GI effects®

The Microbiome: Understanding Infection and Dysbiosis

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Medical Education Specialist| Genova Diagnostics

GENOVA DIAGNOSTICS®

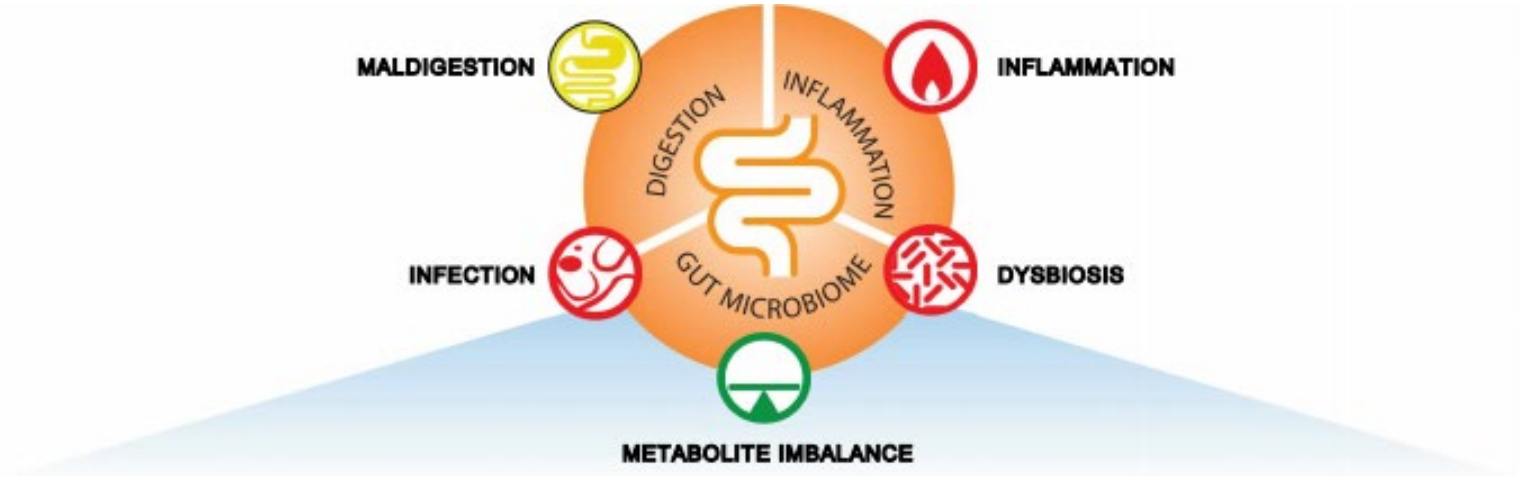
Core GI Functions

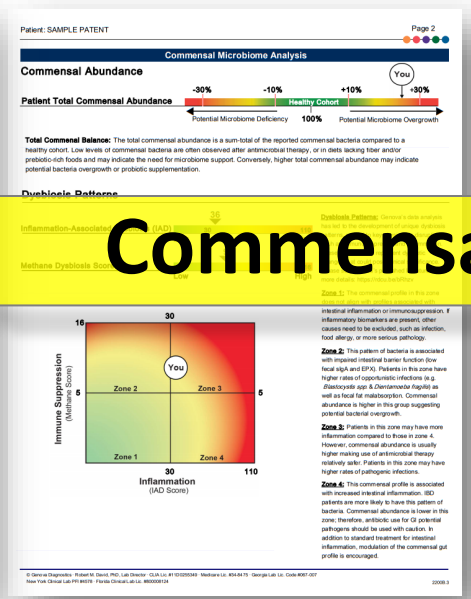
Digestion

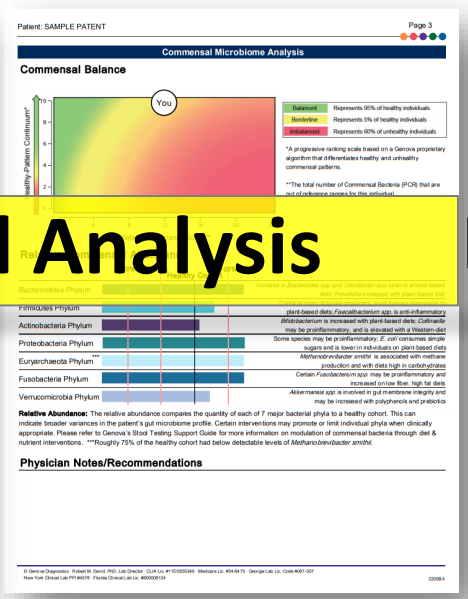
Inflammation/Immune

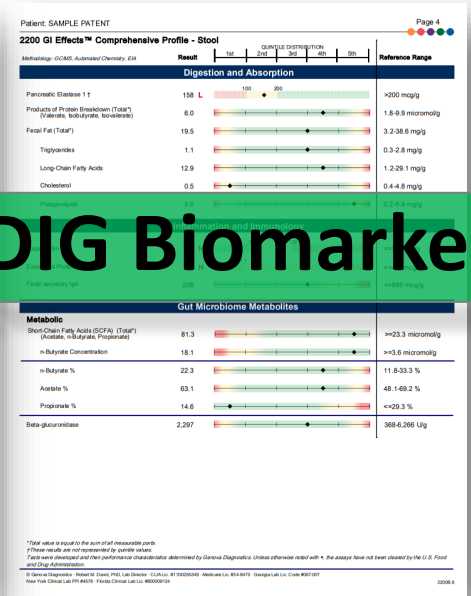
Gut Microbiome

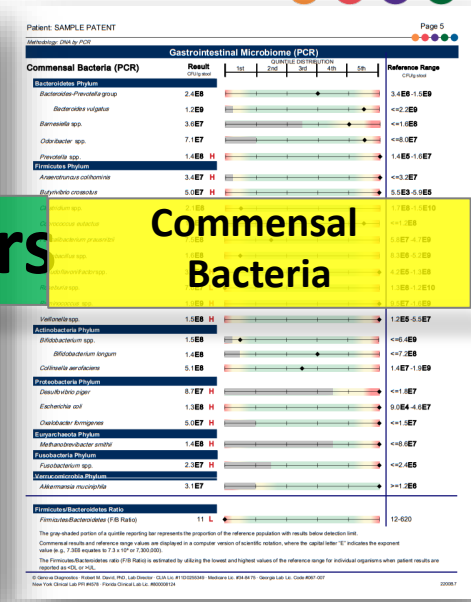
- Infection
- Metabolite Imbalance
- Dysbiosis

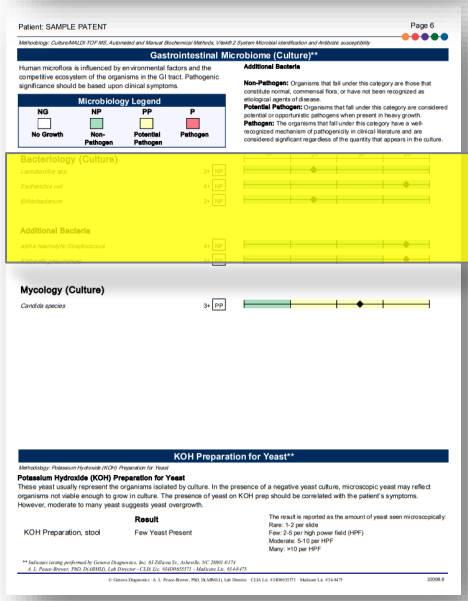


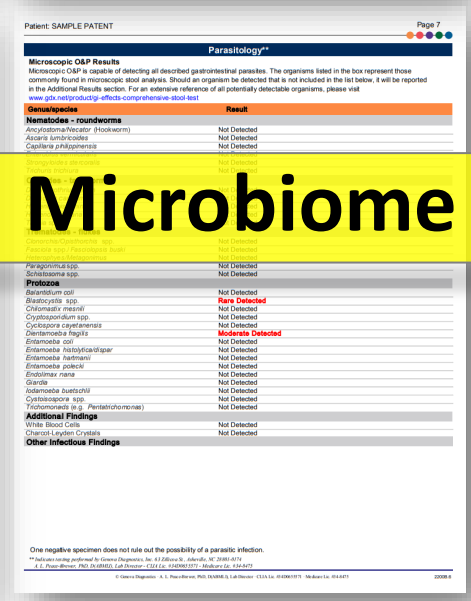


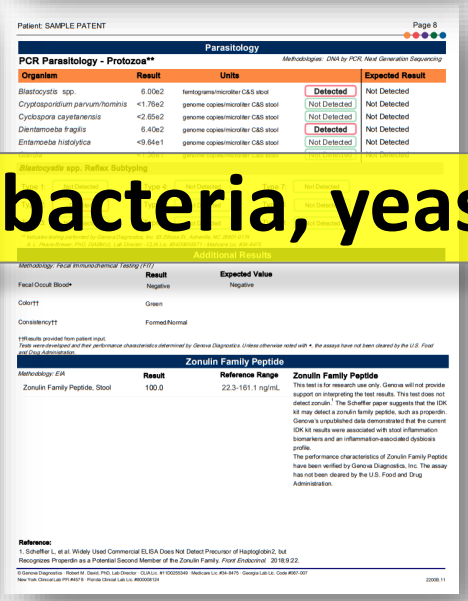


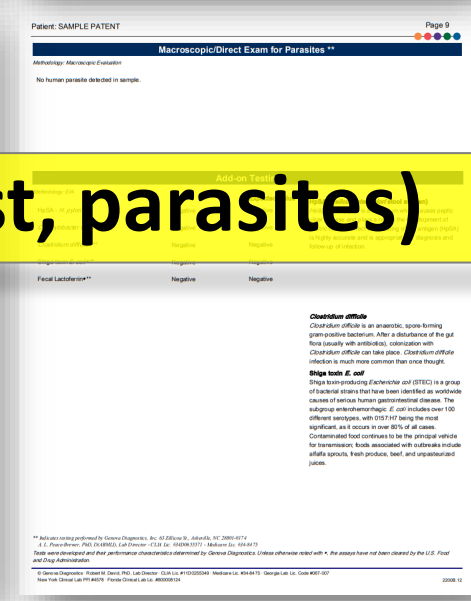


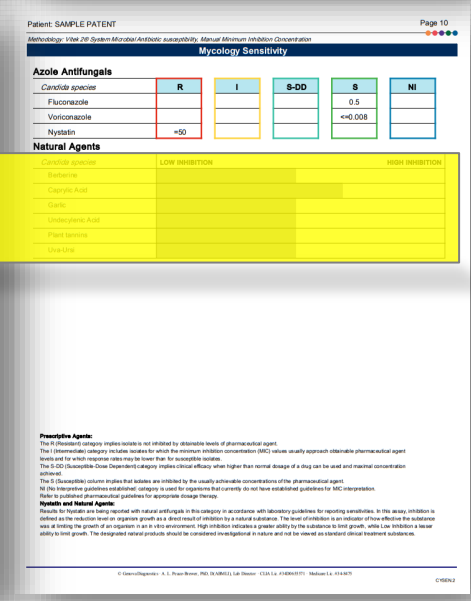












Overview

Commensal Analysis

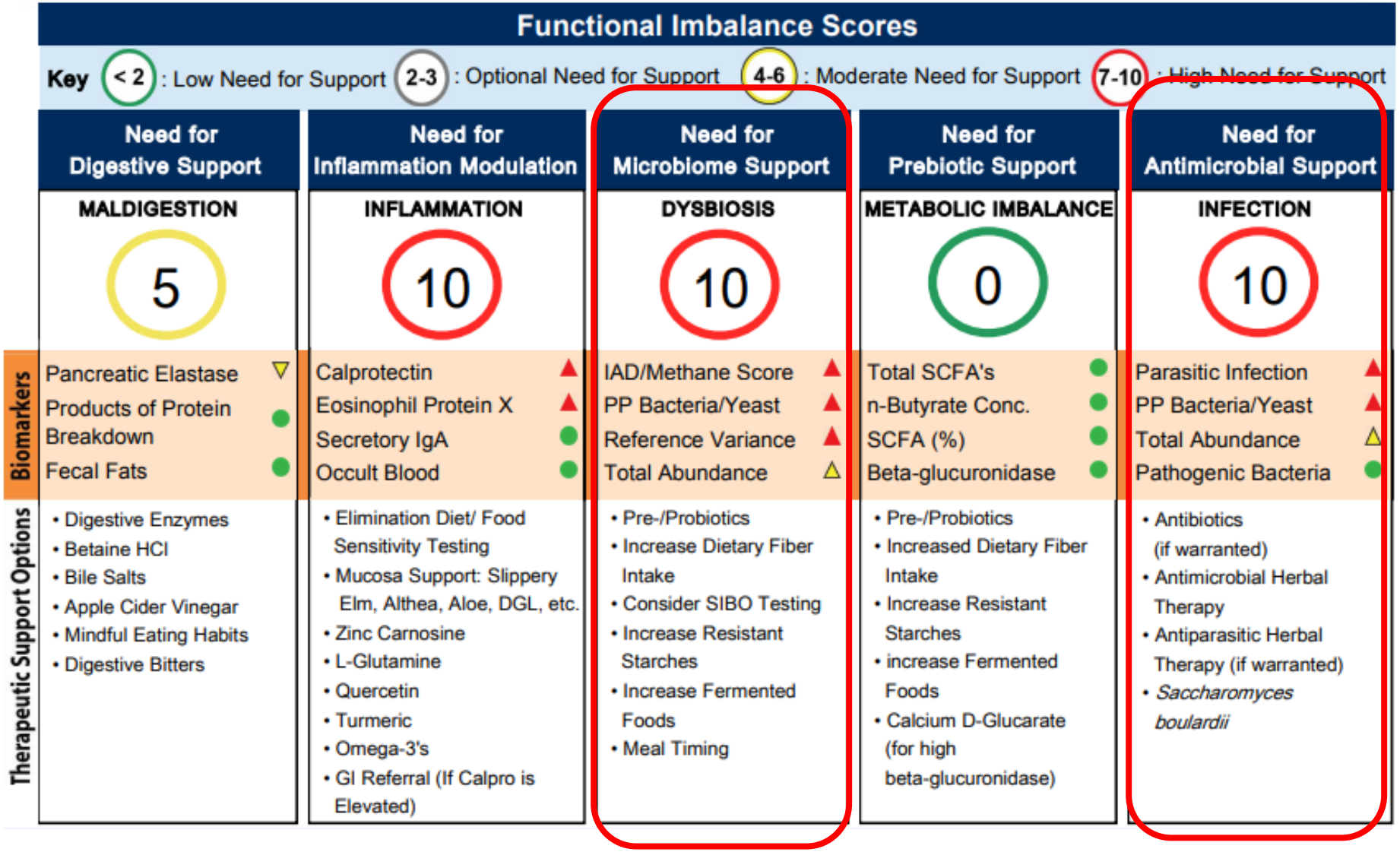
DIG Biomarkers

Commensal Bacteria

Microbiome (bacteria, yeast, parasites)

GENOVA DIAGNOSTICS

Functional Imbalance Scores



GENOVA DIAGNOSTICS

GI Effects Comprehensive Profile
Microbiome Analysis

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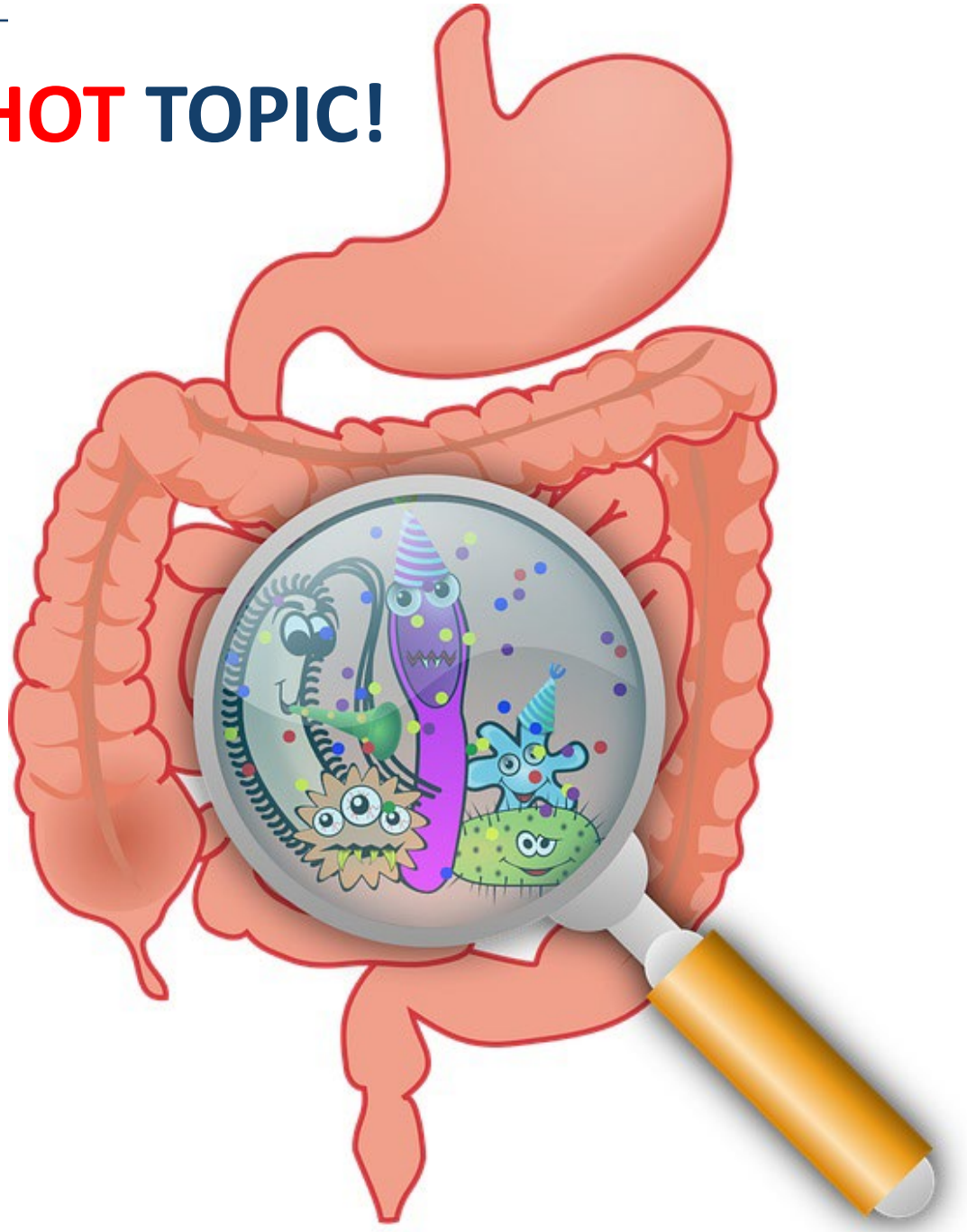
GENOVA DIAGNOSTICS

Microbiome = HOT TOPIC!



GENOVA DIAGNOSTICS

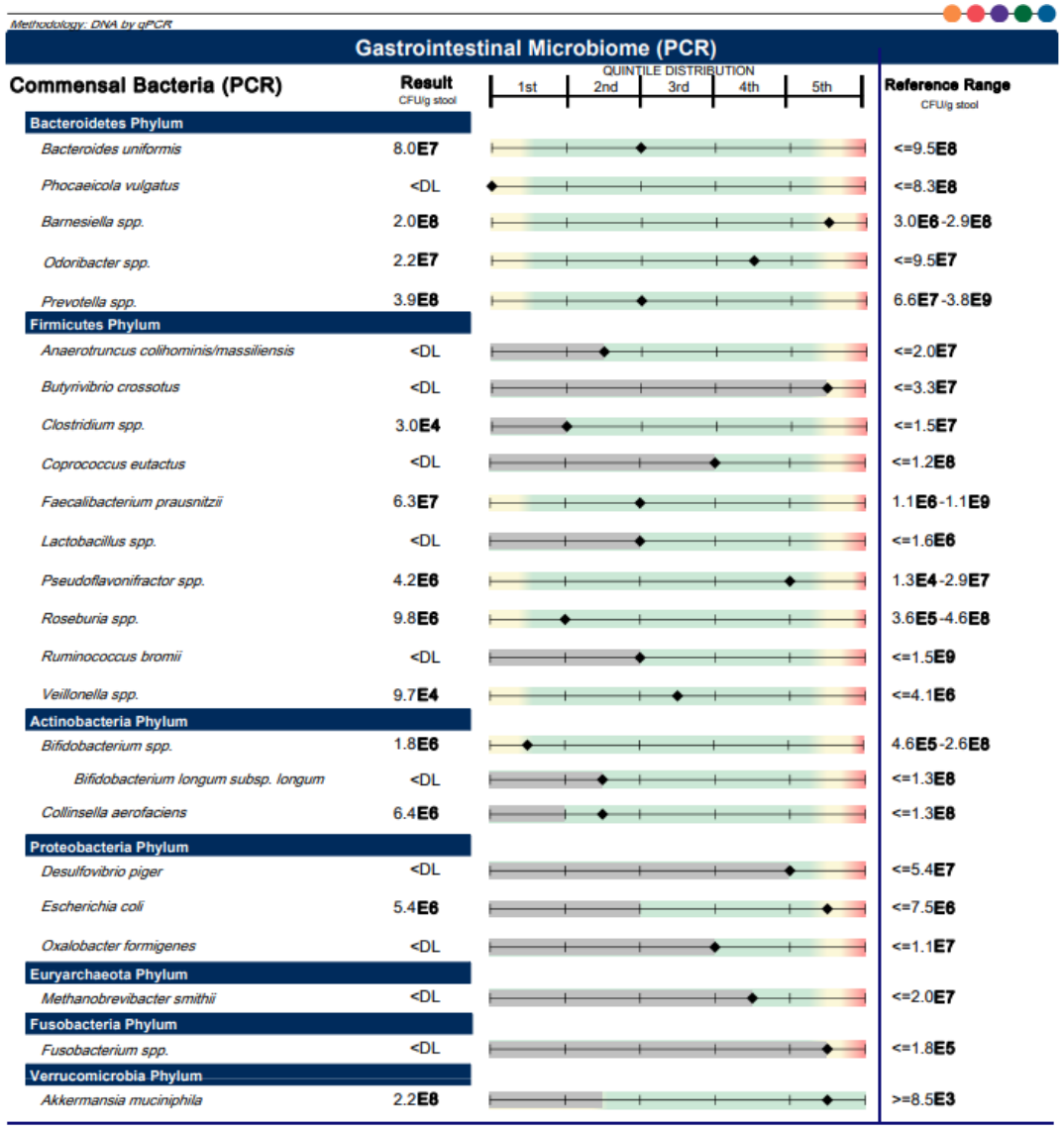
Microbiomix

A more complete picture

Adding **Microbiomix** to the **GI Effects** offers a more complete picture of overall gut health. **Microbiomix** complements the information provided on the GI Effects. This additional information may reveal treatable abnormalities that are not seen on GI Effects.

GENOVA DIAGNOSTICS

Commensal Bacteria?



Methodology: DNA by qPCR

Gastrointestinal Microbiome (PCR)

Commensal Bacteria (PCR)	Result CFU/g stool	QUINTILE DISTRIBUTION 1st 2nd 3rd 4th 5th	Reference Range CFU/g stool
Bacteroidetes Phylum			
Bacteroides uniformis	8.0**E7**		<=9.5**E8**
Phocaeicola vulgatus	<DL		<=8.3**E8**
Barnesiella spp.	2.0**E8**		3.0**E6**-2.9**E8**
Odoribacter spp.	2.2**E7**		<=9.5**E7**
Prevotella spp.	3.9**E8**		6.6**E7**-3.8**E9**
Firmicutes Phylum			
Anaerotruncus colihominis/massiliensis	<DL		<=2.0**E7**
Butyrivibrio crossotus	<DL		<=3.3**E7**
Clostridium spp.	3.0**E4**		<=1.5**E7**
Coprococcus eutactus	<DL		<=1.2**E8**
Faecalibacterium prausnitzii	6.3**E7**		1.1**E6**-1.1**E9**
Lactobacillus spp.	<DL		<=1.6**E6**
Pseudoflavonifractor spp.	4.2**E6**		1.3**E4**-2.9**E7**
Roseburia spp.	9.8**E6**		3.6**E5**-4.6**E8**
Ruminococcus bromii	<DL		<=1.5**E9**
Veillonella spp.	9.7**E4**		<=4.1**E6**
Actinobacteria Phylum			
Bifidobacterium spp.	1.8**E6**		4.6**E5**-2.6**E8**
Bifidobacterium longum subsp. longum	<DL		<=1.3**E8**
Collinsella aerofaciens	6.4**E6**		<=1.3**E8**
Proteobacteria Phylum			
Desulfovibrio piger	<DL		<=5.4**E7**
Escherichia coli	5.4**E6**		<=7.5**E6**
Oxalobacter formigenes	<DL		<=1.1**E7**
Euryarchaeota Phylum			
Methanobrevibacter smithii	<DL		<=2.0**E7**
Fusobacteria Phylum			
Fusobacterium spp.	<DL		<=1.8**E5**
Verrucomicrobia Phylum			
Akkermansia muciniphila	2.2**E8**		>=8.5**E3**

- Clinicians often struggle with what to do with DNA PCR analysis of commensal bacteria

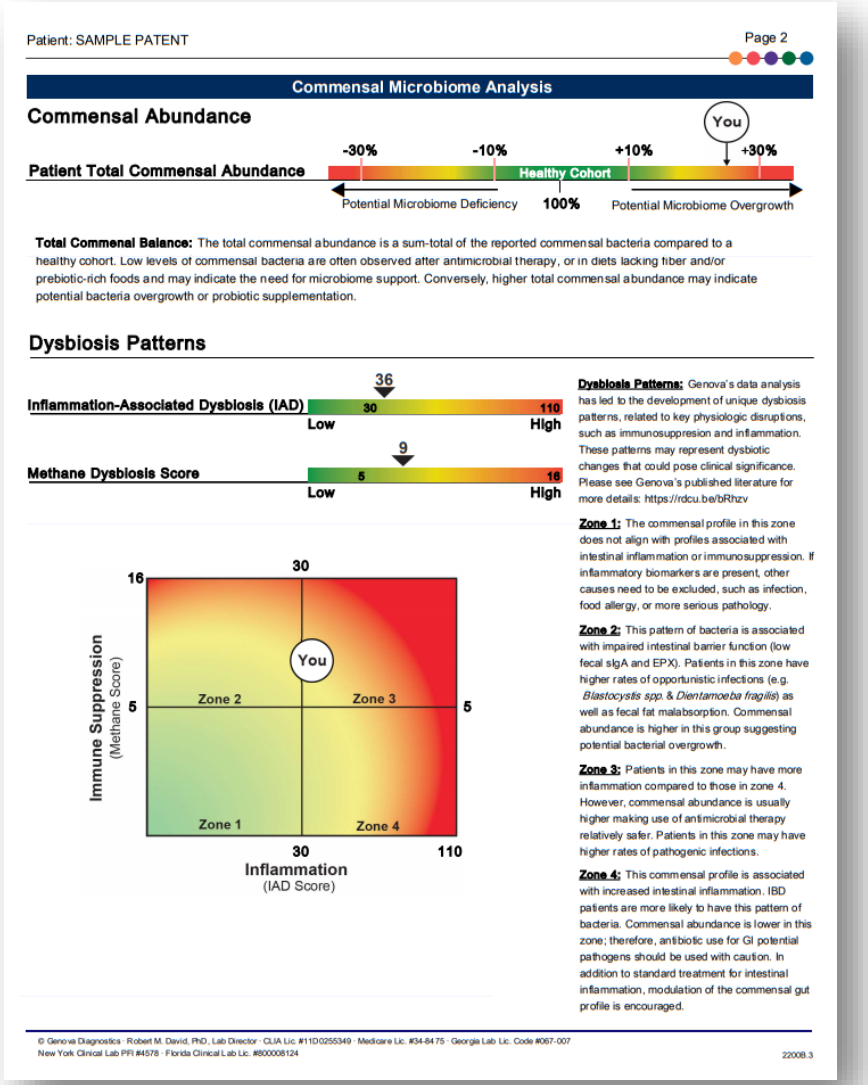
- Historical limitations
  - Methodologies differ in literature
  - Discrepant results in publications
  - Unknown clinical importance of individual bacteria
  - Limited research into bacterial patterns

Genova's AI-Supported Data Analysis

- Genova has profiled thousands of GI Effects commensal bacteria results
- Cluster analysis has helped us pave the way toward understanding shifts in the microbiome patterns that are associated with clinical symptoms
- You can directly compare your patients' results to these clinical associations
  - Same methodology
  - Same DNA probes
  - Same commensal bacteria

A Novel Approach to Microbiome Analysis

1. Abundance
2. Pattern
3. Balance



Patient: SAMPLE PATENT

Page 2

Commensal Microbiome Analysis

Commensal Abundance

Total Commensal Balance: The total commensal abundance is a sum-total of the reported commensal bacteria compared to a healthy cohort. 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 bacteria overgrowth or probiotic supplementation.

Dysbiosis Patterns

Dysbiosis Patterns: Genova's data analysis has led to the development of unique dysbiosis patterns, related to key physiologic disruptions, such as immunosuppresion and inflammation. These patterns may represent dysbiotic changes that could pose clinical significance. Please see Genova's published literature for more details: https://rdcu.be/bRhzv

Zone 1: The commensal profile in this zone does not align with profiles associated with intestinal inflammation or immunosuppression. If inflammatory biomarkers are present, other causes need to be excluded, such as infection, food allergy, or more serious pathology.

Zone 2: This pattern of bacteria is associated with impaired intestinal barrier function (low fecal sIgA and EPX). Patients in this zone have higher rates of opportunistic infections (e.g. *Blastocystis spp.* & *Dientamoeba fragilis*) as well as fecal fat malabsorption. Commensal abundance is higher in this group suggesting potential bacterial overgrowth.

Zone 3: 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: This commensal profile is associated with increased intestinal inflammation. IBD patients are more likely to have this pattern of bacteria. Commensal abundance is lower in this zone; therefore, 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.

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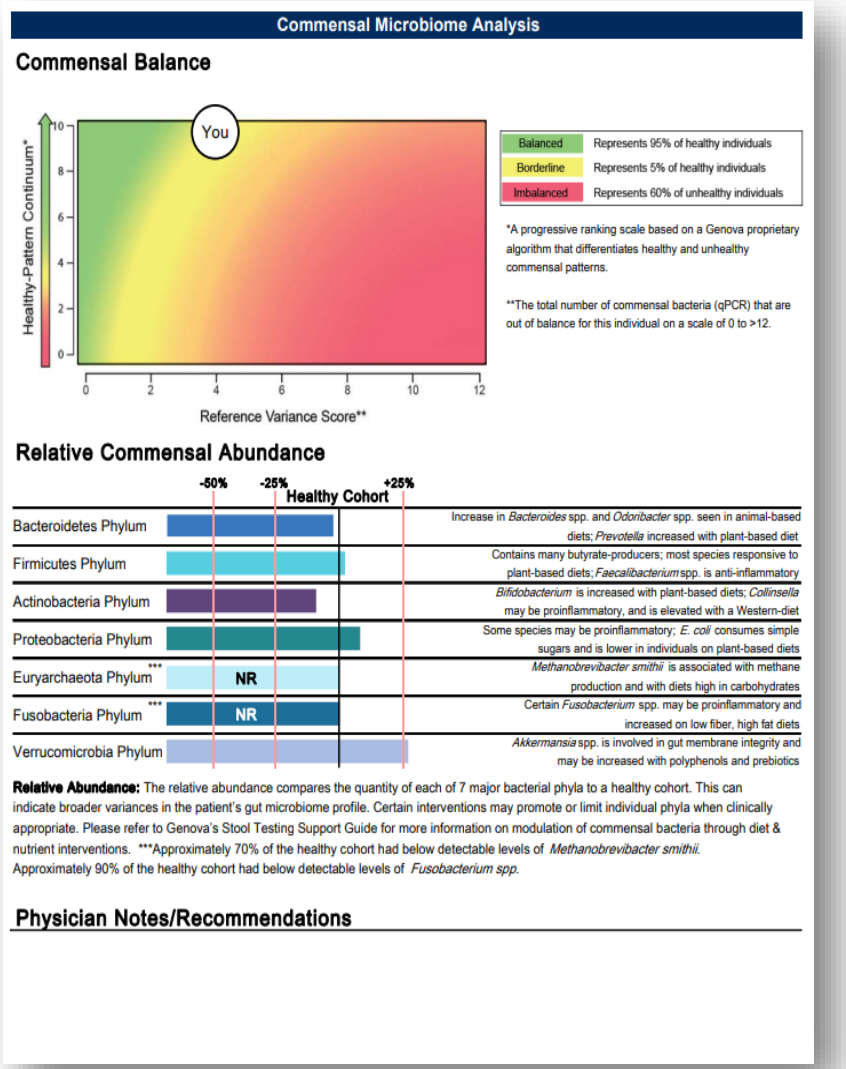

Commensal Microbiome Analysis

Commensal Balance

*A progressive ranking scale based on a Genova proprietary algorithm that differentiates healthy and unhealthy commensal patterns.

**The total number of commensal bacteria (qPCR) that are out of balance for this individual on a scale of 0 to >12.

Relative Commensal Abundance

Relative Abundance: The relative abundance compares the quantity of each of 7 major bacterial phyla to a healthy cohort. This can indicate broader variances in the patient's gut microbiome profile. Certain interventions may promote or limit individual phyla when clinically appropriate. Please refer to Genova's Stool Testing Support Guide for more information on modulation of commensal bacteria through diet & nutrient interventions. ***Approximately 70% of the healthy cohort had below detectable levels of *Methanobrevibacter smithii*. Approximately 90% of the healthy cohort had below detectable levels of *Fusobacterium spp.*

Physician Notes/Recommendations

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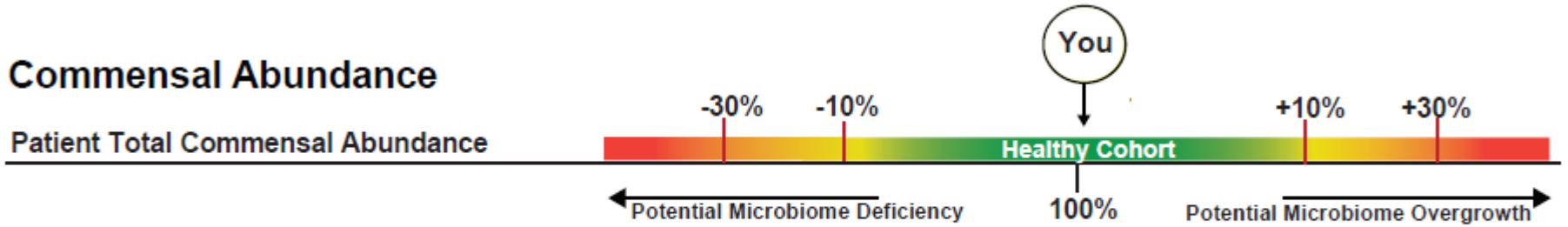
Total Commensal *Abundance*

- Shift-to-the-Right: Patient has more overall commensal bacteria
  - May be indicative of potential microbial overgrowth
  - May also be due to recent supplementation with probiotics
- Shift-to-the-Left: Patient has less overall commensal bacteria
  - May be indicative of potential microbiome deficiency, such as following antibiotic use
  - May indicate a diet low in fiber and prebiotic foods

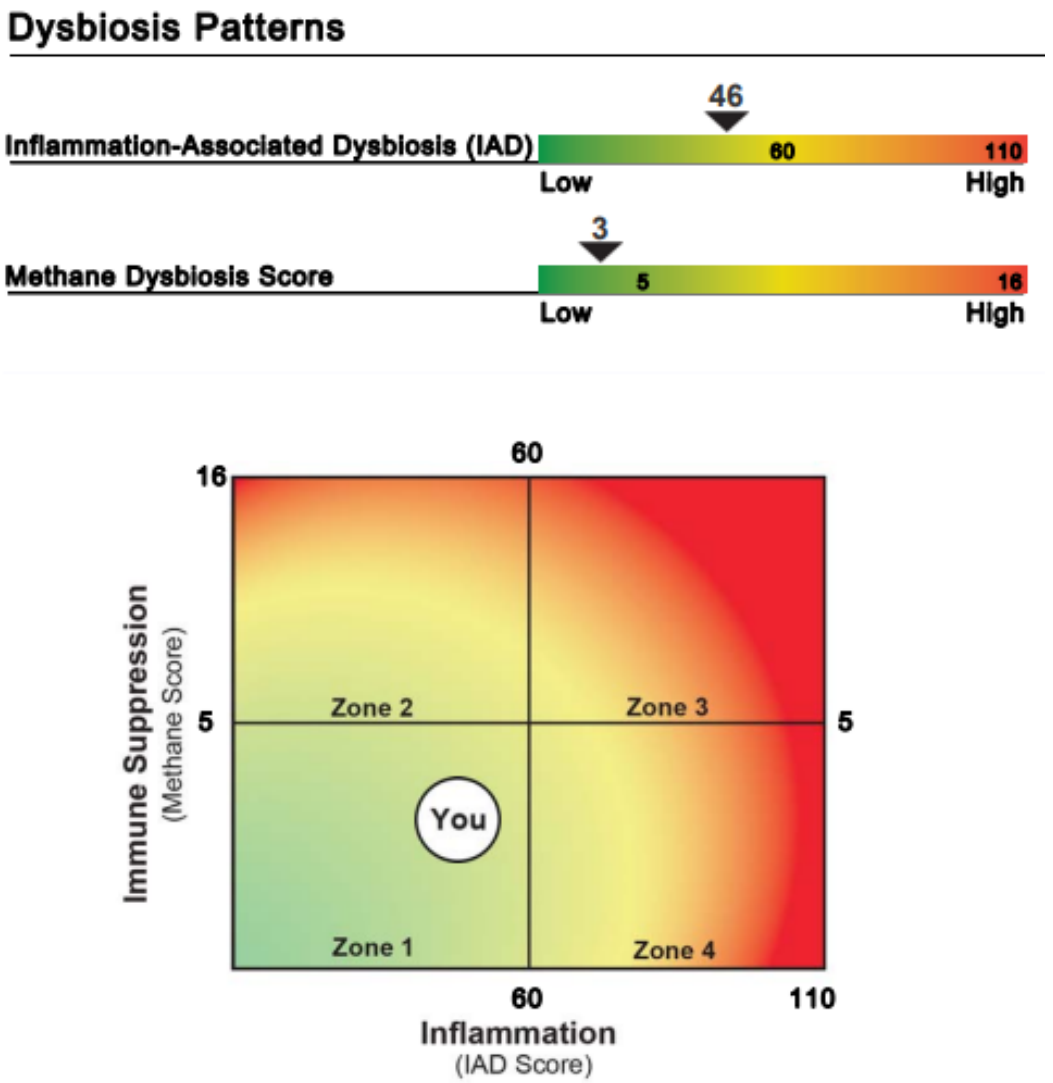


Total Commensal Abundance: The total commensal abundance is a sum-total of the commensal bacteria compared to a healthy cohort. Low levels of commensal bacteria may indicate need for microbiome support, whereas higher levels may indicate potential overgrowth.

GENOVA DIAGNOSTICS

Dysbiosis *Patterns*

- Novel biomarkers
  - Unique to Genova's GI Effects
  - Based on internal data analysis of commensal patterns
- Inflammation-Associated Dysbiosis Score
  - An indicator of a dysbiotic pattern associated with GI inflammation
- Methane Dysbiosis Score
  - An indicator of a dysbiotic pattern associated with methane production



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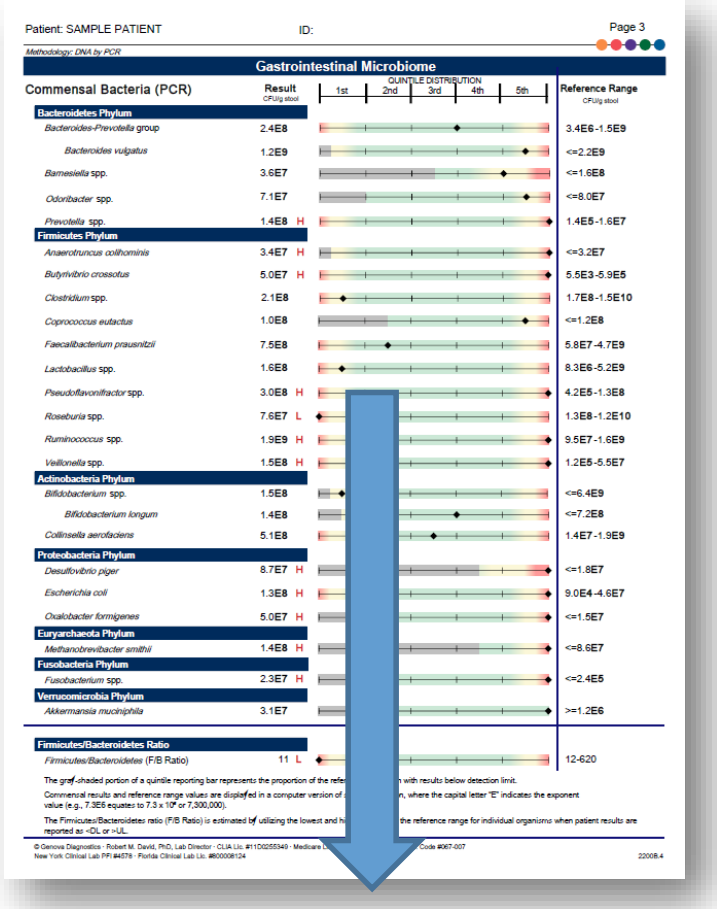
Inflammation-Associated Dysbiosis Score (IAD)

- Specific dysbiosis pattern that is associated with inflammation
- Correlated with inflammatory biomarkers
  - Calprotectin
  - Eosinophil Protein X
  - Secretory IgA
- Algorithm-derived from commensal bacteria analysis


Patient: SAMPLE PATIENT ID: Page 3

Methodology: DNA by PCR

Gastrointestinal Microbiome

Commensal Bacteria (PCR)	Result CFU/g stool	QUINTILE DISTRIBUTION 1st 2nd 3rd 4th 5th	Reference Range CFU/g stool
Bacteroidetes Phylum			
Bacteroides-Prevotella group	2.4E8		3.4E6-1.5E9
Bacteroides vulgatus	1.2E9		<=2.2E9
Barnesiella spp.	3.6E7		<=1.6E8
Odoribacter spp.	7.1E7		<=8.0E7
Prevotella spp.	1.4E8 H		1.4E5-1.6E7
Firmicutes Phylum			
Anaerotruncus colihominis	3.4E7 H		<=3.2E7
Butyrivibrio crossotus	5.0E7 H		5.5E3-5.9E5
Clostridium spp.	2.1E8		1.7E8-1.5E10
Coprococcus eutactus	1.0E8		<=1.2E8
Faecalibacterium prausnitzii	7.5E8		5.8E7-4.7E9
Lactobacillus spp.	1.6E8		8.3E6-5.2E9
Pseudoflavonifractor spp.	3.0E8 H		4.2E5-1.3E8
Roseburia spp.	7.6E7 L		1.3E8-1.2E10
Ruminococcus spp.	1.9E9 H		9.5E7-1.6E9
Veillonella spp.	1.5E8 H		1.2E5-5.5E7
Actinobacteria Phylum			
Bifidobacterium spp.	1.5E8		<=6.4E9
Bifidobacterium longum	1.4E8		<=7.2E8
Collinsella aerofaciens	5.1E8		1.4E7-1.9E9
Proteobacteria Phylum			
Desulfovibrio piger	8.7E7 H		<=1.8E7
Escherichia coli	1.3E8 H		9.0E4-4.6E7
Oxalobacter formigenes	5.0E7 H		<=1.5E7
Euryarchaeota Phylum			
Methanobrevibacter smithii	1.4E8 H		<=8.6E7
Fusobacteria Phylum			
Fusobacterium spp.	2.3E7 H		<=2.4E5
Verrucomicrobia Phylum			
Akkermansia muciniphila	3.1E7		>=1.2E6
Firmicutes/Bacteroidetes Ratio			
Firmicutes/Bacteroidetes (F/B Ratio)	11 L		12-620

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

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

The Firmicutes/Bacteroidetes ratio (F/B Ratio) is estimated by utilizing the lowest and h… the reference range for individual organisms when patient results are reported as <DL or >UL.

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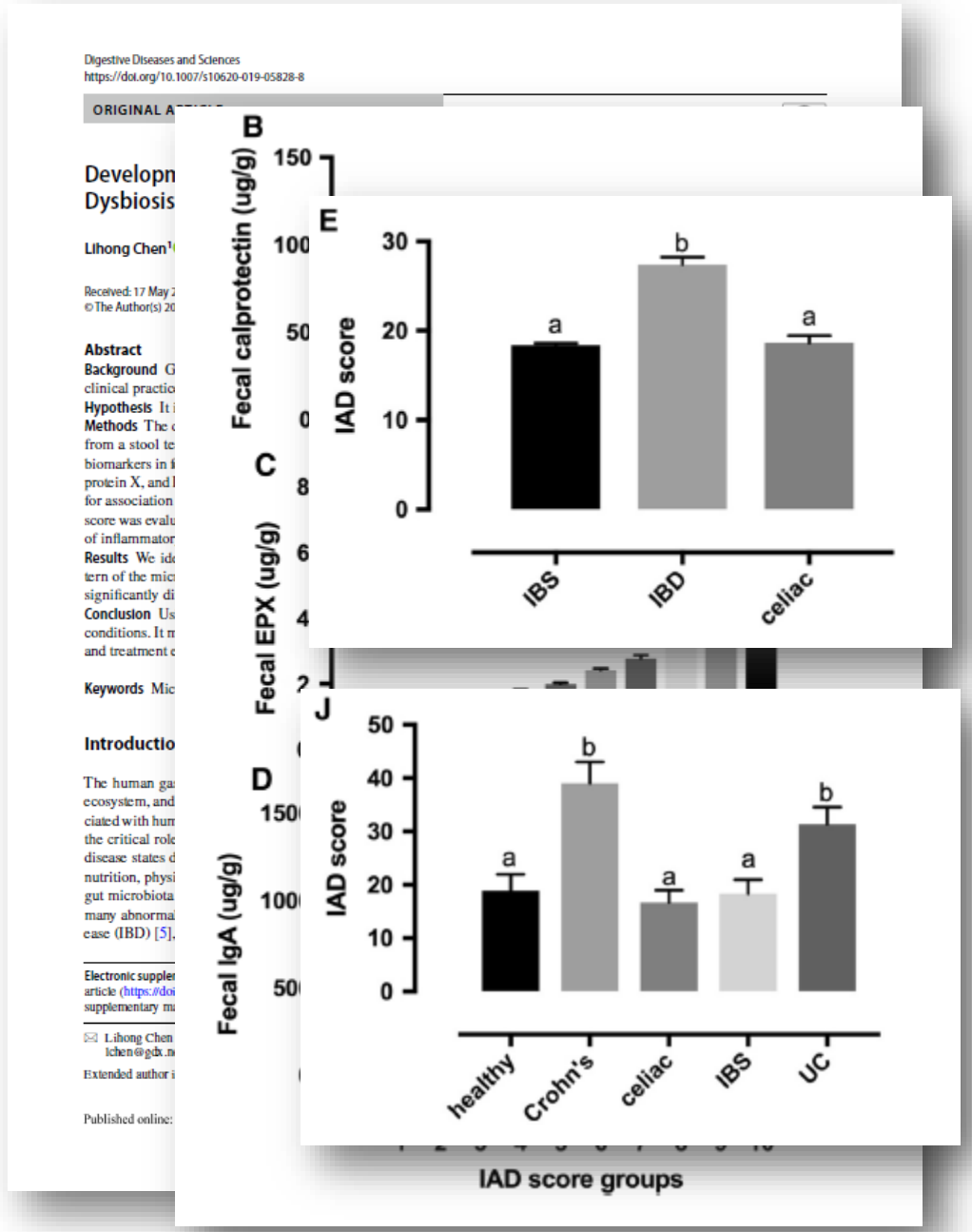
GENOVA DIAGNOSTICS

IAD Score

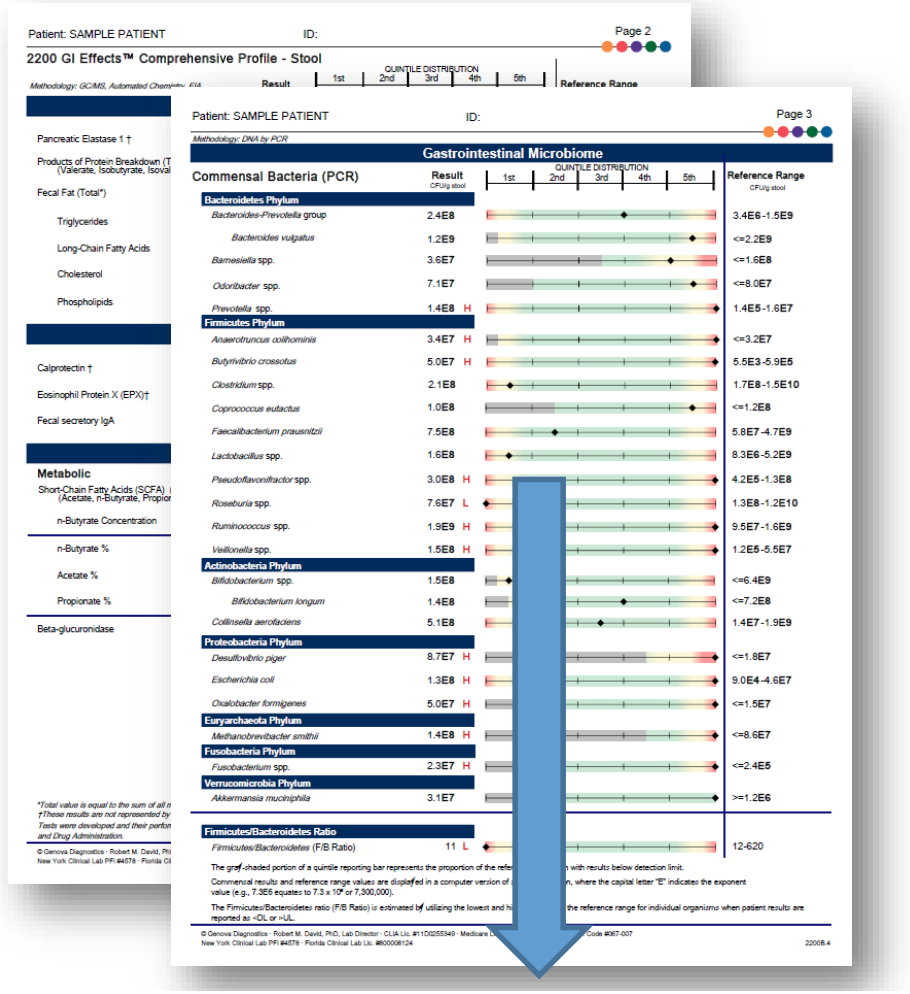
- Published article on 2 separate studies
  - Study 1: Using Genova Database (n=~7000)
  - Study 2: UCLA Medical Center (n=161)
- Demonstrated that IAD score correlated with inflammatory biomarkers
- IAD score distinguished between disease cohorts with inflammatory bowel disease vs IBS/Celiac



GENOVA DIAGNOSTICS

Methane Dysbiosis Score

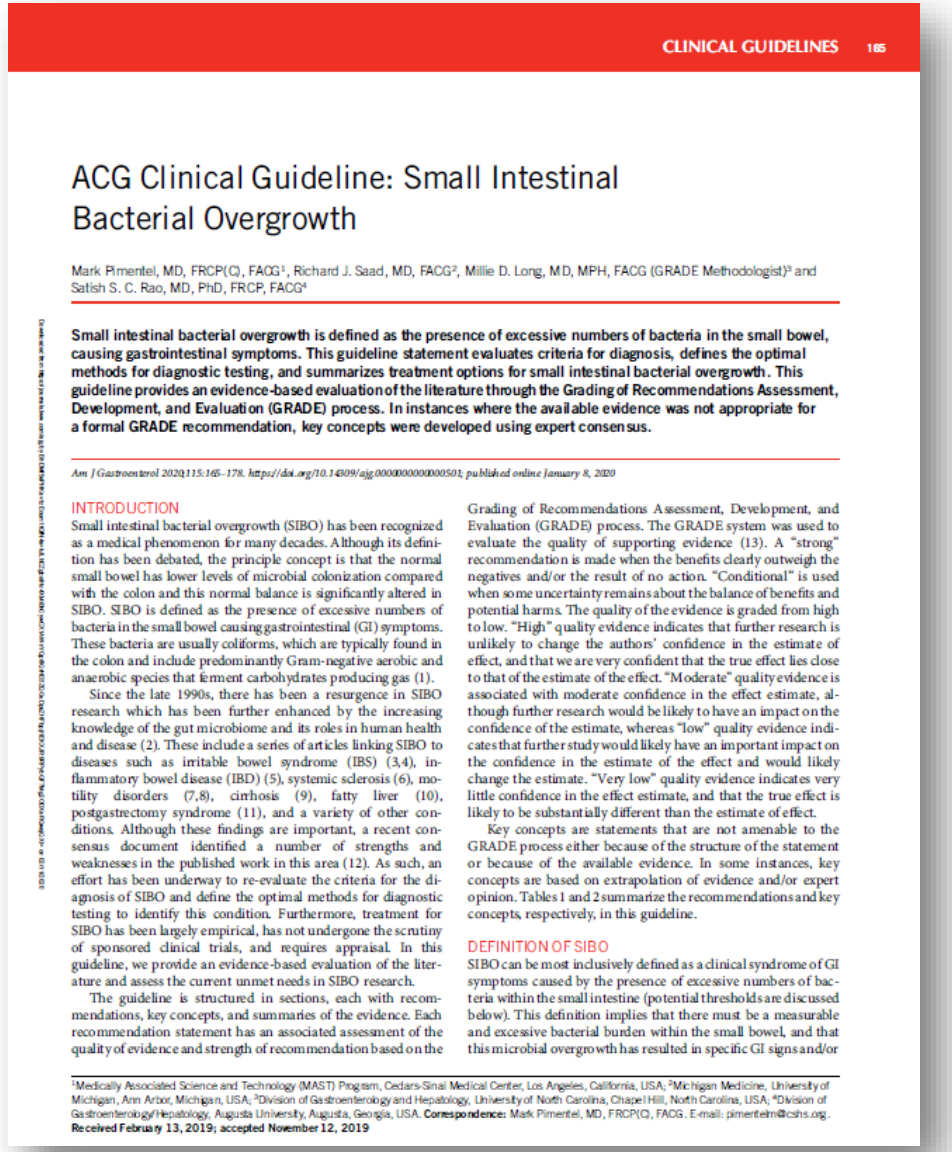
- Specific dysbiosis pattern that is associated with methane production
- Correlated with methane production on SIBO tests
- Based both on commensal bacterial profile and stool biomarkers
- Developed an algorithm-derived score to predict higher methane production in the GI tract



GENOVA DIAGNOSTICS

GI Methanogenesis

- Methane is produced in the GI tract through the consumption of hydrogen produced from other bacteria
  - The predominant methanogen in the GI tract is *Methanobrevibacter smithii*
- Intestinal methane production is associated with slowed transit time/constipation
- 2020 ACG paper suggests naming condition *Intestinal Methanogen Overgrowth (IMO)* to represent elevated methane production on breath test



ACG Clinical Guideline: Small Intestinal Bacterial Overgrowth

Mark Pimentel, MD, FRCP(C), FACG[1], Richard J. Saad, MD, FACG[2], Millie D. Long, MD, MPH, FACG (GRADE Methodologist)[3] and Satish S. C. Rao, MD, PhD, FRCP, FACG[4]

Small intestinal bacterial overgrowth is defined as the presence of excessive numbers of bacteria in the small bowel, causing gastrointestinal symptoms. This guideline statement evaluates criteria for diagnosis, defines the optimal methods for diagnostic testing, and summarizes treatment options for small intestinal bacterial overgrowth. This guideline provides an evidence-based evaluation of the literature through the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process. In instances where the available evidence was not appropriate for a formal GRADE recommendation, key concepts were developed using expert consensus.

Am J Gastroenterol 2020;115:165–178. https://doi.org/10.14309/ajg.0000000000000501; published online January 8, 2020

INTRODUCTION

Small intestinal bacterial overgrowth (SIBO) has been recognized as a medical phenomenon for many decades. Although its definition has been debated, the principle concept is that the normal small bowel has lower levels of microbial colonization compared with the colon and this normal balance is significantly altered in SIBO. SIBO is defined as the presence of excessive numbers of bacteria in the small bowel causing gastrointestinal (GI) symptoms. These bacteria are usually coliforms, which are typically found in the colon and include predominantly Gram-negative aerobic and anaerobic species that ferment carbohydrates producing gas (1).

Since the late 1990s, there has been a resurgence in SIBO research which has been further enhanced by the increasing knowledge of the gut microbiome and its roles in human health and disease (2). These include a series of articles linking SIBO to diseases such as irritable bowel syndrome (IBS) (3,4), inflammatory bowel disease (IBD) (5), systemic sclerosis (6), motility disorders (7,8), cirrhosis (9), fatty liver (10), postgastrectomy syndrome (11), and a variety of other conditions. Although these findings are important, a recent consensus document identified a number of strengths and weaknesses in the published work in this area (12). As such, an effort has been underway to re-evaluate the criteria for the diagnosis of SIBO and define the optimal methods for diagnostic testing to identify this condition. Furthermore, treatment for SIBO has been largely empirical, has not undergone the scrutiny of sponsored clinical trials, and requires appraisal. In this guideline, we provide an evidence-based evaluation of the literature and assess the current unmet needs in SIBO research.

The guideline is structured in sections, each with recommendations, key concepts, and summaries of the evidence. Each recommendation statement has an associated assessment of the quality of evidence and strength of recommendation based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process. The GRADE system was used to evaluate the quality of supporting evidence (13). A "strong" recommendation is made when the benefits clearly outweigh the negatives and/or the result of no action. "Conditional" is used when some uncertainty remains about the balance of benefits and potential harms. The quality of the evidence is graded from high to low. "High" quality evidence indicates that further research is unlikely to change the authors' confidence in the estimate of effect, and that we are very confident that the true effect lies close to that of the estimate of the effect. "Moderate" quality evidence is associated with moderate confidence in the effect estimate, although further research would be likely to have an impact on the confidence of the estimate, whereas "low" quality evidence indicates that further study would likely have an important impact on the confidence in the estimate of the effect and would likely change the estimate. "Very low" quality evidence indicates very little confidence in the effect estimate, and that the true effect is likely to be substantially different than the estimate of effect.

Key concepts are statements that are not amenable to the GRADE process either because of the structure of the statement or because of the available evidence. In some instances, key concepts are based on extrapolation of evidence and/or expert opinion. Tables 1 and 2 summarize the recommendations and key concepts, respectively, in this guideline.

DEFINITION OF SIBO

SIBO can be most inclusively defined as a clinical syndrome of GI symptoms caused by the presence of excessive numbers of bacteria within the small intestine (potential thresholds are discussed below). This definition implies that there must be a measurable and excessive bacterial burden within the small bowel, and that this microbial overgrowth has resulted in specific GI signs and/or

[1]Medically Associated Science and Technology (MAST) Program, Cedars-Sinai Medical Center, Los Angeles, California, USA; [2]Michigan Medicine, University of Michigan, Ann Arbor, Michigan, USA; [3]Division of Gastroenterology and Hepatology, University of North Carolina, Chapel Hill, North Carolina, USA; [4]Division of Gastroenterology/Hepatology, Augusta University, Augusta, Georgia, USA. **Correspondence:** Mark Pimentel, MD, FRCP(C), FACG. E-mail: pimentelm@cshs.org.

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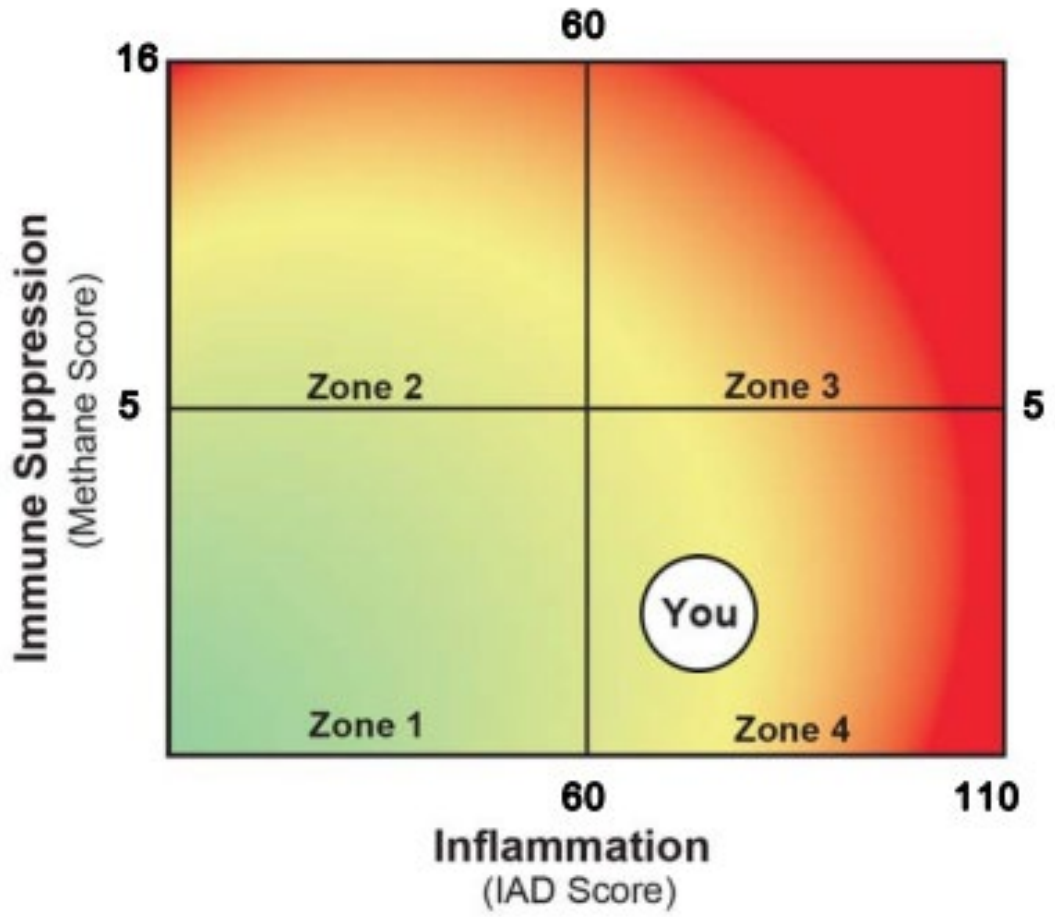
GENOVA DIAGNOSTICS

Dysbiosis Pattern Zones



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Zone 1: The commensal profile in this zone does not align with profiles associated with intestinal inflammation or immunosuppression. If inflammatory biomarkers are present, other causes need to be excluded, such as infection, food allergy, or more serious pathology.

Zone 4: This commensal profile is associated with increased intestinal inflammation. IBD patients are more likely to have this pattern of bacteria. Commensal abundance is lower in this zone; therefore, 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.

relatively safer. Patients in this zone may have higher rates of pathogenic infections.

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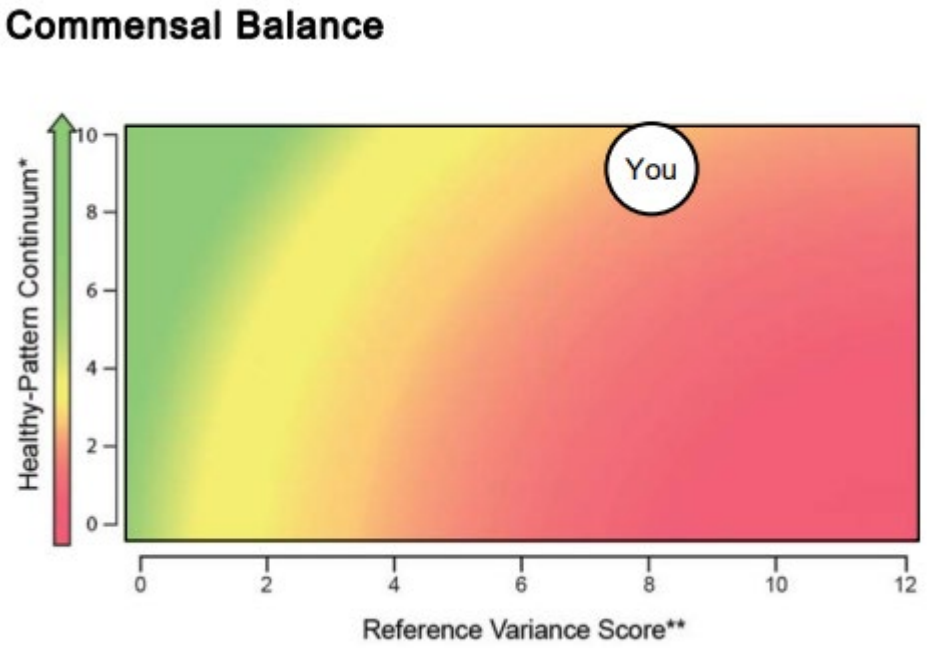
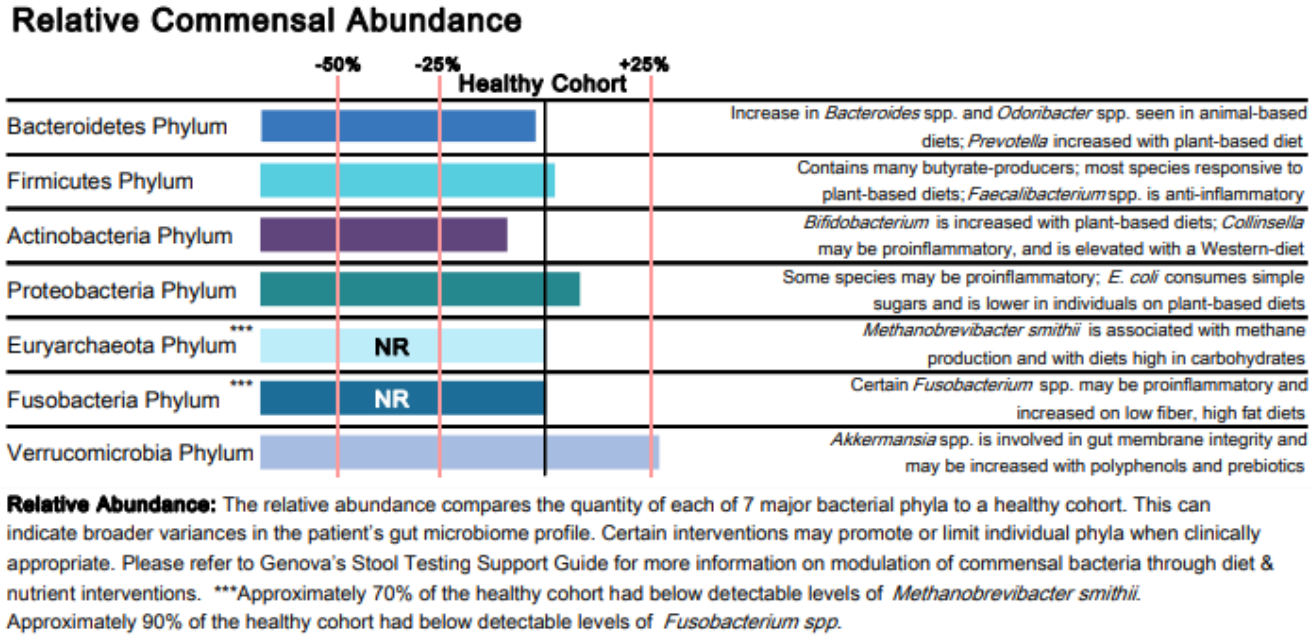
GENOVA DIAGNOSTICS

Commensal *Balance*

- The GI Effects looks at balance in two different ways:
  - Commensal Balance Graphic: Based on clinical populations vs healthy cohort
  - Relative Commensal Abundance: Based on phylum abundance compared to healthy cohort

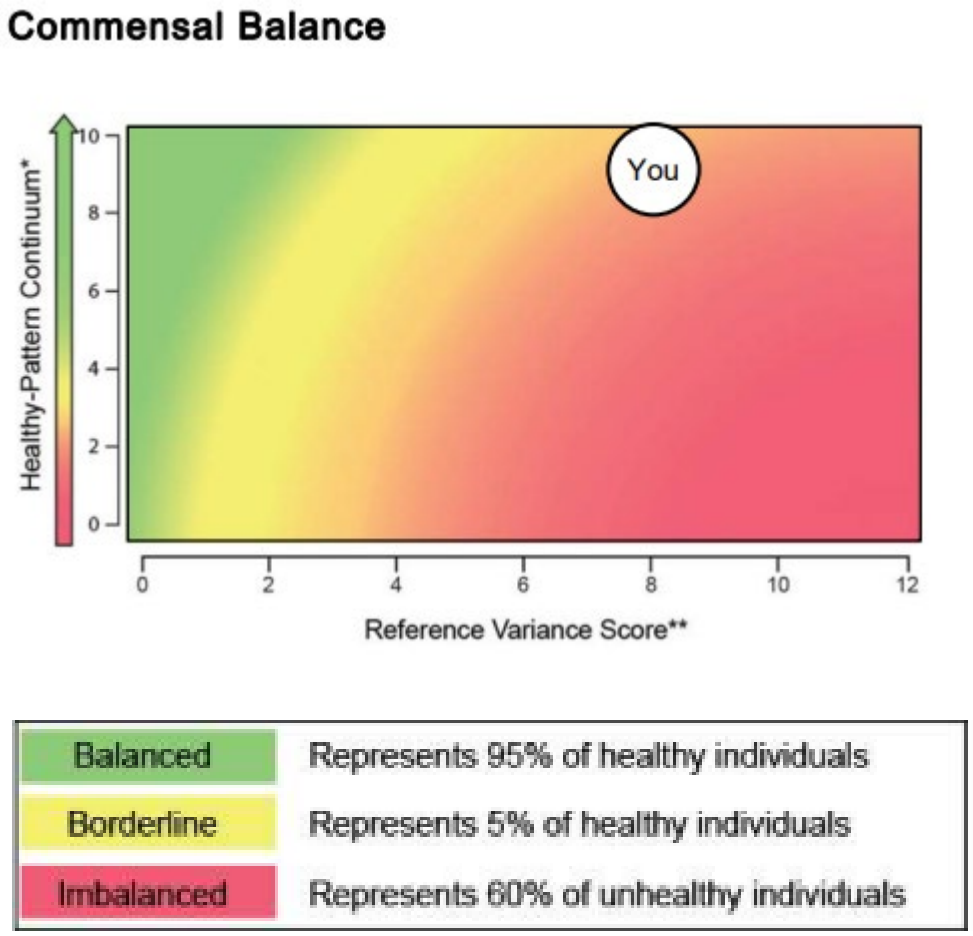




Relative Abundance: The relative abundance compares the quantity of each of 7 major bacterial phyla to a healthy cohort. This can indicate broader variances in the patient's gut microbiome profile. Certain interventions may promote or limit individual phyla when clinically appropriate. Please refer to Genova's Stool Testing Support Guide for more information on modulation of commensal bacteria through diet & nutrient interventions. ***Approximately 70% of the healthy cohort had below detectable levels of *Methanobrevibacter smithii*. Approximately 90% of the healthy cohort had below detectable levels of *Fusobacterium spp.*

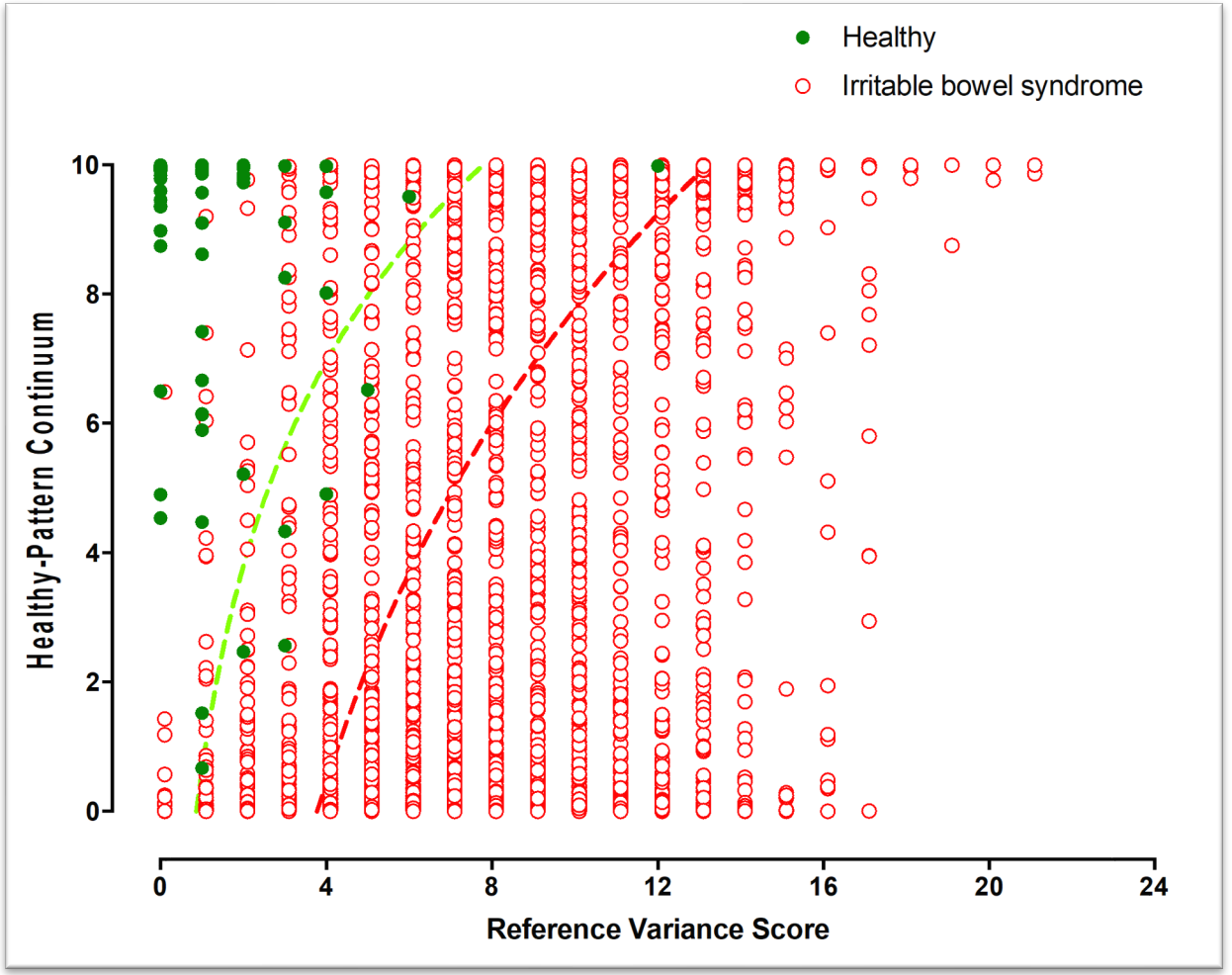
Commensal Balance Graphic

- The **Commensal Balance** is a composite of two measures:
  - 'Y-axis': The **Healthy-Pattern Continuum** is a progressive ranking scale which differentiates healthy and unhealthy commensal patterns.
  - 'X-axis': The **Reference Variance Score** reflects the total number of an individual patient's commensal bacteria (PCR) results that are out of balance on a scale of 0 to >12.



GENOVA DIAGNOSTICS

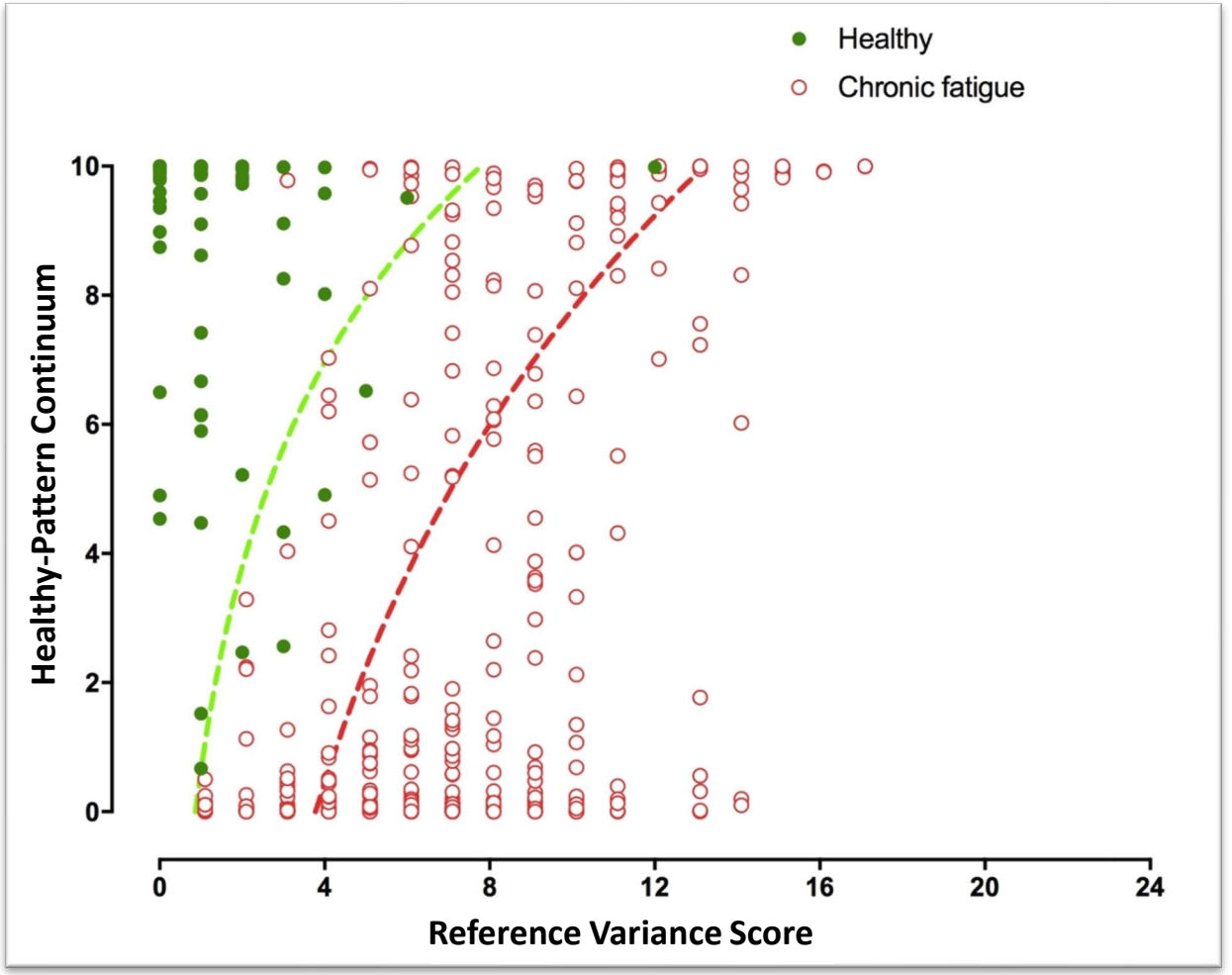
Differential Distribution Between Healthy and IBS Cohorts



GENOVA DIAGNOSTICS

Unpublished data

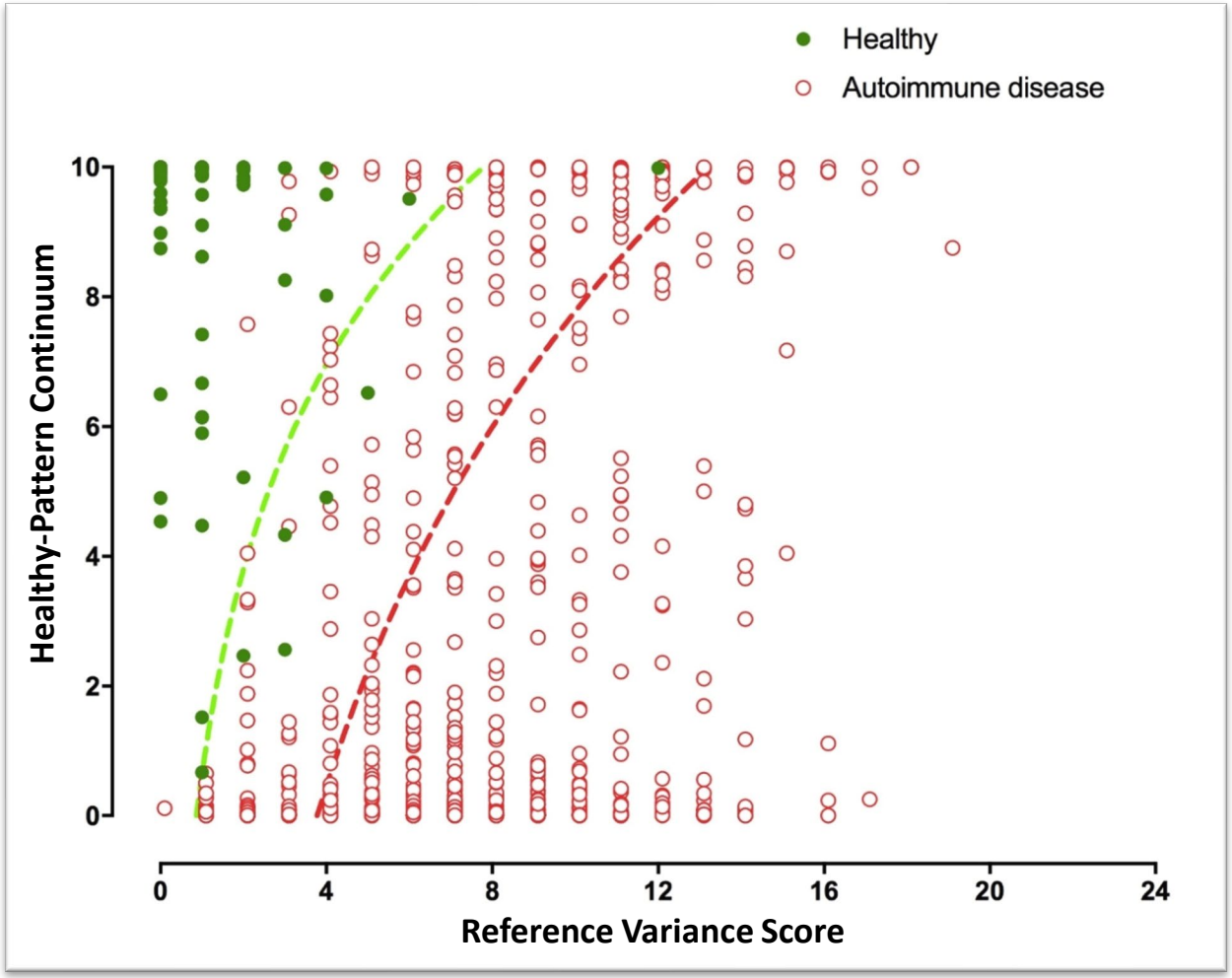
Differential Distribution Between Healthy and Chronic Fatigue Cohorts



GENOVA DIAGNOSTICS

Unpublished data

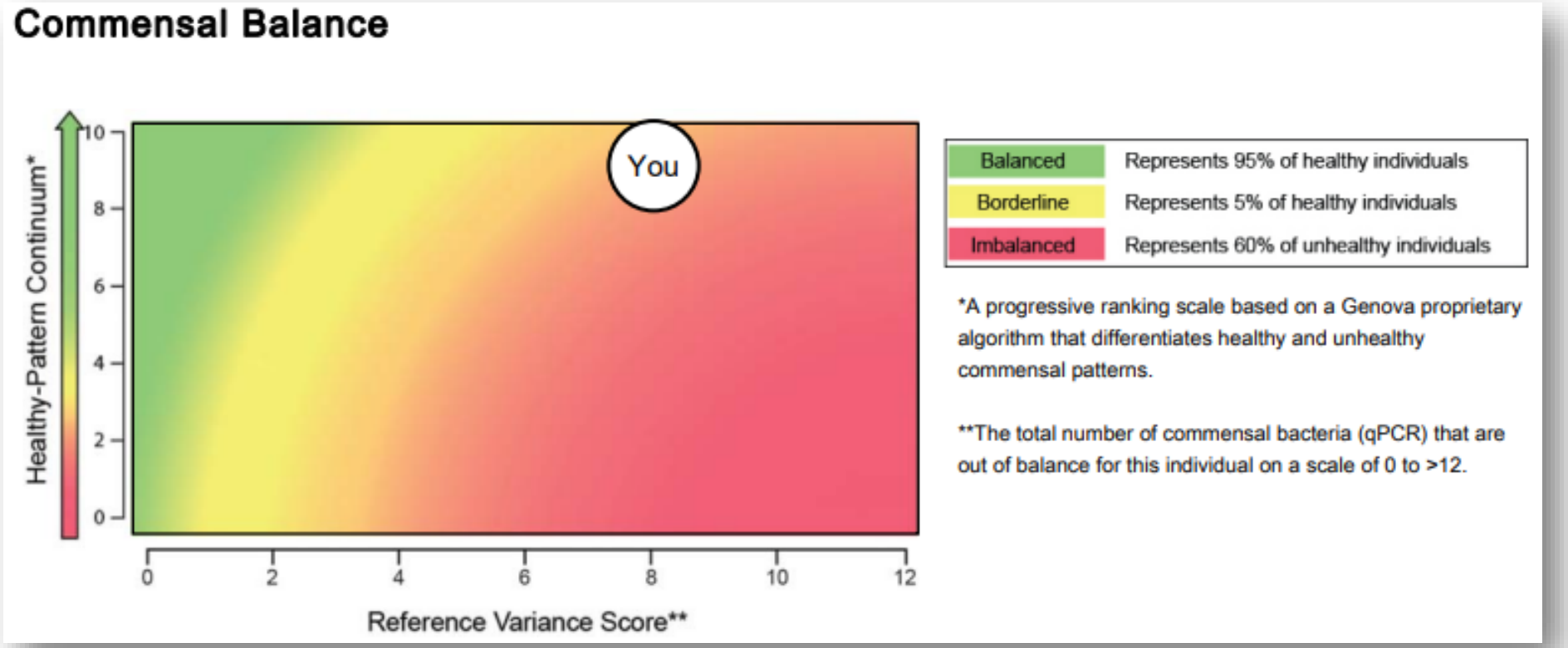
Differential Distribution Between Healthy and Autoimmune Cohorts



GENOVA DIAGNOSTICS

Unpublished data

Patient's Result is Not Dependent on Specific Bacteria

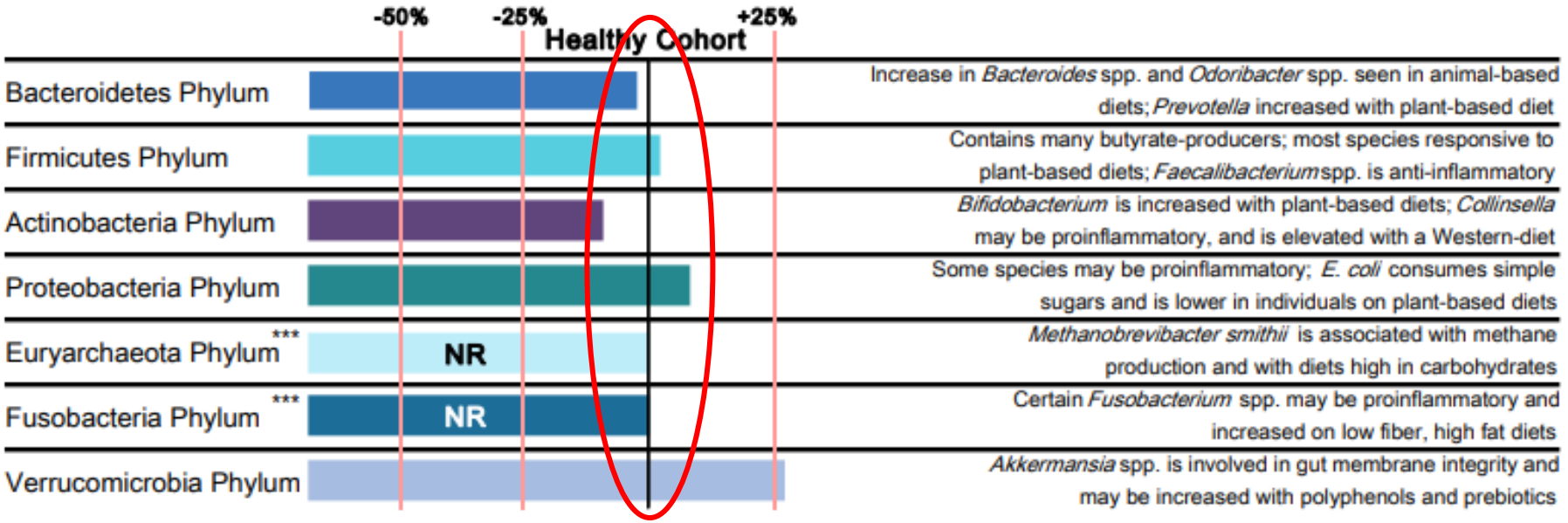


GENOVA DIAGNOSTICS

Relative Commensal Abundance

Patient Results

Clinical Commentary



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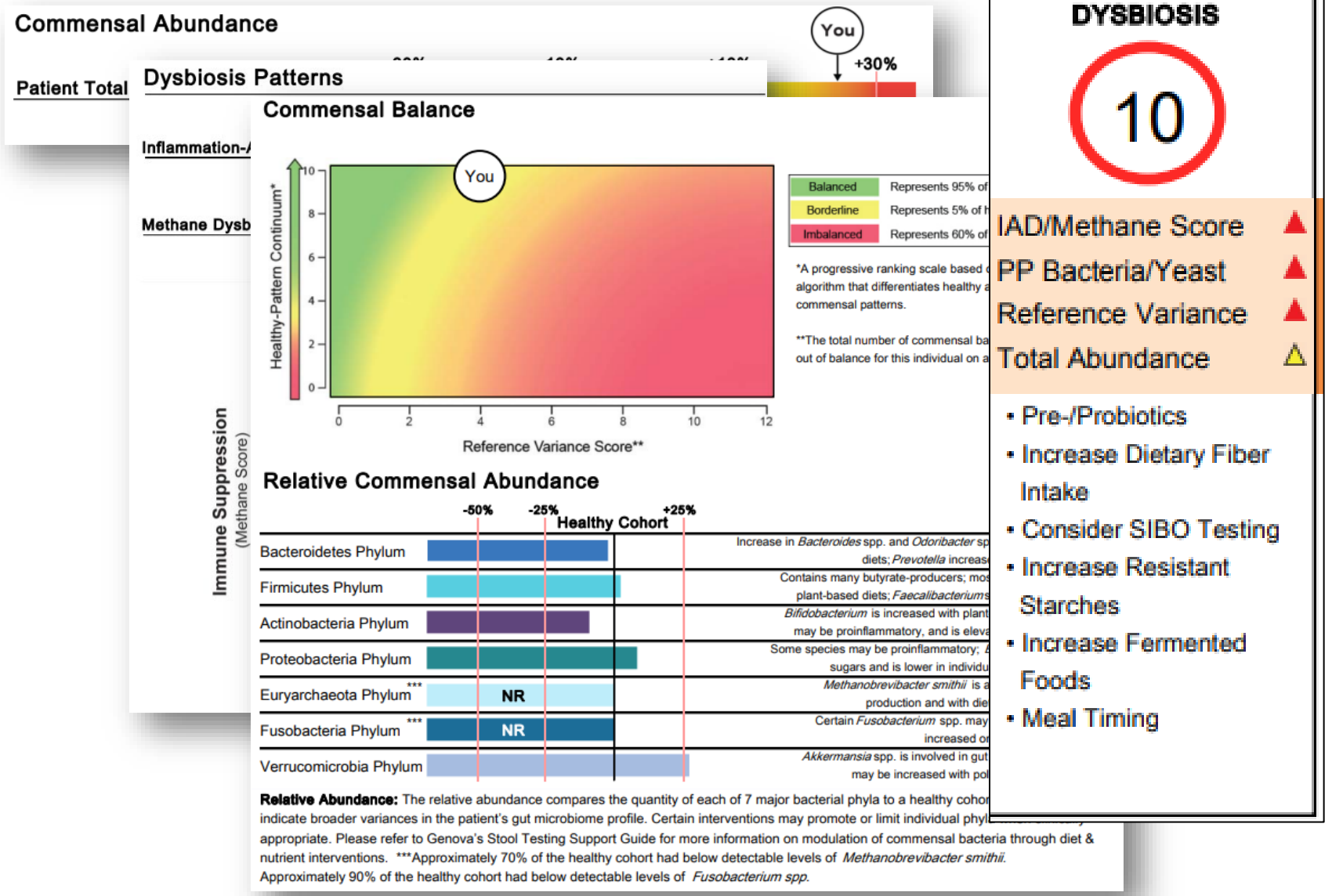
GENOVA DIAGNOSTICS

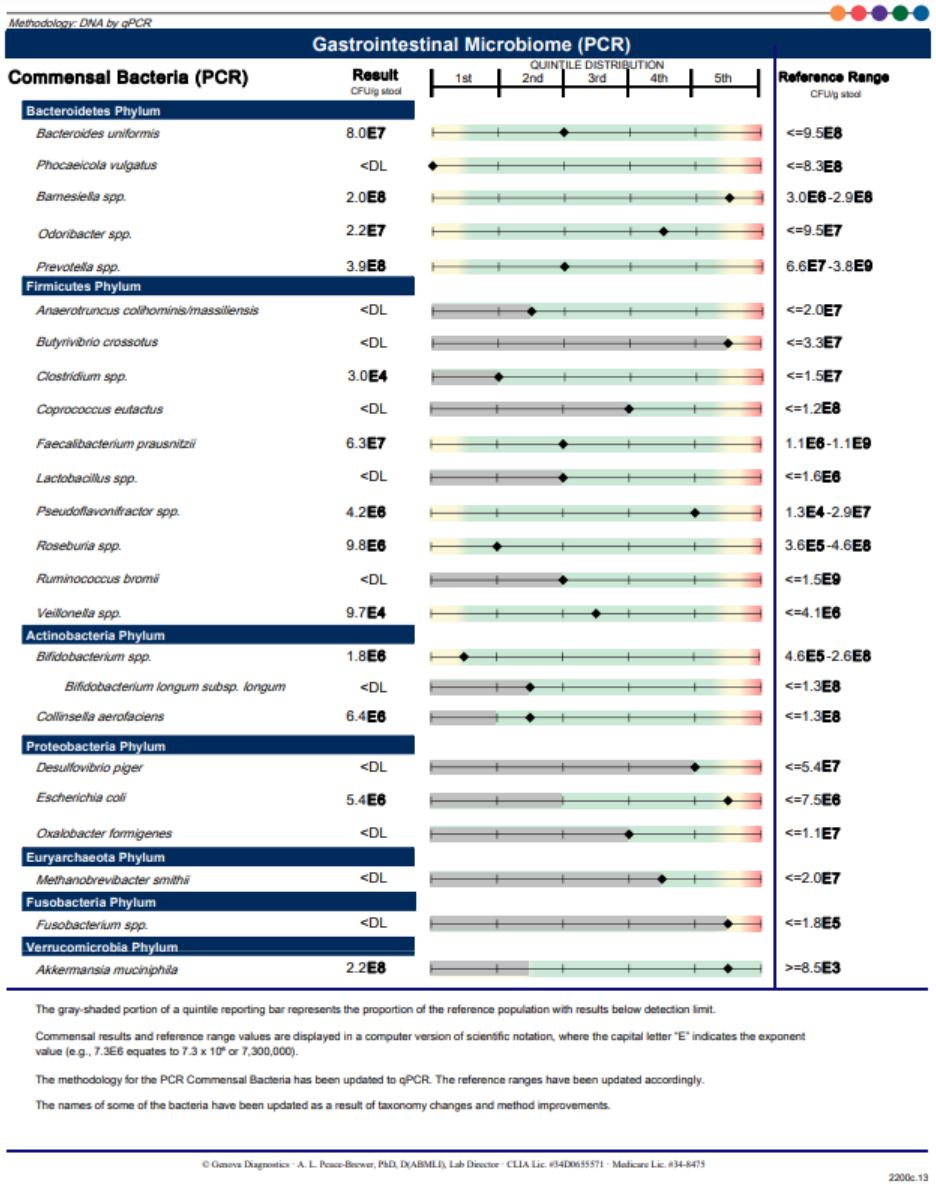
Microbiome Synthesis Recap

1. Abundance
2. Pattern
3. Balance



GENOVA DIAGNOSTICS

Commensal Bacteria



Methodology: DNA by qPCR

Gastrointestinal Microbiome (PCR)

Commensal Bacteria (PCR)	Result (CFU/g stool)	Reference Range (CFU/g stool)
Bacteroidetes Phylum		
Bacteroides uniformis	8.0E7	<=9.5E8
Phocaeicola vulgatus	<DL	<=8.3E8
Barnesiella spp.	2.0E8	3.0E6-2.9E8
Odoribacter spp.	2.2E7	<=9.5E7
Prevotella spp.	3.9E8	6.6E7-3.8E9
Firmicutes Phylum		
Anaerotruncus colihominis/massiliensis	<DL	<=2.0E7
Butyrivibrio crossotus	<DL	<=3.3E7
Clostridium spp.	3.0E4	<=1.5E7
Coprococcus eutactus	<DL	<=1.2E8
Faecalibacterium prausnitzii	6.3E7	1.1E6-1.1E9
Lactobacillus spp.	<DL	<=1.6E6
Pseudoflavonifractor spp.	4.2E6	1.3E4-2.9E7
Roseburia spp.	9.8E6	3.6E5-4.6E8
Ruminococcus bromii	<DL	<=1.5E9
Veillonella spp.	9.7E4	<=4.1E6
Actinobacteria Phylum		
Bifidobacterium spp.	1.8E6	4.6E5-2.6E8
Bifidobacterium longum subsp. longum	<DL	<=1.3E8
Collinsella aerofaciens	6.4E6	<=1.3E8
Proteobacteria Phylum		
Desulfovibrio piger	<DL	<=5.4E7
Escherichia coli	5.4E6	<=7.5E6
Oxalobacter formigenes	<DL	<=1.1E7
Euryarchaeota Phylum		
Methanobrevibacter smithii	<DL	<=2.0E7
Fusobacteria Phylum		
Fusobacterium spp.	<DL	<=1.8E5
Verrucomicrobia Phylum		
Akkermansia muciniphila	2.2E8	>=8.5E3

QUINTILE DISTRIBUTION: 1st | 2nd | 3rd | 4th | 5th

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 10^6 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.

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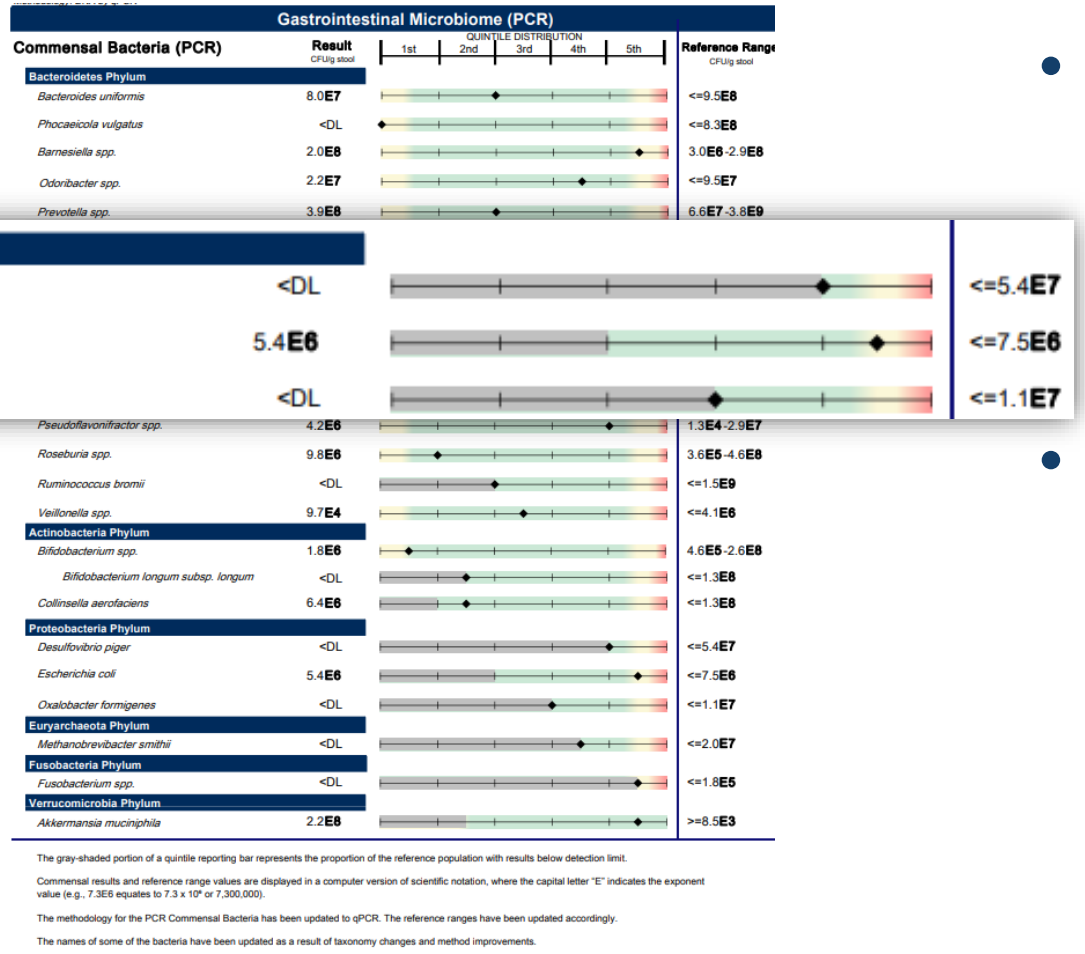
- Used to create microbiome synthesis pages 2-3
- Individual bacteria have unique clinical associations and importance to GI health

Commensal Bacteria



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Prevotella spp.	3.9**E8**		6.6**E7**-3.8**E9**
Proteobacteria Phylum			
Desulfovibrio piger	<DL		<=5.4**E7**
Escherichia coli	5.4**E6**		<=7.5**E6**
Oxalobacter formigenes	<DL		<=1.1**E7**
Pseudoflavonifractor spp.	4.2**E6**		1.3**E4**-2.9**E7**
Roseburia spp.	9.8**E6**		3.6**E5**-4.6**E8**
Ruminococcus bromii	<DL		<=1.5**E9**
Veillonella spp.	9.7**E4**		<=4.1**E6**
Actinobacteria Phylum			
Bifidobacterium spp.	1.8**E6**		4.6**E5**-2.6**E8**
Bifidobacterium longum subsp. longum	<DL		<=1.3**E8**
Collinsella aerofaciens	6.4**E6**		<=1.3**E8**
Proteobacteria Phylum			
Desulfovibrio piger	<DL		<=5.4**E7**
Escherichia coli	5.4**E6**		<=7.5**E6**
Oxalobacter formigenes	<DL		<=1.1**E7**
Euryarchaeota Phylum			
Methanobrevibacter smithii	<DL		<=2.0**E7**
Fusobacteria Phylum			
Fusobacterium spp.	<DL		<=1.8**E5**
Verrucomicrobia Phylum			
Akkermansia muciniphila	2.2**E8**		>=8.5**E3**

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- Gray bar – proportion of the reference population with results below detection limit
- Capital letter "E" indicates the exponent value (e.g., 7.3E6 equates to 7.3 x 10^6 or 7,300,000

GENOVA DIAGNOSTICS

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.

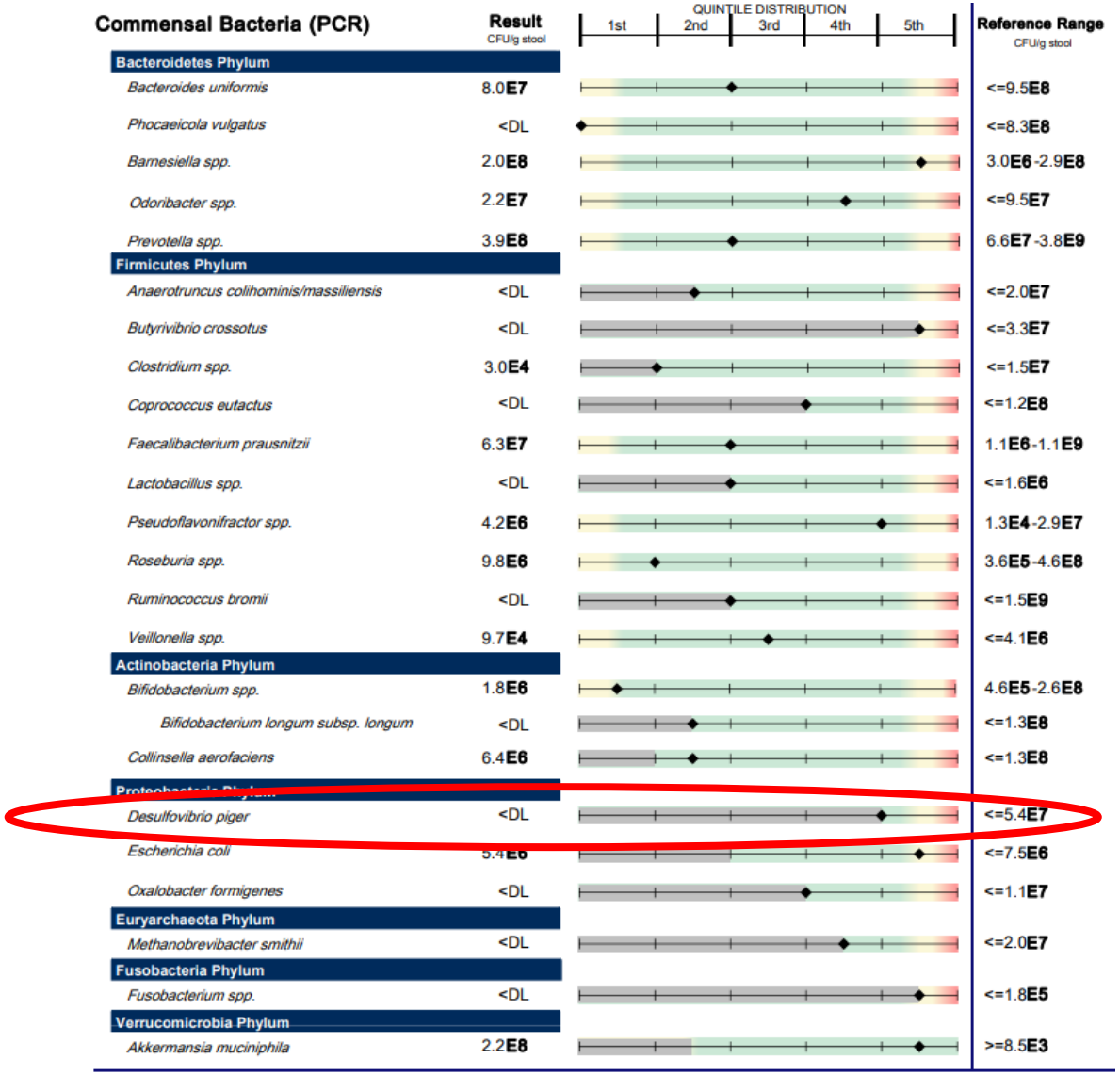
* Under certain conditions, environmental factors may influence specific commensals to become pathobionts. Pathobionts are distinguished from true infectious agents; they are potential pathogens under certain conditions. It is unknown whether these organisms play a causative role in disease or are a 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
Bacteroides-Prevotella group	*Bacteroides* historically included multiple taxonomic groups including *Prevotella* and others. New classification has separated them into *Bacteroides, Prevotella,* and other groups, however it is challenging to separate many of the species. For this reason, the *Bacteroides-Prevotella* group includes mainly *Bacteroides* and some *Prevotella.*[4-6] Displays flexibility to adapt to many environmental conditions/diets *Bacteroides* consist of bile-tolerant organisms and has the capability of utilizing polysaccharides and mucins.[7-9] Produces beta glucuronidase,[10] secondary bile acids,[11] acetate, propionate,[12,13] products of protein breakdown,[9] and is involved in vitamin metabolism[7] Associated with reduced bacterial gene richness[14] Along with *Methanobrevibacter smithii*, certain *Clostridium* and *Bacteroides* spp. can produce methane gas.[15] Generally associated with industrialized populations consuming a Western diet[16] *Bacteroides* growth in culture and propionate formation is favored at a close-to-neutral pH of 6.5, in contrast to butyrate-producing *Faecalibacterium prausnitzii* and *Roseburia* spp., which are favored at a lower pH of 5.5.[17] Pathobiont* some species	A *Bacteroides*-dominated microbiome is positively correlated with long-term diets rich in animal protein and saturated fat.[9,18] A small study on 11 healthy volunteers showed that an animal-based diet increased the abundance of bile-tolerant microorganisms (*Alistipes, Bilophila* and *Bacteroides*) and decreased the levels of Firmicutes that metabolize dietary plant polysaccharides (*Roseburia, Eubacterium rectale* and *Ruminococcus bromii*).[9] Tart cherry juice may normalize high or low levels.[19] Increased in obese adolescents who lost more than 4 kg on a calorie-restricted diet[20] Increased in overweight men drinking low glycinin soymilk compared to regular soymilk or bovine milk[21] Levels of *Bacteroides, Faecalibacterium, Odoribacter,* and others enriched after pomegranate extract consumption in overweight-obese subjects. Serum endotoxemia marker LBP was reduced.[22] Four bacteria are enriched with aspirin use versus no medication and includes *Bacteroides* spp., *Prevotella* spp., *Barnesiella* spp. and the family Ruminococcaceae. Furthermore, *Bacteroides* spp. was seen with other medications including NSAIDs with PPIs, and NSAIDs with antidepressants and laxatives.[23] Cigarette smoking is associated with increased levels.[24] Red wine was positively associated with the relative abundance of *Bacteroides* in 23 allergic patients,[25] and in 10 healthy males.[26] A high beef diet was associated with increases in *Bacteroides fragilis, B. vulgatus* and *Clostridium* spp. in 10 volunteers.[27] A ketogenic low-carbohydrate high-fat diet was associated with a reduction of *Faecalibacterium* and abundance of *Bacteroides* and *Dorea* spp. in race walkers.[28]	Tart cherry juice may normalize high or low levels.[19] Reduced with inulin from Jerusalem artichoke or chicory.[29] A systematic review of inulin supplementation in humans showed an increase in *Bifidobacterium*, and a relative increase in *Faecalibacterium* and *Lactobacillus*, and decrease in relative abundance of *Bacteroides.*[30] *Lactobacillus kefiri* was given to 20 healthy volunteers for one month and after the probiotic was discontinued for a month, *Bacteroides, Barnesiella, Clostridium, Veillonella* and other species were significantly reduced compared to baseline samples.[31] A study on 250 vegetarian and vegan individuals showed lower counts of *Bifidobacterium* spp. (vegan), *Bacteroides* spp. (vegan) and *E. coli* (vegan and vegetarian).[32]

GENOVA DIAGNOSTICS

Desulfovibrio piger

- Hydrogen sulfide gas producer, decreases butyrate
- Increased risk of IBD, CRC, visceral nerve sensitivity
- Increased
  - Animal studies: High-fat/high-sugar diet, chondroitin sulfate
- Decreased
  - Human: *Lactobacillus plantarum*
  - In-vitro: lower pH



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Fusobacteria Phylum			
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Verrucomicrobia Phylum			
Akkermansia muciniphila	2.2E8		>=8.5E3

Kushkevych I, et. al. *Open Med.* 2019;14:66-74.

Rey F, et. al. *Proc Natl Acad Sci USA.* 2013;110(33):13582-13587.

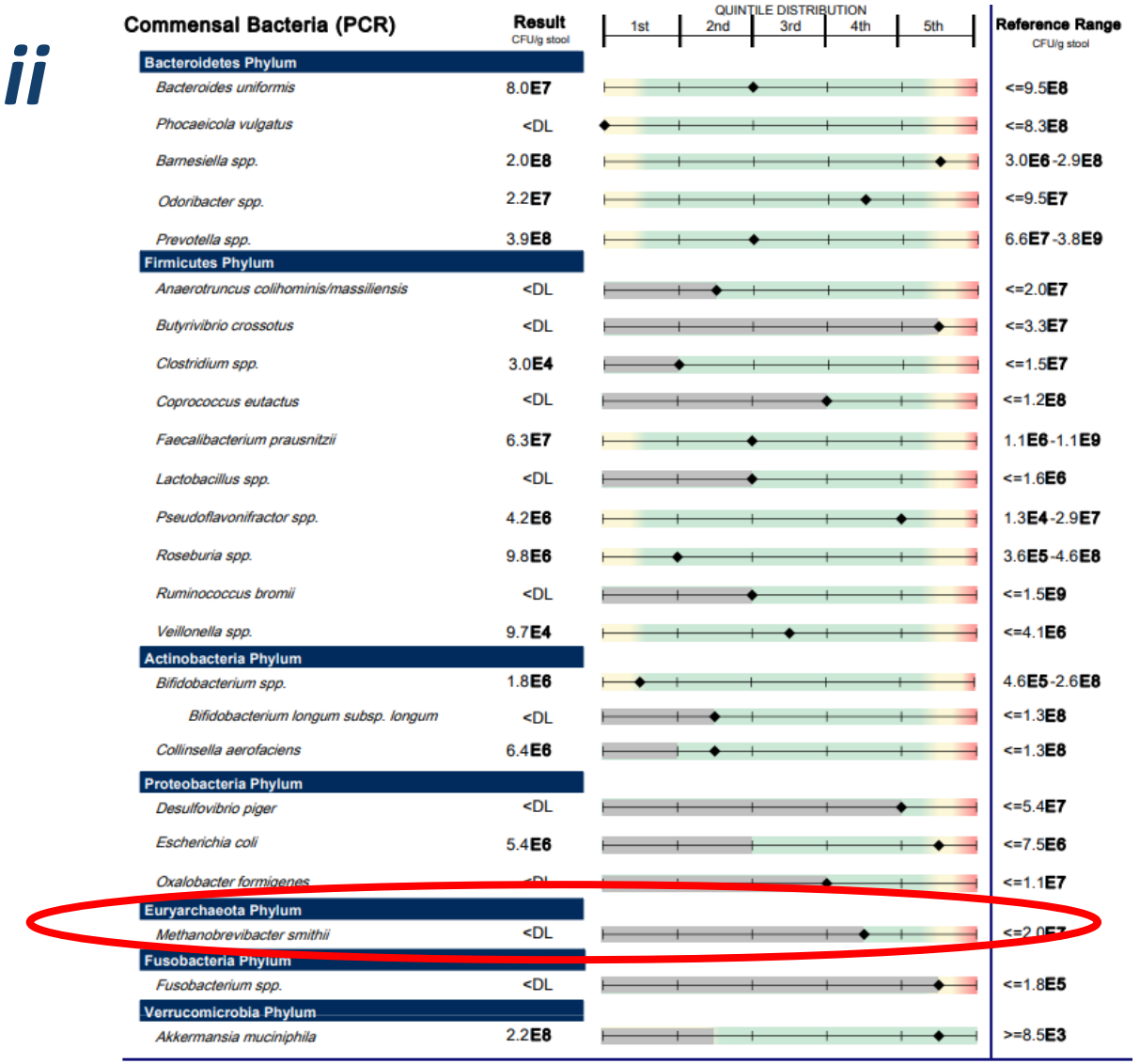
Singh S, Lin H. *Microorganisms.* 2015;3(4):866-889.

Wang L et. al. *Nutr.* 2014;30(7-8):776-83.

GENOVA DIAGNOSTICS

Methanobrevibacter smithii

- Hydrogen-consuming, methane gas-producing archaea (not a bacteria)
- Methane associated with obesity, prediabetes, constipation
- Decreased
  - Rifaximin+Neomycin, statins, probiotics with Lactobacillus and Bifidobacterium strains, garlic (breath methane levels)



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Gottlieb K, et. al. *Aliment Pharmacol Ther.* 2016;43(2):197-212.

Mathur R, et. al. *Obesity.* 2016;24(3):576-582.

Pimentel M, et.al. *Am J Gastroenterol Suppl.* 2012;1:28-33.

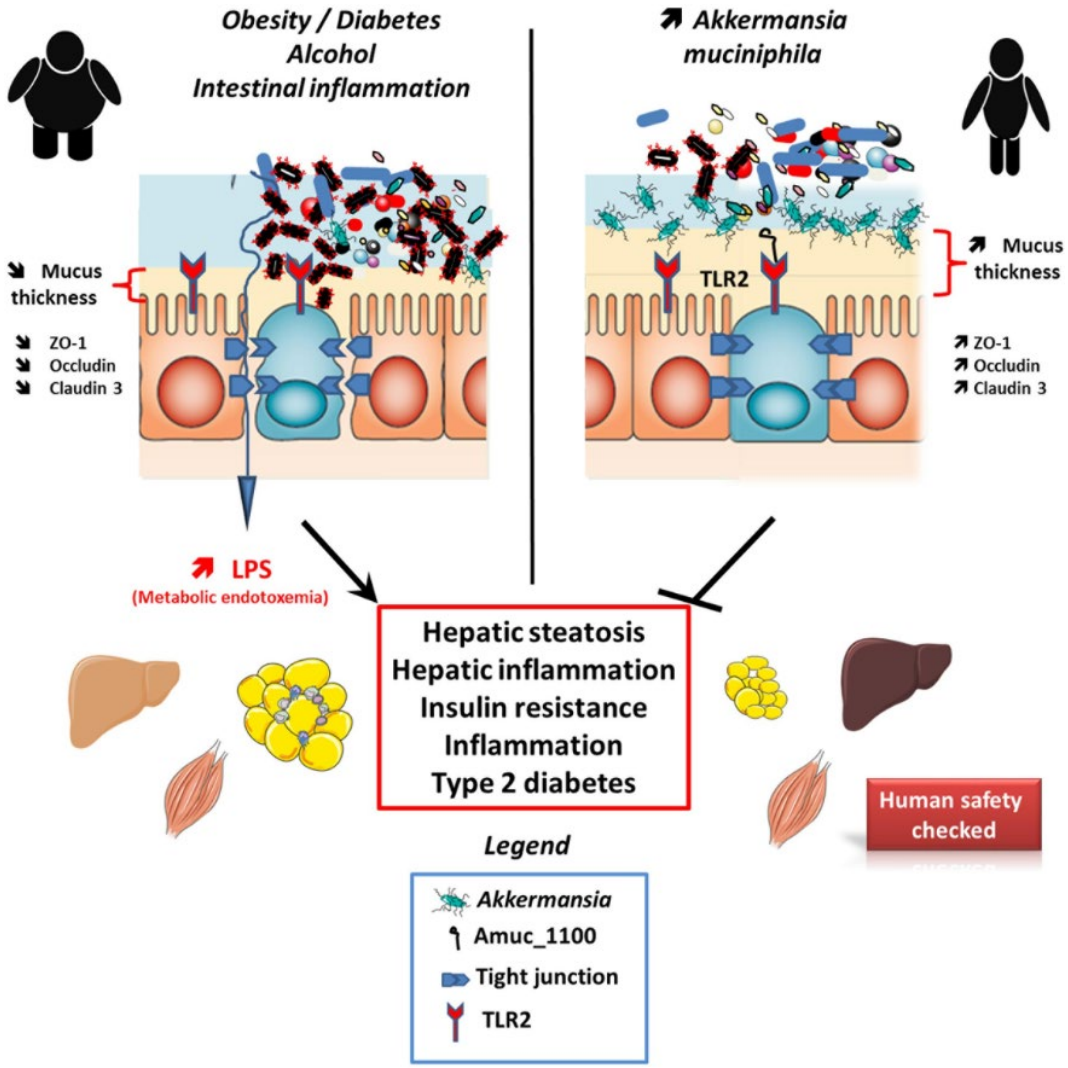
Pimentel M, et. al. *Dig Dis Sci.* 2014;59(6):1278-85.

Seo M, et.al. *PLoS One.* 2017;12(9):e0184547.

GENOVA DIAGNOSTICS

Akkermansia muciniphila

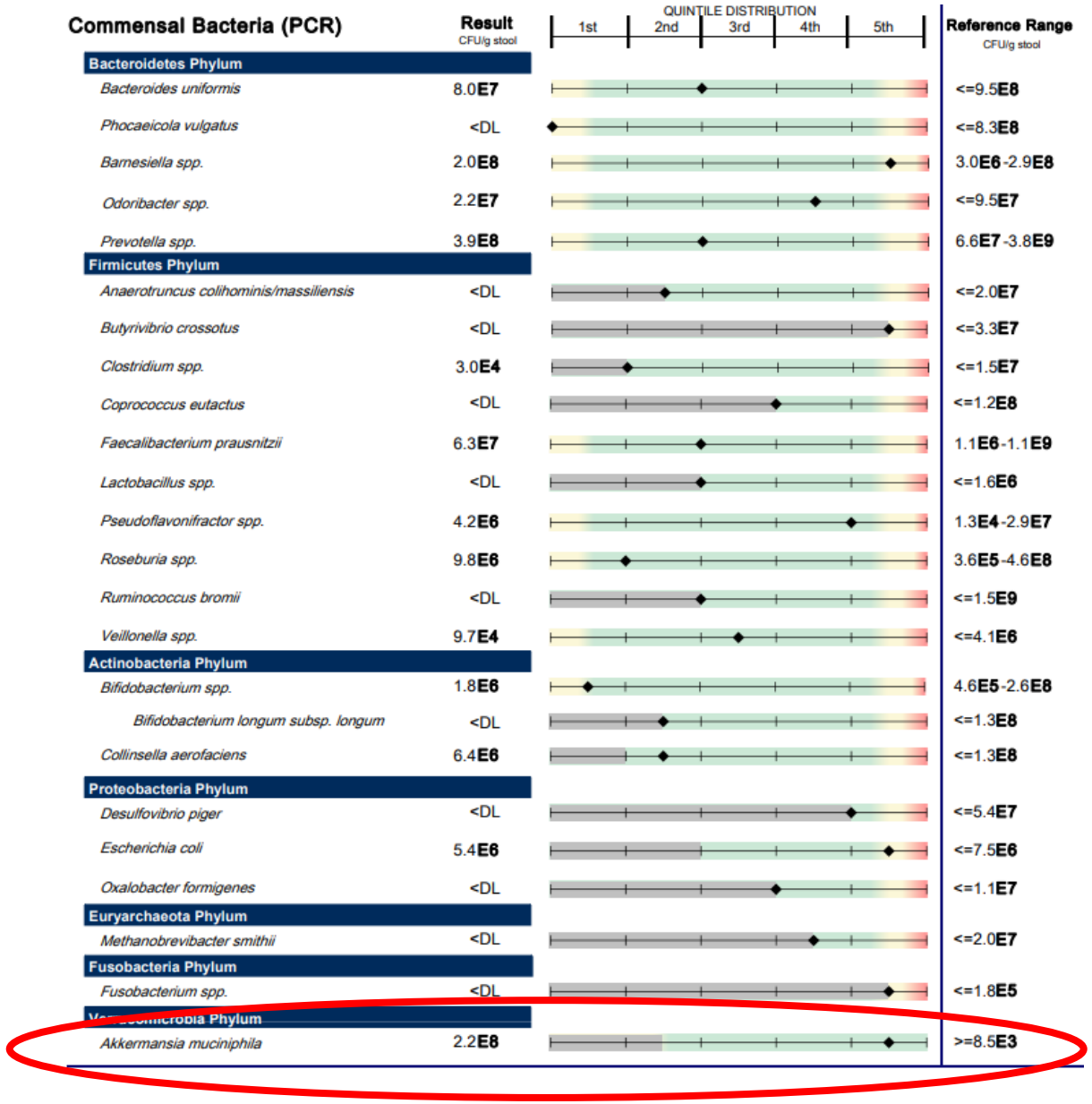
- Low levels associated with obesity, diabetes, inflammation, insulin resistance, hepatic inflammation, gut permeability
- Mucin degrader, produces acetate and propionate
- Improves intestinal barrier integrity
- May limit toxicity of sulfate-reducing bacteria
- A probiotic supplement



Depommier C, et. al. *Nat Med.* 2019;25(7):1096-1103.
Cani P, de Vos WM. *Front Microbiol.* 2017;8:1765.
Hiippala K, et. al. *Nutrients.* 2018;10(8):988.

Akkermansia muciniphila

- Increased
  - Pomegranate, caloric restriction, resveratrol, polydextrose, inulin, sodium butyrate
- Decreased
  - Low FODMAP diet



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Coprococcus eutactus	<DL		<=1.2**E8**
Faecalibacterium prausnitzii	6.3**E7**		1.1**E6**-1.1**E9**
Lactobacillus spp.	<DL		<=1.6**E6**
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Collinsella aerofaciens	6.4**E6**		<=1.3**E8**
Proteobacteria Phylum			
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Escherichia coli	5.4**E6**		<=7.5**E6**
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GENOVA DIAGNOSTICS

Verhoog S et. al. *Nutrients.* 2019;11(7):1565.
Zhou K. *J Funct Foods.* 2017;33:194-201.

GI Effects Comprehensive Profile
Microbiome Analysis

Pages 6-11

GENOVA DIAGNOSTICS

Gastrointestinal Microbiome (Culture)

Human microflora is influenced by environmental factors and the competitive ecosystem of the organisms in the GI tract. Pathogenic significance should be based upon clinical symptoms.

Microbiology Legend

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

Bacteriology (Culture)

Lactobacillus spp.		NG
Escherichia coli		NG
Bifidobacterium (Anaerobic Culture)	3+	NP

Additional Bacteria

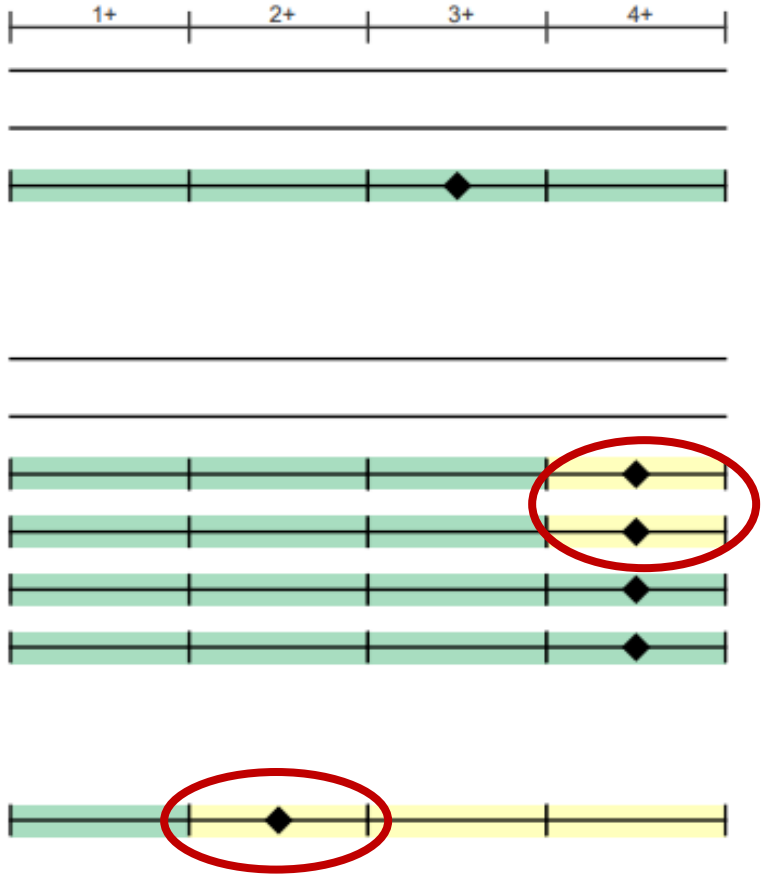
Salmonella spp.		NG
Shigella spp.		NG
Citrobacter braakii	4+	PP
Klebsiella oxytoca	4+	PP
Hafnia paralvei	4+	NP
Enterococcus faecalis	4+	NP

Mycology (Culture)

Candida parapsilosis	2+	PP

Additional Bacteria

Non-Pathogen: Organisms that fall under this category are those that constitute normal, commensal flora, or have not been recognized as etiological agents of disease.
Potential Pathogen: Organisms that fall under this category are considered potential or opportunistic pathogens when present in heavy growth.
Pathogen: The organisms that fall under this category have a well-recognized mechanism of pathogenicity in clinical literature and are considered significant regardless of the quantity that appears in the culture.



Need for Antimicrobial Support

INFECTION

10

- Parasitic Infection
- PP Bacteria/Yeast
- Total Abundance
- Pathogenic Bacteria

- Antibiotics (if warranted)
- Antimicrobial Herbal Therapy
- Antiparasitic Herbal Therapy (if warranted)
- *Saccharomyces boulardii*

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Pathogenic Bacteria & Yeast

Genus/Organism	Description	Habitat/Sources of Isolation	Pathogenicity	GI Symptoms
Aeromonas *Aeromonas hydrophilia* *Aeromonas caviae* *Aeromonas veronii* *Aeromonas jandaei* *Aeromonas schuberti*	*Aeromonas* is a facultatively anaerobic, Gram-negative rod.[1] *Aeromonas* species share many biochemical properties with *Vibrio* species and were jointly classified in the *Vibrionaceae* family until genotypic information provided new insights.[2] (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 *A. hydrophilia*.[1]	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]	*Aeromonas* has been associated with a wide variety of human infectious diseases, including gastroenteritis, wound infections, septicemia, respiratory infections, and urinary tract infections.[2] However, *Aeromonas* 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]
Bacillus anthracis	*B. anthracis* is a spore-forming, Gram-positive bacterium which causes anthrax.[4] In humans, there are three major forms of anthrax as delineated by the spore exposure route: cutaneous, gastrointestinal, and inhalational.[5] (P)	*B. anthracis* 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]	Spores are ingested and germinate within the GI tract epithelium. *B. anthracis* then uses a toxin called anthrolysin to disrupt the GI barrier.[6]	GI anthrax can present clinically as either intestinal or, less commonly, oropharyngeal infection. The incubation period is typically 1-6 days. 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]
Bacillus cereus	*B. cereus* is a Gram-positive, aerobic (or facultative aerobic), spore-forming, rod-shaped bacterium.[7] (PP)	*B. cereus* 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]	*B. cereus* produces several toxin types: hemolysin, phospholipase, cereulide (emetic toxin), and enterotoxins. The incubation time averages 12 hours, and the duration of signs/symptoms is between 12-24 hours.[7]	*B. cereus* infectious symptoms include gastroenteritis and vomiting, but the illness is self-limiting and usually lasts less than 24 hours.[7]

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Candida Susceptibility Profile for Azoles*

Organism	Number of Isolates	% Sensitive	
		Fluconazole	Voriconazole
Candida albicans	25561	99.19%	99.51%
Candida parapsilosis	8777	98.64%	99.33%
Candida kruseii	3420	0.23%	97.79%
Candida tropicalis	1076	93.22%	90.57%
Candida glabrata	2898	27.1%	90.9%

Non-absorbed Antifungals

Candida parapsilosis	LOW INHIBITION	HIGH INHIBITION
Nystatin		

Natural Agents

Candida parapsilosis	LOW INHIBITION	HIGH INHIBITION
Berberine		
Caprylic Acid		
Garlic		
Undecylenic Acid		
Uva-Ursi		

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Prescriptive Agents

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

Natural Agents

Klebsiella oxytoca	LOW INHIBITION	HIGH INHIBITION
Berberine		
Oregano		
Uva-Ursi		

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Add-on Pathogenic Bacteria EIA

Add-on Testing		
Methodology: EIA	**Result**	**Expected Value**
HpSA - *H. pylori*	Negative	Negative
Campylobacter spp.*	Negative	Negative
*Clostridium difficile**	Negative	Negative
Shiga toxin *E. coli**	Negative	Negative

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H. Pylori indications

Table 1. Indications for Diagnosis and Treatment of *H. pylori*

Established

- Active peptic ulcer disease (gastric or duodenal ulcer)
- Confirmed history of peptic ulcer disease (not previously treated for *H. pylori*)
- Gastric MALT lymphoma (low grade)
- After endoscopic resection of early gastric cancer
- Uninvestigated dyspepsia (depending upon *H. pylori* prevalence)

Controversial

- Nonulcer dyspepsia
- Gastroesophageal reflux disease
- Persons using nonsteroidal antiinflammatory drugs
- Unexplained iron deficiency anemia
- Populations at higher risk for gastric cancer

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Chey, W & Wong, B. American College of Gastroenterology Guideline on the Management of *Helicobacter pylori* Infection. *Amer J Gastro* 102(8):p 1808-1825, Aug 2007.

Add-on KOH Preparation for Yeast

KOH Preparation for Yeast

Methodology: Potassium Hydroxide (KOH) Preparation for Yeast

Potassium Hydroxide (KOH) Preparation for Yeast

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

	Result	
KOH Preparation, stool	Rare Yeast Present	The result is reported as the amount of yeast seen microscopically: Rare: 1-2 per slide Few: 2-5 per high power field (HPF) Moderate: 5-10 per HPF Many: >10 per HPF

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G/Gastrointestinal Microbiome – Parasitology

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

PCR Parasitology - Protozoa

Methodologies: DNA by PCR, Next Generation Sequencing

Organism	Result	Units		Expected Result
Blastocystis spp.	3.90e4	femtograms/microliter C&S stool	**Detected**	Not Detected
Cryptosporidium parvum/hominis	<1.76e2	genome copies/microliter C&S stool	Not Detected	Not Detected
Cyclospora cayetanensis	<2.65e2	genome copies/microliter C&S stool	Not Detected	Not Detected
Dientamoeba fragilis	<1.84e2	genome copies/microliter C&S stool	Not Detected	Not Detected
Entamoeba histolytica	<9.64e1	genome copies/microliter C&S stool	Not Detected	Not Detected
Giardia	<1.36e1	genome copies/microliter C&S stool	Not Detected	Not Detected

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

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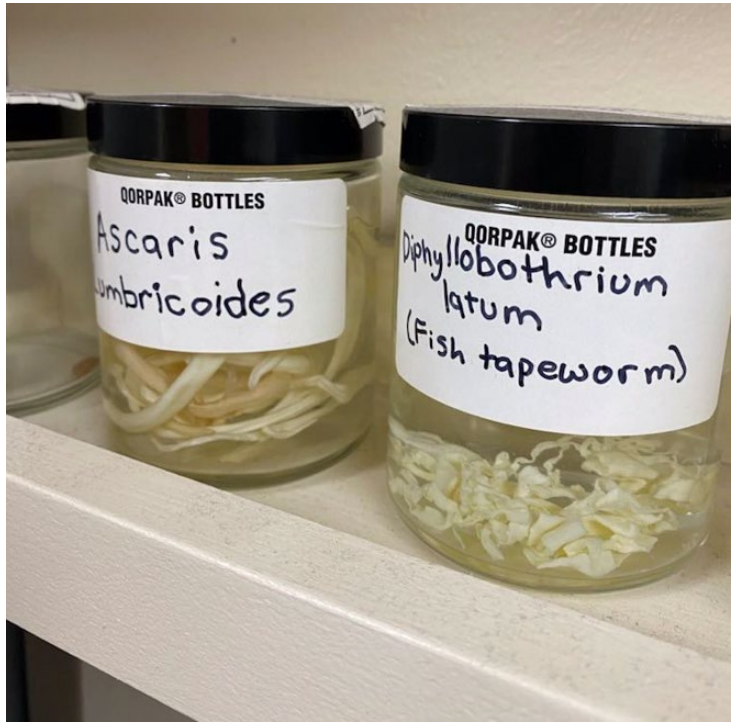
Add-on Macroscopic/Direct Exam for Parasites

Macroscopic/Direct Exam for Parasites

Methodology: Macroscopic Evaluation

No human parasite detected in sample.



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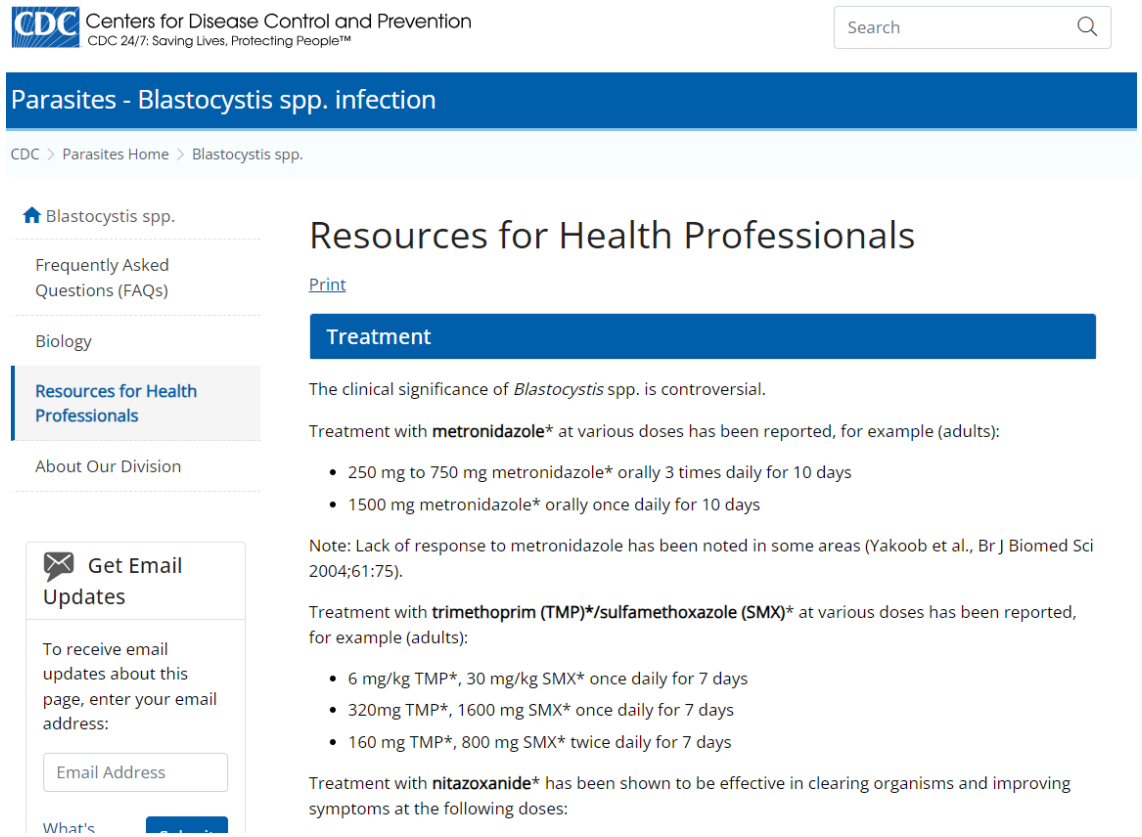
Parasitic Organisms

NEMATODES – ROUNDWORMS

Organism	Description	Epidemiology/Transmission	Pathogenicity	Symptoms
Ancylostoma -Necator *Ancylostoma duodenale* *Necator americanus*	Hookworms Soil-transmitted nematodes (P)	Found in tropical and subtropical climates, as well as in areas where sanitation and hygiene are poor.[1] Infection occurs when individuals come into contact with soil containing fecal matter of infected hosts.[2]	*Necator* can only be transmitted through penetration of the skin, whereas *Ancylostoma* can be transmitted through the skin and orally. *Necator* attaches to the intestinal mucosa and feeds on host mucosa and blood.[2] *Ancylostoma* eggs pass from the host's stool to soil. Larvae can penetrate the skin, enter the lymphatics, and migrate to heart and lungs.[3]	Some are asymptomatic, though a heavy burden is associated with anemia, fever, diarrhea, nausea, vomiting, rash, and abdominal pain.[2] During the invasion stages, local skin irritation, elevated ridges due to tunneling, and rash lesions are seen.[3] *Ancylostoma* and *Necator* are associated with iron deficiency anemia.[1,2]
Ascaris lumbricoides	Soil-transmitted nematode Most common human worm infection (P)	Common in Sub-Saharan Africa, South America, Asia, and the Western Pacific. In non-endemic areas, infection occurs in immigrants and travelers. It is associated with poor personal hygiene, crowding, poor sanitation, and places where human feces are used as fertilizer. Transmission is via the fecal-oral route.[4]	*Ascaris* 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]	Most patients are asymptomatic or have only mild abdominal discomfort, nausea, dyspepsia, or loss of appetite. Complications include obstruction, appendicitis, right upper quadrant pain, and biliary colic.[4] 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]
Capillaria philippinensis	Fish-borne nematode (P)	Although rare in the US, it is more common in Asia (Thailand and the Philippines)[4] Infection occurs from eating raw or undercooked fish containing larvae.	Ingested larvae reside in the human small intestine, where the female deposits eggs, which then develop, causing autoinfection and hyperinfection.[4]	Diarrhea, anorexia, malaise, and vomiting.[4] Capillariasis can mimic IBD and other causes of protein losing enteropathy.[6]
Enterobius vermicularis	Pinworm The most common worm infection in children ages 5-10 in the US (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	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]	Some infections are asymptomatic. Symptoms may include itching and irritation. Occasional migration of the worm to distant organs can cause dysuria, vaginal discharge, enuresis, and peritoneal granulomas.[4] Enterobiasis can mimic hemorrhoids and IBD.[6]

Treating Parasites

- Why doesn't Genova run sensitivities to parasites?
  - They're dead!
- CDC for conventional Tx information
  - https://www.cdc.gov/dpdx/az.html
- PubMed or supplement companies for natural Rx



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Parasitology – Multiple Methodologies

- The GI Effects is the first stool test to combine microscopic O&P technology with PCR technology
  - Each methodology has its limitations
    - PCR technology is used for most common pathogenic parasites
    - Microscopic O&P is important to rule out other infections
  - Performing both has improved our detection rates
  - Given us some interesting data, including >95% correlation from O&P to PCR

- 3-day or 1-day?
  - Organisms can shed at different times, so if a parasite is suspected, order 3-day

Additional Educational Resources

www.GDX.net

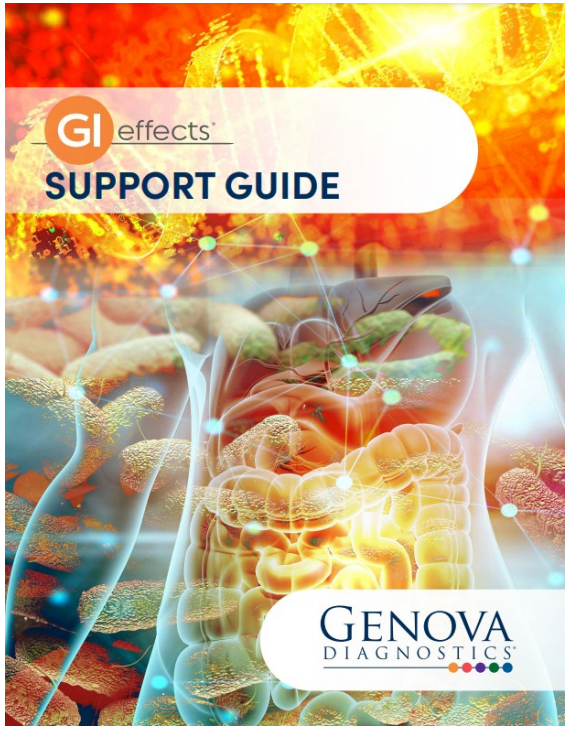
- GI Effects Support Guide and organism charts
- Learning Library video modules
- Test Prep information – supplement/medication FAQs

The Lab Report Podcast

- Available on Apple Podcasts and GDX.net

Medical Education Consultations

- Schedule online through myGDX
- Call Client Services 800-522-4762
- 1:1 and group consultations



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GI effects®

The Microbiome: Understanding Infection and Dysbiosis

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Medical Education Specialist| Genova Diagnostics

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Frontline Gastroenterol. 2023 Feb 9;14(5):371-376. doi: 10.1136/flgastro-2022-102271. eCollection 2023.

What is the significance of a faecal elastase-1 level between 200 and 500µg/g?

Alok Mathew [1], Darren Fernandes [2 3], H Jervoise N Andreyev [2 4]

Affiliations + expand

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DOI: 10.1136/flgastro-2022-102271

Abstract

Background: Pancreatic exocrine insufficiency is a cause of malabsorption. It is generally diagnosed if faecal elastase-1 (FE-1) levels are below 200 µg/g. Pancreatic function is assumed to be normal when faecal elastase levels are >500 µg/g. The significance of faecal elastase levels above 200 µg/g but less than 500 µg/g is unclear.

Methods: This retrospective study reports the response to treatment in patients who had an FE-1 level between 200 and 500 µg/g.

Results: Of these 82 patients, 28 were offered pancreatic enzyme replacement therapy (PERT). A clinical response, defined as an improvement in their initial symptoms after commencing PERT, was seen in 20 patients (71%), 7 with potentially predisposing conditions and 13 with functional diarrhoea. PERT particularly abolished or improved diarrhoea, steatorrhoea and flatulence.

Conclusion: Clinicians should, therefore, be aware that a trial of PERT given to patients with FE-1 levels between 200 and 500 µg/g may lead to improvement in gastrointestinal symptoms.

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