IBS, SIBO & Histamine Intolerance

Insights with GI-MAP

Thomas Fabian, PhD CNTP

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Q&A to ask the panel questions

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Recording will be available for a limited time

Poll 1: Which Best Describes you?

- ❑ Physician (MD, ND, DO, DC, etc…)
- ❑ Physician’s Assistant or Nurse Practitioner
- ❑ Nutrition professional
- ❑ Pharmacist
- ❑ Student
- ❑ Other

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- Teach-Ins with expert colleagues
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Key Topics

- Common GI symptoms & conditions involving symptoms that overlap with SIBO & IBS
- Underlying causes & contributors: digestive deficiencies, dysbiosis, & diet
- Key insights from advanced stool testing
- Evolving perspectives and clinical implications

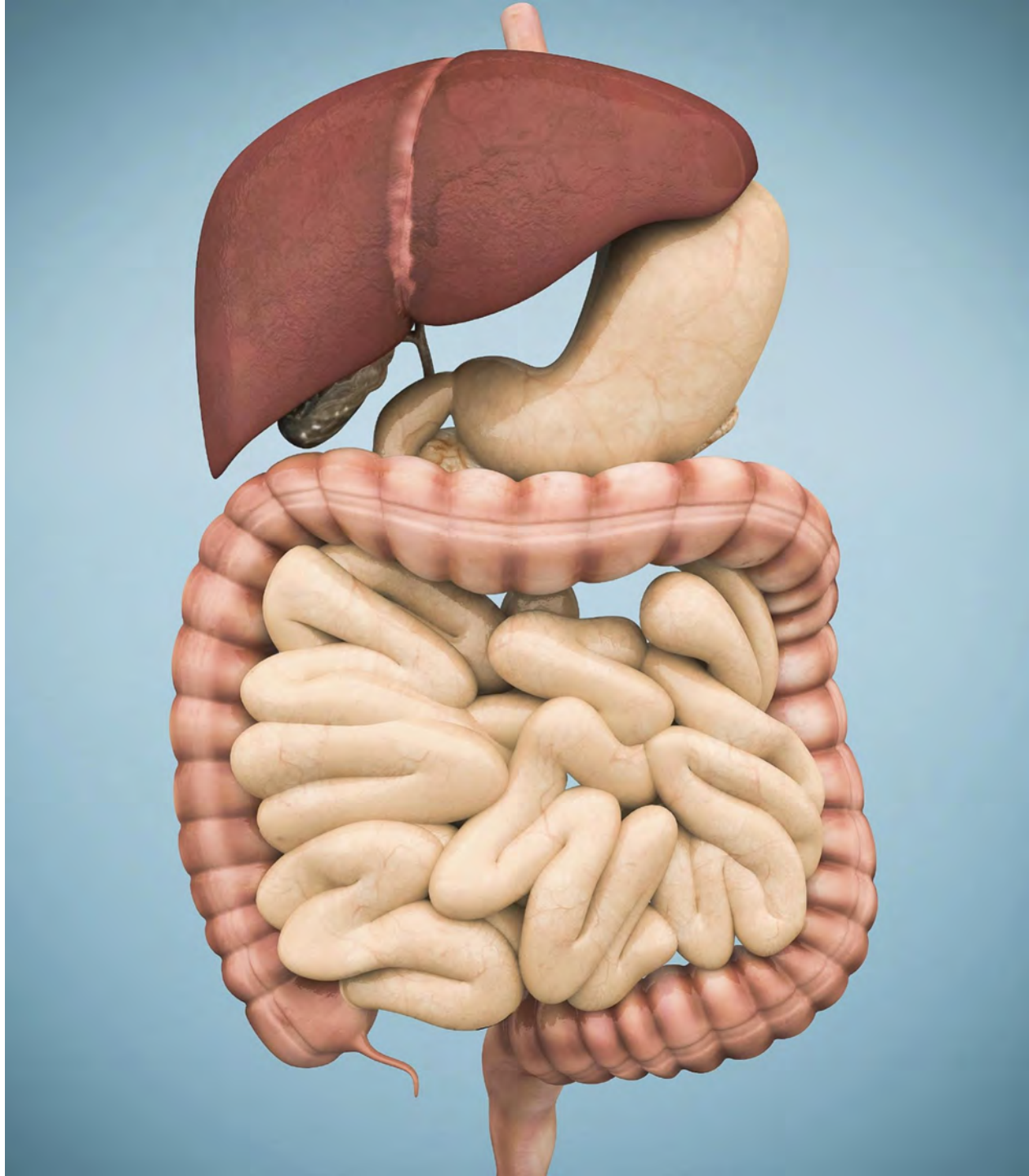
Common GI Symptoms

Bloating / distension

Excessive gas

Abdominal discomfort or pain

Diarrhea / constipation



Review > World J Gastroenterol. 2019 Aug 21;25(31):4414-4426.

Gastrointestinal motility and absorptive disorders in patients with inflammatory bowel diseases: Prevalence, diagnosis and treatment

Table 1 Common symptoms of overlapping gastrointestinal disorders in inflammatory bowel disease patients

Disease	Symptoms
Bile-acid malabsorption	Diarrhea, urgency
Exocrine pancreatic insufficiency	Abdominal discomfort, bloating, diarrhea, greasy stools
Carbohydrates intolerance	Abdominal discomfort, bloating, diarrhea
Small intestinal bacterial overgrowth	Abdominal discomfort, bloating, constipation, diarrhea, distention, sensation of incomplete evacuation, urgency
Small intestinal fungal overgrowth	Abdominal discomfort, bloating, diarrhea, distention, urgency
Dyssynergic defecation	Abdominal discomfort, bloating, constipation, diarrhea, distention, sensation of incomplete evacuation, straining, urgency
Ehlers-Danlos syndromes-hypermobility type	Abdominal pain, bloating, constipation, distention, sensation of incomplete evacuation, straining, pelvic floor dysfunction
Mast cell activation syndrome	Abdominal discomfort, bloating, dynamic allergies, diarrhea, distention, sensation of incomplete evacuation, urgency
Eosinophilic gastroenteritis	Abdominal pain, bloating, diarrhea
Intra-abdominal adhesions	Abdominal pain, bloating, distention
Irritable bowel syndrome	Abdominal discomfort, bloating, diarrhea /constipation, distention, sensation of incomplete evacuation, urgency
Celiac disease	Abdominal discomfort, bloating, diarrhea

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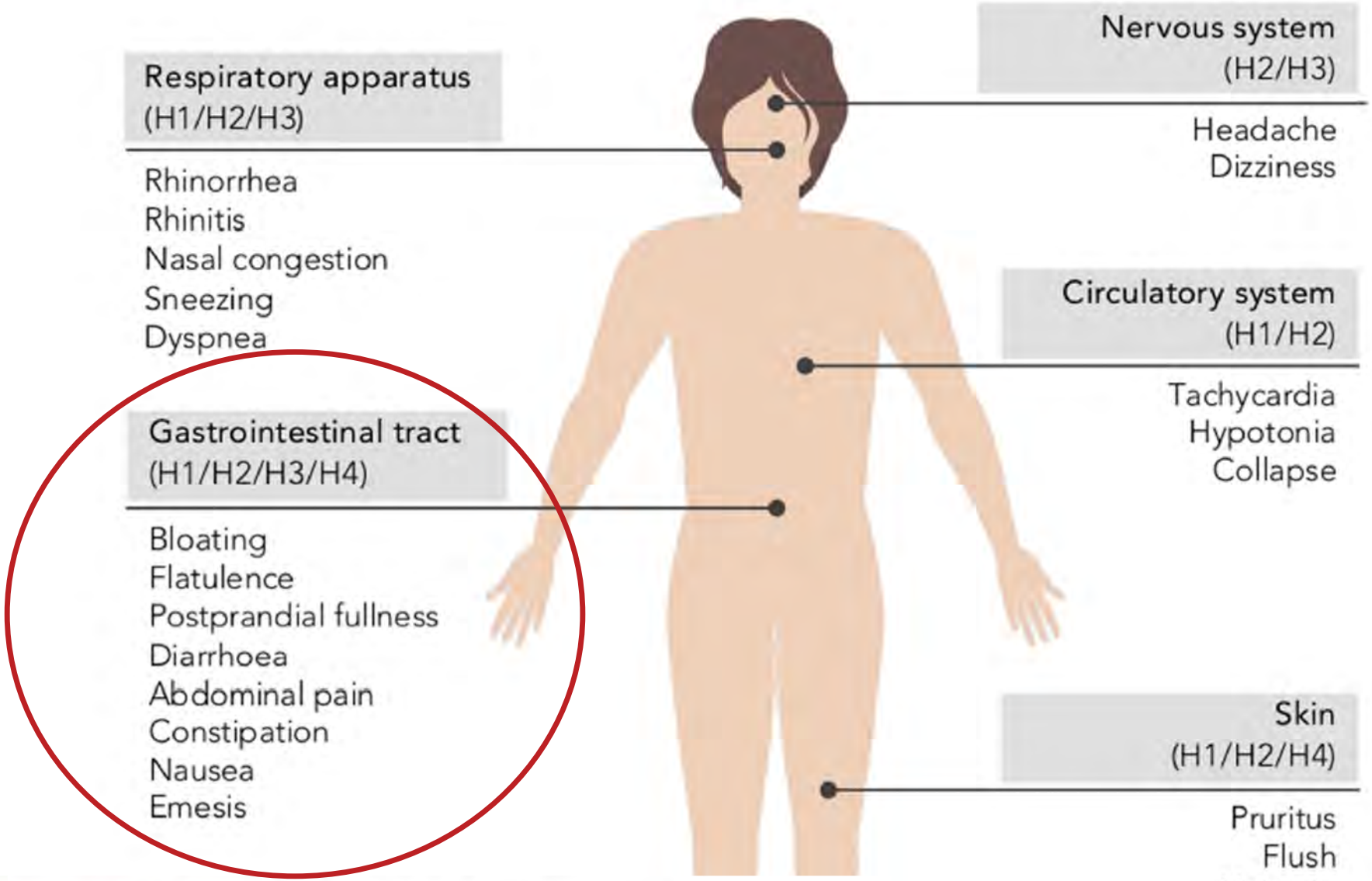
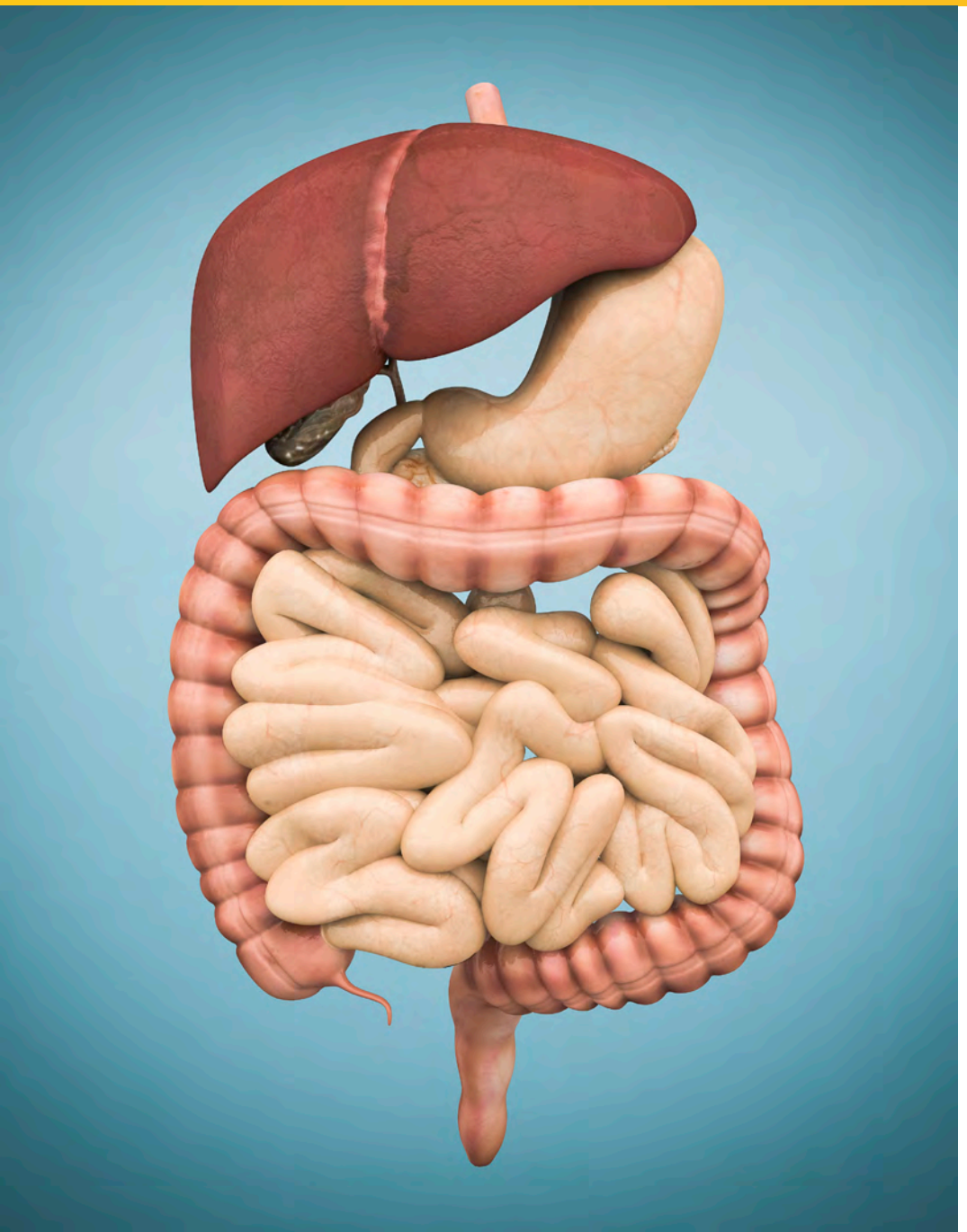
Giardiasis	Abdominal discomfort, bloating, diarrhea



Review > Biomolecules. 2020 Aug 14;10(8):1181. doi: 10.3390/biom10081181.

Histamine Intolerance: The Current State of the Art

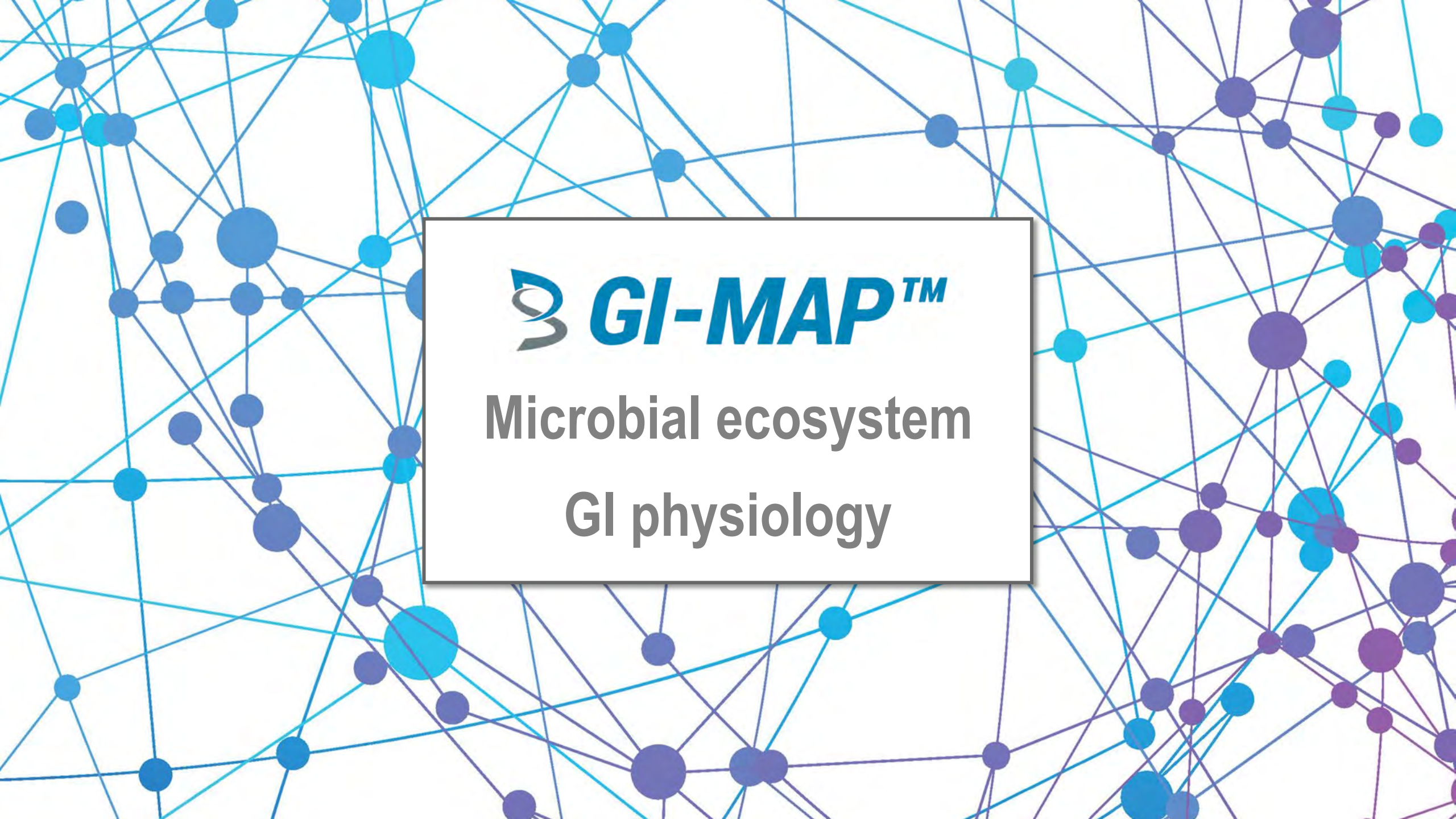


Common GI Symptoms: Key Causes & Contributors

Diet

Digestive Dysfunction
(+ digestive, immune, nervous system, etc.)

Dysbiosis

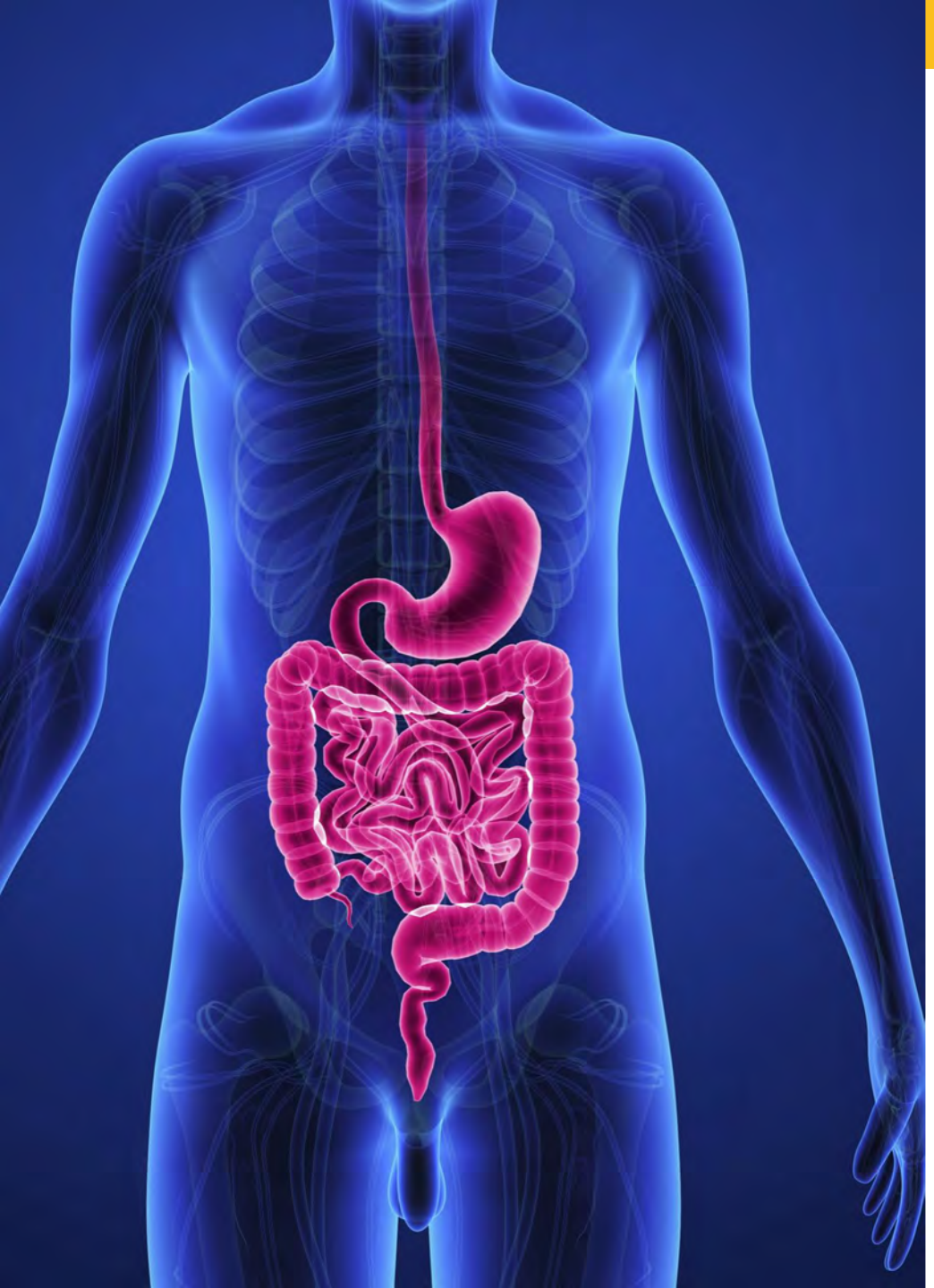

GI-MAP™
Microbial ecosystem
GI physiology

Common GI-MAP Dysbiosis Patterns

Insufficiency dysbiosis

Inflammatory dysbiosis

Digestive dysfunction dysbiosis



Digestive Dysfunction

Bile acid insufficiency

Pancreatic enzyme deficiency / EPI

Hypochlorhydria

Brush border enzyme deficiency
(small intestinal dysfunction)

Intestinal Health

Digestion	Result		Normal
Steatocrit	33	High	<15 %
Elastase-1	187	Low	>200 ug/g

GI Markers	Result	Normal
b-Glucuronidase	**1693**	<2486 U/mL
Occult Blood - FIT	**0**	<10 ug/g

Immune Response	Result		Normal
Secretory IgA	81	Low	510 - 2010 ug/g
Anti-gliadin IgA	**73**		0 - 157 U/L

Inflammation	Result	Normal
Calprotectin	**14**	<173 ug/g

H. pylori

	Result		Normal
Helicobacter pylori	6.9e3	High	<1.0e3
Virulence Factor, babA	**Negative**		Negative
Virulence Factor, cagA	**Positive**		Negative
Virulence Factor, dupA	**Negative**		Negative
Virulence Factor, iceA	**Negative**		Negative
Virulence Factor, oipA	**Positive**		Negative
Virulence Factor, vacA	**Negative**		Negative
Virulence Factor, virB	**Negative**		Negative
Virulence Factor, virD	**Negative**		Negative

Normal Bacterial Flora

	Result		Normal
Bacteroides fragilis	**1.68e10**		1.60e9 - 2.50e11
Bifidobacterium spp.	**1.99e10**		>6.70e7
Enterococcus spp.	**6.39e6**		1.9e5 - 2.00e8
Escherichia spp.	**4.36e6**		3.70e6 - 3.80e9
Lactobacillus spp.	**9.25e7**		8.6e5 - 6.20e8
Clostridia (class)	**2.03e8**	**High**	5.00e6 - 5.00e7
Enterobacter spp.	**2.73e8**	**High**	1.00e6 - 5.00e7
Akkermansia muciniphila	**2.61e5**	**High**	1.00e1 - 5.00e4
Faecalibacterium prausnitzii	**1.40e6**		1.00e3 - 5.00e8

Phyla Microbiota	Result		Normal
Bacteroidetes	**8.66e12**	**High**	8.61e11 - 3.31e12
Firmicutes	**4.46e11**	**High**	5.70e10 - 3.04e11
Firmicutes:Bacteroidetes Ratio	**0.05**		<1.00

Opportunistic Bacteria

Additional Dysbiotic/Overgrowth Bacteria	Result		Normal
Bacillus spp.	1.37e7	High	<1.50e5
Enterococcus faecalis	1.92e7	High	<1.00e4
Enterococcus faecium	5.39e4	High	<1.00e4
Morganella spp.	<dl		<1.00e3
Pseudomonas spp.	4.39e8	High	<1.00e4
Pseudomonas aeruginosa	3.49e5	High	<5.00e2
Staphylococcus spp.	<dl		<1.00e4
Staphylococcus aureus	2.06e3	High	<5.00e2
Streptococcus spp.	2.14e3	High	<1.00e3
Methanobacteriaceae (family)	1.55e9		<5.00e9

Potential Autoimmune Triggers	Result		Normal
Citrobacter spp.	<dl		<5.00e6
Citrobacter freundii	<dl		<5.00e5
Klelbsiella spp.	2.95e4	High	<5.00e3
Klebsiella pneumoniae	4.84e5	High	<5.00e4
Mycobacterium tuberculosis (avium)	<dl		<5.00e3
Prevotella copri	<dl		<1.00e7
Proteus spp.	<dl		<5.00e4
Proteus mirabilis	1.02e4	High	<1.00e3

Major Microbiome Products

Short-chain fatty acids

Gases

Bile acids & metabolites

Amino acid metabolites

Biogenic amines
(histamine, putrescine, tyramine, TMA, etc)

Disease	Symptoms
Bile-acid malabsorption	Diarrhea, urgency
Exocrine pancreatic insufficiency	Abdominal discomfort, bloating, diarrhea, greasy stools
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Giardiasis	Abdominal discomfort, bloating, diarrhea

Intestinal Health

Digestion	Result		Normal
Steatocrit	**<dl**		<15 %
Elastase-1	196	Low	>200 ug/g

GI Markers	Result	Normal
b-Glucuronidase	**874**	<2486 U/mL
Occult Blood - FIT	**1**	<10 ug/g

Immune Response	Result	Normal
Secretory IgA	**525**	510 - 2010 ug/g
Anti-gliadin IgA	**22**	0 - 157 U/L

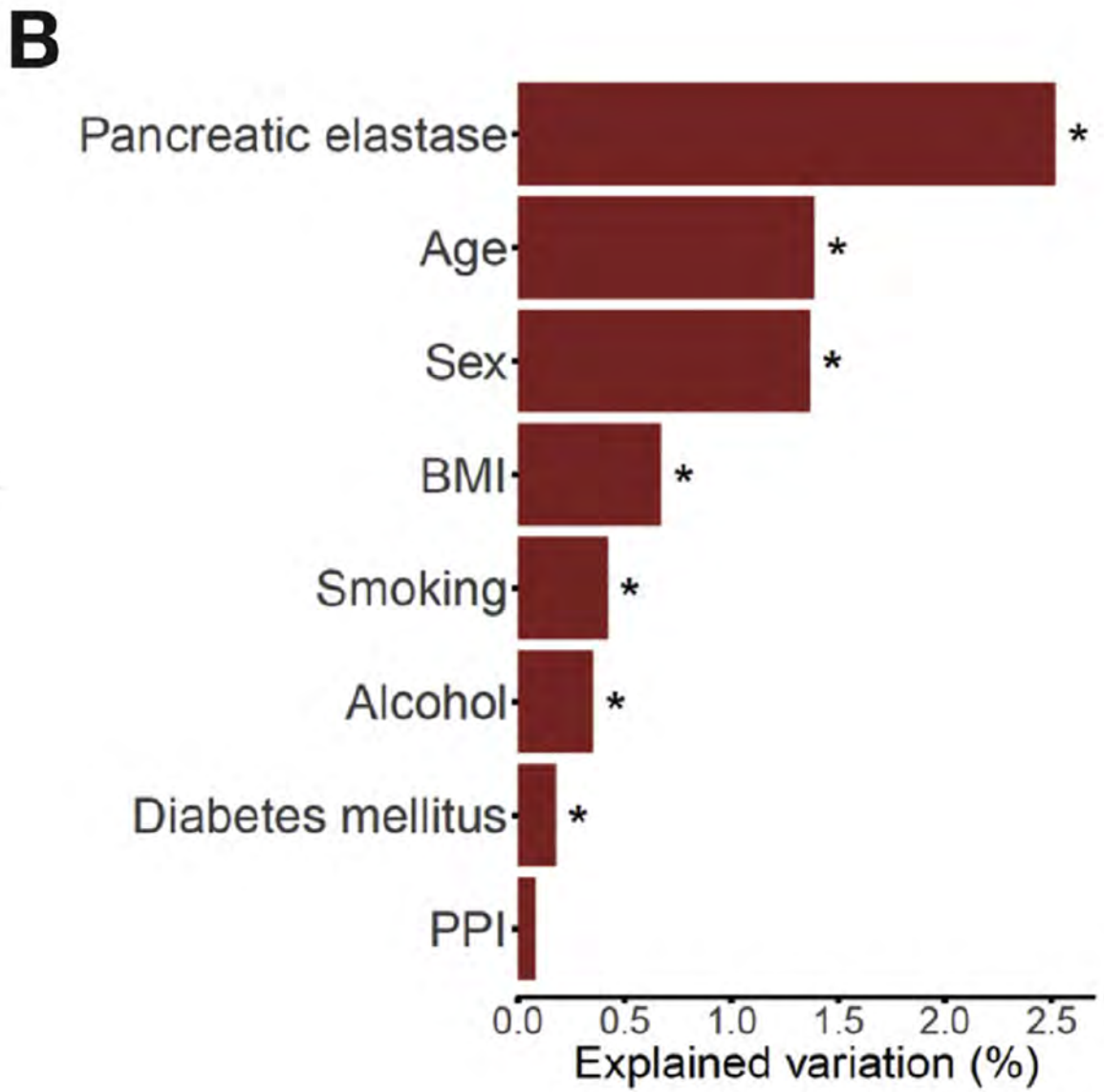
Inflammation	Result	Normal
Calprotectin	**22**	<173 ug/g

DR. KARA FITZGERALD

> Gastroenterology. 2019 Mar;156(4):1010-1015. doi: 10.1053/j.gastro.2018.10.047.
Epub 2018 Nov 2.

Impaired Exocrine Pancreatic Function Associates With Changes in Intestinal Microbiota Composition and Diversity

"To summarize, this is the first population-based study providing evidence that exocrine pancreatic function is the most important host factor involved in shaping the human intestinal microbiome known so far."


B
Pancreatic elastase
Age
Sex
BMI
Smoking
Alcohol
Diabetes mellitus
PPI
*
0.0
0.5
1.0
1.5
2.0
2.5
Explained variation (%)

Observational Study > Clin Transl Gastroenterol. 2020 Sep;11(9):e00232.
doi: 10.14309/ctg.0000000000000232.

The Gut Microbiome in Patients With Chronic Pancreatitis Is Characterized by Significant Dysbiosis and Overgrowth by Opportunistic Pathogens

"Patients with CP exhibited severely reduced microbial diversity (Shannon diversity index and Simpson diversity number, $P < 0.001$) with an increased abundance of facultative pathogenic organisms ($P < 0.001$) such as Enterococcus ($q < 0.001$), Streptococcus ($q < 0.001$), and Escherichia/Shigella ($q = 0.002$)."

> Aliment Pharmacol Ther. 2020 Mar;51(5):505-526. doi: 10.1111/apt.15604. Epub 2020 Jan 28.

Systematic review: the effects of proton pump inhibitors on the microbiome of the digestive tract–evidence from next-generation sequencing studies

- In a review of 19 eligible studies, higher levels of the following were found in stool of PPI users:
  - *Streptococcus*
  - *Enterococcus*
  - *Staphylococcus*
  - *Bacillus*
  - Lactobacillus
  - Enterobacteriaceae (E. coli, Klebsiella, etc.)

Opportunistic Bacteria

Additional Dysbiotic/Overgrowth Bacteria	Result		Normal
Bacillus spp.	1.37e7	High	<1.50e5
Enterococcus faecalis	1.92e7	High	<1.00e4
Enterococcus faecium	5.39e4	High	<1.00e4
Morganella spp.	<dl		<1.00e3
Pseudomonas spp.	4.39e8	High	<1.00e4
Pseudomonas aeruginosa	3.49e5	High	<5.00e2
Staphylococcus spp.	<dl		<1.00e4
Staphylococcus aureus	2.06e3	High	<5.00e2
Streptococcus spp.	2.14e3	High	<1.00e3
Methanobacteriaceae (family)	1.55e9		<5.00e9

Potential Autoimmune Triggers	Result		Normal
Citrobacter spp.	<dl		<5.00e6
Citrobacter freundii	<dl		<5.00e5
Klelbsiella spp.	2.95e4	High	<5.00e3
Klebsiella pneumoniae	4.84e5	High	<5.00e4
Mycobacterium tuberculosis (avium)	<dl		<5.00e3
Prevotella copri	<dl		<1.00e7
Proteus spp.	<dl		<5.00e4
Proteus mirabilis	1.02e4	High	<1.00e3

Normal Bacterial Flora

	Result		Normal
Bacteroides fragilis	**1.68e10**		1.60e9 - 2.50e11
Bifidobacterium spp.	**1.99e10**		>6.70e7
Enterococcus spp.	**6.39e6**		1.9e5 - 2.00e8
Escherichia spp.	**4.36e6**		3.70e6 - 3.80e9
Lactobacillus spp.	**9.25e7**		8.6e5 - 6.20e8
Clostridia (class)	**2.03e8**	**High**	5.00e6 - 5.00e7
Enterobacter spp.	**2.73e8**	**High**	1.00e6 - 5.00e7
Akkermansia muciniphila	**2.61e5**	**High**	1.00e1 - 5.00e4
Faecalibacterium prausnitzii	**1.40e6**		1.00e3 - 5.00e8

Phyla Microbiota	Result		Normal
Bacteroidetes	**8.66e12**	**High**	8.61e11 - 3.31e12
Firmicutes	**4.46e11**	**High**	5.70e10 - 3.04e11
Firmicutes:Bacteroidetes Ratio	**0.05**		<1.00

“Most patients chronically infected with H. pylori manifest a pan-gastritis with hypochlorhydria.”

Curr Top Microbiol Immunol. 2017;400:227-252. doi: 10.1007/978-3-319-50520-6_10.

Helicobacter pylori-Induced Changes in Gastric Acid Secretion and Upper Gastrointestinal Disease.

H. pylori

	Result		Normal
Helicobacter pylori	6.9e3	High	<1.0e3
Virulence Factor, babA	**Negative**		Negative
Virulence Factor, cagA	**Positive**		Negative
Virulence Factor, dupA	**Negative**		Negative
Virulence Factor, iceA	**Negative**		Negative
Virulence Factor, oipA	**Positive**		Negative
Virulence Factor, vacA	**Negative**		Negative
Virulence Factor, virB	**Negative**		Negative
Virulence Factor, virD	**Negative**		Negative

Disease	Symptoms
Bile-acid malabsorption	Diarrhea, urgency
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Celiac disease	Abdominal discomfort, bloating, diarrhea
Giardiasis	Abdominal discomfort, bloating, diarrhea

Review > Nat Rev Gastroenterol Hepatol. 2019 Dec;16(12):733-747.

Intestinal gases: influence on gut disorders and the role of dietary manipulations

Kourosh Kalantar-Zadeh[1]*, *Kyle J. Berean*[1,2,3], *Rebecca E. Burgell*[4], *Jane G. Muir*[4] and *Peter R. Gibson*[4]*

Abstract | The inner workings of the intestines, in which the body and microbiome intersect to influence gut function and systemic health, remain elusive. Carbon dioxide, hydrogen, methane and hydrogen sulfide, as well as a variety of trace gases, are generated by the chemical interactions and microbiota within the gut. Profiling of these intestinal gases and their responses to dietary changes can reveal the products and functions of the gut microbiota and their influence on human health. Indeed, different tools for measuring these intestinal gases have been developed, including newly developed gas-sensing capsule technology. Gases can, according to their type, concentration and volume, induce or relieve abdominal symptoms, and might also

Dietary disaccharides (such as lactose and sucrose) and oligosaccharides released from the amylase-mediated digestion of starch require digestion by brush border enzymes prior to absorption. Thus, their absorption fails when the activity of these enzymes is low, as occurs in lactase or sucrase–isomaltase deficiency[132]. Other oligosaccharides (such as fructo-oligosaccharides and galacto-oligosaccharides) and non-starch polysaccharides that are not digested due to the lack of suitable hydrolases in the small intestine are, therefore, not absorbed at all[133].

Unabsorbed carbohydrates reach the bacteria-rich colon, where they can be fermented. In general, carbohydrates of short chain lengths are fermented more rapidly than those with a long chain length (that is, those with a degree of polymerization (DP) of >10), yielding larger quantities of gas over a shorter period of time[99,134]. Non-

> Dig Dis Sci. 2020 Feb;65(2):534-540. doi: 10.1007/s10620-019-05780-7. Epub 2019 Sep 6.

Sucrase-Isomaltase Deficiency as a Potential Masquerader in Irritable Bowel Syndrome

"SID [sucrase-isomaltase deficiency] was found in 35% of patients with presumed IBS-D/M and should be considered in the differential diagnosis of patients presenting with abdominal pain, diarrhea, or bloating."

Review > Nutrients. 2021 Feb 9;13(2):575. doi: 10.3390/nu13020575.

Impact of Diet on Symptoms of the Irritable Bowel Syndrome

"FODMAPs, being poorly absorbed, enter the colon, where they are rapidly fermented. This can be readily visualised by MRI, which shows how the osmotically active fructose distends the small bowel with fluid and subsequently the colon, where it produces gas along with a rise in breath hydrogen."

> Gut Microbes. 2016 May 3;7(3):235-45. doi: 10.1080/19490976.2016.1182288.

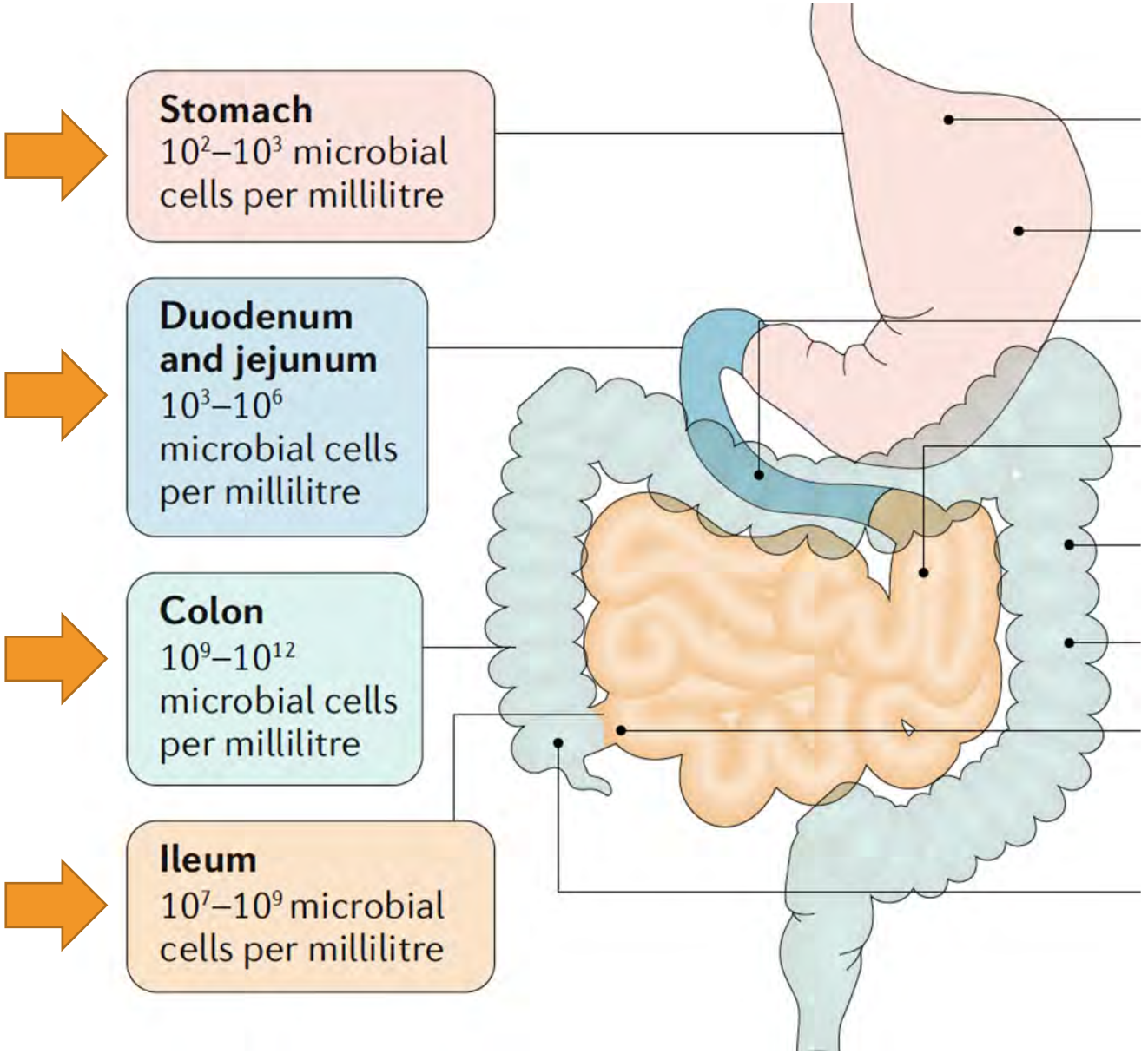
H2 metabolism is widespread and diverse among human colonic microbes

This study concluded that: “the predominant mechanism of H_2 evolution [production] in this ecosystem is through fermentative processes mediated by ***Bacteroidetes and Clostridial members of the Firmicutes***.”

Normal Bacterial Flora

	Result		Normal
Bacteroides fragilis	**1.68e10**		1.60e9 - 2.50e11
Bifidobacterium spp.	**1.99e10**		>6.70e7
Enterococcus spp.	**6.39e6**		1.9e5 - 2.00e8
Escherichia spp.	**4.36e6**		3.70e6 - 3.80e9
Lactobacillus spp.	**9.25e7**		8.6e5 - 6.20e8
Clostridia (class)	**2.03e8**	**High**	5.00e6 - 5.00e7
Enterobacter spp.	**2.73e8**	**High**	1.00e6 - 5.00e7
Akkermansia muciniphila	**2.61e5**	**High**	1.00e1 - 5.00e4
Faecalibacterium prausnitzii	**1.40e6**		1.00e3 - 5.00e8

Phyla Microbiota	Result		Normal
Bacteroidetes	**8.66e12**	**High**	8.61e11 - 3.31e12
Firmicutes	**4.46e11**	**High**	5.70e10 - 3.04e11
Firmicutes:Bacteroidetes Ratio	**0.05**		<1.00


Stomach
10^2–10^3 microbial cells per millilitre
Duodenum and jejunum
10^3–10^6 microbial cells per millilitre
Colon
10^9–10^{12} microbial cells per millilitre
Ileum
10^7–10^9 microbial cells per millilitre

Opportunistic Bacteria

Additional Dysbiotic/Overgrowth Bacteria	Result		Normal
Bacillus spp.	**6.47e4**		<1.50e5
Enterococcus faecalis	**<dl**		<1.00e4
Enterococcus faecium	**1.13e3**		<1.00e4
Morganella spp.	**<dl**		<1.00e3
Pseudomonas spp.	**2.45e5**	**High**	<1.00e4
Pseudomonas aeruginosa	**3.00e3**	**High**	<5.00e2
Staphylococcus spp.	**<dl**		<1.00e4
Staphylococcus aureus	**2.52e3**	**High**	<5.00e2
Streptococcus spp.	**2.17e4**	**High**	<1.00e3
Methanobacteriaceae (family)	**5.47e9**	**High**	<5.00e9

In the human gastrointestinal tract, *Methanobrevibacter smithii* is the major methanogen responsible for the conversion of CO_2 and H_2 into CH_4 (REF.[66]). The detection of CH_4 in the breath has led to classification of individuals as 'CH_4 producers' or 'CH_4 non-producers' (REF.[67]). However, as methanogens are still found in the faeces of many CH_4 non-producers[68], such a classification seems to be artificial, and the detection of CH_4 is probably related to whether sufficient levels are produced for detection in the breath. The existence of methanogens at concentrations of $>1 \times 10^8$ colony-forming units (CFU) per gram of stool has been suggested to be required to result in detectable levels of CH_4 in the breath[69,70].

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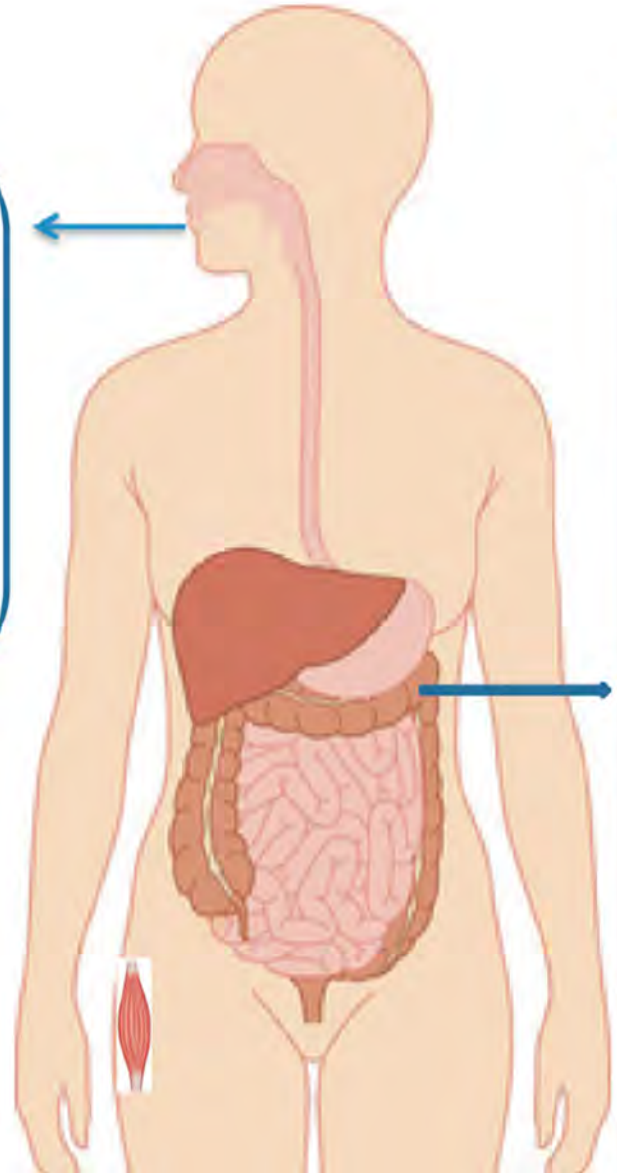
Human Microbiome Journal 3 (2017) 1–8

Archaea: Essential inhabitants of the human digestive microbiota

Oral cavity

Methanobrevibacter oralis (48%)
Methanobrevibacter smithii
Methanobrevibacter massiliense
Methanosarcinia mazei
Methanobacterium congolense
*Methanoculleus bourgensis**
Candidatus Nitrososphaera evergladensis*
*Methanomassilicoccus luminyensis**



Microbiota

Methanogens

Methanobreviacter smithii (94%)
Methanosphaera stadtmanae (27%)
Methanomassilicoccus luminyensis (4%)
Methanobrevibacter arboriphilicus
Methanobrevibacter oralis
Methanobrevibacter millerae
Methanocellus chikugoensis
Candidatus Methanomassilococcus intestinalis
Candidatus Methanomethylophilus alvus

Halophilic archaea

Haloferax massiliense
Haloferax alexandrinus
Halorubrum koreense
Halorubrum alimentarium
Halocuccus morrhuae
Halorubrum saccharovorum
Halorubrum sp.
Halorubrum norisence
Halorubrum orientale
Halorubrum kribbense
Halosimplex carisbadense
Halococcus sp.
Natrorubrum sp.

> Sci Rep. 2021 Jan 8;11(1):26. doi: 10.1038/s41598-020-79554-x.

Hydrogen–methane breath testing results influenced by oral hygiene

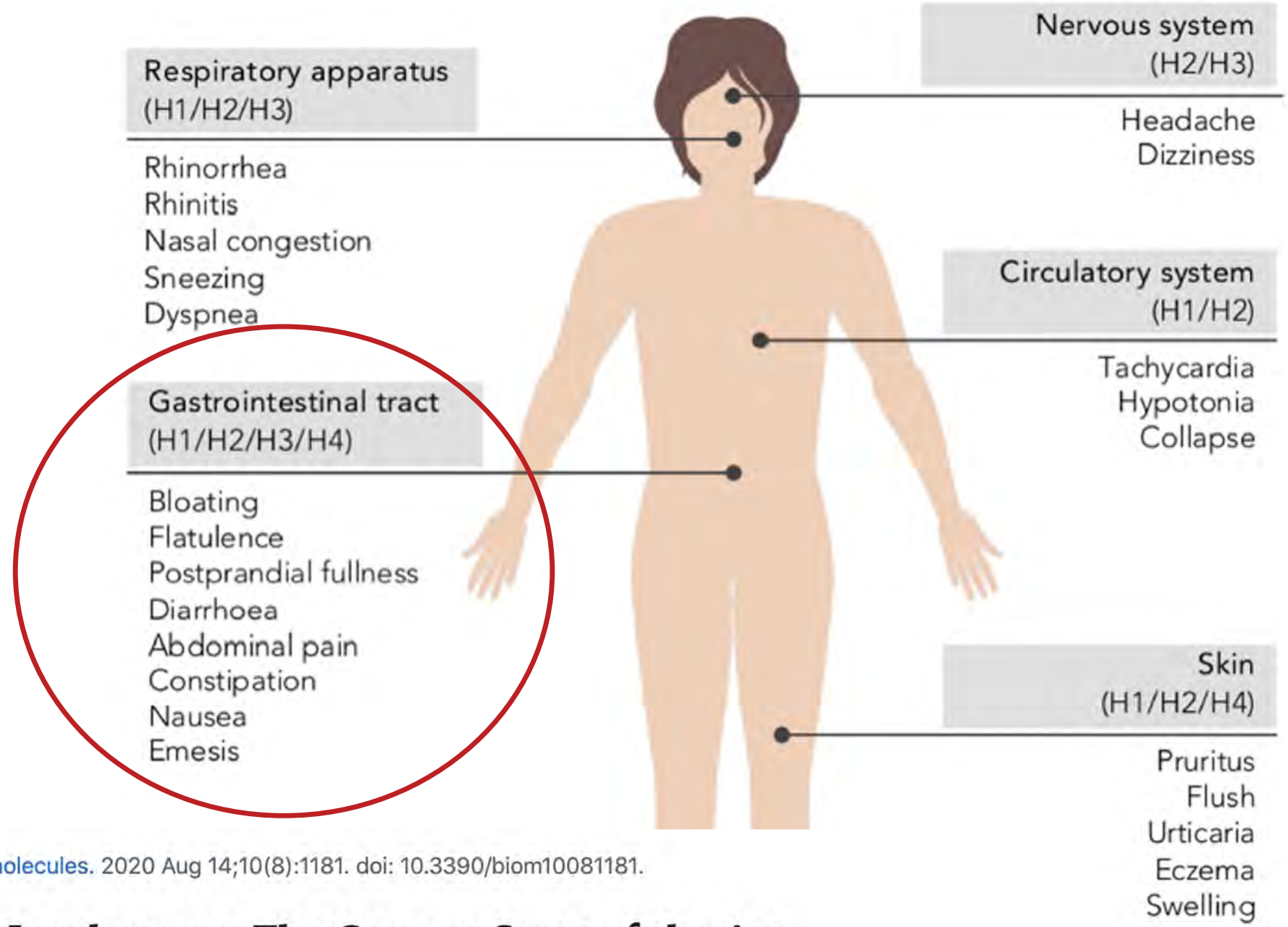
"Conclusion: Baseline elevations of expired hydrogen or methane seen in breath testing may be due to the oral microbiota, including methanogens. Variations in gas production such as those seen in this study has significant implications on test interpretation and subsequently on diagnosis."

Histamine & Histamine Intolerance

- Sensitivity to dietary histamine due to impaired histamine breakdown (intestinal diamine oxidase)
- Gut microbes & immune responses (mast cells) also contribute to histamine levels
- Symptom overlap with other common GI conditions

Brush Border Deficiencies

- Diamine oxidase (DAO) >> Histamine intolerance
- Disaccharidases >> carbohydrate intolerance
- Peptidases >> allergens, protein fermentation
- Intestinal alkaline phosphatase >> LPS
- Transporters for absorption



Review > Biomolecules. 2020 Aug 14;10(8):1181. doi: 10.3390/biom10081181.

Histamine Intolerance: The Current State of the Art

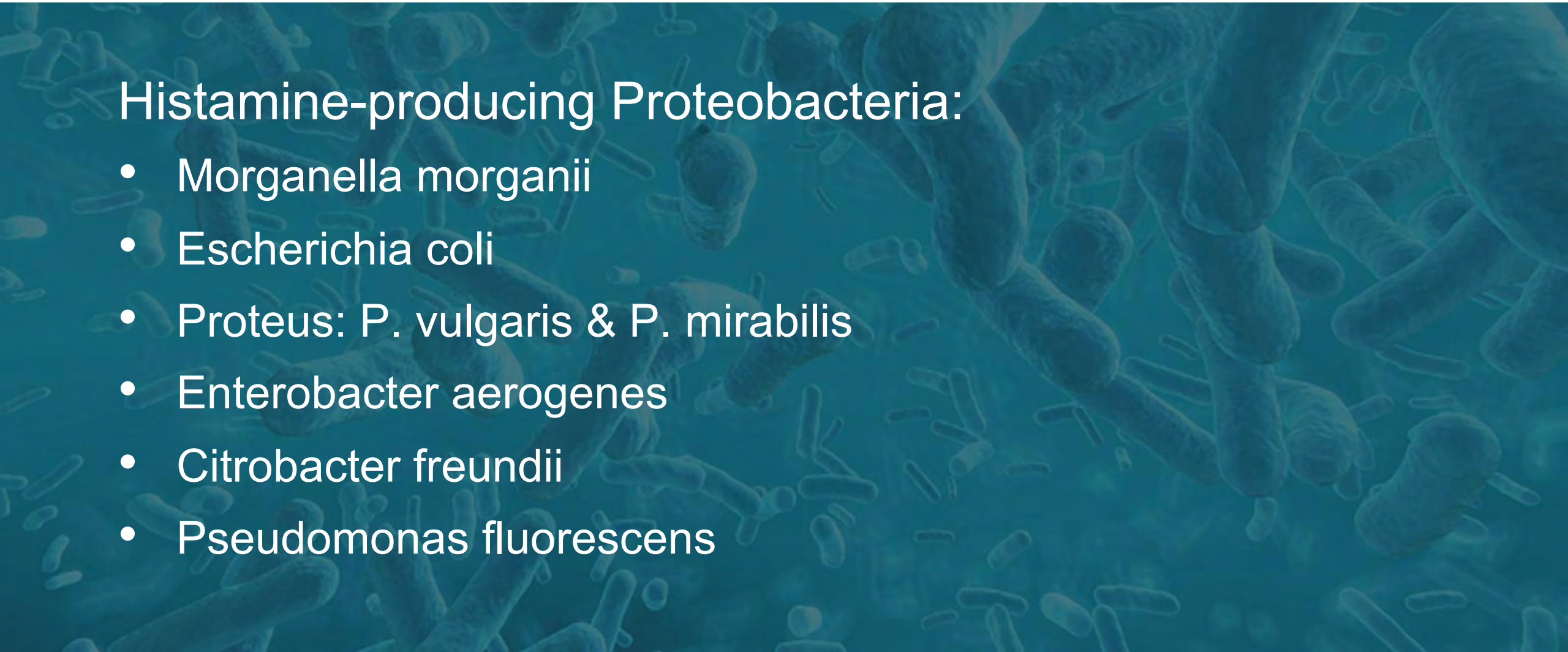
Review > Biomolecules. 2020 Aug 14;10(8):1181. doi: 10.3390/biom10081181.

Histamine Intolerance: The Current State of the Art

"Specifically, the Enterobacteriaceae species Hafnai aluei, Morganella morganii and Klebsiella pneumoniae have been identified as some of the most prolific histamine-forming bacteria ... "

Review > Curr Opin Immunol. 2017 Oct;48:108-113. doi: 10.1016/j.coi.2017.08.011.

Immune regulation by histamine and histamine-secreting bacteria



Histamine-producing Proteobacteria:

- Morganella morganii
- Escherichia coli
- Proteus: P. vulgaris & P. mirabilis
- Enterobacter aerogenes
- Citrobacter freundii
- Pseudomonas fluorescens

Normal Bacterial Flora

	Result		Normal
Bacteroides fragilis	**1.68e10**		1.60e9 - 2.50e11
Bifidobacterium spp.	**1.99e10**		>6.70e7
Enterococcus spp.	**6.39e6**		1.9e5 - 2.00e8
Escherichia spp.	**4.36e6**		3.70e6 - 3.80e9
Lactobacillus spp.	**9.25e7**		8.6e5 - 6.20e8
Clostridia (class)	**2.03e8**	**High**	5.00e6 - 5.00e7
Enterobacter spp.	**2.73e8**	**High**	1.00e6 - 5.00e7
Akkermansia muciniphila	**2.61e5**	**High**	1.00e1 - 5.00e4
Faecalibacterium prausnitzii	**1.40e6**		1.00e3 - 5.00e8

Phyla Microbiota	Result		Normal
Bacteroidetes	**8.66e12**	**High**	8.61e11 - 3.31e12
Firmicutes	**4.46e11**	**High**	5.70e10 - 3.04e11
Firmicutes:Bacteroidetes Ratio	**0.05**		<1.00

Opportunistic Bacteria

Additional Dysbiotic/Overgrowth Bacteria	Result		Normal
Bacillus spp.	5.86e5	High	<1.50e5
Enterococcus faecalis	<dl		<1.00e4
Enterococcus faecium	<dl		<1.00e4
Morganella spp.	1.69e5	High	<1.00e3
Pseudomonas spp.	3.35e6	High	<1.00e4
Pseudomonas aeruginosa	4.71e3	High	<5.00e2
Staphylococcus spp.	<dl		<1.00e4
Staphylococcus aureus	<dl		<5.00e2
Streptococcus spp.	3.22e3	High	<1.00e3
Methanobacteriaceae (family)	3.02e8		<5.00e9

Potential Autoimmune Triggers	Result		Normal
Citrobacter spp.	<dl		<5.00e6
Citrobacter freundii	<dl		<5.00e5
Klelbsiella spp.	2.95e4	High	<5.00e3
Klebsiella pneumoniae	4.84e5	High	<5.00e4
Mycobacterium tuberculosis (avium)	<dl		<5.00e3
Prevotella copri	<dl		<1.00e7
Proteus spp.	<dl		<5.00e4
Proteus mirabilis	1.02e4	High	<1.00e3

> Crit Rev Food Sci Nutr. 2020 Jul 9;1-8. doi: 10.1080/10408398.2020.1791049.

Considering histamine in functional gastrointestinal disorders

"There is an imprecise clinical overlap between irritable bowel syndrome (IBS) and other IBS-like disorders. … Generally, there is a lack of specificity of symptoms, therefore symptoms alone or symptom complexes are hardly, if ever, diagnostic. It is suspected that various pathogenetic mechanisms may be responsible for IBS. However, 80% of IBS patients identified food, including histamine, as a possible trigger for their symptoms."

> Can J Gastroenterol Hepatol. 2016;2016:4893501. doi: 10.1155/2016/4893501.
Epub 2016 Nov 30.

Concomitant Prevalence of Low Serum Diamine Oxidase Activity and Carbohydrate Malabsorption

"Interestingly, 89 out of 241 (36.9%) individuals with carbohydrate malabsorption were also diagnosed with HI."

"Mucosal damage in the small intestine caused by GI conditions …may reduce DAO and lactase activity, respectively."

Box 2 | Causes of small intestinal villous atrophy

Immune disorders

- Coeliac disease
- Autoimmune enteropathy
- Inflammatory bowel disease

Immune deficiencies

- Common variable immunodeficiency

Infections

- *Helicobacter pylori*
- Giardiasis
- Cryptosporidiosis
- HIV
- Viral gastroenteritis

Nutritional deficiencies

- Malnutrition
- Vitamin B_{12}, folic acid or zinc deficiencies

Malignancies

- Enteropathy-associated T cell lymphoma

Other

- Peptic duodenitis
- Eosinophilic gastroenteritis
- Olmesartan medication and other angiotensin II blockers
- NSAIDs
- Radiation and chemotherapy
- Allergy to cow's milk
- Small intestine bacterial overgrowth

Data are from REFS[104,219,220].

Nat Rev Dis Primers. 2019 Jan 10;5(1):4. doi: 10.1038/s41572-019-0059-2.

Coeliac disease.

Brush Border Deficiencies

- Diamine oxidase (DAO) >> Histamine intolerance
- Disaccharidases >> carbohydrate intolerance
- Peptidases >> allergens, protein fermentation
- Intestinal alkaline phosphatase >> LPS
- Transporters for absorption

Randomized Controlled Trial > Gut. 2017 Jul;66(7):1241-1251.

FODMAPs alter symptoms and the metabolome of patients with IBS: a randomised controlled trial

- Thirty-seven patients completed the 3-week diet (19 low-FODMAP, 18 high-FODMAP).
- Lactulose breath tests showed a minor decrease in H2 production in the low FODMAP compared with the high FODMAP group.
- Histamine, a measure of immune activation, was reduced eightfold in the low FODMAP group ($p<0.05$)

Summary: Key Topics

- Common GI symptoms & conditions involving symptoms that overlap with SIBO & IBS
- Underlying causes & contributors: digestive deficiencies, dysbiosis, & diet
- Key insights from advanced stool testing
- Evolving perspectives and clinical implications

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NATURE COMMUNICATIONS | (2019)10:2012 |

ARTICLE

https://doi.org/10.1038/s41467-019-09964-7 OPEN

Small intestinal microbial dysbiosis underlies symptoms associated with functional gastrointestinal disorders

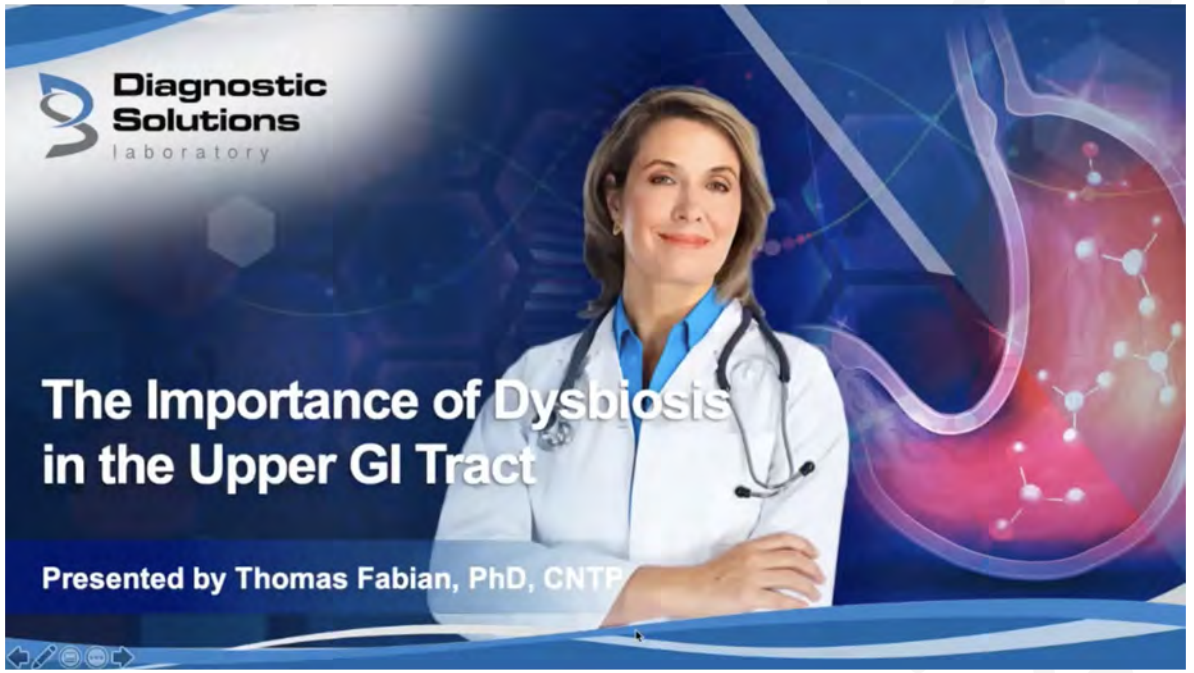
George B. Saffouri[1,14], Robin R. Shields-Cutler[2,3,14], Jun Chen[4], Yi Yang[5], Heather R. Lekatz[1], Vanessa L. Hale[6], Janice M. Cho[7], Eric J. Battaglioli[1], Yogesh Bhattarai[1], Kevin J. Thompson[4], Krishna K. Kalari[4], Gaurav Behera[1], Jonathan C. Berry[8], Stephanie A. Peters[1], Robin Patel[8], Audrey N. Schuetz[8], Jeremiah J. Faith[9], Michael Camilleri[1,10], Justin L. Sonnenburg[11], Gianrico Farrugia[12], Jonathan R. Swann[5], Madhusudan Grover[1,10], Dan Knights[2,13] & Purna C. Kashyap[1,10]

Small intestinal bacterial overgrowth (SIBO) has been implicated in symptoms associated with functional gastrointestinal disorders (FGIDs), though mechanisms remain poorly defined and treatment involves non-specific antibiotics. Here we show that SIBO based on duodenal aspirate culture reflects an overgrowth of anaerobes, does not correspond with patient

Upper GI / Small Intestine Dysbiosis

- H. pylori
- Giardia
- Cryptosporidium
- Enterotoxigenic E. coli
- Vibrio cholerae
- Yersinia enterocolitica
- Norovirus
- Ancyclostoma duodenale
- Necator americanus

- Candida
- Streptococcus
- Lactobacillus
- Pseudomonas
- Staphylococcus
- Klebsiella
- Citrobacter
- Enterobacter (+ colon)
- Fusobacterium
- E. coli (+ colon)



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Integrative Perspective

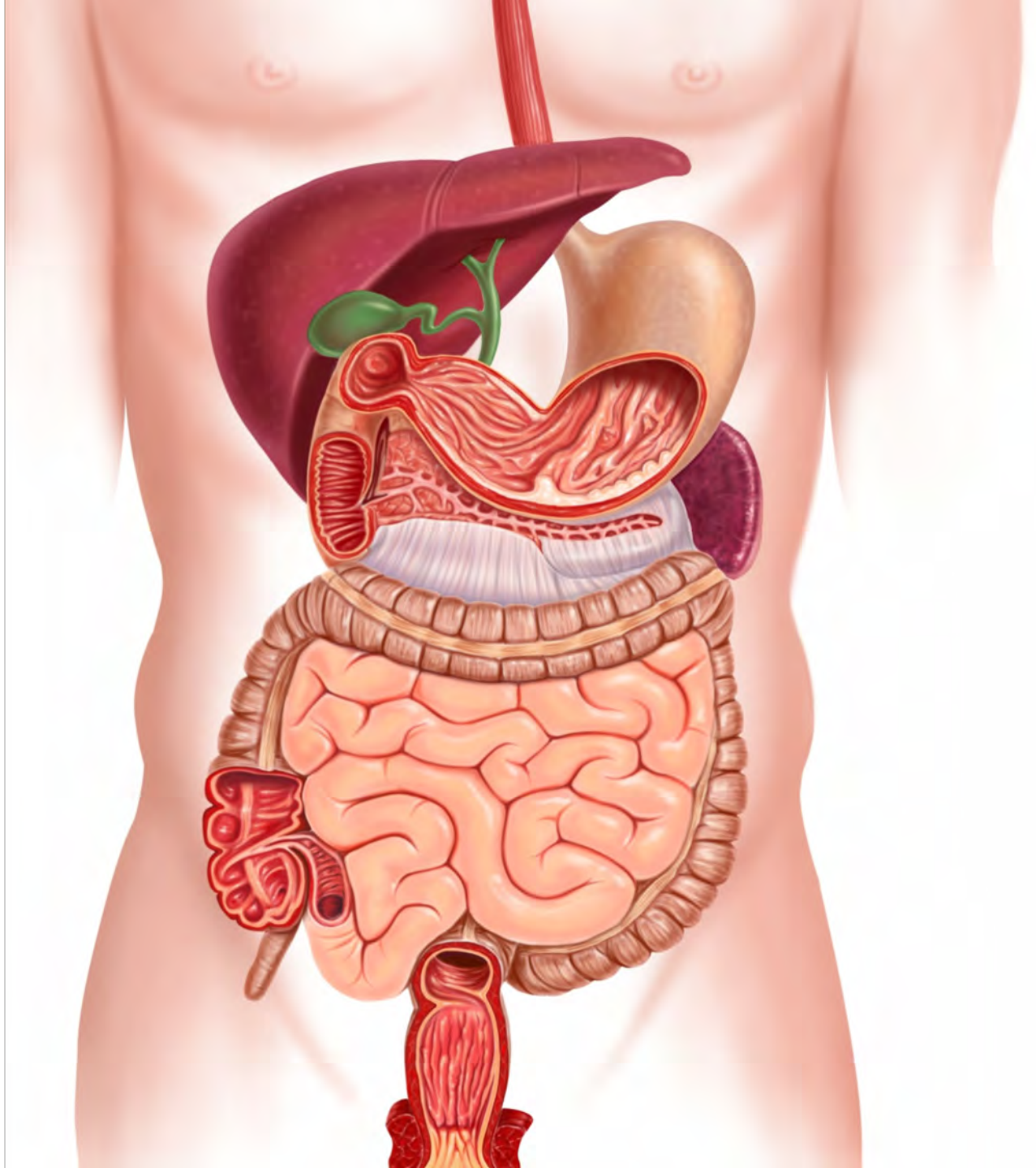
Oral cavity

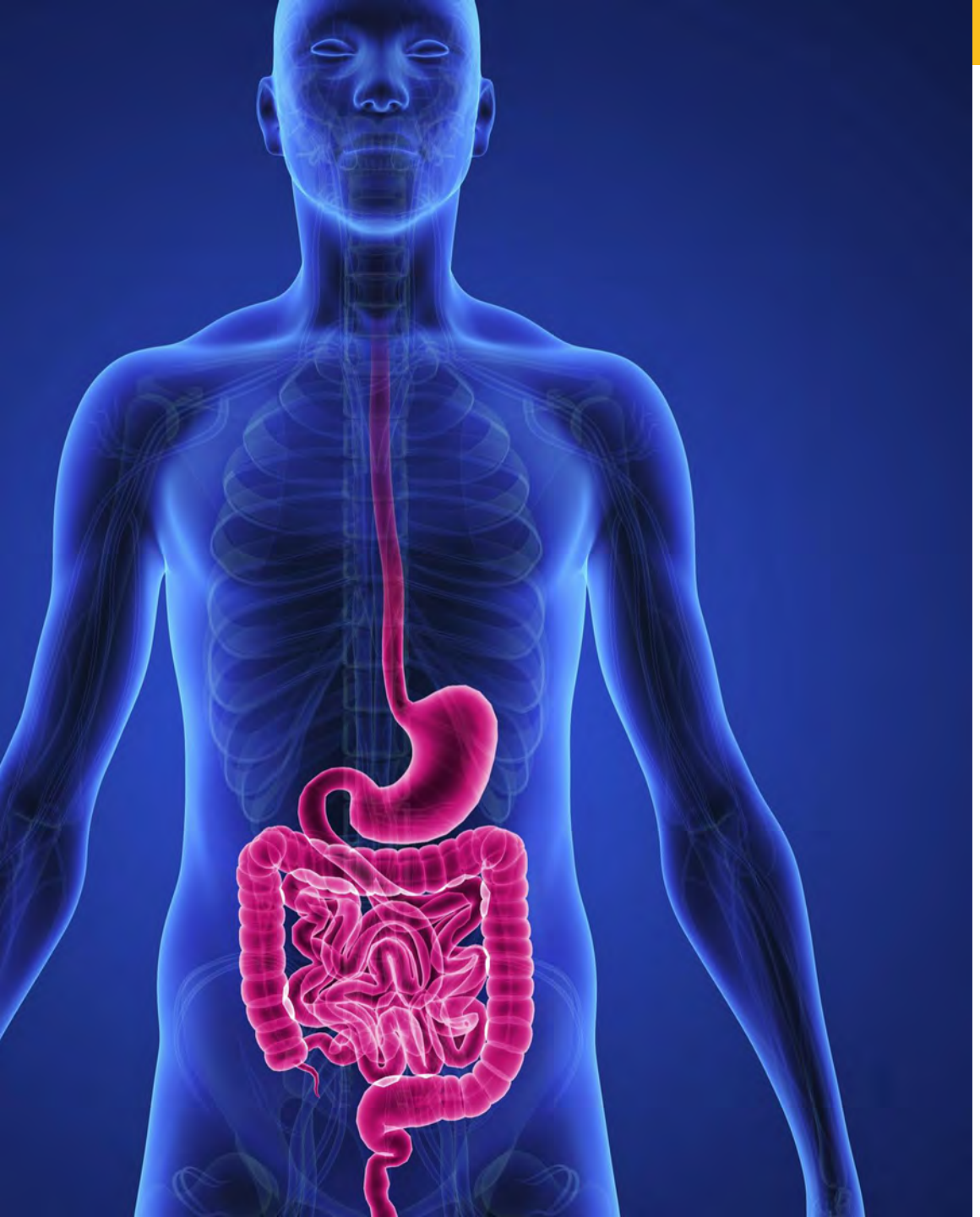
Stomach

Small intestine

Large intestine

Systemic





Causes & Contributors: Implications for Treatment

Diet

Dysbiosis

Digestive Dysfunction
(+ immune, nervous system, etc.)

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Bonus! PDF Companion Guide

This exclusive resource for practitioners guides on common functional groups of microbes on GI-MAP that are related to common GI symptoms, including:

- ✓ Bacteria associated with hypochlorhydria and low pancreatic enzymes
- ✓ Histamine-producing bacteria
- ✓ Gas-producing microbes:
  - ➢ Hydrogen
  - ➢ Methane
  - ➢ Hydrogen sulfide

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Thank you!

Additional resources:

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