastric bypass⁸⁹⁻⁹¹

Therapeutic considerations for elevated calprotectin

- Eicosapentaenoic acid (EPA) from fish oil^{92,93}

Calprotectin 50 to 100 mcg/g

Address cause of inflammation:

- Infection
- Suspected or history of IBD
- Chronic NSAID, PPI use

Recheck calprotectin in 4-6 weeks

Calprotectin >100 mcg/g

- Refer to GI specialist to rule out IBD, malignancy, or other cause of significant GI inflammation
- ***NOTE: All patients over 50 should have independent colorectal cancer screening per USPSTF recommendations. Although a normal fecal calprotectin does have a high negative predictive value for colorectal cancer, no single biomarker on the GI Effects panel is intended to exclusively rule out or to diagnose cancer.

Eosinophil Protein X (EPX)

EPX, also known as eosinophil-derived neurotoxin (EDN), is one of the four basic eosinophil granule proteins (i.e., major basic protein, eosinophil cationic protein, EPX, and eosinophil peroxidase).

Biomarker Key Points

Under steady-state conditions, the digestive tract's mucosa harbors a substantial number of eosinophils, which, if need be, are activated and exert several effector and immunoregulatory functions.⁹⁴

While small-intestinal eosinophils are anti-inflammatory, large-intestinal eosinophils, when activated, secrete proinflammatory cytokines that can aggravate colitis. Although eosinophils are present throughout the intestine, large-intestinal eosinophils are scarce in a steady state. They can dramatically increase only under intestinal inflammatory conditions.⁹⁴

Causes of EPX elevation

- Immune-mediated food hypersensitivity, atopic dermatitis, and food allergies^{95,96}
- IBD^{97,98}
- Certain parasitic infections⁹⁹
 - » According to Genova's data analysis, stool inflammatory biomarker levels were parasite specific. In general, *Giardia* and *Cryptosporidium* were associated with high calprotectin, EPX, and sIgA. Additionally, Genova's analysis showed lower EPX in patient groups positive for *Blastocystis* and *Dientamoeba fragilis*. EPX was higher in the *Cryptosporidium* group compared to a healthy cohort or parasite negative group. Due to the low incidence of intestinal worms in the U.S. population at large, Genova's data set did not allow for a conclusion as to whether EPX would be expected to be elevated with all, or only certain worm infections.
- Microscopic colitis
 - » A definitive diagnosis of microscopic colitis is only possible by histological analysis, which further classify these clinical entities as collagenous colitis (CC), lymphocytic colitis (LC), or other conditions.
 - » Elevated fecal EPX, without neutrophilic inflammation, may predict CC but not LC.¹⁰⁰

- Eosinophilic gastrointestinal disorders
 - » Eosinophilic gastroenteritis, eosinophilic esophagitis, and eosinophilic colitis make up a group of disorders called eosinophilic gastrointestinal disorders. Currently, there are no specific studies that evaluated EPX stool levels in these diseases. However, these are conditions worthy of consideration, especially when the patient is not responding to an elimination diet.
- Age (children younger than 4 years old)¹⁰¹

Therapeutic considerations for elevated EPX

Target evaluation and treatment for etiologies for EPX abnormalities

- IgE-mediated allergy (Consider IgE Food Antibody panel - If positive consider elimination diet)
- IBD (review Calprotectin level)
- Evaluate for parasitic infection

Fecal secretory IgA

As the most abundant class of antibody found in the human intestinal lumen, **secretory IgA (sIgA)** is recognized as a first line of defense in protecting the intestinal epithelium from enteric pathogens and toxins. It is used to assess gastrointestinal barrier function.

Biomarker Key Points

As part of the gut epithelial barrier, sIgA is important in the development of immune tolerance for normal, beneficial commensal gut organisms, as well as common molecular epitopes found in foods.¹⁰²⁻¹⁰⁶

Early studies of sIgA focused on immune exclusion (the prevention of pathological material and organisms from entering the general circulation). Recent studies also show sIgA plays a role in immune inclusion (delivery of commensal bacteria and their products to the gut and systemic immune system) for recognition. This leads to the development of immune tolerance. Immune inclusion spares beneficial organisms from destruction by the immune system which helps to support the immune system in a noninflammatory way to preserve local homeostasis.^{103,106}

Although secretory IgA is the major antibody in the intestinal mucosa, the prevalence of GI disorders in patients with systemic IgA deficiency is not as high as one might expect. It is thought that the transportation of IgM from the mucosa can compensate for a lack of IgA.¹⁰⁷

In people with genetic immunodeficiency of systemic sIgA, GI symptoms such as diarrhea have been reported.¹⁰⁸ Systemically IgA-deficient patients more often have airway infections since compensatory sIgM is lacking in the airways (in contrast to the gut). Adaptive sIgA responses may allow the host to respond to fluctuations in commensal bacteria to favor mucosal homeostasis.¹⁰⁹

Causes of elevated fecal sIgA

- Any defective epithelial barrier¹¹⁰⁻¹¹²
 - » A defective epithelial barrier allows bacterial and microbial penetration, which is the strongest stimulator of sIgA production.
- Celiac disease¹¹³
- Colon cancer¹¹⁴

- Infections
- IBS (especially the diarrhea subtype)

Therapeutic considerations for elevated fecal sIgA

Assess for and treat root causes of immune upregulation / inflammation:

- Infection (bacterial, parasitic, and/or viral pathogen, potential pathogen)
- Compromised intestinal barrier function (i.e., intestinal permeability)
- Heightened response to noninfectious stimuli (i.e., food sensitivity/allergy, etc.)
 - » Consider Food Antibody testing
 - › If positive, consider elimination diet

Considerations for low fecal sIgA

Because of the lack of clinical evidence, there is no clear cut-off value for low fecal sIgA.

Patients with systemic IgA deficiency can have low levels of fecal secretory IgA. There is a demonstrated link between IgA deficiency and several GI diseases, including celiac disease, giardiasis, nodular lymphoid hyperplasia, ulcerative colitis, Crohn's disease, pernicious anemia, and gastric and colonic adenocarcinoma. Low sIgA may reflect a loss of GI immune response resiliency.

Fecal sIgA may be low in severe/prolonged IBD patients due to a switch from intestinal IgA to IgG production as well as a deficiency in producing IgA dimers and polymers.¹⁰⁶

Secretory IgA demonstrates an array of activities integral to the maintenance of intestinal homeostasis. It influences the composition of intestinal microbiota, down-regulates pro-inflammatory responses normally associated with the uptake of highly pathogenic bacteria and potentially allergenic antigens, and promotes the retro-transport of antigens across the intestinal epithelium to gut-associated lymphoid tissue (GALT). Therefore, a low sIgA is clinically significant.¹⁰⁹ This test result should be considered together with the patient's medical condition, other biomarkers, and microbiome profiles when interpreting the data.

Probiotics have been shown to support sIgA levels.¹¹⁵⁻¹¹⁸

Fecal Lactoferrin

Lactoferrin is an iron-binding glycoprotein secreted by mucosal membranes as a granular component of neutrophils. It is liberated by neutrophils in response to inflammation.

Biomarker Key Points

Lactoferrin can also be found in most exocrine secretions, including breast milk, tears, nasal secretions, saliva, intestinal mucus, and genital secretions.¹¹⁹

Lactoferrin has antimicrobial properties by depriving pathogens of iron or disrupting their plasma membranes through its highly cationic charge. It also exhibits immunomodulatory activities by up- and down-regulating innate and adaptive immune cells.¹¹⁹

Genova's assessment uses an enzyme immunoassay to assess polyclonal antibodies to lactoferrin. The result is qualitative and expressed as a positive or negative finding. Subsequent calprotectin testing can provide additional useful information and assist in triage for endoscopic referral.

GASTROINTESTINAL (GI) MICROBIOME

The **GI microbiome biomarkers** provide information regarding the health, function, and diversity of the trillions of GI tract microbial cells. They indicate how well the microbiome is performing the metabolic functions that are shared with the human host.

There are several different GI microbiome stool biomarker categories on Genova's stool profiles:

Metabolic Indicators: This category includes β -glucuronidase and short chain fatty acids (butyrate, acetate, and propionate). These biomarkers reflect specific and vital metabolic functions performed by the microbiota.

Commensal Bacteria: GI Effects measures 24 commensal bacteria using real-time polymerase chain reaction (qPCR). More than 95% of commensal gut organisms are anaerobic and are difficult to recover by traditional (aerobic) culture techniques. Genova's proprietary algorithms produce dysbiosis scores as well as scores for composition and relative abundance of stool bacteria.

Bacteriology and Mycology Culture with

Sensitivities: Culture demonstrates the presence of specific live beneficial and pathogenic organisms. Sensitivities to prescriptive and natural antimicrobial agents are provided to guide therapeutic interventions when clinically indicated. Culture is the only method that accurately and reproducibly evaluates an organism's response to prescriptive and natural antimicrobial agents.

Potassium Hydroxide (KOH) Preparation: KOH prep is offered as standard on the Gut Pathogen Profile. It is an add-on to other stool profiles. This microscopic evaluation reflects all yeast regardless of viability.

Parasitology: Genova's assessment includes comprehensive testing for all parasites on every parasitology exam ordered. Microscopic ova and parasite (O&P) examination is offered on all parasitology profiles, while certain GI Effects profiles also offer qPCR detection. Six targets are chosen to detect common protozoan parasites. These include *Blastocystis* spp., *Cryptosporidium parvum/hominis*, *Cyclospora cayetanensis*, *Dientamoeba fragilis*, *Entamoeba histolytica*, and *Giardia*. qPCR for pathogenic organisms has emerged as a preferred, highly sensitive method for infectious organism detection. By utilizing multiple detection tools, Genova offers the most comprehensive parasitology examination currently available.

Macroscopic evaluation for worms is offered as standard on the Gut Pathogen Profile, and as an add-on to other stool profiles.

Microbiomix: Genova's whole genome sequencing (WGS) profile offers information about a patient's entire gut microbiome and its potential functions. Microbiomix is an add-on to the GI Effects Comprehensive profile. Metagenomics is considered the gold standard for complete microbiome assessment.¹²⁰

METABOLIC INDICATORS

Metabolic			
Short-Chain Fatty Acids (SCFA) (Total*) (Acetate, n-Butyrate, Propionate)	29.3		>=23.3 micromol/g
n-Butyrate Concentration	6.7		>=3.6 micromol/g
n-Butyrate %	22.9		11.8-33.3 %
Acetate %	59.2		48.1-69.2 %
Propionate %	18.1		<=29.3 %
Beta-glucuronidase	1,547		368-6,266 U/g

Short Chain Fatty Acids (SCFAs)

Short chain fatty acids (SCFAs) are organic acids that consist of one to six carbons, of which **acetate, propionate, and butyrate** are the most abundant ($\geq 95\%$). Acetate, propionate, and butyrate are produced by bacterial fermentation of dietary fiber and resistant starch. They can also be produced using endogenous epithelial-derived mucus by specific colonic anaerobic bacteria.^{121,122}

SCFAs function to:

1. Maintain intestinal barrier function
2. Provide fuel for colonocytes
3. Regulate colonic absorption of water, electrolytes, and nutrients
4. Salvage unabsorbed carbohydrates
5. Support commensal bacteria
6. Modulate anti-inflammatory and antimicrobial activities

Biomarker Key Points

It is important to note that fecal SCFA results may not completely reflect how much of the SCFA was produced and absorbed in the intestine. A low fecal SCFA test result can be a consequence of low production or high absorption. A high fecal SCFA test result can be a consequence of high production or low absorption.

Results are reported as total SCFA concentration, n-butyrate concentration, and n-butyrate, acetate, and propionate percentages of the total concentration. The total concentration is important to focus on, with causes of elevated or low levels outlined below. Skewed percentages of the individual SCFAs may reflect an imbalanced microbiome or diet.

Literature-Based Short Chain Fatty Acid Production		
Butyrate Producer (C4:0)	Acetate Producer (C2:0)	Propionate Producer (C3:0)
<i>F. prausnitzii</i> <i>B. crossotus</i> <i>A. colihominis</i> <i>Clostridium</i> spp. <i>C. eutactus</i> <i>Roseburia</i> spp. <i>B. uniformis</i>	<i>Prevotella</i> spp. <i>Odoribacter</i> spp. <i>A. colihominis</i> <i>Clostridium</i> spp. <i>C. eutactus</i> <i>Lactobacillus</i> spp. <i>R. bromii</i> <i>Veillonella</i> spp. <i>Bifidobacterium</i> spp. <i>A. muciniphila</i>	<i>Phocaeicola vulgatus</i> <i>Prevotella</i> spp. <i>Odoribacter</i> spp. <i>Clostridium</i> spp. <i>Veillonella</i> spp. <i>A. muciniphila</i>
Butyrate Utilizer	Acetate Utilizer	Propionate Utilizer
<i>Clostridium</i> spp.	<i>Roseburia</i> spp.	<i>Clostridium</i> spp.

SCFA production from fiber is dependent on the specific enzymes each gut bacteria possesses.¹²²

The table below lists the commensal bacteria listed on the GI Effects profile, and the type of short chain fatty acid they primarily produce, based on literature. When bacteria are imbalanced, SCFA may also be imbalanced.

Butyrate

Butyrate is the primary fuel source for colonocytes. Inadequate levels are associated with disordered colonic health.^{123,124}

Based on the literature, the three major butyrate-producers are *Faecalibacterium*, *Eubacterium*, and *Roseburia*.¹²¹

Various mixtures of dietary fibers, some types of resistant starch, fructooligosaccharides (FOS), and beta glucan are important for butyrate production.¹²⁵

Acetate

Acetate is the most abundant SCFA in the colon and makes up more than half of the total SCFAs.

Acetate has two main routes of production. The primary route is carbohydrate fermentation by enteric bacteria. Acetate is formed directly from acetyl-CoA, gets released into systemic circulation, and is taken up by the liver. It is then used as an energy source, as well as a substrate for the synthesis of cholesterol and long-chain fatty acids.¹²⁶

Acetate is recognized as a volatile signal for biofilm formation.¹²⁷

Inulin supplementation has been shown to increase acetate levels.¹²⁸ Pectin is also an important substrate for acetate production.¹²⁵

Propionate

Propionate is a minor energy source for the colonocytes, though it has anti-inflammatory effects.¹²⁹

Propionate acts as a precursor for gluconeogenesis in the liver.¹²⁶

Systemic propionate inhibits acetate incorporation into cholesterol.¹²⁸

Guar gum can support propionate levels.¹²⁵

Causes of low SCFAs

- Diarrhea (rapid transit leading to decreased SCFA production)
- Constipation (increased SCFA absorption)
- Inflammation (high calprotectin and/or high EPX/sIgA)
- Chronic antibiotic use
- Decreased carbohydrate/fiber consumption¹³⁰⁻¹³²
- Chronic illness with restricted diet (e.g., low fermentable fiber)
- Severe dysbiosis (e.g., some commensal bacteria are very high, while others are very low)

Therapeutic considerations for low SCFAs

- Dietary fiber, resistant starches (e.g., seeds and legumes, whole grains, green bananas, potatoes) and/or butyrate supplementation
- Arabinogalactans and β -glucan, as found in whole-grains¹³³
- Inulin supplementation¹²⁸
- Probiotics and fermented foods to balance the microbiome

Causes of elevated SCFAs

- Elevated commensal bacteria abundance or bacterial overgrowth¹³⁴
- High dietary intake of fiber and resistant starches

Optimal levels of SCFAs have not been established. However, in general, higher levels are considered beneficial.

Therapeutic considerations for high SCFAs

- May be optimal
- Consider SIBO testing if any of these apply
 - » Total abundance of commensal bacteria is high
 - » Products of Protein Breakdown are elevated
 - » Fecal fats are elevated
 - » *Methanobrevibacter smithii* is high via qPCR

Beta-glucuronidase

Beta-glucuronidase is an enzyme which is produced by colonocytes and by some intestinal bacteria (particularly *E. coli*, but also *Ruminococcus*, *Bacteroides*, *Eubacterium*, *Peptostreptococcus*, *Staphylococcus*, and *Clostridium*).¹³⁵

Biomarker Key Points

Beta-glucuronidase breaks down complex carbohydrates and increases the bioavailability and reabsorption of plant polyphenols (lignans, flavonoids, ceramides, and glycyrrhetic acid).¹³⁶ Beta-glucuronidase deconjugates glucuronide molecules from a variety of toxins, carcinogens, hormones (i.e., estrogens) and drugs. Deconjugation permits reabsorption via enterohepatic circulation, with the potential to elevate systemic levels of potentially harmful compounds and hormones.¹³⁵ The intestinal bacterial microbiome related to estrogen metabolism is collectively called the 'estrobolome' and is illustrated in the figure below.¹³⁷

Limited research suggests an association between elevated fecal beta-glucuronidase and cancer risk, primarily colorectal and breast cancer.¹³⁸⁻¹⁴¹

Evaluating beta-glucuronidase may be of specific interest to clinicians interested in evaluating levels of important substances such as hormones, vitamin D, and phytonutrients.

Causes of elevated beta-glucuronidase

- Dysbiosis
- Western diet, high in red meat and protein^{135,142}

Therapeutic considerations for elevated beta-glucuronidase

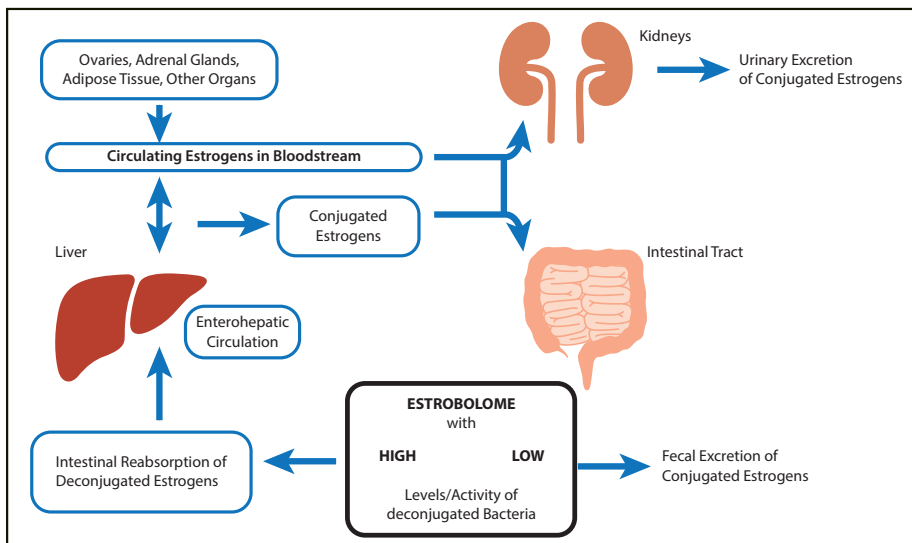
- Probiotics^{143,144}
- Dietary fiber, prebiotics¹⁴³⁻¹⁴⁶
- Calcium-D-glucarate
 - » Calcium-D-glucarate is the calcium salt of D-glucaric acid. It is found in fruits and vegetables (oranges, apples, grapefruit, and cruciferous vegetables).¹⁴⁷
 - » Oral supplementation inhibits the enzymatic activity of beta-glucuronidase.¹⁴⁷
- Milk thistle^{148,149}
- Low-calorie and vegetarian diets^{135,150}

Causes of low beta-glucuronidase

- Dysbiosis
- Antibiotic use^{151,152}

Therapeutic considerations for low beta-glucuronidase

Abnormally low levels may diminish the bioavailability of many phytonutrients. There is no literature indicating the need to treat low fecal β -glucuronidase. However, because it is produced in the intestinal endothelium and by commensal bacteria, maintaining a healthy commensal balance may be helpful to optimize levels.



COMMENSAL BACTERIA

The vast majority of microorganisms within the body reside in the colon and are called ‘**microbiota**’; their genetic components are collectively termed ‘**the microbiome**.’ The microbiome is viewed as an integral part of the body that is essential to proper organ function. The individual species in these communities were long considered “**commensal**” organisms—literally “at the same table”—with the implication that such microorganisms were neither pathogenic nor particularly harmful when in their natural site and in a proper amount.

After a child reaches 2–3 years old, a relative stability in gut microbiota composition has been demonstrated. Richness and diversity of gut microbiota shaped in early life characterize a healthy gut microbiome.¹⁵³ However, optimal healthy gut microbiota composition is different for each individual. The composition of each person’s microbiome is highly variable and can change according to age, ethnicity, location, diet, lifestyle, medications, and environmental factors.¹⁵³

Rather than concentrating on any one commensal bacteria, understanding overall microbiome patterns is essential in connecting dysbiosis to clinical symptomatology. **Genova’s GI Effects Comprehensive Stool Profile** and the **Microbial Ecology Profile** assess 24 commensal gut bacteria (at genus or species levels) using qPCR methodology.

**Please refer to the Commensal Bacteria Chart regarding these 24 measured commensal bacteria.*

The commensal gut microbiota interacts extensively with the host, influencing multiple metabolic and physiological functions, such as: ¹⁵⁴⁻¹⁵⁶

- regulating the gut’s development
- facilitating digestion
- producing SCFAs
- shaping the immune system
- preventing the growth of harmful microflora species
- synthesizing nutrients (such as B-vitamins and vitamin K)
- neutralizing toxins
- stimulating the intestinal immune system
- modulating gastrointestinal hormone production
- oxidative response
- barrier function

Metabolomics of the commensal bacteria reveal the interaction between the microbiome and its host. Commensal bacteria and SCFAs are closely related. Commensal bacteria each have differing functions. The balance of products and processes helps to establish partnerships, depending on which bacteria are in the gut. There are many literature-based associations between commensal bacteria and important bacterial fermentation end products.

The gray-shaded portion of a quintile reporting bar represents the proportion of the reference population with results below detection limit. Studies show that there are times when it is acceptable to not have an organism present in the GI tract and be considered healthy. There are thousands of bacteria in the GI tract that can perform the same metabolic function.



Gastrointestinal Microbiome (PCR)

Commensal Bacteria (PCR)	Result CFU/g stool	QUINTILE DISTRIBUTION					Reference Range CFU/g stool
		1st	2nd	3rd	4th	5th	
Bacteroidetes Phylum							
<i>Bacteroides uniformis</i>	3.5E8						<=9.5E8
<i>Phocaeicola vulgatus</i>	2.8E8						<=8.3E8
<i>Barnesiella spp.</i>	3.6E7						3.0E6-2.9E8
<i>Odoribacter spp.</i>	<DL						<=9.5E7
<i>Prevotella spp.</i>	1.2E9						6.6E7-3.8E9
Firmicutes Phylum							
<i>Anaerotruncus colihominis/massiliensis</i>	1.6E7						<=2.0E7
<i>Butyrivibrio crossotus</i>	<DL						<=3.3E7
<i>Clostridium spp.</i>	<DL						<=1.5E7
<i>Coproccoccus eutactus</i>	<DL						<=1.2E8
<i>Faecalibacterium prausnitzii</i>	2.4E8						1.1E6-1.1E9
<i>Lactobacillus spp.</i>	5.6E3						<=1.6E6
<i>Pseudoflavonifractor spp.</i>	1.4E6						1.3E4-2.9E7
<i>Roseburia spp.</i>	7.4E7						3.6E5-4.6E8
<i>Ruminococcus bromii</i>	4.6E8						<=1.5E9
<i>Veillonella spp.</i>	4.6E5						<=4.1E6
Actinobacteria Phylum							
<i>Bifidobacterium spp.</i>	5.0E7						4.6E5-2.6E8
<i>Bifidobacterium longum subsp. longum</i>	<DL						<=1.3E8
<i>Collinsella aerofaciens</i>	<DL						<=1.3E8
Proteobacteria Phylum							
<i>Desulfovibrio piger</i>	<DL						<=5.4E7
<i>Escherichia coli</i>	2.1E4						<=7.5E6
<i>Oxalobacter formigenes</i>	<DL						<=1.1E7
Euryarchaeota Phylum							
<i>Methanobrevibacter smithii</i>	<DL						<=2.0E7
Fusobacteria Phylum							
<i>Fusobacterium spp.</i>	<DL						<=1.8E5
Verrucomicrobia Phylum							
<i>Akkermansia muciniphila</i>	5.9E5						>=8.5E3

The gray-shaded portion of a quintile reporting bar represents the proportion of the reference population with results below detection limit.

Commensal results and reference range values are displayed in a computer version of scientific notation, where the capital letter "E" indicates the exponent value (e.g., 7.3E6 equates to 7.3 x 10⁶ or 7,300,000).

The methodology for the PCR Commensal Bacteria has been updated to qPCR. The reference ranges have been updated accordingly.

The names of some of the bacteria have been updated as a result of taxonomy changes and method improvements.

<p>Butyrate Producer (C4:0) Increases with fermentation of starch and inulin-type fructans.¹⁵⁷</p>	<p>Acetate Producer (C2:0) Acetate is produced by most enteric bacteria from carbohydrate fermentation. One-third of acetate comes from acetogenic bacteria, which synthesize acetate from hydrogen and carbon dioxide or formic acid.¹²¹</p>	<p>Propionate Producer (C3:0) Increases with fermentation of oat bran and β-glucan, pectin, pulses, wheat dextrin, and pyrodextrins.¹⁵⁷</p>
<p><i>F. prausnitzii</i> <i>B. crossotus</i> <i>A. colihominis</i> <i>Clostridium</i> spp. <i>C. eutactus</i> <i>Roseburia</i> spp. <i>B. uniformis</i></p>	<p><i>Prevotella</i> spp. <i>Odoribacter</i> spp. <i>A. colihominis</i> <i>Clostridium</i> spp. <i>C. eutactus</i> <i>Lactobacillus</i> spp. <i>Ruminococcus bromii</i> <i>Veillonella</i> spp. <i>Bifidobacterium</i> spp. <i>A. muciniphila</i></p>	<p><i>P. vulgatus</i> <i>Prevotella</i> spp. <i>Odoribacter</i> spp. <i>Clostridium</i> spp. <i>Veillonella</i> spp. <i>A. muciniphila</i></p>
<p>Lactate Producer Higher concentrations of lactate have been noted in IBD. Lactate is converted to acetate, butyrate, and propionate, generally at a higher pH, and there may be reduced conversion and lactate accumulation at a lower pH.¹⁵⁸</p>	<p>H₂-producing (hydrogenogenic) H₂ is a primary by-product of human microbiota biology. Endogenous H₂ is either passed in flatus or absorbed into the circulation and released by respiration. New research is evaluating it as an anti-inflammatory biomolecule that safeguards against tissue injury.¹⁵⁹ H₂ is used by intestinal bacterial methanogens, acetogens, and SRB.</p>	<p>Sulfate reducing bacteria (SRB) H₂S Producer: AA metabolism utilizes sulfate (SO₄²⁻) and reduces it to hydrogen sulfide (H₂S). SRB are part of a normal gut microbiota, though increased levels may contribute to disease. Excess is not absorbed and is available for rapid exogenous H₂S production by the SRB.^{160,161}</p>
<p><i>P. vulgatus</i> <i>B. crossotus</i> <i>Lactobacillus</i> spp. <i>Bifidobacterium</i> spp. <i>B. longum</i></p>	<p><i>Odoribacter</i> spp. <i>Clostridium</i> spp. <i>R. bromii</i> <i>E. coli</i></p>	<p><i>Odoribacter</i> spp. <i>D. piger</i></p>
<p>Degrades Lactate Lactate-Utilizing Bacteria (LUB) metabolize lactate to form different end-products. The balance between H₂-producing and H₂-utilizing LUB might contribute to colic symptoms.¹⁶²</p>	<p>H₂-using (hydrogenotrophic) H₂ consumers include reductive acetogens, methanogenic archaea, and sulfate-reducing bacteria [SRB].</p>	<p>Methane Producer – Methanogens Methane producers produce methane by utilizing hydrogen and carbon dioxide. Approximately 30% to 62% of individuals harbor methane-producing bacteria.¹⁶³</p>
<p><i>Roseburia</i> spp. <i>Veillonella</i> spp.</p>	<p><i>D. piger</i> <i>M. smithii</i></p>	<p><i>M. smithii</i></p>

Dysbiosis

The term '**dysbiosis**' is often used to describe altered microbiome patterns as compared to a healthy cohort.¹⁶⁴ Others define dysbiosis as the changes in gut microbiota composition associated with disease.¹⁶⁵ Genova's data analysis reveals that dysbiosis and commensal microbial patterns may contribute to, and be a root cause of, many clinical conditions. In Genova's data analysis, statistically significant correlations were found between commensal bacteria and self-reported clinical conditions such as inflammatory bowel disease, metabolic syndrome, chronic fatigue, autoimmune dysfunction, type 2 diabetes mellitus, high blood pressure, mood disorder, and ROME III criteria irritable bowel syndrome.

Dysbiosis can result from medication use (antibiotics, PPIs, etc.), stress, alcohol, disruption in circadian rhythms, and poor diet.¹⁶⁶⁻¹⁷⁰

On the **GI Effects Comprehensive Profile**, the Commensal Microbiome Analysis section assesses dysbiosis. These graphics were outlined previously.





Therapeutic considerations

Therapeutic interventions, such as dietary macronutrient content, fiber supplementation, prebiotics, probiotics, symbiotics, lifestyle modification, and the environment have been shown to modulate the individual microbiome.^{171,172}

BACTERIOLOGY AND MYCOLOGY CULTURE WITH SENSITIVITIES

Traditional culture complements DNA-based testing by providing a more complete survey of a patient's gut microbiota beyond the specific organisms targeted by qPCR. Culture methods have established clinical utility and are recognized as the 'gold standard' in traditional clinical diagnostics. Culture is necessary to determine therapeutic interventions, such as sensitivities to pharmaceutical or botanical antimicrobial agents.

Bacteriology and mycology culture results are reported as 'No Growth' (NG) or growth using quantification (1+, 2+, 3+ 4+) and a color-coding system: Non-pathogen (NP) in green, potential pathogen (PP) in yellow, or known Pathogen (P) in red.

Microbiology Legend			
NG	NP	PP	P
			
No Growth	Non-Pathogen	Potential Pathogen	Pathogen

Non-pathogens are normal, commensal flora which have not been recognized as disease-causing. Potential pathogens are considered opportunistic organisms capable of causing symptoms. Pathogens are organisms which are well-recognized in literature to cause disease regardless of the quantity. Since the human microflora is influenced by many factors, pathogenic significance should be based on the patient's clinical presentation.

Beneficial Bacteria Culture

Lactobacillus, *Escherichia coli*, and *Bifidobacterium* are cultured to offer a more complete microbiome assessment. They are also measured via qPCR for quantification.

Lactobacillus, *Escherichia coli*, and *Bifidobacterium* are known to exert positive local and systemic effects in the microbiome.¹⁷³⁻¹⁷⁶

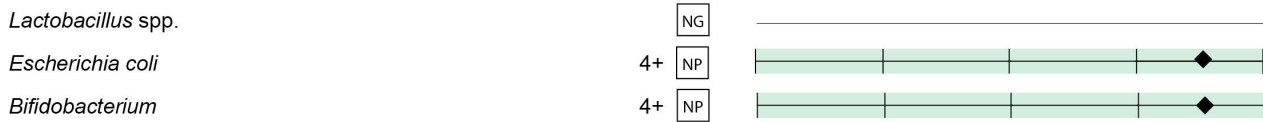
Lower levels of these beneficial bacteria have been associated with disease.^{177,178}

Additional Bacteria and Mycology Culture

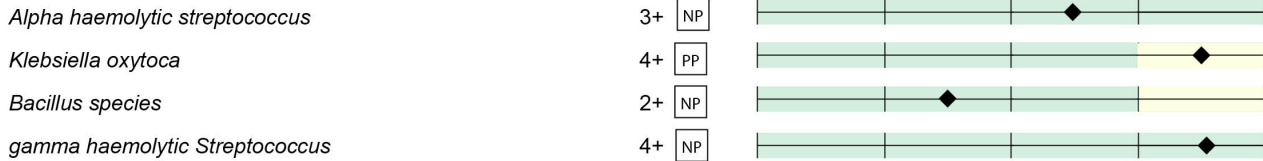
Any aerobic bacteria or yeast that is grown in culture will be identified using matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF) and a Vitek-MS library. Vitek-MS using MALDI-TOF relies on the most extensive FDA-cleared library of microbial targets available on the market, which can accurately identify approximately 200 different additional bacteria and yeast. It should be noted that the technology can identify a limitless number of organisms. Any organism identified will be reported.

Gastrointestinal Microbiome

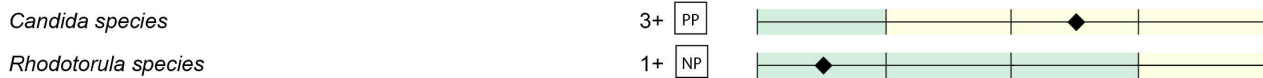
Bacteriology (Culture)



Additional Bacteria



Mycology (Culture)



**Please refer to the Pathogenic Bacteria and Yeast Chart regarding specific pathogenic or potentially pathogenic bacteria and yeast.*

Antimicrobial sensitivities to both pharmaceutical and botanical agents are automatically offered for any pathogenic or potentially pathogenic organism to help guide therapy. The decision to treat should be based on the patient's clinical presentation and symptoms.

Prescriptive Agents

<i>Klebsiella oxytoca</i>	R	I	S-DD	S	NI
Ampicillin	R				
Amox./Clavulanic Acid				S	
Cephalothin				S	
Ciprofloxacin				S	
Tetracycline				S	
Trimethoprim/Sulfa				S	

Natural Agents

<i>Klebsiella oxytoca</i>	LOW INHIBITION	HIGH INHIBITION
Berberine		
Oregano		
Uva Ursi		

For prescriptive agents, an 'R' for resistant or 'S' for sensitive will be placed in the appropriate column:

R – (Resistant) category implies the isolated organism is not inhibited by that prescriptive agent.

I – (Intermediate) category includes isolates which have minimum inhibitory concentration (MIC) values that are obtainable but may be lower than for susceptible isolates.

S-DD (Susceptible- Dose Dependent) category implies better clinical efficacy when a higher-than-normal drug dosage is used to achieve maximal concentration.

S – (Susceptible) column implies that the isolated organism is inhibited by the prescriptive agent.

NI – (No Interpretive Guidelines Established) category is used for organisms that currently do not have established guidelines for MIC interpretation. Any numerical value placed in this column signifies some inhibition.

For natural agents, inhibition levels indicate how effective the substance was at limiting the organism's growth in vitro. Higher inhibition reflects a greater ability by the substance to limit growth.

The decision to treat any pathogen or potential pathogen should be based on the patient's clinical presentation.

Potassium Hydroxide (KOH) Prep for Yeast

Potassium hydroxide (KOH) is a strong alkali used to clear cellular material and better visualize fungal elements. Results are reported as the amount of yeast detected microscopically:

- **Rare:** 1-2 per slide
- **Few:** 2-5 per high power field (HPF)
- **Moderate:** 5-10 per HPF
- **Many:** >10 per HPF

These yeasts usually represent the organisms isolated by culture. In the presence of a negative yeast culture, microscopic yeast reflects organisms not viable enough to grow in culture. The presence of yeast on the KOH prep should be correlated with the patient's symptoms. However, moderate yeast suggests overgrowth.

Pathogenic Bacteria EIA Testing

The utility of pathogenic bacteria EIA testing is best placed in the context of appropriate differential diagnosis. Clinicians should consider a patient's symptoms and establish a high index of suspicion for a clinically known syndrome or symptom complex. Testing of non-symptomatic patients is not recommended.

**Please refer to the Pathogenic Bacteria and Yeast Chart regarding specific pathogenic or potentially pathogenic bacteria and yeast.*

- ***Clostridium difficile* (Toxin A/B)**

- » *C. difficile* is an opportunistic anaerobic bacterium which causes symptoms ranging from mild diarrhea to pseudomembranous colitis when the normal flora has been altered (as in antibiotic use).
- » *C. difficile* produces two toxins. Toxin A is a tissue-damaging enterotoxin, while toxin B is referred to as a cytotoxin.
- » A prerequisite for *C. difficile* EIA toxin testing is a stool consistency of 7 on the Bristol stool scale, whereby the samples take the shape of the container.
- » Genova's EIA kit measures antibodies to both toxin A and B. Clinical relevance is determined by the presence of toxin A/B. When these toxins are present, correlation with patient symptoms is recommended.

- **Shiga toxin *E. coli***

- » Most *E. coli* harmlessly colonize the GI tract as normal flora. However, some have acquired virulence factors such as Shiga toxin.
- » Shiga toxin *E. coli* symptoms include bloody diarrhea, vomiting, and can progress to hemolytic uremic syndrome (HUS).
- » All enterohemorrhagic *E. coli* (EHEC) can produce Shiga toxin (ST). ST-1 and ST-2 are the most common and EHEC can produce both or either. Therefore, ST detection is a better diagnostic strategy than serotype in the determination of EHEC associated disease.
- » Genova's enzyme immunoassay measures monoclonal anti-Shiga toxin antibodies.

- ***Campylobacter* spp.**

- » *Campylobacter* is bacterial pathogen associated with a wide range of symptoms and gastrointestinal conditions. It can cause watery or bloody diarrhea, fever, nausea, and abdominal pain. It is also associated with IBD, Barrett's esophagus, colorectal cancer, and reactive arthritis.¹⁷⁹
- » Genova's enzyme immunoassay measures a *Campylobacter*-specific antigen.

- ***Helicobacter pylori***

- » *H. pylori* is an important cause of peptic ulcer disease (PUD) and gastric cancer. It may also have a role in functional dyspepsia, ulcer risk in patients taking low-dose aspirin or starting NSAID therapy, unexplained iron deficiency anemia, and idiopathic thrombocytopenic purpura (ITP).
- » According to the American College of Gastroenterology, the indications to test for *H. pylori* infection include active PUD, a history of PUD, low-grade mucosa-associated lymphoid tissue (MALT) lymphoma, or endoscopic early gastric cancer. Patients initiating chronic aspirin or NSAID treatment, those with unexplained iron deficiency anemia, and patients with ITP should be tested.¹⁸⁰
- » Patients with typical GERD symptoms without a history of PUD, need not be tested for *H. pylori*; however, those who are tested and found to be infected should be treated.¹⁸⁰
- » Genova uses an enzyme-immunoassay platform that utilizes antibodies to detect *H. pylori* antigen present in the stool sample.

PARASITOLOGY

Currently, there is not one methodology that provides a complete examination for all parasites. The most effective approach is to provide a combination of methodologies to account for varying sensitivities and specificities for all parasitic organisms. Utilizing a single technology cannot fully capture the complex dynamics of the microbiome. Genova's stool profiles offer the most comprehensive parasitology assessment available including:

- **Microscopic ova and parasites (O&P)**
- **qPCR for 6 protozoan targets**
- **Macroscopic examination for worms**

When clinical suspicion for a parasitic infection is high, a three-day sample collection is recommended. This traditional recommendation in textbooks and lab manuals to collect at least three samples has been challenged, to reduce cost and improve patient ease of use.¹⁸¹⁻¹⁸³ Many intestinal protozoa irregularly shed. Data suggests that a single stool specimen submitted for microscopic examination will detect 58 to 72% of protozoa present. The three specimen evaluation increases the yield by 22.7% for *E. histolytica*, 11.3% for *Giardia*, and 31.1% for *D. fragilis*.¹⁸⁴ However, older studies demonstrated that in at least 90% of cases, examination of only one stool sample was sufficient to detect an enteric parasite.¹⁸¹

Purge testing refers to the administration of a laxative prior to sample collection, with the assumption that parasite recovery will be enhanced. Genova has not noted any significant difference in parasite recovery when comparing purged with non-purged specimens. Therefore, it is not necessary to purge prior to specimen collection.

**Please refer to the Parasitic Organisms Chart regarding specific pathogenic or potentially pathogenic parasites.*

Microscopic Ova & Parasites (O&P)

Microscopic examination of stool specimens for ova and parasites (O&P) is considered the gold-standard stool parasite testing methodology for traditional laboratories.

Factors that influence the sensitivity of microscopic parasite examinations include the specimen collection interval, patient medications, and stool preservation prior to testing.¹⁸⁴

The organism's correct identification is subjective, and highly dependent on the technician's training and experience. Genova's microbiology staff is highly trained and employs technicians with decades of experience. Based on Genova's proficiency test scores, our sensitivity (detecting a parasite present) is >97%, and our accuracy (correctly identifying it) is >98%.

While the O&P exam can detect all parasites, some parasites are more difficult to detect due to their small size, irregular shedding schedules, etc. Additional testing methods are recommended to enhance sensitivity, such as qPCR.

A negative O&P microscopy result is reported as "Not Detected." A positive finding is reported as the amount of that organism (rare, few, moderate, many), followed by the organism's morphology characteristics (trophozoites, cysts, ova.)

- **Rare: 1-2 per slide**
- **Few: 1-2 per high powered field (HPF)**
- **Moderate: 2-5 per HPF**
- **Many: >5 per HPF**

Parasitology

Microscopic O&P Results

Microscopic O&P is capable of detecting all described gastrointestinal parasites. The organisms listed in the box represent those commonly found in microscopic stool analysis. Should an organism be detected that is not included in the list below, it will be reported in the Additional Results section. These results were obtained using wet preparation(s) and trichrome stained smear. For an extensive reference of all potentially detectable organisms, please visit www.gdx.net/product/gi-effects-comprehensive-stool-test

Genus/species	Result
Nematodes - roundworms	
<i>Ancylostoma/Necator</i> (Hookworm)	Not Detected
<i>Ascaris lumbricoides</i>	Not Detected
<i>Capillaria philippinensis</i>	Not Detected
<i>Enterobius vermicularis</i>	Not Detected
<i>Strongyloides stercoralis</i>	Not Detected
<i>Trichuris trichiura</i>	Not Detected
Cestodes - tapeworms	
<i>Diphyllobothrium latum</i>	Not Detected
<i>Dipylidium caninum</i>	Not Detected
<i>Hymenolepis diminuta</i>	Not Detected
<i>Hymenolepis nana</i>	Not Detected
<i>Taenia</i> spp.	Not Detected
Trematodes - flukes	
<i>Clonorchis/Opisthorchis</i> spp.	Not Detected
<i>Fasciola</i> spp./ <i>Fasciolopsis buski</i>	Not Detected
<i>Heterophyes/Metagonimus</i>	Not Detected
<i>Paragonimus</i> spp.	Not Detected
<i>Schistosoma</i> spp.	Not Detected
Protozoa	
<i>Balantidium coli</i>	Not Detected
<i>Blastocystis</i> spp.	Many Detected
<i>Chilomastix mesnili</i>	Not Detected
<i>Cryptosporidium</i> spp.	Not Detected
<i>Cyclospora cayetanensis</i>	Not Detected
<i>Dientamoeba fragilis</i>	Not Detected
<i>Entamoeba coli</i>	Not Detected
<i>Entamoeba histolytica/dispar</i>	Not Detected
<i>Entamoeba hartmanii</i>	Not Detected
<i>Entamoeba polecki</i>	Not Detected
<i>Endolimax nana</i>	Not Detected
<i>Giardia</i>	Not Detected
<i>Iodamoeba buetschlii</i>	Not Detected
<i>Cystoisospora</i> spp.	Not Detected
<i>Trichomonads</i> (e.g. <i>Pentatrichomonas</i>)	Not Detected
Additional Findings	
White Blood Cells	Not Detected
Charcot-Leyden Crystals	Not Detected
Other Infectious Findings	

Other Microscopic Findings

Charcot-Leyden crystals may be seen under the microscope. This is an eosinophil breakdown product and is present in patients with tissue-invading parasites and allergic conditions.^{185,186} They are observed more commonly in the sputum of asthmatics, but are rarely found in the stool.¹⁸⁷ Studies show that Charcot-Leyden crystals can be present with *E. histolytica* and *Blastocystis* infections.¹⁸⁸ Allergy assessment may be warranted in symptomatic patients that do not have a parasite and may include ordering a serum IgE allergy

panel. While rare, Charcot-Leyden crystals may indicate eosinophilic gastroenteritis which requires evaluation with endoscopy.^{187,189}

White blood cells (WBC) indicate an immune response that can be seen in infectious conditions or inflammatory bowel disease (IBD).

Red blood cells (RBC) indicate blood in the stool. RBCs can be seen with bleeding hemorrhoids or menstrual blood, as well as serious conditions such as malignancy or IBD. If a serious condition is suspected, a follow-up fecal occult blood test

or colonoscopy is recommended. *Entamoeba histolytica* can engulf RBCs which can distinguish the pathogenic *E. histolytica* from the non-pathogenic *E. dispar*.¹⁹⁰

Vegetable and meat fibers are undigested food particles that are sometimes seen microscopically or macroscopically. They may indicate maldigestion and/or malabsorption. Correlation with symptoms and other biomarkers of maldigestion/malabsorption is recommended. Biomarkers of maldigestion and malabsorption include pancreatic elastase 1, products of protein breakdown, and fecal fats.

Polymerase Chain Reaction (qPCR)

qPCR is a method that utilizes probes targeting specific DNA segments, which allow identification of specific organisms. It is sometimes called “molecular photocopying” since small DNA segments are amplified, or copied.¹⁹¹

Genova’s 6 parasite targets include *Cryptosporidium parvum/hominis*, *Entamoeba histolytica*, *Giardia*, *Blastocystis* spp., *Cyclospora cayetanensis*, and *Dientamoeba fragilis*. They are assessed via real-time PCR (also known as quantitative PCR, or qPCR.)

Certain organisms are difficult to recover or visualize microscopically. PCR offers enhanced sensitivity. This is especially important for those organisms that present a public health concern, such as *Entamoeba histolytica*, *Cyclospora cayetanensis* or *Cryptosporidium parvum/hominis*.

Until all potential human parasitic pathogens are included in molecular panels, PCR will remain highly sensitive but will fail to detect the scope of possible pathogens that can be found via an O&P microscopic exam.¹⁹²

The PCR results for the 6 organisms are reported as detected or not detected.

Positive PCR, negative microscopy

A positive PCR means the organism’s DNA was detected, but the organism itself could not be found or visualized under the microscope. In the case of irregular organism shedding, it can be difficult to detect an organism microscopically. Additionally, parasite DNA may be detected regardless of organism viability; it is possible the organism was dead upon transmission. Correlation with symptoms is always recommended regardless of any test findings. The clinical effect of nonviable parasite DNA passing through the host organism is not known.

Parasitology				
PCR Parasitology - Protozoa				Methodologies: DNA by PCR
Organism	Result	Units		Expected Result
<i>Blastocystis</i> spp.	<2.14e2	femtograms/microliter C&S stool	Detected	Not Detected
<i>Cryptosporidium parvum/hominis</i>	<1.76e2	genome copies/microliter C&S stool	Not Detected	Not Detected
<i>Cyclospora cayetanensis</i>	<2.65e2	genome copies/microliter C&S stool	Not Detected	Not Detected
<i>Dientamoeba fragilis</i>	<1.84e2	genome copies/microliter C&S stool	Not Detected	Not Detected
<i>Entamoeba histolytica</i>	<9.64e1	genome copies/microliter C&S stool	Not Detected	Not Detected
<i>Giardia</i>	<1.36e1	genome copies/microliter C&S stool	Not Detected	Not Detected

Negative PCR, positive microscopy

Possible reasons for this finding include sample mishandling, interfering substances, PCR assay step failure, or misidentification on microscopic exam. Additionally, the PCR testing is performed on the third-day vial, while microscopy is performed using a homogenized sample mixing all three days of stool. If a parasite intermittently sheds, it may be possible to miss in PCR since only one stool sample is tested.

Additionally, approximately 15% of samples submitted for parasite detection via PCR will demonstrate inhibition of the PCR reaction. This inhibition rate can be due to many factors, such as medications, excessive unrelated DNA, and other constituent stool factors. With dilution of the extracted DNA, the rate of reaction inhibition can be cut in half. This has been documented in peer reviewed literature as well as studies supporting FDA approval of these commercial assays. Genova's internal data review and external validation studies have confirmed a similar inhibition rate for our laboratory developed assay. Genova performs sample dilution to lower the percentage of inhibition, however, for those samples continuing to exhibit inhibition we will not report results. This is because further dilution will adversely impact the limit of detection and may result in false negatives. Additionally, Genova will not increase the number of amplification cycles to compensate for the reduced sensitivity due to dilution. This approach may result in amplification of artifact and thus generate false positives.

With any laboratory-developed test, it is critical that there be agreement with a proven, clinically valid FDA method. PCR parasitology should always be validated by comparison to proven standards, such as enzyme-linked immunoassay or microscopic ova and parasite methods.

Genova combines microscopic parasite detection with PCR for relevant parasites. This multi-pronged approach results in a comprehensive, highly sensitive, and highly specific assessment of parasite infection. It also helps mitigate the impact of sporadic shedding, rare parasite presence and PCR inhibition that can adversely impact the results given when using a single technology.

This PCR assay inhibition is rarely seen when reporting results for commensal bacterial DNA. This is due to the much higher concentration of these bacteria relative to the low levels of parasites in stool specimens. Thus, dilution of these samples can overcome inhibition of the PCR reaction but not at the expense of the detection limit of the assay.

Macroscopic Examination for Worms

Most nematodes (roundworms), trematodes (flukes), and cestodes (tapeworms) to a lesser degree, are primarily diagnosed by ova in the stool during the microscopic O&P exam.

The technician performs a gross examination of the entire specimen to look for macroscopic evidence of proglottids (tapeworm segments) or whole worms prior to doing the microscopic examination.

If a patient sees worms in the stool, they should remove the worm from the stool and place it in the vial clean of any stool, or in a separate container for transport to the lab.

While pinworm eggs can be seen in a stool sample submitted for O&P exam, there is often a low yield. The best way to diagnose pinworms is the “tape test,” or “Scotch tape test.”

Therapeutic considerations for Parasitology

**Please refer to the Parasitic Organisms Chart regarding specific pathogenic or potentially pathogenic parasites.*

Correct identification of the organism allows the clinician to choose appropriate treatment protocols aimed toward infection resolution. Treatment should be patient specific.

Genova is unable to provide sensitivities for parasitic organisms. The collection vial contains a fixative/preservative such that the organism arrives dead. Only live organisms can be cultured for sensitivities.

Intestinal parasites are spread via soil, food, water, and surfaces that are contaminated with feces from infected humans or animals.¹⁹³ Optimizing personal and community hygiene, in addition to sanitary measures to prevent contamination with fecal material, are essential (i.e. hand washing, washing and peeling raw vegetables and fruit, avoiding unboiled tap water when traveling).^{192,194}

The following resources provide valuable insight into the practical, clinical management of parasitic infections:

- **The Sanford Guide to Antimicrobial Therapy**
- **Centers for Disease Control** – monographs on individual parasites <https://www.cdc.gov/dpdx/>
- **World Health Organization** – maps showing geographic prevalence <http://www.who.int/>
- **American Journal of Gastroenterology** 2018 article “Beyond O&P Times Three.” This article outlines multiple organisms, their symptomatology, and differential diagnoses, and discusses testing and management.¹⁸³
- Garcia, et al. 2018 article “Laboratory Diagnosis of Parasites from the Gastrointestinal Tract.” This is an 81-page guide on lab diagnosis, versus clinical features.¹⁸⁵
- **CDC hotline** for healthcare providers with questions regarding parasites:
 - » Parasitic Diseases Hotline (M-F; 8am-4pm EST) 404-718-4745
 - » Emergency, after-hours hotline 770-488-7100

Generally, symptom resolution does not warrant follow-up testing.¹⁹⁵ Retesting PCR should not be used to document cure.^{196,197}

Additional Tests

Several additional tests have long been used in the analysis of stool. These include stool color and consistency, as well as the presence or absence of occult blood.

Color: Stool color is primarily associated with diet and medication use, though it may indicate various GI health conditions.

Consistency: Stool consistency may vary from hard to watery. This is self-reported by the patients upon submission of the stool sample. The technical ability to measure diagnostic biomarkers from stool may be influenced by consistency extremes.

Occult Blood

The term '**occult blood**' simply means blood that is not evident to the naked eye and present in microscopic quantities only. Genova uses the Hemosure diagnostic kit to measure occult blood.

The Hemosure diagnostic kit uses fecal immunochemical testing (FIT). It has higher specificity than common guaiac testing because of its use of mono- and polyclonal antibodies specific to human hemoglobin.

FIT-based diagnostics have been recommended by the American College of Gastroenterology as the preferred test for colorectal cancer screening/detection.

Zonulin Family Peptide

Intestinal barrier transport is mainly regulated by structures of the paracellular pathway called tight junctions, which form barriers between epithelial cells and regulate the transport of ions and small molecules across the intestinal lumen. **Zonulin** has been identified as a tight junction regulating protein.

Biomarker Key Points

In this assessment, Genova uses a kit from the manufacturer Immundiagnostik (IDK). A research paper published in *Frontiers in Endocrinology* by Scheffler et.al. suggested that the zonulin kits from IDK do not detect zonulin (a precursor of haptoglobin 2). This issue was further confirmed by the kit manufacturer in a statement released to clinical laboratories.¹⁹⁸

To the best of Genova's knowledge, the Scheffler paper has impacted the zonulin assay across the United States, including Genova's stool zonulin test. Because some researchers are conducting studies and have received data from the current zonulin kits, Genova has decided to provide the test for research use only with the manufacturer's suggested name: "zonulin family peptide."

The Scheffler paper suggests that the kits may detect properdin, a protein involved in the alternative complement pathway and inflammation. Preliminary study results from an external investigator suggest that properdin may be structurally and functionally similar to zonulin. Another study confirmed that zonulin was not detected, but possibly complement C3, which plays a role in the modulation of intestinal epithelial barrier integrity. The structural similarity of these proteins makes identification challenging.¹⁹⁹

Several papers have been published using the IDK kit and clinical associations range from metabolic and liver diseases to mood disorders. The majority of studies have focused on serum concentrations.

Genova's unpublished data analysis (of 13,613 tests) demonstrated that the test results of the current stool zonulin kit (now called zonulin family peptide) were strongly and positively associated with stool EPX and sIgA (but not calprotectin). Levels of zonulin family peptide detected by this kit were also associated with a commensal bacterial profile related to intestinal inflammation. In addition, they were also positively associated with stool biomarkers such as fecal PE-1 and cholesterol. Some biomarkers, such as stool fat and short-chain fatty acids, showed "bell-shaped" distributions. High or low levels of the zonulin family peptide were associated with low levels of stool fat and short-chain fatty acids.

Therapeutic considerations for zonulin family peptide

- The clinical significance of an elevated zonulin family peptide is unknown. It may relate to increased intestinal permeability and results should be confirmed with a follow up lactulose/mannitol **Intestinal Permeability Assessment**. Studies on athletes show a reduction in stool zonulin family peptide levels with colostrum and probiotics.^{200,201}
- A normal or low zonulin family peptide finding does not necessarily rule out intestinal permeability. A follow up lactulose/mannitol Intestinal Permeability Assessment should be considered if intestinal permeability is suspected.

REFERENCES

1. Chen L, Reynolds C, David R, Peace Brewer A. Development of an Index Score for Intestinal Inflammation-Associated Dysbiosis Using Real-World Stool Test Results. *Dig Dis Sci*. 2019.
2. Löser C, Möllgaard A, Fölsch U. Faecal elastase 1: a novel, highly sensitive, and specific tubeless pancreatic function test. *Gut*. 1996;39(4):580-586.
3. Domínguez-Muñoz JE, Hardt PD, Lerch MM, Löhr MJ. Potential for screening for pancreatic exocrine insufficiency using the fecal elastase-1 test. *Dig Dis Scis*. 2017;62(5):1119-1130.
4. Carroccio A, Fontana M, Spagnuolo MI, et al. Pancreatic dysfunction and its association with fat malabsorption in HIV infected children. *Gut*. 1998;43(4):558-563.
5. Carroccio A, Iacono G, Ippolito S, et al. Usefulness of faecal elastase-1 assay in monitoring pancreatic function in childhood coeliac disease. *Ital J Gastroenterol Hepatol*. 1998;30(5):500-504.
6. Icks A, Haastert B, Giani G, Rathmann W. Low fecal elastase-1 in type I diabetes mellitus. *Z Gastroenterol*. 2001;39(10):823-830.
7. Sziegoleit A, Linder D. Studies on the sterol-binding capacity of human pancreatic elastase 1. *Gastroenterology*. 1991;100(3):768-774.
8. Singh VK, Haupt ME, Geller DE, Hall JA, Quintana Diez PM. Less common etiologies of exocrine pancreatic insufficiency. *World J Gastroenterol*. 2017;23(39):7059-7076.
9. Othman MO, Harb D, Barkin JA. Introduction and practical approach to exocrine pancreatic insufficiency for the practicing clinician. *Int J Clin Pract*. 2018.
10. Struyvenberg MR, Martin CR, Freedman SD. Practical guide to exocrine pancreatic insufficiency - Breaking the myths. *BMC Med*. 2017;15(1):29.
11. Lindkvist B. Diagnosis and treatment of pancreatic exocrine insufficiency. *World J Gastroenterol*. 2013;19(42):7258-7266.
12. Elborn JS. Cystic fibrosis. *Lancet*. 2016;388(10059):2519-2531.
13. Majumder S, Chari ST. Chronic pancreatitis. *Lancet*. 2016;387(10031):1957-1966.
14. Ghaneh P, Neoptolemos JP. Exocrine pancreatic function following pancreatectomy. *Ann New York Acad Scis*. 1999;880:308-318.
15. Dominguez-Munoz JE, P DH, Lerch MM, Lohr MJ. Potential for Screening for Pancreatic Exocrine Insufficiency Using the Fecal Elastase-1 Test. *Dig Dis Sci*. 2017;62(5):1119-1130.
16. Hardt PD, Bretz L, Krauss A, et al. Pathological pancreatic exocrine function and duct morphology in patients with cholelithiasis. *Dig Dis Sci*. 2001;46(3):536-539.
17. Vujasinovic M, Valente R, Del Chiaro M, Permert J, Lohr JM. Pancreatic Exocrine Insufficiency in Pancreatic Cancer. *Nutrients*. 2017;9(3).
18. Vujasinovic M, Valente R, Thorell A, et al. Pancreatic Exocrine Insufficiency after Bariatric Surgery. *Nutrients*. 2017;9(11).
19. Nousia-Arvanitakis S, Fotoulaki M, Tendzidou K, Vassilaki C, Agguridaki C, Karamouzis M. Subclinical exocrine pancreatic dysfunction resulting from decreased cholecystokinin secretion in the presence of intestinal villous atrophy. *J Ped Gastroenterol Nutr*. 2006;43(3):307-312.
20. Vujasinovic M, Tepes B, Volfand J, Rudolf S. Exocrine pancreatic insufficiency, MRI of the pancreas and serum nutritional markers in patients with coeliac disease. *Postgrad Med J*. 2015;91(1079):497-500.
21. Leeds JS, Hopper AD, Hurlstone DP, et al. Is exocrine pancreatic insufficiency in adult coeliac disease a cause of persisting symptoms? *Alim Pharmacol Therap*. 2007;25(3):265-271.
22. Walkowiak J, Herzig KH. Fecal elastase-1 is decreased in villous atrophy regardless of the underlying disease. *Eur J Clin Invest*. 2001;31(5):425-430.
23. Gomez JC, Moran CE, Maurino EC, Bai JC. Exocrine pancreatic insufficiency in celiac disease. *Gastroenterology*. 1998;114(3):621-623.
24. Pitchumoni CS, Rubin A, Das K. Pancreatitis in inflammatory bowel diseases. *J Clin Gastroenterol*. 2010;44(4):246-253.
25. Othman MO, Harb D, Barkin JA. Introduction and practical approach to exocrine pancreatic insufficiency for the practicing clinician. *Int J Clin Pract*. 2018;72(2).
26. Baffy G, Boyle JM. Association of Zollinger-Ellison syndrome with pancreatitis: report of five cases. *Dig Dis Sci*. 2000;45(8):1531-1534.
27. Herzig KH, Purhonen AK, Rasanen KM, et al. Fecal pancreatic elastase-1 levels in older individuals without known gastrointestinal diseases or diabetes mellitus. *BMC Geriatrics*. 2011;11:4.

28. Conwell DL, Lee LS, Yadav D, et al. American Pancreatic Association Practice Guidelines in Chronic Pancreatitis: evidence-based report on diagnostic guidelines. *Pancreas*. 2014;43(8):1143-1162.
29. Capurso G, Signoretti M, Archibugi L, Stigliano S, Delle Fave G. Systematic review and meta-analysis: Small intestinal bacterial overgrowth in chronic pancreatitis. *United Eur Gastroenterol J*. 2016;4(5):697-705.
30. Bures J, Cyrany J, Kohoutova D, et al. Small intestinal bacterial overgrowth syndrome. *World J Gastroenterol*. 2010;16(24):2978-2990.
31. Lappinga PJ, Abraham SC, Murray JA, Vetter EA, Patel R, Wu TT. Small intestinal bacterial overgrowth: histopathologic features and clinical correlates in an underrecognized entity. *Arch Pathol Lab Med*. 2010;134(2):264-270.
32. El Kurdi B, Babar S, El Iskandarani M, et al. Factors That Affect Prevalence of Small Intestinal Bacterial Overgrowth in Chronic Pancreatitis: A Systematic Review, Meta-Analysis, and Meta-Regression. *Clin Transl Gastroenterol*. 2019;10(9):e00072.
33. Teichmann J, Riemann JF, Lange U. Prevalence of exocrine pancreatic insufficiency in women with obesity syndrome: assessment by pancreatic fecal elastase 1. *ISRN Gastroenterol*. 2011;2011:951686.
34. Walkowiak J, Madry E, Lisowska A, et al. Adaptive changes of pancreatic protease secretion to a short-term vegan diet: influence of reduced intake and modification of protein. *Br J Nutr*. 2012;107(2):272-276.
35. Piciucchi M, Capurso G, Archibugi L, Delle Fave MM, Capasso M, Delle Fave G. Exocrine pancreatic insufficiency in diabetic patients: prevalence, mechanisms, and treatment. *Int J Endocrinol*. 2015;2015:595649.
36. Rathmann W, Haastert B, Oscarsson J, Berglind N, Lindkvist B, Wareham NJ. Association of faecal elastase 1 with non-fasting triglycerides in type 2 diabetes. *Pancreatol*. 2016;16(4):563-569.
37. Salvatore S, Finazzi S, Barassi A, et al. Low fecal elastase: potentially related to transient small bowel damage resulting from enteric pathogens. *J Ped Gastroenterol Nutr*. 2003;36(3):392-396.
38. Raybould HE. Mechanisms of CCK signaling from gut to brain. *Curr Op Pharmacol*. 2007;7(6):570-574.
39. Lohr JM, Oliver MR, Frulloni L. Synopsis of recent guidelines on pancreatic exocrine insufficiency. *United European Gastroenterol J*. 2013;1(2):79-83.
40. Durie P, Baillargeon JD, Bouchard S, Donnellan F, Zepeda-Gomez S, Teshima C. Diagnosis and management of pancreatic exocrine insufficiency (PEI) in primary care: consensus guidance of a Canadian expert panel. *Curr Med Res Opin*. 2018;34(1):25-33.
41. Yao CK, Muir JG, Gibson PR. Review article: insights into colonic protein fermentation, its modulation and potential health implications. *Alim Pharmacol Therap*. 2016;43(2):181-196.
42. Wang X, Wang J, Rao B, Deng L. Gut flora profiling and fecal metabolite composition of colorectal cancer patients and healthy individuals. *Exp Therap Med*. 2017;13(6):2848-2854.
43. Amiot A, Dona AC, Wijeyesekera A, et al. (1)H NMR Spectroscopy of Fecal Extracts Enables Detection of Advanced Colorectal Neoplasia. *J Proteome Res*. 2015;14(9):3871-3881.
44. Niccolai E, Baldi S, Ricci F, et al. Evaluation and comparison of short chain fatty acids composition in gut diseases. *World J Gastroenterol*. 2019;25(36):5543-5558.
45. Szczesniak O, Hestad KA, Hanssen JF, Rudi K. Isovaleric acid in stool correlates with human depression. *Nutr Neurosci*. 2016;19(7):279-283.
46. Hoverstad T, Bjorneklett A, Fausa O, Midtvedt T. Short-chain fatty acids in the small-bowel bacterial overgrowth syndrome. *Scand J Gastroenterol*. 1985;20(4):492-499.
47. Kotani A, Miyaguchi Y, Kohama M, Ohtsuka T, Shiratori T, Kusu F. Determination of short-chain fatty acids in rat and human feces by high-performance liquid chromatography with electrochemical detection. *Analyt Sci*. 2009;25(8):1007-1011.
48. Geypens B, Claus D, Evenepoel P, et al. Influence of dietary protein supplements on the formation of bacterial metabolites in the colon. *Gut*. 1997;41(1):70-76.
49. Tursi A, Mastromarino P, Capobianco D, et al. Assessment of Fecal Microbiota and Fecal Metabolome in Symptomatic Uncomplicated Diverticular Disease of the Colon. *J Clin Gastroenterol*. 2016;50 Suppl 1:S9-s12.
50. Caminero A, Nistal E, Herran AR, et al. Differences in gluten metabolism among healthy volunteers, coeliac disease patients and first-degree relatives. *Br J Nutr*. 2015;114(8):1157-1167.
51. Liu S, Li E, Sun Z, et al. Altered gut microbiota and short chain fatty acids in Chinese children with autism spectrum disorder. *Sci Rep*. 2019;9(1):287.

52. Holtug K, Rasmussen HS, Mortensen PB. Short chain fatty acids in inflammatory bowel disease. The effect of bacterial fermentation of blood. *Scand J Clin Lab Invest.* 1988;48(7):667-671.
53. Nakamura T, Tabeke K, Terada A, et al. Short-chain carboxylic acid in the feces in patients with pancreatic insufficiency. *Acta gastro-enterol Belgica.* 1993;56(5-6):326-331.
54. Farup PG, Valeur J. Changes in Faecal Short-Chain Fatty Acids after Weight-Loss Interventions in Subjects with Morbid Obesity. *Nutrients.* 2020;12(3).
55. Pezzilli R, Andriulli A, Bassi C, et al. Exocrine pancreatic insufficiency in adults: a shared position statement of the Italian Association for the Study of the Pancreas. *World J Gastroenterol.* 2013;19(44):7930-7946.
56. Bures J, Cyrany J, Kohoutova D, et al. Small intestinal bacterial overgrowth syndrome. *World J Gastroenterol.* 2010;16(24):2978-2990.
57. Revaiah PC, Kochhar R, Rana SV, et al. Risk of small intestinal bacterial overgrowth in patients receiving proton pump inhibitors versus proton pump inhibitors plus prokinetics. *JGH Open.* 2018;2(2):47-53.
58. Rios-Covian D, González S, Nogacka AM, et al. An Overview on Fecal Branched Short-Chain Fatty Acids Along Human Life and as Related With Body Mass Index: Associated Dietary and Anthropometric Factors. *Front Microbiol.* 2020;11:973.
59. Thorsgaard PN. Estimation of assimilation of simultaneously ingested 14C-triolein and 3H-oleic acid as a test of pancreatic digestive function. *Scand J Gastroenterol.* 1984;19(2):6.
60. Thorsgaard PN, Halgreen, H. Simultaneous assessment of fat maldigestion and fat malabsorption by a double-isotope method using fecal radioactivity. *Gastroenterology.* 1985;88(1 Pt 1):8.
61. van der Velde AE, Vrins CL, van den Oever K, et al. Direct intestinal cholesterol secretion contributes significantly to total fecal neutral sterol excretion in mice. *Gastroenterology.* 2007;133(3):967-975.
62. Turroni S, Fiori J, Rampelli S, et al. Fecal metabolome of the Hadza hunter-gatherers: a host-microbiome integrative view. *Sci Rep.* 2016;6:32826.
63. Alkaade S, Vareedayah AA. A primer on exocrine pancreatic insufficiency, fat malabsorption, and fatty acid abnormalities. *Am J Manag Care.* 2017;23(12 Suppl):s203-s209.
64. Milovic V. Gastrointestinal disease and dosage form performance. In: *Oral Drug Absorption.* CRC Press; 2016:141-151.
65. Foltz E, Azad S, Everett ML, et al. An assessment of human gastric fluid composition as a function of PPI usage. *Physiol Rep.* 2015;3(1).
66. Grace E, Shaw C, Whelan K, Andreyev H. small intestinal bacterial overgrowth—prevalence, clinical features, current and developing diagnostic tests, and treatment. *Alim Pharmacol Therap.* 2013;38(7):674-688.
67. Berceanu D, Bucur D, Diaconu C. Type 2 diabetes and liver disease: a frequent and harmful connection. *Arch Balkan Med Union vol.* 2016;51(4):506-511.
68. Rana SV, Malik A, Bhadada SK, Sachdeva N, Morya RK, Sharma G. Malabsorption, Orocecal Transit Time and Small Intestinal Bacterial Overgrowth in Type 2 Diabetic Patients: A Connection. *Indian J Clin Biochem.* 2017;32(1):84-89.
69. Mohapatra S, Singh DP, Alcid D, Pitchumoni CS. Beyond O&P Times Three. *Am J Gastroenterol.* 2018;1.
70. O'Keefe SJD, Rakitt T, Ou J, et al. Pancreatic and Intestinal Function Post Roux-en-Y Gastric Bypass Surgery for Obesity. *Clin Transl Gastroenterol.* 2017;8(8):e112.
71. Watson L, Lalji A, Bodla S, Muls A, Andreyev HJ, Shaw C. Management of bile acid malabsorption using low-fat dietary interventions: a useful strategy applicable to some patients with diarrhoea-predominant irritable bowel syndrome? *Clin Med.* 2015;15(6):536-540.
72. Mourad FH, Barada KA, Saade NE. Impairment of Small Intestinal Function in Ulcerative Colitis: Role of Enteric Innervation. *J Crohns Colitis.* 2017;11(3):369-377.
73. Gujral N, Freeman HJ, Thomson ABR. Celiac disease: prevalence, diagnosis, pathogenesis and treatment. *World J Gastroenterol.* 2012;18(42):6036-6059.
74. Nakashige TG, Zhang B, Krebs C, Nolan EM. Human calprotectin is an iron-sequestering host-defense protein. *Nat Chem Biol.* 2015;11(10):765-771.
75. Steinbakk M, Naess-Andresen CF, Lingaas E, Dale I, Brandtzaeg P, Fagerhol MK. Antimicrobial actions of calcium binding leucocyte L1 protein, calprotectin. *Lancet.* 1990;336(8718):763-765.
76. Lasson A, Stotzer PO, Ohman L, Isaksson S, Sapnara M, Strid H. The intra-individual variability of faecal calprotectin: a prospective study in patients with active ulcerative colitis. *J Crohns Colitis.* 2015;9(1):26-32

77. Manceau H, Chicha-Cattoir V, Puy H, Peoc'h K. Faecal calprotectin in inflammatory bowel diseases: update and perspectives. *Clin Chem Lab Med*. 2017;55(4):474-483.
78. Joshi S, Lewis SJ, Creanor S, Ayling RM. Age-related faecal calprotectin, lactoferrin and tumour M2-PK concentrations in healthy volunteers. *Ann Clin Biochem*. 2010;47(Pt 3):259-263.
79. Orfei M, Gasparetto M, Hensel KO, Zellweger F, Heuschkel RB, Zilbauer M. Guidance on the interpretation of faecal calprotectin levels in children. *PloS one*. 2021;16(2):e0246091.
80. Davidson F, Lock RJ. Paediatric reference ranges for faecal calprotectin: a UK study. *Ann Clin Biochem*. 2017;54(2):214-218.
81. Roca M, Rodriguez Varela A, Carvajal E, et al. Faecal calprotectin in healthy children aged 4-16 years. *Sci Rep*. 2020;10(1):20565.
82. Joshi S, Lewis SJ, Creanor S, Ayling RM. Age-related faecal calprotectin, lactoferrin and tumour M2-PK concentrations in healthy volunteers. *Ann Clin Biochem*. 2010;47(3):259-263.
83. D'Angelo F, Felley C, Frossard JL. Calprotectin in Daily Practice: Where Do We Stand in 2017? *Digestion*. 2017;95(4):293-301.
84. Meling TR, Aabakken L, Roseth A, Osnes M. Faecal calprotectin shedding after short-term treatment with non-steroidal anti-inflammatory drugs. *Scand J Gastroenterol*. 1996;31(4):339-344.
85. Gallo A, Ianiro G, Montalto M, Cammarota G. The Role of Biomarkers in Diverticular Disease. *J Clin Gastroenterol*. 2016;50 Suppl 1:S26-28.
86. Stimac D, Nardone G, Mazzari A, et al. What's New in Diagnosing Diverticular Disease. *J Gastro Liver Dis*. 2020;28 suppl.1:17-22.
87. Hoekman DR, Zeevenhooven J, D'Haens GR, Benninga MA. The prevalence of irritable bowel syndrome-type symptoms in inflammatory bowel disease patients in remission. *Eur J Gastroenterol Hepatol*. 2017;29(9):1086-1090.
88. Lundgren D, Eklof V, Palmqvist R, Hultdin J, Karling P. Proton pump inhibitor use is associated with elevated faecal calprotectin levels. A cross-sectional study on subjects referred for colonoscopy. *Scand J Gastroenterol*. 2019;54(2):152-157.
89. Boerlage TC, Westerink F, Poland DC, Huibregtse IL, Acherman YI, Gerdes VE. Faecal Calprotectin, Elastase, and Alpha-1-Antitrypsin Levels After Roux-en-Y Gastric Bypass; Calprotectin Is Significantly Elevated in the Majority of Patients. *Obesity Surg*. 2016;26(12):2974-2980.
90. Westerink F, Huibregtse I, De Hoog M, et al. Faecal Inflammatory Biomarkers and Gastrointestinal Symptoms after Bariatric Surgery: A Longitudinal Study. *Inflamm Intestin Dis*. 2021;6(2):109-116.
91. Brcic I, Todoroff A, Baumgartner K, Langner C, Gröchenig H. P547 Is there an association between bariatric surgery and Crohn's disease? *J Crohns Colitis*. 2017;11(suppl_1).
92. Scaioli E, Sartini A, Bellanova M, et al. Eicosapentaenoic Acid Reduces Faecal Levels of Calprotectin and Prevents Relapse in Patients With Ulcerative Colitis. *Clinical Gastroenterol Hepatol*. 2018;16(8):1268-1275.e1262.
93. Prossomariti A, Scaioli E, Piazzini G, et al. Short-term treatment with eicosapentaenoic acid improves inflammation and affects colonic differentiation markers and microbiota in patients with ulcerative colitis. *Sci Rep*. 2017;7(1):7458.
94. Yang BG, Seoh JY, Jang MH. Regulatory Eosinophils in Inflammation and Metabolic Disorders. *Immune Netw*. 2017;17(1):41-47.
95. Majamaa H, Laine S, Miettinen A. Eosinophil protein X and eosinophil cationic protein as indicators of intestinal inflammation in infants with atopic eczema and food allergy. *Clin Exp Allergy*. 1999;29(11):1502-1506.
96. van Odijk J, Peterson CG, Ahlstedt S, et al. Measurements of eosinophil activation before and after food challenges in adults with food hypersensitivity. *Int Arch Allergy Immunol*. 2006;140(4):334-341.
97. Bischoff SC, Grabowsky J, Manns MP. Quantification of inflammatory mediators in stool samples of patients with inflammatory bowel disorders and controls. *Dig Dis Sci*. 1997;42(2):394-403.
98. Amcoff K, Cao Y, Zhulina Y, Lampinen M, Halfvarson J, Carlson M. Prognostic significance of faecal eosinophil granule proteins in inflammatory bowel disease. *Scand J Gastroenterol*. 2019;54(10):1237-1244.
99. Jung Y, Rothenberg ME. Roles and regulation of gastrointestinal eosinophils in immunity and disease. *J Immunol*. 2014;193(3):999-1005.
100. Wagner M, Sjoberg K, Vigren L, et al. Elevated faecal levels of eosinophil granule proteins predict collagenous colitis in patients referred to colonoscopy due to chronic non-bloody diarrhea. *Scand J Gastroenterol*. 2016;51(7):835-841.
101. Roca M, Rodriguez Varela A, Donat E, et al. Faecal Calprotectin and Eosinophil-derived Neurotoxin in Healthy Children Between 0 and 12 Years. *J Ped Gastroenterol Nutr*. 2017;65(4):394-398.

102. Mantis NJ, Rol N, Corthesy B. Secretory IgA's complex roles in immunity and mucosal homeostasis in the gut. *Mucosal Immunol.* 2011;4(6):603-611.
103. Corthesy B. Secretory immunoglobulin A: well beyond immune exclusion at mucosal surfaces. *Immunopharmacol Immunotoxicol.* 2009;31(2):174-179.
104. Mantis NJ, Forbes SJ. Secretory IgA: arresting microbial pathogens at epithelial borders. *Immunol Invest.* 2010;39(4-5):383-406.
105. Bemark M, Boysen P, Lycke NY. Induction of gut IgA production through T cell-dependent and T cell-independent pathways. *Ann New York Acad Sci.* 2012;1247:97-116.
106. Brandtzaeg P. Update on mucosal immunoglobulin A in gastrointestinal disease. *Curr Opin Gastroenterol.* 2010;26(6):554-563.
107. Agarwal S, Mayer L. Pathogenesis and treatment of gastrointestinal disease in antibody deficiency syndromes. *J All Clin Immunol.* 2009;124(4):658-664.
108. Ray A, Dittel BN. Interrelatedness between dysbiosis in the gut microbiota due to immunodeficiency and disease penetrance of colitis. *Immunology.* 2015;146(3):359-368.
109. Mantis NJ, Rol N, Corthesy B. Secretory IgA's complex roles in immunity and mucosal homeostasis in the gut. *Mucosal Immunol.* 2011;4(6):603-611.
110. Brandtzaeg P, Carlsen HS, Halstensen TS. The B-cell system in inflammatory bowel disease. *Adv Exp Med Biol.* 2006;579:149-167.
111. Chalkias A, Nikotian G, Koutsovasilis A, et al. Patients with colorectal cancer are characterized by increased concentration of fecal hb-hp complex, myeloperoxidase, and secretory IgA. *Am J Clin Oncol.* 2011;34(6):561-566.
112. Dzunkova M, Moya A, Vazquez-Castellanos JF, et al. Active and Secretory IgA-Coated Bacterial Fractions Elucidate Dysbiosis in *Clostridium difficile* Infection. *mSphere.* 2016;1(3).
113. Matysiak-Budnik T, Moura IC, Arcos-Fajardo M, et al. Secretory IgA mediates retrotranscytosis of intact gliadin peptides via the transferrin receptor in celiac disease. *J Exp Med.* 2008;205(1):143-154.
114. Chalkias A, Nikotian G, Koutsovasilis A, et al. Patients With Colorectal Cancer Are Characterized by Increased Concentration of Fecal Hb-Hp Complex, Myeloperoxidase, and Secretory IgA. *Am J Clin Oncol.* 2011;34(6):561-566.
115. Soldi S, Tagliacarne SC, Valsecchi C, et al. Effect of a multistrain probiotic (Lactoflorene((R)) Plus) on inflammatory parameters and microbiota composition in subjects with stress-related symptoms. *Neurobiol Stress.* 2019;10:100138.
116. Kusumo PD, Bela B, Wibowo H, Munasir Z, Surono IS. *Lactobacillus plantarum* IS-10506 supplementation increases faecal sIgA and immune response in children younger than two years. *Beneficial Microb.* 2019;10(3):245-252.
117. Wang L, Zhang J, Guo Z, et al. Effect of oral consumption of probiotic *Lactobacillus planatarum* P-8 on fecal microbiota, SIgA, SCFAs, and TBAs of adults of different ages. *Nutrition.* 2014;30(7-8):776-783.e771.
118. Baldassarre ME, Di Mauro A, Mastromarino P, et al. Administration of a Multi-Strain Probiotic Product to Women in the Perinatal Period Differentially Affects the Breast Milk Cytokine Profile and May Have Beneficial Effects on Neonatal Gastrointestinal Functional Symptoms. A Randomized Clinical Trial. *Nutrients.* 2016;8(11).
119. Drago-Serrano ME, Campos-Rodríguez R, Carrero JC, de la Garza M. Lactoferrin: Balancing Ups and Downs of Inflammation Due to Microbial Infections. *Int J Mol Sci.* 2017;18(3):501.
120. Amrane S, Hocquart M, Afouda P, et al. Metagenomic and culturomic analysis of gut microbiota dysbiosis during *Clostridium difficile* infection. *Sci Rep.* 2019;9(1):12807.
121. Rios-Covian D, Ruas-Madiedo P, Margolles A, Gueimonde M, de Los Reyes-Gavilan CG, Salazar N. Intestinal Short Chain Fatty Acids and their Link with Diet and Human Health. *Front Microbiol.* 2016;7:185.
122. Tan J, McKenzie C, Potamitis M, Thorburn AN, Mackay CR, Macia L. The role of short-chain fatty acids in health and disease. *Adv Immunol.* 2014;121:91-119.
123. Mortensen PB, Clausen MR. Short-chain fatty acids in the human colon: relation to gastrointestinal health and disease. *Scand J Gastroenterol Suppl.* 1996;216:132-148.
124. Velazquez OC, Lederer HM, Rombeau JL. Butyrate and the colonocyte. Production, absorption, metabolism, and therapeutic implications. *Adv Exp Med Biol.* 1997;427:123-134.
125. Basson A, Trotter A, Rodriguez-Palacios A, Cominelli F. Mucosal Interactions between Genetics, Diet, and Microbiome in Inflammatory Bowel Disease. *Front Immunol.* 2016;7:290.
126. den Besten G, van Eunen K, Groen AK, Venema K, Reijngoud DJ, Bakker BM. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. *J Lipid Res.* 2013;54(9):2325-2340.

127. Chen Y, Gozzi K, Yan F, Chai Y. Acetic Acid Acts as a Volatile Signal To Stimulate Bacterial Biofilm Formation. *mBio*. 2015;6(3):e00392.
128. Boets E, Deroover L, Houben E, et al. Quantification of in Vivo Colonic Short Chain Fatty Acid Production from Inulin. *Nutrients*. 2015;7(11):8916–8929.
129. Riviere A, Selak M, Lantin D, Leroy F, De Vuyst L. Bifidobacteria and Butyrate-Producing Colon Bacteria: Importance and Strategies for Their Stimulation in the Human Gut. *Front Microbiol*. 2016;7:979.
130. Wong JM, de Souza R, Kendall CW, Emam A, Jenkins DJ. Colonic health: fermentation and short chain fatty acids. *J Clin Gastroenterol*. 2006;40(3):235–243.
131. Valeur J, Roseth AG, Knudsen T, et al. Fecal Fermentation in Irritable Bowel Syndrome: Influence of Dietary Restriction of Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols. *Digestion*. 2016;94(1):50–56.
132. Varju P, Farkas N, Hegyi P, et al. Low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) diet improves symptoms in adults suffering from irritable bowel syndrome (IBS) compared to standard IBS diet: A meta-analysis of clinical studies. *PLoS One*. 2017;12(8):e0182942.
133. Bach Knudsen KE. Microbial degradation of whole-grain complex carbohydrates and impact on short-chain fatty acids and health. *Adv Nutr*. 2015;6(2):206–213.
134. Ghoshal UC, Shukla R, Ghoshal U. Small Intestinal Bacterial Overgrowth and Irritable Bowel Syndrome: A Bridge between Functional Organic Dichotomy. *Gut Liver*. 2017;11(2):196–208.
135. Mroczynska M, Galecka M, Szachta P, Kamoda D, Libudzisz Z, Roszak D. Beta-glucuronidase and Beta-glucosidase activity in stool specimens of children with inflammatory bowel disease. *Pol J Microbiol*. 2013;62(3):319–325.
136. Flores R, Shi J, Gail MH, Gajer P, Ravel J, Goedert JJ. Association of fecal microbial diversity and taxonomy with selected enzymatic functions. *PLoS One*. 2012;7(6):e39745.
137. Kwa M, Plottel CS, Blaser MJ, Adams S. The Intestinal Microbiome and Estrogen Receptor-Positive Female Breast Cancer. *J Nat Cancer Inst*. 2016;108(8).
138. Kim DH, Jin YH. Intestinal bacterial beta-glucuronidase activity of patients with colon cancer. *Arch Pharmacol Res*. 2001;24(6):564–567.
139. Flores R, Shi J, Gail MH, Gajer P, Ravel J, Goedert JJ. Association of fecal microbial diversity and taxonomy with selected enzymatic functions. *PLoS one*. 2012;7(6):e39745–e39745.
140. Thompson KJ, Ingle JN, Tang X, et al. A comprehensive analysis of breast cancer microbiota and host gene expression. *PLoS one*. 2017;12(11):e0188873–e0188873.
141. Sivieri K, Bedani R, Cavallini DCU, Rossi EA. Probiotics and intestinal microbiota: implications in colon cancer prevention. In: *Lactic Acid Bacteria-R & D for Food, Health and Livestock Purposes*. IntechOpen; 2013.
142. Goldin BR, Swenson L, Dwyer J, Sexton M, Gorbach SL. Effect of diet and *Lactobacillus acidophilus* supplements on human fecal bacterial enzymes. *J Natl Cancer Inst*. 1980;64(2):255–261.
143. De Preter V, Raemen H, Cloetens L, Houben E, Rutgeerts P, Verbeke K. Effect of dietary intervention with different pre- and probiotics on intestinal bacterial enzyme activities. *Eur J Clin Nutr*. 2008;62(2):225–231.
144. Valerio F, Russo F, de Candia S, et al. Effects of probiotic *Lactobacillus paracasei*-enriched artichokes on constipated patients: a pilot study. *J Clin Gastroenterol*. 2010;44 Suppl 1:S49–53.
145. Liu Z, Lin X, Huang G, Zhang W, Rao P, Ni L. Prebiotic effects of almonds and almond skins on intestinal microbiota in healthy adult humans. *Anaerobe*. 2014;26:1–6.
146. Molan AL, Liu Z, Plimmer G. Evaluation of the effect of blackcurrant products on gut microbiota and on markers of risk for colon cancer in humans. *Phytother Res*. 2014;28(3):416–422.
147. Calcium-D-glucarate. *Altern Med Rev*. 2002;7(4):336–339.
148. Křen V, Walterova D. Silybin and silymarin—new effects and applications. *Biomed Papers*. 2005;149(1):29–41.
149. Kim DH, Jin YH, Park JB, Kobashi K. Silymarin and its components are inhibitors of beta-glucuronidase. *Biol Pharmaceut Bull*. 1994;17(3):443–445.
150. Azcarate-Peril MA, Sikes M, Bruno-Barcena JM. The intestinal microbiota, gastrointestinal environment and colorectal cancer: a putative role for probiotics in prevention of colorectal cancer? *Am J Physiol Gastrointest Liver Physiol*. 2011;301(3):G401–424.

151. Koning CJ, Jonkers DM, Stobberingh EE, Mulder L, Rombouts FM, Stockbrugger RW. The effect of a multispecies probiotic on the intestinal microbiota and bowel movements in healthy volunteers taking the antibiotic amoxicillin. *Am J Gastroenterol.* 2008;103(1):178-189.
152. Zhanel GG, Siemens S, Slayter K, Mandell L. Antibiotic and oral contraceptive drug interactions: Is there a need for concern? *Can J Infect Dis.* 1999;10(6):429-433.
153. Rinninella E, Raoul P, Cintoni M, et al. What is the Healthy Gut Microbiota Composition? A Changing Ecosystem across Age, Environment, Diet, and Diseases. *Microorganisms.* 2019;7(1):14.
154. Clemente JC, Manasson J, Scher JU. The role of the gut microbiome in systemic inflammatory disease. *BMJ.* 2018;360:j5145.
155. Fava F, Danese S. Intestinal microbiota in inflammatory bowel disease: friend of foe? *World J Gastroenterol.* 2011;17(5):557-566.
156. Rowland I, Gibson G, Heinken A, et al. Gut microbiota functions: metabolism of nutrients and other food components. *Eur J Nutr.* 2018;57(1):1-24.
157. Verbeke KA, Boobis AR, Chiodini A, et al. Towards microbial fermentation metabolites as markers for health benefits of prebiotics. *Nutr Res Rev.* 2015;28(1):42-66.
158. Belenguer A, Duncan SH, Holtrop G, Anderson SE, Lobley GE, Flint HJ. Impact of pH on lactate formation and utilization by human fecal microbial communities. *Appl Environ Microbiol.* 2007;73(20):6526-6533.
159. Ostojic SM. Non-gut microbiota as a source of bioactive hydrogen. *Postgrad Med J.* 2017;93(1097):170.
160. Figliuolo VR, Dos Santos LM, Abalo A, et al. Sulfate-reducing bacteria stimulate gut immune responses and contribute to inflammation in experimental colitis. *Life Sci.* 2017;189:29-38.
161. Stroot PG. The primary cause of oxidative stress is ultra-exogenous sulfide formation (USF). *Med Hypotheses.* 2014;83(6):766-768.
162. Pham VT, Lacroix C, Braegger CP, Chassard C. Lactate-utilizing community is associated with gut microbiota dysbiosis in colicky infants. *Sci Rep.* 2017;7(1):11176.
163. Ghoshal U, Shukla R, Srivastava D, Ghoshal UC. Irritable Bowel Syndrome, Particularly the Constipation-Predominant Form, Involves an Increase in *Methanobrevibacter smithii*, Which Is Associated with Higher Methane Production. *Gut Liver.* 2016;10(6):932-938.
164. Petersen C, Round JL. Defining dysbiosis and its influence on host immunity and disease. *Cell Microbiol.* 2014;16(7):1024-1033.
165. Tang WHW, Kitai T, Hazen SL. Gut Microbiota in Cardiovascular Health and Disease. *Circulation Res.* 2017;120(7):1183-1196.
166. Imhann F, Bonder MJ, Vich Vila A, et al. Proton pump inhibitors affect the gut microbiome. *Gut.* 2016;65(5):740-748.
167. Valdes AM, Walter J, Segal E, Spector TD. Role of the gut microbiota in nutrition and health. *BMJ.* 2018;361:k2179.
168. Myers SP. The causes of intestinal dysbiosis: a review. *Alternative medicine review : a journal of clinical therapeutic.* 2004;9(2):180-197.
169. Engen PA, Green SJ, Voigt RM, Forsyth CB, Keshavarzian A. The Gastrointestinal Microbiome: Alcohol Effects on the Composition of Intestinal Microbiota. *Alc Res.* 2015;37(2):223-236.
170. Rea K, Dinan TG, Cryan JF. The microbiome: a key regulator of stress and neuroinflammation. *Neurobiol Stress.* 2016;4:23-33.
171. Houghton D, Stewart CJ, Day CP, Trenell M. Gut Microbiota and Lifestyle Interventions in NAFLD. *Int J Mol Sci.* 2016;17(4):447.
172. Allen AP, Dinan TG, Clarke G, Cryan JF. A psychology of the human brain-gut-microbiome axis. *Soc Personal Psychol Compass.* 2017;11(4):e12309.
173. Frei R, Akdis M, O'Mahony L. Prebiotics, probiotics, synbiotics, and the immune system: experimental data and clinical evidence. *Curr Op Gastroenterol.* 2015;31(2):153-158.
174. Sassone-Corsi M, Raffatellu M. No vacancy: how beneficial microbes cooperate with immunity to provide colonization resistance to pathogens. *J Immunol.* 2015;194(9):4081-4087.
175. Tojo R, Suárez A, Clemente MG, et al. Intestinal microbiota in health and disease: role of bifidobacteria in gut homeostasis. *World J Gastroenterol.* 2014;20(41):15163.
176. Kechagia M, Basoulis D, Konstantopoulou S, et al. Health benefits of probiotics: a review. *ISRN Nutr.* 2013;2013.

177. Heeney DD, Gareau MG, Marco ML. Intestinal Lactobacillus in health and disease, a driver or just along for the ride? *Curr Op Biotechnol.* 2018;49:140-147.
178. Matsuoka K, Kanai T. The gut microbiota and inflammatory bowel disease. Paper presented at: Seminars in immunopathology 2015.
179. Kaakoush NO, Castano-Rodriguez N, Mitchell HM, Man SM. Global Epidemiology of Campylobacter Infection. *Clin Microbiol Rev.* 2015;28(3):687-720.
180. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG clinical guideline: treatment of Helicobacter pylori infection. *Am J Gastroenterol.* 2017;112(2):212.
181. Senay H, MacPherson D. Parasitology: diagnostic yield of stool examination. *CMAJ.* 1989;140(11):1329-1331.
182. Cartwright CP. Utility of multiple-stool-specimen ova and parasite examinations in a high-prevalence setting. *J Clin Microbiol.* 1999;37(8):2408-2411.
183. Mohapatra S, Singh DP, Alcid D, Pitchumoni CS. Beyond O&P Times Three. *Am J Gastroenterol.* 2018;113(6):805-818.
184. McHardy IH, Wu M, Shimizu-Cohen R, Couturier MR, Humphries RM. Detection of intestinal protozoa in the clinical laboratory. *J Clin Microbiol.* 2014;52(3):712-720.
185. Garcia LS, Arrowood M, Kokoskin E, et al. Laboratory Diagnosis of Parasites from the Gastrointestinal Tract. *Clin Microbiol Rev.* 2018;31(1).
186. CDC. Artifacts. DPDx - Laboratory Identification of Parasites of Public Health Concern 2016;. Accessed November 15, 2018.
187. Siddique SM, Gilotra NA. Crystal clear: a unique clue to diagnosis in a patient with recurrent nausea and vomiting. *Gastroenterology.* 2014;147(2):e1-2.
188. Tan KS. New insights on classification, identification, and clinical relevance of Blastocystis spp. *Clin Microbiol Rev.* 2008;21(4):639-665.
189. Zuo L, Rothenberg ME. Gastrointestinal eosinophilia. *Immunol Allergy Clin North Am.* 2007;27(3):443-455.
190. CDC. Amebiasis. DPDx - Laboratory Identification of Parasites of Public Health Concern 2017; <https://www.cdc.gov/dpdx/amebiasis/index.html>. Accessed November 14, 2018.
191. NIH. Polymerase Chain Reaction (PCR). Fact Sheets 2015; <https://www.genome.gov/10000207/polymerase-chain-reaction-pcr-fact-sheet/>. Accessed October 30, 2018.
192. Garcia LS. Dientamoeba fragilis, One of the Neglected Intestinal Protozoa. *J Clin Microbiol.* 2016;54(9):2243-2250.
193. CDC. Parasites - Cryptosporidium (also known as "Crypto"). 2017; <https://www.cdc.gov/parasites/crypto/>. Accessed October 15, 2018.
194. Popruk S, Pintong A-r, Radomyos P. Diversity of Blastocystis subtypes in humans. *J Trop Med Parasitol.* 2013;36:88-97.
195. Fullerton KYJ. Chapter 3 - Giardiasis Trav Health 2017; <https://wwwnc.cdc.gov/travel/yellowbook/2018/infectious-diseases-related-to-travel/giardiasis>. Accessed November 2, 2018.
196. Park S, Hitchcock MM, Gomez CA, Banaei N. Is Follow-up Testing with FilmArray Gastrointestinal Multiplex PCR Panel Necessary? *J Clin Microbiol.* 2017;JCM. 02354-02316.
197. Rijsman LH, Monkelbaan JF, Kusters JG. Clinical consequences of polymerase chain reaction-based diagnosis of intestinal parasitic infections. *J Gastroenterol Hepatol.* 2016;31(11):1808-1815.
198. Scheffler L, Crane A, Heyne H, et al. Widely Used Commercial ELISA Does Not Detect Precursor of Haptoglobin2, but Recognizes Properdin as a Potential Second Member of the Zonulin Family. *Front Endocrinol.* 2018;9(22).
199. Ajamian M, Steer D, Rosella G, Gibson PR. Serum zonulin as a marker of intestinal mucosal barrier function: May not be what it seems. *PLoS one.* 2019;14(1):e0210728.
200. Lamprecht M, Bogner S, Schippinger G, et al. Probiotic supplementation affects markers of intestinal barrier, oxidation, and inflammation in trained men; a randomized, double-blinded, placebo-controlled trial. *J Int Soc Sports Nutr.* 2012;9(1):45.
201. Halasa M, Maciejewska D, Baskiewicz-Halasa M, Machalinski B, Safranow K, Stachowska E. Oral Supplementation with Bovine Colostrum Decreases Intestinal Permeability and Stool Concentrations of Zonulin in Athletes. *Nutrients.* 2017;9(4).

APPENDIX

Commensal Bacteria

The most current, literature-based information on human studies related to increased or decreased levels of the commensal bacteria is summarized in the following chart. Note that the findings in the literature may not be consistent with Genova's findings due to different methodologies, thus treatment efficacy may vary. Most therapeutic interventions do not work in isolation, meaning they do not exclusively only target that one organism. Genova has not conducted outcome studies on the impact of certain therapeutics on the microbiome markers. Clinician discretion is advised for appropriateness of therapeutics.

Under certain conditions, environmental factors may influence specific commensals to become pathobionts. Pathobionts are distinguished from true infectious agents; they are potential pathogens under certain conditions. It is unknown whether these organisms play a causative role in disease or are a consequence of a disease state. Literature is evolving regarding the definition of a pathobiont and the role of commensal bacteria.¹⁻³

Organism	Description	Increased Levels	Decreased Levels
<i>Bacteroides uniformis</i>	<p><i>Bacteroides uniformis</i> is a fiber-degrading bacteria. It colonizes the gut in early infancy and is promoted by breast feeding.⁴</p> <p>Thought to enhance the gut barrier through the production of butyrate and GABA.^{5,6} Also produces beta glucuronidase, degrades mucin, and produces folate.^{4,7,8}</p> <p>Studied in preclinical trials as a potential probiotic for use in inflammatory and metabolic disorders.⁹⁻¹¹ <i>B. uniformis</i> was found to be decreased in obese patients as compared to healthy or lean groups.^{12,13} It was higher in healthy controls as compared to patients with ulcerative colitis.¹⁴</p> <p>Enriched in healthy individuals versus colorectal cancer patients.¹⁵</p> <p>Associated with degradation of the isoflavone genistein, which then becomes less bioavailable to the human.¹⁶</p>	<p>In ten healthy males, the consumption of red wine polyphenols for 4 weeks significantly increased the amount of <i>Bacteroides uniformis</i> as well as other commensal bacteria species.¹⁷</p> <p>Higher levels of insoluble fiber are associated with higher levels of <i>B. uniformis</i>.¹⁸</p> <p>A more favorable metabolic risk profile in men on a healthy plant-based diet was seen with a certain microbial profile featuring increased <i>B. uniformis</i> and decreased <i>Prevotella copri</i>. The healthy diet was characterized by a higher intake of fiber, plant proteins, whole grains, fruits, vegetables, nuts, and legumes, and a lower intake of energy, animal proteins, refined grains, potatoes, sweets, animal fat, egg, dairy, and meats.¹⁹</p> <p>A small study (n=13) showed the presence of <i>B. uniformis</i> and other <i>Bacteroides</i> species in non-vegetarians, versus vegetarians.²⁰</p>	<p>Higher fiber intake from beans is associated with lower abundance of <i>B. uniformis</i>.²¹</p>
<i>Phocaeicola vulgatus</i>	<p>Generally considered a beneficial gut commensal, although is capable of attaching to and invading colonic epithelial cells and inducing pro-inflammatory cytokines.²²</p> <p>Produces beta-glucuronidase, succinate, lactate, acetate, formate, and propionate.^{23,24}</p>	<p>A high beef diet was associated with increases in <i>Bacteroides fragilis</i>, <i>B. vulgatus</i> and <i>Clostridium</i> spp. in 10 volunteers.²⁷</p>	<p>Decreased levels were found in 7-12-year olds who consumed oligofructose-enriched inulin (<i>BENEOS</i>'s prebiotic fiber <i>Synergy1</i>) for 16 weeks in a double-blind-controlled trial.²⁸</p>

Commensal Bacteria

Organism	Description	Increased Levels	Decreased Levels
	<p>Associated with insulin resistance.²⁵</p> <p>Contains bile salt hydrolases to metabolize bile.²⁶</p> <p>Formerly named <i>Bacteroides vulgatus</i></p>		<p>Dietary inulin-type fructan prebiotics decreased <i>Bacteroides vulgatus</i> in obese women which positively correlated with changes in body composition and glucose homeostasis.²⁹</p>
<i>Barnesiella</i> spp.	<p><i>Barnesiella</i> spp. is a small group made up of two species with <i>B. intestinhominis</i> isolated in humans.^{30,31}</p> <p><i>B. intestinhominis</i> is found in individuals in industrialized populations versus hunter-gatherer societies and generally correlates with beneficial effects on the human gut.^{32,33}</p> <p><i>Barnesiella</i> colonization correlates with reduced antibiotic-resistant <i>Enterococcus</i> species,³⁴ eradication of <i>Klebsiella pneumoniae</i>,³⁵ and has other beneficial immunoregulatory effects including potential applications in cancer treatment.^{36,37} Positively correlates with plasma cholesterol in mice.³⁸</p>	<p>4 bacteria are enriched with aspirin use versus no medication and includes <i>Bacteroides</i> spp., <i>Prevotella</i> spp., <i>Barnesiella</i> spp. and the family Ruminococaceae.³⁹</p>	<p><i>Lactobacillus kefir</i> was given to 20 healthy volunteers for one month and after the probiotic was discontinued for a month, <i>Bacteroides</i>, <i>Barnesiella</i>, <i>Clostridium</i>, <i>Veillonella</i> and other species were significantly reduced compared to baseline samples.⁴⁰</p>
<i>Odoribacter</i> spp.	<p>This genus includes three species: <i>O. denticanis</i>, <i>O. laneus</i>, <i>O. splanchnicus</i>.⁴¹</p> <p>Produces butyrate, acetate, propionate, indole from tryptophan, products of protein breakdown, hydrogen and H₂S.⁴¹</p>	<p>Animal based diets have been found to increase <i>Odoribacter</i> spp.⁴²</p> <p>Levels of <i>Bacteroides</i>, <i>Faecalibacterium</i>, <i>Odoribacter</i>, and others enriched after pomegranate extract consumption in overweight-obese subjects. Serum endotoxemia marker LBP was reduced.⁴³</p>	<p>Higher fiber intake is associated with lower abundance of <i>Odoribacter</i>.²¹</p>
<i>Prevotella</i> spp.	<p>The <i>Prevotella</i> genus is comprised of more than 40 species, and three predominate in the gut with <i>P. copri</i> being most abundant. The majority of <i>Prevotella</i> spp. are found in the oral cavity.⁴⁴</p> <p><i>Prevotella</i> has been linked with chronic inflammatory conditions and insulin resistance,⁴⁴ however others have linked <i>P. copri</i> with improved glucose tolerance in diets rich in fiber. <i>Prevotella</i> effects may be diet-dependent. For example, <i>P. copri</i> strains associated with an omnivorous diet may result in higher BCAA synthesis, a risk factor for</p>	<p>A <i>Prevotella</i>-dominated microbiome is richer in response to plant-based, complex carb, high-fiber diet.⁵¹</p> <p>Individuals with a high <i>Prevotella</i>-to-<i>Bacteroides</i> ratio lost more body weight and body fat compared to individuals with low P/B, confirming that individuals with a high P/B are more susceptible to weight loss on a diet rich in dietary fiber (30+grams).⁵⁰</p> <p>4 bacteria are enriched with aspirin use versus no medication and includes <i>Bacteroides</i> spp., <i>Prevotella</i> spp., <i>Barnesiella</i> spp. and the family Ruminococaceae.³⁹</p> <p>Cigarette smoking is associated with increased levels.⁵²</p>	<p><i>Lactobacillus kefir</i> was given to 20 healthy volunteers and at the end of one month, <i>Prevotella</i> and other species were reduced compared to baseline samples.⁴⁰</p> <p>A Standard American Diet (low-fiber/high-animal based) has been associated with reduced levels and less diversity of <i>Prevotella</i>.⁵³</p>

Commensal Bacteria

Organism	Description	Increased Levels	Decreased Levels
	<p>glucose intolerance and DM2, whereas fiber-rich diets were linked to <i>P. copri</i> types with enhanced potential for carbohydrate metabolism.^{45,46}</p> <p>Acetate, propionate, and succinate producer;^{47,48} mucin degrader.⁴⁹</p> <p>Generally associated with traditional, agrarian diets across Africa, Asia, and South America.⁵⁰</p>	<p>Red wine polyphenol intake for 4 weeks in 10 healthy males was associated with increased <i>Prevotella</i>.¹⁷</p>	
<i>Anaerotruncus colihominis/massiliensis</i>	<p>The genus <i>Anaerotruncus</i> includes species <i>Anaerotruncus colihominis</i> and <i>Anaerotruncus massiliensis</i>.</p> <p><i>A. colihominis</i> is a butyrate and acetate producer.⁵⁴ Abundance is associated with higher bacterial gene richness in the gut.⁵⁵</p> <p><i>A. colihominis</i> is increased in healthy individuals and presumed to be anti-inflammatory.⁵⁶ There is an inverse correlation with high BMI and elevated serum triglycerides in older Amish adults.⁵⁷</p> <p>There is an inverse relationship with <i>A. colihominis</i> abundance and cognitive function scores in patients with Alzheimer's disease.⁵⁸</p> <p><i>A. massiliensis</i> is a newly identified strain similar to <i>A. colihominis</i>.^{59,60} They both ferment amino acids and carbohydrates and are mucin degraders.⁶¹</p>	<p><i>Anaerotruncus</i> abundance is associated with high saturated fat consumption in a study on healthy individuals.⁶²</p> <p>In a study on older men, adherence to a Western diet is associated with higher relative abundance of several bacteria including the genus <i>Anaerotruncus</i>.⁶³</p>	
<i>Butyrivibrio crossotus</i>	<p>Butyrate producer.⁵⁵</p> <p>Abundance may help protect against weight gain.⁵⁵</p> <p>Abundance associated with higher bacterial gene richness in the gut.⁵⁵</p>	<p><i>B. crossotus</i> correlated with xylanase/xylosidase enzymes that break down complex carbohydrates, mainly from grains.⁶⁴</p> <p>Higher counts of <i>Butyrivibrio</i> spp. appear to be associated with a diet richer in complex carbohydrates than animal protein.⁶⁵</p>	
<i>Clostridium</i> spp.	<p><i>Clostridium</i> spp. is a genus belonging to the phylum Firmicutes. While interpreting the literature, careful attention should be paid to the phylogenetic classification of this group due to minor spelling differences between the</p>	<p>Cigarette smoking is associated with increased levels.⁵²</p> <p>Coffee was positively associated with the relative abundance of <i>Clostridium</i>, <i>Lactobacillus</i>, and <i>Lactococcus</i> in 23 allergic patients.⁷¹</p>	<p><i>Lactobacillus kefir</i> was given to 20 healthy volunteers for one month and after the probiotic was discontinued for a month, <i>Bacteroides</i>, <i>Barnesiella</i>, <i>Clostridium</i>, <i>Veillonella</i> and other</p>

Commensal Bacteria

Organism	Description	Increased Levels	Decreased Levels
	<p>taxonomic levels. Beyond the phylum level, it is broken down as follows: Class: Clostridia, Order: Clostridiales, Family: Clostridiaceae, and finally, Genus: <i>Clostridium</i>. The <i>Clostridium</i> genus contains more than 100 species, most of which are commensal, however it does include pathogens. The literature discusses Clostridial clusters, which may include other species belonging to <i>Eubacterium</i>, <i>Ruminococcus</i>, <i>Roseburia</i>, <i>Butyrivibrio</i>, <i>Faecalibacterium</i> and other genera. These clusters exist due to historic issues with classification, where unclassified species would be moved into the <i>Clostridium</i> category.^{66,67}</p> <p>The <i>Clostridium</i> spp. probe is not meant to diagnose pathogenic <i>Clostridium</i> infections. An add-on <i>Clostridium difficile</i> EIA stool test is available if patient symptoms warrant testing.</p> <p>Produces butyrate, acetate, hydrogen, secondary bile acids, beta-glucuronidase.^{23,68,69}</p> <p>Along with <i>Methanobrevibacter smithii</i>, certain <i>Clostridium</i> and <i>Bacteroides</i> spp. can produce methane gas.⁷⁰</p> <p>Necessary for immune homeostasis.⁶⁶</p> <p>Many of its species are associated with lower bacterial gene richness.²⁵</p>	<p>A high beef diet was associated with increases in <i>Bacteroides</i> and <i>Clostridium</i> spp. in 10 volunteers.²⁷</p>	<p>species were significantly reduced compared to baseline samples.⁴⁰</p> <p>After 12 weeks, a significant increase in <i>Bifidobacteria</i>, and decrease in pathogenic <i>Clostridium</i> spp. (<i>C. histolyticum</i> and <i>C. coccoides</i> clusters) were observed in 57 HIV positive adults supplemented with a prebiotic oligosaccharide powder (15 or 30 g short chain galactooligosaccharides/long chain fructooligosaccharides/pectin hydrolysate-derived acidic oligosaccharides (scGOS/lcFOS/pAOS)).⁷²</p>
<i>Coprococcus eutactus</i>	<p>Butyrate producer.^{47,73}</p> <p>Abundance associated with greater bacterial gene richness in the gut.⁵⁵</p>	<p>Higher abundance was seen on a very low protein diet supplemented with select amino acids in patients with chronic kidney disease. <i>C. eutactus</i> correlated with fiber, vegetable proteins, potassium, and ketoanalogs.⁷⁴</p>	
<i>Faecalibacterium prausnitzii</i>	<p><i>Faecalibacterium prausnitzii</i> belongs to the <i>Clostridium</i> cluster IV, also known as the <i>Clostridium leptum</i> group.^{67,75}</p> <p>Predominant butyrate-producer contributing to a healthy mucosa and barrier function. Controls inflammation through inflammatory cytokine inhibition. <i>F. prausnitzii</i> produces an anti-inflammatory protein called Microbial Anti-</p>	<p>There are many studies on the beneficial effects of fiber and prebiotics on increasing <i>F. prausnitzii</i> levels, however some studies show mixed results in various populations. This may be due to the many strains of <i>F. prausnitzii</i> responding to different substrates.^{75,76}</p> <p>Higher fiber intake is associated with higher abundance of <i>Faecalibacterium</i>.^{21,77}</p>	<p>A small study of 10 healthy subjects showed reduced <i>F. prausnitzii</i> after 1 month on a gluten-free diet (GFD).⁸⁸ Another study did not find a change in <i>F. prausnitzii</i> levels on a GFD in healthy individuals, but did observe a decrease in abundance of other butyrate-producing bacteria in the Firmicutes phylum.⁸⁹</p>

Commensal Bacteria

Organism	Description	Increased Levels	Decreased Levels
	<p>inflammatory Molecule (MAM) which inhibits the activation of NF-κB.^{76,77}</p> <p>There are many strains of <i>F. prausnitzii</i> that respond to different substrates including simple carbohydrates, amino acids, pectin, non-digestive polysaccharides, and host-derived mucosal substrates.⁷⁶ It ferments glucose and acetate to produce formate, D-lactate, and butyrate.⁷⁷</p> <p><i>F. prausnitzii</i> is an extremely oxygen-sensitive anaerobe. Therefore, the development of a therapeutic supplement proves challenging.⁷⁷</p> <p><i>F. prausnitzii</i> growth and butyrate production is favored at a lower pH in culture, around 5.7 to 6.7.^{76,78}</p>	<p>Long-term consumption of a low-fat, high complex carbohydrate diet was associated with increased abundance of <i>F. prausnitzii</i>, in an obese population.⁷⁹</p> <p>Levels of <i>Bacteroides</i>, <i>Faecalibacterium</i>, <i>Odoribacter</i>, and others enriched after pomegranate extract consumption in overweight-obese subjects. Serum endotoxemia marker LBP was reduced.⁴³</p> <p>Levels increased after polydextrose and soluble corn fiber intake.⁸⁰</p> <p><i>F. prausnitzii</i> was more abundant in a raffinose and chick pea diet compared to controls.⁷⁵</p> <p>Inulin and inulin-type fructans increased <i>Bifidobacterium</i> and <i>F. prausnitzii</i>.^{29,77,81} A systematic review of inulin supplementation in humans showed an increase in <i>Bifidobacterium</i>, and a relative increase in <i>Faecalibacterium</i> and <i>Lactobacillus</i>, and decrease in relative abundance of <i>Bacteroides</i>.⁸²</p> <p>Red wine consumption was associated with an increased abundance of <i>F. prausnitzii</i>.⁸³ In ten metabolic syndrome patients, red wine polyphenols significantly increased the number of fecal <i>Bifidobacteria</i> and <i>Lactobacillus</i> (intestinal barrier protectors) and butyrate-producing bacteria (<i>Faecalibacterium prausnitzii</i> and <i>Roseburia</i>) at the expense of less desirable groups of bacteria such as LPS producers (<i>Escherichia coli</i> and <i>Enterobacter cloacae</i>).⁸⁴</p> <p>Most strains can grow on apple pectin.⁷⁶</p> <p>A decline in <i>F. prausnitzii</i> in 20 patients with IBS on a low FODMAP diet can be recovered with supplementation of prebiotic fructo-oligosaccharides (FOS).⁸⁵</p> <p>Physical activity at doses as low as the minimum recommended by the WHO may increase health-promoting species including <i>Bifidobacterium</i> spp., <i>Roseburia hominis</i>, <i>Akkermansia muciniphila</i> and <i>Faecalibacterium prausnitzii</i>. However, in a study</p>	<p>A low FODMAP diet in 52 IBD patients resulted in lower <i>Bifidobacterium adolescentis</i>, <i>Bifidobacterium longum</i>, and <i>Faecalibacterium prausnitzii</i> than patients on a control diet. However, microbiome diversity and markers of inflammation did not differ between the IBD and control groups.⁹⁰ Lower <i>F. prausnitzii</i> and <i>Bifidobacterium</i> was observed in 20 patients with IBS-D or IBS-M on a low FODMAP diet. Additionally, total SCFAs and n-butyrate were lower.⁸⁵</p> <p>Excess bile salt.⁷⁶</p> <p>A ketogenic, low-carbohydrate, high-fat diet was associated with a reduction of <i>Faecalibacterium</i> and abundance of <i>Bacteroides</i> and <i>Dorea</i> spp. in competitive race walkers.⁹¹ However another study on a ketogenic diet in 6 patients with GLUT1 Deficiency Syndrome did not have an effect on <i>F. prausnitzii</i>.⁹²</p> <p>Oral versus IV iron supplementation in iron-deficient IBD patients resulted in decreased abundances of <i>Faecalibacterium prausnitzii</i>, <i>Ruminococcus bromii</i>, <i>Dorea</i> spp., and <i>Collinsella aerofaciens</i>.⁹³</p>

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Organism	Description	Increased Levels	Decreased Levels
		<p>comparing sedentary to active women, dietary differences were noted, which may account for the bacterial differences. The active group consumed more fiber, fruits and vegetables, and the sedentary group consumed more processed meats.⁸⁶</p> <p>The poorly absorbed antibiotic rifaximin was associated with increases in beneficial bacteria <i>F. prausnitzii</i>, <i>Bifidobacterium</i>, and <i>Lactobacillus</i> in human studies.⁸⁷</p>	
<i>Lactobacillus</i> spp.	<p>There are over 170 species of <i>Lactobacillus</i>.⁹⁴ Many species and strains are found in probiotic supplements and fermented foods. There are numerous studies on the therapeutic benefits of probiotics.⁹⁵</p> <p>Ferments carbohydrates to produce lactic acid, inhibits the colonization of pathogens, enhances barrier integrity, and beneficially modulates the immune system.⁹⁵</p> <p>Both <i>Lactobacillus</i> and <i>Bifidobacterium</i> (probiotic bacteria) are involved in the process of converting polyphenols to phytoestrogens, converting glucosinolates from cruciferous vegetables to isothiocyanates which are cytoprotective and antioxidative, B vitamin production, and SCFA production.⁹⁶ Along with <i>Oxalobacter formigenes</i>, <i>Lactobacillus</i> and <i>Bifidobacterium</i> are also capable of consuming oxalate.⁹⁷</p>	<p>Whey and pea protein, a Mediterranean diet, polyphenols (catechins, flavonols, flavones, anthocyanins, proanthocyanidins, phenolic acids found in fruits, seeds, vegetables, tea, cocoa, wine) increase beneficial bacteria <i>Lactobacillus</i> and <i>Bifidobacterium</i>.⁹⁸</p> <p>A study using a partially hydrolyzed guar gum preparation was administered to 15 constipated women for 3 weeks. <i>Lactobacillus</i> spp. increased and constipation improved.⁹⁹</p> <p>In ten metabolic syndrome patients, red wine polyphenols significantly increased the number of fecal <i>Bifidobacteria</i> and <i>Lactobacillus</i> (intestinal barrier protectors) and butyrate-producing bacteria (<i>Faecalibacterium prausnitzii</i> and <i>Roseburia</i>) at the expense of less desirable groups of bacteria such as LPS producers (<i>Escherichia coli</i> and <i>Enterobacter cloacae</i>).⁸⁴</p> <p>A systematic review of inulin supplementation in humans showed an increase in <i>Bifidobacterium</i>, and a relative increase in <i>Faecalibacterium</i> and <i>Lactobacillus</i>, and decrease in relative abundance of <i>Bacteroides</i>.⁸²</p> <p>Coffee was positively associated with the relative abundance of <i>Clostridium</i>, <i>Lactobacillus</i>, and <i>Lactococcus</i> in 23 allergic patients.⁷¹</p> <p>The poorly absorbed antibiotic rifaximin was associated with increases in beneficial bacteria <i>F. prausnitzii</i>, <i>Bifidobacterium</i>, and <i>Lactobacillus</i> in human studies.⁸⁷</p>	<p>A small study of 10 healthy subjects showed reduced <i>Lactobacillus</i>, <i>Bifidobacterium</i> and <i>Bifidobacterium longum</i> after 1 month on a gluten-free diet (GFD).⁸⁸</p> <p>High saturated and trans-fat, found in a Western diet, increases the risk of cardiovascular disease and reduces <i>Lactobacillus</i>.⁹⁶</p> <p>A Western diet is associated with decreased <i>Lactobacilli</i> and <i>Bifidobacteria</i>.⁹⁸</p>
<i>Pseudoflavonifractor</i> spp.	<p>Small group made up of two species: <i>Pseudoflavonifractor capillosus</i> and <i>Pseudoflavonifractor phocaeensis</i>.¹⁰⁰</p>		<p>Decreased in long-term users of proton pump inhibitors.¹⁰²</p>

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Organism	Description	Increased Levels	Decreased Levels
	Study participants who succeeded in losing weight consistently had a microbiota enriched in <i>Pseudoflavonifractor</i> at baseline. ¹⁰¹		
<i>Roseburia</i> spp.	<p>The genus <i>Roseburia</i> includes 5 species: <i>Roseburia intestinalis</i>, <i>R. hominis</i>, <i>R. inulinivorans</i>, <i>R. faecis</i> and <i>R. cecicola</i>.^{77,103}</p> <p>The <i>Roseburia</i> genus, along with <i>Faecalibacterium</i> are the predominant butyrate producers in the human GI tract.¹⁰⁴ <i>Roseburia</i> is involved in immune maintenance and is anti-inflammatory.¹⁰³</p>	<p>Higher <i>Roseburia</i> is associated with consuming a plant-based diet, Mediterranean diet and fiber-rich foods.^{79,105,106}</p> <p><i>Roseburia</i> increased on resistant starch diet.¹⁰⁷</p> <p>In ten metabolic syndrome patients, red wine polyphenols significantly increased the number of fecal <i>Bifidobacteria</i> and <i>Lactobacillus</i> (intestinal barrier protectors) and butyrate-producing bacteria (<i>Faecalibacterium prausnitzii</i> and <i>Roseburia</i>) at the expense of less desirable groups of bacteria such as LPS producers (<i>Escherichia coli</i> and <i>Enterobacter cloacae</i>).⁸⁴</p> <p>Physical activity at doses as low as the minimum recommended by the WHO may increase health-promoting species including <i>Bifidobacterium</i> spp., <i>Roseburia hominis</i>, <i>Akkermansia muciniphila</i> and <i>Faecalibacterium prausnitzii</i>. However, in a study comparing sedentary to active women, dietary differences were noted, which may account for the bacterial differences. The active group consumed more fiber, fruits and vegetables, and the sedentary group consumed more processed meats.⁸⁶</p>	<p><i>R. faecis</i> decreased on a gluten-free diet in 21 healthy volunteers.⁸⁹</p> <p>A small study on 11 healthy volunteers showed that an animal-based diet increased the abundance of bile-tolerant microorganisms (<i>Alistipes</i>, <i>Bilophila</i> and <i>Bacteroides</i>) and decreased the levels of Firmicutes that metabolize dietary plant polysaccharides (<i>Roseburia</i>, <i>Eubacterium rectale</i> and <i>Ruminococcus bromii</i>).¹⁰⁸</p> <p><i>Roseburia</i> decreased on a high-protein, low-carbohydrate weight loss diet in 14 overweight men.¹⁰⁷</p>
<i>Ruminococcus bromii</i>	<p><i>R. bromii</i> ferments resistant starch which is correlated with increased butyrate production downstream.^{109,110} The major fermentation products include acetate, H₂, and CO₂.¹¹⁰</p> <p>The byproducts of the degradation of resistant starch are used by bacterial species. Therefore, <i>R. bromii</i> supports microbiome diversity through cross-feeding.¹¹¹</p> <p>One study showed that five species, including <i>R. bromii</i>, were significantly more abundant in stool samples from obese individuals versus non-obese individuals.¹¹²</p> <p><i>R. bromii</i> is enriched in healthy twins versus those with food allergies.¹¹³ An infant study</p>	<p><i>R. bromii</i> increased on a resistant starch diet.^{89,107}</p> <p>In a study on 360 Spanish adults with different levels of adherence to a Mediterranean diet, legume consumption was shown to enhance <i>R. bromii</i>.¹¹⁵</p> <p>In a population study on 156 asymptomatic Mexican adults, <i>Blastocystis</i> colonization was strongly correlated with an increase in <i>R. bromii</i>.¹¹⁶</p>	<p><i>R. bromii</i> decreased on a gluten-free diet in 21 healthy volunteers.⁸⁹</p> <p>A small study on 11 healthy volunteers showed that an animal-based diet increased the abundance of bile-tolerant microorganisms (<i>Alistipes</i>, <i>Bilophila</i> and <i>Bacteroides</i>) and decreased the levels of Firmicutes that metabolize dietary plant polysaccharides (<i>Roseburia</i>, <i>Eubacterium rectale</i> and <i>Ruminococcus bromii</i>).¹⁰⁸</p> <p>Oral versus IV iron supplementation in iron deficient IBD patients resulted in decreased abundances of</p>

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Organism	Description	Increased Levels	Decreased Levels
	showed that depletion of <i>R. bromii</i> and <i>Akkermansia muciniphila</i> was associated with reduced butyrate and the development of atopic dermatitis. ¹¹⁴		<i>Faecalibacterium prausnitzii</i> , <i>Ruminococcus bromii</i> , <i>Dorea</i> spp., and <i>Collinsella aerofaciens</i> . ⁹³ A study on 409 type 2 diabetes Chinese patients demonstrated the reduction of <i>R. bromii</i> with berberine. It is thought that the hypoglycemic effect of berberine is mediated by the inhibition of secondary bile acid biotransformation by <i>R. bromii</i> . ¹¹⁷
<i>Veillonella</i> spp.	The genera <i>Veillonella</i> contains 12 Gram-negative species. This phylogenetic grouping is unusual as the larger Firmicutes phylum is comprised of Gram-positive bacteria. ¹¹⁸ <i>V. parvula</i> is often isolated from the human oral cavity and has also been found in the intestinal tract. Like other gram-negative bacteria, it produces LPS and in the oral cavity it is known to produce biofilm. ^{119,120} Utilizes lactate to produce SCFAs acetate and propionate; ^{68,121} H ₂ producer. ¹²²	Postprandial levels of lactose after milk intake in 14 healthy men were positively correlated with the abundance of <i>Veillonella</i> . ¹²³ The family <i>Veillonellaceae</i> increased with supplemental polydextrose and soluble corn fiber in 20 healthy adult males. ¹²⁴ This family includes genera other than <i>Veillonella</i> , although <i>Veillonella</i> represents the majority of this family. ¹¹⁸ <i>Veillonella</i> spp. increased following Roux-en-Y gastric bypass RYGB within the first 3 months and remained elevated for the first year. ¹²⁵	<i>Lactobacillus kefir</i> was given to 20 healthy volunteers for one month and after the probiotic was discontinued for a month, <i>Bacteroides</i> , <i>Barnesiella</i> , <i>Clostridium</i> , <i>Veillonella</i> and other species were significantly reduced compared to baseline samples. ⁴⁰ The family <i>Veillonellaceae</i> was decreased on a gluten-free diet in 21 healthy volunteers. ⁸⁹ This family includes genera other than <i>Veillonella</i> , although <i>Veillonella</i> represents the majority of this family. ¹¹⁸
<i>Bifidobacterium</i> spp.	Many species and strains are found in probiotic supplements and there are extensive studies on the therapeutic benefits of probiotics. Probiotics can beneficially modulate the microbiome and immune system. ¹²⁶ Both <i>Lactobacillus</i> and <i>Bifidobacterium</i> (probiotic bacteria) are involved in the process of converting polyphenols to phytoestrogens, converting glucosinolates from cruciferous vegetables to isothiocyanates which are cytoprotective and antioxidative, B vitamin production, and SCFA production. ⁹⁶ Along with <i>Oxalobacter formigenes</i> , <i>Lactobacillus</i> and <i>Bifidobacterium</i> are also capable of consuming oxalate. ⁹⁷ <i>Bifidobacteria</i> can prevent GI infections by competitive exclusion of pathogens. ¹²⁶ They are equipped with genes related to carbohydrate metabolism from	Whey and pea protein increase beneficial bacteria <i>Lactobacillus</i> and <i>Bifidobacterium</i> . ⁹⁸ Human studies on individuals consuming partially hydrolyzed guar gum show an increase in <i>Bifidobacterium</i> and butyrate-producing bacteria. ¹²⁹⁻¹³¹ Daily walnut consumption (43 g) in 194 healthy individuals was associated with increased abundance of <i>Ruminococcus</i> and <i>Bifidobacterium</i> . ¹³² Red wine polyphenol intake for 4 weeks in 10 healthy males was associated with increased <i>Bifidobacterium</i> . ¹⁷ In ten metabolic syndrome patients, red wine polyphenols significantly increased the number of fecal <i>Bifidobacteria</i> and <i>Lactobacillus</i> (intestinal barrier protectors) and butyrate-producing bacteria (<i>Faecalibacterium prausnitzii</i> and <i>Roseburia</i>) at the expense of less desirable groups of	Cigarette smoking is associated with decreased levels. ⁵² A high beef diet was associated with a decrease in <i>B. adolescentis</i> in 10 volunteers. ²⁷ A low FODMAP diet in 52 IBD patients resulted in lower <i>Bifidobacterium adolescentis</i> , <i>Bifidobacterium longum</i> , and <i>Faecalibacterium prausnitzii</i> than in patients on a control diet. However, microbiome diversity and markers of inflammation did not differ between the IBD and control groups. ⁹⁰ Lower <i>F. prausnitzii</i> and <i>Bifidobacterium</i> was observed in 20 patients with IBS-D or IBS-M on a low FODMAP diet. Additionally, total SCFAs and n-butyrate

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Organism	Description	Increased Levels	Decreased Levels
	<p>plants in the diet, milk oligosaccharides, and host-derived glycans. They produce acetate that facilitates the cross-feeding of other bacteria, including butyrate-producers.⁷⁷ They also produce lactic acid.¹²⁷</p> <p>Along with <i>Collinsella</i>, can modify bile acids to modulate the virulence and pathogenicity of enteric pathogens.¹²⁸</p>	<p>bacteria such as LPS producers (<i>Escherichia coli</i> and <i>Enterobacter cloacae</i>).⁸⁴</p> <p>The prebiotic effects of FOS, GOS, inulin, and lactulose have been thoroughly assessed in human trials and suggest a beneficial impact on the microbiome by increasing <i>Bifidobacterial</i> levels and decreasing <i>E. coli</i> and enterococci.¹²⁶ A systematic review of inulin supplementation in humans showed an increase in <i>Bifidobacterium</i>, and a relative increase in <i>Faecalibacterium</i> and <i>Lactobacillus</i>, and decrease in relative abundance of <i>Bacteroides</i>.⁸²</p> <p>Physical activity at doses as low as the minimum recommended by the WHO may increase health-promoting species including <i>Bifidobacterium</i> spp., <i>Roseburia hominis</i>, <i>Akkermansia muciniphila</i> and <i>Faecalibacterium prausnitzii</i>. However, in a study comparing sedentary to active women, dietary differences were noted, which may account for the bacterial differences. The active group consumed more fiber, fruits and vegetables, and the sedentary group consumed more processed meats.⁸⁶</p> <p>The poorly absorbed antibiotic rifaximin was associated with increases in beneficial bacteria <i>F. prausnitzii</i>, <i>Bifidobacterium</i>, and <i>Lactobacillus</i> in human studies.⁸⁷</p>	<p>were lower.⁸⁵ Another study in patients with functional GI disorders with flatulence compared a low FODMAP diet with the effects of a prebiotic supplement. <i>Bifidobacterium</i> was reduced in the low FODMAP group and increased in the prebiotic group.¹³³</p> <p>A small study of 10 healthy subjects showed reduced <i>Lactobacillus</i>, <i>Bifidobacterium</i> and <i>Bifidobacterium longum</i> after 1 month on a gluten-free diet (GFD).⁸⁸</p> <p>A study on 250 vegetarian and vegan individuals showed lower counts of <i>Bifidobacterium</i> spp. (vegan), <i>Bacteroides</i> spp. (vegan) and <i>E. coli</i> (vegan and vegetarian).¹³⁴</p>
<i>Bifidobacterium longum</i>	<p><i>Bifidobacterium longum</i> is comprised of multiple subspecies the beneficially modulate the immune system.^{126,135} It is found in probiotic supplements and fermented foods.</p> <p>Lactate producer; acetate producer. Utilizes diet-derived carbohydrates.¹²⁶</p>	<p>Long-term consumption of Mediterranean diet partially restored <i>B. longum</i> in metabolic syndrome patients.¹³⁶</p>	<p><i>B. longum</i> and <i>B. adolescentis</i> suppressed by rice in 26 Mongolian individuals who consumed wheat, rice, and oat as the sole carbohydrate staple food for a week each.⁶⁴</p> <p>A low FODMAP diet in 52 IBD patients resulted in lower <i>Bifidobacterium adolescentis</i>, <i>Bifidobacterium longum</i>, and <i>Faecalibacterium prausnitzii</i> than patients on a control diet. However, microbiome diversity and markers of inflammation did not differ between the IBD and control groups.⁹⁰</p> <p>A small study of 10 healthy subjects showed reduced <i>Lactobacillus</i>,</p>

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Organism	Description	Increased Levels	Decreased Levels
			<i>Bifidobacterium</i> and <i>Bifidobacterium longum</i> after 1 month on a gluten-free diet (GFD). ⁸⁸
<i>Collinsella aerofaciens</i>	<p>Possibly proinflammatory, may play a role in altering intestinal barrier integrity.^{137,138}</p> <p>Produces H₂, ethanol, short-chain fatty acids including butyrate, and lactate and is a major utilizer of lactose.^{128,139} Contains bile salt hydrolases to metabolize bile,²⁶ and along with <i>Bifidobacterium</i>, can modify bile acids to modulate the virulence and pathogenicity of enteric pathogens.¹²⁸</p> <p>Consumes oligosaccharides and simple sugars.¹⁴⁰</p>	<p><i>C. aerofaciens</i> higher levels in healthy adults consuming a whole grain diet (40 g fiber) compared to a red meat diet.¹⁴¹ Studies are mixed on the association with fiber and the <i>Collinsella</i> genus,¹⁴² which contains at least 6 species.¹⁴³</p> <p>Higher levels found in non-vegetarian versus vegetarian Thai adults that were healthy.¹⁴⁴</p>	<p>Decreased on a high-protein, low-carb weight loss diet in a study in 14 overweight men.¹⁰⁷</p> <p><i>C. aerofaciens</i> reduced in elderly subjects taking NSAIDs compared to elderly subjects not taking NSAIDs, or in young adults.¹⁴⁵</p> <p>Oral versus IV iron supplementation in iron-deficient IBD patients resulted in decreased abundances of <i>Faecalibacterium prausnitzii</i>, <i>Ruminococcus bromii</i>, <i>Dorea</i> spp., and <i>Collinsella aerofaciens</i>.⁹³</p>
<i>Desulfovibrio piger</i>	<p><i>Desulfovibrio piger</i> is Gram-negative and the most common sulfate-reducing bacteria (SRB) in healthy adults. Although SRB are positively associated with inflammation, both pro- and anti-inflammatory signaling have been attributed to H₂S.¹⁴⁰</p> <p>Utilizes H₂ and lactate and releases acetate and hydrogen sulfide (H₂S). H₂S is highly toxic to colonic mucosa. H₂S may create colonic cellular energy deficiency by inhibiting the beta-oxidation of butyrate.^{146,147} May work together with <i>Collinsella aerofaciens</i>, a hydrogen producer.¹⁴⁰</p> <p>H₂S can be derived from sulfur compounds in the diet including sulfur-containing amino acids or endogenous mucin.¹⁴⁶ Sulfate and sulfite are used as preservatives, additives and antioxidants in foods such as bread, preserved meat, dried fruit, carrageenan, and wine, and is also present in the supplement chondroitin sulfate.¹⁴⁰</p>	<p>A study on sigmoid biopsies from 9 healthy subjects over 9 months showed correlation with <i>Desulfovibrio</i> spp. and red meat and cholesterol intake.¹⁴⁹ The <i>Desulfovibrio</i> genus contains several species, so it is not clear whether this correlation pertains to <i>D. piger</i>, specifically.</p>	<p><i>D. piger</i> was reduced with supplemental <i>Lactobacillus plantarum</i>.¹⁵⁰</p> <p>A study on 10 healthy individuals showed reduction of H₂S with bismuth subsalicylate. The study only looked at H₂S levels, not bacterial composition.¹⁵¹</p> <p>A diet containing whole grains, traditional Chinese medicinal foods and prebiotics was given to 93 overweight individuals and resulted in a decrease in the family <i>Desulfovibrionaceae</i>.¹⁵² The <i>Desulfovibrionaceae</i> family contains several species, so it is not clear whether this correlation pertains to <i>D. piger</i>, specifically.</p>

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Organism	Description	Increased Levels	Decreased Levels
	Displays resistance to most broad-spectrum antibiotics, as H ₂ S is a defense mechanism against antimicrobials. ¹⁴⁸		
<i>Escherichia coli</i>	<p><i>Escherichia coli</i> is a Gram-negative facultative anaerobe.¹⁵³ Many strains belong to the species <i>Escherichia coli</i>, and most strains are harmless, normal GI inhabitants. The <i>Escherichia coli</i> probe is not meant to diagnose pathogenic <i>E. coli</i> infections. An add-on shiga-toxin producing <i>E. coli</i> EIA stool test is available if patient symptoms warrant testing.</p> <p>H₂S producer.¹⁴⁸ Ethanol producer which may promote gut permeability.¹⁵⁴ Both commensal and pathogenic strains capable of biofilm production. The presence of mucin stimulates biofilm formation and <i>E. coli</i> utilizes mono-, disaccharides and other simple glycoprotein degradation molecules to form the biofilm.¹⁵⁵ Produces vitamin K and vitamin B12.¹⁵³</p> <p><i>E. coli</i> has been associated with intestinal inflammatory disorders in animal and human studies.¹⁵⁵</p> <p>Consumes oligosaccharides and simple sugars and ferments amino acids.¹⁴⁰ Consumes oxygen, thus maintaining an environment for strictly anaerobic bacteria. Competitively excludes pathogens.¹⁵³</p> <p><i>E. coli</i> Nissle is a probiotic that has a protective effect on the intestinal barrier and can ameliorate certain GI disorders.^{156,157}</p> <p><i>E. coli</i> thrives in higher stool pH environments, as seen in omnivorous diets higher in animal protein.¹³⁴</p>	A small study of 10 healthy subjects showed increased <i>E. coli</i> and reduced <i>Lactobacillus</i> , <i>Bifidobacterium</i> and <i>Bifidobacterium longum</i> after 1 month on a gluten-free diet (GFD). ⁸⁸	<p>In ten metabolic syndrome patients, red wine polyphenols significantly increased the number of fecal <i>Bifidobacteria</i> and <i>Lactobacillus</i> (intestinal barrier protectors) and butyrate-producing bacteria (<i>Faecalibacterium prausnitzii</i> and <i>Roseburia</i>) at the expense of less desirable groups of bacteria such as LPS producers (<i>Escherichia coli</i> and <i>Enterobacter cloacae</i>).⁸⁴</p> <p>A study on 250 vegetarian and vegan individuals showed lower counts of <i>Bifidobacterium</i> spp. (vegan), <i>Bacteroides</i> spp. (vegan) and <i>E. coli</i> (vegan and vegetarian). <i>E. coli</i> was lower in groups with lower stool pH, as seen in higher carbohydrate and fiber diets.¹³⁴</p> <p>The prebiotic effects of FOS, GOS, inulin, and lactulose have been thoroughly assessed in human trials and suggest a beneficial impact on the microbiome by increasing <i>Bifidobacterial</i> levels and decreasing <i>E. coli</i> and enterococci.¹²⁶</p>
<i>Oxalobacter formigenes</i>	Gram negative anaerobic bacteria that depends on oxalate metabolism for energy. Key bacterium responsible for the degradation of oxalate, therefore reducing oxalate absorption, oxalate excretion in urine, and the risk of calcium oxalate kidney stones developing. ^{97,158}		Sensitive to and reduced with commonly used antibiotics. ⁹⁷

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Organism	Description	Increased Levels	Decreased Levels
	Lactobacillus and Bifidobacterium are also capable of consuming oxalate. ⁹⁷		
<i>Methanobrevibacter smithii</i>	<p><i>Methanobrevibacter smithii</i> is not a bacteria, but rather an archaea, and is the most common methanogen in humans.¹⁵⁹ It uses CO₂ and H₂ to produce methane gas.¹⁶⁰ <i>M. smithii</i> levels correlate with breath methane levels.¹⁵⁹ (This correlation was also observed in an internal Genova data analysis.)</p> <p>Certain <i>Clostridium</i> and <i>Bacteroides</i> spp. can produce methane gas.⁷⁰</p> <p>Methane has been associated with constipation, possibly due to the gasotransmitter effect on intestinal transit.⁷⁰</p> <p>It is suggested that since methanogens consume hydrogen, flatulence is reduced through a 4:1 conversion of hydrogen gas to methane gas.¹⁶¹</p> <p><i>M. smithii</i> is strongly associated with the presence of the parasite <i>Blastocystis</i>.¹⁶² (This correlation was also observed in an internal Genova data analysis.)</p>	<p><i>M. smithii</i> is present in milk products and their consumption may determine archaeal gut colonization in children.¹⁶³</p> <p>Methanobrevibacter levels were positively associated with diets high in carbohydrates.¹⁶⁴</p>	<p>A smaller study on 11 prediabetic, obese patients who were treated with Rifaximin and Neomycin eradicated <i>M. smithii</i> and lowered breath methane levels. Additionally, LDL, total cholesterol, and insulin levels improved.¹⁶⁵</p> <p>Statins are being studied for their ability to lower methanogen and thus, methane levels.¹⁶⁰</p> <p>Twenty-one healthy adults received a probiotic containing <i>Lactobacillus</i> and <i>Bifidobacterium</i> strains for 60 days and abundance of <i>Methanobrevibacter</i> was reduced.¹⁶⁶</p>
<i>Fusobacterium</i> spp.	<p>The genus <i>Fusobacterium</i> has approximately 20 species.¹⁶⁷ Though most of the members of the <i>Fusobacterium</i> genus are normal commensals, the genus also comprises some questionably pathogenic species – (<i>F. nucleatum</i> has some association with colorectal cancer). Although the prevalence of <i>Fusobacterium</i> is higher in fecal samples in patients with CRC, <i>Fusobacterium</i> is a passenger that multiplies in the more favorable conditions caused by malignancy rather than a causal factor in cancer development. Commensal <i>Fusobacterium</i> are also found in the oral cavity and have been implicated in periodontal disease.¹⁶⁸</p> <p>May be proinflammatory; some species produce butyrate and H₂S.^{148,169}</p>	<p>Low fiber, high fat diet in Africans was associated with an increase of <i>F. nucleatum</i>.¹⁷⁰</p>	<p>The green and black tea extracts (EGCG) and theaflavins decreased the adherence of <i>F. nucleatum</i> to oral epithelial cells and attenuated <i>F. nucleatum</i>-mediated hemolysis and H₂S production.¹⁷¹</p> <p>Levels of Fusobacteria decreased after ingestion of barley β-glucans (whole grain barley pasta and durum wheat flour).¹⁷²</p> <p>No statistically significant associations were found between dietary and lifestyle exposures except for a positive association between higher BMI and inverse association between vegetable</p>

Commensal Bacteria

Organism	Description	Increased Levels	Decreased Levels
<i>Akkermansia muciniphila</i>	<p>Mucin degrading bacteria.¹⁷³ Low levels associated with obesity, diabetes, inflammation, and gut permeability.⁷⁷</p> <p>Produces acetate and propionate – supports the growth of butyrate producers by degrading mucin and providing acetate. Can use pseudovitamin B12 produced by other bacteria for its propionate production.¹⁷³</p> <p>May limit toxicity of sulfate-reducing bacteria – there is a release of sulfate during mucin degradation. This sulfate might be used by sulfate-reducing bacteria, producing hydrogen sulfide. In turn, <i>A. muciniphila</i> predictively harbors genes in L-cysteine biosynthesis using hydrogen sulfide, suggesting that it has a role in the detoxification of hydrogen sulfide in the intestines.¹⁷⁴</p> <p>In development as a probiotic supplement for metabolic conditions.¹⁷⁵</p>	<p>Resveratrol supplementation led to increased <i>A. muciniphila</i> in obese, insulin-resistant USA Caucasians, but not other ethnic groups.¹⁷⁶</p> <p>Pomegranate (1000 mg of pomegranate extract daily) increased levels of <i>Akkermansia</i> in 20 healthy participants.¹⁷⁷</p> <p>Significant increase in <i>A. muciniphila</i> after inulin and butyrate supplementation in 60 overweight and obese diabetic patients.¹⁷⁸</p> <p><i>Akkermansia</i> increased with polydextrose – but lowered <i>Ruminococcus</i> and <i>Coprococcus</i>.⁸⁰</p> <p>A study on 28 patients with diabetes, those taking metformin had higher <i>Akkermansia</i> compared to those not taking metformin.¹⁷⁹</p> <p>Physical activity at doses as low as the minimum recommended by the WHO may increase health-promoting species including <i>Bifidobacterium</i> spp., <i>Roseburia hominis</i>, <i>Akkermansia muciniphila</i> and <i>Faecalibacterium prausnitzii</i>. However, in a study comparing sedentary to active women, dietary differences were noted, which may account for the bacterial differences. The active group consumed more fiber, fruits and vegetables, and the sedentary group consumed more processed meats.⁸⁶ A study on a group of 40 rugby players showed higher proportions of <i>Akkermansia</i> compared with higher BMI controls. Athletes consumed more protein in the form of meat and protein supplements, as well as more vegetables, fiber, and mono/polyunsaturated fats.¹⁸⁰</p>	<p>consumption and <i>Fusobacterium</i> in advanced adenoma patients.¹⁶⁸</p> <p>Lower abundance on low FODMAP diet.^{67,181}</p>

REFERENCES

1. Hornel M. Pathogens, commensal symbionts, and pathobionts: discovery and functional effects on the host. *ILAR J*. 2015;56(2):159-162.
2. Chow J, Tang H, Mazmanian SK. Pathobionts of the gastrointestinal microbiota and inflammatory disease. *Curr Opin Immunol*. 2011;23(4):473-480.
3. Buret AG, Motta J-P, Allain T, Ferraz J, Wallace JL. Pathobiont release from dysbiotic gut microbiota biofilms in intestinal inflammatory diseases: a role for iron? *J Biomed Sci*. 2019;26(1):1.
4. Benítez-Páez A, Gómez Del Pulgar EM, Sanz Y. The Glycolytic Versatility of *Bacteroides uniformis* CECT 7771 and Its Genome Response to Oligo and Polysaccharides. *Front Cell Infect Microbiol*. 2017;7:383.
5. Xing C, Du Y, Duan T, et al. Interaction between microbiota and immunity and its implication in colorectal cancer. *Front Immunol*. 2022;13:963819.
6. Takahashi K, Nishida A, Fujimoto T, et al. Reduced Abundance of Butyrate-Producing Bacteria Species in the Fecal Microbial Community in Crohn's Disease. *Digestion*. 2016;93(1):59-65.
7. Pellock SJ, Walton WG, Biernat KA, et al. Three structurally and functionally distinct β -glucuronidases from the human gut microbe *Bacteroides uniformis*. *J Biol Chem*. 2018;293(48):18559-18573.
8. Qiao S, Bao L, Wang K, et al. Activation of a Specific Gut Bacteroides-Folate-Liver Axis Benefits for the Alleviation of Nonalcoholic Hepatic Steatosis. *Cell Rep*. 2020;32(6):108005.
9. Neef A, Sanz Y. Future for probiotic science in functional food and dietary supplement development. *Curr Opin Clin Nutr Metab Care*. 2013;16(6):679-687.
10. El Hage R, Hernandez-Sanabria E, Van de Wiele T. Emerging Trends in "Smart Probiotics": Functional Consideration for the Development of Novel Health and Industrial Applications. *Front Microbiol*. 2017;8:1889.
11. López-Almela J, Romani-Pérez M, Bullich-Vilarrubias C, et al. *Bacteroides uniformis* combined with fiber amplifies metabolic and immune benefits in obese mice. *Gut Microbes*. 2021;13(1):1-20.
12. Duan M, Wang Y, Zhang Q, Zou R, Guo M, Zheng H. Characteristics of gut microbiota in people with obesity. *PLoS one*. 2021;16(8):e0255446.
13. Dugas LR, Bernabé BP, Priyadarshini M, et al. Decreased microbial co-occurrence network stability and SCFA receptor level correlates with obesity in African-origin women. *Sci Rep*. 2018;8(1):17135.
14. Nomura K, Ishikawa D, Okahara K, et al. *Bacteroides* Species Are Correlated with Disease Activity in Ulcerative Colitis. *J Clin Med*. 2021;10(8).
15. Wang T, Cai G, Qiu Y, et al. Structural segregation of gut microbiota between colorectal cancer patients and healthy volunteers. *ISME J*. 2012;6(2):320-329.
16. Renouf M, Hendrich S. *Bacteroides uniformis* is a putative bacterial species associated with the degradation of the isoflavone genistein in human feces. *J Nutr*. 2011;141(6):1120-1126.
17. Queipo-Ortuno MI, Boto-Ordóñez M, Murri M, et al. Influence of red wine polyphenols and ethanol on the gut microbiota ecology and biochemical biomarkers. *Am J Clin Nutr*. 2012;95(6):1323-1334.
18. Zengul AG, Demark-Wahnefried W, Barnes S, et al. Associations between Dietary Fiber, the Fecal Microbiota and Estrogen Metabolism in Postmenopausal Women with Breast Cancer. *Nutr Cancer*. 2021;73(7):1108-1117.
19. Li Y, Wang DD, Satija A, et al. Plant-Based Diet Index and Metabolic Risk in Men: Exploring the Role of the Gut Microbiome. *Nutr*. 2021;151(9):2780-2789.
20. Ruengsomwong S, Korenori Y, Sakamoto N, Wannissorn B, Nakayama J, Nitisinprasert S. Senior Thai fecal microbiota comparison between vegetarians and non-vegetarians using PCR-DGGE and real-time PCR. *J Microbiol Biotechnol*. 2014;24(8):1026-1033.
21. Lin D, Peters BA, Friedlander C, et al. Association of dietary fibre intake and gut microbiota in adults. *Br J Nutr*. 2018;120(9):1014-1022.
22. Cuiv PO, Klaassens ES, Durkin AS, et al. Draft genome sequence of *Bacteroides vulgatus* PCS10, a strain isolated from human feces. *J Bacteriol*. 2011;193(15):4025-4026.
23. Mroczynska M, Galecka M, Szachta P, Kamoda D, Libudzisz Z, Roszak D. Beta-glucuronidase and Beta-glucosidase activity in stool specimens of children with inflammatory bowel disease. *Pol J Microbiol*. 2013;62(3):319-325.
24. Lück R, Deppenmeier U. Genetic tools for the redirection of the central carbon flow towards the production of lactate in the human gut bacterium *Phocaeicola* (*Bacteroides*) *vulgatus*. *Appl Microbiol Biotechnol*. 2022;106(3):1211-1225.
25. Leite AZ, Rodrigues NC, Gonzaga MI, et al. Detection of Increased Plasma Interleukin-6 Levels and Prevalence of *Prevotella copri* and *Bacteroides vulgatus* in the Feces of Type 2 Diabetes Patients. *Front Immunol*. 2017;8:1107.
26. Mullish BH, McDonald JAK, Pechlivanis A, et al. Microbial bile salt hydrolases mediate the efficacy of faecal microbiota transplant in the treatment of recurrent *Clostridioides difficile* infection. *Gut*. 2019;68(10):1791-1800.
27. Hentges DJ, Maier BR, Burton GC, Flynn MA, Tsutakawa RK. Effect of a high-beef diet on the fecal bacterial flora of humans. *Cancer Res*. 1977;37(2):568-571.
28. Nicolucci AC, Hume MP, Martinez J, Mayengbam S, Walter J, Reimer RA. Probiotics Reduce Body Fat and Alter Intestinal Microbiota in Children Who Are Overweight or With Obesity. *Gastroenterology*. 2017;153(3):711-722.
29. Dewulf EM, Cani PD, Claus SP, et al. Insight into the prebiotic concept: lessons from an exploratory, double blind intervention study with inulin-type fructans in obese women. *Gut*. 2013;62(8):1112-1121.
30. Wylie KM, Truty RM, Sharpton TJ, et al. Novel bacterial taxa in the human microbiome. *PLoS one*. 2012;7(6):e35294.
31. Morotomi M, Nagai F, Sakon H, Tanaka R. *Dialister succinatiphilus* sp. nov. and *Barnesiella intestinihominis* sp. nov., isolated from human faeces. *Int J System Evol Microbiol*. 2008;58(Pt 12):2716-2720.
32. Mancabelli L, Milani C, Lugli GA, et al. Meta-analysis of the human gut microbiome from urbanized and pre-agricultural populations. *Environ Microbiol*. 2017;19(4):1379-1390.
33. Mancabelli L, Milani C, Lugli GA, et al. Identification of universal gut microbial biomarkers of common human intestinal diseases by meta-analysis. *FEMS Microbiol Ecol*. 2017;93(12).
34. Ubeda C, Buccì V, Caballero S, et al. Intestinal microbiota containing *Barnesiella* species cures vancomycin-resistant *Enterococcus faecium* colonization. *Infect Immun*. 2013;81(3):965-973.
35. Bilinski J, Grzesiowski P, Sorensen N, et al. Fecal Microbiota Transplantation in Patients With Blood Disorders Inhibits Gut Colonization With Antibiotic-Resistant Bacteria: Results of a Prospective, Single-Center Study. *Clin Infect Dis*. 2017;65(3):364-370.
36. Leal-Lopes C, Velloso FJ, Campopiano JC, Sogayar MC, Correa RG. Roles of Commensal Microbiota in Pancreas Homeostasis and Pancreatic Pathologies. *J Diab Res*. 2015;2015:284680.
37. Daillere R, Vetzou M, Waldschmitt N, et al. *Enterococcus hirae* and *Barnesiella intestinihominis* Facilitate Cyclophosphamide-Induced Therapeutic Immunomodulatory Effects. *Immunity*. 2016;45(4):931-943.
38. Le Roy T, Lecuyer E, Chassaing B, et al. The intestinal microbiota regulates host cholesterol homeostasis. *BMC Biol*. 2019;17(1):94.
39. Rogers MAM, Aronoff DM. The influence of non-steroidal anti-inflammatory drugs on the gut microbiome. *Clin Microbiol Infect*. 2016;22(2):178.e171-178.e179.
40. Toscano M, De Grandi R, Miniello VL, Mattina R, Drago L. Ability of *Lactobacillus kefir* LKF01 (DSM32079) to colonize the intestinal environment and modify the gut microbiota composition of healthy individuals. *Dig Liver Dis*. 2017;49(3):261-267.
41. Goker M, Gronow S, Zeytun A, et al. Complete genome sequence of *Odoribacter splanchnicus* type strain (1651/6). *Stand Genom Sci*. 2011;4(2):200-209.
42. Odamaki T, Kato K, Sugahara H, Xiao JZ, Abe F, Benno Y. Effect of probiotic yoghurt on animal-based diet-induced change in gut microbiota: an open, randomised, parallel-group study. *Ben Microbes*. 2016;7(4):473-484.
43. Gonzalez-Sarrias A, Romo-Vaquero M, Garcia-Villalba R, Cortes-Martin A, Selma MV, Espin JC. The Endotoxemia Marker Lipopolysaccharide-Binding Protein is Reduced in Overweight-Obese Subjects Consuming Pomegranate Extract by Modulating the Gut Microbiota: A Randomized Clinical Trial. *Mol Nutr Food Res*. 2018;62(11):e1800160.
44. Ley RE. Gut microbiota in 2015: *Prevotella* in the gut: choose carefully. *Nat Rev Gastroenterol Hepatol*. 2016;13(2):69-70.
45. Tett A, Huang KD, Asnicar F, et al. The *Prevotella copri* Complex Comprises Four Distinct Clades Underrepresented in Westernized Populations. *Cell Host Microbe*. 2019;26(5):666-679.e667.
46. De Filippis F, Pasolli E, Tett A, et al. Distinct Genetic and Functional Traits of Human Intestinal *Prevotella copri* Strains Are Associated with Different Habitual Diets. *Cell Host Microbe*. 2019;25(3):444-453.e443.
47. Koh A, De Vadder F, Kovatcheva-Datchary P, Backhed F. From Dietary Fiber to Host Physiology: Short-Chain Fatty Acids as Key Bacterial Metabolites. *Cell*. 2016;165(6):1332-1345.
48. Chen T, Long W, Zhang C, Liu S, Zhao L, Hamaker BR. Fiber-utilizing capacity varies in *Prevotella*-versus *Bacteroides*-dominated gut microbiota. *Sci Rep*. 2017;7(1):2594.
49. Arumugam M, Raes J, Pelletier E, et al. Enterotypes of the human gut microbiome. *Nature*. 2011;473(7346):174-180.
50. Hjorth MF, Blaedel T, Bendtsen LQ, et al. *Prevotella*-to-*Bacteroides* ratio predicts body weight and fat loss success on 24-week diets varying in macronutrient composition and dietary fiber: results from a post-hoc analysis. *Int J Obesity* (2005). 2019;43(1):149-157.
51. Wu GD, Chen J, Hoffmann C, et al. Linking long-term dietary patterns with gut microbial enterotypes. *Science*. 2011;334(6052):105-108.
52. Savin Z, Kivity S, Yonath H, Yehuda S. Smoking and the intestinal microbiome. *Arch Microbiol*. 2018;200(5):677-684.
53. Amato KR, Yeoman CJ, Cerda G, et al. Variable responses of human and non-human primate gut microbiomes to a Western diet. *Microbiome*. 2015;3:53.
54. Lawson PA, Song Y, Liu C, et al. *Anaerotruncus colihominis* gen. nov., sp. nov., from human faeces. *Int J System Evol Microbiol*. 2004;54(Pt 2):413-417.
55. Le Chatelier E, Nielsen T, Qin J, et al. Richness of human gut microbiome correlates with metabolic markers. *Nature*. 2013;500(7464):541-546.
56. Satokari R, Fuentes S, Mattila E, Jalanka J, de Vos WM, Arkkila P. Fecal transplantation treatment of antibiotic-induced, noninfectious colitis and long-term microbiota follow-up. *Case Rep Med*. 2014;2014:913867.

REFERENCES

57. Zupancic ML, Cantarel BL, Liu Z, et al. Analysis of the gut microbiota in the old order Amish and its relation to the metabolic syndrome. *PLoS one*. 2012;7(8):e43052.
58. Jeong S, Huang LK, Tsai MJ, et al. Cognitive Function Associated with Gut Microbial Abundance in Sucrose and S-Adenosyl-L-Methionine (SAME) Metabolic Pathways. *JAD*. 2022;87(3):1115-1130.
59. Togo AH, Diop A, Dubourg G, et al. *Anaerotruncus massiliensis* sp. nov., a succinate-producing bacterium isolated from human stool from an obese patient after bariatric surgery. *New Microb New Infect*. 2019;29:100508.
60. Togo AH, Valero R, Delerce J, Raoult D, Million M. "Anaerotruncus massiliensis", a new species identified from human stool from an obese patient after bariatric surgery. *New Microb New Infect*. 2016;14:56-57.
61. Raimondi S, Musmeci E, Candelieri F, Amaretti A, Rossi M. Identification of mucin degraders of the human gut microbiota. *Sci Rep*. 2021;11(1):11094.
62. Bailén M, Bressa C, Martínez-López S, et al. Microbiota Features Associated With a High-Fat/Low-Fiber Diet in Healthy Adults. *Front Nutr*. 2020;7:583608.
63. Shikany JM, Demmer RT, Johnson AJ, et al. Association of dietary patterns with the gut microbiota in older, community-dwelling men. *Am J Clin Nutr*. 2019;110(4):1003-1014.
64. Li J, Hou Q, Zhang J, et al. Carbohydrate Staple Food Modulates Gut Microbiota of Mongolians in China. *Front Microbiol*. 2017;8:484.
65. Lin A, Bik EM, Costello EK, et al. Distinct distal gut microbiome diversity and composition in healthy children from Bangladesh and the United States. *PLoS one*. 2013;8(1):e53838.
66. Lopetuso LR, Scaldaferrri F, Petito V, Gasbarrini A. Commensal Clostridia: leading players in the maintenance of gut homeostasis. *Gut Path*. 2013;5(1):23.
67. Halmos EP, Christophersen CT, Bird AR, Shepherd SJ, Gibson PR, Muir JG. Diets that differ in their FODMAP content alter the colonic luminal microenvironment. *Gut*. 2015;64(1):93-100.
68. Basson A, Trotter A, Rodriguez-Palacios A, Cominelli F. Mucosal Interactions between Genetics, Diet, and Microbiome in Inflammatory Bowel Disease. *Front Immunol*. 2016;7:290.
69. Lin P-Y, Whang L-M, Wu Y-R, et al. Biological hydrogen production of the genus *Clostridium*: metabolic study and mathematical model simulation. *Int J Hydrog Energ*. 2007;32(12):1728-1735.
70. Triantafyllou K, Chang C, Pimentel M. Methanogens, methane and gastrointestinal motility. *J Neurogastroenterol Motil*. 2014;20(1):31-40.
71. Cuerdo A, Hevia A, Lopez P, et al. Phenolic compounds from red wine and coffee are associated with specific intestinal microorganisms in allergic subjects. *Food Function*. 2016;7(1):104-109.
72. Gori A, Rizzardini G, Van't Land B, et al. Specific prebiotics modulate gut microbiota and immune activation in HAART-naïve HIV-infected adults: results of the "COPA" pilot randomized trial. *Mucosal Immunol*. 2011;4(5):554-563.
73. Nylund L, Nermes M, Isolauri E, Salminen S, de Vos WM, Satokari R. Severity of atopic disease inversely correlates with intestinal microbiota diversity and butyrate-producing bacteria. *Allergy*. 2015;70(2):241-244.
74. Di Iorio BR, Rocchetti MT, De Angelis M, et al. Nutritional Therapy Modulates Intestinal Microbiota and Reduces Serum Levels of Total and Free Indoxyl Sulfate and P-Cresyl Sulfate in Chronic Kidney Disease (Medika Study). *J Clin Med*. 2019;8(9).
75. Verhoog S, Taneri PE, Roa Diaz ZM, et al. Dietary Factors and Modulation of Bacteria Strains of *Akkermansia muciniphila* and *Faecalibacterium prausnitzii*: A Systematic Review. *Nutrients*. 2019;11(7).
76. Lopez-Siles M, Duncan SH, Garcia-Gil LJ, Martinez-Medina M. *Faecalibacterium prausnitzii*: from microbiology to diagnostics and prognostics. *ISME J*. 2017;11(4):841-852.
77. Hiipapala K, Jouhten H, Ronkainen A, et al. The Potential of Gut Commensals in Reinforcing Intestinal Barrier Function and Alleviating Inflammation. *Nutrients*. 2018;10(8).
78. Walker AW, Duncan SH, McWilliam Leitch EC, Child MW, Flint HJ. pH and peptide supply can radically alter bacterial populations and short-chain fatty acid ratios within microbial communities from the human colon. *Appl Environ Microbiol*. 2005;71(7):3692-3700.
79. Haro C, Montes-Borrego M, Rangel-Zuniga OA, et al. Two Healthy Diets Modulate Gut Microbial Community Improving Insulin Sensitivity in a Human Obese Population. *J Clin Endocrinol Metab*. 2016;101(1):233-242.
80. Hooda S, Boler BMV, Seroo MCR, et al. 454 Pyrosequencing Reveals a Shift in Fecal Microbiota of Healthy Adult Men Consuming Polydextrose or Soluble Corn Fiber. *J Nutr*. 2012;142(7):1259-1265.
81. Ramirez-Farias C, Slezak K, Fuller Z, Duncan A, Holtrop G, Louis P. Effect of inulin on the human gut microbiota: stimulation of *Bifidobacterium adolescentis* and *Faecalibacterium prausnitzii*. *Br J Nutr*. 2009;101(4):541-550.
82. Le Bastard Q, Chapelet G, Javaudin F, Lepelletier D, Batard E, Montassier E. The effects of inulin on gut microbial composition: a systematic review of evidence from human studies. *Eur J Clin Microbiol Infect Dis*. 2019.
83. Zhernakova A, Kurilshikov A, Bonder MJ, et al. Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity. *Science*. 2016;352(6285):565-569.
84. Moreno-Indias I, Sanchez-Alcoholado L, Perez-Martinez P, et al. Red wine polyphenols modulate fecal microbiota and reduce markers of the metabolic syndrome in obese patients. *Food Function*. 2016;7(4):1775-1787.
85. Hustofi TN, Hausken T, Ystad SO, et al. Effects of varying dietary content of fermentable short-chain carbohydrates on symptoms, faecal microenvironment, and cytokine profiles in patients with irritable bowel syndrome. *Neurogastroenterol Motil*. 2017;29(4).
86. Bressa C, Bailen-Andrino M, Perez-Santiago J, et al. Differences in gut microbiota profile between women with active lifestyle and sedentary women. *PLoS one*. 2017;12(2):e0171352.
87. Ponziani FR, Zocco MA, D'Aversa F, Pompili M, Gasbarrini A. Eubiotic properties of rifaximin: Disruption of the traditional concepts in gut microbiota modulation. *WJG*. 2017;23(25):4491-4499.
88. De Palma G, Nadal I, Collado MC, Sanz Y. Effects of a gluten-free diet on gut microbiota and immune function in healthy adult human subjects. *Br J Nutr*. 2009;102(8):1154-1160.
89. Bonder MJ, Tigchelner EF, Cai X, et al. The influence of a short-term gluten-free diet on the human gut microbiome. *Genome Med*. 2016;8(1):45.
90. Cox SR, Lindsay JQ, Fromentin S, et al. Effects of Low FODMAP Diet on Symptoms, Fecal Microbiome, and Markers of Inflammation in Patients With Quiescent Inflammatory Bowel Disease in a Randomized Trial. *Gastroenterology*. 2020;158(1):176-188. e177.
91. Murtaza N, Burke LM, Vlahovich N, et al. The Effects of Dietary Pattern during Intensified Training on Stool Microbiota of Elite Race Walkers. *Nutrients*. 2019;11(2).
92. Tagliabue A, Ferraris C, Uggeri F, et al. Short-term impact of a classical ketogenic diet on gut microbiota in GLUT1 Deficiency Syndrome: A 3-month prospective observational study. *Clin Nutr ESPEN*. 2017;17:33-37.
93. Lee T, Clavel T, Smirnov K, et al. Oral versus intravenous iron replacement therapy distinctly alters the gut microbiota and metabolome in patients with IBD. *Gut*. 2017;66(5):863-871.
94. Goldstein EJ, Tyrrell KL, Citron DM. *Lactobacillus* species: taxonomic complexity and controversial susceptibilities. *Clin Infect Dis*. 2015;60 Suppl 2:S98-107.
95. Zhang Z, Lv J, Pan L, Zhang Y. Roles and applications of probiotic *Lactobacillus* strains. *Appl Microbiol Biotechnol*. 2018;102(19):8135-8143.
96. Tomova A, Bukovsky I, Rembert E, et al. The Effects of Vegetarian and Vegan Diets on Gut Microbiota. *Front Nutr*. 2019;6:47.
97. Kelly JF, Curhan GC, Cave DR, Anderson TE, Kaufman DW. Factors related to colonization with *Oxalobacter formigenes* in U.S. adults. *J Endourol*. 2011;25(4):673-679.
98. Singh RK, Chang HW, Yan D, et al. Influence of diet on the gut microbiome and implications for human health. *J Transl Med*. 2017;15(1):73.
99. Takahashi H, Wako N, Okubo T, Ishihara N, Yamanaka J, Yamamoto T. Influence of partially hydrolyzed guar gum on constipation in women. *J Nutr Sci Vitaminol*. 1994;40(3):251-259.
100. Ricaboni D, Mailhe M, Benezzech A, Andrieu C, Fournier PE, Raoult D. "Pseudoflavonifactor phocaensis" gen. nov., sp. nov., isolated from human left colon. *New Microb New Infect*. 2017;17:15-17.
101. Louis S, Tappu RM, Damms-Machado A, Hudson DH, Bischoff SC. Characterization of the Gut Microbial Community of Obese Patients Following a Weight-Loss Intervention Using Whole Metagenome Shotgun Sequencing. *PLoS one*. 2016;11(2):e0149564.
102. Clooney AG, Bernstein CN, Leslie WD, et al. A comparison of the gut microbiome between long-term users and non-users of proton pump inhibitors. *Aliment Pharmacol Therap*. 2016;43(9):974-984.
103. Tamanai-Shacoori Z, Srida I, Bousarghin L, et al. *Roseburia* spp.: a marker of health? *Fut Microbiol*. 2017;12:157-170.
104. Scott KP, Antoine JM, Midtvedt T, van Hemert S. Manipulating the gut microbiota to maintain health and treat disease. *Microb Ecol Health Dis*. 2015;26:25877.
105. De Filippis F, Pellegrini N, Vannini L, et al. High-level adherence to a Mediterranean diet beneficially impacts the gut microbiota and associated metabolome. *Gut*. 2016;65(11):1812-1821.
106. David LA, Materna AC, Friedman J, et al. Host lifestyle affects human microbiota on daily timescales. *Genome Biol*. 2014;15(7):R89.
107. Walker AW, Ince J, Duncan SH, et al. Dominant and diet-responsive groups of bacteria within the human colonic microbiota. *ISME J*. 2011;5(2):220-230.
108. David LA, Maurice CF, Carmody RN, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature*. 2014;505(7484):559-563.
109. Morrison DJ, Preston T. Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. *Gut Microb*. 2016;7(3):189-200.
110. Baxter NT, Schmidt AW, Venkataraman A, Kim KS, Waldron C, Schmidt TM. Dynamics of Human Gut Microbiota and Short-Chain Fatty Acids in Response to Dietary Interventions with Three Fermentable Fibers. *mBio*. 2019;10(1).
111. Rangarajan AA, Chia HE, Azaldegui CA, et al. *Ruminococcus bromii* enables the growth of proximal *Bacteroides thetaiotaomicron* by releasing glucose during starch degradation. *Microbiology*. 2022;168(4).
112. Kasai C, Sugimoto K, Moritani I, et al. Comparison of the gut microbiota composition between obese and non-obese individuals in a Japanese population, as analyzed by terminal restriction fragment length polymorphism and next-generation sequencing. *BMC Gastroenterol*. 2015;15:100.
113. Bao R, Hesser LA, He Z, Zhou X, Nadeau KC, Nagler CR. Fecal microbiome and metabolome differ in healthy and food-allergic twins. *J Clinical Invest*. 2021;131(2).
114. Sasaki M, Schwab C, Ramirez Garcia A, et al. The abundance of *Ruminococcus bromii* is associated with faecal butyrate levels and atopic dermatitis in infancy. *Allergy*. 2022.
115. Rosés C, Cuevas-Sierra A, Quintana S, et al. Gut Microbiota Bacterial Species Associated with Mediterranean Diet-Related Food Groups in a Northern Spanish Population. *Nutrients*. 2021;13(2).
116. Nieves-Ramirez ME, Partida-Rodríguez O, Lافorest-Lapointe I, et al. Asymptomatic Intestinal Colonization with Protist *Blastocystis* Is Strongly Associated with Distinct Microbiome Ecological Patterns. *mSystems*. 2018;3(3).
117. Zhang Y, Gu Y, Ren H, et al. Gut microbiome-related effects of berberine and probiotics on type 2 diabetes (the PREMOTEST study). *Nat Comm*. 2020;11(1):5015.
118. Marchandin H, Jumas-Bilak E. The family *Veillonellaceae*. The Prokaryotes: Firmicutes and Tenericutes. 2014:433-453.
119. Liu S, Chen M, Wang Y, et al. Effect of *Veillonella parvula* on the physiological activity of *Streptococcus mutans*. *Arch Oral Biol*. 2020;109:104578.
120. Poppleton DJ, Duchateau M, Hourdel V, et al. Outer Membrane Proteome of *Veillonella parvula*: A Diderm Firmicute of the Human Microbiome. *Front Microbiol*. 2017;8:1215.
121. Gronow S, Welnitz S, Lapidus A, et al. Complete genome sequence of *Veillonella parvula* type strain (Te3). *Stand Genom Sci*. 2010;2(1):57-65.
122. Pham VT, Lacroix C, Braegger CP, Chassard C. Lactate-utilizing community is associated with gut microbiota dysbiosis in colicky infants. *Sci Rep*. 2017;7(1):11176.
123. Pimentel G, Burton KJ, Rosikiewicz M, et al. Blood lactose after dairy product intake in healthy men. *Br J Nutr*. 2017;118(12):1070-1077.
124. Hooda S, Boler BM, Seroo MC, et al. 454 pyrosequencing reveals a shift in fecal microbiota of healthy adult men consuming polydextrose or soluble corn fiber. *J Nutr*. 2012;142(7):1259-1265.
125. Palleja A, Kashani A, Allin KH, et al. Roux-en-Y gastric bypass surgery of morbidly obese patients induces swift and persistent changes of the individual gut microbiota. *Genome Med*. 2016;8(1):67.

REFERENCES

126. O'Callaghan A, van Sinderen D. Bifidobacteria and Their Role as Members of the Human Gut Microbiota. *Front Microbiol*. 2016;7:925.
127. Yuan J, Zhu L, Liu X, et al. A proteome reference map and proteomic analysis of *Bifidobacterium longum* NCC2705. *Mol Cell Proteom*. 2006;5(6):1105-1118.
128. Bag S, Ghosh TS, Das B. Complete Genome Sequence of *Collinsella aerofaciens* Isolated from the Gut of a Healthy Indian Subject. *Genome Announce*. 2017;5(47).
129. Ohashi Y, Sumitani K, Tokunaga M, Ishihara N, Okubo T, Fujisawa T. Consumption of partially hydrolysed guar gum stimulates Bifidobacteria and butyrate-producing bacteria in the human large intestine. *Ben Microbes*. 2015;6(4):451-455.
130. Yasukawa Z, Inoue R, Ozeki M, et al. Effect of Repeated Consumption of Partially Hydrolyzed Guar Gum on Fecal Characteristics and Gut Microbiota: A Randomized, Double-Blind, Placebo-Controlled, and Parallel-Group Clinical Trial. *Nutrients*. 2019;11(9).
131. Tuohy KM, Kolida S, Lustenberger AM, Gibson GR. The prebiotic effects of biscuits containing partially hydrolysed guar gum and fructo-oligosaccharides—a human volunteer study. *Br J Nutr*. 2001;86(3):341-348.
132. Bamberger C, Rossmeyer A, Lechner K, et al. A Walnut-Enriched Diet Affects Gut Microbiome in Healthy Caucasian Subjects: A Randomized, Controlled Trial. *Nutrients*. 2018;10(2).
133. Huaman JW, Mego M, Manichanh C, et al. Effects of Probiotics vs a Diet Low in FODMAPs in Patients With Functional Gut Disorders. *Gastroenterology*. 2018;155(4):1004-1007.
134. Zimmer J, Lange B, Frick JS, et al. A vegan or vegetarian diet substantially alters the human colonic faecal microbiota. *Eur J Clin Nutr*. 2012;66(1):53-60.
135. Wong CB, Odamak T, Xiao J-z. Beneficial effects of *Bifidobacterium longum* subsp. *longum* BB536 on human health: Modulation of gut microbiome as the principal action. *J Function Foods*. 2019;54:506-519.
136. Haro C, García-Carpintero S, Alcalá-Díaz JF, et al. The gut microbial community in metabolic syndrome patients is modified by diet. *J Nutr Biochem*. 2016;27:27-31.
137. Kalinkovich A, Livshits G. A cross talk between dysbiosis and gut-associated immune system governs the development of inflammatory arthropathies. *Sem Arthr Rheum*. 2019;49(3):474-484.
138. Chen J, Wright K, Davis JM, et al. An expansion of rare lineage intestinal microbes characterizes rheumatoid arthritis. *Genome Med*. 2016;8(1):43.
139. Qin P, Zou Y, Dai Y, Luo G, Zhang X, Xiao L. Characterization of a Novel Butyric Acid-Producing Bacterium *Collinsella aerofaciens* Subsp. *Shenzhenensis* Subsp. *Nov*. *Microorganisms*. 2019;7(3).
140. Rey FE, Gonzalez MD, Cheng J, Wu M, Ahern PP, Gordon JI. Metabolic niche of a prominent sulfate-reducing human gut bacterium. *Proc Natl Acad Sci USA*. 2013;110(33):13582-13587.
141. Foerster J, Mskarinec G, Reichardt N, et al. The influence of whole grain products and red meat on intestinal microbiota composition in normal weight adults: a randomized crossover intervention trial. *PLoS one*. 2014;9(10):e109606.
142. Gomez-Arango LF, Barrett HL, Wilkinson SA, et al. Low dietary fiber intake increases *Collinsella* abundance in the gut microbiota of overweight and obese pregnant women. *Gut Microbes*. 2018;9(3):189-201.
143. Bilen M, Beye M, Mbogning Fonkou MD, et al. Genomic and phenotypic description of the newly isolated human species *Collinsella bouchedurhonenensis* sp. nov. *Microbiol Open*. 2018;7(5):e00580.
144. Ruengsomwong S, La-Ongkham O, Jiang J, Wannissom B, Nakayama J, Nitisinprasert S. Microbial Community of Healthy Thai Vegetarians and Non-Vegetarians, Their Core Gut Microbiota, and Pathogen Risk. *J Microbiol Biotechnol*. 2016;26(10):1723-1735.
145. Makivuokko H, Tiihonen K, Tynkynen S, Paulin L, Rautonen N. The effect of age and non-steroidal anti-inflammatory drugs on human intestinal microbiota composition. *Br J Nutr*. 2010;103(2):227-234.
146. Marquet P, Duncan SH, Chassard C, Bernalier-Donadille A, Flint HJ. Lactate has the potential to promote hydrogen sulphide formation in the human colon. *FEMS Microbiol Lett*. 2009;299(2):128-134.
147. Kuskhevych I, Dordevic D, Vitezova M. Analysis of pH Dose-dependent Growth of Sulfate-reducing Bacteria. *Open Med*. 2019;14:66-74.
148. Singh SB, Lin HC. Hydrogen Sulfide in Physiology and Diseases of the Digestive Tract. *Microorganisms*. 2015;3(4):866-889.
149. Wolf P, Cummings P, Shah N, Gaskins HR, Mutlu E. Sulfidogenic Bacteria Abundance in Colonic Mucosa is Positively Correlated with Milk and Animal Fat Intake and Negatively Correlated with Mono and Polyunsaturated Fatty Acids. *FASEB J*. 2015;29(11_supplement):598.510.
150. Wang L, Zhang J, Guo Z, et al. Effect of oral consumption of probiotic *Lactobacillus plantarum* P-8 on fecal microbiota, SIgA, SCFAs, and TBAs of adults of different ages. *Nutrition*. 2014;30(7-8):776-783.e771.
151. Suarez FL, Fume JK, Springfield J, Levitt MD. Bismuth subsalicylate markedly decreases hydrogen sulfide release in the human colon. *Gastroenterology*. 1998;114(5):923-929.
152. Xiao S, Fei N, Pang X, et al. A gut microbiota-targeted dietary intervention for amelioration of chronic inflammation underlying metabolic syndrome. *FEMS Microbiol Ecol*. 2014;87(2):357-367.
153. Blount ZD. The unexhausted potential of *E. coli*. *eLife*. 2015;4.
154. Miura K, Ohnishi H. Role of gut microbiota and Toll-like receptors in nonalcoholic fatty liver disease. *WJG*. 2014;20(23):7381-7391.
155. Rossi E, Cimdins A, Luthje P, et al. "It's a gut feeling" - *Escherichia coli* biofilm formation in the gastrointestinal tract environment. *Crit Rev Microbiol*. 2018;44(1):1-30.
156. Jia K, Tong X, Wang R, Song X. The clinical effects of probiotics for inflammatory bowel disease: A meta-analysis. *Medicine*. 2018;97(51):e13792.
157. Guo S, Chen S, Ma J, et al. *Escherichia coli* Nissle 1917 Protects Intestinal Barrier Function by Inhibiting NF- κ B-Mediated Activation of the MLCK-P-MLC Signaling Pathway. *Med Inflamm*. 2019;2019:5796491.
158. Ticinesi A, Nouvenne A, Meschi T. Gut microbiome and kidney stone disease: not just an Oxalobacter story. *Kidney international*. 2019;96(1):25-27.
159. Basser RJ, Basser B, Pimentel M, et al. Intestinal methane production in obese individuals is associated with a higher body mass index. *Gastroenterol Hepatol*. 2012;8(1):22-28.
160. Gottlieb K, Wacher V, Sliman J, Pimentel M. Review article: inhibition of methanogenic archaea by statins as a targeted management strategy for constipation and related disorders. *Aliment Pharmacol Therap*. 2016;43(2):197-212.
161. Pimentel M, Gunsalus RP, Rao SS, Zhang H. Methanogens in human health and disease. *Am J Gastroenterol Suppl*. 2012;1(1):28.
162. Beghini F, Pasoli E, Truong TD, Putignani L, Caccio SM, Segata N. Large-scale comparative metagenomics of Blastocystis, a common member of the human gut microbiome. *ISME J*. 2017;11(12):2848-2863.
163. van de Pol JAA, van Best N, Mbakwa CA, et al. Gut Colonization by Methanogenic Archaea Is Associated with Organic Dairy Consumption in Children. *Front Microbiol*. 2017;8(355).
164. Hoffmann C, Dollive S, Grunberg S, et al. Archaea and Fungi of the Human Gut Microbiome: Correlations with Diet and Bacterial Residents. *PLOS ONE*. 2013;8(6):e66019.
165. Mathur R, Chua KS, Mamelak M, et al. Metabolic effects of eradicating breath methane using antibiotics in prediabetic subjects with obesity. *Obesity*. 2016;24(3):576-582.
166. Seo M, Heo J, Yoon J, et al. Methanobrevibacter attenuation via probiotic intervention reduces flatulence in adult human: A non-randomised paired-design clinical trial of efficacy. *PLoS one*. 2017;12(9):e0184547.
167. Afra K, Laupland K, Leal J, Lloyd T, Gregson D. Incidence, risk factors, and outcomes of *Fusobacterium* species bacteremia. *BMC Infect Dis*. 2013;13:264.
168. Amitay EL, Werner S, Vital M, et al. *Fusobacterium* and colorectal cancer: causal factor or passenger? Results from a large colorectal cancer screening study. *Carcinogenesis*. 2017;38(8):781-788.
169. Brook I. *Fusobacterium*, Infection and Immunity. 1998.
170. O'Keefe SJ, Li JV, Lahti L, et al. Fat, fibre and cancer risk in African Americans and rural Africans. *Nature Comm*. 2015;6:6342.
171. Ben Lagha A, Haas B, Grenier D. Tea polyphenols inhibit the growth and virulence properties of *Fusobacterium nucleatum*. *Sci Rep*. 2017;7:44815.
172. De Angelis M, Montemurro E, Vannini L, et al. Effect of whole-grain barley on the human fecal microbiota and metabolome. *Appl Environ Microbiol*. 2015;81(22):7945-7956.
173. Derrien M, Vaughan EE, Plugge CM, de Vos WM. *Akkermansia muciniphila* gen. nov., sp. nov., a human intestinal mucin-degrading bacterium. *Int J System Evolut Microbiol*. 2004;54(5):1469-1476.
174. Geerlings SY, Kostopoulos I, De Vos WM, Belzer C. *Akkermansia muciniphila* in the human gastrointestinal tract: when, where, and how? *Microorganisms*. 2018;6(3):75.
175. Depommier C, Everard A, Druart C, et al. Supplementation with *Akkermansia muciniphila* in overweight and obese human volunteers: a proof-of-concept exploratory study. *Nat Med*. 2019;25(7):1096-1103.
176. Walker JM, Eckardt P, Aleman JO, et al. The effects of trans-resveratrol on insulin resistance, inflammation, and microbiota in men with the metabolic syndrome: A pilot randomized, placebo-controlled clinical trial. *J Clin Transl Res*. 2019;4(2):122-135.
177. Li Z, Henning SM, Lee RP, et al. Pomegranate extract induces ellagitannin metabolite formation and changes stool microbiota in healthy volunteers. *Food Function*. 2015;6(8):2487-2495.
178. Roshanravan N, Mahdavi R, Alizadeh E, et al. The effects of sodium butyrate and inulin supplementation on angiotensin signaling pathway via promotion of *Akkermansia muciniphila* abundance in type 2 diabetes: A randomized, double-blind, placebo-controlled trial. *J Cardiovasc Thorac Res*. 2017;9(4):183-190.
179. de la Cuesta-Zuluaga J, Mueller NT, Corrales-Agudelo V, et al. Metformin Is Associated With Higher Relative Abundance of Mucin-Degrading *Akkermansia muciniphila* and Several Short-Chain Fatty Acid-Producing Microbiota in the Gut. *Diab Care*. 2017;40(1):54-62.
180. Clarke SF, Murphy EF, O'Sullivan O, et al. Exercise and associated dietary extremes impact on gut microbial diversity. *Gut*. 2014;63(12):1913-1920.
181. Zhou K. Strategies to promote abundance of *Akkermansia muciniphila*, an emerging probiotics in the gut, evidence from dietary intervention studies. *J Funct Foods*. 2017;33:194-201.

Pathogenic Bacteria & Yeast

Genus/Organism	Description	Habitat/Sources of Isolation	Pathogenicity	GI Symptoms
<p><i>Aeromonas</i></p> <p><i>Aeromonas hydrophilia</i></p> <p><i>Aeromonas caviae</i></p> <p><i>Aeromonas veronii</i></p> <p><i>Aeromonas jandaei</i></p> <p><i>Aeromonas schuberti</i></p>	<p><i>Aeromonas</i> is a facultatively anaerobic, Gram-negative rod.¹</p> <p><i>Aeromonas</i> species share many biochemical properties with <i>Vibrio</i> species and were jointly classified in the <i>Vibrionaceae</i> family until genotypic information provided new insights.²</p> <p>(P)</p>	<p>Aeromonads normally inhabit the aquatic environment, though they have been isolated from a variety of foods, such as fish, meat, milk, and vegetables. The foodborne isolations are predominantly <i>A. hydrophilia</i>.¹</p>	<p>Aeromonads possess virulence factors, such as enterotoxins, cytotoxins, and hemolysins. They have the ability to adhere to and invade cells, and produce various enzymes that are regarded as pathogenic mechanisms.³</p>	<p><i>Aeromonas</i> has been associated with a wide variety of human infectious diseases, including gastroenteritis, wound infections, septicemia, respiratory infections, and urinary tract infections.²</p> <p>However, <i>Aeromonas</i> is most commonly associated with gastrointestinal enteropathy. Symptoms include watery diarrhea (with a self-limiting course), fever, abdominal pain, vomiting, bloody diarrhea, and possible secondary dehydration.²</p>
<p><i>Bacillus anthracis</i></p>	<p><i>B. anthracis</i> is a spore-forming, Gram-positive bacterium which causes anthrax.⁴</p> <p>In humans, there are three major forms of anthrax as delineated by the spore exposure route: cutaneous, gastrointestinal, and inhalational.⁵</p> <p>(P)</p>	<p><i>B. anthracis</i> spores primarily infect grazing animals, but humans may be exposed to anthrax through the handling of infected animals and animal products or tainted meat consumption.⁴</p>	<p>Spores are ingested and germinate within the GI tract epithelium. <i>B. anthracis</i> then uses a toxin called anthrolysin to disrupt the GI barrier.⁶</p>	<p>GI anthrax can present clinically as either intestinal or, less commonly, oropharyngeal infection. The incubation period is typically 1-6 days.</p> <p>Intestinal anthrax manifests with ileal or cecal ulcerations. Illness begins with anorexia, nausea, vomiting, and fever; this progresses to severe abdominal pain, hematemesis, melena, and/or frank blood in the stool.⁶</p>
<p><i>Bacillus cereus</i></p>	<p><i>B. cereus</i> is a Gram-positive, aerobic (or facultative aerobic), spore-forming, rod-shaped bacterium.⁷</p> <p>(PP)</p>	<p><i>B. cereus</i> is ubiquitous in soil and freshwater environments in all temperate zones. It is capable of contaminating many food products, including rice, chicken, vegetables, spices, and dairy products.⁷</p>	<p><i>B. cereus</i> produces several toxin types: hemolysin, phospholipase, cereulide (emetic toxin), and enterotoxins.</p> <p>The incubation time averages 12 hours, and the duration of signs/symptoms is between 12-24 hours.⁷</p>	<p><i>B. cereus</i> infectious symptoms include gastroenteritis and vomiting, but the illness is self-limiting and usually lasts less than 24 hours.⁷</p>

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Genus/Organism	Description	Habitat/Sources of Isolation	Pathogenicity	GI Symptoms
<i>Bacillus</i> species	<p><i>Bacillus</i> species are Gram-positive aerobic (or facultatively aerobic) rods.⁸</p> <p>Most human non-anthraxis <i>Bacillus</i> spp. infections are caused by <i>B. cereus</i>.</p> <p>Not all isolates are associated with disease. Many <i>Bacillus</i> species are used in spore- and soil-based probiotics, such as <i>B. subtilis</i>, <i>B. coagulans</i>, and <i>B. licheniformis</i>.⁹</p> <p>(PP)</p>	<p><i>Bacillus</i> organisms are widely distributed in the environment, though the primary habitats are soil and water.</p> <p>Many <i>Bacillus</i> species are beneficial and used in probiotics and in biocidal environmental insecticides.^{9,10}</p>	<p>Different <i>Bacillus</i> species produce various extracellular products, including antimicrobial substances, enzymes, pigments, and toxins.</p> <p>Except for a select few species, most <i>Bacillus</i> species have no pathogenic potential and are not associated with disease.⁸</p>	<p><i>Bacillus</i> infection is not always pathogenic and often asymptomatic.</p> <p>Infections caused by the <i>Bacillus</i> species include self-limiting gastroenteritis (<i>B. cereus</i>), localized infections due to trauma, ocular infections, and rarely systemic illness as seen in <i>B. anthracis</i>.⁸</p>
<p><i>Campylobacter</i> spp.</p> <p><i>Campylobacter jejuni</i></p> <p><i>Campylobacter coli</i></p>	<p><i>Campylobacter</i> species are non-spore-forming, Gram-negative, helical, rod-shaped, or curved bacteria.¹¹</p> <p><i>Campylobacter</i> genus belongs to the family <i>Campylobacteraceae</i>.¹²</p> <p>(P)</p>	<p><i>Campylobacter</i> has a world-wide distribution and international travel is a risk factor for infection.</p> <p><i>Campylobacter</i> is a confirmed foodborne bacterial pathogen. Infection occurs after consumption of contaminated food, particularly poultry, unpasteurized milk, and water.^{12,13}</p>	<p><i>Campylobacter</i>'s helical shape and flagella are thought to be responsible for their ability to colonize the intestinal tract, and for adhesion and invasion into epithelial cells.¹¹ Additionally, cytotoxin production leads to cell death, damage to mucosal surfaces, and subsequent diarrhea.¹⁴</p> <p>The onset of symptoms usually occurs 24-72 hours following ingestion.¹²</p>	<p><i>C. jejuni</i> and <i>C. coli</i> are established causes of gastroenteritis world-wide. <i>C. jejuni</i> can also lead to autoimmune conditions like Guillain-Barre' syndrome and Miller Fischer syndrome. Patients with <i>C. jejuni</i> or <i>C. coli</i> experience acute watery or bloody diarrhea, weight loss, and abdominal cramping.¹²</p> <p>Many <i>Campylobacter</i> species are known pathogens associated with a wide range of gastrointestinal conditions, including inflammatory bowel disease, Barrett's esophagus, and colorectal cancer. They have also been known to cause extra-gastrointestinal manifestations, including bacteremia, lung infections, brain abscesses, meningitis, and reactive arthritis.¹²</p>

Pathogenic Bacteria & Yeast

Genus/Organism	Description	Habitat/Sources of Isolation	Pathogenicity	GI Symptoms
<p><i>Candida</i> spp.</p> <p><i>Candida albicans</i></p> <p><i>Candida</i> species, not <i>albicans</i></p> <p><i>Candida auris</i></p> <p><i>Candida dubliniensis</i></p> <p><i>Candida famata</i></p> <p><i>Candida glabrata</i></p> <p><i>Candida guilliermondii</i></p> <p><i>Candida krusei</i></p> <p><i>Candida lusitanae</i></p> <p><i>Candida parapsilosis</i></p> <p><i>Candida pseudotropicalis</i></p> <p><i>Candida rugosa</i></p> <p><i>Candida stellatoidea</i></p> <p><i>Candida tropicalis</i></p> <p><i>Candida zeylanoides</i></p>	<p><i>Candida</i> spp. have commonly been identified as part of the healthy human mycobiome. Host defense interruption, or immunocompromise, is required for them to act as pathogens.¹⁵</p> <p><i>Candida albicans</i> is the most prevalent among the <i>Candida</i> spp.¹⁵</p> <p>(PP)</p>	<p>Fungi, including <i>Candida</i>, are ubiquitous in our environment and are part of natural foods and industrial processes, including antibiotic production, bread, cheese, alcoholic beverages, decomposing natural debris, fruits, and soil nutrients.¹⁶</p> <p><i>Candida</i> is present in the gut of up to 70% of healthy adults, but certain factors, including diabetes, antibiotics, antacid, and steroid inhaler use, promote overgrowth.¹⁷</p> <p><i>Candida</i> growth in the GI tract is positively correlated with carbohydrate consumption.¹⁸</p>	<p><i>Candida</i> pathogenesis depends on virulence factor expression, like germ tube formation, adhesions, phenotypic switching, biofilm formation, and hydrolytic enzyme production. Most <i>Candida</i> disease processes are primarily due to biofilm formation.¹⁵</p> <p>During overgrowth, <i>Candida</i> produces pseudohyphae that push their way into the intestinal lining, destroying cells and brush borders, and may eventually send toxic metabolic by-products through the intestinal wall into the blood.¹⁹</p> <p>High-level <i>Candida</i> colonization is frequently observed in ulcer and IBD patients. This may in part reflect common treatments for these conditions. In addition, the presence of <i>Candida</i> delays healing and exacerbates disease.²⁰</p>	<p>As noted, most patients are asymptomatic, and <i>Candida</i> is considered a commensal organism.</p> <p>Depending on the host's immune status and comorbidities, symptoms will vary. <i>Candida</i> overgrowth in the GI tract has been shown to cause diarrheal illness.²¹ Other GI symptoms sometimes seen include thrush, bloating, gas, intestinal cramps, rectal itching, and altered bowel habits.²²</p> <p>Some generalized symptoms of patients with yeast infections include chronic fatigue, mood disorders, and malaise.²²</p>

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Genus/Organism	Description	Habitat/Sources of Isolation	Pathogenicity	GI Symptoms
<p><i>Citrobacter</i> spp.</p> <p><i>Citrobacter amalonaticus</i></p> <p><i>Citrobacter braakii</i></p> <p><i>Citrobacter freundii</i></p> <p><i>Citrobacter youngae</i></p> <p><i>Citrobacter koseri/diversus</i></p>	<p><i>Citrobacter</i> are Gram-negative, non-spore-forming, facultatively anaerobic bacilli.</p> <p><i>Citrobacter</i> fall within the <i>Enterobacteriaceae</i> family.²³</p> <p><i>Citrobacter</i> is considered a commensal bacteria; however, depending on the clinical picture, it is also known to be an opportunistic pathogen.²⁴</p> <p>(PP)</p>	<p><i>Citrobacter</i> species are found in water, soil, food, and commonly in the human intestinal tract.²³</p> <p><i>Citrobacter</i> infections can also be nosocomial.²³</p>	<p>Although considered a commensal, some <i>Citrobacter</i> isolates have virulent toxins, such as Shiga-like toxins, heat-stable toxins, and cholera B toxin B subunit homologs.²⁵</p>	<p><i>Citrobacter</i> is most often asymptomatic but can cause diarrhea.²⁴</p>
<p><i>Clostridium difficile</i></p>	<p><i>C. difficile</i> is an anaerobic, Gram-positive, spore-forming, toxin-producing bacillus.²⁶</p> <p>(P/PP) * See GI Symptoms column</p> <p>Genova measures <i>C. difficile</i> toxin via EIA. A prerequisite for <i>C. difficile</i> EIA toxin testing is a stool consistency of 7 on the Bristol stool scale, whereby the sample takes the shape of the container.</p> <p>Clinical relevance is determined by the presence of toxin A/B. When these toxins are present, correlation with patient symptoms is recommended.²⁷</p>	<p><i>C. difficile</i> spores are frequently found in healthcare facilities, and are found in lower levels in the environment and food supply. Infection can be nosocomial or community transmitted.²⁶</p>	<p><i>C. difficile</i> spores are resistant to heat, acid, and antibiotics. They colonize the large intestine and release two protein exotoxins (A, B). These exotoxins cause colonocyte death, barrier function loss, and neutrophilic colitis.²⁶</p> <p>Colonization is prevented by barrier properties of the microbiota; weakening of this barrier by antibiotics is the major risk factor for disease.^{26,28}</p>	<p>Not all colonized patients develop symptoms.²⁷ A majority of infants are colonized with <i>C. difficile</i> and are asymptomatic.²⁶</p> <p>When present, <i>C. difficile</i> infection presents with bloody and non-bloody diarrhea, fever, abdominal pain, vomiting, ileus, and dehydration. Toxic megacolon and peritonitis are significant complications of advanced infections.²⁶</p> <p>Of note, many successfully treated patients will continue to test positive for weeks or months after symptom resolution; additional treatment is neither required nor effective.²⁶</p>

Pathogenic Bacteria & Yeast

Genus/Organism	Description	Habitat/Sources of Isolation	Pathogenicity	GI Symptoms
<p><i>Cryptococcus albidus</i></p> <p><i>Cryptococcus gattii</i></p> <p><i>Cryptococcus humicolus</i></p> <p><i>Cryptococcus laurentii</i></p> <p><i>Cryptococcus luteolus</i></p> <p><i>Cryptococcus neoformans</i></p>	<p><i>Cryptococcus</i> is a fungus. Although there are more than 30 species of <i>Cryptococcus</i>, only two commonly affect humans and animals: <i>C. neoformans</i> and <i>C. gattii</i>.²⁹</p> <p>95% of cryptococcal infections are caused by <i>C. neoformans</i>.³⁰</p> <p>(PP)</p>	<p>Cryptococcosis has a worldwide distribution. Cryptococcosis occurs through the inhalation of fungal cells from soil, plants, and decaying natural materials, though zoonotic transmission is possible. The yeast may incidentally enter the gastrointestinal tract, though this is less likely.³⁰</p>	<p>There are prominent virulence factors attributed to <i>Cryptococcus</i>, including capsule formation, thermotolerance, and melanin pigment production, which protects the yeast from host oxidative stresses. An effective host immune response is common, using helper T cell reactions; therefore, any weakening of that response allows <i>Cryptococcus</i> to survive and thrive.³⁰</p>	<p>Cryptococcal infection primarily affects the lungs or central nervous system, though GI tract infection causing diarrhea is increasing among immunocompromised patients (HIV/AIDS).²⁹</p>
<p><i>Edwardsiella tarda</i></p>	<p><i>E. tarda</i> is a Gram-negative, facultatively anaerobic rod.³¹ It is a member of the <i>Enterobacteriaceae</i> family.</p> <p>(PP)</p>	<p><i>E. tarda</i> exists widely in nature and is isolated from lakes, streams, seawater, and aquatic animals/fish.³¹</p> <p>Infection results from the consumption of contaminated meat/fish, though human infection is rare.³²</p>	<p>Pathogenicity of <i>E. tarda</i> is associated with many virulence factors, such as hemolysins, which enable the bacteria to have access to essential nutrient elements in order to colonize.³³</p>	<p>Gastroenteritis, with fever and vomiting, is the most common symptom of <i>E. tarda</i> infection, ranging from mild secretory enteritis to chronic enterocolitis. Symptoms can be self-limiting; however, extraintestinal manifestations can include systemic abscesses and septicemia.^{32,33}</p>
<p><i>Enterobacter cloacae</i></p>	<p><i>E. cloacae</i> is a Gram-negative, non-spore-forming, enteric bacilli belonging to the <i>Enterobacteriaceae</i> family.</p> <p><i>Enterobacteriaceae</i> are not considered primary human pathogens, but are capable of causing opportunistic infections.³⁴</p> <p>(PP)</p>	<p><i>Enterobacter</i> have a ubiquitous environmental distribution (trees, plants, crops, soil, water, and foods). They are also part of the normal flora of the GI tract.³⁴</p> <p>It can also be a common nosocomial infection.³⁵</p>	<p><i>Enterobacter's</i> ability to form biofilms and to secrete various cytotoxins, such as enterotoxins and hemolysins, contribute to its pathogenicity.³⁵</p>	<p>Most patients with an <i>E. cloacae</i> infection are asymptomatic. However, when present, symptoms can include nausea, vomiting, diarrhea, and abdominal cramps.³⁶</p>

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<i>Escherichia coli</i> O157:H7 Shiga toxin producing	<p><i>E. coli</i> is a Gram-negative, rod-shaped, facultative anaerobe.</p> <p>Most <i>E. coli</i> harmlessly colonize the GI tract as normal flora. However, some strains have evolved and acquired virulence factors, which are characterized by serotypes. <i>E. coli</i> O157:H7 has become one of the most virulent foodborne pathogens.³⁷</p> <p>(P)</p>	<p><i>E. coli</i> O157 is transmitted to humans through contaminated food and water, directly between persons, and through contact with animals. The most common reservoir is cattle, and the most frequently identified mode of transmission is through ground beef consumption.³⁸</p>	<p><i>E. coli</i> O157's ability to induce injury is a result of its ability to produce Shiga toxin, which is cytotoxic. Additionally, it produces other proteins which aid in the attachment and colonization in the intestinal wall and can lyse red blood cells to liberate iron to support its own metabolism.</p> <p>It should be noted that there are other organisms which can also produce Shiga-like toxin.</p> <p>The characteristic histopathological lesions caused by <i>E. coli</i> O157:H7 are called attaching and effacing (A/E) lesions. Microvilli are effaced and bacteria adhere to the epithelium.³⁷</p>	<p>Signs and symptoms associated with Shiga-toxin producing <i>E. coli</i> O157 include bloody diarrhea, stomach cramping, and vomiting. This can progress to hemolytic uremic syndrome and death.³⁸</p>
<i>Geotrichum</i> species <i>Geotrichum candidum</i> <i>Geotrichum capitum</i>	<p><i>Geotrichum</i> is a eukaryotic, aerobic, Gram-positive, non-capsulated fungus.</p> <p><i>Geotrichum</i> is considered a common commensal in the human GI tract, though opportunistic infections are seen in immunocompromised patients.³⁹</p> <p>(PP)</p>	<p><i>Geotrichum</i> is ubiquitous and is commonly found on fruits, vegetables, cheeses, mil, soil, water, air, and in the human digestive tract.⁴⁰</p> <p>Transmission is through inhalation of fungal cells or ingestion of contaminated foods.³⁹</p>	<p><i>Geotrichum</i> infection is rare and, in general, <i>Geotrichum</i> has low virulence. In patients with normal immunity, it is not pathogenic.⁴¹</p>	<p>Clinical manifestations are very similar to candidiasis. Many patients are asymptomatic; when present, symptoms include diarrhea, abdominal pain, and mucus in the stool.³⁹</p>
<i>Hafnia alvei</i>	<p><i>H. alvei</i> is a Gram-negative, facultatively anaerobic bacillus that belongs to the <i>Enterobacteriaceae</i> family.</p> <p>Though rare, it is considered an opportunistic pathogen.⁴²</p> <p>(PP)</p>	<p><i>H. alvei</i> is most commonly isolated from vacuum-packed meat, raw milk, raw fish, and other foods. Transmission is via ingestion of contaminated foods, but nosocomial infections have been seen.⁴²</p>	<p><i>H. alvei</i> pathogenicity is in biofilm formation and cellulose production; this aids in colonization and mediates cell-cell interaction. It also produces adhesins and toxins which contribute to symptoms and antimicrobial resistance.⁴²</p>	<p><i>H. alvei</i>'s clinical relevance is not clear. It has been isolated from feces in asymptomatic patients, yet is also known to cause gastroenteritis, necrotizing enterocolitis, and extra-intestinal illnesses.⁴³</p>

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<p><i>Hansenula anomala</i></p> <p>Also known as <i>Pichia anomala</i> and <i>Wickerhamomyces anomalus</i></p>	<p><i>H. anomala/W. anomalus</i> is an ascomycete yeast.⁴⁴</p> <p>Although useful in food processing, it has been shown to be a very rare opportunistic and nosocomial pathogen in humans, mainly neonates and immunocompromised patients.^{44,45}</p> <p>(PP)</p>	<p><i>H. anomala/W. anomalus</i> is frequently found in natural environments (plants, soil, fruit, animals) and is useful in wine fermentation.⁴⁵ It also has antimicrobial properties and has been used as a biocontrol agent. It can be found on the skin and as normal flora in the human gastrointestinal tract.⁴⁴</p>	<p><i>H. anomala/W. anomalus</i> are classed as biosafety level 1 by the European Food Safety Authority, and there are no reports in the literature regarding hazardous mycotoxin formation or allergic reactions to spores from this yeast. However, rare isolates from immunocompromised patients are emerging with no clear specific pathogenicity.⁴⁴</p>	<p><i>H. anomala/W. anomalus</i> are considered normal flora and very rarely cause disease, but they have been known to cause sepsis, fungal arthritis, pneumonia, and endocarditis in immunocompromised patients.⁴⁶</p>
<p><i>Helicobacter pylori</i></p>	<p><i>H. pylori</i> is a Gram-negative, aerophilic bacterium.</p> <p><i>H. pylori</i> infection is one of the most common chronic bacterial infections affecting humans.⁴⁷</p> <p>(P)</p> <p>Genova uses an enzyme immunoassay platform that utilizes antibodies to detect <i>H. pylori</i> antigen present in the stool sample.</p>	<p><i>H. pylori</i> infection is chronic and is usually acquired in childhood. The exact means of infection is not clear.⁴⁷</p>	<p>After entering the host stomach, <i>H. pylori</i> uses its urease activity to neutralize the acidic environment. It has a flagella-mediated motility to help it move toward the gastric epithelium. Specific bacterial adhesin proteins lead to colonization and persistent infection. It finally releases effector proteins and toxins causing host tissue damage.⁴⁸</p>	<p><i>H. pylori</i> is an important cause of peptic ulcer disease (PUD) and gastric cancer. It may also have a role in functional dyspepsia, ulcer risk in patients taking low-dose aspirin or starting NSAID therapy, unexplained iron deficiency anemia, and idiopathic thrombocytopenic purpura (ITP).⁴⁷</p> <p>According to the American College of Gastroenterology, the indications to test for <i>H. pylori</i> include active PUD, a history of PUD, low-grade mucosa-associated lymphoid tissue (MALT) lymphoma, or endoscopic early gastric cancer. Patients initiating chronic aspirin or NSAID treatment, those with unexplained iron deficiency, and patients with ITP, should be tested.⁴⁷</p> <p>Patients with typical GERD symptoms without a history of PUD, need not be tested for <i>H. pylori</i>; however, those who are tested and found to be infected should be treated.⁴⁷</p>

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<p><i>Klebsiella oxytoca</i></p> <p><i>Klebsiella pneumoniae</i></p>	<p><i>Klebsiella</i> are non-motile, Gram-negative rods that belong to the <i>Enterobacteriaceae</i> family.</p> <p><i>Klebsiella</i> bacteria are considered commensal but act as opportunistic bacteria in the GI tract. <i>Klebsiella</i> is a leading cause of hospital-acquired infections.⁴⁹</p> <p>(PP)</p>	<p><i>Klebsiella</i> is part of the normal intestinal flora. The environment likely acts as a reservoir for human acquisition, either as colonization or infection. It is frequently found in water, sewage, soil, and plant surfaces.⁵⁰</p>	<p><i>Klebsiella</i> possesses virulence factors, such as a capsule, lipopolysaccharides, and pili. <i>Klebsiella</i> translocates across the intestinal epithelium via a transcellular mechanism by active bacterial invasion. This allows it to penetrate the intestinal barrier and enter systemic circulation causing extraintestinal disease.⁵¹</p> <p>Cytotoxins produced by <i>Klebsiella oxytoca</i> are associated with antibiotic-associated hemorrhagic colitis (AAHC).⁵²</p> <p>Ankylosing spondylitis and Crohn's disease have been shown to be triggered by <i>Klebsiella pneumoniae</i>. Increased starch consumption by genetically susceptible patients (HLA-B27 allelotypes) could trigger disease by enhancing the growth of <i>Klebsiella</i> in the gut. The cross-reactive antibodies between <i>Klebsiella</i> and AS/Crohn's trigger inflammatory cascades, such as the complement system, as well as producing various cytokines causing pathologic changes.⁵³</p>	<p><i>Klebsiella</i> can asymptotically colonize the GI tract. However, depending on host factors and immunocompetence, it may cause diarrhea and systemic illnesses.^{49,50}</p>
<p><i>Listeria monocytogenes</i></p>	<p><i>Listeria</i> is a Gram-positive, facultative intracellular bacterium.⁵⁴</p> <p>(P)</p>	<p><i>Listeria</i> is ubiquitous in the environment. It is the causative agent of Listeriosis, a rare but fatal foodborne disease.^{54,55}</p>	<p><i>Listeria</i> can cross several physiological barriers, including the intestinal epithelium and placenta, and survive in multiple cell types. Following internalization into the host cell, the bacterium escapes its membrane-bound vacuole using the toxin listeriolysin. It then replicates within the cytosol and can multiply and spread from cell to cell.⁵⁵</p>	<p>Ingestion of <i>L. monocytogenes</i>-contaminated food by immune-competent individuals is often limited to gastroenteritis that resolves in a few days, with pathogenic clearance from the intestine.⁵⁴</p> <p>Severe complications include systemic dissemination causing septicemia, meningitis, and chorioamnionitis; all are associated with high mortality.⁵⁴</p>

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<i>Moellerella wisconsensis</i>	<p><i>Moellerella wisconsensis</i> is a Gram-negative bacilli from the <i>Enterobacteriaceae</i> family.⁵⁶</p> <p>(PP)</p>	<p><i>M. wisconsensis</i> has been recovered from various sources, such as water, food, and animals.⁵⁶</p> <p>Isolation of this bacteria in clinical samples is very rare. The majority of <i>M. wisconsensis</i> isolates from human clinical samples have been from stool, though bronchial aspirates, biliary samples, and peritoneal exudates have been seen.^{56,57}</p>	Pathogenicity is unclear due to the scarcity of human infection.	Though rare, isolated case reports show that <i>M. wisconsensis</i> has been associated with diarrhea. ^{56,57}
<i>Morganella morganii</i>	<p><i>M. morganii</i> is a facultative anaerobic, Gram-negative, enteric bacterium which belongs to the <i>Enterobacteriaceae</i> family.</p> <p><i>M. morganii</i> is an opportunistic pathogen often isolated as a cause of nosocomial infections in adults.⁴³</p> <p>(PP)</p>	<i>M. morganii</i> is found in the environment and colonizes the human intestinal tract as part of the normal flora. ⁵⁸	<i>Morganella</i> produces a urease that predisposes to encrustation of urinary catheters. It may also produce a hemolysin, which enhances virulence by lysing erythrocytes. ⁵⁸	Although <i>Morganella</i> is part of the normal intestinal flora, it has been implicated in various diseases, including diarrhea, urinary tract infections, and wound infections. Serious infections, like meningitis in AIDS patients, have been reported. ⁴³
<p><i>Pichia ohmeri</i></p> <p>More recently known as <i>Kodamaea ohmeri</i></p>	<p><i>K. ohmeri</i> is a fungus that belongs to the <i>Saccharomycetes</i> family, which acts as a very rare opportunistic pathogen.⁵⁹</p> <p>(PP)</p>	<p><i>K. ohmeri</i> is widely used in the food industry for the fermentation of fruits, pickles, and rinds.⁵⁹ In the past, <i>Kodamaea ohmeri</i> was considered a food contaminant, but is now recognized as an emerging opportunistic pathogen in immunocompromised patients.⁶⁰</p>	Pathogenicity is not yet clearly defined due to the rarity of human infection.	<p><i>K. ohmeri</i> infection is rarely reported to cause human infection, with only isolated case reports seen in the literature; these are primarily in infants and immunocompromised patients.⁶⁰⁻⁶²</p> <p>Systemic fungemia has been rarely seen in association with indwelling catheters, phlebitis, wound infections, endocarditis, and outbreaks in intensive care units.⁶⁰</p>
<i>Plesiomonas shigelloides</i>	<p><i>P. shigelloides</i> is an anerobic, Gram-negative bacillus, belonging to the <i>Enterobacteriaceae</i> family.</p> <p>(P)</p>	<p><i>Plesiomonas</i> is a global pathogen with worldwide distribution. It is most often isolated in aquatic environments.</p> <p>Infection occurs primarily by undercooked freshwater fish consumption.⁶³</p>	<i>Plesiomonas</i> contains a Shigella phase I antigen, cholera-like toxins, hemolysins, and cytotoxic lipopolysaccharides.	<i>P. shigelloides</i> causes gastroenteritis, which ranges from a secretory enteritis to a cholera-like diarrhea. Extraintestinal manifestations can occur with bacteremia and sepsis. ⁶³

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<i>Providencia alcalifaciens</i>	<p><i>P. alcalifaciens</i> is a Gram-negative rod that belongs to the <i>Enterobacteriaceae</i> family. It is usually considered to be a commensal bacteria, but can also be an opportunistic pathogen and a cause of traveler's diarrhea.⁶⁴</p> <p>(PP)</p>	<p><i>P. alcalifaciens</i> is found throughout the environment, and as a commensal bacteria in the large intestine. Food contamination and human transmission has been shown to be via the fecal-oral route, lack of sanitation, and poor food storage.⁶⁴</p>	<p><i>P. alcalifaciens</i> has lipopolysaccharides that cause epithelial barrier dysfunction and endothelial apoptosis.⁶⁵</p>	<p>Although often considered a commensal bacteria, <i>P. alcalifaciens</i> has been shown to cause diarrhea.⁶⁴</p>
<p><i>Proteus mirabilis</i></p> <p><i>Proteus penneri</i></p> <p><i>Proteus vulgaris</i></p>	<p><i>Proteus</i> is Gram-negative bacteria belonging to the <i>Enterobacteriaceae</i> family.</p> <p><i>Proteus</i> spp. are considered opportunistic pathogens, isolated from urine, stool, and wounds.^{66,67} <i>Proteus</i> are a common cause of nosocomial infections in patients with impaired immunity.</p> <p>(PP)</p>	<p><i>Proteus</i> is widespread in the environment and considered part of the normal GI flora.</p> <p><i>Proteus</i> spp. are found in soil or water habitats and are often regarded as indicators of fecal contamination.⁶⁷</p>	<p>The chemical structure of <i>Proteus'</i> lipopolysaccharides plays an important role in how it adapts to the environment and its pathogenicity.</p> <p>In impaired immunity, <i>Proteus</i> bacteria become opportunistic. Cross infection with the urinary tract is common.⁶⁷</p>	<p><i>Proteus</i> species in the stool are considered normal flora, but have been shown to cause diarrheal illness.⁶⁷</p>
<i>Pseudomonas aeruginosa</i>	<p><i>P. aeruginosa</i> is a Gram-negative aerobic bacilli. Although seen as part of the normal healthy intestinal flora, it is considered a potential pathogen.</p> <p>It is generally not a common cause of infectious diarrhea in a healthy host. Patients with chronic disease, chronic antibiotic use, or immunocompromise are at highest risk for infection.⁶⁸</p> <p>(PP)</p>	<p><i>Pseudomonas aeruginosa</i> is readily found in the environment (soil and water) and in the healthy gastrointestinal tract.</p>	<p><i>P. aeruginosa</i> induces pro-inflammatory responses and anti-microbial peptides within intestinal epithelial cells. It also has cytotoxic activity. Disruption of the intestinal epithelial protective mechanisms allow for disease progression.⁶⁹</p>	<p>Most patients are asymptomatic, though <i>P. aeruginosa</i> can cause mild diarrhea. A rare complication is Shanghai Fever, which is characterized by fever, diarrhea, and sepsis.</p> <p><i>P. aeruginosa</i> has also been associated with antibiotic-related diarrhea.⁶⁸</p>

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<p><i>Pseudomonas pseudomallei</i></p> <p>Also known as <i>Burkholderia pseudomallei</i></p>	<p><i>P. pseudomallei</i> is a Gram-negative, aerobic, saprophytic bacillus.</p> <p>It causes the rare, often fatal disease, melioidosis.⁷⁰</p> <p>There are fears that <i>P. pseudomallei</i> can be used as a biological weapon.⁷¹</p> <p>(P)</p>	<p><i>Pseudomonas/Burkholderia pseudomallei</i> is widespread in South, Central, and North America; it is also common in Southeast Asia.</p> <p>Infection occurs through contact with soil and water in endemic areas through inhalation, skin inoculation, or ingestion.⁷⁰</p>	<p><i>P. pseudomallei</i> possesses several secretion systems essential for its dissemination. Pathogenicity is due to its endotoxins inducing apoptosis.</p> <p>Most infections occur in the lung, though systemic disease is possible.⁷¹</p> <p>It is likely to be consumed in water and food in settings where the organism is present in the environment. It can colonize the gastrointestinal tract without clinical features for months or years.</p>	<p>Most symptoms of melioidosis are pulmonary, though colonization, shedding, and carriage through the GI tract are possible. Systemic disseminated abscesses are common.⁷¹</p>
<p><i>Rhodotorula</i> spp.</p> <p><i>Rhodotorula glutinis</i></p> <p><i>Rhodotorula rubra</i></p>	<p><i>Rhodotorula</i> is a saprophytic yeast. Previously considered non-pathogenic, it has emerged as an opportunistic pathogen.</p> <p>(PP)</p>	<p><i>Rhodotorula</i> is a common, ubiquitous yeast that is found in air, soil, lakes, ocean water, food, and beverages.⁷²</p>	<p>It has been shown that <i>Rhodotorula</i> species are able to form biofilms which may play a role in its pathogenicity. Antibiotics and cytotoxic agent exposure increases intestinal colonization and mucosal damage.</p>	<p>Isolation from non-sterile sites, like skin and stool, are more commonly contaminant or colonization. Specific gastrointestinal symptoms are not well studied. Systemic infections and fungemia are possible in immunocompromised patients.⁷³</p>
<p><i>Saccharomyces cerevisiae</i></p>	<p><i>Saccharomyces cerevisiae</i> and <i>Saccharomyces boulardii</i> are two closely related strains of non-spore-forming yeast which are nearly identical at the molecular level.</p> <p>Classically considered a safe, nonpathogen, <i>S. cerevisiae</i> can cause disease in immunocompromised patients.⁷⁴</p> <p>(PP)</p>	<p><i>S. cerevisiae</i> commonly colonizes the human respiratory, gastrointestinal, and urinary tracts.</p> <p><i>S. cerevisiae</i> is found in many niches in the environment, but is commonly known as baker's yeast, and is frequently used in the industrial fermentation of bread, beer, and wine.⁷⁴</p> <p><i>S. cerevisiae</i> is also commercially available as a nutritional supplement and is used to treat antibiotic-related diarrhea and IBS.⁷⁵</p>	<p><i>S. cerevisiae</i> uses adhesin proteins to penetrate disrupted epithelial or endothelial barriers. Most fungal pathogens display resistance to the reactive oxygen species used by human cells to resist infection.⁷⁴</p>	<p>Immunosuppression can lead to <i>S. cerevisiae</i> infection, though indwelling catheters, chronic antibiotic therapy, and nosocomial spread are common risk factors. <i>S. cerevisiae</i> infection can cause a wide variety of clinical syndromes, such as fungemia, pneumonia, abscess, esophagitis, and fever. It has been associated with Crohn's disease and ulcerative colitis.⁷⁶</p>

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<p><i>Salmonella typhi</i></p> <p><i>Salmonella</i> species</p> <p><i>S. arizonae</i></p> <p><i>Salmonella</i> group A, B, C, D, E, E+G, C+D</p> <p><i>S. paratyphi</i> A, B, C</p>	<p><i>Salmonella</i> is a facultative intracellular, Gram-negative bacteria within the <i>Enterobacteriaceae</i> family. It is the causative agent of human typhoid fever.^{77,78}</p> <p>(P)</p>	<p>Humans are typically infected with <i>Salmonella</i> after consuming food or drinking water contaminated with bacteria, and transmission is often fecal-oral.⁷⁷</p>	<p>After oral ingestion, <i>Salmonella</i> invades the epithelial cells in the distal ileum and invades Peyer's patches. <i>Salmonella</i> travels via the afferent lymphatics to gain access to the blood and systemic tissues.⁷⁷</p>	<p>Depending on the serotype, <i>Salmonella</i> symptoms can vary from a self-limiting gastroenteritis and diarrhea, to systemic infection with fever, respiratory distress, hepatic and splenic complications, and neurologic damage.⁷⁸</p>
<p><i>Serratia marcescens</i></p>	<p><i>Serratia</i> are non-spore-forming, Gram-negative rods, and are part of the <i>Enterobacteriaceae</i> family.</p> <p><i>S. marcescens</i> is an opportunistic pathogen, which is generally thought not to be pathogenic in the intestine, but is emerging as a frequent nosocomial infectious agent.^{79,80}</p> <p>(PP)</p>	<p><i>Serratia</i> species are ubiquitous in the environment, and found in water, soil, plants, insects, humans, and other animals.⁸¹</p> <p>Infection is acquired through ingestion of contaminated food or contact with hospital equipment and personnel.⁸⁰</p>	<p><i>S. marcescens</i> has the potential for adhesion, invasion, cytotoxicity, perturbation of intestinal barrier function, cytokine release, and alteration of cellular morphology.⁸⁰</p>	<p>Patients most at risk for <i>S. marcescens</i> infection include those with immunocompromise, patients on broad spectrum antibiotics, or hospitalized patients subjected to invasive instrumentation/catheters.</p> <p>Most patients are asymptomatic carriers, though <i>S. marcescens</i> infection symptoms may include diarrhea and rarely necrotizing enterocolitis.⁸⁰</p>
<p><i>Shigella</i> species</p> <p><i>Shigella boydii</i></p> <p><i>Shigella dysenteriae</i></p> <p><i>Shigella flexneri</i></p> <p><i>Shigella sonnei</i></p>	<p><i>Shigella</i> are Gram-negative pathogenic bacteria that belong to the <i>Enterobacteriaceae</i> family.⁸²</p> <p><i>Shigella</i> is the causative organism of Shigellosis, accounting for the majority of dysentery worldwide.⁸²</p> <p>(P)</p>	<p><i>Shigella</i> species are transmitted via the fecal-oral route. They are easily transmitted by personal contact with an infected person or consumption of contaminated food or water.⁸³</p> <p><i>Shigella</i> species are geographically stratified based on the level of economic development in a given country. <i>S. flexneri</i> is the primary infectious species in the developing world, whereas <i>S. sonnei</i> rates increase with economic development. <i>S. boydii</i> is restricted to Bangladesh and Southeast Asia. <i>S. dysenteriae</i> occurs sporadically worldwide.⁸²</p>	<p>The <i>Shigella</i> bacteria invades colonic mucosa, then can multiply causing epithelial cell death, and spread laterally to cause mucosal ulcers, bleeding, and inflammation.⁸³</p>	<p>Symptoms of shigellosis include fever, bloody diarrhea, and abdominal cramping. Infection is usually restricted to the gastrointestinal tract, though extra-intestinal manifestations (reactive arthritis, hemolytic-uremic syndrome, and neurologic complications) can be seen.⁸³</p>

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Genus/Organism	Description	Habitat/Sources of Isolation	Pathogenicity	GI Symptoms
<i>Staphylococcus aureus</i>	<p><i>S. aureus</i> in the GI tract is a commensal Gram-positive bacterium, which can be responsible for opportunistic toxigenic infections.⁸⁴</p> <p>(PP)</p>	<p><i>S. aureus</i> is a common cause of food-borne disease. Though ubiquitous in the environment, and a commensal found on the skin, nasopharynx, and gastrointestinal tract, it can be transmitted via contaminated food or water consumption.⁸⁵</p> <p>Fecal carriage is considered an important risk factor for hospital- and community-acquired infections.⁸⁶</p>	<p><i>S. aureus</i> produces varying enterotoxins and contains several virulence genes.⁸⁷</p>	<p>Asymptomatic fecal <i>S. aureus</i> carriage is common. However, <i>S. aureus</i> GI infection symptoms include nausea, vomiting, and abdominal cramping, with or without diarrhea.⁸⁵ The foodborne illness can be self-limiting with resolution after 24-48 hours. Severe disease often requires hospitalization.⁸⁷</p> <p>Colonization with <i>S. aureus</i> increases the risk of systemic infection and bacteremia.⁸⁴</p>
<p><i>Trichosporon</i> species</p> <p><i>Trichosporon beigelii</i></p> <p><i>Trichosporon pullulans</i></p>	<p><i>Trichosporon</i> are amorphic fungi. Though considered a commensal yeast, they are increasingly recognized as opportunistic pathogens in immunocompromised individuals.⁸⁸</p> <p>(PP)</p>	<p><i>Trichosporon</i> fungi are commonly found in nature and can reside harmlessly as commensals on the skin and in healthy individuals' gastrointestinal tracts.⁸⁸</p>	<p><i>Trichosporon's</i> ability to invade the skin and other tissues includes several virulence factors, including yeast-to-hyphae transition, biofilm formation, lipases and proteases, and cell wall plasticity.⁸⁸</p>	<p><i>Trichosporon</i> is a commensal yeast in the GI tract and is usually asymptomatic.</p> <p>Changes in nutrient availability may influence <i>Trichosporon</i> spp. abundance and diversity and underlie gut mycobiome dysbiosis. This can potentially lead to inflammatory pathologies, such as inflammatory bowel disease. Invasive and systemic trichosporonosis is seen in immunocompromised hosts.⁸⁸</p>
<i>Vibrio cholerae</i>	<p><i>Vibrio cholerae</i> is a Gram-negative, facultative anaerobic bacterium that is responsible for epidemic cholera, a severe diarrheal disease.^{89,90}</p> <p>(P)</p>	<p><i>V. cholerae</i> naturally inhabits aquatic environments. Epidemic cholera is transmitted to humans by contaminated water and food consumption.⁸⁹</p> <p>Cholera is associated with unsanitary conditions and countries with poor infrastructure.⁹⁰</p>	<p><i>V. cholerae</i> are ingested and colonize the intestinal mucosa using adhesin proteins and mucinase enzymes. The incubation period is between 12 hours and 5 days. Once a certain concentration of cells is reached, enterotoxin cascades are produced. After being shed, cells can be found in a hyperinfectious state, which make secondary infection to others prevalent.⁸⁹</p>	<p>When mild, cholera symptoms are often indistinguishable from other diarrheal causes. However, more commonly, patients develop severe dehydration or die due to acute watery diarrhea.⁹⁰</p>
<i>Vibrio fluvialis</i>	<p><i>V. fluvialis</i> is a Gram-negative rod known to be pathogenic in humans.⁹¹</p> <p>(P)</p>	<p><i>V. fluvialis</i> occurs widely in the aquatic environment. It is one of the emerging foodborne pathogens throughout the world. <i>V. fluvialis</i> is often associated with raw or undercooked fish consumption.⁹²</p>	<p>Upon ingestion into the GI tract, the prevalent virulence factors in <i>V. fluvialis</i> infection are hemolysin and cytotoxins.⁹²</p>	<p><i>V. fluvialis</i> is found to be associated with cholera-like diarrhea. Rare complications include biliary tract infection, suppurative cholangitis, peritonitis, and other extraintestinal manifestations.⁹²</p>

Pathogenic Bacteria & Yeast

Genus/Organism	Description	Habitat/Sources of Isolation	Pathogenicity	GI Symptoms
<i>Vibrio furnissii</i>	<i>V. furnissii</i> is a Gram-negative rod. Initially it was assigned and named as a subgroup of <i>V. fluvialis</i> , but it is now considered a separate species. It is considered pathogenic, but rare. ⁹³ (P)	<i>V. furnissii</i> is ubiquitous in aquatic marine environments. Infection is associated with ingestion of contaminated seafood, or exposure to coastal waters. ⁹³	Flagellum are one virulence factor in <i>Vibrio</i> infections, in addition to proteases, hemagglutinins, and hydrolytic exoenzymes. ⁹³	<i>V. furnissii</i> has been associated with gastroenteritis in humans. ⁹³
<i>Vibrio hollisae</i> Now reclassified as <i>Grimontia hollisae</i>	<i>G. hollisae</i> is a Gram-negative, aerobic, rod-shaped bacteria, which belongs to the Vibrionaceae family. ⁹⁴ (P)	Infection usually follows the ingestion of raw, undercooked, or contaminated seafood. ⁹⁴	<i>G. hollisae</i> shares a pathogenic gene cluster with the entire <i>Vibrio</i> genus. It releases a thermostable hemolysin toxin, which is absorbed in the intestines after ingestion. ⁹⁵	<i>V. hollisae</i> causes severe gastroenteritis, hypovolemia, and septicemia. It is associated with hepatotoxicity. ⁹⁵
<i>Vibrio metschnikovii</i>	<i>V. metschnikovii</i> is a Gram-negative rod. It is a very rare species with only a small number of cases reported. ⁹⁶ (P)	Nonhuman sources include shrimp, crab, birds, water, sewage, and other seafood. ⁹⁶	As with other members of the <i>Vibrio</i> genus, hemolysin and cytotoxins contribute to pathogenicity. ⁹⁶	Presentation includes diarrhea and vomiting, though infections with <i>V. metschnikovii</i> can be fatal in patients with significant comorbidities. ⁹⁶
<i>Vibrio mimicus</i>	<i>V. mimicus</i> is a Gram-negative rod closely related to <i>V. cholerae</i> . ⁹⁷ (P)	The natural habitat of <i>V. mimicus</i> is similar to <i>V. cholerae</i> —the aquatic ecosystem. Infection usually occurs from the consumption of infected seafood. ⁹⁸	Many <i>V. mimicus</i> virulence factors have been identified, including enterotoxin, hemolysin, proteases, and hemagglutinin. ⁹⁷	<i>V. mimicus</i> gastroenteritis is characterized by diarrhea, nausea, vomiting, abdominal cramping, and fever. However, unlike <i>V. cholerae</i> , it is not associated with cholera epidemics since most isolates do not produce cholera toxin. ⁹⁸
<i>Vibrio parahaemolyticus</i>	<i>V. parahaemolyticus</i> is a Gram-negative rod belonging to the Vibrionaceae family. (P)	<i>V. parahaemolyticus</i> grows in warm, low salinity marine water and is the most prevalent food poisoning bacterium associated with seafood consumption. ⁹⁹	The vast majority of <i>V. parahaemolyticus</i> strains have hemolysin, causing hemolysis in the initiation of disease. ⁹⁹	Infection usually causes acute gastroenteritis and is generally self-limiting. Common characteristics include abdominal cramps, nausea, headaches, diarrhea, fever, and chills. ⁹⁹

Pathogenic Bacteria & Yeast

Genus/Organism	Description	Habitat/Sources of Isolation	Pathogenicity	GI Symptoms
<p><i>Yersinia enterocolitica</i></p> <p><i>Yersinia pseudotuberculosis</i></p>	<p><i>Yersinia</i> is a Gram-negative bacillus belonging to the <i>Enterobacteriaceae</i> family.</p> <p>Genus <i>Yersinia</i> includes three bacteria that cause human pathology: <i>Y. enterocolitica</i>, <i>Y. pseudotuberculosis</i>, and <i>Y. pestis</i>.</p> <p><i>Y. pestis</i> causes plague and is transmitted via flea bites.</p> <p><i>Y. enterocolitica</i> and <i>Y. pseudotuberculosis</i> cause gastroenteritis and are mainly transmitted via contaminated food and water.¹⁰⁰</p> <p>(P)</p>	<p>Yersiniosis has been detected on all continents. <i>Yersinia enterocolitica</i> has been associated with contamination of a variety of foods, including milk and milk products, raw meats, poultry, eggs, vegetables, seafood, and others.</p> <p><i>Yersinia</i> species are able to propagate in vacuum-packed foods and at refrigeration temperatures.¹⁰¹</p>	<p>Following ingestion, approximately 10% of bacteria survive the acidic gastric environment and translocate the gut barrier, which compromises the Peyer's patches in the small bowel and lymphoid follicles in the large bowel. <i>Yersinia</i> then drains to neighboring lymph nodes and possibly the portal blood stream.¹⁰¹</p> <p>It has been postulated that <i>Yersinia</i> species contribute to the occurrence or persistence of gut inflammation in Crohn's disease.¹⁰¹</p>	<p><i>Y. enterocolitica</i> and <i>Y. pseudotuberculosis</i> can both cause acute watery or bloody diarrhea and gastroenteritis.</p> <p>Although gastroenteritis from <i>Yersinia</i> is often self-limiting, some patients develop chronic infections, such as reactive arthritis, erythema nodosum, glomerulonephritis, or myocarditis.¹⁰⁰</p>

TREATMENT RESOURCES:

The decision to treat potentially pathogenic organisms should be based on the patient's clinical presentation.

The following resources provide valuable insight into the clinical management of pathogenic and potentially pathogenic bacteria and yeast:

- Sanford Guide – infectious disease treatment guidelines: <https://www.sanfordguide.com/>
- Johns Hopkins Antibiotic Guide – subscription service for in depth information on pathogens, treatment, and clinical implications: https://www.hopkinsguides.com/hopkins/index/Johns_Hopkins_ABX_Guide/All_Topics/A
- PubMed – literature search engine for up to date clinical and treatment information: <https://www.ncbi.nlm.nih.gov/pubmed/>
- Mayo Clinic – conditions search engine: <https://www.mayoclinic.org/>
- Merck Manual – treatment and clinical implications of infectious diseases: <https://www.merckmanuals.com/professional>

REFERENCES

1. Stratev D, Odeyemi OA. Antimicrobial resistance of *Aeromonas hydrophila* isolated from different food sources: A mini-review. *Journal of infection and public health*. 2016;9(5):535-544.
2. van Zwetelaar M, Nyombi B, Sonda T, et al. *Aeromonas caviae* mimicking *Vibrio cholerae* infectious enteropathy in a cholera-endemic region with possible public health consequences: two case reports. *Journal of medical case reports*. 2018;12(1):71-71.
3. Ghenghesh KS, Ahmed SF, Cappuccinelli P, Klena JD. Genespecies and virulence factors of *Aeromonas* species in different sources in a North African country. *Libyan Journal of Medicine*. 2014;9(1):25497.
4. Lightfoot YL, Yang T, Sahay B, et al. Colonic immune suppression, barrier dysfunction, and dysbiosis by gastrointestinal bacillus anthracis infection. *PLoS One*. 2014;9(6):e100532.
5. Cote C, Welkos S. Anthrax toxins in context of *Bacillus anthracis* spores and spore germination. *Toxins*. 2015;7(8):3167-3178.
6. Owen JL, Yang T, Mohamadzadeh M. New insights into gastrointestinal anthrax infection. *Trends in molecular medicine*. 2015;21(3):154-163.
7. Beer MR, McKillip JL. *Bacillus cereus*: a bacterial species of environmental and clinical significance. *Journal for the Liberal Arts and Sciences*. 2014;18(2):21.
8. Tuazon CU. *Bacillus* species. Last accessed on. 2016.
9. Horosheva TV, Vodyanov Y, Sorokulova I. Efficacy of *Bacillus* probiotics in prevention of antibiotic-associated diarrhoea: a randomized, double-blind, placebo-controlled clinical trial. *JMM Case Reports*. 2014;1(3).
10. Narkhede C, Patil C, Suryawanshi R, Koli S, Mohite B, Patil S. Synergistic effect of certain insecticides combined with *Bacillus thuringiensis* on mosquito larvae. *Journal of Entomological and Acarological Research*. 2017;49(1).
11. Stahl M, Friedich E, Vermeulen J, et al. The helical shape of *Campylobacter jejuni* promotes in vivo pathogenesis by aiding its transit through intestinal mucus and colonization of crypts. *Infection and immunity*. 2016;84(10):00751-00756.
12. Kaakoush NO, Castaño-Rodríguez N, Mitchell HM, Man SM. Global epidemiology of *Campylobacter* infection. *Clinical microbiology reviews*. 2015;28(3):687-720.
13. Harrison LM. Beyond *Campylobacter jejuni*: understanding *Campylobacter coli* infections in a systemic model of disease. *Vivulence*. 2015;6(6):537-538.
14. Ghunaim H, Behnke JM, Aigha I, et al. Analysis of resistance to antimicrobials and presence of virulence/stress response genes in *Campylobacter* isolates from patients with severe diarrhoea. *PLoS one*. 2015;10(3):e0119268.
15. Marak MB, Dhanashree B. Antifungal Susceptibility and Biofilm Production of *Candida* spp. Isolated from Clinical Samples. *International journal of microbiology*. 2018;2018.
16. Nash AK, Auchtung TA, Wong MC, et al. The gut mycobiome of the Human Microbiome Project healthy cohort. *Microbiome*. 2017;5(1):153.
17. Schelenz S. Fungal diseases of the gastrointestinal tract. *Oxford Textbook of Medical Mycology*. 2017.
18. Mukherjee PK, Sendid B, Hoarau G, Colombel J-F, Poulain D, Ghannoum MA. Mycobiota in gastrointestinal diseases. *Nature reviews Gastroenterology and hepatology*. 2015;12(2):77.
19. Ezeonu IM, Ntun NW, Ugwu KO. Intestinal candidiasis and antibiotic usage in children: case study of Nsukka, South Eastern Nigeria. *African Health Sciences*. 2017;17(4):1178-1184.
20. Kumamoto CA. Inflammation and gastrointestinal *Candida* colonization. *Current opinion in microbiology*. 2011;14(4):386-391.
21. Uppal B, Panda P, Kishor S, Sharma S, Ferooqi F. Speciation of *Candida* isolates obtained from diarrheal stool. *The Egyptian Journal of Internal Medicine*. 2016;28(2):66-66.
22. Martins N, Ferreira IC, Barros L, Silva S, Henriques M. Candidiasis: predisposing factors, prevention, diagnosis and alternative treatment. *Mycopathologia*. 2014;177(5-6):223-240.
23. Wang J-T, Chang S-C. *Citrobacter* species. In: 2016.
24. Lan R, Xu J. Genetic diversity, multidrug resistance and virulence of *Citrobacter freundii* from diarrheal patients and healthy individuals. *Frontiers in cellular and infection microbiology*. 2018;8:233.
25. Liu L, Chen D, Liu L, et al. Genetic Diversity, Multidrug Resistance, and Virulence of *Citrobacter freundii* From Diarrheal Patients and Healthy Individuals. *Frontiers in cellular and infection microbiology*. 2018;8:233-233.
26. Leffler DA, Lamont JT. *Clostridium difficile* infection. *New England Journal of Medicine*. 2015;372(16):1539-1548.
27. Fang FC, Polage CR, Wilcox MH. Point-Counterpoint: What is the optimal approach for detection of *Clostridium difficile* infection? *Journal of clinical microbiology*. 2017;55(10):02463-02463.
28. Polage CR, Gyorke CE, Kennedy MA, et al. Overdiagnosis of *Clostridium difficile* infection in the molecular test era. *JAMA internal medicine*. 2015;175(11):1792-1801.
29. May RC, Stone NRH, Wiesner DL, Brican T, Nielsen K. *Cryptococcus*: from environmental saprophyte to global pathogen. *Nature reviews Microbiology*. 2016;14(2):106-117.
30. Maziarz EK, Perfect JR. *Cryptococcosis*. *Infectious disease clinics of North America*. 2016;30(1):179-206.
31. Xu T, Zhang X-H. *Edwardsiella tarda*: an intriguing problem in aquaculture. *Aquaculture*. 2014;431:129-135.
32. Hirai Y, Asahata-Tago S, Ainoeda Y, Fujita T, Kikuchi K. *Edwardsiella tarda* bacteremia. A rare but fatal water- and foodborne infection: Review of the literature and clinical cases from a single centre. *The Canadian journal of infectious diseases & medical microbiology = Journal canadien des maladies infectieuses et de la microbiologie medicale*. 2015;26(6):313-318.
33. Verjan N, Iregui C, Hirono L. Adhesion and invasion-related genes of *Edwardsiella tarda* ETS154. *Genes relacionados con la adhesión e invasión de Edwardsiella tarda ETS154*. *Revista Colombiana de Ciencia Animal*. 2013;6(1):26-35.
34. Patel KK, Patel S. *Enterobacter* spp.—An emerging nosocomial infection. *IJAR*. 2016;2(11):532-538.
35. Davin-Regli A, Pagès J-M. *Enterobacter* aerogenes and *Enterobacter cloacae*: versatile bacterial pathogens confronting antibiotic treatment. *Frontiers in microbiology*. 2015;6:392-392.
36. Liu F, Wang F, Du L, et al. Antibacterial and antibiofilm activity of phenylacetic acid against *Enterobacter cloacae*. *Food Control*. 2018;84:442-448.
37. Lim JY, Yoon J, Hovde CJ. A brief overview of *Escherichia coli* O157:H7 and its plasmid O157. *Journal of microbiology and biotechnology*. 2010;20(1):5-14.
38. Heiman KE, Mody RK, Johnson SD, Griffin PM, Gould LH. *Escherichia coli* O157 Outbreaks in the United States, 2003-2012. *Emerging infectious diseases*. 2015;21(8):1293-1301.
39. Pal M, Sejira S, Sejira A, Tesfaye S. Geotrichosis: an opportunistic mycosis of humans and animals. *Int J Livest Res*. 2013;3(2):38-44.
40. Myint T, Dykhuizen MJ, McDonald CH, Ribes JA. Post operative fungal endophthalmitis due to *Geotrichum candidum*. *Med Mycol Case Rep*. 2015;10:4-6.
41. Gao G-X, Tang H-L, Zhang X, Xin X-L, Feng J, Chen X-Q. Invasive fungal infection caused by *geotrichum capitatum* in patients with acute lymphoblastic leukemia: a case study and literature review. *International journal of clinical and experimental medicine*. 2015;8(8):14228-14235.
42. Chapartegui-González I, Lázaro-Díez M, Redondo-Salvo S, Amaro-Prellezo E, Esteban-Rodríguez E, Ramos-Vivas J. Biofilm formation in *Hafnia alvei* HUMV-5920, a human isolate. *AIMS Microbiol*. 2016;2(4):412-421.
43. Dos Santos G, Solidonio E, Costa M, et al. Study of the Enterobacteriaceae group CESP (*Citrobacter*, *Enterobacter*, *Serratia*, *Providencia*, *Morganella* and *Hafnia*): a review. *The Battle Against Microbial Pathogens: Basic Science, Technological Advances and Educational Programs*. 2015;2:794-805.
44. Epis S, Capone A, Martin E, et al. A rapid qPCR method to investigate the circulation of the yeast *Wickerhamomyces anomalus* in humans. *The new microbiologica*. 2015;38(4):577-581.
45. Huang CH, Chang MT, Huang L. Species identification of *Wickerhamomyces anomalus* and related taxa using β -tubulin (β Tub) DNA barcode marker. *Yeast*. 2012;29(12):531-535.
46. Choi S-W, Lee T-J, Kim M-K, Lee M, Jung J-H. A case of fungal arthritis caused by *Hansenula anomala*. *Clinics in orthopedic surgery*. 2010;2(1):59-62.
47. Chey WD, Leontidis GI, Howden CW, Moss SF. ACG clinical guideline: treatment of *Helicobacter pylori* infection. *The American journal of gastroenterology*. 2017;112(2):212.
48. Kao C-Y, Sheu B-S, Wu J-J. *Helicobacter pylori* infection: An overview of bacterial virulence factors and pathogenesis. *Biomedicine*. 2016;39(1):14-23.
49. Gorrie CL, Mireta M, Wick RR, et al. Gastrointestinal Carriage Is a Major Reservoir of *Klebsiella pneumoniae* Infection in Intensive Care Patients. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2017;65(2):208-215.
50. Martin RM, Bachman MA. Colonization, Infection, and the Accessory Genome of *Klebsiella pneumoniae*. *Frontiers in cellular and infection microbiology*. 2018;8:4-4.
51. Hsu C-R, Pan Y-J, Liu J-Y, Chen C-T, Lin T-L, Wang J-T. *Klebsiella pneumoniae* translocates across the intestinal epithelium via Rho GTPase- and phosphatidylinositol 3-kinase/Akt-dependent cell invasion. *Infection and immunity*. 2015;83(2):769-779.
52. Tse H, Gu Q, Sze K-H, et al. A tricyclic pyrrolobenzodiazepine produced by *Klebsiella oxytoca* is associated with cytotoxicity in antibiotic-associated hemorrhagic colitis. *The Journal of biological chemistry*. 2017;292(47):19503-19520.
53. Rashid T, Wilson C, Ebringer A. The link between ankylosing spondylitis, Crohn's disease, *Klebsiella*, and starch consumption. *Clinical & developmental immunology*. 2013;2013:872632-872632.
54. Becattini S, Littmann ER, Carter RA, et al. Commensal microbes provide first line defense against *Listeria monocytogenes* infection. *Journal of Experimental Medicine*. 2017;214(7):1973-1989.
55. David DJV, Cossart P. Recent advances in understanding *Listeria monocytogenes* infection: the importance of subcellular and physiological context. *F1000Research*. 2017;6:F1000 Faculty Rev-1126.
56. Zaveri Anuiraq ea. *Moellerella wisconsinensis* Isolated from Stool Sample Having Prolonged History of Diarrhea. *International Microbiology Research*. 2018;10(2):773-775.
57. Aller A, Castro C, Medina M, et al. Isolation of *Moellerella wisconsinensis* from blood culture from a patient with acute cholecystitis. *Clinical Microbiology and Infection*. 2009;15(12):1193-1194.
58. Lin T-Y, Kak V, Chang FY. *Morganella* species.
59. Al-Sweih N, Khan ZU, Ahmad S, et al. *Kodamaea ohmeri* as an emerging pathogen: a case report and review of the literature. *Medical Mycology*. 2011;49(7):766-770.
60. Vivas R, Beltran C, Munera MI, Trujillo M, Restrepo A, Garcés C. Fungemia due to *Kodamaea ohmeri* in a young infant and review of the literature. *Medical mycology case reports*. 2016;13:5-8.
61. Tashiro A, Nei T, Sugimoto R, et al. *Kodamaea ohmeri* fungemia in severe burn: Case study and literature review. *Medical mycology case reports*. 2018;2:21-23.
62. Chakrabarti A, Rudramurthy S, Kale P, et al. Epidemiological study of a large cluster of fungaemia cases due to *Kodamaea ohmeri* in an Indian tertiary care centre. *Clinical Microbiology and Infection*. 2014;20(2):083-089.
63. Janda JM, Abbott SL, McIver CI. *Plesiomonas shigelloides* revisited. *Clinical microbiology reviews*. 2016;29(2):349-374.
64. Shah MM, Oboyo E, Larson PS, et al. First Report of a Foodborne *Providencia alkalifaciens* Outbreak in Kenya. *The American journal of tropical medicine and hygiene*. 2015;93(3):497-500.
65. Asakura H, Momose Y, Ryu CH, et al. *Providencia alkalifaciens* causes barrier dysfunction and apoptosis in tissue cell culture: potent role of lipopolysaccharides on diarrheagenicity. *Food additives & contaminants Part A, Chemistry, analysis, control, exposure & risk assessment*. 2013;30(8):1459-1466.
66. Prasad RR, Shree V, Sagar S, Kumar S, Kumar P. Prevalence and Antimicrobial Susceptibility Pattern of *Proteus* Species in Clinical Samples. *Int J Curr Microbiol App Sci*. 2016;5(4):962-968.
67. Drzewiecka D. Significance and Roles of *Proteus* spp. Bacteria in Natural Environments. *Microbial Ecology*. 2016;72(4):741-758.
68. Chuang C-H, Wang Y-H, Chang H-J, et al. Shanghai fever: a distinct *Pseudomonas aeruginosa* enteric disease. *Gut*. 2014;63(5):736-743.
69. Huang F-C. Differential regulation of interleukin-8 and human beta-defensin 2 in *Pseudomonas aeruginosa*-infected intestinal epithelial cells. *BMC microbiology*. 2014;14:275-275.
70. Benoit TJ, Blaney DD, Doker TJ, et al. A Review of Melioidosis Cases in the Americas. *The American journal of tropical medicine and hygiene*. 2015;93(6):1134-1139.
71. Perumal Samy R, Stiles BG, Sethi G, Lim LHK. Melioidosis: Clinical impact and public health threat in the tropics. *PLoS neglected tropical diseases*. 2017;11(5):e0004738-e0004738.
72. Wirth F, Goldani LZ. Epidemiology of *Rhodotorula*: an emerging pathogen. *Interdisciplinary perspectives on infectious diseases*. 2012;2012:465717-465717.
73. Ramos A, Redelman G, Brown A, Seo S. *Rhodotorula* species. 2015.

REFERENCES

74. Pérez-Torrado R, Querol A. Opportunistic Strains of *Saccharomyces cerevisiae*: A Potential Risk Sold in Food Products. *Frontiers in microbiology*. 2016;6:1522-1522.
75. Pineton de Chambrun G, Neut C, Chau A, et al. A randomized clinical trial of *Saccharomyces cerevisiae* versus placebo in the irritable bowel syndrome. *Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver*. 2015;47(2):119-124.
76. Muñoz P, Bouza E, Cuenca-Estrella M, et al. *Saccharomyces cerevisiae* Fungemia: An Emerging Infectious Disease. *Vol 40* 2005.
77. Pham OH, McSorley SJ. Protective host immune responses to *Salmonella* infection. *Future microbiology*. 2015;10(1):101-110.
78. Gayet R, Bioley G, Rochereau N, Paul S, Corthésy B. Vaccination against *Salmonella* infection: the mucosal way. *Microbiology and Molecular Biology Reviews*. 2017;81(3):e00007-00017.
79. Herra C, Falkner FR. *Serratia marcescens*. *Antimicrobial Therapy and Vaccines*. 2017;1.
80. Ochieng JB, Boisen N, Lindsay B, et al. *Serratia marcescens* is injurious to intestinal epithelial cells. *Gut microbes*. 2014;5(6):729-736.
81. Iguchi A, Nagaya Y, Pradel E, et al. Genome Evolution and Plasticity of *Serratia marcescens*, an Important Multidrug-Resistant Nosocomial Pathogen. *Genome Biology and Evolution*. 2014;6(8):2096-2110.
82. Anderson M, Sansonetti PJ, Marteyn BS. *Shigella* Diversity and Changing Landscape: Insights for the Twenty-First Century. *Frontiers in cellular and infection microbiology*. 2016;6:45-45.
83. Puzari M, Sharma M, Chetia P. Emergence of antibiotic resistant *Shigella* species: A matter of concern. *Journal of infection and public health*. 2018;11(4):451-454.
84. Missiakas D, Schneewind O. *Staphylococcus aureus* vaccines: Deviating from the carol. *Journal of Experimental Medicine*. 2016;213(9):1645-1653.
85. Kadariya J, Smith TC, Thapaliya D. *Staphylococcus aureus* and staphylococcal food-borne disease: an ongoing challenge in public health. *BioMed research international*. 2014;2014.
86. Claassen-Weitz S, Shittu AO, Ngwarai MR, Thabane L, Nicol MP, Kaba M. Fecal carriage of *Staphylococcus aureus* in the hospital and community setting: A systematic review. *Frontiers in microbiology*. 2016;7:449.
87. Puah SM, Chua KH, Tan JAMA. Virulence factors and antibiotic susceptibility of *Staphylococcus aureus* isolates in ready-to-eat foods: detection of *S. aureus* contamination and a high prevalence of virulence genes. *International journal of environmental research and public health*. 2016;13(2):199.
88. Duarte-Oliveira C, Rodrigues F, Gonçalves SM, Goldman GH, Carvalho A, Cunha C. The Cell Biology of the *Trichosporon*-Host Interaction. *Frontiers in cellular and infection microbiology*. 2017;7:118-118.
89. Almagro-Moreno S, Pruss K, Taylor RK. Intestinal colonization dynamics of *Vibrio cholerae*. *PLoS pathogens*. 2015;11(5):e1004787.
90. Learoyd TP, Gaut RM. Cholera: under diagnosis and differentiation from other diarrhoeal diseases. *Journal of Travel Medicine*. 2018;25(suppl_1):S46-S51.
91. Osuobale O, Okoh A. Isolation and antibiotic profile of *Vibrio* spp. final effluents of two wastewater treatment plants in the Eastern Cape of South Africa. *bioRxiv*. 2018:330456.
92. Ramamurthy T, Chowdhury G, Pazhani G, Shinoda S. *Vibrio fluvialis*: an emerging human pathogen. *Frontiers in Microbiology*. 2014;5(91).
93. Ballal M, Shetty V, Bangera SR, Prabhu M, Umakanth S. *Vibrio furnissii*, an emerging pathogen causing acute gastroenteritis: a Case Report. *JMM case reports*. 2017;4(9):e005111-e005111.
94. Singh A, Vaidya B, Khatri I, et al. *Grimontia indica* AK16(T), sp. nov., isolated from a seawater sample reports the presence of pathogenic genes similar to *Vibrio* genus. *PLoS one*. 2014;9(1):e85590-e85590.
95. Lin Y-R, Chen Y-L, Wang K-B, et al. The thermostable direct hemolysin from *Grimontia hollisae* causes acute hepatotoxicity in vitro and in vivo. *PLoS one*. 2013;8(2):e56226-e56226.
96. Jensen J, Jellinge ME. Severe septic shock and cardiac arrest in a patient with *Vibrio metschnikovii*: a case report. *Journal of Medical Case Reports*. 2014;8(1):348.
97. Mizuno T, Nanko A, Maehara Y, Shinoda S, Miyoshi SL. A novel extracellular protease of *Vibrio mimicus* that mediates maturation of an endogenous hemolysin. *Microbiology and immunology*. 2014;58(9):503-512.
98. Hasan NA, Grim CJ, Haley BJ, et al. Comparative genomics of clinical and environmental *Vibrio mimicus*. *Proceedings of the National Academy of Sciences*. 2010;107(49):21134-21139.
99. Baker-Austin C, Trinanes J, Gonzalez-Escalona N, Martinez-Urtaza J. Non-cholera vibrios: the microbial barometer of climate change. *Trends in microbiology*. 2017;25(1):76-84.
100. Wielkoszynski T, Moghaddam A, Bäckman A, et al. Novel diagnostic ELISA test for discrimination between infections with *Yersinia enterocolitica* and *Yersinia pseudotuberculosis*. *European Journal of Clinical Microbiology & Infectious Diseases*. 2018;37(12):2301-2306.
101. Le Baut G, O'Brien C, Pavli P, et al. Prevalence of *Yersinia* Species in the Ileum of Crohn's Disease Patients and Controls. *Frontiers in cellular and infection microbiology*. 2018;8:336-336.

Parasitic Organisms

NEMATODES – ROUNDWORMS

Organism	Description	Epidemiology/Transmission	Pathogenicity	Symptoms
<p><i>Ancylostoma -Necator</i></p> <p><i>Ancylostoma duodenale</i></p> <p><i>Necator americanus</i></p>	<p>Hookworms</p> <p>Soil-transmitted nematodes</p> <p>(P)</p>	<p>Found in tropical and subtropical climates, as well as in areas where sanitation and hygiene are poor.¹</p> <p>Infection occurs when individuals come into contact with soil containing fecal matter of infected hosts.²</p>	<p><i>Necator</i> can only be transmitted through penetration of the skin, whereas <i>Ancylostoma</i> can be transmitted through the skin and orally.</p> <p><i>Necator</i> attaches to the intestinal mucosa and feeds on host mucosa and blood.²</p> <p><i>Ancylostoma</i> eggs pass from the host's stool to soil. Larvae can penetrate the skin, enter the lymphatics, and migrate to heart and lungs.³</p>	<p>Some are asymptomatic, though a heavy burden is associated with anemia, fever, diarrhea, nausea, vomiting, rash, and abdominal pain.²</p> <p>During the invasion stages, local skin irritation, elevated ridges due to tunneling, and rash lesions are seen.³</p> <p><i>Ancylostoma</i> and <i>Necator</i> are associated with iron deficiency anemia.^{1,2}</p>
<p><i>Ascaris lumbricoides</i></p>	<p>Soil-transmitted nematode</p> <p>Most common human worm infection</p> <p>(P)</p>	<p>Common in Sub-Saharan Africa, South America, Asia, and the Western Pacific. In non-endemic areas, infection occurs in immigrants and travelers.</p> <p>It is associated with poor personal hygiene, crowding, poor sanitation, and places where human feces are used as fertilizer.</p> <p>Transmission is via the fecal-oral route.⁴</p>	<p><i>Ascaris</i> eggs attach to the small intestinal mucosa. Larvae migrate via the portal circulation into the pulmonary circuit, to the alveoli, causing a pneumonitis-like illness. They are coughed up and enter back into the GI tract, causing obstructive symptoms.⁵</p>	<p>Most patients are asymptomatic or have only mild abdominal discomfort, nausea, dyspepsia, or loss of appetite.</p> <p>Complications include obstruction, appendicitis, right upper quadrant pain, and biliary colic.⁴</p> <p>Intestinal ascariasis can mimic intestinal obstruction, bowel infarction, intussusception, and volvulus. Hepatic and pancreatic ascariasis can mimic biliary colic, acute acalculous cholecystitis, hepatic abscess, acute pancreatitis, and ascending cholangitis. Appendicular ascariasis can mimic appendicular colic, appendicitis, appendicular gangrene. Gastric ascariasis can mimic pyloric obstruction.⁶</p>
<p><i>Capillaria philippinensis</i></p>	<p>Fish-borne nematode</p> <p>(P)</p>	<p>Although rare in the US, it is more common in Asia (Thailand and the Philippines)⁴</p> <p>Infection occurs from eating raw or undercooked fish containing larvae.</p>	<p>Ingested larvae reside in the human small intestine, where the female deposits eggs, which then develop, causing autoinfection and hyperinfection.⁴</p>	<p>Diarrhea, anorexia, malaise, and vomiting.⁴</p> <p>Capillariasis can mimic IBD and other causes of protein losing enteropathy.⁶</p>
<p><i>Enterobius vermicularis</i></p>	<p>Pinworm</p> <p>The most common worm infection in children ages 5-10 in the US</p> <p>(P)</p>	<p>Compared to other intestinal parasites, the transmission of pinworm is limited because their eggs are unable to survive in the environment. The main routes of infection are autoinfection from eggs or larvae deposited on the anus, contamination from bed sheets, clothing, door handles, and inhalation of eggs from</p>	<p>Eggs are deposited around the anus by the worm. Autoinfection occurs due to scratching the perineal area, then thumb-sucking or nail-biting. Pinworms reside in the intestine but can migrate to distant organs.⁴</p>	<p>Some infections are asymptomatic.</p> <p>Symptoms may include itching and irritation. Occasional migration of the worm to distant organs can cause dysuria, vaginal discharge, enuresis, and peritoneal granulomas.⁴</p> <p>Enterobiasis can mimic hemorrhoids and IBD.⁶</p>

Parasitic Organisms

NEMATODES – ROUNDWORMS

Organism	Description	Epidemiology/Transmission	Pathogenicity	Symptoms
		<p>hands, bed mattresses, or dust. As a result, infections tend to be limited to families and individuals in close proximity, like nurseries and boarding schools.⁷</p> <p>Spread by overcrowding and poor hygiene.</p>		
<i>Strongyloides stercoralis</i>	<p>Soil-transmitted nematode</p> <p>(P)</p>	<p>Endemic to the tropics and temperate subtropics where poor sanitation facilitates fecal contamination. Also found in poorer areas of the US: Appalachian mountain communities, Kentucky, and rural Tennessee.¹</p> <p>Transmission is from contaminated soil.⁸</p>	<p>Infection occurs from skin penetration where the organism then travels systemically (blood, lung, GI tract).⁸</p> <p><i>Strongyloides stercoralis</i> is unique among nematodes infections in humans because larvae passing in the feces can give rise to a free-living generation of worms. The potential for autoinfection exists if larvae attain infectivity while in the host.⁴</p>	<p>Most patients have subclinical or asymptomatic infections. They are commonly chronic and longstanding due to the autoinfective lifecycle.⁴</p> <p>Irritation, edema, and urticaria at the site of skin penetration.⁸</p> <p>Diarrhea, constipation, abdominal pain, anorexia.</p> <p>Dry cough, tracheal irritation, recurrent asthma.⁸</p> <p>Strongyloidiasis can mimic IBD and eosinophilic enterocolitis.⁶</p>
<i>Trichuris trichiura</i>	<p>Whipworm</p> <p>Soil-transmitted nematode</p> <p>The third most common roundworm in humans⁴</p> <p>(P)</p>	<p>Found in areas where human feces is used as fertilizer. Found in the tropics and places with poor sanitation.</p> <p>Transmitted via the fecal-oral route.⁴</p>	<p>A human host consumes eggs, sometimes in food. Once the eggs are ingested, the larvae hatch in the small intestine. From there they migrate to the large intestine, where the anterior ends lodge within the mucosa. This leads to cell destruction and activation of the host immune system, recruiting eosinophils, lymphocytes, and plasma cells. This causes the typical symptoms of rectal bleeding and abdominal pain.⁹</p>	<p>Mild infections are usually asymptomatic. Heavy worm burden causes painful defecation with mucus, water, and blood (Trichuris dysentery syndrome). Rectal prolapse is also seen.⁹</p> <p>Children develop iron deficiency anemia, growth retardations, and impaired cognitive development.⁴</p> <p>Trichuriasis can mimic IBD, bacillary dysentery and acute intestinal amebiasis.⁶</p>

Parasitic Organisms

CESTODES – TAPEWORMS

Organism	Description	Epidemiology/Transmission	Pathogenicity	Symptoms
<i>Dipylidium caninum</i>	Dog (or cat) tapeworm (P)	Human infection is rare but can occur in those who kiss or are licked by their infected pets. ¹⁰	Fleas ingest <i>D. caninum</i> eggs. Adult fleas are ingested by pets and establish in the small intestine where the eggs develop into the adult tapeworm. The tapeworm sheds proglottids, which are found in the stool. Humans are infected by accidental ingestion of infected dog or cat fleas. ¹⁰	Most are asymptomatic. When present, symptoms include weight loss, colic, and vomiting. ¹¹
<i>Diphyllobothrium latum</i>	Fish tapeworm (P)	<i>D. latum</i> occurs in freshwater fish throughout much of the northern hemisphere; intermediate hosts include bears, pigs, cats, dogs, foxes, and wolves. Humans become infected after eating raw or undercooked fish. ¹¹	After ingestion, in humans the adult helminth can live up to 20 years in the small intestine. It adheres to the mucosa and can eliminate millions of eggs each day. Diagnosis is made by the demonstration of eggs or proglottids in the stool. ¹²	Mostly asymptomatic, but signs and symptoms can include nausea, vomiting, diarrhea, abdominal pain, and weight loss. ¹¹ Can cause megaloblastic anemia. ⁶
<i>Hymenolepis diminuta</i>	Rat tapeworm (P)	Human infection with <i>H. diminuta</i> is rare with only a few hundred cases reported, mainly in children. <i>H. diminuta</i> is prevalent worldwide in temperate to tropical conditions with poor sanitation. ¹³ <i>H. diminuta</i> infection requires an intermediate host (usually rodents, but also insects). Humans become infected by ingesting food contaminated with larvae, or by direct hand contact. ¹⁴	Once ingested, <i>H. diminuta</i> grows to adult form and sheds eggs through the stool. It attaches to the mucosal surface of the intestine and grows to approximately 20-50 cm. in length.	Infection is usually asymptomatic, though may cause abdominal pain, diarrhea, and irritability. ¹⁴
<i>Hymenolepis nana</i>	Dwarf tapeworm (P)	<i>H. nana</i> is one of the most common parasitic tapeworm infections worldwide, found mainly in children. It does not require an intermediary host and can be transmitted human to human, though rodents can also carry <i>H. nana</i> . ¹⁵ It has fecal-oral transmission from food and water in areas of poor sanitation. ¹⁶	<i>H. nana</i> eggs are immediately infective when passed through the stool and cannot last more than 10 days in the environment. Once ingested, larvae penetrate intestinal villi and develop into adults that measure 15-40 cm. in length. Eggs pass into stool or can reside within the intestinal villi and cause continual autoinfection. ¹⁷	Symptoms include abdominal pain, diarrhea, anorexia, weight loss, malnutrition, and anemia. ¹⁸

Parasitic Organisms

CESTODES – TAPEWORMS

Organism	Description	Epidemiology/Transmission	Pathogenicity	Symptoms
<i>Taenia</i> spp. <i>Taenia saginata</i> <i>Taenia solium</i>	Tapeworm (P)	This tapeworm is found in people who have traveled outside of the US where the infection is endemic, or in Latin American immigrants. Locally acquired infections are rare but have been diagnosed in Los Angeles, New York, Chicago, and Oregon. Infection occurs upon ingestion of raw or undercooked meat. ⁴	Ingested parasite cysts reach the intestine and develop into adult tapeworms, releasing motile segments and/or eggs in the stool. ¹⁹ One adult tapeworm can expel a minimum of 100,000 eggs per day. The enclosed larvae penetrate the intestinal wall and are transported via the bloodstream to various tissues where they undergo multiple development stages to become cysticerci. ²⁰	The adult tapeworm stage is relatively innocuous and does not have human pathogenic effects. However, some species' intermediate stages can develop in human brains causing neurocysticercosis, a major cause of neurologic disease in developing countries. Cysticercosis can develop in other organs causing intramuscular, ocular, subcutaneous, and spinal cysticercoses. ¹⁹ Taeniasis can mimic IBS. ⁶

TREMATODES – FLUKES

Organism	Description	Epidemiology/Transmission	Pathogenicity	Symptoms
<i>Clonorchis</i> - <i>Opisthorchis</i> spp.	Liver flukes (P)	<i>Clonorchis</i> and <i>Opisthorchis</i> infections have been reported in many parts of east Asia, Thailand, Laos, Cambodia, and Japan. ²¹ These flukes live in freshwater snails and fish. Humans are infected by eating raw or partially cooked, infected fish.	Adult flukes attach to bile ducts where they feed for as long as 10-30 years, resulting in chronic inflammation, epithelial hyperplasia, fibrosis, and granuloma. ²² Both are classified as Group 1 carcinogens. Infection by these parasites is frequently asymptomatic and rarely diagnosed during early exposure. Persistent infection is associated with parasite-associated cancer. The mechanism of this transformation is yet to be fully defined. ²³	Early infection is often asymptomatic. Chronic infection is associated with cholangitis, obstructive jaundice, biliary fibrosis, cholecystitis, and cholangiocarcinoma. ²⁴
<i>Fasciola</i> spp.- <i>Fasciolopsis buski</i> ova	Plant-borne intestinal fluke <i>F. buski</i> is known as the giant intestinal fluke, and is one of the largest flukes to infect humans. ²⁵ <i>F. hepatica</i> is a liver fluke. (P)	Largely confined to Asian countries, including China. ²⁵ Humans are infected by ingesting eggs adhering to the surface of edible water plants. ²⁵	After ingestion, gastric juices aid the release of the worm. The worm migrates to the small intestine, and produces eggs, which are passed in feces. ²⁶	Light infections are often asymptomatic. Moderate to heavy infection causes abdominal pain, diarrhea, nausea, vomiting, and fever. Extensive intestinal inflammation, erosions, ulceration, abscess, and hemorrhage are possible. ²⁶
<i>Heterophyes</i> - <i>Metagonimus</i> ova	Fish-borne intestinal fluke (P)	These are mostly seen in Far East and Asian countries. ²⁷ These flukes are exclusively fish-borne and are contracted by humans by ingesting raw or improperly cooked freshwater or brackish fish.	Mechanical irritation is caused by movement of the worms causing mucosal villous atrophy. Chemical excretory/secretory proteins acts as active antigens and toxins, provoking a systemic immune response. ²⁷	Mucosal changes lead to nutrient malabsorption, intestinal permeability, and watery diarrhea. ²⁷ Abdominal pain, weight loss, and anorexia are also seen. ²⁷

Parasitic Organisms

TREMATODES – FLUKES

Organism	Description	Epidemiology/Transmission	Pathogenicity	Symptoms
<i>Paragonimus</i> spp.	Lung fluke (P)	There are roughly 9 species that cause clinical disease in humans, but only <i>P. kellicotti</i> is endemic to North America, where it is found in streams and rivers in the Mississippi River Basin, including the central United States west to the Rocky Mountains. ¹¹ Infection is caused by ingestion of raw or undercooked crabs or crayfish. ²⁸	After ingestion of infected crabs or crayfish, the fluke resides in the small intestine and migrates through the intestinal wall into the peritoneal space and eventually into the pleural space. ¹¹	Patients are often asymptomatic after ingestion and during the initial migration phase. Some patients may develop abdominal pain and diarrhea. After migration to the pleural space, inflammatory pulmonary symptoms begin. ¹¹ Typical features of pulmonary paragonimiasis include cough, hemoptysis, chest pain, and dyspnea. ²⁸
<i>Schistosoma</i> spp. <i>Schistosoma mansoni</i> <i>Schistosoma japonicum</i> <i>Schistosoma haematobium</i> <i>Schistosoma mekongi</i>	Blood fluke <i>S. mansoni</i> , <i>S. japonicum</i> , and <i>S. mekongi</i> cause intestinal disease ²⁹ <i>S. haematobium</i> causes urinary disease (P)	This organism is prevalent in the tropics and subtropics where poor sanitation is common. ³⁰ <i>S. mekongi</i> is primarily limited to the Mekong River Basin stretching from Laos to Cambodia. ²⁹ Humans contract the infection via water sources. ³⁰	Humans acquire the infection by direct contact with water sources containing infectious larvae. The larvae penetrate skin and enter the circulation via the capillaries and lymphatics. ³⁰	Schistosome egg deposition and fluke burden can occur in any ectopic site, giving rise to site-specific symptoms and disease. These include dermatitis, abdominal pain, diarrhea, ascites, GI bleeding, and urinary obstructive symptoms. ³⁰ Intestinal schistosomiasis can mimic diverticulitis and IBD. Hepatic schistosomiasis can mimic alcoholic liver disease and liver cirrhosis. ⁶

Parasitic Organisms

PROTOZOA

Organism	Description	Epidemiology/Transmission	Pathogenicity	Symptoms
<i>Balantidium coli</i>	Ciliate protozoan (PP)	<i>Balantidium</i> is reported worldwide, but is more prevalent in temperate and tropical regions. Human infections are related to poor sanitation and drinking water contaminated with human and animal (swine) feces. ⁴	Trophozoites inhabit the intestine, feeding on bacteria and other intestinal contents. In most cases, infections are asymptomatic and the infected host shows no clinical signs, suggesting that this ciliate is an opportunistic parasite that could take advantage of the host's weakened status caused by other infections or diseases. In such cases, the parasite could invade the intestinal wall, causing the disease known as balantidiasis or balantidial dysentery. ³¹	Often asymptomatic, but in the acute form symptoms may include mucus and blood in feces. In severe cases, hemorrhages and perforation could occur. Chronic infection may present with unspecific abdominal disorders (diarrhea, abdominal pain), cramping rectal pain, nausea, and vomiting. ³¹ Balantidiasis can mimic traveler's diarrhea, invasive amebiasis, bacterial dysentery and IBD. ⁶
<i>Blastocystis</i> spp.	Although there are 17 different <i>Blastocystis</i> subtypes, subtypes 1-9 are the only subtypes found in humans. Subtypes 1-4 make up 90%. Subtype 3 is most common. Subtypes have geographic distribution. (PP)	<i>Blastocystis</i> is one of the most common parasites, affecting 1.5-30% of those in industrialized countries and 30-76% in developing countries. ^{32,33} <i>Blastocystis</i> transmission is via the fecal-oral route by ingesting contaminated food or water, exposure to daycare environments, and exposure to domestic and wild animals. ^{34,35} Various subtypes have different zoonotic transmissions.	<i>Blastocystis</i> resides in the ileum and cecum, adheres to mucus' outer layer, and uses certain bacteria as a nutritional source. (30) Its pathogenicity is controversial. ³² It is associated with higher microbial diversity, and may be regarded as a commensal organism. ³³ Literature-based conclusions about disease associations and subtype pathogenicity is conflicting, but evolving.	<i>Blastocystis</i> is often asymptomatic. When present, symptoms include nausea, anorexia, abdominal pain, flatulence, acute/chronic diarrhea, constipation, anal itching, fatigue, joint pain, and urticaria. It is associated with irritable bowel syndrome (IBS), and is three times higher in patients with IBS-D. ³⁶ Blastocystosis can mimic acute viral enteritis, and traveler's diarrhea. ⁶
<i>Chilomastix mesnili</i>	Non-pathogenic parasite (NP)	<i>C. mesnili</i> is found in about 3.5% of the US population. ³⁷ Transmission is fecal-oral via the ingestion of mature cysts from contaminated water or food.	<i>C. mesnili</i> lives in the cecum and colon, but is noninvasive and nonpathogenic. ³⁷	Although <i>C. mesnili</i> is nonpathogenic, and causes no symptoms, it often occurs with other parasitic infections. ³⁷
<i>Cryptosporidium</i> spp.	Coccidian parasite (P)	<i>Cryptosporidium</i> is endemic to North, Central, and South America, Africa, and Australia. Infection is spread via the fecal-oral route and indirectly through contaminated water. <i>Cryptosporidium</i> is a common cause of food and water-borne outbreaks. ⁴	The parasite adheres to intestinal epithelial cells. The intestinal epithelium releases cytokines to incite an immune response and causes cell apoptosis and villous atrophy. <i>Cryptosporidium</i> has developed ways to slow this protective mechanism; therefore, host immune competency determines pathogenicity. ³⁸	In immunocompetent patients, infection is self-limiting with 2 weeks of watery diarrhea. Other symptoms include fever, nausea, vomiting, and abdominal pain. Symptoms can be cyclical. ^{39,40} It can be life threatening in immunocompromised patients. ⁴⁴¹ Enteric cryptosporidiosis can mimic malabsorption syndrome, Giardiasis, and viral diarrhea. Biliary cryptosporidiosis can mimic acute cholangitis. ⁶

Parasitic Organisms

PROTOZOA

Organism	Description	Epidemiology/Transmission	Pathogenicity	Symptoms
<i>Cyclospora cayentanensis</i>	Food- and waterborne coccidian parasite (P)	<i>Cyclospora</i> is endemic to Nepal, Haiti, Peru, and Guatemala, but it has been found as a cause of traveler's diarrhea worldwide. There have been many US outbreaks related to imported fruits and vegetables. ^{4,42} In the US, increased cases are reported during the spring and summer months. Transmission is fecal-oral via ingestion of contaminated water or food.	Individuals with <i>Cyclospora</i> infection excrete unsporulated oocysts in their feces. These oocysts require 7 to 15 days to sporulate and become infectious to a susceptible host. When food or water contaminated with infectious oocysts is ingested by a susceptible host, the oocysts excyst and sporozoites are released and infect epithelial cells of the duodenum and jejunum. ⁴³	Cyclosporiasis is marked by profuse, non-bloody, watery diarrhea, anorexia, fatigue, weight loss, nausea, flatulence, abdominal cramping, myalgias, vomiting, and low grade fever. Symptoms start approximately 7 days after ingestion. If left untreated, it can last weeks to months, with remitting and relapsing symptoms. ⁴ Cyclosporiasis can mimic acute viral enteritis and traveler's diarrhea. ⁶
<i>Cystoisospora</i> spp. <i>Cystoisospora belli</i>	Coccidian parasite Previously referred to as <i>Isoospora</i> ⁴⁴ (P)	<i>Cystoisospora</i> is an uncommon human intestinal parasite. It has a worldwide distribution. <i>Cystoisospora</i> is frequently found in tropical and subtropical regions. ⁴⁵ Transmission is through the fecal-oral route by the ingestion of contaminated water and food. ⁴⁶	<i>Cystoisospora</i> releases sporozoites that penetrate the small intestinal columnar epithelium. ⁴⁷	Some <i>Cystoisospora</i> infections are asymptomatic. When present, infections are usually mild and self-limiting, consisting of diarrhea and abdominal pain. ⁴⁵ It can cause severe chronic diarrhea in immunocompromised AIDS patients. It has also been reported to be a cause of traveler's diarrhea in the normal host and can mimic giardiasis or cryptosporidiosis. ⁴⁸
<i>Dientamoeba fragilis</i>	Flagellate protozoan parasite (P)	<i>D. fragilis</i> has a worldwide distribution, and is transmitted via the fecal-oral route. Transmission via helminth eggs (<i>Ascaris</i> , <i>Enterobius</i>) has also been postulated, but is still being investigated.	The role of <i>D. fragilis</i> as a pathogen is controversial because the trophozoites are not invasive and patients are commonly asymptomatic. ⁴	Although many patients are asymptomatic, <i>D. fragilis</i> has been associated with diarrhea, abdominal pain, nausea, weight loss, anorexia, and flatulence. ⁴ Dientamebiasis can mimic eosinophilic colitis and IBD. ⁶
<i>Entamoeba coli</i>	Non-pathogenic amoeba (NP)	<i>E. coli</i> is cosmopolitan in distribution and has been postulated to occur in approximately 50% of the population. ⁴⁹ Transmission is fecal-oral via the ingestion of contaminated water or food. ⁴⁹	<i>E. coli</i> lives inside the large intestine but never enters the mucosa or sub-mucosal intestinal layers.	The presence of <i>E. coli</i> is not cause to seek treatment and is harmless. However, when a patient is infected with this benign amoeba, introduction of other pathogenic organisms is possible and may cause symptoms. ³⁷
<i>Entamoeba dispar</i>	Non-pathogenic amoeba <i>E. dispar</i> is morphologically and genetically similar to the virulent <i>E. histolytica</i> ; therefore, other laboratory methods are necessary to distinguish the two. ⁵⁰ (NP)	It is speculated that this species is responsible for most infections that were previously considered to be <i>E. histolytica</i> . <i>E. dispar</i> has a high worldwide prevalence. ⁵⁰ Transmission is fecal-oral via the ingestion of contaminated water or food. ⁵¹	<i>E. dispar</i> is noninvasive and considered non-pathogenic. ⁵⁰	<i>E. dispar</i> infection is not associated with clinical symptoms.

Parasitic Organisms

PROTOZOA

Organism	Description	Epidemiology/Transmission	Pathogenicity	Symptoms
<i>Entamoeba hartmanni</i>	<p>Non-pathogenic amoeba</p> <p><i>E. hartmanni</i> can be distinguished from the virulent <i>E. histolytica</i> by the much smaller cyst size.⁵²</p> <p>(NP)</p>	<p><i>E. hartmanni</i> has a worldwide distribution, but is most common in developing countries with poor sanitation.⁵³</p> <p>Transmission is fecal-oral via the ingestion of mature cysts from contaminated water or food.⁵²</p>	<p><i>E. hartmanni</i> is non-pathogenic.⁵³</p>	<p><i>E. hartmanni</i> infection is not associated with clinical symptoms.</p>
<i>Entamoeba histolytica</i>	<p>The leading parasitic cause of mortality globally,⁵² and the third most common parasitic infection in the US.⁴</p> <p>Erythrophagocytosis has been used as a diagnostic indicator of invasive <i>E. histolytica</i> by microscopy.⁵⁴</p> <p>(P)</p>	<p><i>E. histolytica</i> has a worldwide distribution, but is most common in developing countries with poor sanitation.⁵³</p> <p>Transmission is fecal-oral via ingestion of mature cysts from contaminated water or food, or contaminated individuals.⁵³</p>	<p>Cysts are ingested and excystation occurs. Colonization usually happens in the large bowel, but the cecum is most common. It penetrates the endothelium causing ulceration. Host factors appear to promote a more invasive, systemic disease, leading to dysentery, liver abscess, pleuropulmonary involvement, and many other systemic complications.⁵³</p>	<p>Although many cases are asymptomatic, it is likely that misdiagnosis is the cause (failure to identify <i>E. dispar/hartmanni</i>).</p> <p>Symptoms of <i>E. histolytica</i> infection (amoebiasis) include hemorrhagic diarrhea, fatigue, nausea, fever, weight loss.⁵⁵</p> <p>Intestinal amebiasis can mimic infectious diarrhea, IBD, ischemic colitis, diverticulitis, AV malformation. Amoeboma can mimic colon carcinoma. Amebic strictures can mimic lymphogranuloma venereum (chlamydia) and malignancy. Hepatic amebiasis can mimic pyogenic liver abscess, necrotic hepatoma and echinococcal cyst.⁶</p>
<i>Entamoeba polecki</i>	<p>Non-pathogenic amoeba</p> <p><i>E. polecki</i> can be distinguished from other Entamoeba species by microscopy. It is the only uninucleated species.⁵⁶ <i>E. polecki</i> comprises four subtypes, all of which are found in humans.⁵⁶</p> <p>(NP)</p>	<p>Infection with <i>E. polecki</i> is rare, though its prevalence and distribution are often confused with those of the other Entamoeba species.^{56,57}</p> <p><i>E. polecki</i>, much like all Entamoeba species, is transmitted through the fecal-oral route by the ingestion of contaminated food or water.⁵⁶</p>	<p><i>E. polecki</i> is non-pathogenic.</p>	<p><i>E. polecki</i> infection is not associated with clinical symptoms.</p>
<i>Endolimax nana</i>	<p>Non-pathogenic protozoa</p> <p>(NP)</p>	<p><i>E. nana</i> has a global distribution.</p> <p><i>E. nana</i> is transmitted through the fecal-oral route through ingestion of contaminated food or water.⁵⁸</p>	<p><i>E. nana</i> inhabits the colon and has been found in the appendix. <i>E. nana</i> feeds on bacteria and is non-invasive.⁵⁸</p>	<p><i>Endolimax</i> is an indicator of fecal contamination, which often entails co-infection by other organisms capable of causing diarrhea. There are rare cases of associations with urticaria, polyarthritis, and diarrhea. However, there is too little evidence to support pathogenicity.⁵⁸</p>

Parasitic Organisms

PROTOZOA

Organism	Description	Epidemiology/Transmission	Pathogenicity	Symptoms
<i>Giardia</i>	Flagellate protozoa (P)	<i>Giardia</i> has a worldwide distribution. In the US, it is more frequently reported in children aged 1-9. ⁵⁹ <i>Giardia</i> is transmitted through the fecal-oral route by the ingestion of contaminated water and food. ⁵⁹	<i>Giardia</i> (via secretory and excretory proteases) may alter the structure and composition of human intestinal microbiota biofilms. Bacteria from these dysbiotic microbiota in turn can cause epithelial and intestinal abnormalities after the enteropathogen has been cleared. ⁶⁰	<i>Giardia</i> is a leading cause of diarrhea worldwide. Some cases may be asymptomatic; when present symptoms include diarrhea, bloating, malabsorption, nausea, vomiting, and abdominal cramping. Infections are normally self-limiting, but chronic diarrhea may occur in children. ⁵⁹ It is emerging as a prominent precursor to post-infectious irritable bowel syndrome and a variety of chronic extra-intestinal disturbances, such as reactive arthritis and chronic fatigue. ⁶⁰ Acute giardiasis can mimic acute viral enteritis, bacillary dysentery, acute intestinal amebiasis and IBD. ⁶
<i>Iodamoeba butschlii</i>	Non-pathogenic amoeba <i>Iodamoeba</i> gets its name from its appearance when stained with iodine. ³⁷ (NP)	<i>Iodamoeba</i> has a worldwide distribution. Humans have a low prevalence of <i>Iodamoeba butschlii</i> . Transmission is through the fecal-oral route by the ingestion of contaminated water and food. ³⁷	<i>Iodamoeba</i> is usually found in the large intestine and are non-invasive. ³⁷	<i>Iodamoeba</i> is not associated with symptoms. However, it is an indicator of fecal contamination, which often entails co-infection by other organisms capable of causing diarrhea. ³⁷
<i>Trichomonads-</i> <i>Pentatrichomonas</i> <i>Pentatrichomonas hominis</i> <i>Enteromonis hominis</i> <i>Retortamonas intestinalis</i>	Flagellate parasite <i>Trichomonas tenax</i> is usually found in oral/periodontal infections and cannot survive intestinal passage. <i>Pentatrichomonas hominis</i> (also known as <i>Trichomonas hominis</i>) will not survive in the oral cavity or genitourinary tract. It is considered a non-pathogenic parasite. ³⁷ <i>Trichomonas vaginalis</i> is confined to the urogenital system. Among trichomonads, there is a habitat restriction: each can survive only in its site-specific location. ³⁷ (NP)	Trichomonads have worldwide distribution. <i>E. hominis</i> , <i>P. hominis</i> , and <i>R. intestinalis</i> are transmitted via the fecal-oral route by the ingestion of contaminated water, food, and flies. ³⁷	<i>P. hominis</i> , <i>R. intestinalis</i> , and <i>E. hominis</i> are considered non-pathogenic commensals found in the cecum and colon. ³⁷	Trichomonads in the stool are not related to gastrointestinal illness. ³⁷ The presence of trichomonad trophozoites in the stool can be an indicator of fecal contamination, and therefore doesn't rule out other infections as a cause of symptoms. ³⁷

TREATMENT RESOURCES:

The decision to treat parasitic organisms should be based on the patient's clinical presentation.

The following resources provide valuable insight into the clinical management of parasitic infections:

- Center for Disease Control – monographs on individual parasites and treatment protocols: <https://www.cdc.gov/parasites/>
- Sanford Guide - infectious disease treatment guidelines: <https://www.sanfordguide.com/>
- CDC hotline for healthcare providers with questions regarding parasites:
 - Parasitic Diseases Hotline (M-F; 8am-4pm EST) 404-718-4745
 - Emergency, after-hours hotline 770-488-7100
- Mayo Clinic – conditions search engine: <https://www.mayoclinic.org/>
- PubMed – literature search engine: <https://www.ncbi.nlm.nih.gov/pubmed/>

REFERENCES

1. McKenna ML, McAtee S, Bryan PE, et al. Human intestinal parasite burden and poor sanitation in rural Alabama. The American journal of tropical medicine and hygiene. 2017;97(5):1623-1628.
2. Chauhan VM, Scurr DJ, Christie T, Telford G, Aylott JW, Pritchard DJ. The physicochemical fingerprint of *Necator americanus*. PLoS neglected tropical diseases. 2017;11(12):e0005971.
3. Aziz MH, Ramphul K. *Ancylostoma*. In: StatPearls [Internet]. StatPearls Publishing; 2018.
4. Mohapatra S, Singh DP, Alcid D, Pitchumoni CS. Beyond O&P Times Three. The American journal of gastroenterology. 2018;113(6):805-818.
5. Midha A, Janek K, Niewianda A, et al. The Intestinal Roundworm *Ascaris suum* Releases Antimicrobial Factors Which Interfere With Bacterial Growth and Biofilm Formation. Frontiers in cellular and infection microbiology. 2018;8:271.
6. Mohapatra S, Singh DP, Alcid D, Pitchumoni CS. Beyond O&P Times Three. The American journal of gastroenterology. 2018;113(6):805-818.
7. Taylor A, Saichua P, Rhongbutsri P, Tiengtip R, Kitvatanachai S, Taylor WRJ. A preliminary epidemiological study of pinworm infection in Thaklong Municipal Early Childhood Development Center and Rangsit Babies' Home, Pathum Thani, Thailand. BMC Research Notes. 2018;11(1):603.
8. Nutman TB. Human infection with *Strongyloides stercoralis* and other related *Strongyloides* species. Parasitology. 2017;144(3):263-273.
9. Viswanath A, Williams M. *Trichuris trichiura* (Whipworm, Roundworm). In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2018.
10. Jiang P, Zhang X, Liu RD, Wang ZQ, Cui J. A Human Case of Zoonotic Dog Tapeworm, *Dipylidium caninum* (Eucestoda: Dilepididae), in China. The Korean journal of parasitology. 2017;55(1):61-64.
11. Mathison BA, Pritt BS. A Systematic Overview of Zoonotic Helminth Infections in North America. Laboratory Medicine. 2018;49(4):e61-e93.
12. Rosas R, Weitzel T. [Diphyllobothrium latum]. Revista chilena de infectología : organo oficial de la Sociedad Chilena de Infectología. 2014;31(2):211-212.
13. Tiwari S, Karuna T, Rautaraya B. <i>Hymenolepis diminuta</i> infection in a child from a rural area: A rare case report. Journal of Laboratory Physicians. 2014;6(1):58-59.
14. Kotodziej P, Rzymowska J, Stepien-Rukasz H, Lorencowicz R, Lucifarska M, Dzióbek M. Analysis of a child infected with <i>Hymenolepis diminuta</i> in Poland. Annals of Agricultural and Environmental Medicine. 2014;21(3):510-511.
15. Thompson RC. Neglected zoonotic helminths: *Hymenolepis nana*, *Echinococcus canadensis* and *Ancylostoma ceylanicum*. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases. 2015;21(5):426-432.
16. Vilchez Barreto PM, Gamboa R, Santiviáñez S, et al. Prevalence, Age Profile, and Associated Risk Factors for *Hymenolepis nana* Infection in a Large Population-Based Study in Northern Peru. The American journal of tropical medicine and hygiene. 2017;97(2):583-586.
17. Kim BJ, Song KS, Kong H-H, Cha H-J, Ock M. Heavy *Hymenolepis nana* infection possibly through organic foods: report of a case. The Korean journal of parasitology. 2014;52(1):85-87.
18. Cabada MM, Morales ML, Lopez M, et al. *Hymenolepis nana* Impact Among Children in the Highlands of Cusco, Peru: An Emerging Neglected Parasite Infection. The American journal of tropical medicine and hygiene. 2016;95(5):1031-1036.
19. Jabbar A, Gauzi C, Lightowler MW. Diagnosis of human taeniasis. Microbiology Australia. 2016;37(1):43-45.
20. Gripper LB, Welburn SC. Neurocysticercosis infection and disease—A review. Acta tropica. 2017;166:218-224.
21. Doanh PN, Nawa Y. *Clonorchis sinensis* and *Opisthorchis* spp. in Vietnam: current status and prospects. Transactions of The Royal Society of Tropical Medicine and Hygiene. 2016;110(1):13-20.
22. Feng M, Cheng X. Parasite-Associated Cancers (Blood Flukes/Liver Flukes). Advances in experimental medicine and biology. 2017;1018:193-205.
23. Buisson Y. Vaincre la distomatose à *Opisthorchis viverrini* pour prévenir le cholangiocarcinome. Bulletin de la Société de pathologie exotique. 2017;110(1):61-67.
24. Brindley PJ, da Costa JMC, Srija B. Why does infection with some helminths cause cancer? Trends in cancer. 2015;1(3):174-182.
25. Ma J, Sun M-M, He J-J, et al. Fasciolopsis buski (Digenea: Fasciolidae) from China and India may represent distinct taxa based on mitochondrial and nuclear ribosomal DNA sequences. Parasites & Vectors. 2017;10(1):101.
26. Achra A, Prakash P, Shankar R. Fasciolopsiasis: Endemic focus of a neglected parasitic disease in Bihar. Indian journal of medical microbiology. 2015;33(3):364-368.
27. Chai J-Y, Jung B-K. Fishborne zoonotic heterophyid infections: An update. Food and Waterborne Parasitology. 2017;8:33-63.
28. Luo J, Wang M-Y, Liu D, et al. Pulmonary Paragonimiasis Mimicking Tuberculous Pleuritis: A Case Report. Medicine. 2016;95(15):e3436-e3436.
29. Ohmae H, Snuon M, Kirinoki M, et al. Schistosomiasis mekongi: from discovery to control. Parasitology international. 2004;53(2):135-142.
30. Weerakoon KG, Gobert GN, Cai P, McManus DP. Advances in the diagnosis of human schistosomiasis. Clinical microbiology reviews. 2015;28(4):939-967.
31. Ponce-Gordo F, Irkd-Pornabiko A, K. 2017. *Balantidium coli*. Global Water Pathogens Pro ect <http://www.waterpathogens.org> (R. Faer and W. Akubowski, eds) Part 3) <http://www.waterpathogens.org/book/balantidium-coli> Michigan State Univ. ersit, E. Lansing, MI, UNESCO cknowledgements: KRL oung, Pro ect Design editor. 2017.
32. Mohamed AM, Ahmed MA, Ahmed SA, Al-Semary SA, Alghamdi SS, Zaglool DA. Predominance and association risk of *Blastocystis hominis* subtype I in colorectal cancer: a case control study. Infectious agents and cancer. 2017;12(1):21.
33. Nieves-Ramirez M, Partida-Rodríguez Q, Laforet-Lapointe J, et al. Asymptomatic Intestinal Colonization with Protist *Blastocystis* Strongly Associated with Distinct Microbiome Ecological Patterns. mSystems. 2018;3(3):e00007-00018.
34. Salehi R, Haghghi A, Stensvold CR, et al. Prevalence and subtype identification of *Blastocystis* isolated from humans in Ahvaz, Southwestern Iran. Gastroenterology and hepatology from bed to bench. 2017;10(3):235.
35. Barbosa CV, Barreto MM, de Jesus Andrade R, et al. Intestinal parasite infections in a rural community of Rio de Janeiro (Brazil): Prevalence and genetic diversity of *Blastocystis* subtypes. PLoS one. 2018;13(3):e0193860.
36. Nagel R, Traub RJ, Kwan MM, Bielefeldt-Olmann H. *Blastocystis* specific serum immunoglobulin in patients with irritable bowel syndrome (IBS) versus healthy controls. Parasites & vectors. 2015;8(1):453.
37. Issa R. Non-pathogenic protozoa. Int J Pharm Pharm Sci. 2014;6(12):30-40.
38. Laurent F, Lacroix-Lamande S. Innate immune responses play a key role in controlling infection of the intestinal epithelium by *Cryptosporidium*. International journal for parasitology. 2017;47(12):711-721.
39. Janssen B, Snowden J. *Cryptosporidiosis*. In: StatPearls [Internet]. StatPearls Publishing; 2017.
40. Shin J-H, Lee S-E, Kim TS, Ma D-W, Chai J-Y, Shin E-H. Multiplex-touchdown pcr to simultaneously detect *Cryptosporidium parvum*, *Giardia lamblia*, and *Cyclospora cayentensis*, the major causes of traveler's diarrhea. The Korean journal of parasitology. 2016;54(5):631.
41. Bouzid M, Kintz E, Hunter PR. Risk factors for *Cryptosporidium* infection in low and middle income countries: A systematic review and meta-analysis. PLoS neglected tropical diseases. 2018;12(6):e0006553-e0006553.
42. Sánchez-Vega JT, Cabrera-Fuentes HA, Romero-Olmedo AJ, Ortiz-Frías JL, Sokolina F, Barreto G. *Cyclospora cayentensis*: this emerging protozoan pathogen in Mexico. The American journal of tropical medicine and hygiene. 2014;90(2):351-353.
43. Ortega YR, Sanchez R. Update on *Cyclospora cayentensis*, a food-borne and waterborne parasite. Clinical microbiology reviews. 2010;23(1):218-234.
44. Legua P, Seas C. *Cystoisospora* and *Cyclospora*. Current opinion in infectious diseases. 2013;26(5):479-483.
45. Wang Z-D, Liu Q, Liu H-H, et al. Prevalence of *Cryptosporidium*, *microsporidia* and *Isoospora* infection in HIV-infected people: a global systematic review and meta-analysis. Parasites & vectors. 2018;11(1):28.
46. Chiu K-W, Chiou S-S, Lu L-S, Wu C-K, Eng H-L. Molecular Identification of Biliary *Isoospora belli*: A Case Report. Medicine. 2016;95(10).
47. Mudholkar V, Namey R. Heavy infestation of <i>Isoospora belli</i> causing severe watery diarrhea. Indian Journal of Pathology and Microbiology. 2010;53(4):824-825.
48. Sodeman Jr WA. Intestinal protozoa: amebae. 1996.
49. Hamad MN, Bkhairi ME, Elfaki TM. *Entamoeba coli* as a Potent Phagocytic Microorganism. Global Journal of Medical Research. 2018.
50. Oliveira FMS, Neumann E, Gomes MA, Caliani MV. *Entamoeba dispar*: Could it be pathogenic. Tropical parasitology. 2015;5(1):9-14.
51. Calegar DA, Nunes BC, Monteiro KL, et al. Frequency and molecular characterisation of *Entamoeba histolytica*, *Entamoeba dispar*, *Entamoeba moshkovskii*, and *Entamoeba hartmanni* in the context of water scarcity in northeastern Brazil. Memórias do Instituto Oswaldo Cruz. 2016;111(2):114-119.
52. Gomes Tdos S, Garcia MC, de Souza Cunha F, Wemeck de Macedo H, Peralta JM, Peralta RH. Differential diagnosis of *Entamoeba* spp. in clinical stool samples using SYBR green real-time polymerase chain reaction. TheScientificWorldJournal. 2014;2014:645084.
53. Wolfe MS. Amebiasis. In: Netter's Infectious Diseases. Elsevier; 2012:452-457.
54. Boettner DR, Huston CD, Linford AS, et al. *Entamoeba histolytica* phagocytosis of human erythrocytes involves PATMK, a member of the transmembrane kinase family. PLoS pathogens. 2008;4(1):e8.
55. Herberiger K-H, Fleischmann E, Weber C, Petrona P, Löscher T, Bretzel G. Epidemiological, clinical, and diagnostic data on intestinal infections with *Entamoeba histolytica* and *Entamoeba dispar* among returning travelers. Infection. 2011;39(6):527-535.
56. Stensvold CR, Winiecka-Krusnell J, Liet T, Lebbad M. Evaluation of a PCR method for detection of *Entamoeba polecki*, with an overview of its molecular epidemiology. Journal of clinical microbiology. 2018;JCM.00154-00118.
57. Van Den Broecke S, Verschueren J, Van Esbroeck M, Bottieau E, Van den Ende J. Clinical and microscopic predictors of *Entamoeba histolytica* intestinal infection in travelers and migrants diagnosed with *Entamoeba histolytica*/*dispar* infection. PLoS neglected tropical diseases. 2018;12(10):e0006892.
58. Poulsen CS, Stensvold CR. Systematic review on *Endolimax nana*: A less well studied intestinal ameba. Trop Parasitol. 2016;6(1):8-29.
59. Carra VA, Mathison BA. Infections by Intestinal Coccidia and *Giardia duodenalis*. Clinics in laboratory medicine. 2015;35(2):423-444.
60. Beatty JK, Akkerman SV, Motta JP, et al. *Giardia duodenalis* induces dysbiosis of human intestinal microbiota biofilms. International journal for parasitology. 2017;47(6):311-326.



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