IBS and Specialty Diagnostics

Practical Tools to Support Clinical Management

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Goals for the Conversation

- IBS as a model of common, chronic illness
  - Defining IBS and its impact
  - Exploring the Differential Diagnosis & Associated Disease States
- Conventional Diagnostics & Treatments
- Functional Diagnostics & Treatments
  - 'DIG' framework
  - Clinical Utility of Stool Based Biomarker for IBS
  - Additional Diagnostic considerations: GI, Immune, Nutritional
- Functional Testing & Outcomes Research

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Medical maxim …

“Death begins in the colon.”

Practical application …

“When in doubt, treat the gut.”

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IBS as a Common Chronic Illness: Impact on Patients

What is IBS?

Signs and Symptoms

Clinical Impact

IBS Statistics

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What is IBS? Irritable Bowel Syndrome

- Irritable bowel syndrome or IBS affects up to 55 million Americans, mostly women. To date there has been no single cause of IBS indentified, it is thought to have many potential underlying causes.
- Considered a functional gastrointestinal disorder (FGIDs), disorders of the digestive system in which symptoms cannot be explained by the presence of structural or tissue abnormality.
- Signs and Symptoms are often similar to those of IBD, however it is not considered an inflammatory disease.

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What is IBS?

- Rome III Criteria for diagnosis of IBS:
  - Recurrent abdominal pain or discomfort** at least 3 days/month in the last 3 months associated with *two or more* of the following:
    - Improvement with defecation
    - Onset associated with a change in frequency of stool
    - Onset associated with a change in form (appearance) of stool
  - The criteria must be fulfilled for at least the past 3 months with symptom onset at least 6 months prior to diagnosis

  ** "Discomfort" means an uncomfortable sensation not described as pain.

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Drossman DA. The functional gastrointestinal disorders and the Rome III process. *Gastroenterology.* Apr 2006;130(5):1377-1390.

What is IBS?

- Some clinicians view IBS as a ‘diagnosis of exclusion’, meaning after an extensive workup, after everything else has been ruled out, they are left with a diagnosis of IBS.
- Classifications:
  - IBS-D: Diarrhea predominant
  - IBS-C: Constipation predominant
  - IBS-M: Alternating or mixed constipation and diarrhea
  - IBS-U: Unable to meet criteria
- Tends to be more common in
  - People who have a history of physical or sexual abuse or other psychological trauma.
  - People with other conditions such as depression, migraines, and fibromyalgia.

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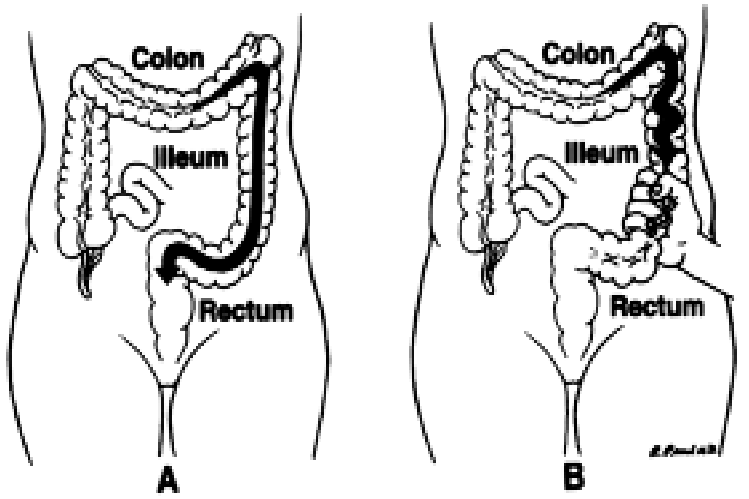
Spiegel BM, Farid M, Esrailian E, Talley J, Chang L. Is irritable bowel syndrome a diagnosis of exclusion?: a survey of primary care providers, gastroenterologists, and IBS experts. *The American journal of gastroenterology.* Apr 2010;105(4):848-858.
http://digestive.niddk.nih.gov/ddiseases/pubs/ibs/

IBS Signs and Symptoms

- Abdominal pain or discomfort
- Diarrhea/ loose or watery stools
- Constipation/ hard or lumpy stools
- Feeling of incomplete bowel movement
- Passing mucous
- Abdominal bloating and distension
- Urgency
- Straining during a bowel movement

Classifications:

- IBS-D: Diarrhea predominant
- IBS-C: Constipation predominant
- IBS-M: Alternating or mixed constipation and diarrhea
- IBS-U: Unable to meet criteria



Although there is no physical obstruction, a patient may perceive cramps or functional blockage.

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http://digestive.niddk.nih.gov/ddiseases/pubs/ibs/

Clinical Impact

IBS symptoms are not well controlled in most patients.

- No single well established therapy is available
- Patients typically report extensive self-experimentation

Evaluation and management of IBS is unstructured, prolonged, and frustrating.

- Patients typically report that years elapsed between first onset of symptoms and final diagnosis of IBS
- Leads to “doctor-shopping” for more testing

"I'm afraid that your irritable bowel syndrome has progressed. You now have furious and vindictive bowel syndrome."

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Major Clinical Impact

A 2002 study found that two-thirds to three-quarters of patients still had IBS 10 years later.

Cash B and Chey W. Diagnosis of Irritable Bowel Syndrome. *Practical Gastroenterology*, 2002.

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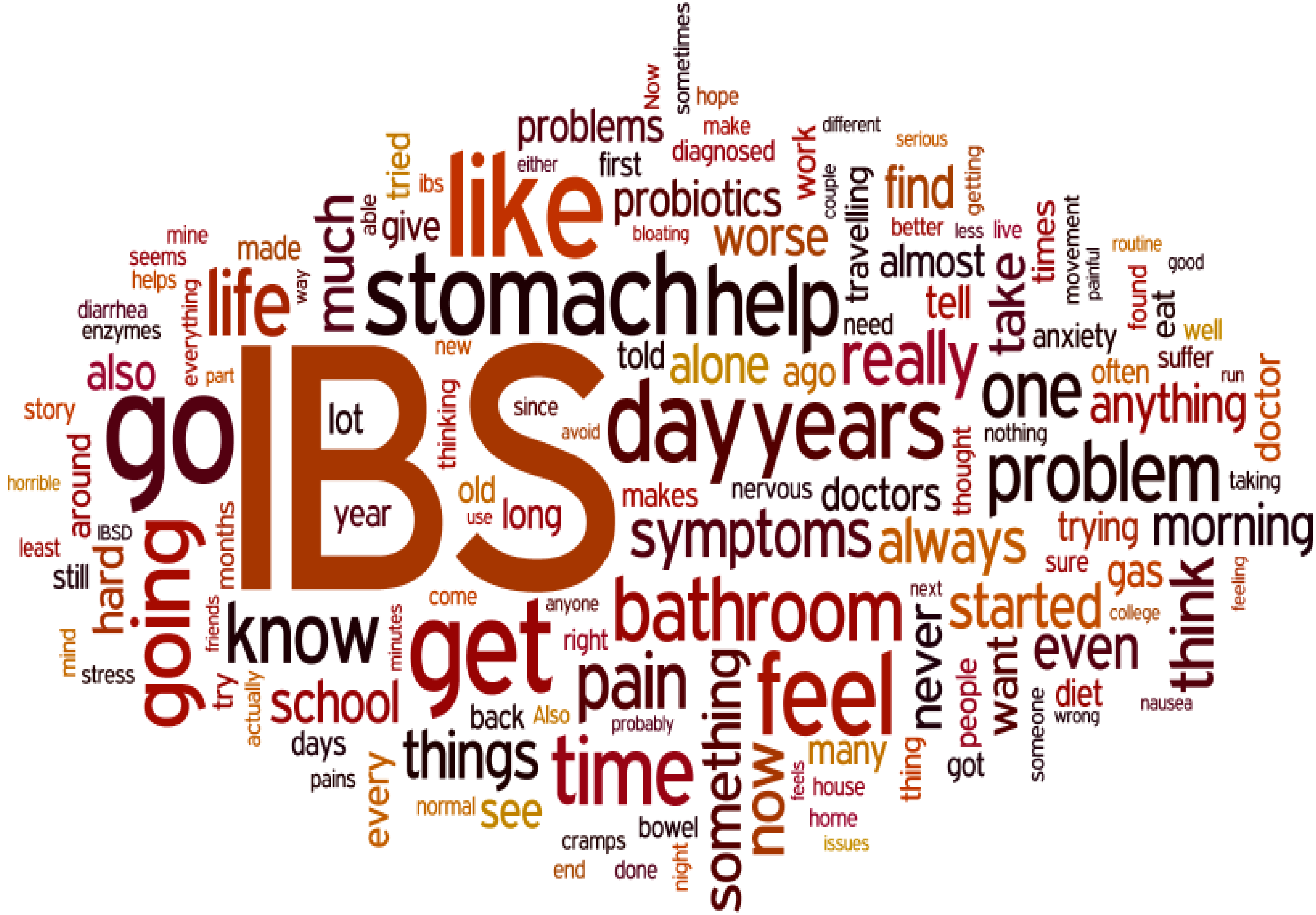

IBS
stomach
help
like
go
day
years
going
get
feel
bathroom
know
time
problem
one
life
much
probiotics
problems
worse
find
really
symptoms
always
things
pain
something
now
think
morning
anything
started
even
school
take
almost
alone
also
doctors
doctor
never
want
sometimes
Now
hope
make
diagnosed
work
different
serious
first
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bloating
couple
travelling
getting
better
less
live
times
movement
painful
routine
good
mine
seems
helps
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way
everything
diarrhea
enzymes
tell
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anxiety
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new
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ago
suffer
often
run
story
part
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avoid
thinking
nothing
taking
horrible
around
thought
year
old
use
long
makes
nervous
trying
IBSD
least
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sure
gas
feeling
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treatment
therapy
chronic
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care
medical
psychiatric
syndrome
irritable
successful
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illness
anxiety
difficult
results
bowel
well
bring
cognitive-behavioural
utilization
perceived
multiple
management
doubt
coexisting
complaints
Bowel
pain
intensity
stepped
Nevertheless
also
approach
investigations
presenting
Anxiety
encounters
Somatic
severity
effective
unexplained
existed
syndromes
thought
common
outpatient
Syndrome
depressive
strongly
described
expects
recent
global
useful
physician
multicomponent
initially
co-morbidity
recurrent
review
leading
psychology
visits
etc
good
primary
headache
unknown
different
predictors
Antidepressants
comorbidity
reason
fibromyalgia
cause
least
stress
interdisciplinary
approaches
higher
hypersensitivity
Depression
psychotherapeutic
include
medically
Hypnotherapy
healthcare
etiology
epidemiology
symptom
best
errors
Psychoanalysis
Unexplained
colonic
predominant
self-rated
difficulty
added
obtained
functional
lower
high
methodological
cognitive
Diverse
Medicine
Irritable
option
number
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consists
health
Patients
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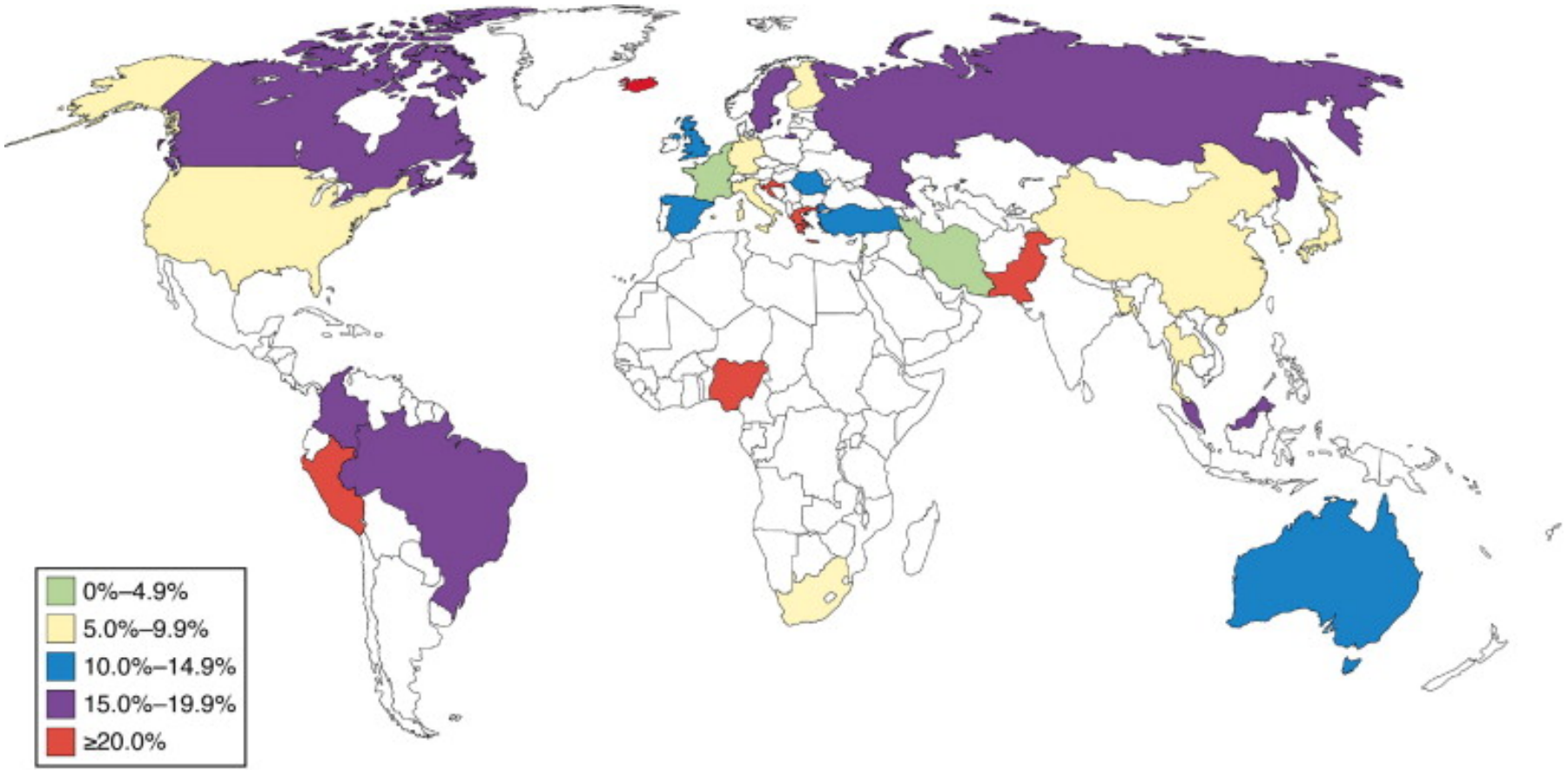
three
vision
phases
put

IBS Statistics- Prevalence according to country



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Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. *Clin Gastroenterol Hepatol*, 2012 Jul;10(7):712-721.e4.

IBS Statistics

20%

IBS affects up to 20% of Americans, affecting those in their prime years of productivity and employment[1]

55M

IBS sufferers in the US, making IBS the 4th most prevalent GI condition[2]

$20 Billion

Annual direct and indirect costs of IBS in the US[3]

#2

IBS is the second leading cause of workplace absenteeism, behind only the common cold[1]

[1]Cash B, Sullivan S, Barghout V. Total costs of IBS: employer and managed care perspective. *The American journal of managed care.* Apr 2005;11(1 Suppl):S7-16.

[2]Sandler RS, Everhart JE, Donowitz M, et al. The burden of selected digestive diseases in the United States. *Gastroenterology.* May 2002;122(5):1500-1511.

[3]Brandt LJ, Chey WD, Foxx-Orenstein AE, et al. An evidence-based position statement on the management of irritable bowel syndrome. *The American Journal of Gastroenterology.* Jan 2009;104 Suppl 1:S1-35.

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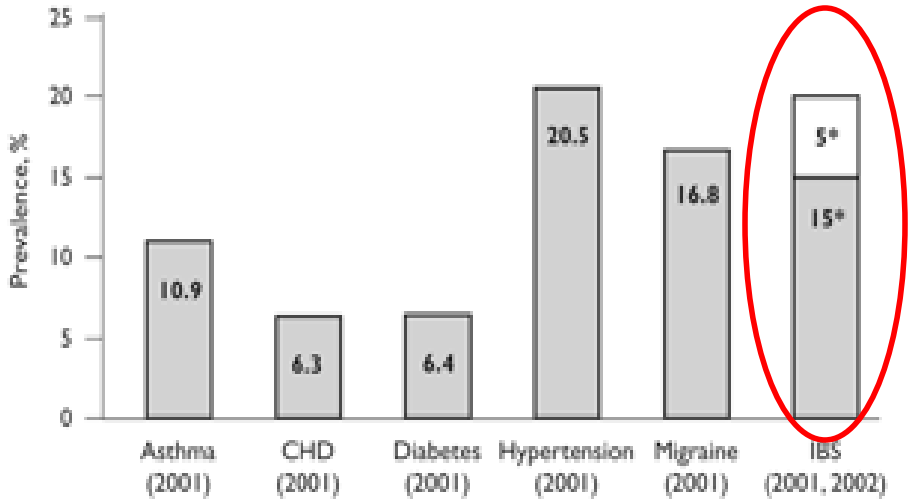
IBS Compared to Other Conditions

Figure 1. Prevalence of Common Long-term Conditions in the United States



*IBS prevalence is depicted as a range, with 15% as an accepted consensus value and an additional 5% to total 20%, as has been found in some studies. CHD indicates coronary heart disease; IBS, irritable bowel syndrome.

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Cash B, Sullivan S, Barghout V. Total costs of IBS: employer and managed care perspective. *The American journal of managed care.* Apr 2005;11(1 Suppl):S7-16.

Patient Impact

- IBS is a clinical diagnosis (based on ROME III criteria).
- IBS is a prevalent and costly condition.
  - Affects up to 20% of Americans
  - Higher prevalence than asthma or diabetes
  - $20 billion annual direct and indirect costs
- IBS symptoms are not well controlled in most patients.
- Evaluation and management of IBS is unstructured, prolonged, and frustrating for both patients and clinicians.

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Conventional Diagnostics

Differential Diagnosis

Labs

Standard Treatment

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Diagnosis of IBS

- Diagnosis based on identifying positive symptoms (i.e. ROME III Criteria)

- Diagnostic studies may include stool (ova and parasites, occult blood), full blood count, sedimentation rate, thyroid function tests and serum chemistries.
- Other diagnostic studies will depend on the symptom subtype.
  - IBS-C Evaluation for obstruction
  - IBS-D Lactose Intolerance, Celiac

- Some clinicians view IBS as a 'diagnosis of exclusion', meaning after an extensive workup, after everything else has been ruled out, they are left with a diagnosis of IBS.

IBS: Differential Diagnosis

Maldigestion/ Malabsorption
- Celiac disease
- Pancreatic insufficiency

Dietary Factors
- Lactose Intolerance
- Caffeine, EtOH, Fats
- Gas-producing foods

Infection
- Bacteria
- Parasites
- Candida

IBD
- UC/ Crohns
- Microscopic Colitis
- C. Difficile

Psychologic Disorders
- Anxiety/ Panic
- Depression
- Somatization

NeuroEndocrine Change
- Visceral Sensitivity
- Intestinal Contractility

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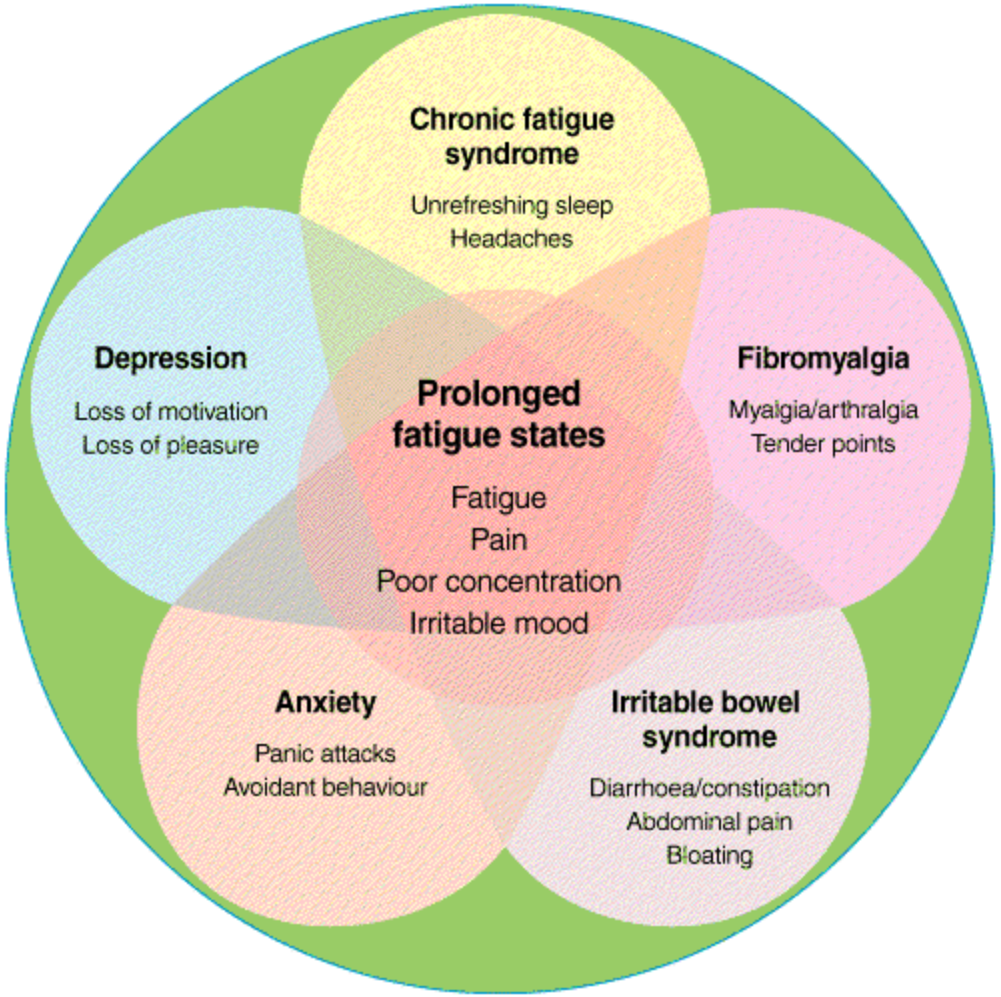
Associated Disease States



[5]

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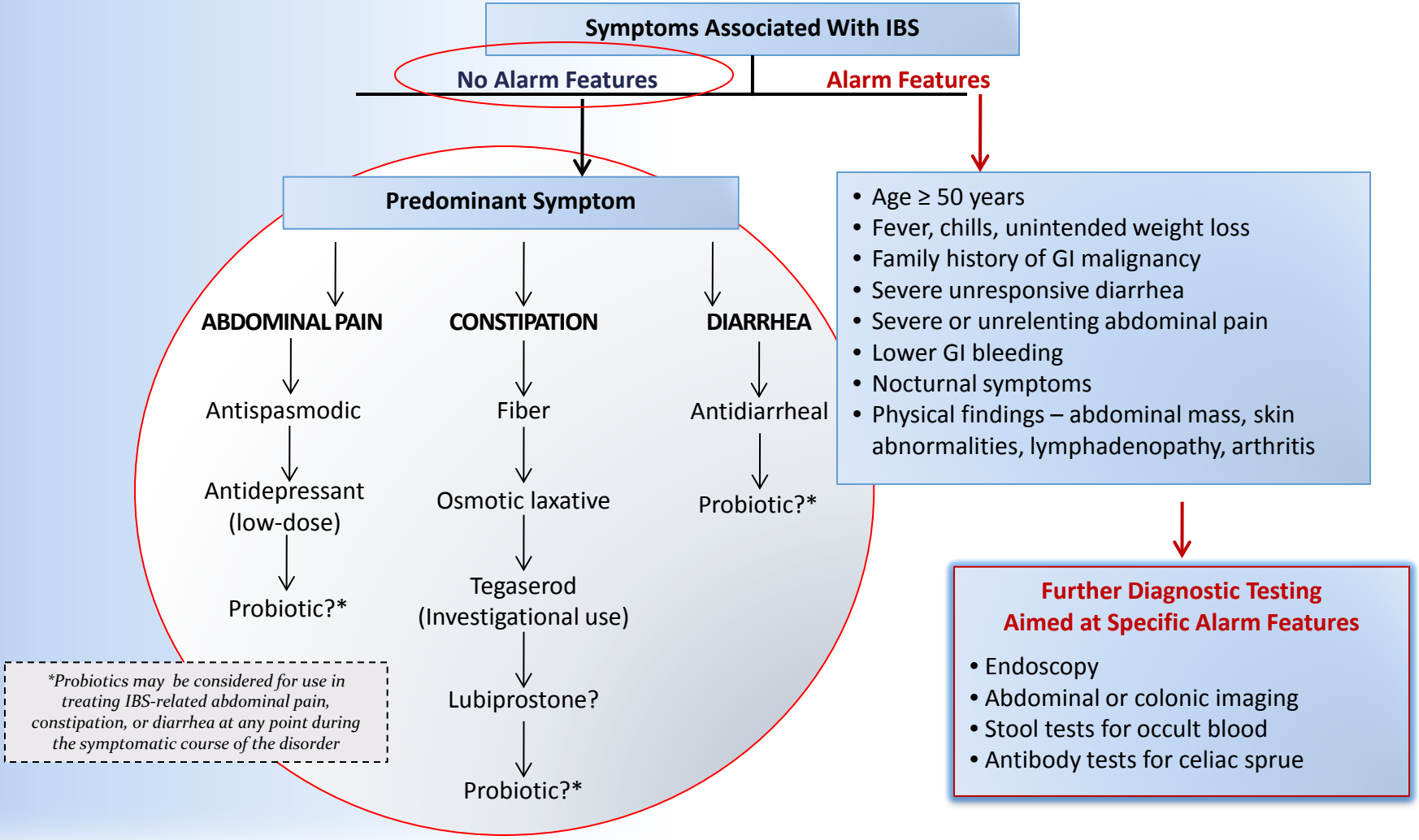
Approach to the patient with suspected IBS



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Flowchart Source: Cash BD, Chey WD., *Gastroenterology Clinical North Am*. 34 (2005): 205-220
Cash BD, Furman DL. "The Role of Diagnostic Testing in Irritable Bowel Syndrome". *Gastroenterology Clinical North Am.* 40 (2011) 105-119

IBS Workup

- GI-specific procedures are performed at high rates in patients with IBS to exclude low prevalence, but serious conditions
- Over 95% of GI specific procedures are normal in patients with IBS

	IBS	Control
Radiologic Tests		
Abdominal X-ray	30,249 (21.4%)	12,791 (9.1%)
Barium enema	23,960 (17.0%)	5,767 (4.1%)
Computed tomography, pelvis	27,900 (19.7%)	12,666 (9.0%)
Computed tomography, abdomen	32,206 (22.8%)	14,671 (10.4%)
Magnetic resonance imaging, pelvis	699 (0.5%)	449 (0.3%)
Magnetic resonance imaging, abdomen	675 (0.5%)	317 (0.2%)
Ultrasound, pelvis	36,797 (26.0%)	21,194 (15.0%)
Ultrasound, abdomen	49,857 (35.3%)	22,440 (15.9%)
Upper gastrointestinal series	18,734 (13.3%)	5,334 (3.8%)
Small bowel follow-through	5,903 (4.2%)	1,065 (0.8%)

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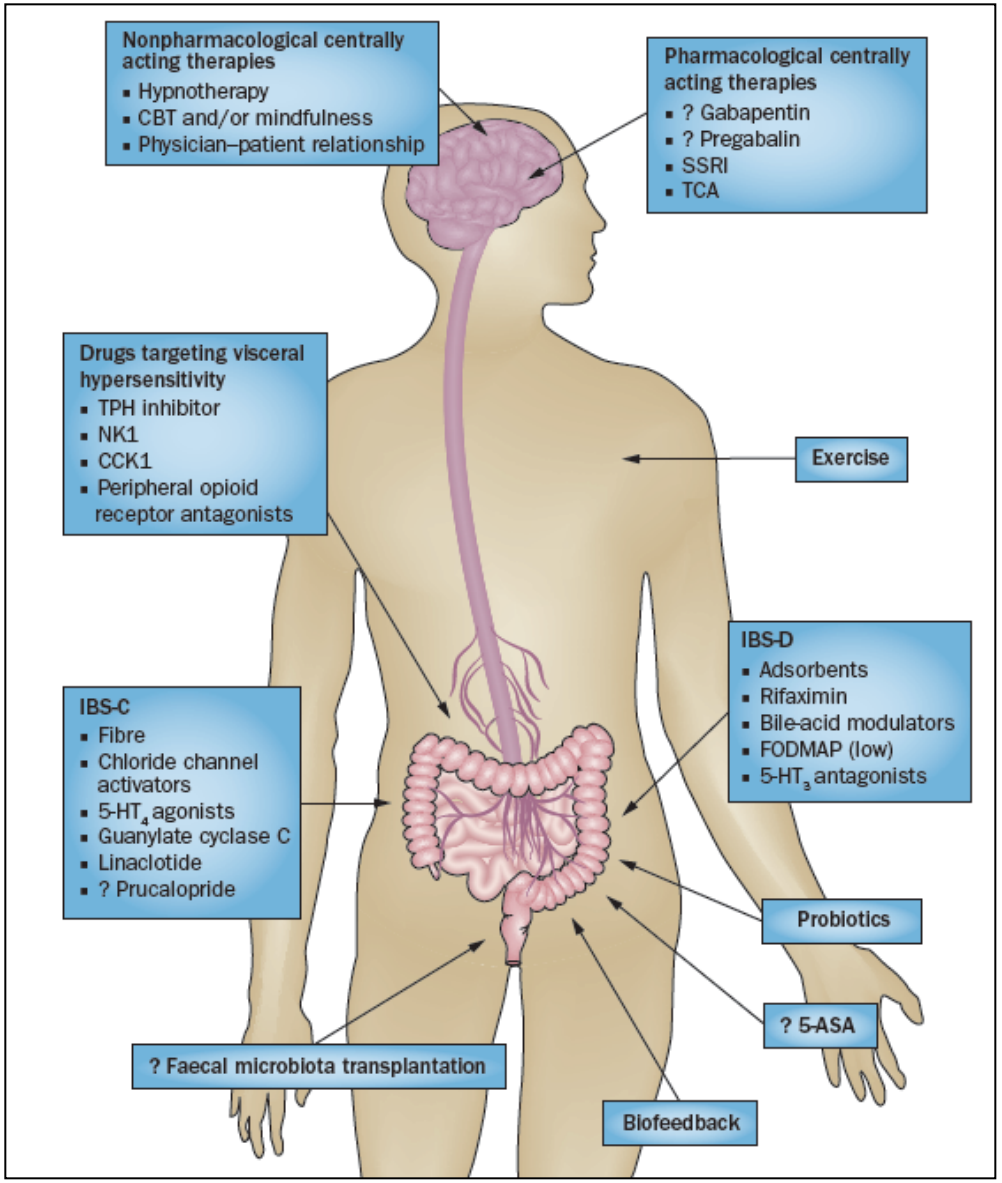
IBS Treatments

- The treatment strategy is based on the nature and severity of the symptoms, the characteristics and degree of functional impairment, and the presence of psychosocial difficulties affecting the course of the illness.

- Treatment for IBS is focused on managing symptoms.
  - Many classes of drugs are used.

- Complementary or integrative strategies, such as biofeedback or exercise are sometimes recommended.



Halland M, Talley NJ. New treatments for IBS. *Nat Rev Gastroenterol Hepatol.* Dec 11 2012;10(1):13-23.

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IBS Conventional RX Treatments

Drugs Used in Management of Irritable Bowel Syndrome
Predominantly central acting drugs:
Selective Serotonin reuptake inhibitors (SSRIs)
Central and peripheral acting drugs:
Neurokinin receptor antagonists
Serotonin receptor modulators
Drugs with opioid action
Neurotrophins
Corticotropin releasing factor (CRF) antagonists
Somatostatin analogues
Drugs acting predominantly in the periphery:
Antibiotics
Selective chloride channel activators
Cholecystokinin (CCK) antagonists
Natural products
Peripheral receptor modulators: guanylate cyclase

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Conventional Diagnostics & Treatments

- Diagnosis of IBS includes assessing the presences of alarm signs and identifying symptoms based on ROME III Criteria.
- GI specific procedures are performed at high rates in patients with IBS to exclude low prevalence, but serious conditions.
  - As many as 50% of patients being evaluated for IBS will undergo colonoscopy; 25% of all colonoscopies performed in the US are done for evaluation of IBS
- Over 95% of these GI-specific procedures in IBS patients show normal findings.
- Treatment includes many drug classifications and is focused on managing symptoms.

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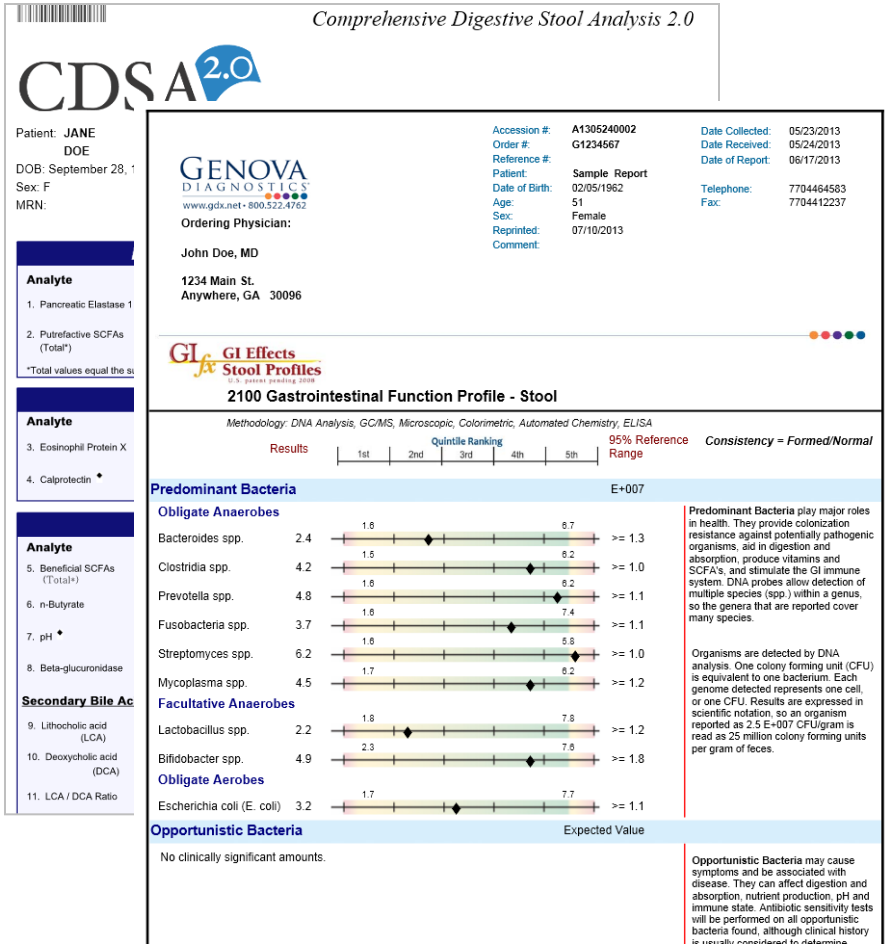
Functional Diagnostics

Relevant Tests

- Featured profile (Comprehensive Stool Testing)
- Additional profiles for consideration

Targeted Treatments



Comprehensive Digestive Stool Analysis 2.0

CDSA 2.0

Patient: JANE DOE
DOB: September 28, 1
Sex: F
MRN:

Analyte
1. Pancreatic Elastase 1
2. Putrefactive SCFAs (Total*)
*Total values equal the s

Analyte
3. Eosinophil Protein X
4. Calprotectin ◆

Analyte
5. Beneficial SCFAs (Total*)
6. n-Butyrate
7. pH ◆
8. Beta-glucuronidase
Secondary Bile Ac
9. Lithocholic acid (LCA)
10. Deoxycholic acid (DCA)
11. LCA / DCA Ratio

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Ordering Physician:

John Doe, MD

1234 Main St.
Anywhere, GA 30096

Accession #:	A1305240002	Date Collected:	05/23/2013
Order #:	G1234567	Date Received:	05/24/2013
Reference #:		Date of Report:	06/17/2013
Patient:	Sample Report		
Date of Birth:	02/05/1962	Telephone:	7704464583
Age:	51	Fax:	7704412237
Sex:	Female		
Reprinted:	07/10/2013		
Comment:			

GI fx GI Effects Stool Profiles

2100 Gastrointestinal Function Profile - Stool

Methodology: DNA Analysis, GC/MS, Microscopic, Colorimetric, Automated Chemistry, ELISA

Consistency = Formed/Normal

Results	Quintile Ranking (1st 2nd 3rd 4th 5th)	95% Reference Range
Predominant Bacteria	E+007	
Obligate Anaerobes		
Bacteroides spp. 2.4	1.6 – 6.7	>= 1.3
Clostridia spp. 4.2	1.5 – 6.2	>= 1.0
Prevotella spp. 4.8	1.6 – 6.2	>= 1.1
Fusobacteria spp. 3.7	1.6 – 7.4	>= 1.1
Streptomyces spp. 6.2	1.6 – 5.8	>= 1.0
Mycoplasma spp. 4.5	1.7 – 6.2	>= 1.2
Facultative Anaerobes		
Lactobacillus spp. 2.2	1.8 – 7.8	>= 1.2
Bifidobacter spp. 4.9	2.3 – 7.6	>= 1.8
Obligate Aerobes		
Escherichia coli (E. coli) 3.2	1.7 – 7.7	>= 1.1
Opportunistic Bacteria	Expected Value	
No clinically significant amounts.		

Predominant Bacteria play major roles in health. They provide colonization resistance against potentially pathogenic organisms, aid in digestion and absorption, produce vitamins and SCFA's, and stimulate the GI immune system. DNA probes allow detection of multiple species (spp.) within a genus, so the genera that are reported cover many species.

Organisms are detected by DNA analysis. One colony forming unit (CFU) is equivalent to one bacterium. Each genome detected represents one cell, or one CFU. Results are expressed in scientific notation, so an organism reported as 2.5 E+007 CFU/gram is read as 25 million colony forming units per gram of feces.

Opportunistic Bacteria may cause symptoms and be associated with disease. They can affect digestion and absorption, nutrient production, pH and immune state. Antibiotic sensitivity tests will be performed on all opportunistic bacteria found, although clinical history

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Approaching IBS through the DIG framework

- Applying the DIG framework
  - **D**igestion and Absorption
  - **I**nflammation and Gut Immune Function
  - **G**astrointestinal microbiology (gut microflora balance, as well as presence of parasitic organisms and yeast/fungi).
- Select Biomarkers and Stool Test Review

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Stool Biomarkers

Applying the DIG Framework to Identify the Root Cause of IBS

There are multiple evaluations that could be performed as part of an IBS work-up, related to the following areas:

Clinical Area	Type of Evaluation
Digestion	Measure pancreatic insufficiency **(Pancreatic Elastase 1)**
Inflammation	Evaluate GI inflammation **(fecal Calprotectin)**
	Evaluate allergic component **(Eosinophil Protein X)**
	Test occult bleeding **(Hemoccult)**
Gut Microbiome	Evaluate stool for infection **(*C. difficile*, parasitic EIA & microscopy, *H. pylori*)**
	Microbiology **(altered gut flora/dysbiosis)**

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Stool Biomarkers

Stool testing identifies underlying causes of IBS that can be treated using relatively low-cost therapies or issues needing further investigation:

Clinical Area	Treatment/ Additional Workup
Digestion	Pancreatic insufficiency - **Pancreatic Enzymes; R/O causes of pancreatic insufficiency**
Inflammation	GI inflammation **(fecal Calprotectin) – ID cause of inflammation address with appropriate treatment; possible GI referral**
	Allergic component **(Eosinophil Protein X) – ID and remove dietary allergens**
	Occult bleeding **(Hemoccult) - ID cause of bleeding; possible GI referral**
Gut Microbiome	Infection**(*C. difficile*, parasitic EIA & microscopy, *H. pylori*) - Address with appropriate anti-microbial or anti-parasitic therapies**
	Microbiology **(altered gut flora/dysbiosis) – Probiotics and/or anti-microbials**

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DIG: Digestion & Absorption

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Pancreatic Elastase 1 (PE 1) may be used clinically to demonstrate Exocrine Pancreatic Insufficiency

- Pancreatic exocrine insufficiency is a major consequence of:
  - Pancreatic diseases (e. g. chronic pancreatitis and Cystic Fibrosis);
  - Extra-pancreatic diseases like celiac disease & Crohn's disease;
  - Gastrointestinal and pancreatic surgical resections.

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Pancreatic Elastase 1 (PE 1) & Pancreatic Exocrine Insufficiency

> 350 µg/gm	68%	Normal
201-350 µg/gm	22%	Mild insufficiency
101-200 µg/gm	6%	Moderate insufficiency
< 100 µg/gm	3%	Severe insufficiency

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Pancreatic Elastase 1 (PE 1) & Pancreatic Exocrine Insufficiency

> 350 µg/gm 68% Normal

201-350 µg/gm 22% Mild insufficiency

Rx → OTC or Pancreatic Enzymes (Creon-6 qAC)

101-200 µg/gm 6% Moderate insufficiency

Rx → Pancreatic Enzymes (Creon-12 qAC)

< 100 µg/gm 3% Severe insufficiency

Rx → Pancreatic Enzymes (Creon-24 qAC)

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DIG: Inflammation & Immune Dysregulation

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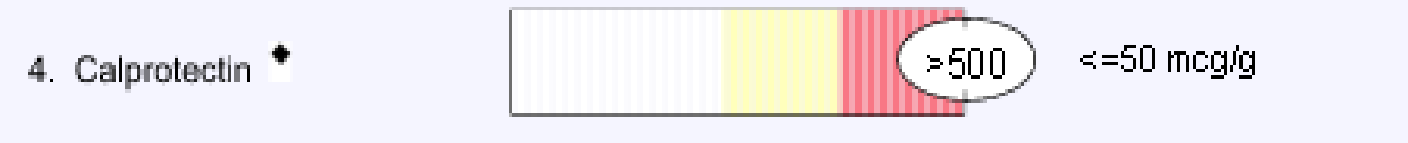
DIG: Inflammation and Immune Dysregulation



Fecal Calprotectin

- Reliable, highly accurate biomarker for the presence of infectious, inflammatory or malignant disease
- FDA-cleared marker to distinguish between Inflammatory Bowel Disease (IBD) and IBS and to monitor treatment for IBD

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Fecal Calprotectin

- Provides an objective & quantifiable indicator of GI-specific inflammation
- FDA-cleared to reliably distinguish Inflammatory Bowel Disease (IBD) from Irritable Bowel Syndrome (IBS).
- Correlates well with histologic and endoscopic grading of IBD disease activity.
- Is better at discriminating low levels of inflammation
- Is unaffected by (most) medications and dietary supplements
- Is resistant to enzymatic degradation in the gut.
- Is stable in stool for up to one week at room temperature

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Fecal Calprotectin

- May be elevated in:
  - Inflammatory Bowel Disease
  - Post-Infectious Irritable Bowel Syndrome
  - Certain GI infections
  - NSAID enteropathy
  - Food allergy
  - Chronic Pancreatitis
  - Colorectal cancer

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Poullis A, et al. *J Gastroenterol Hepatol.* 2003;18:756-762

Fecal Calprotectin

- Marker of neutrophilic activity in the gut
- Neutrophils are mobilized and activated in the gut in response to:
  - Cell or tissue damage
  - Increased permeability of the mucosa
  - Infectious processes

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Aadland E, Fagerhol MK. *Eur J Gastro Hepatol 2002, 14:823-825*

IBD vs. IBS

A person with positive Rome criteria and a normal Calprotectin (< 50 µg/g) has virtually

***NO CHANCE* of having IBD**

FDA-cleared biomarker, Calprotectin, which is highly accurate, and capable of differentiating IBS from IBD.

Remember, a workup for IBD includes colonoscopy, an expensive and invasive procedure.

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Calprotectin

- A meta-analysis published in 2010 evaluated the clinical impact of utilizing a biomarker like Calprotectin to assess concern for IBD in patients with IBS.

- This paper, which evaluated 13 studies from the primary literature, found that in adults being evaluated for IBD, ***screening by measuring calprotectin levels would produce a 67% reduction in the number of adults undergoing endoscopy.***

van Rheenen PF, Van de Vijver E, Fidler V. Faecal calprotectin for screening of patients with suspected inflammatory bowel disease: diagnostic meta-analysis. *BMJ (Clinical research ed.* 2010;341:c3369.

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Calprotectin Treatment Options

- <50 ug/g No significant inflammation
- 50-120 ug/g Indicates some GI inflammation: IBD, infection, polyps, neoplasia, NSAIDS
- >120 ug/g Significant inflammation: referral may be indicated to determine pathology
- >250 ug/g Active disease present: predicts imminent relapse in treated patients

- Adjunctive therapeutics include: Probiotics, fish oils, N-acetylglucosamine, rutin, anti-inflammatory agents such as leukotriene inhibitors or TNF-alpha antagonists

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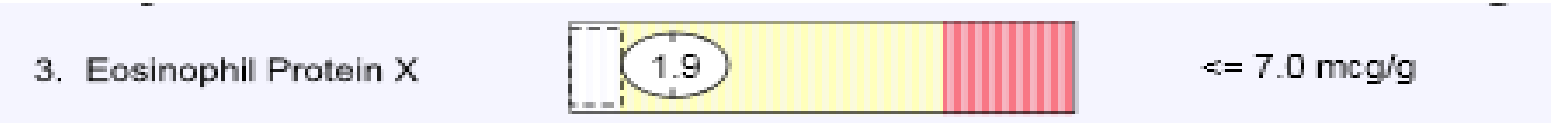
Eosinophil Protein X



- Reflects IgE-mediated inflammation and/or tissue damage of the GI tract
- An elevation may be caused by IgE-mediated food allergies, inflammatory bowel disease, parasitic or worm infections, and collagenous colitis.

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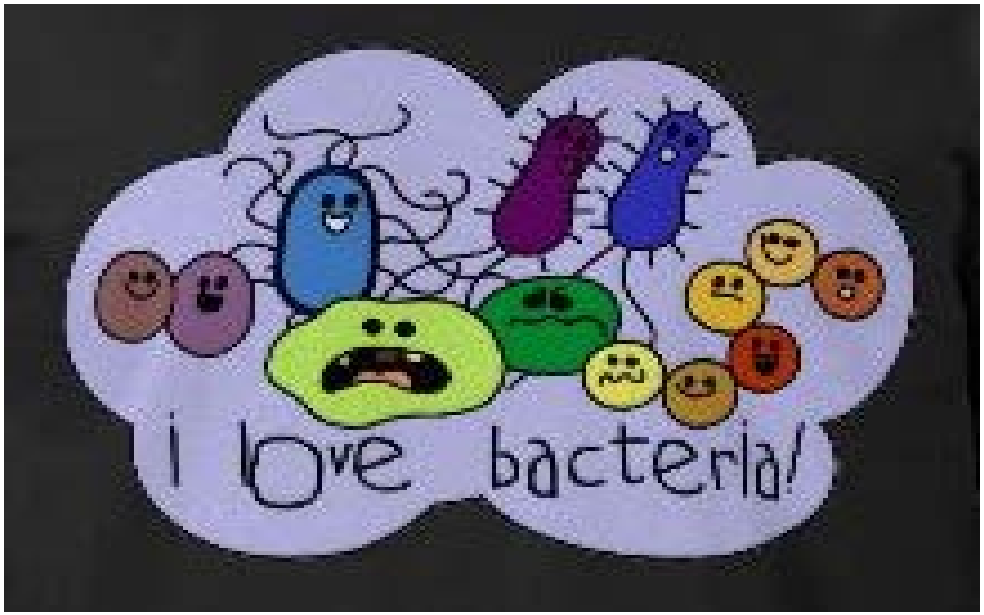
Eosinophil Protein X Treatment Options

- If elevated may consider
  - Probiotics, fish oils, N-acetylglucosamine, quercetin
  - Anti-inflammatory agents such as leukotriene inhibitors or TNF-alpha antagonists
  - Elimination Diet and/or food antibody assessment
  - Treatment of parasitic infection

DIG: Gut Microbiome



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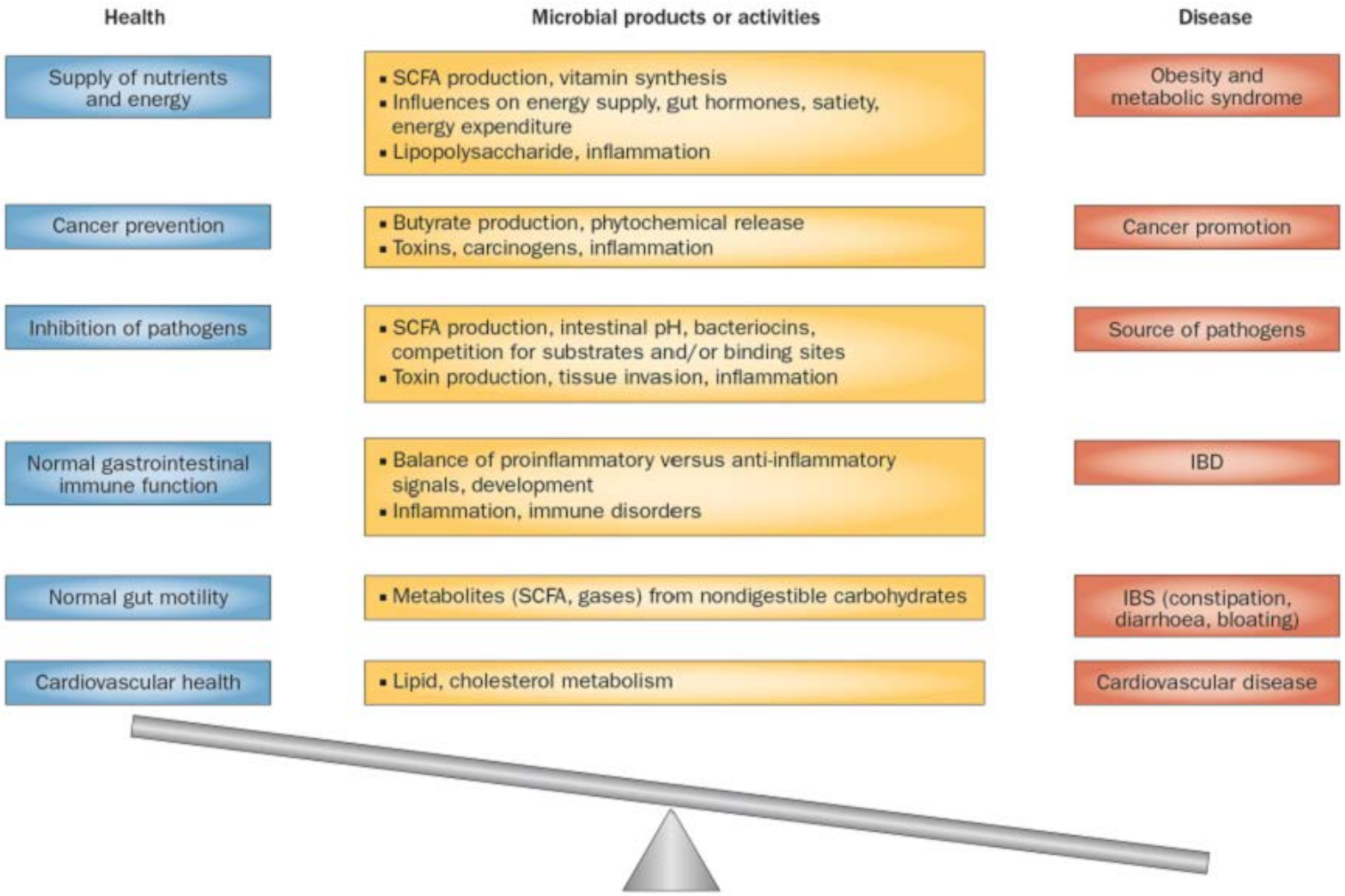

Figure 1 | Influence of gut microbial communities on health. Most of the microbial activities indicated in the centre column are functions of the whole community of gut microbiota rather than being attributable to a single species. The balance of the community and its output determines the net contribution to health or disease. Abbreviation: SCFA, short-chain fatty acid.

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Flint, H. J. *et al.* The role of the gut microbiota in nutrition and health. *Nat. Rev. Gastroenterol. Hepatol.* 2012.

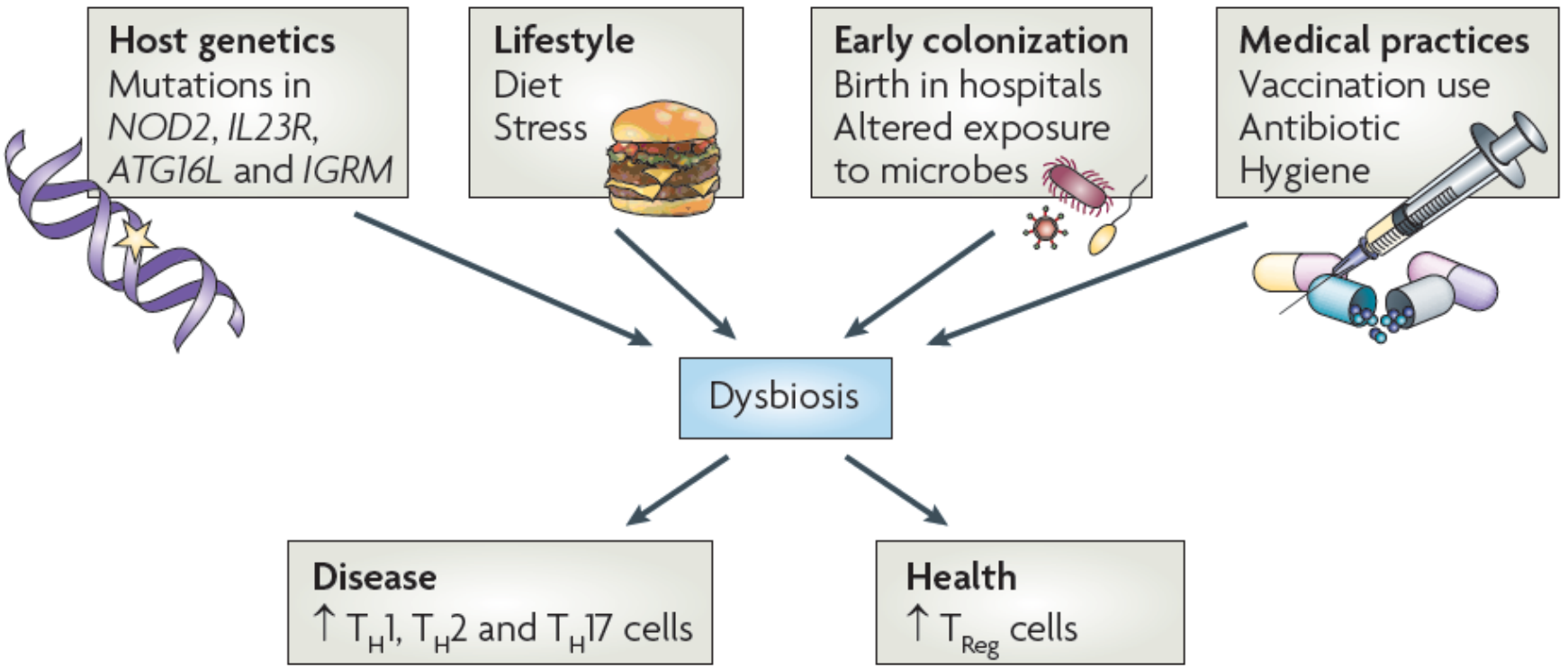
Gut Microbiome Imbalance: 'Dysbiosis'

- A state of imbalanced microbial ecology that contributes to disease.

- The overgrowth of micro-organisms of low intrinsic virulence induces disease by altering
  - the nutritional status
  - the immune response
  - the elimination capacity of the host

Proposed causes of dysbiosis of the microbiota.

The composition of microbiota can shape a healthy immune response or predispose to disease.



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Analysis of the Gut Microbiome: Culture-based Technology

Additional Tests (if ordered)

	Inside	Outside	Reference Range
Campylobacter specific antigen	Not Ordered		Negative
Enterohemorrhagic Escherichia coli Shiga-like Toxin	Not Ordered		Negative

Microbiology

Bacteriology

12. Beneficial Bacteria

Lactobacillus species	3+
Escherichia coli	3+
Bifidobacterium	4+

13. Additional Bacteria

gamma haemolytic Streptococcus	NP	2+
alpha haemolytic Streptococcus	NP	2+
Klebsiella pneumoniae	NP	3+
Staphylococcus aureus	NP	1+

14. Mycology

*NG *NG

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

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

GENOVA DIAGNOSTICS

Analysis of the Gut Microbiome: DNA-based Technology

Predominant Bacteria

E+007

Obligate Anaerobes

Bacteroides spp.	2.4	1.6 – 6.7	>= 1.3
Clostridia spp.	4.2	1.5 – 6.2	>= 1.0
Prevotella spp.	4.8	1.6 – 6.2	>= 1.1
Fusobacteria spp.	3.7	1.6	
Streptomyces spp.	6.2	1.6	
Mycoplasma spp.	4.5	1.7	

Facultative Anaerobes

Lactobacillus spp.	2.2	1.8	
Bifidobacter spp.	4.9	2.3	

Obligate Aerobes

Escherichia coli (E. coli)	3.2	1.7	

Predominant Bacteria play major roles in health. They provide colonization resistance against potentially pathogenic organisms, aid in digestion and absorption, produce vitamins and SCFA's, and stimulate the GI immune system. DNA probes allow detection of multiple species (spp.) within a genus, so the genera that are reported cover

Opportunistic Bacteria

No clinically significant amounts.

Pathogenic Bacteria

		Expected Value
Helicobacter pylori - Molecular Probe	Positive	Negative
Helicobacter pylori - EIA	Positive	Negative
Campylobacter spp. - Molecular Probe	Negative	Negative
Shiga toxin E. coli*	Negative	Negative
Clostridium difficile*	Negative	Negative

*Positive results are confirmed by EIA

Yeast/Fungi

Expected Value

No clinically significant amounts.

Yeast/Fungi
Yeast overgrowth has been linked to many chronic conditions, in part because of antigenic responses in some patients to even low rates of yeast growth. Potential symptoms include diarrhea, headache, bloating, atopic dermatitis and fatigue. Positives are reported as +1, +2, +3 or +4 indicating >100, >1000, >10000 or >100000 pg DNA/g.

Parasites

Expected Value

		Expected Value
Parasite present; taxonomy unavailable	Positive	Negative

Parasites
Parasite infections are a major cause of non-viral diarrhea. Symptoms may include constipation, gas, bloating, increased allergy response, colitis, nausea and distention.

Adiposity Index

Expected Value

Firmicutes %	70		<= 80 %
Bacteroidetes %	30		>= 20 %

The **Adiposity Index** is derived by using DNA probes that detect multiple genera of the phyla Firmicutes and Bacteroidetes. Abnormalities of these phyla may be associated with increased caloric extraction from food.

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Dysbiosis Treatment Decision Matrix

Symptoms Present?	WNL Beneficial/ WNL Additional	WNL Beneficial/ ABNL Additional	ABNL Beneficial/ ABNL Additional	ABNL Beneficial/ WNL Additional
YES	5 – 10 B CFUs/day; R/O BOSI	Antibiotics & Probiotics	Probiotics (50 – 100 B CFUs/d) & Antibiotics	Probiotics (50 – 100 B CFUs/day)
NO	5 – 10 B CFUs/day	Antimicrobial Botanicals & Probiotics	Probiotics (50 – 100 B CFUs/d) & Antimicrobial Botanicals	Probiotics (25 – 50 B CFUs/day)

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PCR & Culture: Microbiology

PCR

- High analytical sensitivity
  - ONLY identifies '**targeted**' bacteria
  - Eliminate errors due to transport
- Ability to identify anaerobic bacteria well, broader picture of predominant (commensal) bacteria
  - No diagnosis established, but low risk treatments
- Pathogen diagnosis via PCR not established
  - Consequences of overtreatment = microbial resistance

CULTURE

- Lower analytical sensitivity
- Can identify a wide range of microbes without the need for a technology-driven, specific target.
- Established clinical utility
  - Reasonable parameters that have defined "normal" for established clinical diagnostics
- Diagnostic for Pathogens
  - High risk treatments

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Functional Diagnostic Tests Relevant to the Irritable Bowel Syndrome Patient Population

Product Line	Profile	Clinical Consideration
GI	Comprehensive Stool Diagnostics	Assesses underlying GI dysfunction utilizing several biomarkers.
	Intestinal Permeability Assessment	Identifies patients with altered intestinal barrier integrity that can be caused by various factors.
	Bacterial Overgrowth of the Small Intestine Breath Test	A subset of patients with IBS have small intestinal bacterial overgrowth and eradication of bacteria can greatly improve symptoms.
	Lactose Intolerance Breath Test	Lactose intolerance can cause common IBS symptoms.
Nutritional	Nutritional Testing	With digestive concerns, patients may not be digesting and absorbing nutrients.
Immune	Celiac and Gluten Sensitivity	Patients with IBS tend to have higher rates of Celiac disease. Elimination of gluten can resolve symptoms.
	IgG and IgE Food Antibodies	Food allergies and sensitivities can irritate the lining of the digestive tract and can cause symptoms.

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Additional Test Considerations

GI Diagnostics

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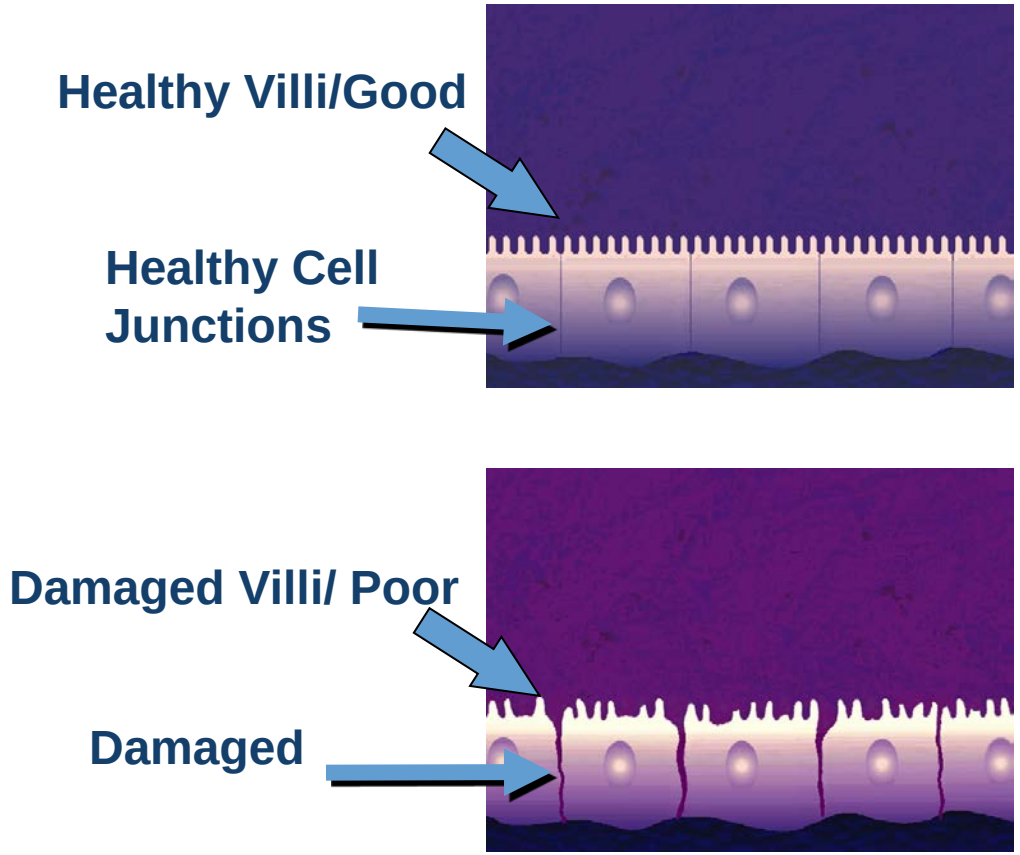
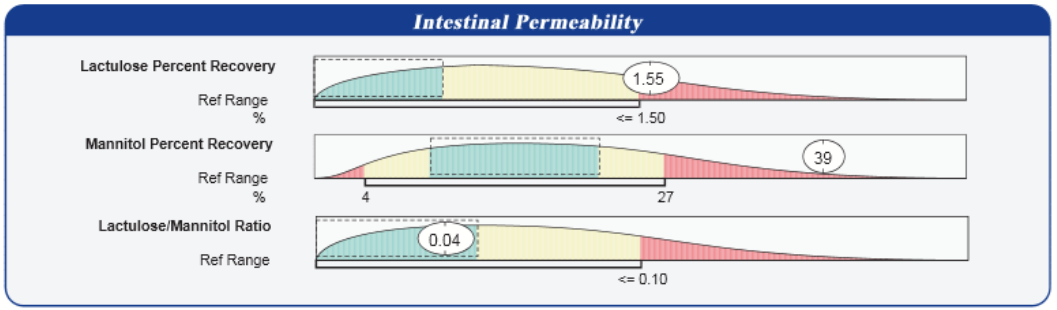
GI Diagnostics: Intestinal Permeability

•Also called “Leaky Gut Syndrome”

•Many factors contribute to intestinal permeability including stress, food sensitivities and allergies, bile acids, infection, dysbiosis, hormones and more

•Treating this condition would involve identifying and addressing the cause of permeability, as well as employing therapies that heal the gut lining





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Increased Intestinal Permeability- Treatment Options

Endogenous Protection:

- sIgA (blocks potentially antigenic proteins)
- Mucin

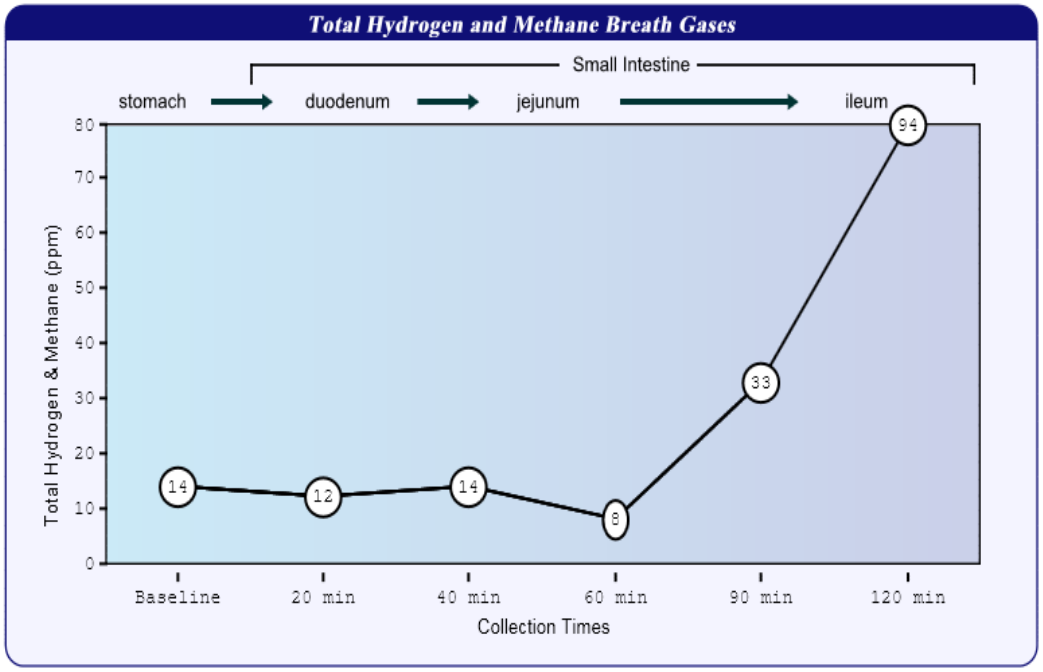
Exogenous Protection:

- Probiotics (normalize gut flora and increase sIgA)
- Quercetin (anti-inflammatory)
- N-acetylglucosamine (mucous enhancement)
- L-Glutamine (supports enterocytes and microvilli)

GI Diagnostics: Bacterial Overgrowth of the Small Intestine

- Symptoms can resolve with balancing the gut microflora.

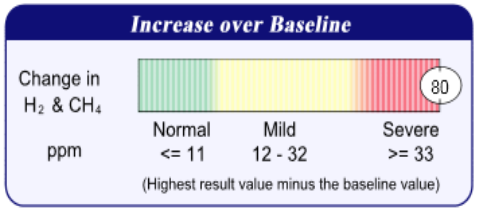
- As high as 37.5% of patients evaluated for IBS may suffer from a quantitative increase in bacteria in the small bowel (SIBO), especially following enteric infections.

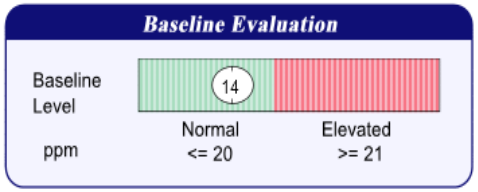


Hydrogen & Methane (ppm)

Minutes	Base-line	20	40	60	90	120
Hydrogen (H_2)	11	8	11	4	30	89
Methane (CH_4)	3	4	3	4	3	5
Total	14	12	14	8	33	94

This test was developed and its performance characteristics determined by Genova Diagnostics, Inc. It has not been cleared or approved by the U.S. Food and Drug Administration.





TBO63 RMS 1040 Rev 2

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Pyleris E, Giamarellos-Bourboulis EJ, Tzivras D, Koussoulas V, Barbatzas C, Pimentel M. The prevalence of overgrowth by aerobic bacteria in the small intestine by small bowel culture: relationship with irritable bowel syndrome. *Dig Dis Sci.* May 2012;57(5):

Bacterial Overgrowth of the Small Intestine - Treatment Options

- Flora in SBBO is typically comprised of both coliforms and strict anaerobes
- Non-absorbed antibiotics may minimize side effects: Rifaximin
  - 7 day course of Rifaximin (400 mg TID) normalized breath H_2 in 70% of pts;
  - TCN normalized breath H_2 in 27% of pts.
- Probiotics to minimize side effects

Bacterial Overgrowth of the Small Intestine - Treatment Options

Probiotics to minimize side effects

- Natural approach:
  - Broad-spectrum botanicals
  - Lactobacillus acidophilus and L. casei
- Address underlying causes!
  - Stasis, slow transit time, low stomach acid (betaine HCl, stop PPIs), maldigestion, lactose intolerance
- Temporarily restrict CHOs, especially disaccharides such as lactose

Additional Test Considerations

Immune Diagnostics

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Immune Diagnostics: Celiac and Gluten Sensitivity

- Testing for Celiac Disease is usually part of the conventional workup for a patient with IBS symptoms

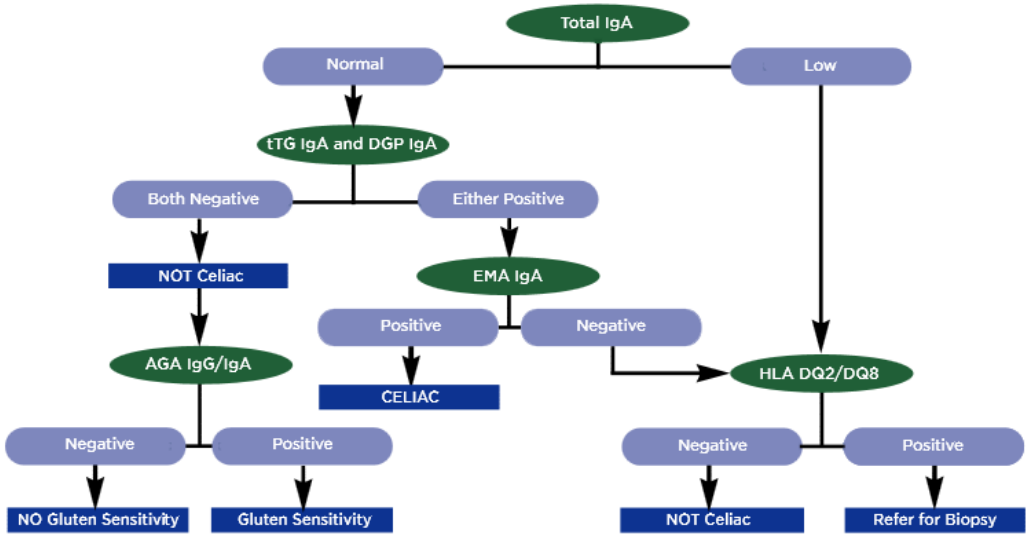
- Treatment may involve eliminating gluten from the diet

Immunologic Markers

Biomarker	Result		Reference Range
Total IgA	139.8	Sufficient	62.0-343.0 mg/dL
Anti-Tissue Transglutaminase IgA (tTG IgA)	2.1	Negative	<=4 U/mL
Anti-Deamidated Gliadin IgA (DGP IgA)	17.2	Negative	<=19 U/mL
Anti-Endomysial IgA (EMA IgA)	Not Detected		Not Detected
Anti-Gliadin IgA (AGA IgA)	21	Weak Positive	<20 U/mL
Anti-Gliadin IgG (AGA IgG)	32	Strong Positive	<20 U/mL

Interpretation

Patient results are consistent with Gluten Sensitivity.



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Celiac and Gluten Sensitivity – Treatment Options

- Celiac: Permanent removal of gluten from diet
- Gluten Sensitivity: Eliminate gluten for 3-6 months, then reintroduce and monitor for symptoms

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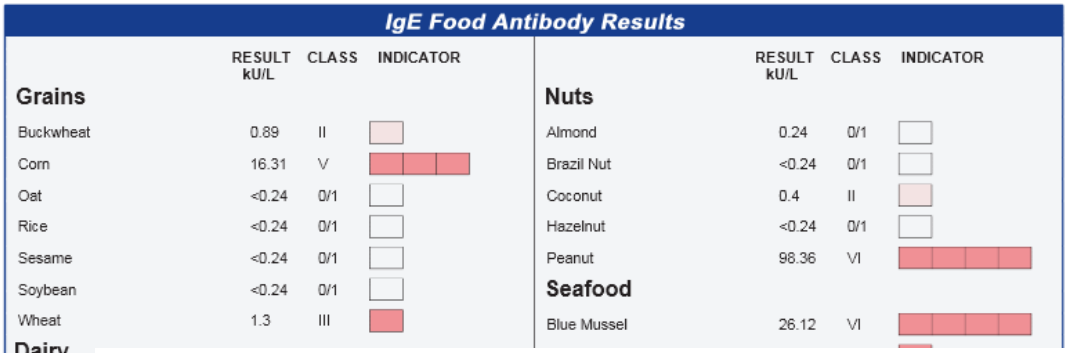
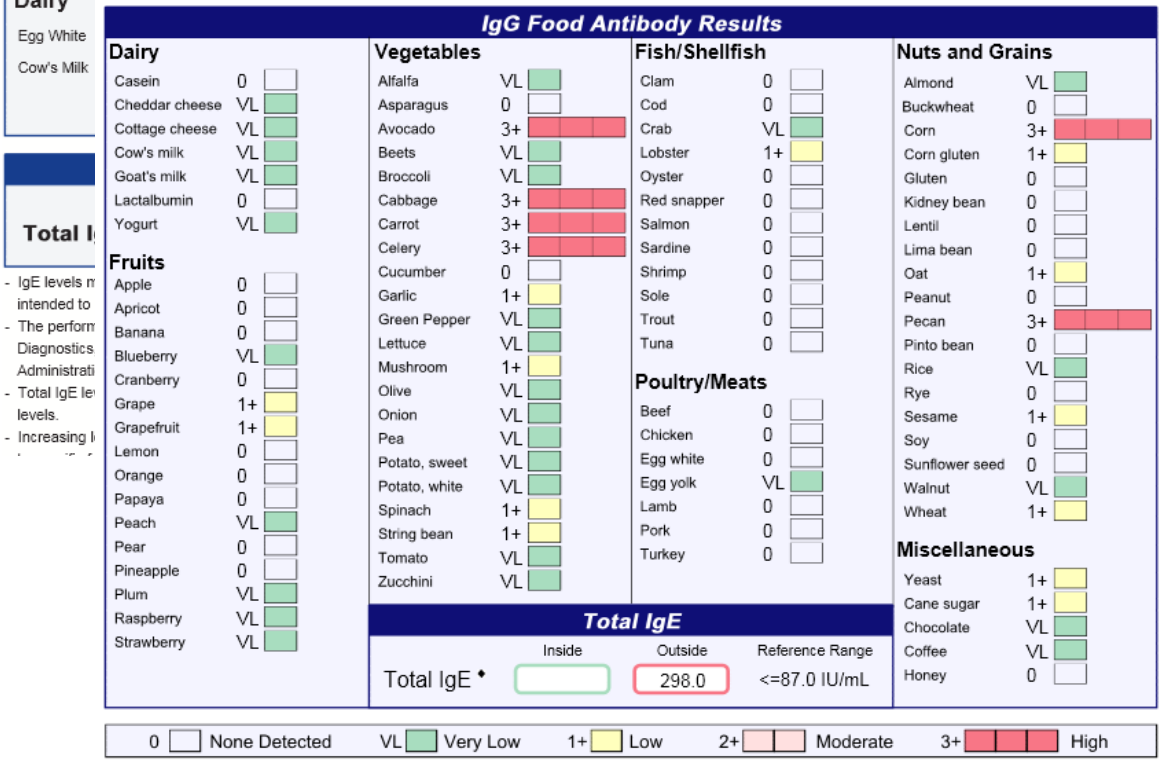
Immune Panels: IgE and IgG Food Antibody Assessments

- IgE food allergies and IgG food sensitivities can cause IBS symptoms
- When offending foods are removed from the diet, symptoms may resolve



IgE Food Antibody Results

	RESULT kU/L	CLASS	INDICATOR
Grains			
Buckwheat	0.89	II	
Corn	16.31	V	
Oat	<0.24	0/1	
Rice	<0.24	0/1	
Sesame	<0.24	0/1	
Soybean	<0.24	0/1	
Wheat	1.3	III	
Dairy			
Egg White			
Cow's Milk			
Nuts			
Almond	0.24	0/1	
Brazil Nut	<0.24	0/1	
Coconut	0.4	II	
Hazelnut	<0.24	0/1	
Peanut	98.36	VI	
Seafood			
Blue Mussel	26.12	VI	



IgG Food Antibody Results

Dairy		Vegetables		Fish/Shellfish		Nuts and Grains	
Casein	0	Alfalfa	VL	Clam	0	Almond	VL
Cheddar cheese	VL	Asparagus	0	Cod	0	Buckwheat	0
Cottage cheese	VL	Avocado	3+	Crab	VL	Corn	3+
Cow's milk	VL	Beets	VL	Lobster	1+	Corn gluten	1+
Goat's milk	VL	Broccoli	VL	Oyster	0	Gluten	0
Lactalbumin	0	Cabbage	3+	Red snapper	0	Kidney bean	0
Yogurt	VL	Carrot	3+	Salmon	0	Lentil	0
Fruits		Celery	3+	Sardine	0	Lima bean	0
Apple	0	Cucumber	0	Shrimp	0	Oat	1+
Apricot	0	Garlic	1+	Sole	0	Peanut	0
Banana	0	Green Pepper	VL	Trout	0	Pecan	3+
Blueberry	VL	Lettuce	VL	Tuna	0	Pinto bean	0
Cranberry	0	Mushroom	1+	**Poultry/Meats**		Rice	VL
Grape	1+	Olive	VL	Beef	0	Rye	0
Grapefruit	1+	Onion	VL	Chicken	0	Sesame	1+
Lemon	0	Pea	VL	Egg white	0	Soy	0
Orange	0	Potato, sweet	VL	Egg yolk	VL	Sunflower seed	0
Papaya	0	Potato, white	VL	Lamb	0	Walnut	VL
Peach	VL	Spinach	1+	Pork	0	Wheat	1+
Pear	0	String bean	1+	Turkey	0	**Miscellaneous**	
Pineapple	0	Tomato	VL			Yeast	1+
Plum	VL	Zucchini	VL			Cane sugar	1+
Raspberry	VL					Chocolate	VL
Strawberry	VL					Coffee	VL
						Honey	0

Total IgE

	Inside	Outside	Reference Range
Total IgE •		298.0	<=87.0 IU/mL

0 None Detected VL Very Low 1+ Low 2+ Moderate 3+ High

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IgE and IgG Food Antibody Assessments - Treatment Options

- IgE- mediated food allergies: permanent removal of that food from the diet
- IgG- mediated food sensitivities:
  - Eliminate the food(s) for 3-6 months, then reintroduce
  - 4- Day rotation diet to minimize exposure to sensitivities
- Quercetin, vitamin C, fish oils decrease inflammation

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Additional Test Considerations

Nutritional Diagnostics

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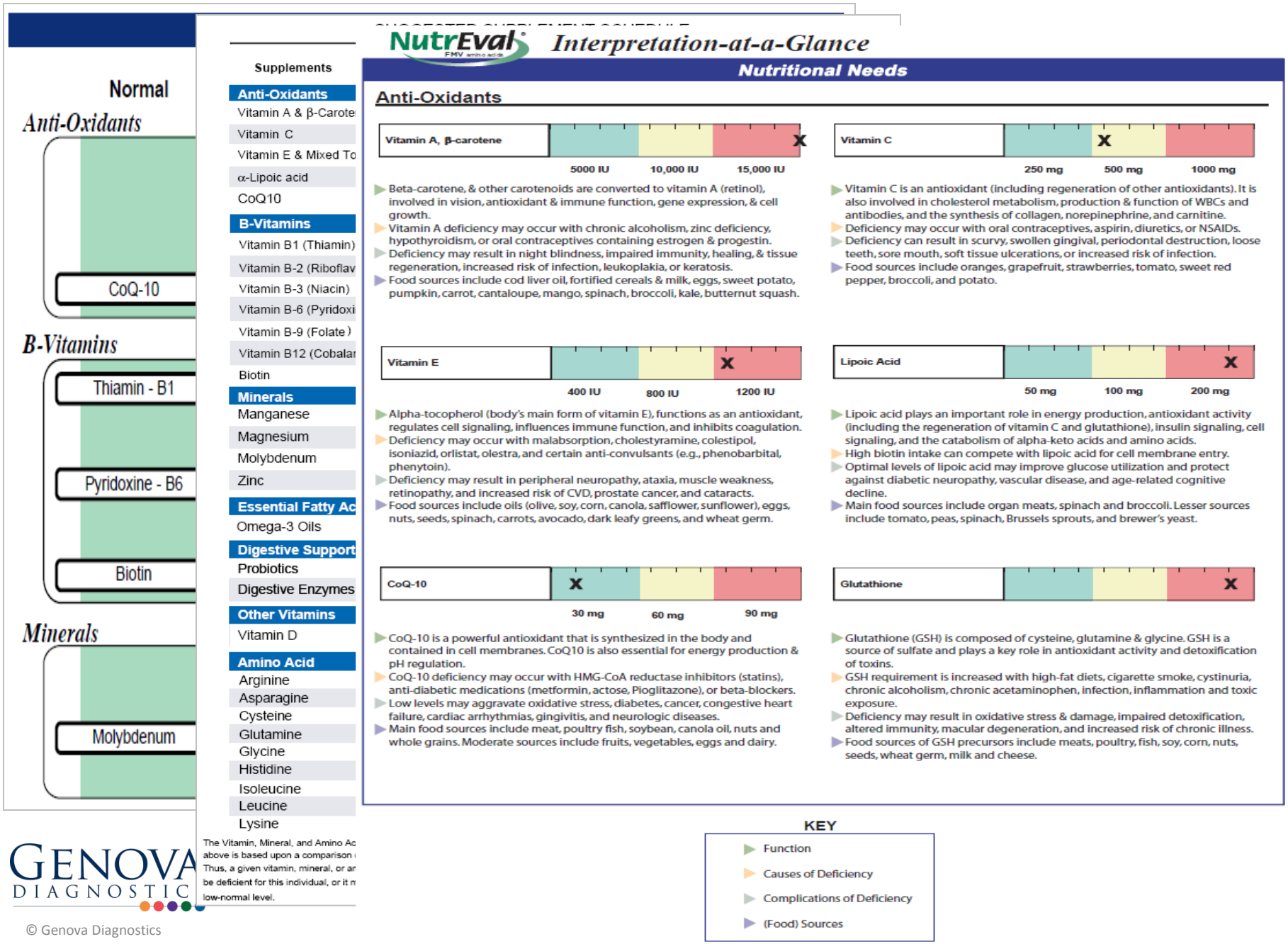
Nutritional Diagnostics

- Nutritional deficiencies can manifest in chronic disease
- IBS patients may not be absorbing nutrients
- There is a need to address the gut as well as deficiencies caused by the condition
- IBS overlaps with multiple other conditions including depression and anxiety
  - nutritional panels assess the need for nutrient cofactors and amino acids that make neurotransmitters
  - essential fatty acids play a role in depression



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Functional Testing

- A number of functional diagnostic products provide the clinician with insight into underlying causes of IBS.
  - Stool testing - DIG
  - Bacterial Overgrowth of the Small Intestine
  - Intestinal Permeability
  - IgG and IgE Food Allergy Testing
  - Nutritional Testing
- Many of the underlying causes can be treated using relatively low-cost therapies.
- Because many other common, chronic illnesses are associated with IBS – such as depresssion, anxiety, chronic fatigue syndrome, prolonged fatigue, and fibromyalgia – diagnostics utilized to address IBS may also illuminate treatment strategies for these chronic concerns as well.

GENOVA DIAGNOSTICS

Diagnostics & Patient Outcomes

Conventional

Case Studies & Functional Diagnostics

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Patient Outcomes with Conventional Diagnostics

- Over 95% of GI-specific procedures in IBS patients show normal findings.
- Patient respondents to a survey typically report that years elapsed between their first onset of symptoms and a final diagnosis of IBS (if one is ever in fact made).
- No single well-established therapy is available for IBS symptom control.
- Traditional therapies for IBS are & have been targeted to provide only symptomatic relief – and have included treatments withdrawn from the market for significant side-effects .

GENOVA DIAGNOSTICS®

Optimizing Gut Function
DIG Case Studies

- Substrate/ Nutrition – Digestion/Absorption
- Defense/ Immune Modulation – Inflammation
- Structure/ Barrier – Intestinal Permeability
- Function/ Metabolism – Gut Microbiome

- Mind/ Body Connection – Neurotransmitters

‘IBS’ Case #1

32 yo Male recently returned from traveling in Asia. Had occasional abdominal discomfort before traveling, now present 2-4x/ month over 3 months.

DIG

- Digestion/ Absorption – no issues noted
- Inflammation/ Immune Regulation/Infection – neutrophilic markers of GI inflammation (Calprotectin) normal
- Gut Microflora – altered microflora with Parasitic Infection (Entamoeba histolytica)

‘IBS’ Case #1

32 yo Male recently returned from traveling in Asia, diagnosed with E. histolytica.

TREATMENT

- Remove Parasites –
  - Nitozoxanide (Alinia) 500mg BID x 7 days
- Reinoculate Gut Flora – Probiotics
- Repair Inflammation
  - Omega-3 Fat (Lovaza) 1gm BID

GENOVA DIAGNOSTICS

‘IBS’ Case #1

32 yo Male recently returned from traveling in Asia, diagnosed with E. histolytica

TREATMENT

- Anti-parasitic pharmaceuticals
- Probiotics
- Omega-3 Fats
- Diet change

FOLLOW-UP @ 6 weeks

- Symptoms resolved completely
- Remained symptom-free @ 1 year

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‘IBS’ Case #2

24 yo Female with intermittent recurrent abdominal pain/discomfort x 5 years. Also with depression and fatigue. Currently being treated with tri-cyclic anti-depressants.

DIG

- Digestion/ Absorption – food not completely digested, exocrine pancreatic function (Pancreatic Elastase) decreased
- Inflammation/ Immune Regulation/Infection – serum tTG (+), confirmed with endomysial IgA (+)
- Gut Microflora – normal

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‘IBS’ Case #2

24 yo Female, newly diagnosed with pancreatic insufficiency & Celiac disease

TREATMENT

- Remove Gluten
- Replace Enzymes –10x USP Pancreatin taken before each meal (Creon-6 or Creon-12)
- Repair Gut Lining – L-Glutamine 1000mg TID

GENOVA DIAGNOSTICS®

‘IBS’ Case #2

24 yo Female, newly diagnosed with pancreatic insufficiency & Celiac disease

TREATMENT

- Pancreatic enzyme supplementation until villous atrophy (2^{o} Celiac disease) resolves
- Totally gluten-free diet – lifetime!
- Repair of ‘leaky gut’

FOLLOW-UP @ 6 & 12 weeks

- Symptoms significantly improved
- Intermittent dietary indiscretions @ 1 year
- Screen for auto-immune diseases

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‘IBS’ Case #3

43 yo Female with a history of GERD x 3 years, currently using a PPI. Also with IBS @ 2 years. Recently developing Restless Leg Syndrome.

DIG

- Digestion/ Absorption – no problems
- Inflammation/ Immune Regulation/Infection – no elevation in neutrophilic markers of inflammation
- Gut Microflora – moderate alterations in bacteria, no parasites present, no C. difficile

‘IBS’ Case #3

43 yo Female with a history of GERD, on PPI. Also with Restless Leg Syndrome.

TREATMENT

- Remove PPI
- Reinoculate gut flora – 25b cfu BID
- Repair – Iberogast (STW 5) 20gtt TID x 4 wks to stimulate gastric emptying

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‘IBS’ Case #3

43yo Female with a history of GERD, on PPI. Also with Restless Leg Syndrome.

TREATMENT

- Remove PPI, add Iberogast for GI motility support
- Probiotics @ 25b cfu BID

FOLLOW-UP @ 6 weeks & 12 weeks

- Little improvement in IBS, GERD improved
- Consider Small Bowel Bacterial Overgrowth
  - Lactulose Breath Testing
    - Rifaxamin 400mg BID x 7 days
- Symptoms resolved @ 12 weeks!

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Case Study #4

- A 48 year old female presents with:
  - History of depression
  - C/o intermittent abdominal pain & cramping over the past 6 months
  - The patient's initial work-up was normal when checking for 'red flag' signs
  - According to ROME III criteria, the patient has IBS

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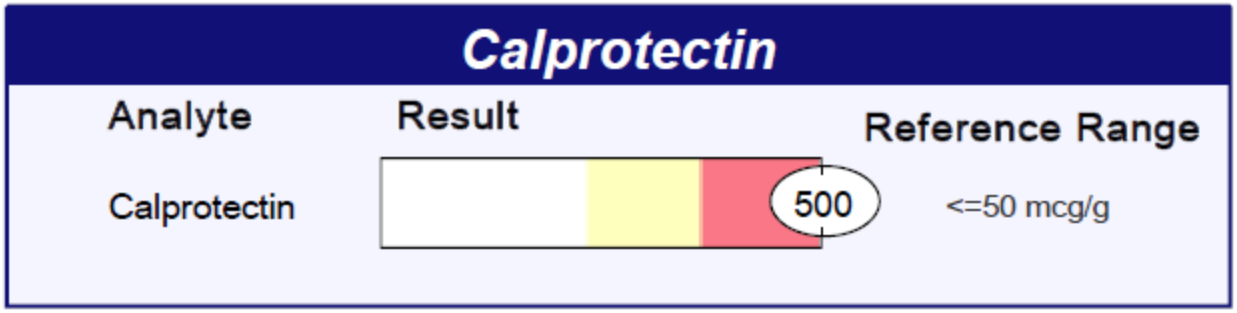
‘IBS’ Case #4



DIG

- Digestion/ Absorption – no problems
- Immune Regulation/ Inflammation – significant elevation in neutrophilic markers of inflammation = Calprotectin 500
- Gut Microflora – no alterations in bacteria, no parasites present, no C. difficile

‘IBS’ Case #4

48yo Female with a history of depression, now with c/o intermittent abdominal pain & cramping over the past 6 months

TREATMENT

- Referred for colonoscopy to determine source of significantly elevated inflammation:
  - R/o Inflammatory Bowel Disease
  - R/o Colorectal Cancer

FOLLOW-UP

- Ulcerative Colitis noted on colonoscopy
  - 5-ASA begun, attempt to spare steroids
  - High dose probiotics @ 3.6 trillion cfu to induce remission

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IBS: Finding the 'Root' Cause

	Digestion/ Absorption	Immune/ Inflammation	GI Flora
IBS #1	No	Yes	Yes
IBS #2	Yes	Yes	No
IBS #3	No	No	Yes
IBS #4	No	Yes	No

GENOVA DIAGNOSTICS

IBS: Treating the 'Root' Cause

	Digestion/ Absorption	Immune/ Inflammation	GI Flora
IBS #1			Anti-parasitics Probiotics
IBS #2	Pancreatic enzymes	Stop ALL Gluten	
IBS #3	Stop PPI Add Iberogast		Probiotics Rifaxamin
IBS #4		Refer to Colonoscopy	

GENOVA DIAGNOSTICS

Functional Diagnostics & Outcomes Research

- Many of the treatable underlying causes of IBS can be accurately diagnosed with simple fecal testing.
- These underlying causes of IBS can be treated using relatively low-cost therapies.
- Treatment of these underlying causes normalizes patient results, and improves symptoms and quality of life in patients with IBS.
- A structured diagnostic testing panel that allows for parallel evaluation of common, treatable underlying causes of IBS symptoms is easier for clinicians to implement and for patients to tolerate, compared to serial testing aimed at eliminating competing diagnoses.
- A structured diagnostic fecal testing panel has been shown to ***reduce the rates of office visits, outpatient visits, laboratory testing, and GI procedures compared to the standard approach – preliminary finding***

GENOVA DIAGNOSTICS®

Goals for the Conversation

- IBS as a model of common, chronic illness
  - Defining IBS and its impact
  - Exploring the Differential Diagnosis & Associated Disease States
- Conventional Diagnostics & Treatments
- Functional Diagnostics & Treatments
  - 'DIG' framework
  - Clinical Utility of Stool Based Biomarker for IBS
  - Additional Diagnostic considerations: GI, Immune, Nutritional
- Functional Testing & Outcomes Research

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IBS and Specialty Diagnostics

Practical Tools to Support Clinical Management

Kathy O'Neil Smith, MD
Pennsylvania Osteopathic Medical Association
3 May 2014

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