GI ReConnect

June 17-19, 2021

Napa Valley, California

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Darren Brenner, MD:

- Consultant, Advisor and Speaker: Allergen, Ironwood, Salix, Alpha Sigma
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Redefining the 4-5: Diagnosing IBS With a 4-5 Minute History and a Maximum 4-5 Tests

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The Problem:

- Common Disorder
  - Affects approx. 5-8% of the USA population (Rome IV)
  - 7th most common diagnosis made by PCPs in USA
- Significant impact on quality of life
  - Life w/IBS-C/D survey (N=3254). What would exchange for 1 month of relief from IBS: >50% caffeine or alcohol, >40% sex, 24.5% cell phones, 21.5% internet for 1 month[1]
  - Individuals with IBS-D willing to accept >10% risk of death for cure
  - International pt survey (N=1966) on ave individuals willing to give up 25% of remaining life for cure (ave loss 15 yrs)
- Undiagnosed too often and for far to long
  - Average time to diagnosis = 4 years
  - ~ 25% of individuals diagnosed with IBS-D/C received the diagnosis >5 yrs after symptoms began
  - > 10% have symptoms for >10 years prior to diagnosis
  - Up to 75% of IBS sufferers remain undiagnosed and this is a MAJOR problem

Palsson OS et al. Gastroenterology 2020;158:1262-1273.

Almario C et al. DDW 2021: Abstract Su 085.

Peery AE et al. Gastroenterology 2015; 149:1731-41.

Ballou S et al. CGH 2019;17(12):2471-2478.

Shah SL et al. 2021;19(1):80-86.

Hungin APS et al. APT 2005;21(11):1365-1375.

Sayuk GS et al. AJG 2017:112:892-899.

Drossman DA et al. J Clin Gastroenterol 2009;43(6):541-550.

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The Differential: Abdominal Pain and Diarrhea are Present in Many GI Conditions

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	EPI	IBS-D	Celiac Disease	SIBO	Disaccharidase Deficiency	Crohn's/ Ulcerative Colitis	Giardia[2]
Diarrhea	✓	✓	✓	✓	✓	✓	✓
Abdominal pain	✓	✓	✓	✓	✓	✓	✓
Bloating	✓	✓	✓	✓	✓		✓
Flatulence	✓	✓		✓	✓		✓

The overlap of symptoms can contribute to misdiagnoses as well as a delayed diagnosis of the appropriate condition[3,4]

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Othman MO, et al. *Int J Clin Pract*. 2018;72(2):e13066. Gardner TB. *Clin Microbiol Rev*. 2001;14(1):114–128.

The IBS Pendulum

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Diagnosis of exclusion[1,2]

72% community GI

23% IBS experts

It's all IBS

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Pimentel M et al. Gastroenterology 2013;144:e1-5.; Spiegel BMR et al. AJG 2010;105:848-58.

The Diagnostic Criteria: Rome IV*

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Recurrent abdominal pain [or discomfort-deleted] on average at least 1 day per week in the last 3 months associated with 2 or more of the following:

**Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis*

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Lacy BE et al., Gastroenterology 2016; 150:1393-1407.

The IBS Subtypes: Rome IV

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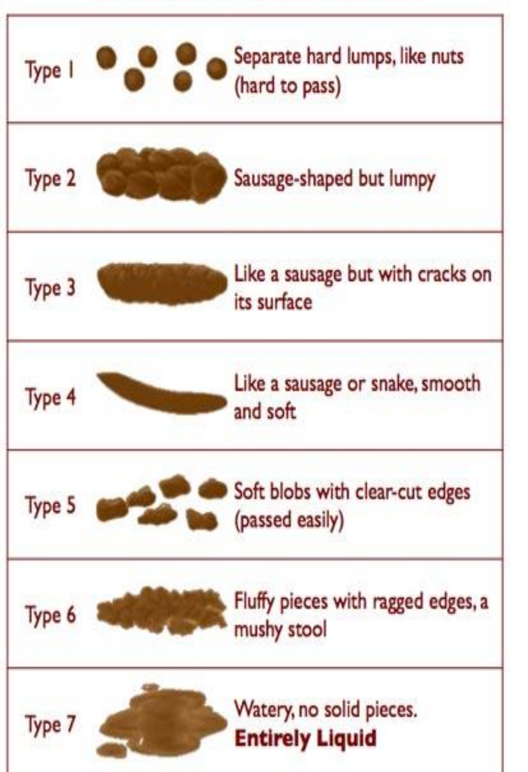

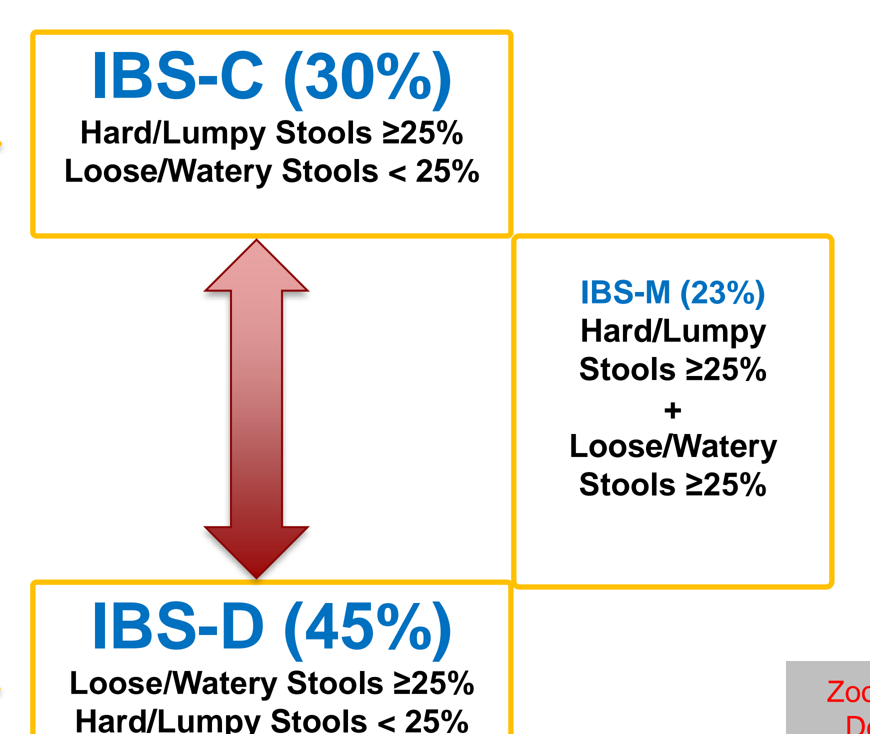

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Lacy BE et al., Gastroenterology 2016; 150:1393-1407 Lovell RM and Ford AC. CHG 2012;10:712-721

The 8 Simple "Rules" For Making An Accurate Diagnosis of IBS

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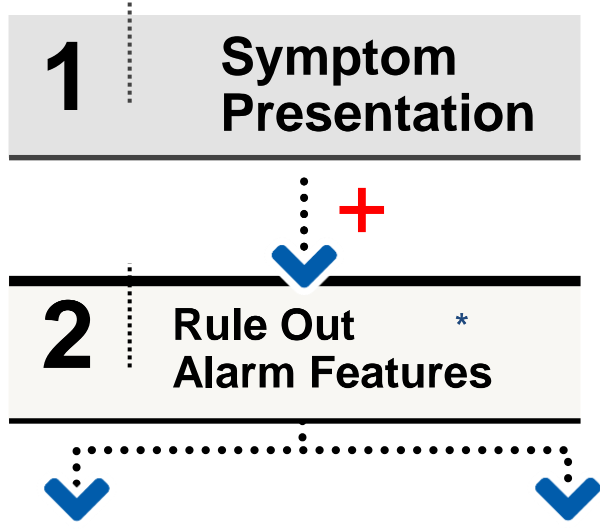

If present*…

Diagnostic testing may be performed to further evaluate patient

If none…

Minimal testing is necessary

Are symptoms consistent with Rome criteria for IBS-?

- Q1. Do you experience pain?
- Q2. Does this pain improve or worsen with bowel movements?
- Q3. When the pain is present is it associated with a change in stool frequency or texture?

Are secondary causes or alarm features present?

- Q4: Is anemia or recurrent bleeding present?
- Q5: Do these symptoms represent an acute change?
- Q6: Is there a family history of Celiac, IBD, or CRC?
- Q7: Have you experienced significant unintentional weight loss?
- Q8: Did the symptoms begin after age 50?

Diagnosis based on symptoms alone potentially accurate in up to 98% of patients

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Cash BD et al. *Am J Gastroenterol*. 2002;97(11):2812-2819.; Vanner SJ et al. *Am J Gastroenterol*. 1999;94(10):2912-2917

The Positive Diagnostic Strategy

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- 302 Pts randomized Rome III IBS no alarm signs/symptoms
  - Positive Diagnostic Strategy (CBC, CRP)
  - DOE (CBC, CRP, Ca, Bili, ALT, AP, Alb, TSH, Ttg, lactase gene, 3 O&P, flex sign + bx)
- Follow-up 4 weeks and 12 months
- Multiple Clinical and economic outcomes
  - Symptom severity compared to baseline (GSRS)
  - Symptom change from baseline
  - Satisfaction with management
  - Use of healthcare resources (practitioners, ER, further diagnostic testing, sick days)

	Baseline		4 weeks			1 year		
	Diagnosis of exclusion (n = 152)	Positive diagnosis (n = 150)	Diagnosis of exclusion (n = 152)	Positive diagnosis (n = 150)	P value[a]	Diagnosis of exclusion (n = 152)	Positive diagnosis (n = 150)	P value[a]
Gastrointestinal symptoms (GSRS-IBS/GSRS)[b]								
Total score,[c] mean (SD)	3.75 (1.06)	3.70 (0.95)	3.22 (1.08)	3.21 (0.93)	.79	3.18 (1.24)	2.95 (1.87)	.17
Pain	3.96 (1.26)	3.95 (1.29)	3.47 (1.26)	3.51 (1.32)	.75	3.37 (1.45)	3.17 (1.31)	.34
Constipation	3.04 (1.70)	3.19 (1.64)	2.68 (1.48)	2.68 (1.48)	.80	2.45 (1.49)	2.54 (1.51)	.37
Diarrhea	3.53 (1.45)	3.32 (1.31)	2.89 (1.28)	2.89 (1.28)	.93	3.01 (1.47)	2.66 (1.20)	.28
Satiety	3.27 (1.80)	3.09 (1.72)	2.88 (1.63)	2.88 (1.63)	.61	2.81 (1.74)	2.54 (1.46)	.35
Bloating	4.72 (1.43)	4.76 (1.34)	4.06 (1.44)	4.06 (1.44)	.36	4.01 (1.52)	3.68 (1.61)	.38
Reflux	1.90 (1.26)	2.01 (1.20)	1.72 (1.08)	1.72 (1.08)	.28	1.76 (1.15)	1.71 (1.05)	.08
Improvement in symptoms compared with baseline, n (%)					P value[d]			P value[d]
Better	—	—	42 (28)	47 (31)	.84	63 (41)	60 (40)	.80
Worse	—	—	24 (16)	25 (18)		13 (9)	15 (10)	
No change	—	—	78 (51)	75 (50)		44 (29)	44 (29)	
Missing	—	—	8 (5)	3 (2)		32 (21)	31 (21)	
Satisfaction with management, n (%)					.59[e]			.06[e]
Very satisfied/satisfied	—	—	132 (87)	134 (89)		104 (68)	93 (62)	
Dissatisfied/very dissatisfied	—	—	1	1		3 (2)	3 (2)	
Not satisfied/not dissatisfied	—	—	5 (3)	4 (3)		7 (5)	12 (8)	
Missing	—	—	14 (9)	11 (7)		38 (25)	42 (28)	

1-yr f/u total costs: $3160 PDS $5075 in DOE strategy P=.12

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Begtrup LM et al. CGH2013;11:956-962.

The Diagnostic Testing To Consider in Patients with Suspected IBS and No Alarm Features

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IBS-D[1,2,3]

- IgA TtG/Quantitative IgA
- Fecal calprotectin/CRP
  Lactoferrin
- Serum C4/FGF-19
- SeHCAT or fecal bile acids
- When colonoscopy performed, obtain random biopsies
- Anti-CdtB/anti-vinculin antibodies

IBS-M[1]

- CRP or fecal calprotectin
- IgA TtG ± quantitative IgA
- Stool diary
- Consider abdominal plain film to assess for fecal loading

IBS-C[1]

- If severe or medically refractory, refer to specialist for physiologic testing

1. Chey WD et al. *JAMA*. 2015;313(9):949-958.
2. Pimentel M et al. *PLoS ONE*. 2015;10(5):e0126438
3. Carrasco-Labra A et al. Gastroenterology 2019;157:859-880.

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The Rule Out: Celiac Disease in IBS?

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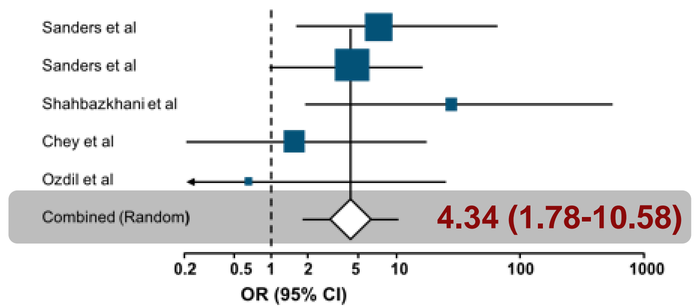
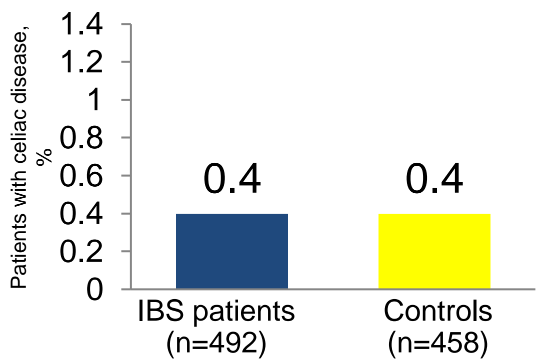
International Meta-analysis[1]
Prevalence of biopsy-proven celiac disease in IBS vs controls



US Prospective Study[2]
Non-constipated IBS patients (Rome II) biopsy-proven celiac disease



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1. Ford A et al. *Archives Int Med.* 2009;169:651
2. Cash BD and Chey WD. *Gastroenterology.* 2011;141:1187

The Rule-out: IBD in IBS With Fecal calprotectin > CRP

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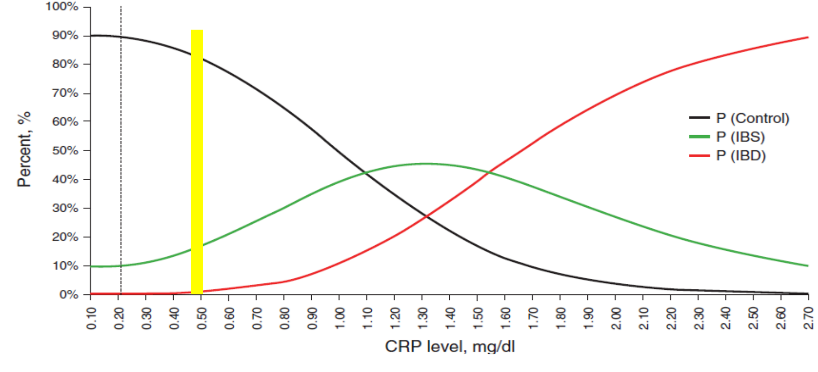
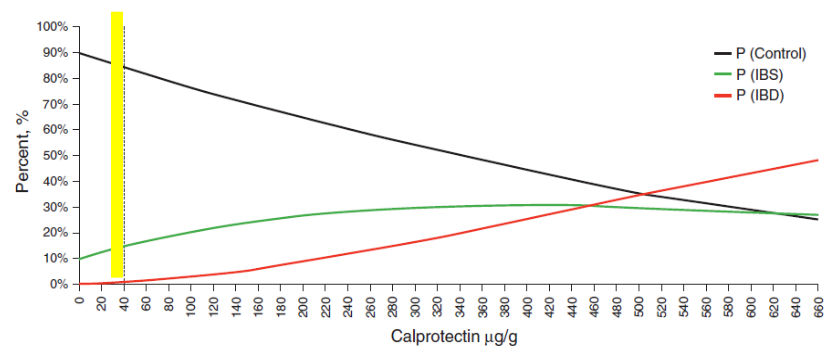
Systematic Review: 12 studies; N=2145:1059 IBD, 595 IBS, 491 controls

Human adult studies: Pts with confirmed IBD compared ESR, CRP, Fecal Calprotectin, Fecal Lactoferrin with IBS or controls

Naïve Bayes statistics to assess probability of having IBS or IBD based on biomarker values





CRP	Percent likelihood HC	Percent likelihood IBS	Percent likelihood IBD
0.1	89.9	9.8	0.2
0.2	89.8	9.9	0.3
0.3	88.4	11.2	0.4
0.4	85.8	13.6	0.6
0.5	82.1	16.8	1.1
0.6	77.4	20.8	1.8
0.7	71.7	25.8	3.0
0.8	65.1	30.2	4.7
0.9	57.9	35.0	7.2
1.0	50.2	39.3	10.6

Calprotectin	Percent likelihood HC	Percent likelihood IBS	Percent likelihood IBD
10	88.6	11.0	0.4
20	87.1	12.4	0.5
30	85.5	13.7	0.8
40	84.1	14.9	1.0
50	82.7	16.0	1.3
60	81.4	17.0	1.6
70	80.1	18.0	1.9
80	78.8	18.9	2.3
90	77.6	19.7	2.7
100	76.3	20.6	3.1

Menees SB et al. AJG 2015;110:444-454.

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The Rule Out Even Performing Most of These: ACG Recommendations for Diagnostic Testing in IBS

Diagnostic Test	ACG Recommendation
CBC, Chemistries, Thyroid Testing	Not recommended but nobody likely to complain
Stool for ova and parasites	Not recommended*
Abdominal imaging	Not recommended
Breath testing for SIBO	Insufficient data to recommend**
Routine colonoscopy	Perform in patients with alarm features and in those aged >45
Allergy/Food sensitivity testing	Not recommended*** unless reproducible symptoms to specific food

*Giardia in individuals from or visiting endemic areas, camping, daycare exposures
**2009 recommendation
***Unless reproducible symptoms to a specific food

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Brandt LJ et al. AJG 2009;104 Suppl 1:S1-35.
Lacy BE et al. AJG 2021: 116:17-44.

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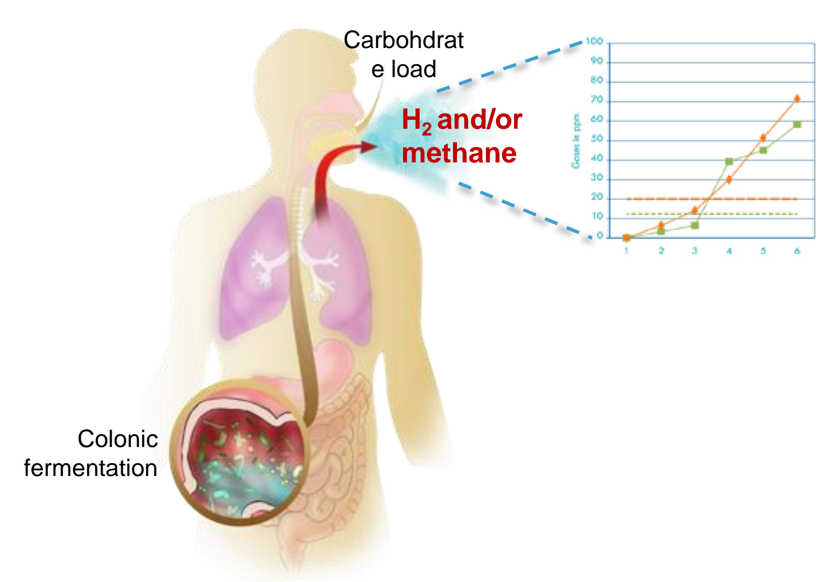
The Rule In: Breath Testing for IBS?



- Simple and safe test to diagnose SIBO
- Useful in assessing conditions associated with bloating like IBS
- Significant heterogeneity in test performance, preparation, indications for testing, and interpretation of results
- ACG IBS Guideline: Not addressed
- ACG SIBO guideline: "We **SUGGEST** the use of breath testing for the diagnosis of SIBO in patients with IBS" (conditional rec/very low level of evidence)

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Pimentel M, et al. *Am J Gastroenterol*. 2020;115:165-178.
Moayyedi P, et al. *Journal Canadian Assoc of Gastroenterology* 2019;2:6-29

Updated MA: Breath Testing for SIBO in IBS

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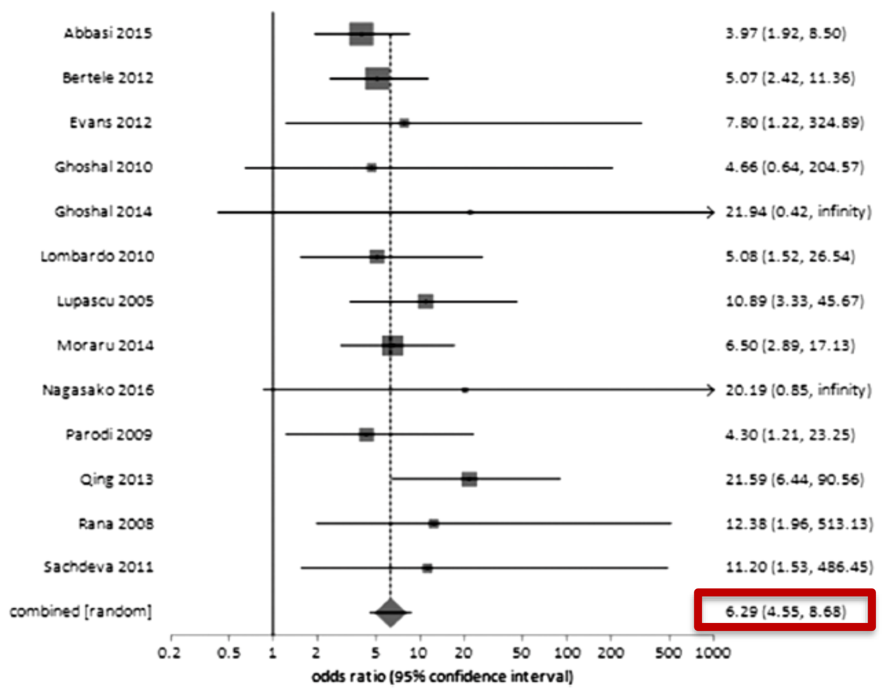

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Moayyedi P et al. Journal Canadian Assoc of Gastroenterology 2019;2:6-29

The Take Home Points:

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- IBS is NOT a coverall for everything in the GI tract
  - Up to 50% of my referrals do not have IBS
- IBS is NOT a diagnosis of exclusion (unless excluding with history)
  - Earlier Rome Criteria PPV w/o alarm signs/symptoms 97-98%
- The 4-5 rule holds: Just not your mother's 4-5
  - 4-5 minutes to ask 8 questions/4-5 studies rule in and out IBS-D/0 studies for IBS-C
  - Avoid superfluous studies
- Confident positive diagnostic strategy will reduce the 75% undiagnosed threshold
- We cannot help what we cannot diagnose

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