



2023 NCSCG
20TH ANNUAL
3 GI SYMPOSIUM

Objectives

- Revisiting Dyspepsia Clinical Guidelines
 - Test & Treat vs. Upfront EGD
 - Personalizing treatment choices
- What's on the horizon?
 - Biomarker directed approach: Ready for primetime?

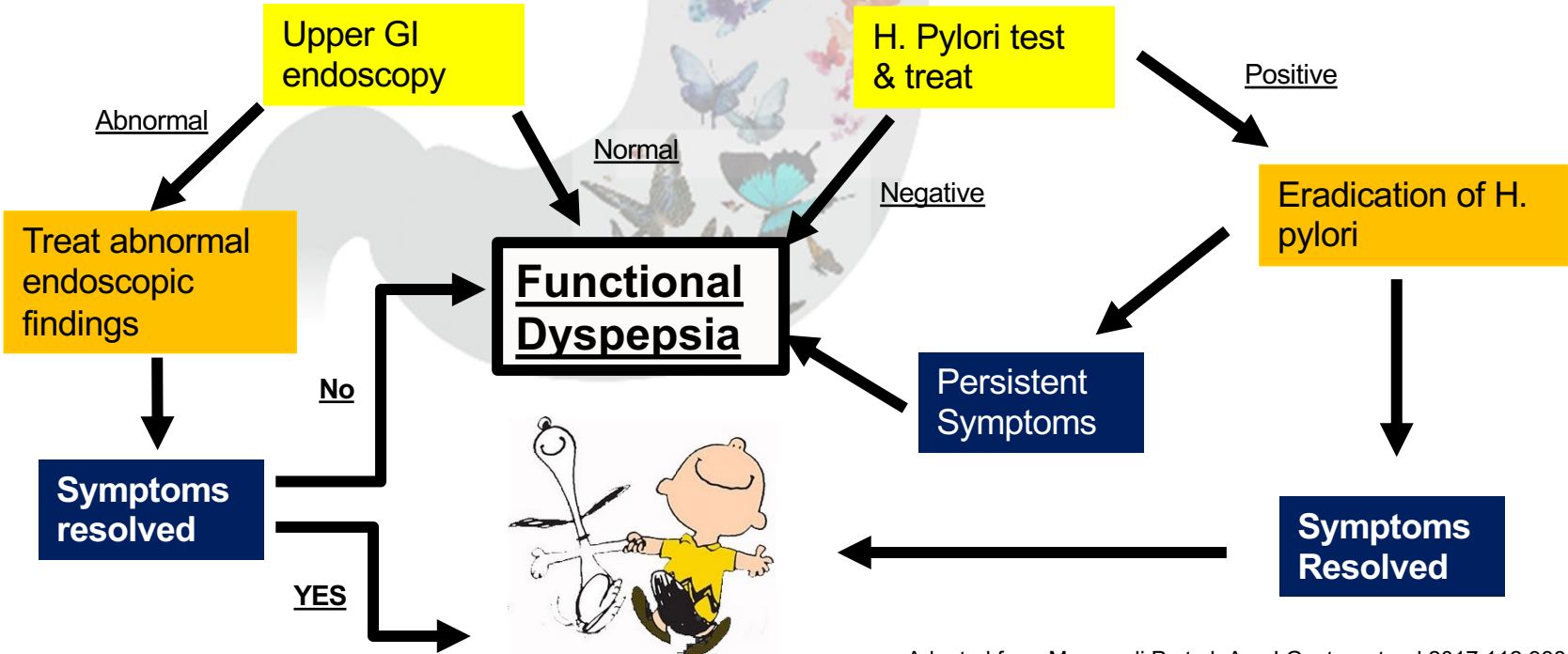
Approach to Dyspepsia

Dyspeptic Symptoms

Alarm features or age > 60

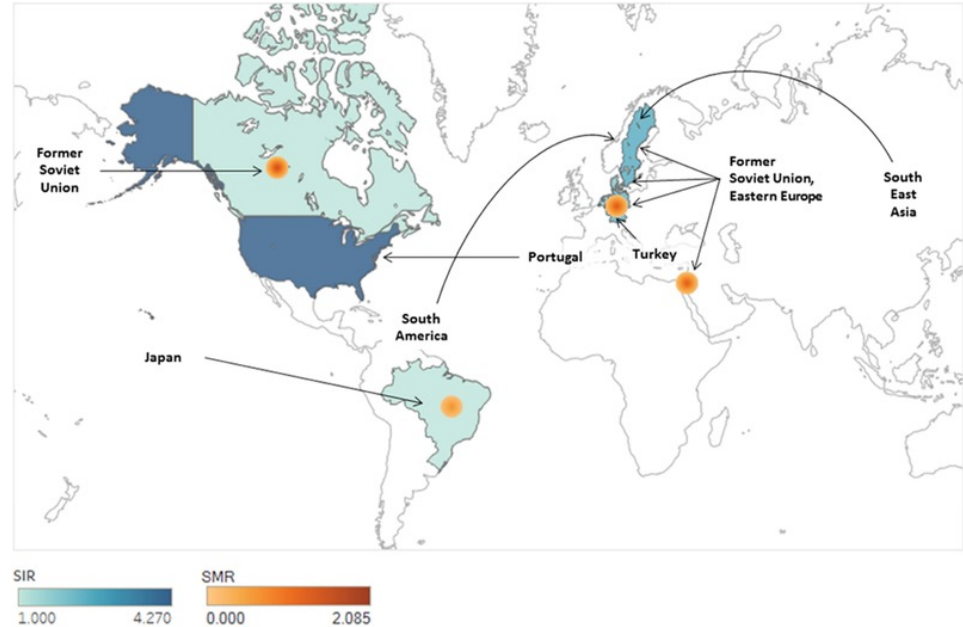
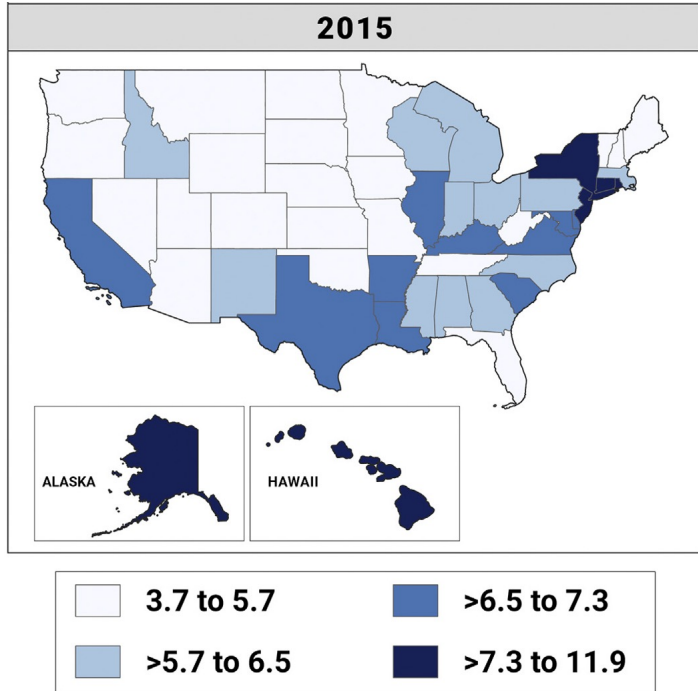
No alarm features and age < 60*

*Age < 45 if Asian Immigrant

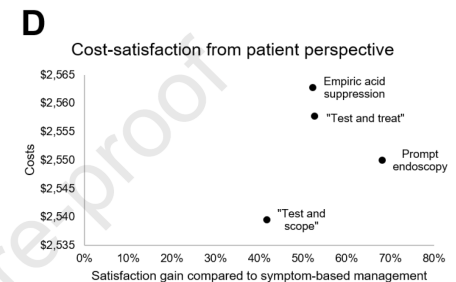
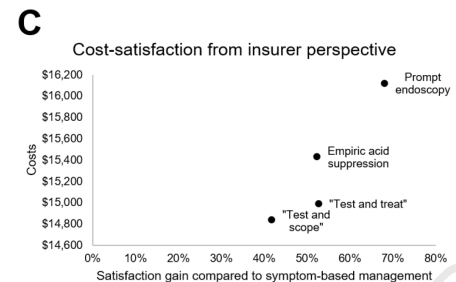
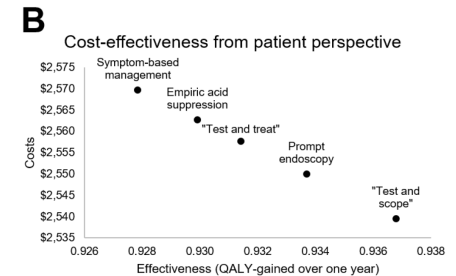
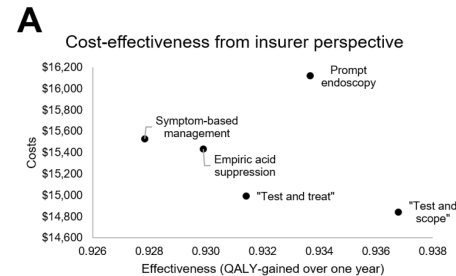
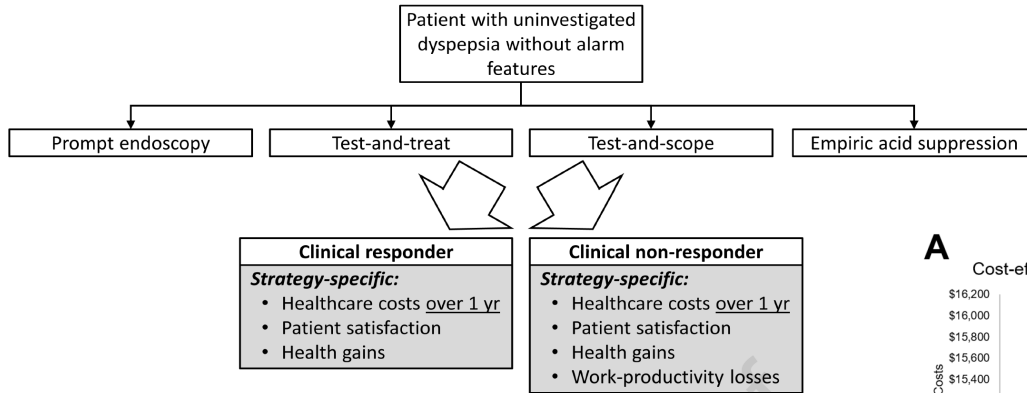


Adapted from Moayyedi P et al. Am J Gastroenterol 2017;112:988-1023

Prevalence of Gastric Cancer

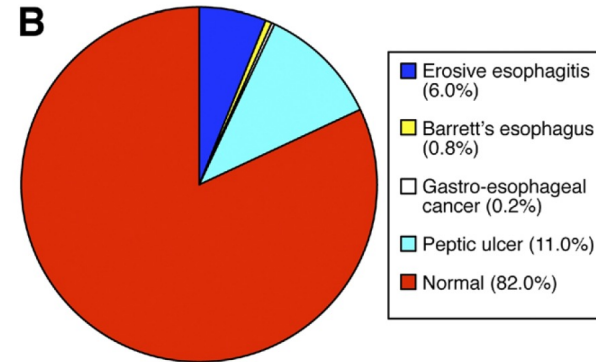
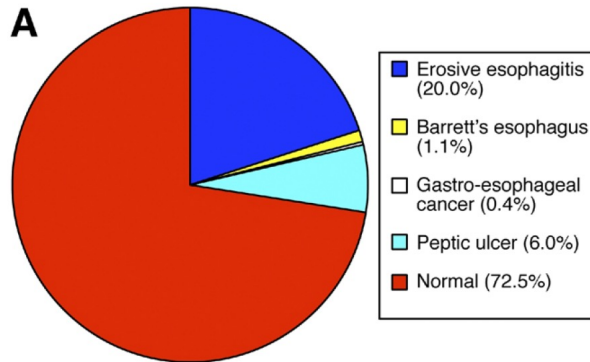


Upfront EGD vs. Test & Treat



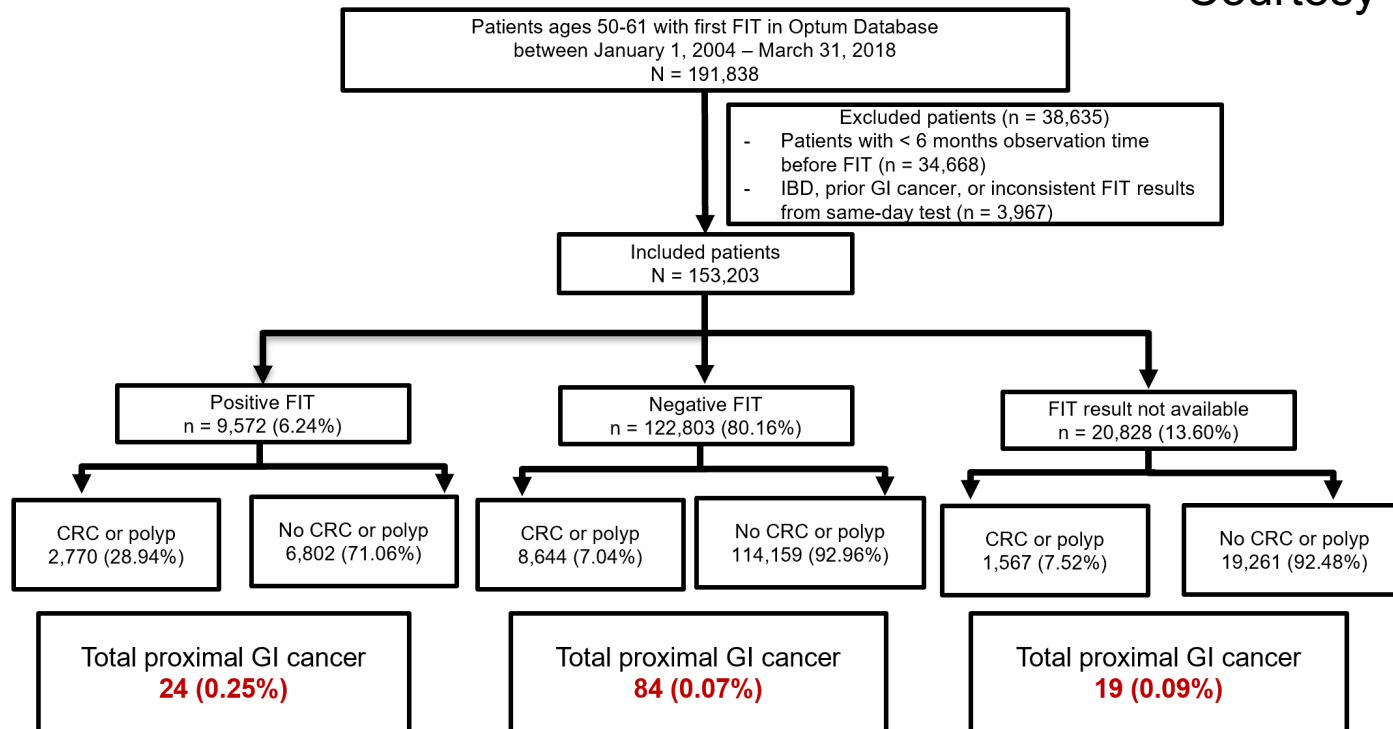
Endoscopic Findings in Patients with Dyspepsia

Endoscopic finding	Number of studies	Number of subjects	Pooled prevalence	95% CI	I ²	P value for I ²
Erosive esophagitis	7	2067	13.4	1.3–35.1	99%	<.001
Barrett's esophagus	6	1982	1.0	0.03–3.4	92%	<.001
Peptic ulcer	9	2597	8.0	6.0–11.0	83%	<.001
Gastric ulcer	6	2284	3.2	2.0–4.7	67%	.007
Duodenal ulcer	6	2284	3.4	1.6–5.9	88%	<.001
Gastric cancer	6	1982	0.25	0.05–0.6	27%	.23
Esophageal cancer	6	1982	0.1	0.02–0.3	0%	.95

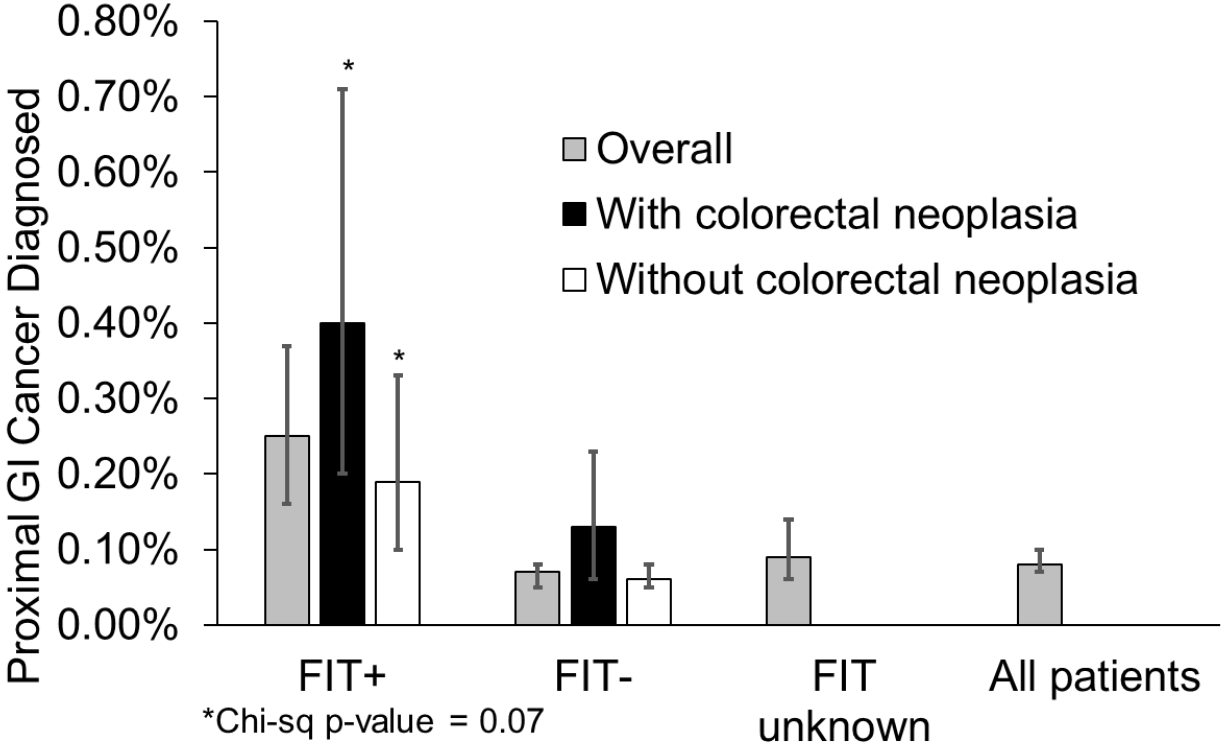


Upper GI Malignancies in FIT+ Patients

*Courtesy of Margaret Zhou



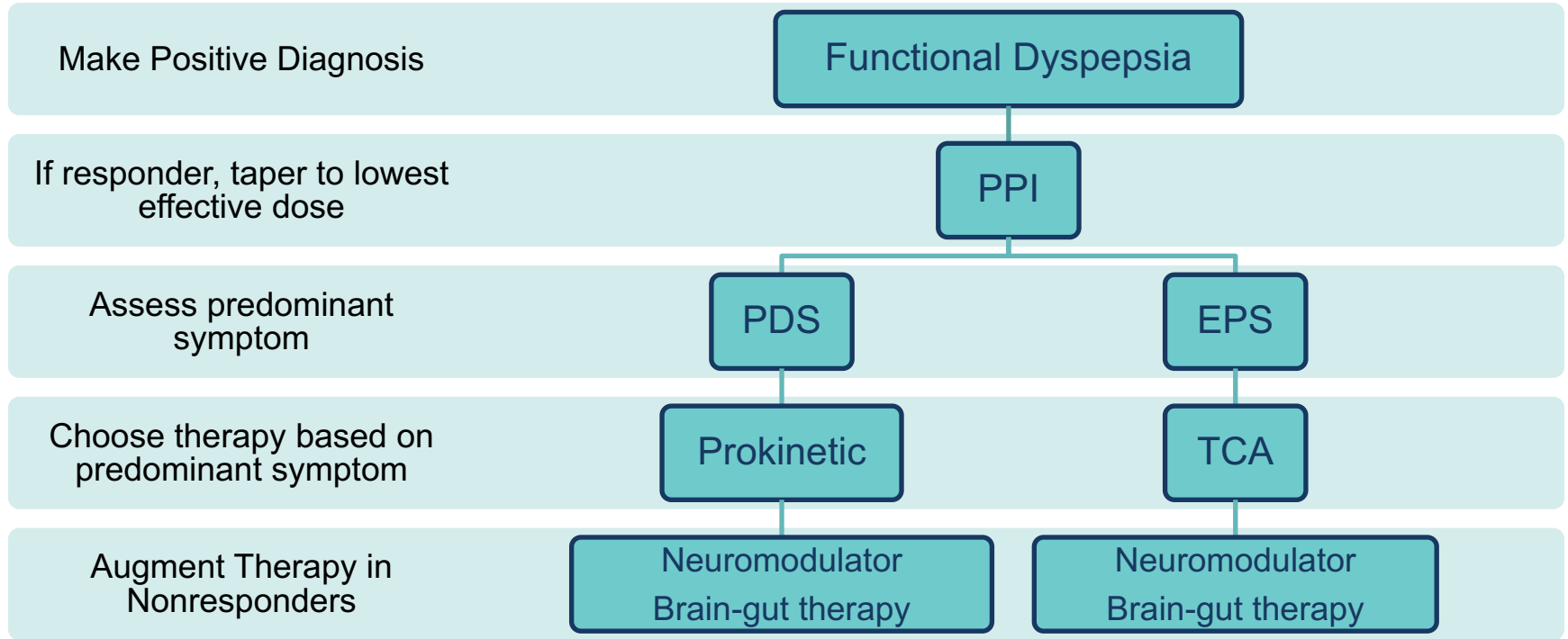
*Courtesy of Margaret Zhou



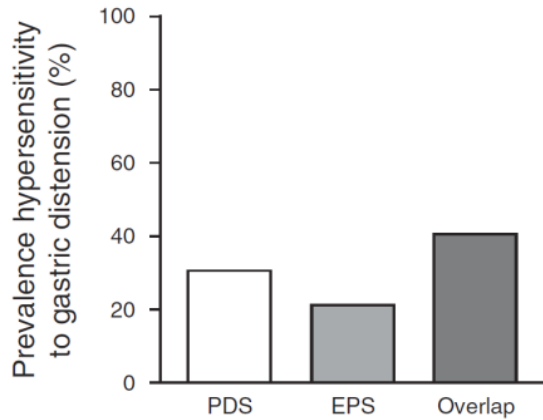


Take Aways

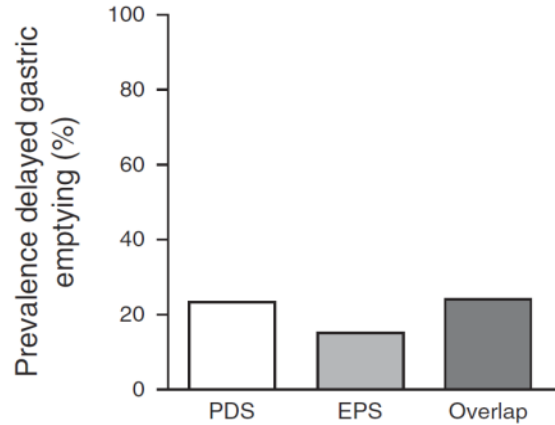
Approach to FD Therapy



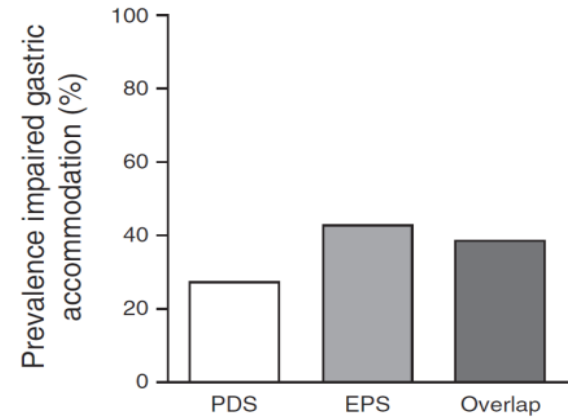
Pathophysiology of Functional Dyspepsia



Visceral Hypersensitivity = 37%



Delayed Gastric Emptying = 23%

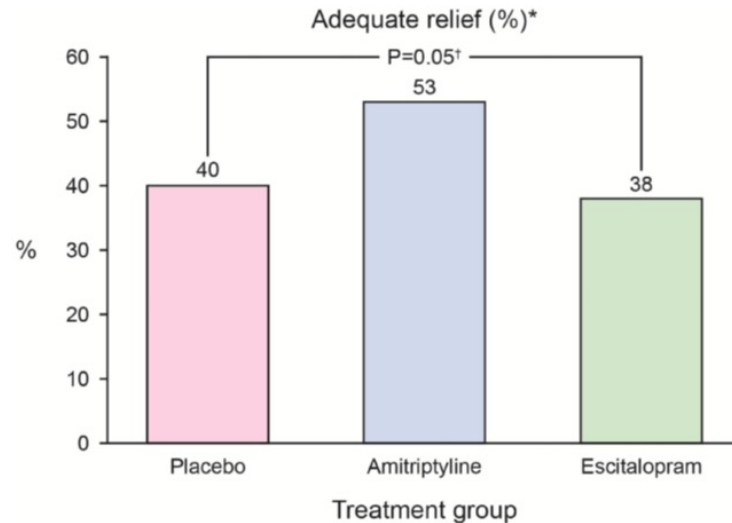


Impaired Accommodation = 37%

Effect of Amitriptyline and Escitalopram on Functional Dyspepsia: a Multi-Center, Randomized, Controlled Study

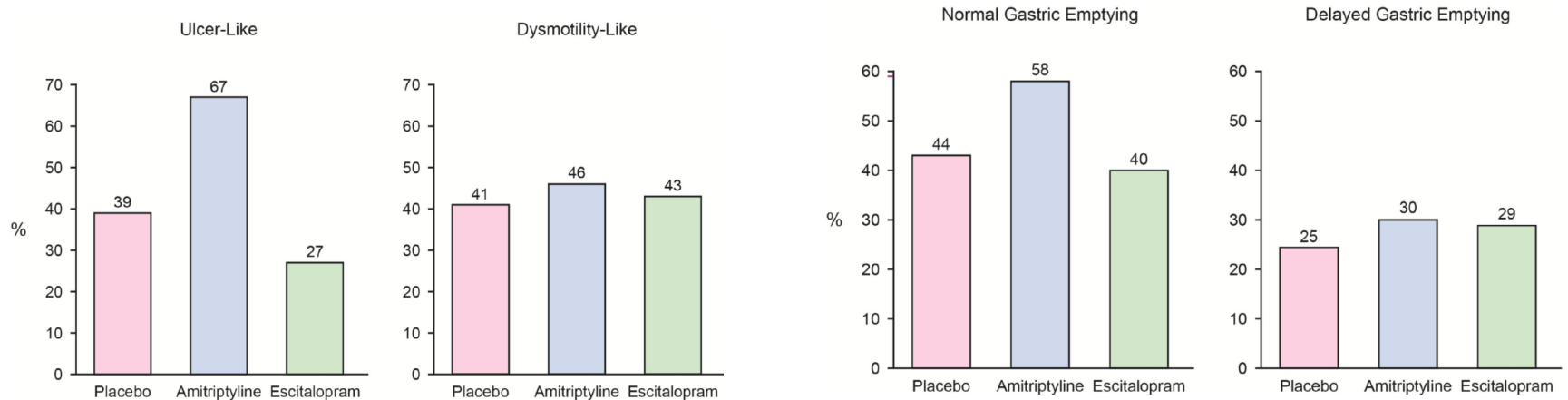
Subject Characteristics, n=292

	PLA n=97	AMI n=97	ESC n=98
Age (years), mean (SD)	45 (16)	43 (15)	45 (15)
Female, n (%)	73 (75%)	72 (74%)	74 (76%)
Caucasian, n (%)	83 (86%)	82 (85%)	85 (87%)
Body mass index (kg/m ²), mean (SD)	26.4 (5.2)	25.7 (6.0)	26.1 (5.6)
HADS score, mean(SD)			
HADS depression	3.1 (2.9)	3.1 (2.7)	3.1 (2.7)
HADS anxiety	5.0 (3.8)	5.2 (3.2)	5.4 (3.8)
Dyspepsia subtype			
Dysmotility-like, n (%)	69 (71%)	67 (69%)	68 (69%)
Ulcer-like, n (%)	28 (29%)	30 (31%)	30 (31%)
Delayed gastric emptying, n (%)	20 (21%)	20 (21%)	21 (21%)
Abnormal satiety, n (%)	55 (57%)	55 (57%)	55 (56%)
<i>H. pylori</i> antibody positive, n (%)	9/92 (10%)	14/96 (15%)	17/94 (18%)
Baseline PPI use, n (%)	18 (19%)	27 (28%)	23(23%)



FD Subtypes Differ in Response to TCA Therapy

- Amitriptyline improves symptoms in “ulcer-like” (EPS) but not “dysmotility-like” (PDS) FD
- FD patients with delayed GE do not respond to amitriptyline



Increased Gastric Mast Cells and Eosinophils in FD

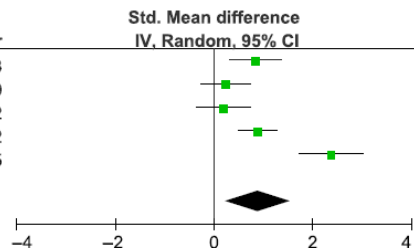
(A)

Study or Subgroup	FD			CON			Weight	Std. Mean difference		Year
	Mean	SD	Total	Mean	SD	Total		IV, Random, 95% CI	Year	
Hall (2003)	213.8	134.4	62	109.4	79.6	20	20.0%	0.84	[0.32, 1.36]	2003
Li (2010)	11.6	20.7	65	7	10.9	20	20.2%	0.24	[-0.26, 0.74]	2010
Binesh (2012)	10.3	10.2	25	8.5	7.9	27	19.8%	0.20	[-0.35, 0.74]	2012
Pignataro (2012)	11.8	12.3	53	4	2.4	56	21.2%	0.89	[0.49, 1.28]	2012
Cheung (2015B)	0.15	0.07	45	0.01	0.02	23	18.7%	2.37	[1.72, 3.02]	2015

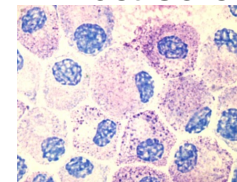
Total (95% CI) 250 146 100.0% 0.89 [0.24, 1.54]

Heterogeneity: $\tau^2 = 0.48$; $\chi^2 = 32.25$, $df = 4$ ($P < .00001$); $I^2 = 88\%$

Test for overall effect: $Z = 2.68$ ($P = .007$)



Mast Cells



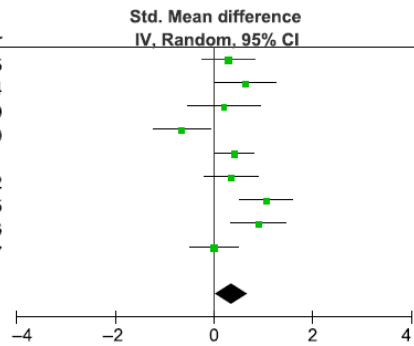
(B)

Study or Subgroup	FD			CON			Weight	Std. Mean difference		Year
	Mean	SD	Total	Mean	SD	Total		IV, Random, 95% CI	Year	
Touken (1985)	8.1	9	27	5.7	7.1	27	11.3%	0.29	[-0.24, 0.83]	1985
Ashorn (1994)	98.3	131.4	54	22.5	20.2	13	10.3%	0.63	[0.01, 1.25]	1994
Bafutto (2009)	7	10.2	36	5.1	3.9	9	8.9%	0.20	[-0.53, 0.93]	2009
Faure (2010)	0.3	0.3	17	0.5	0.3	40	10.8%	-0.66	[-1.24, -0.08]	2010
Pignataro (2011)	24.8	5	50	23	3.5	50	13.3%	0.41	[0.02, 0.81]	2011
Binesh (2012)	7.8	5.7	25	6	4.8	27	11.2%	0.34	[-0.21, 0.89]	2012
Cheung (2015B)	0.09	0.05	45	0.04	0.04	23	11.4%	1.05	[0.52, 1.59]	2015
Lee (2016)	4.2	0.9	43	2	4.2	19	11.0%	0.90	[0.33, 1.46]	2016
Wauters (2017)	3	3.6	31	3	2.2	31	11.9%	0.00	[-0.50, 0.50]	2017

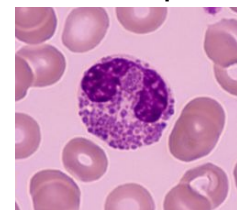
Total (95% CI) 328 239 100.0% 0.36 [0.04, 0.68]

Heterogeneity: $\tau^2 = 0.16$; $\chi^2 = 24.81$, $df = 8$ ($P = .002$); $I^2 = 68\%$

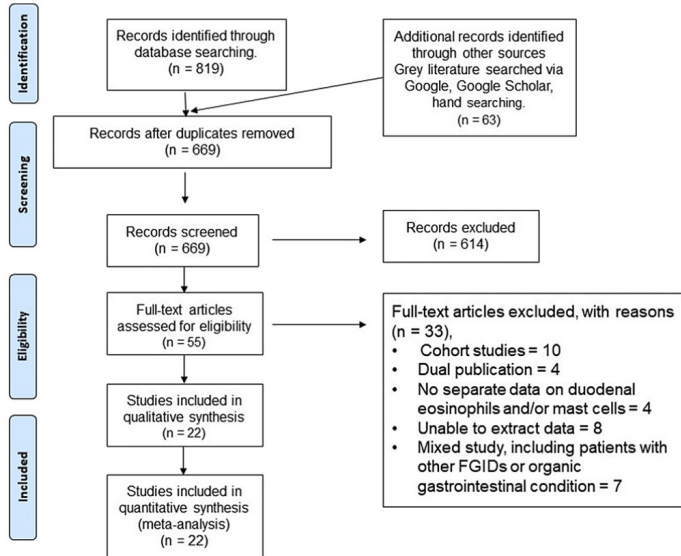
Test for overall effect: $Z = 2.18$ ($P = .03$)



Eosinophil



Meta-analysis of Duodenal Eosinophils & FD



Duodenal eosinophils in FD patients compared to controls

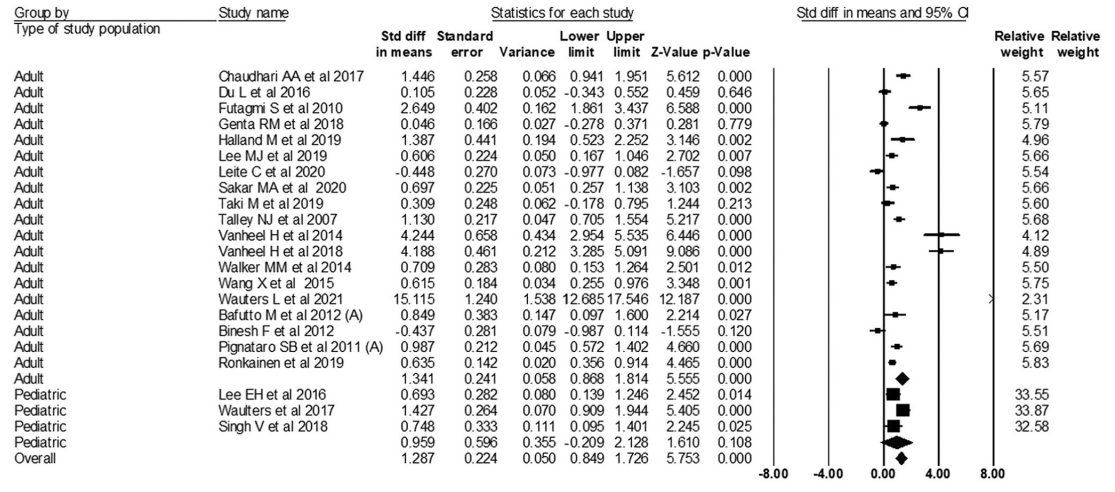
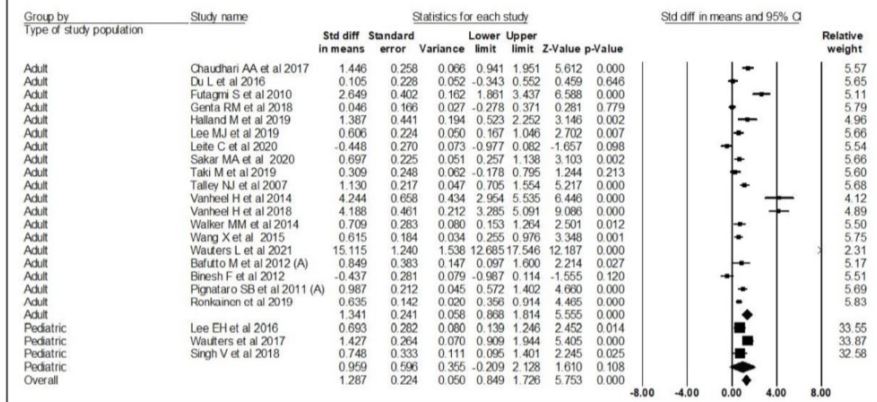


Figure 2. Forest plot of case-control studies showing duodenal eosinophils in functional dyspepsia (FD) patients and controls. FD patients showed increased numbers of duodenal eosinophils (standardized mean difference [SMD], 1.29; 95% CI, 0.85–1.73; $P = .0001$; $I^2 = 93.61$; $P = .0001$). Std diff, standardized difference.

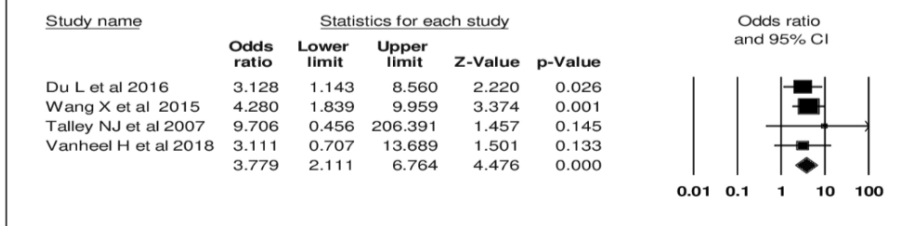
Microscopic Duodenal Inflammation in FD

Duodenal eosinophils in FD patients compared to controls

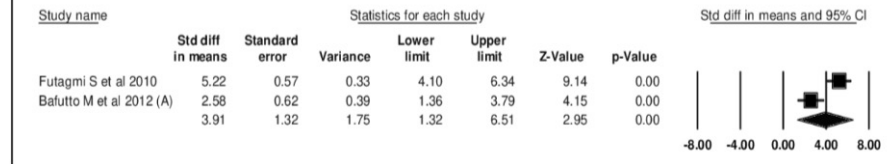


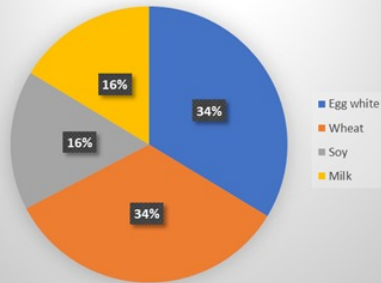
- Degranulated eosinophils higher in FD vs. control (OR 3.78)
- Increased eosinophils is postinfectious FD > noninfectious FD > controls

Degranulation of duodenal eosinophils in FD patients and controls



Duodenal eosinophils in patients with post infectious FD and controls





DDW2023

Digestive Disease Week®

MAY 6-9, 2023 | CHICAGO, IL
EXHIBIT DATES: MAY 7-9, 2023

The six-food elimination diet improves symptoms of functional dyspepsia.

Jolien Schol¹, Karen Routhiau¹, I-Hsuan Huang¹, Karen Van den Heute¹, Joran Tóth¹, Lukas Balsiger¹, Florencia Carbone¹, Tim Vanuytsel¹ and Jan Tack¹
¹ Translational Research Center for Gastrointestinal Disorders, KU Leuven, Leuven, Belgium

INTRODUCTION

Functional dyspepsia is divided by Rome IV criteria into two subtypes (1):

1. Epigastric pain syndrome (EPS)
2. Postprandial distress syndrome (PDS): characterized by early satiety and postprandial fullness

The pathophysiology is complex (2):

- Gastric sensorimotor function
- Duodenal low-grade inflammation
- Decreased duodenal mucosal integrity

Triggers are unknown, but food antigens are a major candidate.

AIM

To evaluate the effect of the six-food elimination diet (6FED) in PDS on:

1. Symptoms
2. Duodenal alterations
3. Gastric sensorimotor function

METHOD

- PDS patients were recruited
- Helicobacter pylori negative
- The six-food elimination diet (6FED) was followed for 8 weeks

1. PDS symptoms

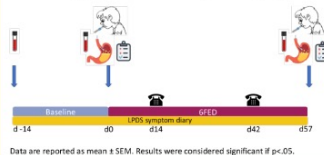
Evaluated using the Leuven Postprandial Distress Scale (LPDS) diary. A change in PDS score of more than 0.7 was considered significant (3).

2. Duodenal alterations with duodenal biopsies:

Permeability: ussing chambers
Inflammation: H&E stained slides

3. Gastric sensorimotor function

Gastric accommodation and sensitivity: gastric barostat
Gastric emptying: 13C octanoic acid gastric emptying test



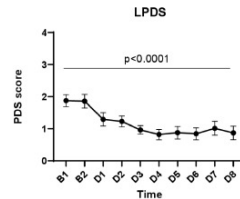
RESULTS

1. SYMPTOMS

- 15 PDS patients 73% women; 33±3 years; BMI 23.9±1.0 kg/m²
- 19% postinfectious onset
- PDS score: ↓ after 6FED (p < 0.0001)
- 73% responder rate.

	Baseline	6FED	p-value
	Mean ± SEM	Mean ± SEM	
Total PDS score	1.9±0.2	0.9±0.2	< 0.0001
Early satiety	1.7±0.2	0.9±0.2	< 0.0001
Postprandial fullness	2.0±0.2	1.0±0.3	< 0.0001
Bloating	2.0±0.2	0.9±0.2	< 0.0001

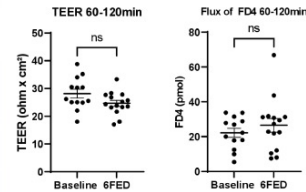
Evolution of PDS score and individual symptoms of the Leuven Postprandial Distress Scale.



Evolution of PDS score. B = baseline period. D = diet period

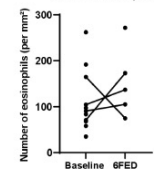
2. DUODENAL ALTERATIONS

- No significant effect on TEER (p=0.16)
- No significant effect on FD4 paracellular flux (p = 0.30)
- No significant effect on duodenal eosinophil count (p = 0.63)



Average of trans-epithelial electrical resistance from 60-120 min before and after the six-food elimination (6FED) diet

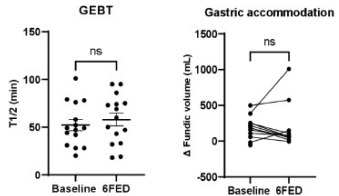
Duodenal eosinophils



Duodenal eosinophil count (preliminary data)

3. GASTRIC SENSORIMOTOR FUNCTION

- No significant effect on gastric emptying (p=0.24)
- No significant effect on gastric accommodation (p=0.37)
- No significant effect on gastric hypersensitivity; two of three patients with hypersensitivity normalized after the diet (p=0.59)



GEBT = gastric emptying breath test
T1/2 = half emptying time

CONCLUSIONS

In PDS patients in an uncontrolled cohort study:

- A 6-food elimination diet improves symptoms of functional dyspepsia

However, the pathophysiological mechanism is uncertain:

- No effect on duodenal permeability or duodenal eosinophils
- No effect on gastric sensorimotor function

REFERENCES

1. Stanghellini V, et al. Gastrointestinal disorders. Gastroenterology. 2016;150(6):1380-92.
2. Wauters, L., et al. Gut. 2020; 69(3): 591.
3. Carbone, F., et al. Alimentary Pharmacology & Therapeutics. 2016; 44(9): 989-1001.

CONTACT INFORMATION

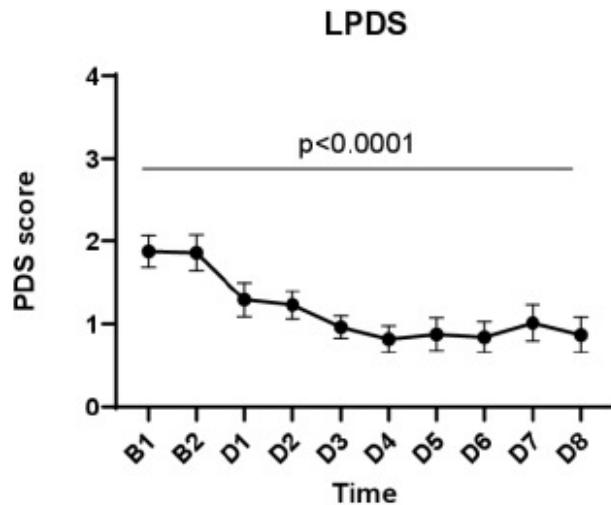
jolien.schol@kuleuven.be
+3216 34 56 63



Results

- 6FED decreases postprandial symptoms in 73% of patients
 - Symptom improvement seen week 1 of 6FED
- 6FED did not change duodenal eosinophil count or permeability
- Diet did not impact gastric emptying, accommodation or sensation

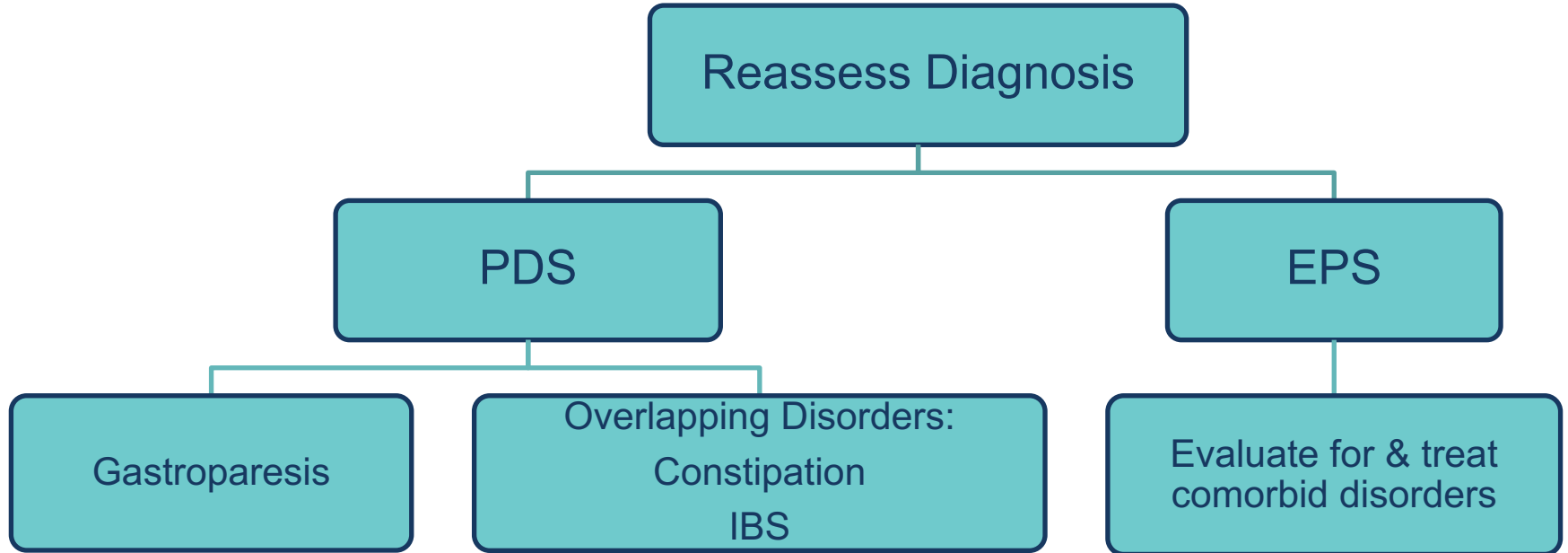
	Baseline Mean \pm SEM	6FED Mean \pm SEM	p-value
Total PDS score	1.9 \pm 0.2	0.9 \pm 0.2	< 0.0001
Early satiation	1.7 \pm 0.2	0.9 \pm 0.2	< 0.0001
Postprandial fullness	2.0 \pm 0.2	1.0 \pm 0.3	< 0.0001
Bloating	2.0 \pm 0.2	0.9 \pm 0.2	< 0.0001





Take Aways

Approach to Refractory FD Symptoms



Clinical Similarities & Differences

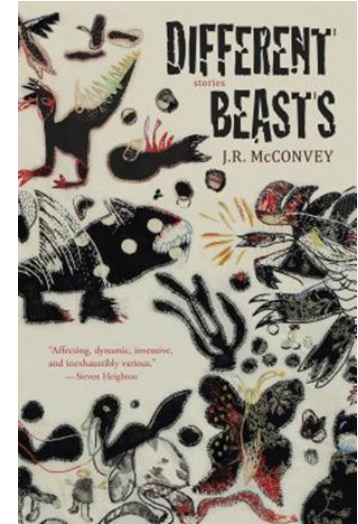
	Gastroparesis	Functional Dyspepsia
Pathophysiology	Antral hypomotility, impaired accommodation, sensory dysfunction, interstitial cells of Cajal loss	Sensory dysfunction, impaired accommodation, antral hypomotility, mucosal inflammation
Predominant symptoms	- Nausea, vomiting & postprandial abdominal pain - Weight loss	- Abdominal pain/burning (postprandial or unrelated to meals), early satiety
Symptom duration	Any	Onset > 6 months with symptoms 3 days/wk
Diagnostic criteria	Delayed Gastric emptying (scintigraphy, Spirulina breath test, C ¹³ breath test, wireless capsule motility)	Rome IV criteria
Gastric Emptying Findings	Delayed	- Delayed = 1/3 - Normal = 2/3 - Rapid < 5%
PPI response	+/- May further delay GE	Helps symptoms (RR =0.75)
TCA therapy	None	Helps
Prokinetic*	Helps (R=0.169)	Not effective

Adapted Moshiree B et al. Gastrointest Endosc Clin N Am. 2019 Jan;29(1):1-14.

* Janssen P et al. Am J Gastroenterol 2013;108:1382-1391

Comparison of the Pathophysiology of FD & GP

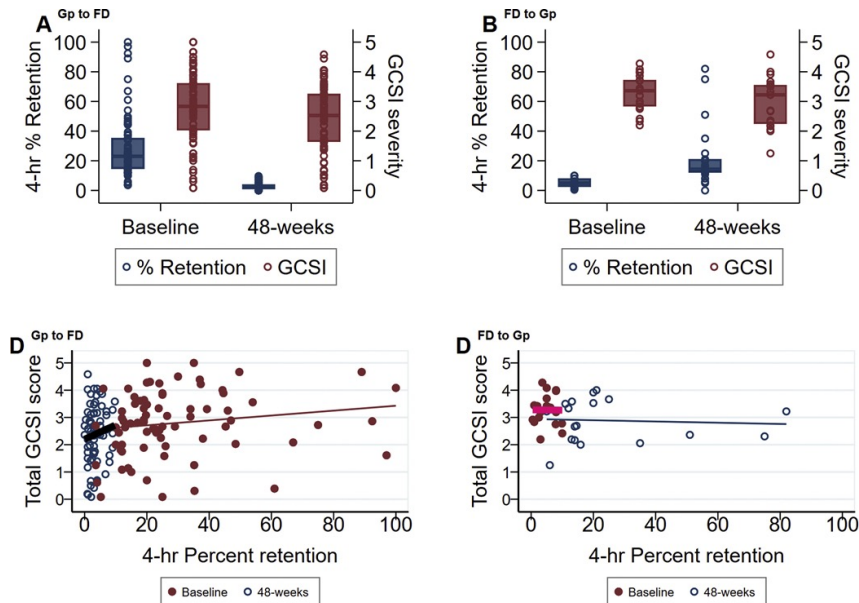
Pathophysiology	Gastroparesis	Functional Dyspepsia
Delayed Gastric Emptying	+	+
Rapid Gastric Emptying		+
Visceral Hypersensitivity	+	+
Impaired Fundic Accommodation	+	+
Antral Hypomotility	+	
Antroduodenal Discoordination	+	+
Duodenal Dysmotility	+	+
Gastric Dysrhythmia	+	+
Duodenal Eosinophilia		+
Aberrant Macrophage Function	+	+
Increased Mucosal Inflammation	+	



1. Vanheel H et al. Am J Gastroenterol 2017;112:132-140
2. Karamanolis G et al. Gut 2007;56:29-36
3. Kim B and Kuo B. J Neurogastroenterol Motil 2019;25:27-35
4. Grover et al. Gut 2019;68:2238-2250
5. Du L et al. Neurogastroenterol Motil 2018
6. Gottfried-Blackmore et al. Clin Trans Gastroenterol 2021

Interpreting Fluctuations in Gastric Emptying

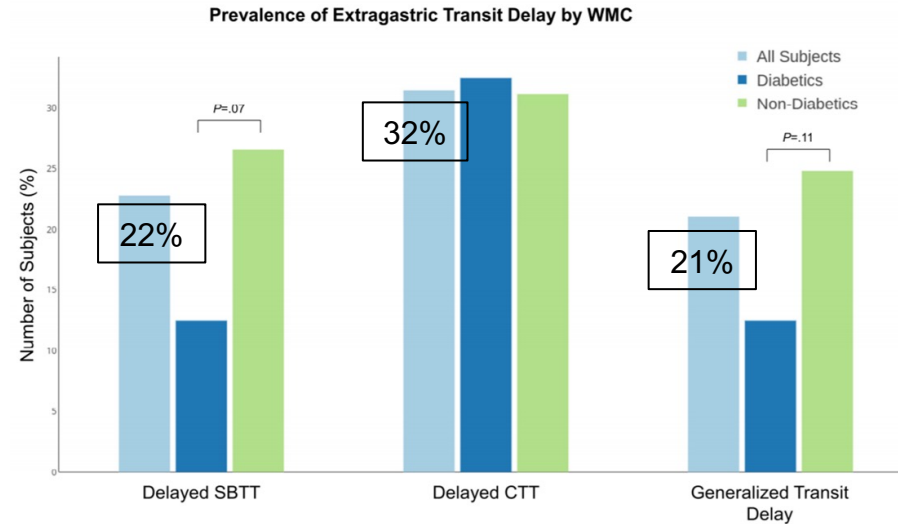
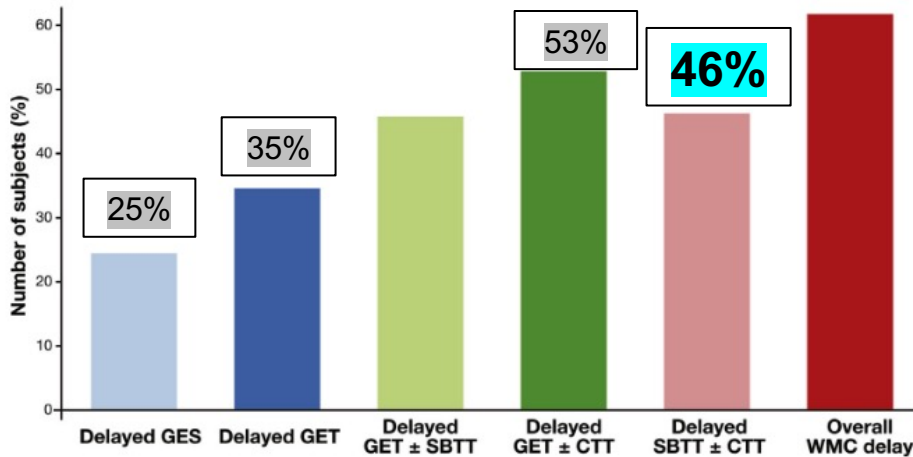
- 42% of GP and 37% of FD patients change categories at 48 weeks
- Change in gastric emptying does NOT correlate with symptoms



	Total patients (n = 249) ^a		
	Baseline	48 Wk	
		Gp	FD
Diagnosis	Gp (n = 189)	110 (58%)	79 (42%)
	Median at 4 h GE	Median at 4 h GE	Median at 4 h GE
Total patients	24.0% (16.0, 40.0)		
Gp to Gp	25.5% (16.5, 42.0)	23.0% (16.0, 38.0)	
Gp to FD	23.0% (14.7, 35.3)		3.0% (1.9, 5.0)
Diagnosis	FD (n = 60)	22 (37%)	38 (63%)
	Median at 4 h GE	Median at 4 h GE	Median at 4 h GE
Total patients	5.0% (2.5, 8.0)		
FD to FD	6.0% (2.5, 8.0)		3.0% (2.0, 5.1)
FD to Gp	5.0% (2.5, 8.0)	14.6% (12.6, 21.0)	
	% Diagnosis changed	41% ([79 + 22]/249)	
	% Unchanged	59% ([110 + 38]/249)	
	P value ^b	.005	

Wireless Capsule Motility Testing

- Consider WCM in patients with extra-gastric symptoms (ie. Constipation)

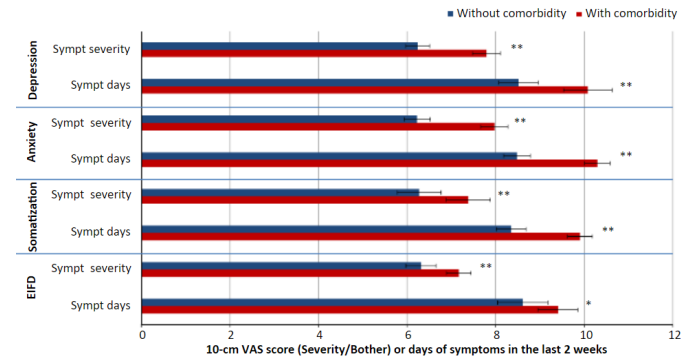
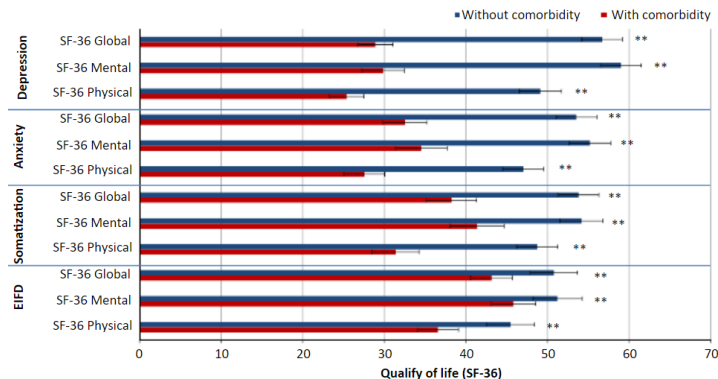


Functional Gastrointestinal Disorders (FGID) Associated with Psychiatric and Extraintestinal Comorbidities

	Non-FGID Control (N=306)	FGID (N=606)	P value
Any Comorbidity	176 (57.5%)	469 (77.4%)	< 0.001
Somatization (PHQ12 \geq 10)	86 (28.1%)	282 (46.7%)	< 0.001
Depression (BDI \geq 14)	42 (13.7%)	208 (34.3%)	< 0.001
Anxiety (BAI \geq 16)	27 (8.8%)	189 (31.2%)	< 0.001
Extraintestinal Functional Disorder*	109 (35.6%)	337 (55.6%)	< 0.001

*EIFD = chronic pelvic pain, interstitial cystitis, CFS, fibromyalgia, migraine HA, chronic HA, mitral valve prolapse, dysmenorrhea, dyspareunia, TMJ

***Somatization** = recurrent and multiple medical symptoms with no discernible organic cause



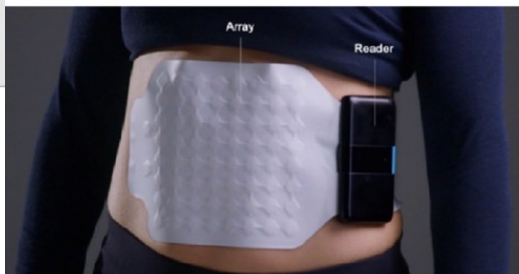


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Gastric dysfunction in patients with chronic nausea and vomiting syndromes defined by a novel non-invasive gastric mapping device

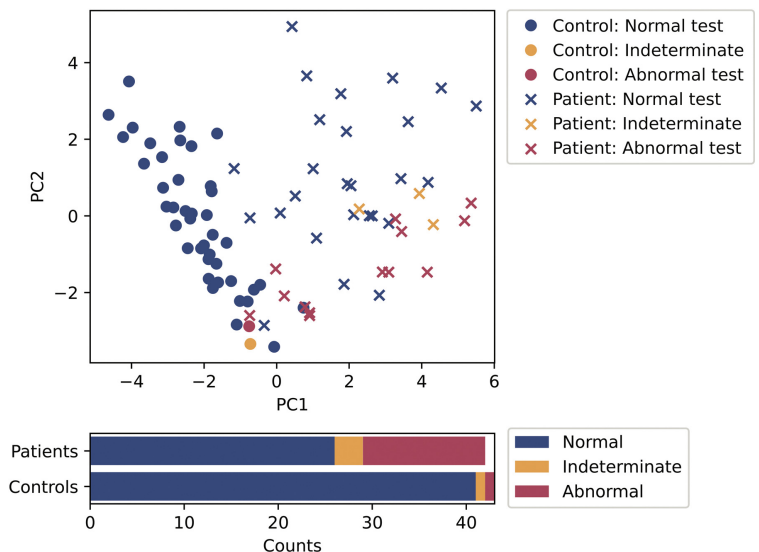
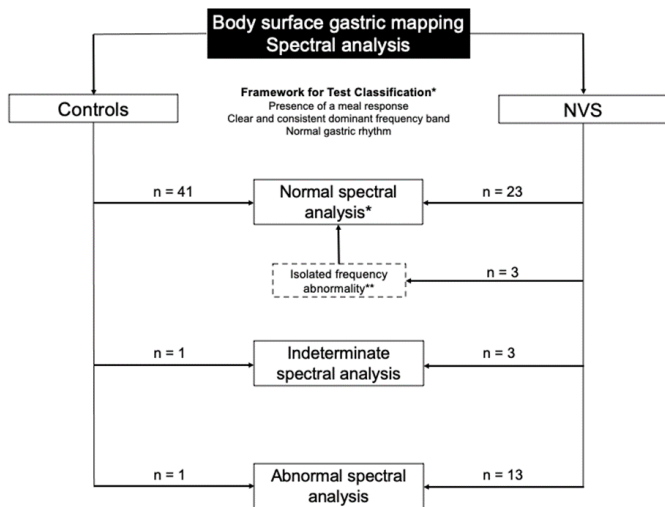
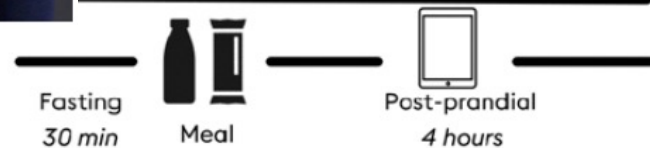
Armen A. Gharibans, PhD^{1,2,3}, Stefan Calder, PhD^{1,2}, Chris Varghese, BMedSc(Hons)¹, Stephen Waite, PhD², Gabriel Schamberg, PhD², Charlotte Daker, FRACP⁴, Peng Du, PhD^{2,3}, Saeed Alighaleh, PhD², Daniel Carson, MBChB¹, Jonathan Woodhead, PhD², Gianrico Farrugia, MD⁵, John A. Windsor, FRACS¹, Christopher N. Andrews, FRCP⁶, Greg O'Grady, FRACS^{1,2,3}



Gastric Data Capture

High-resolution bioelectrical signal acquisition

continuous



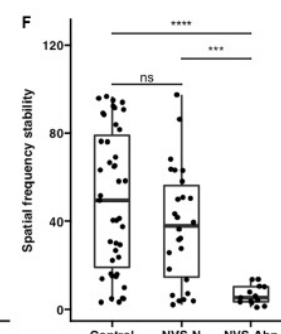
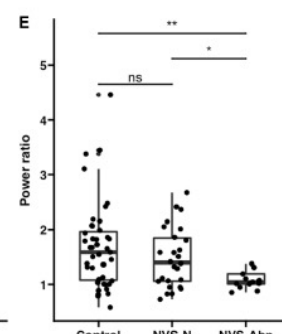
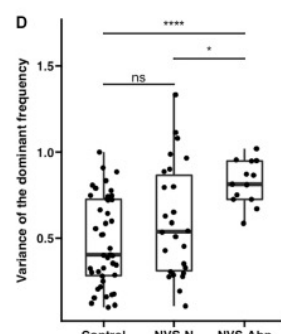
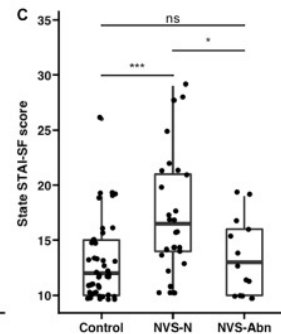
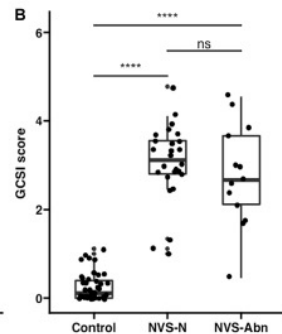
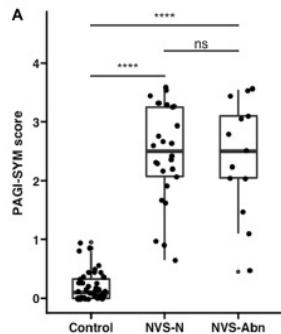
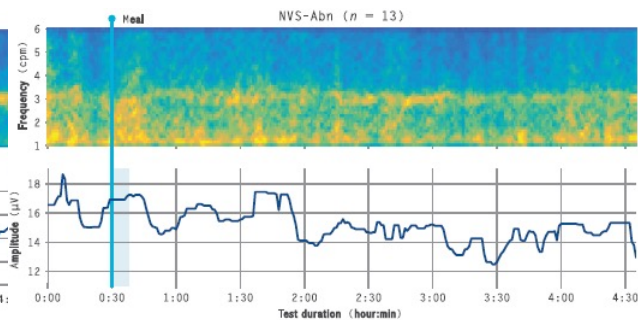
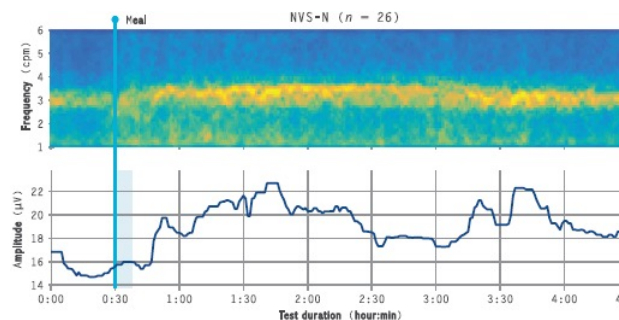
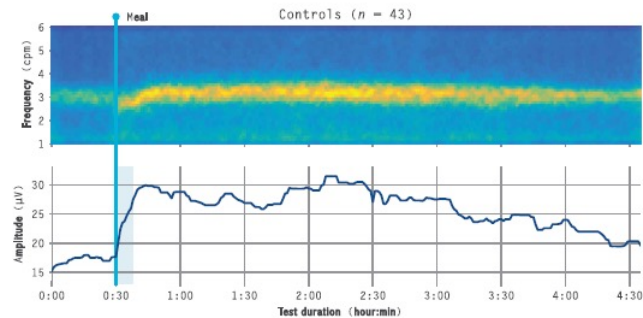
Body Surface Gastric Mapping with Symptom Correlation Differentiates Nausea Vomiting Phenotypes

Gharibans A et al. Sci Transl Med 2022

Healthy

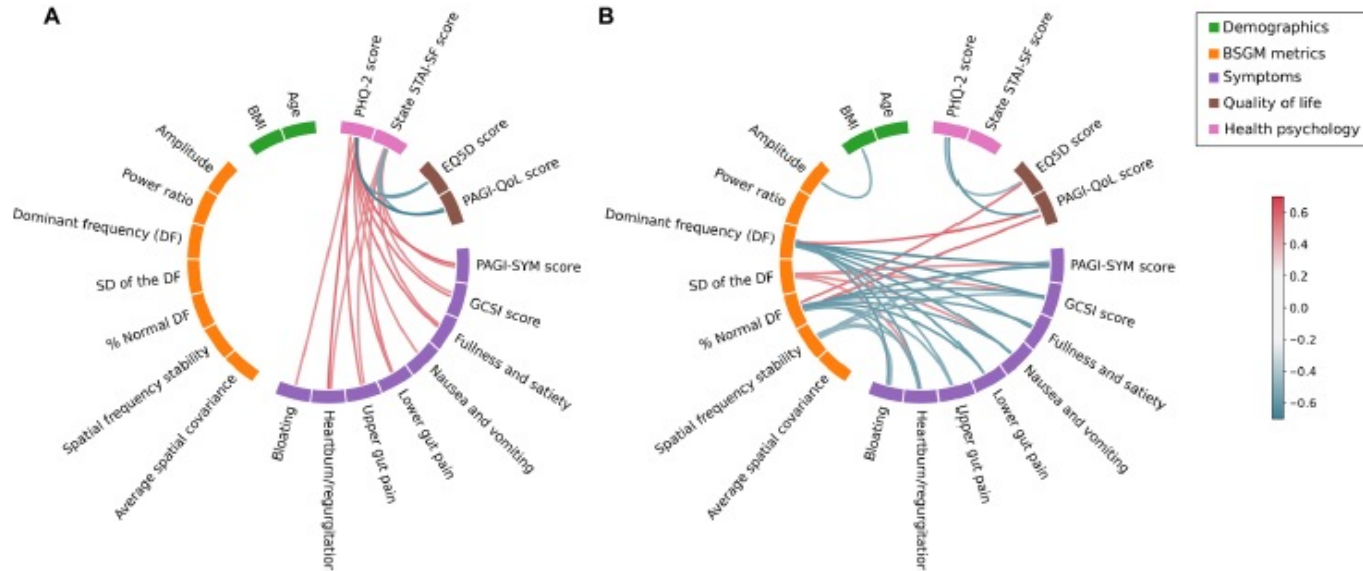
NVS-Normal

NVS-Abnormal



BSGM Identifies Distinct Phenotypes in Patients with Nausea and Vomiting Syndrome

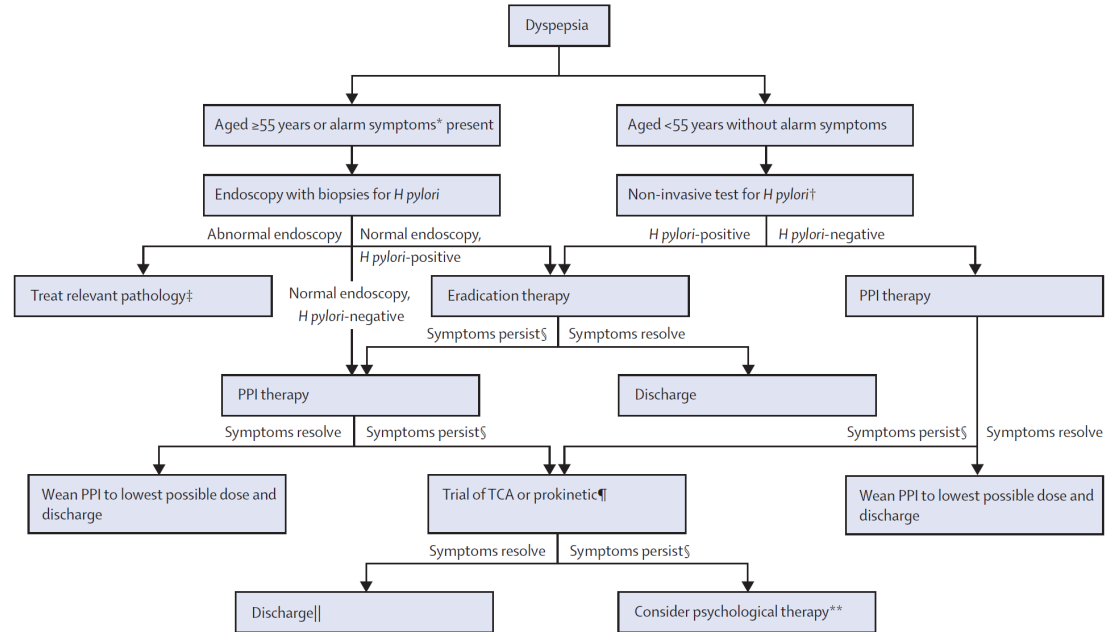
- BSGM able to differentiate gastric neuromuscular dysfunction vs. disordered brain-gut interaction



Uninvestigated Dyspepsia

Diagnose FD

- Avoid overdiagnosis of GP



Immune Activation Model in Functional Dyspepsia

