Casual Friday Series

SIBO – Practical Applications

A Biogenetix Clinical Presentation

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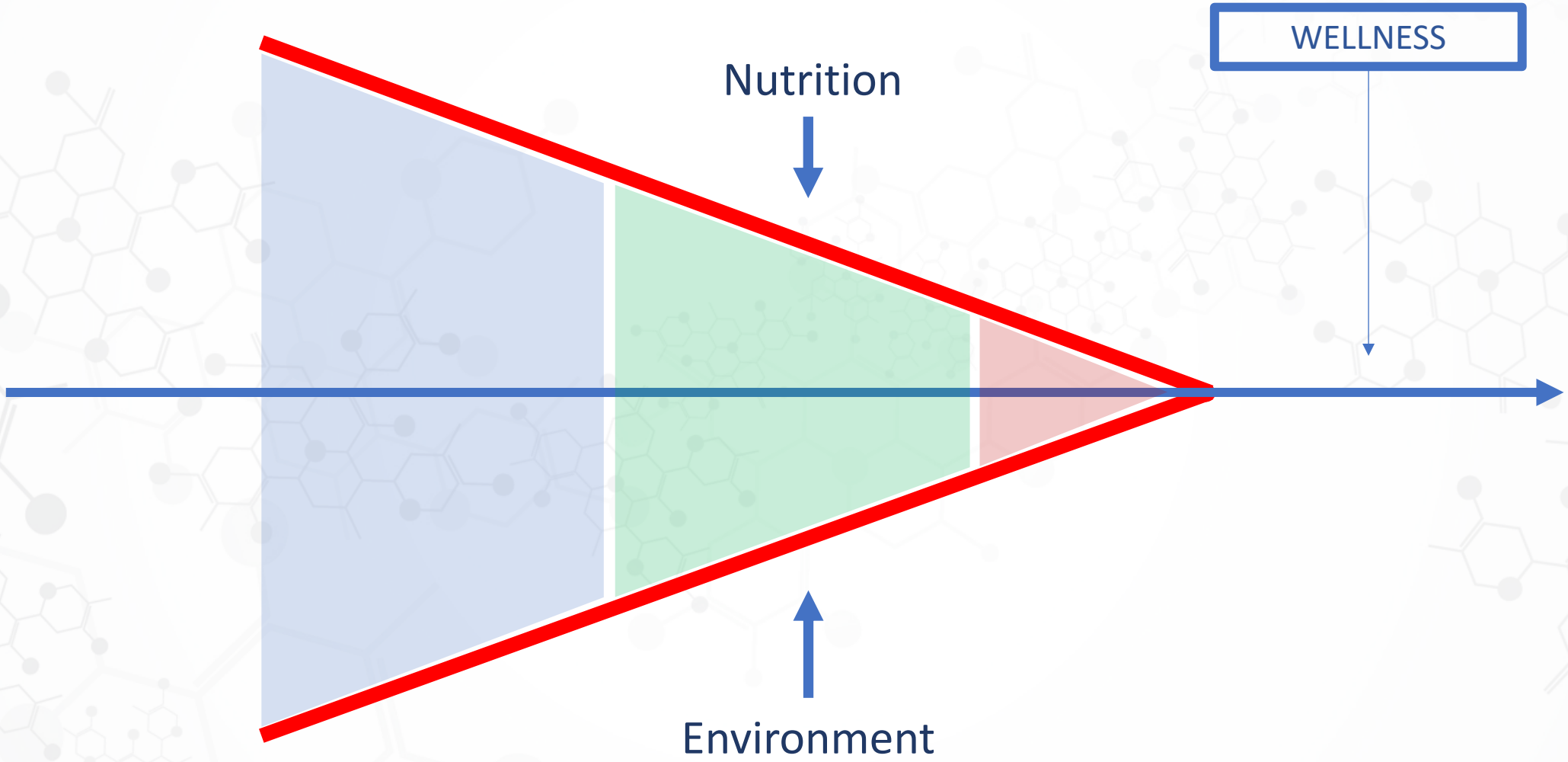
Protocols



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Small Intestinal Bacterial Overgrowth: Comprehensive Review of Diagnosis, Prevention, and Treatment Methods

Monitoring Editor: Alexander Muacevic and John R Adler

Small intestinal bacterial overgrowth (SIBO) is a commonly diagnosed gastrointestinal disorder affecting millions of individuals throughout the United States. It refers to a condition in which there is an excess and imbalance of small intestinal bacteria. Despite its prevalence, it remains underdiagnosed due to the invasive nature of diagnostic testing. Symptoms observed in SIBO, including abdominal distension, bloating, diarrhea, and gas formation, are nonspecific and can overlap with other gastrointestinal disorders. Frequently cited predisposing factors include gastric acid suppression, dysmotility, gastric bypass, and opioids. The diagnostic gold standard remains small bowel aspirate and culture. However, due to its invasive nature, it remains an unpopular method among patients and clinicians alike. Glucose and lactulose breath testing have become the go-to diagnostic method in clinical practice due to its noninvasive nature and low cost. Treatment is guided towards the eradication of bacteria in the small bowel and usually consists of a prolonged course of oral antibiotics. Due to recent advances in our understanding of the human microbiome, we are surely poised for a transformation in our approach to diagnosing and treating this condition.

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Ted George O Achufusi,[1] Anuj Sharma,[2] Ernesto A Zamora,[1] and Divey Manocha[2]

The human gut is inhabited by 10^{14} bacterial cells, which is roughly 10 times higher than the number of cells in the human body [1]. This diverse microbiome is composed of a wide range of organisms, including bacteria, fungi, and viruses. Bacteria compromise the largest portion of this microbiome, with approximately 500 to 1,000 different bacterial species identified to date [2]. The number of bacteria increases with progression from the proximal small intestine to the large intestine. The small intestine is comprised of mainly gram-positive and aerobic bacteria, while the large intestine contains predominantly gram-negative and anaerobic bacteria. The major phyla comprising the gut includes *Bacteroidetes* and *Firmicutes,* whilst *Actinobacteria, Fusobacteria, Verrucomicrobia,* and *Cyanobacteria* are also present, albeit in a smaller proportion [3].

Esophagus pH
< 4.0

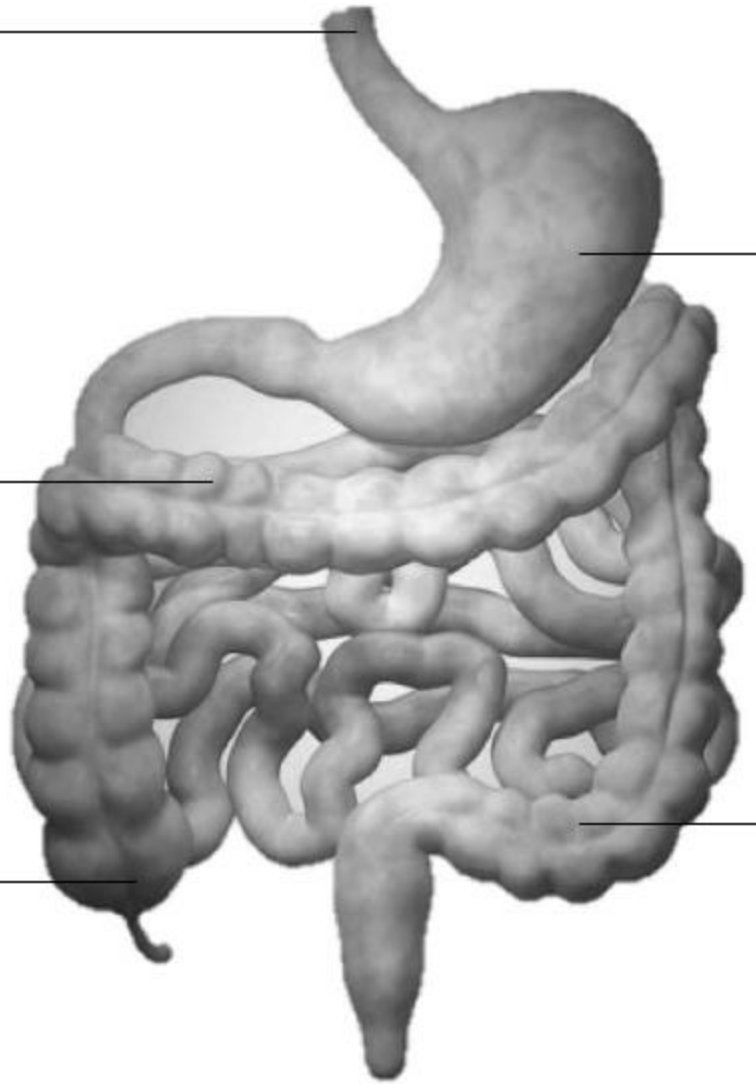
Bacteroides, *Gemella*, *Megasphaera*, *Pseudomonas*, *Prevotella*, *Rothia* sps., *Streptococcus*, *Veillonella*

Colon pH
5-5.7

Bacteroides, *Clostridium*, *Prevotella*, *Porphyromonas*, *Eubacterium*, *Ruminococcus*, *Streptococcus*, *Enterobacterium*, *Enterococcus*, *Lactobacillus*, *Peptostreptococcus*, *Fusobacteria*

Cecum pH
5.7

Lachnospira, *Roseburia*, *Butyrivibrio*, *Ruminococcus*, *Fecalibacterium*, *Fusobacteria*



Stomach pH
2

Streptococcus, *Lactobacillus*, *Prevotella*, *Enterococcus*, *Helicobacter pylori*

Small intestine pH
5-7

Bacteroides, *Clostridium*, *Streptococcus*, *Lactobacillus*, *γ-Proteobacteria*, *Enterococcus*

https://f6publishing.blob.core.windows.net/708d7a28-9674-4604-8b2d-5cad47f3c6bb/WJG-21-8787-g002.jpg

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The prevalence of SIBO among the general population is unknown. However, in most studies, SIBO has been detected anywhere from 0 to 20% of healthy controls [5]. The most common risk factors for abnormal or excessive small bowel bacterial overgrowth include disturbances in the small bowel anatomy and motility. Frequently cited examples include diabetic enteropathy, underlying connective tissue disease, chronic opiate use, diverticula, small bowel adhesions, and blind limbs. Additionally, impairments in the normal biochemical clearance of bacteria also predispose to bacterial overgrowth. This includes hypochloremia caused by chronic proton pump inhibitor (PPI) use and reduced pancreaticobiliary secretions caused by chronic pancreatitis.

A 2019 meta-analysis conducted with the aim to review the prevalence of SIBO among patients with ulcerative colitis and Crohn's disease showed a direct correlation between IBD and SIBO [8]. There were 11 studies included as part of the meta-analysis with combined 1,175 adult patients with IBD and 407 controls. Breath testing was utilized for SIBO diagnosis in each of the 11 studies. The prevalence of SIBO in IBD patients was 22.3% (95% CI 19.92 - 24.68). The OR for SIBO among IBD patients was 9.51 (95% CI 3.39 - 26.68) and significant in both ulcerative colitis (OR = 7.96; 95% CI 1.66 - 38.35) and Crohn's (OR = 10.86; 95% CI 2.76 - 42.69). The results of the study support the idea that IBD does indeed place patients at higher risk for bacterial overgrowth.

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Breath tests are simple, non-invasive, patient-friendly methods for diagnosing bacterial overgrowth. The practical nature of the procedure and low cost have made it the go-to diagnostic tool in clinical practice. The diagnostic role of hydrogen breath tests largely depends on the type of substrate used. For example, lactose hydrogen breath tests are useful in cases of carbohydrate malabsorption, while lactulose and glucose hydrogen breath tests are useful for diagnosing bacterial overgrowth. In patients with carbohydrate malabsorption, the colonic gut flora produces hydrogen and methane gases from the ingested substrates; in patients with SIBO, the small bowel bacteria produce these same gases. The majority of the gases produced are rapidly eliminated with passing flatus. However, about 20% of the gases are absorbed by the lung and then exhaled, which allows for quantitative measurement during breath testing. Contrary to prior studies, where methane level measurement did not increase the yield of hydrogen breath testing, recent data suggest checking methane levels does increase the diagnostic yield of hydrogen breath testing and should be used for diagnostic purposes [3, 16].

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Systemic Antibiotics

Given the limitations of current diagnostic techniques, clinicians often initiate empiric therapy as a diagnostic tool in those with a high level of suspicion for SIBO. In this context, the improvement of symptoms following a trial of antibiotics would lean providers towards making the diagnosis. However, this strategy in itself can be problematic as it exposes patients to risks of antibiotic therapy, including the development of antibiotic-resistant organisms and infections (i.e., *Clostridium difficile* colitis).

Traditionally, the go-to antibiotics for treatment of SIBO consisted of tetracyclines, fluoroquinolones, and co-trimoxazole. However, rifaximin has emerged as the preferred agent among clinicians for SIBO management. Rifaximin is a nonabsorbable antibiotic which acts against Gram-positive and Gram-negative aerobic and anaerobic bacteria. The preferred use of rifaximin stems from its reduced toxicity profile and its utility in irritable bowel syndrome, a diagnosis with significant clinical overlap with SIBO. Furthermore, data shows that rifaximin can act as a “eubotic” agent by preserving colonic flora while increasing the relative abundance of lactobacilli and bifidobacteria in the gut [24]. The eradication rate of SIBO also seems to be dose-related. A previously conducted study reported a dose-dependent eradication rate where higher doses of rifaximin were associated with a higher eradication rate [25]. In a recent meta-analysis aimed at investigating the effectiveness of rifaximin in bacterial overgrowth, the efficacy of rifaximin in eradicating SIBO was 64% as compared to 41% with other systemic antibiotics, including tetracyclines and metronidazole [26]. Another meta-analysis looking at eight studies showed that the effectiveness of rifaximin in the normalization rate of breath testing was 49.5% [27].

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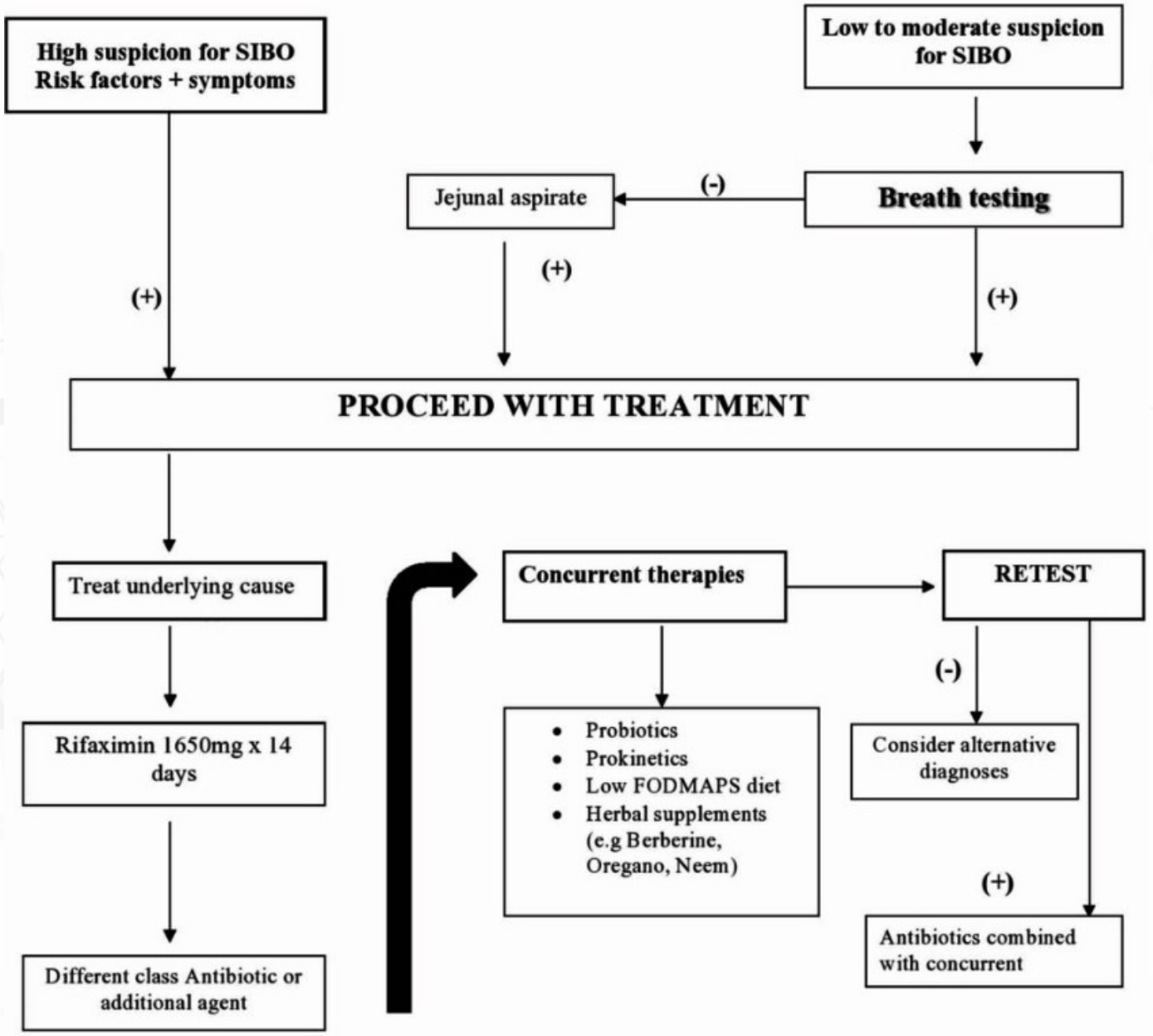
LBT. Results showed that 17/36 subjects on herbal supplementation (46%) had a negative follow-up LBT compared to 23/67 (34%) of rifaximin users. The odds ratio of having a negative LBT after taking herbal therapy as compared to rifaximin was 1.85 (CI = 0.77 - 4.41, P = .17) once adjusted for gender, age, and SIBO risk factors. The same study concluded that herbal therapy has similar efficacy as triple antibiotic therapy for SIBO rescue therapy for rifaximin non-responders [32]. However, it's important to note data regarding herbal supplements for SIBO is extremely limited and products currently available differ significantly in composition and quality.

SIBO MANAGEMENT ALGORITHM



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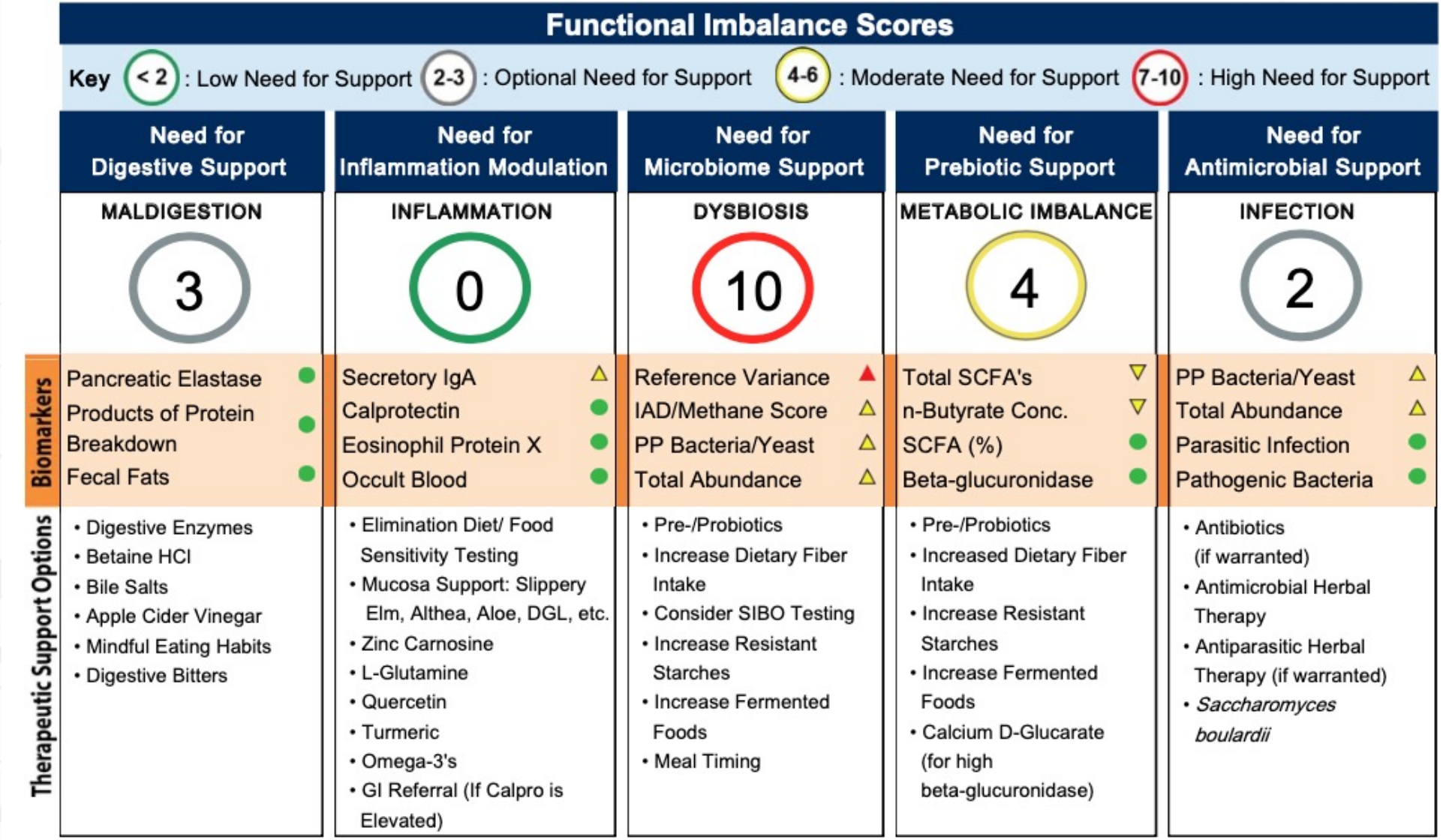
Conclusions

Go to:

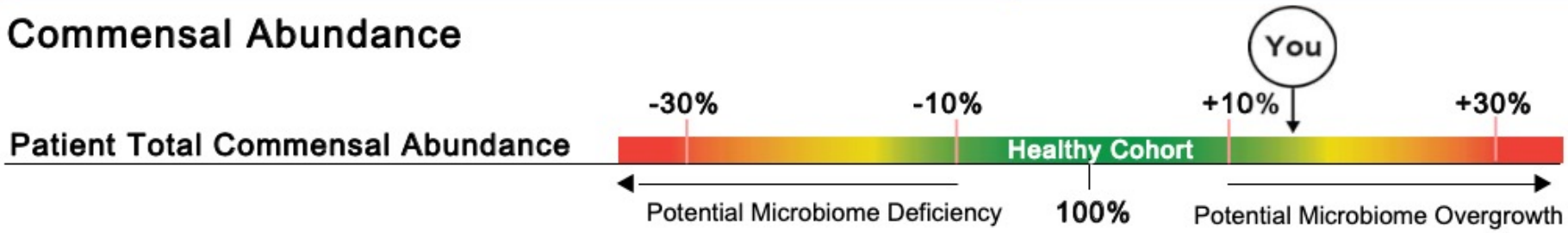
SIBO remains a widely prevalent diagnosis in tertiary referral gastroenterology practice. While there has been significant progress made in our understanding of the condition, efforts to fully unravel this complex diagnosis remain hampered by the limitations of currently available diagnostic tools. Although a perfect diagnostic test for SIBO is lacking, currently available breath testing has proven to be a safe and preferred method in clinical practice. With the lack of clear-cut criteria and diagnostic tools, it is harder to prove the diagnosis of SIBO when it is suspected. This may soon change, however, as the application of molecular techniques to the study of the small intestinal microbiome, coupled with innovative sampling techniques, may soon enable clinicians to truly define the spectrum of SIBO. Additional studies are needed to further characterize contributing pathophysiological mechanisms in SIBO and to investigate optimal treatment for this challenging patient population. While SIBO continues to be a controversial diagnosis, in the era of booming microbiome research, gastroenterologists and other clinicians will surely become increasingly aware of SIBO in the general population, enabling them to provide more effective treatment.

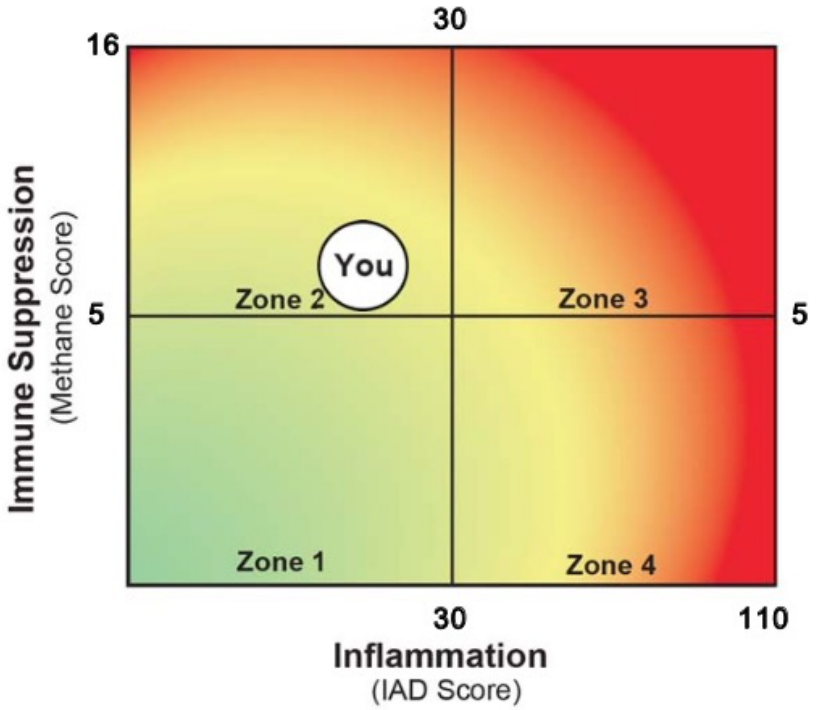


63 yo female: anxiety, fatigue, IBS

Commensal Microbiome Analysis

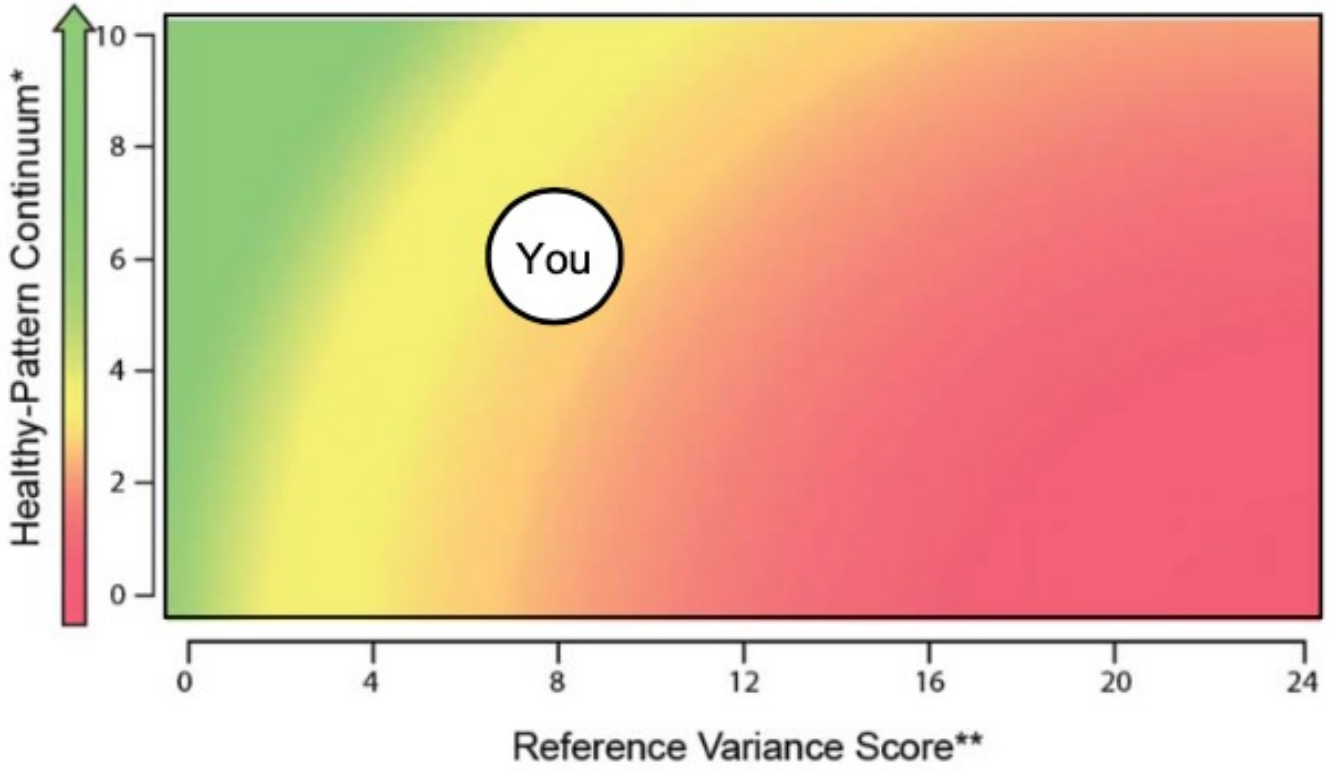
Commensal Abundance





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.

Commensal Balance

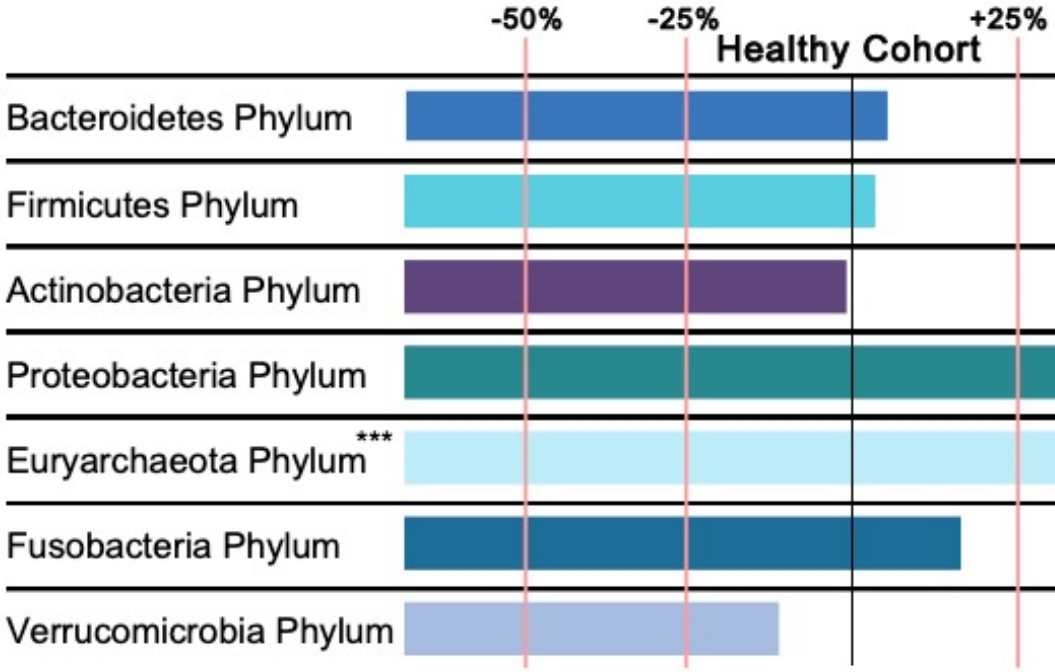


Balanced	Represents 95% of healthy individuals
Borderline	Represents 5% of healthy individuals
Imbalanced	Represents 60% of unhealthy individuals

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

**The total number of Commensal Bacteria (PCR) that are out of reference ranges for this individual.

Relative Commensal Abundance



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

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 75% of the healthy cohort had below detectable levels of *Methanobrevibacter smithii.*

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.	2+	NP
Escherichia coli	4+	NP
Bifidobacterium	2+	NP

Additional Bacteria

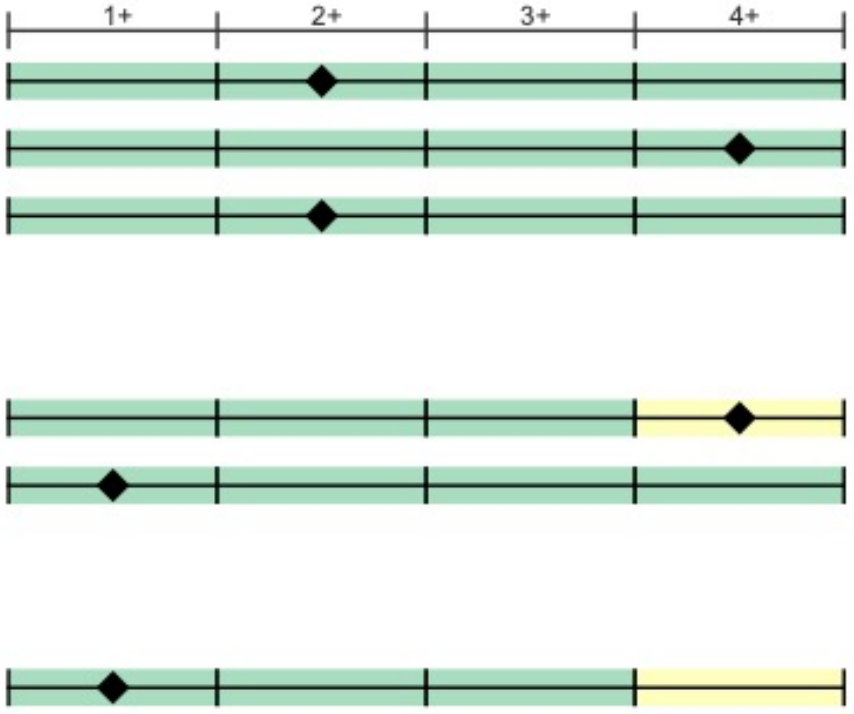
Klebsiella oxytoca	4+	PP
Enterococcus spp	1+	NP

Mycology (Culture)

Rhodotorula species	1+	NP

Additional Bacteria

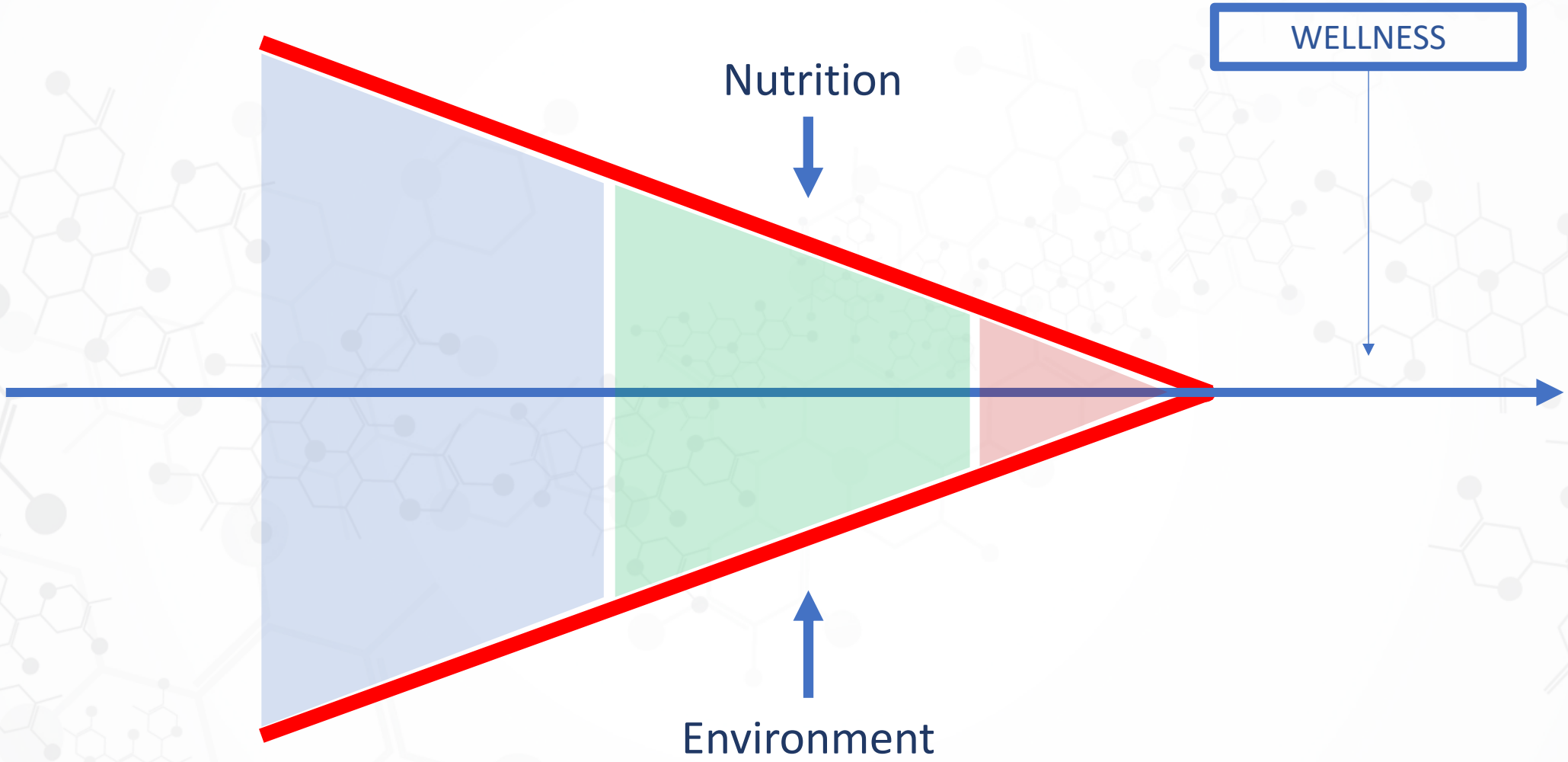
Non-Pathogen: Organisms that fall under this category are those that constitute normal, commensal flora, or have not been recognized as etiological agents of disease.
Potential Pathogen: Organisms that fall under this category are considered potential or opportunistic pathogens when present in heavy 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.



Interpretation At-a-Glance

Commensal Bacteria	Patient Results Out of Reference Range	Genova Diagnostics Commensal Bacteria Clinical Associations*							
		IBS	IBD	Metabolic Syndrome	Chronic Fatigue	Auto-immune	Type 2 Diabetes	High Blood Pressure	Mood Disorders
Bacteroidetes Phylum									
Bacteroides-Prevotella group		↑	↑	↑	↑	↑	↑	↑	↑
Bacteroides vulgatus	H	↑			↑	↑		↑	↑
Barnesiella spp.									
Odoribacter spp.	H								
Prevotella spp.		↑		↑	↑	↑		↑	↑
Firmicutes Phylum									
Anaerotruncus colihominis		↑	↑	↑	↑	↑	↑	↑	↑
Butyrivibrio crossotus	H								
Clostridium spp.									
Coprococcus eutactus		↑			↑	↑		↑	↑
Faecalibacterium prausnitzii	H	↑				↑			↑
Lactobacillus spp.									
Pseudoflavonifractor spp.		↑	↑	↑	↑	↑	↑	↑	↑
Roseburia spp.	L		↓						
Ruminococcus spp.	L	↓↑	↓	↓	↓	↓↑	↓↑	↓↑	↓↑
Veillonella spp.	H	↑	↑	↑	↑	↑	↑		↑
Actinobacteria Phylum									
Bifidobacterium spp.									
Bifidobacterium longum									
Collinsella aerofaciens		↓↑	↓↑	↓	↓↑	↓↑	↓↑	↓↑	↓↑
Proteobacteria Phylum									
Desulfovibrio piger	H								↑
Escherichia coli		↑	↑	↑	↑	↑	↑	↑	↑
Oxalobacter formigenes		↑		↑	↑				↑
Euryarchaeota Phylum									
Methanobrevibacter smithii		↑				↑			↑
Fusobacteria Phylum									
Fusobacterium spp.		↑	↑	↑	↑	↑	↑	↑	↑
Verrucomicrobia Phylum									
Akkermansia muciniphila		↓	↓	↓	↓	↓	↓	↓	↓

Protocols



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