The GI Effects Interpretive Guide has been created to provide a high-level approach to the GI Effects profile, biomarker interpretation, and therapeutic considerations. It is divided into two major sections: an overview of the GI Effects Interpretation At-a-Glance pages; and a more in-depth review of the biomarkers comprising each of the Four Functional Pillars.

**Interpretation At-a-Glance Overview**

Using evidence-based rules and weighted algorithms, the Interpretation At-a-Glance section on the first page of the GI Effects report synthesizes patient test results into key functional areas of clinical significance and provides a directional indication of potential next steps in patient management.

**Four Functional Pillars**

In this section, pertinent biomarkers have been grouped into four clinically actionable areas: Infection, Inflammation, Insufficiency, and Imbalance. The four functional pillars utilize a proprietary algorithm to evaluate key clinical markers in each of these four functional areas. The algorithm takes into account the level of each individual biomarker and its degree of clinical impact. As a result, an overall score of high, medium, or low is provided for each functional pillar. The score is represented by color-coded icons and informational graphics.

The specific biomarkers of concern that are utilized to establish the results for each functional pillar are listed above.
Commensal Balance and Relative Abundance

The Commensal Balance infographic has been designed to provide a more precise view of an individual patient’s commensal bacteria (PCR) results relative to a healthy cohort. It is a composite of two measures:

- **The Healthy-Pattern Continuum** (formerly known as the Diversity Association Index) is a progressive ranking scale based on a Genova proprietary algorithm that 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 and is denoted by the ‘y’ axis of the Commensal Balance infographic.

- **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 24, and is denoted by the ‘x’ axis of the Commensal Balance infographic.

The patient’s result on the Commensal Balance infographic is denoted by a black diamond 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 balanced commensal health status, yellow borderline, and red imbalanced.

**The Relative Abundance (RA)** graphic represents the proportional levels of selected phyla in an individual’s microbiome and is represented relative to similar measures derived from a healthy cohort of individuals.

![Commensal Balance infographic](image)

The remainder of this document will review biomarker interpretation and treatment considerations for each of the Four Pillars in more detail.
Commensal and Biomarker Clinical Associations

To create its Clinical Associations charts, Genova utilized the GI Effects test-results database which allowed comparison of commensal and biomarker results in patients with self-reported clinical conditions (IBD, Metabolic Syndrome, Chronic Fatigue, Autoimmune dysfunction, Type 2 Diabetes, High Blood Pressure, and Mood Disorders and ROME III criteria (IBS)) to those found in the healthy cohort. Differences between the healthy cohort and individuals with clinical conditions are denoted by the arrows in the Clinical Associations charts. In addition, these charts feature patient results marked as high (H) or low (L) compared to the reference range for each commensal bacteria or biomarker.

Clinical Associations Interpretative Key

Statistically significant differences between patients with a clinical condition and the healthy cohort are denoted in the chart with either up or down arrows, or in some instances, a combination of both.

<table>
<thead>
<tr>
<th>Commensal Bacteria</th>
<th>Patient Results Out of Reference Range</th>
<th>Genova Diagnostics</th>
<th>Commensal Bacteria Clinical Associations*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>iBS</td>
<td>IBD</td>
<td>Metabolic Syndrome</td>
</tr>
<tr>
<td>Bacteroidetes Phylum</td>
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<tr>
<td>Bacteroides-Prevotella group</td>
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<tr>
<td>Bacteroides vulgatus</td>
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<td></td>
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<tr>
<td>Bacteroides spp.</td>
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<tr>
<td>Odoribacter spp.</td>
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<tr>
<td>Prevotella spp.</td>
<td>H</td>
<td></td>
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<tr>
<td>Firmicutes Phylum</td>
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</tr>
<tr>
<td>Anaerotruncus coliformis</td>
<td>H</td>
<td></td>
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<tr>
<td>Butyrivibrio catus</td>
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<tr>
<td>Clostridium spp.</td>
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<tr>
<td>Coprococcus eutactus</td>
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<tr>
<td>Faecalibacterium prausnitzii</td>
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<tr>
<td>Lactobacillus spp.</td>
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<tr>
<td>Pseudoflavonifractor spp.</td>
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<td>Roseburia spp.</td>
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<tr>
<td>Ruminococcus spp.</td>
<td>L</td>
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<tr>
<td>Vainaella spp.</td>
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<tr>
<td>Actinobacteria Phylum</td>
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<tr>
<td>Bililbacterium spp.</td>
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<td>Bililbacterium longum</td>
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<td>Collinsella aerofaciens</td>
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<td>Euryarchaeota Phylum</td>
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<td>Methanobrevibacter smithii</td>
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<td>Verrucomicrobia Phylum</td>
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<tr>
<td>Akkermansia muciniphila</td>
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</table>

*Information derived from GDx results data comparing a healthy cohort to various clinical condition cohorts. The chart above shows a comparison of patient results to clinical conditions is meant for informational purposes only. It is not diagnostic, nor does it imply that the patient has a specific clinical diagnosis or condition.

The arrows indicate Genova’s clinical condition cohort test results falling below 🔄 or above 🔄 the reference range that is greater than that of Genova’s healthy cohort.

♩♩ Indicates Genova’s clinical condition cohort test results falling below and above the reference range that are greater than that of Genova’s healthy cohort.

Cells with bolded arrows indicate Genova’s clinical condition cohort had more test results falling above versus below 🔄 or more below versus above 🔄 the reference range compared to that of Genova’s healthy cohort.
4. Displayed in an expanded Interpretation At-a-Glance section, the new report enhancements provide informative data derived from Genova Diagnostics patient results archive. All results were obtained with the same Genova Diagnostics technology platform(s); this allows for an equivalent or ‘like to like’ comparison of an individual patient’s results to various clinical conditions.

<table>
<thead>
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<td>IBS IBD Metabolic Syndrome Chronic Fatigue Autoimmune Type 2 Diabetes High Blood Pressure Mood Disorders</td>
<td></td>
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</table>
| Pancreatic Elastase                    | ↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓↓→
FOUR FUNCTIONAL PILLARS BIOMARKER DETAIL

INFECTION

This pillar is where common infectious microorganisms are reported and includes pathogenic bacteria and intestinal parasites.

- Pathogenic Bacteria Add-on (EIA)
  - *Clostridium difficile* toxin, *Helicobacter pylori*, *Campylobacter* spp., *Shiga* toxin *E. coli*
- Bacteriology (Culture)
- Parasitology (Microscopy, EIA)
  - *Cryptosporidium*, *Giardia*, *Entamoeba*, *Blastocystis*, all others

Antibiotics (if appropriate*)
Natural Agents
Probiotics
Rehydration
See [www.cdc.gov](http://www.cdc.gov) for the most current information

Antiparasitics (if appropriate*)
Natural Agents
Consider probiotic *S. boulardii* in *Blastocystis* infection
See [www.cdc.gov/dpdx/az/html](http://www.cdc.gov/dpdx/az/html) for the most current information

*Some patients may have colonization and treatment decisions must be considered on an individual basis.

INFLAMMATION

This pillar is where biomarkers that indicate inflammatory changes in the GI tract are reported. Biomarkers of GI inflammation and immunology provide information about the GI tract’s interactions with, and responses to, the outside world. They indicate how well the GI tract is maintaining its role as a barrier, as well as whether the GI tract is undergoing pathological responses to external or internal challenges. The biomarkers are *Calprotectin*, a marker of neutrophil-driven inflammation; *Eosinophil Protein X* (EPX), a marker of eosinophil-driven inflammation and allergic response; *Fecal Secretory IgA*, a marker of gut secretory immunity and barrier function; and *Fecal Occult Blood*.

- **Calprotectin 50 to 120 mcg/g**
  - Borderline, suggestive of low-grade GI inflammation
  - Review and treat other biomarkers suggestive of cause of low-grade inflammation:
    - Infection
    - Suspected or hx of IBD
    - Chronic NSAID use
  - Recheck Calprotectin in 4-6 weeks

- **Calprotectin > 120 mcg/g**
  - Clinically relevant GI inflammation
  - 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.

*Some patients may have colonization and treatment decisions must be considered on an individual basis.
Fecal Secretory IgA

**EPX**

- **EPX 1.1 - 4.6 mcg/g**
  - Borderline, suggestive of low-grade GI inflammation

- **EPX > 4.6 mcg/g**
  - Suggestive of clinically relevant GI inflammation

**Target evaluation and treatment for common etiologies for EPX elevation:**
- IgE-mediated allergy (Consider IgE Food Antibody panel)
- IBD (review Calprotectin level)
- Parasitic (especially helminth) infection

**Other less common etiologies and/or clinical associations include:**
- GERD
- Collagenous colitis
- Excessive alcohol intake
- Atopic Dermatitis
- Chronic diarrhea

Fecal Occult Blood

- **Fecal Occult Blood positive**

  **Assess for cause of bleeding**
  (i.e., Ulcers, polyps, diverticulitis, IBD, colorectal cancer, etc.)
INSUFFICIENCY

This pillar is where biomarkers that indicate digestive function are noted. Biomarkers of digestion and absorption provide information about nutrient breakdown and entry into the circulation. They ultimately indicate how well the GI tract is performing its basic digestive functions. The biomarkers are Pancreatic Elastase 1, a marker of exocrine pancreatic function; Products of Protein Breakdown, markers of undigested protein reaching the colon; and Fecal Fat (Total), a marker of fat breakdown.

Pancreatic Elastase 1 (PE1)

Pancreatic Elastase (PE1) >200 mcg/g

Normal exocrine pancreatic function; optimal is considered >500 mcg/g

In patients with levels between 200-500, consider causes of suboptimal function:
- Aging
- Vegan/vegetarian diet
- See list of primary causes of exocrine pancreatic insufficiency
- Assess Products of Protein Breakdown and Fecal Fats; if abnormal, consider a trial of PERT

Pancreatic Elastase (PE1) 100 to 200 mcg/g

Mild-to-moderate exocrine pancreatic insufficiency

Initiate pancreatic enzyme replacement therapy (PERT); Titrate dose to degree of insufficiency and symptom improvement

Evaluate and address lifestyle issues:
- Small, frequent meals for rapid absorption
- Reduce alcohol intake
- Smoking cessation

Pancreatic Elastase (PE1) < 100 mcg/g

Severe exocrine pancreatic insufficiency

Seek primary cause(s) of exocrine pancreatic insufficiency
- Chronic Pancreatitis
- Gallstones
- Diabetes
- Celiac Disease
- Inflammatory Bowel Disease (IBD); see inflammatory markers
- Excessive alcohol consumption
- Cystic Fibrosis

Products of Protein Breakdown (Total)

Total Protein Products < 1.8 micromol/g

May indicate decreased protein intake and/or imbalanced bacterial levels

Assess for and treat root causes of insufficient protein digestion:
- Hypochlorhydria
  » Assess for/reduce use of acid-blocking medications (as clinically indicated)
  » Consider addition of betaine HCl (as clinically indicated)
- Pancreatic exocrine insufficiency
  » Evaluate fecal PE1 and support with PERT as clinically indicated

Total Protein Products > 7.12 micromol/g

May indicate digestive insufficiency of protein and/or excessive delivery of protein to the colon

Assess for excessive delivery of protein to the colon:
- High-protein diet
- Bacterial overgrowth
  » Review, evaluate (if necessary) and treat any abnormal biomarkers in the Inflammation (Calprotectin, EPX, Occult blood) and/or Infection pillars
- GI irritation/inflammation, bleeding
Fecal Fat (Total)

Fecal Fat (Total) > 28.38 mg/g
Suggestive of moderate fat maldigestion and/or malabsorption

Fecal Fat (Total) > 38.62 mg/g
Suggestive of significant fat maldigestion and/or malabsorption

Target evaluation and treatment for common etiologies of fat maldigestion:
- Pancreatic exocrine insufficiency
  » Evaluate fecal PE1 and support with PERT as clinically indicated
- Bile Salt Insufficiency
  » Assess for causes including liver damage, impaired gallbladder function
  » Consider addition of bile salts and/or cholagogues
- Hypochlorhydria
  » Assess for/reduce use of acid-blocking medications (as clinically indicated)
  » Consider addition of betaine HCl (as clinically indicated)
- Small Intestinal Bacterial Overgrowth (SIBO)
  » Results in bacterial deconjugation of bile salts
  » Consider SIBO breath testing
- Medications that impair intestinal lipase activity (i.e., Orlistat, Xenical, Alli)
- Use of synthetic fat-like products indigestible by lipase (i.e., Olestra)

Target evaluation and treatment for common conditions associated with fat malabsorption
- Infection
- Celiac Disease
- IBS (confirm diagnosis via clinical criteria such as Rome IV)
- IBD (review Calprotectin level)
- Food intolerances
- Excessive alcohol ingestion
- Chronic use of NSAIDs
- Rapid transit time
- Gastric bypass, ileal resection or other surgeries that limit absorptive surface area

Further Evaluation:
- May be associated with deficiencies in fat or fat-soluble nutrients
  » Consider nutritional assessment of essential fatty acids, fat-soluble vitamins
This pillar is where imbalances in the population of GI organisms (i.e., dysbiosis) is noted. Biomarkers of the GI Microbiome provide information about the health, function, and abundance of the trillions of microbial cells in the GI tract. They indicate how well the microbiome is performing its shared metabolic functions with the human host. Abnormal results in this pillar may be associated with a large number of conditions and symptoms. The biomarkers which assess gut microbial imbalance are **Metabolic Indicators**, which demonstrate specific and vital metabolic functions performed by the microbiota; **Commensal Bacteria**, a PCR evaluation of 24 key bacterial groups/species; and **Bacterial and Mycologic Culture**, which identifies potentially pathogenic (PP) organisms.

<table>
<thead>
<tr>
<th>Metabolic Indicators</th>
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<tbody>
<tr>
<td>n-Butyrate Concentration</td>
</tr>
<tr>
<td>Total SCFA</td>
</tr>
<tr>
<td>Beta-glucuronidase</td>
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<table>
<thead>
<tr>
<th>Commensal Bacteria (PCR)</th>
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<tbody>
<tr>
<td><em>Lactobacillus</em> (Beneficial)</td>
</tr>
<tr>
<td><em>Bifidobacterium</em> (Beneficial)</td>
</tr>
<tr>
<td><em>E. Coli</em> (Beneficial)</td>
</tr>
<tr>
<td>Commensal Balance</td>
</tr>
<tr>
<td>Relative Abundance (RA)</td>
</tr>
<tr>
<td><em>Firmicutes/Bacteroidetes</em> (F/B) ratio</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Bacterial and Mycologic Culture</th>
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</thead>
<tbody>
<tr>
<td>Treat abnormalities in Infection, Inflammation &amp; Insufficiency pillars</td>
</tr>
<tr>
<td>Dietary Modification to include prebiotic food sources (i.e., FOS, inulin, psyllium, oat bran, xylooligosaccharide, beta-glucan, arabinogalactan), increased intake of fiber and whole, complex carbohydrate and resistant starch</td>
</tr>
<tr>
<td>Apply multi-strain probiotic</td>
</tr>
<tr>
<td>For Beta-glucuronidase elevation also consider calcium-d-glucarate</td>
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<table>
<thead>
<tr>
<th>Severe Imbalance</th>
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<tbody>
<tr>
<td>Moderate Imbalance</td>
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</table>

Treat abnormalities in the Infection, Inflammation & Insufficiency pillars
Consider pharmaceutical or non-pharmaceutical (botanical) antibiotic and/or antifungal agents (based on organism sensitivity)
  » Therapeutic intervention is warranted if the practitioner has a high clinical suspicion that the PP organism is causing the patient’s symptoms.
Apply multi-strain probiotic
Consider addition of prebiotics for low Commensal Balance, RA
Consider addition of fermented foods (i.e., kefir, yogurt, kim chee and other fermented vegetables, miso, etc.)

**Commensal Bacteria and Diet and Lifestyle Influences**
- In general, a high-fat and high-sugar diet, stress and antibiotics shift the gut microbial ecology to contain more pro-inflammatory species and a lower bacterial gene count.
  » Animal-based, high-fat, high-sugar diets have been found to increase *Bacteroides* and *Odoribacter* spp., lower bacterial gene counts and decrease *Barnesiella*, *Prevotella*, *Bifidobacterium*, *Lactobacillus*, and *F. prausnitzii*, as well as lower SCFAs.
- A healthy diet and lifestyle, prebiotics and probiotics produce a favorable shift towards more anti-inflammatory species and increased bacterial gene count.
  » Plant-based, higher fiber diets result in greater *Roseburia*, *Prevotella*, *F. prausnitzii*, greater bacterial gene counts, and decreased *Bacteroides*.
  » A Mediterranean diet increased *F. prausnitzii*, *B. longum*, and *Roseburia*.
- Physical activity can increase gut microbial diversity, as well as health-promoting bacterial species including *F. prausnitzii*, *Roseburia hominis*, and *Akkermansia muciniphila*.
One of the benefits of ordering a comprehensive stool panel like GI Effects is the ability to observe trends across different groups of biomarkers. In addition to patterns discussed within the 4 functional pillars, clinicians commonly observe other patterns including Small Intestinal Bacterial Overgrowth (SIBO), Intestinal Permeability, and Immune Dysregulation/Loss of Resilience. These patterns are not diagnostic, but rather suggestive of these common conditions and further workup may be appropriate.

<table>
<thead>
<tr>
<th>Biomarker pattern, along with associated symptoms suggest</th>
<th>Biomarkers</th>
<th>Next steps</th>
</tr>
</thead>
</table>
| Small Intestinal Bacterial Overgrowth (SIBO)             | ↑ Relative Abundance  
↑ Products of Protein Breakdown  
↑ SCFA  
↑ n-butyrate  
↑ Fecal Fat (total)  
↓ PE1 (limited evidence)  
↑ Methanobrevibacter smithii | • Confirm with SIBO Breath Test |
| Intestinal Permeability                                 | ↑ sIgA  
↑ EPX  
↓ Akkermansia muciniphila | • Confirm with Intestinal Permeability Assessment  
• Determine root cause of permeability  
• Consider GI repair/support  
• Consider IgG and/or IgE Food Antibody testing |
| Immune Dysregulation/Loss of Resilience                  | <DL sIgA  
<DL EPX  
↑ PP bacteria/yeast  
↓ Beneficial bacteria  
↓ Akkermansia muciniphila | • Evaluate root cause of immune dysregulation (i.e., Adrenocortex Stress Profile)  
• Consider prebiotics/probiotics |