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Celiac Disease, Non-celiac Gluten Sensitivity, Wheat Intolerance: What's a Clinician to do?

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Objectives

- Describe the similarities and differences between celiac disease and IBS, including the role of celiac testing in patients with IBS-like symptoms
- Identify the potential causes of non-celiac gluten sensitivity
- Describe the role of dietary modification in managing IBS symptoms

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How often does Celiac Disease Overlap with IBS?

Investigation in IBS Patients Without Alarm Features

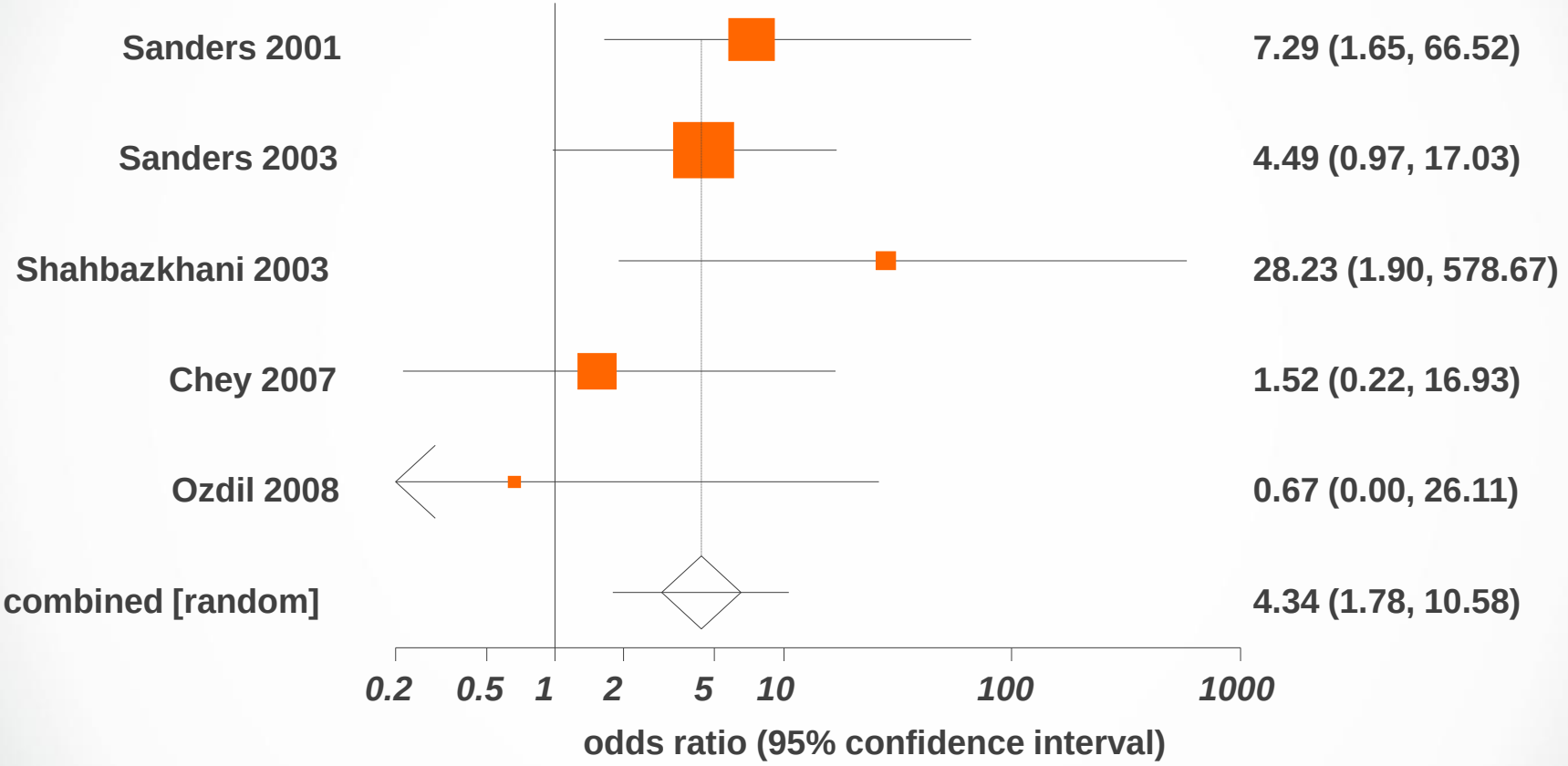
Prevalence of Organic Diseases in Patients Meeting Symptom-based Criteria for IBS

Event	IBS Patients, %	General Population, %
Colitis/IBD	0.51-0.98	0.3-1.2
Colorectal Cancer	0-0.51	0-6 (varies with age)
Thyroid dysfunction	4.2	5-9
GI infection	0-1.5	NA
Celiac sprue	**3.6**	**0.7**
Lactose intolerance	**38**	**26**

Cash BD, et al. *Am J Gastroenterol*. 2002;97:2812-2819.
ACG IBS Task Force. *Am J Gastroenterol*. 2009;104(suppl 1):S1-S35.

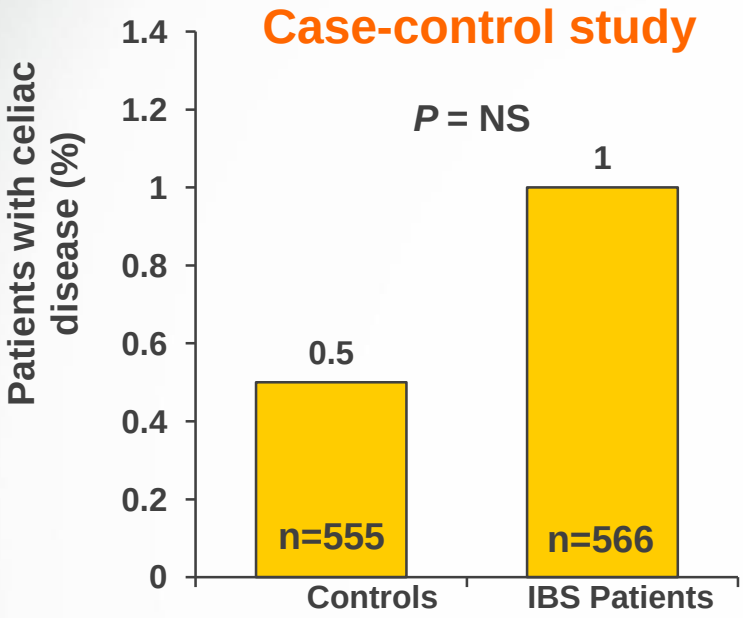
IBS and Celiac Disease (bx proven): Results from a Meta-analysis

Odds ratio meta-analysis plot [random effects]

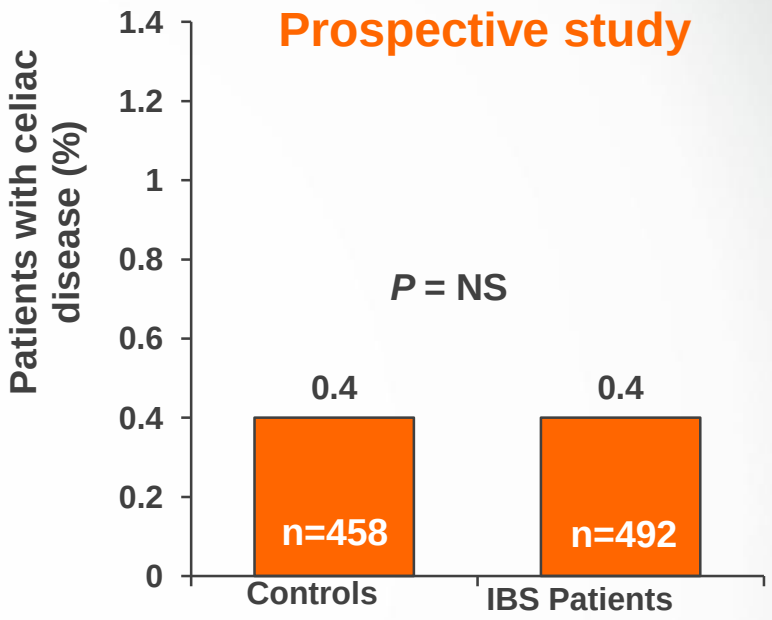


Ford AC et al. *Arch Intern Med.* 2009:169:651-658.

IBS and Celiac Disease: US Data



IBS patients (physician diagnosis)
Positive for both tTGA and EMA
Celiac disease not biopsy-proven



Non-constipated IBS patients (Rome II)
Biopsy-proven celiac disease

- Celiac disease prevalence roughly ≤1% among IBS patients in 2 U.S. studies
- Screening is cost-effective if prevalence is greater than 1%

EMA=anti-endomysium

Saito-Loftus Y et al. *Am J Gastroenterol*. 2008;103(suppl 1):S472. Abstract 1208
Cash BD and Chey WD. *Gastroenterology*, 2011;141:1187-1193.

Is it cost-effective to screen for Celiac Sprue (CS) in IBS?

- Decision analytic model assessed the cost-effectiveness of celiac testing vs empiric IBS therapy in patients with suspected IBS
- Testing cost an incremental $11K for one additional symptomatic improvement
  - ICER $≥= 50K when prevalence of CS<1%
  - Testing dominant when prevalence of CS>8%
- Factors affecting the decision to test:
  - Prevalence of CS, test accuracy, cost of IBS therapy, likelihood that symptoms improve on a gluten-free diet

ICER=incremental cost-effectiveness ratio

Spiegel BM et al. *Gastroenterology.* 2004;126:1721-1732.

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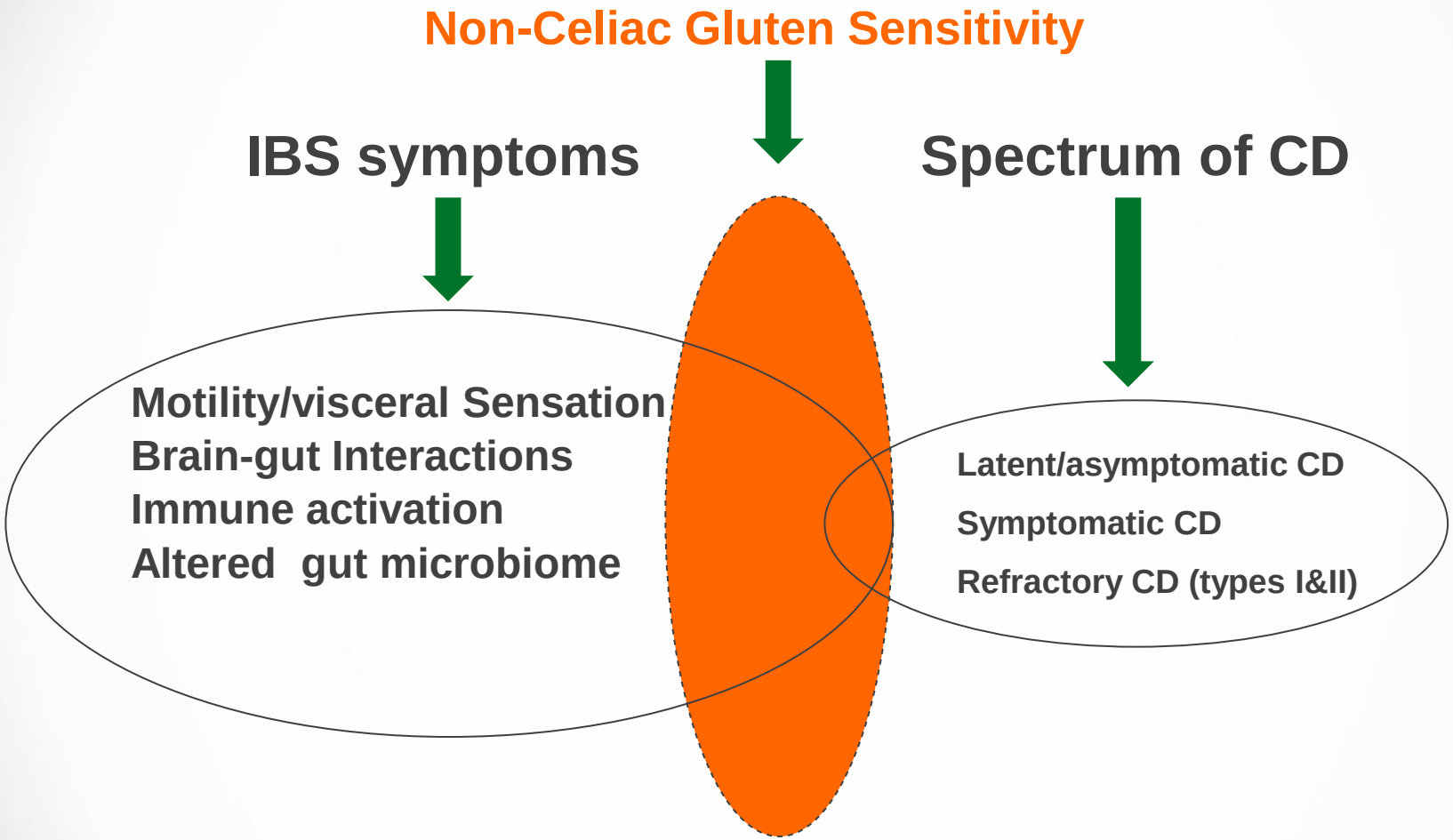
What about “Non-Celiac Gluten Sensitivity”?

Is it IBS, Celiac Disease (CD), or Something in-between?



Adapted from Verdu EF et al. *Am J Gastroenterol.* 2009;104:1587-1594; Ludvigsson JF et al. *Gut.* 2012, online early.

Non-Celiac Gluten Sensitivity

- Gluten sensitivity
- Gluten hypersensitivity
- Gluten intolerance
- Non-Celiac gluten intolerance

Di Sabatino A, Corazza GR. *Ann Intern Med.* 2012;156:309-311.

Non-Celiac Gluten Sensitivity

- Gluten sensitivity
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- Wheat intolerance??

Di Sabatino A, Corazza GR. *Ann Intern Med.* 2012;156:309-311.

Non-Celiac Gluten Sensitivity (NCGS)

- Up to 10% of the general population reports symptoms when ingesting gluten
- NCGS vs. wheat intolerance
- Encompasses a collection of medical conditions in which gluten leads to an adverse effect
- Can be clinically indistinguishable from celiac sprue but testing is negative or inconclusive
  - Not associated with increased intestinal permeability
  - Innate immunity markers TLR2 & FOXP3 altered in gluten sensitivity but not celiac disease
- Improves with a gluten free diet

Eswaren S et al. *GI Clin North Am.* 2011;40:141-146; Sapone S et al. *BMC Medicine.* 2011;9:23-27; Ludvigsson JF et al. *Gut.* 2012, online early.

Possible Causes of NCGS

IgE mediated wheat allergy

Nocebo effect

Innate immune reaction to gluten

Opioid-like activity

Low grade inflammation

Starch/CHO Malabsorption

NCGS=non-celiac gluten sensitivity

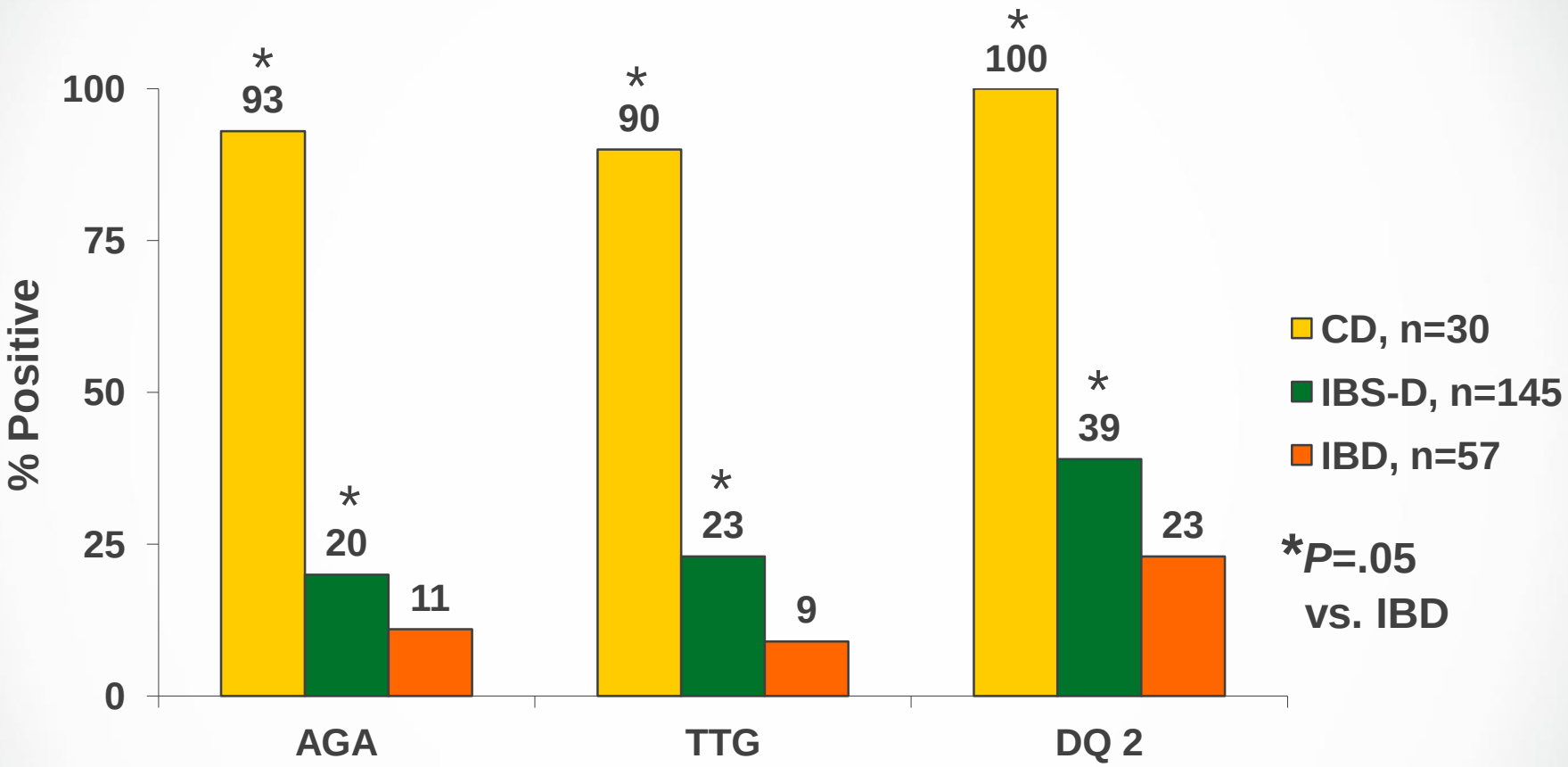
Di Sabatino A, Corazza GR. *Ann Intern Med.* 2012;156:309-311.

Celiac Testing in Suspected IBS:
A US Multi-center Trial

Test	Suspected IBS (n=492), n(%)	Healthy controls (n=458), n(%)	P value	OR (95% CI)
Bx proven celiac disease	2 (0.04)	2 (0.04)	NS	
Any abnormal celiac disease test	36 (7.32)	22 (4.8)	0.25	1.49 (0.76, 2.90)
AGA IgG	24 (4.88)	14 (3.06)	0.70	1.19 (0.5, 2.79)
AGA IgA	8 (1.63)	8 (1.75)	0.54	1.41 (0.47, 4.22)
EMA	3 (0.61)	2 (0.44)	0.66	1.65 (0.17, 15.42)
TTG IgA	6 (1.22)	2 (0.44)	0.15	2.79 (0.61, 24.7)
DQ2	164 (33.33)	180 (39.30)	0.004	0.61 (0.44, 0.86)
DQ8	81 (16.46)	83 (18.12)	0.54	1.14 (0.76, 1.70)

Cash BD et al. *Gastroenterology.* 2011;141:1187-1193.

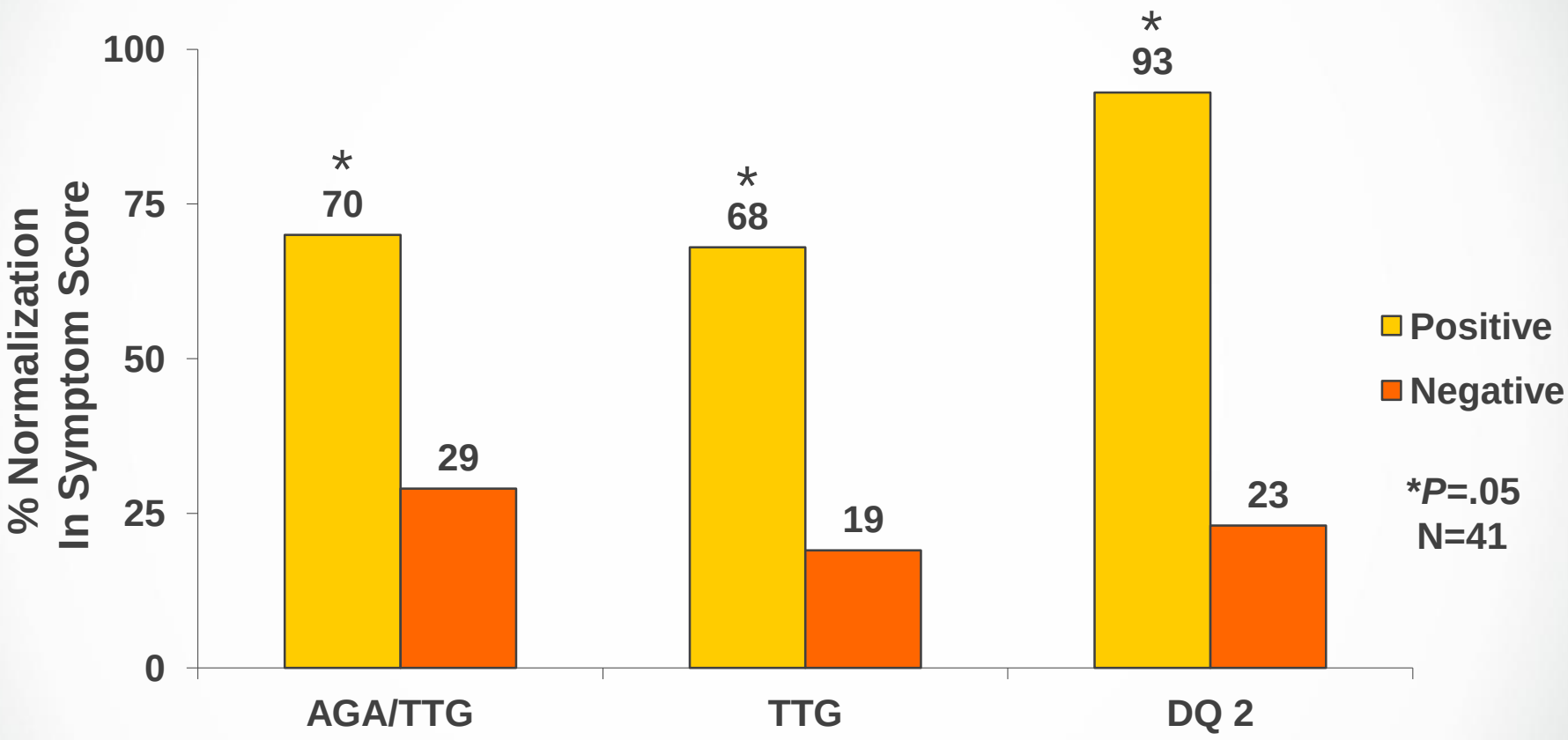
IgG Celiac Antibodies & HLA DQ2 in Celiac Disease, IBS-D, & IBD



IBS-D by Rome II

Wanschaffe U et al. *Clin Gastroenterol Hepatol.* 2007;5:844-850.

Symptom Normalization in IBS-D after a Gluten Free Diet



IBS-D by Rome II

Wanschaffe U et al. *Clin Gastroenterol Hepatol.* 2007;5:844-850.

Food Hypersensitivity in IBS

- Blood from 120 IBS patients (Rome II) analyzed for:
  - Activation of basophils by food allergens (flow cytometry)
  - Total and food-specific IgE
- Patients completed a food hypersensitivity questionnaire and underwent open elimination diet x 4 weeks
  - Milk, wheat, egg, tomato, chocolate
- Responders went on to double-blind placebo controlled food challenges
  - Milk/placebo (2 wks) followed by wheat/placebo proteins (2 wks)

Carroccio A et al. *Clin Gastroenterol Hepatol.* 2010;8:254-260.

Food Hypersensitivity in IBS

- 36% improved with the open-elimination diet
- 20% of IBS patients had food hypersensitivity to milk and/or wheat proteins by double-blind, placebo controlled food challenges
  - 16% both, 3% milk, 2% wheat
  - Problems appeared after median 3 days
  - 50% had to discontinue food challenge related to symptoms
- Patients overestimated and underestimated food hypersensitivity
  - 12/32 (38%) reporting food hypersensitivity improved with double-blind, placebo controlled food challenge
  - Some patients who did not report food hypersensitivity improved with food challenges
  - Basophil activation by flow cytometry (FC) was >85% accurate for food hypersensitivity

FC = Flow cytometry

Carroccio A et al. *Clin Gastroenterol Hepatol.* 2010;8:254-260.

Screening for Celiac Disease

- Routine serologic screening for celiac sprue should be pursued in patients with IBS-D and IBS-M (Grade 1B recommendation).
  - TtG and EMA are very specific
  - Sensitivity reduced in pts with partial villous atrophy or intraepithelial lymphocytosis
  - Many patients with a positive celiac serology (TtG or anti-gliadin antibodies) but normal small bowel biopsies will still improve on a gluten free diet
  - Role of anti-gliadin antibodies to identify nonceliac gluten sensitivity?

EMA=anti-endomysium

ACG IBS Task Force. *Am J Gastroenterol* 2009

Proposed Management of Patients with IBS Symptoms and Possible Celiac Sprue

Symptom	Serology	LD	HLA	Treatment
IBS	+	+	+	Trial of GFD
IBS	-	+	-	Consider other cause
IBS	+	-	+	GFD or follow
IBS	-	-	-	Treat IBS Trial of GFD?

GFD, gluten-free diet; HLA, human leukocyte antigen; IBS, irritable bowel syndrome; LD, lymphocytic duodenosis

Eswaren S, Tack J, Chey WD. *Gastroenterol Clin North* Am. 2011;40:141-162.

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Does a Gluten-free Diet Improve IBS Symptoms?

Gluten Free: More than a fad?

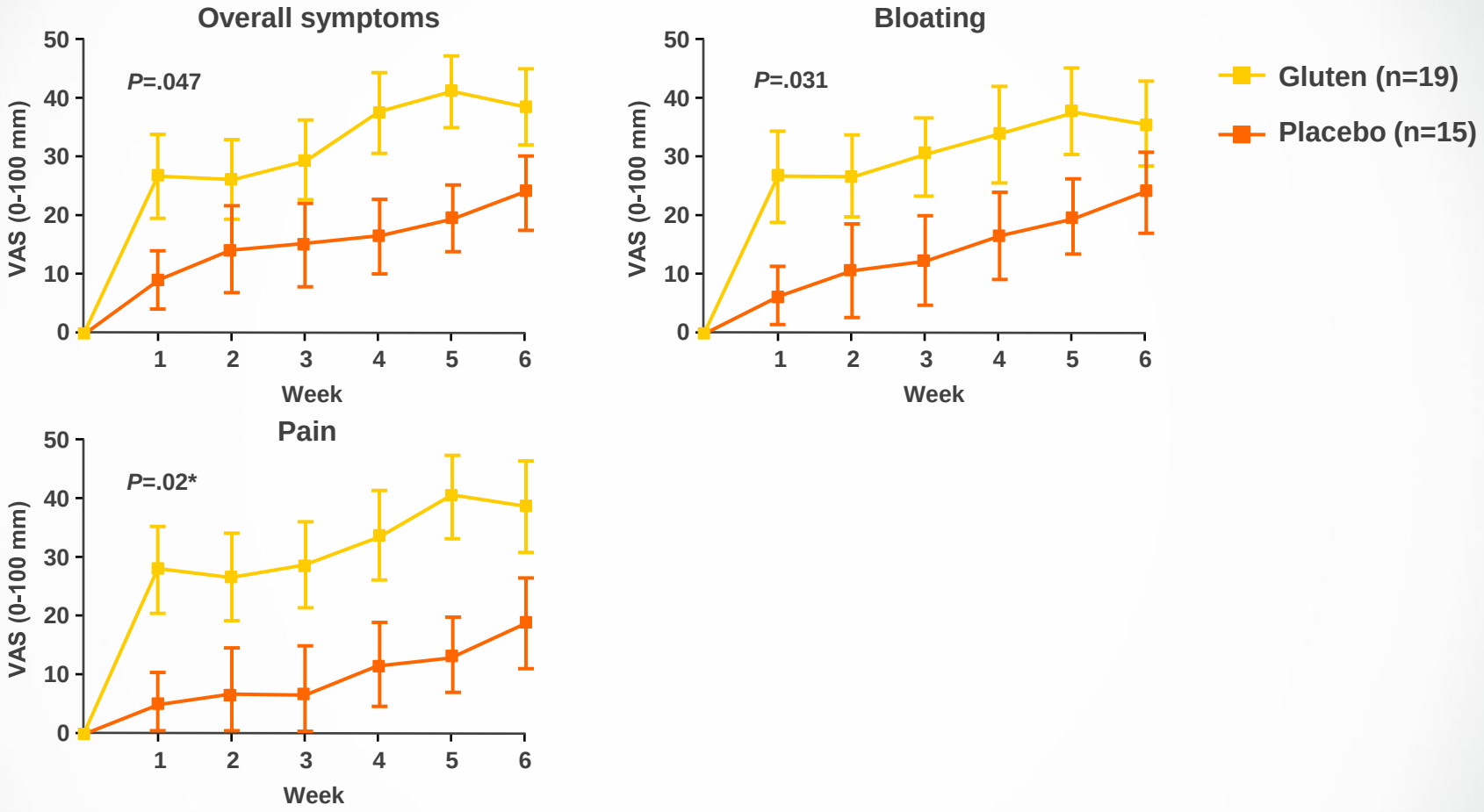
- Euromonitor International forecasts:
  - Sales have more than doubled since 2005
  - 2011 = $1.31 billion US, $2.67 billion worldwide
  - 2015 = $1.68 billion US, $3.38 billion worldwide

  - Big Industry is buying in:
    - General Mills: Chex cereal
    - Betty Crocker: Cake & brownie mixes, Bisquick
    - Anheuser Busch: Gluten free REDBRIDGE beer
    - PF Changs & Subway

Reuters Online – September 29, 2011
Digestive Health SmartBrief – October 5, 2011

Gluten Causes Symptoms in IBS Patients Without Celiac Disease

Mean Change in Symptoms Over 6 Weeks



*P-value for analyses at Week 1 and entire study period.

Adapted from Biesiekierski JR, et al. *Am J Gastroenterol*. 2011;106:508-514.

Gluten Causes Symptoms in IBS Patients Without Celiac Disease

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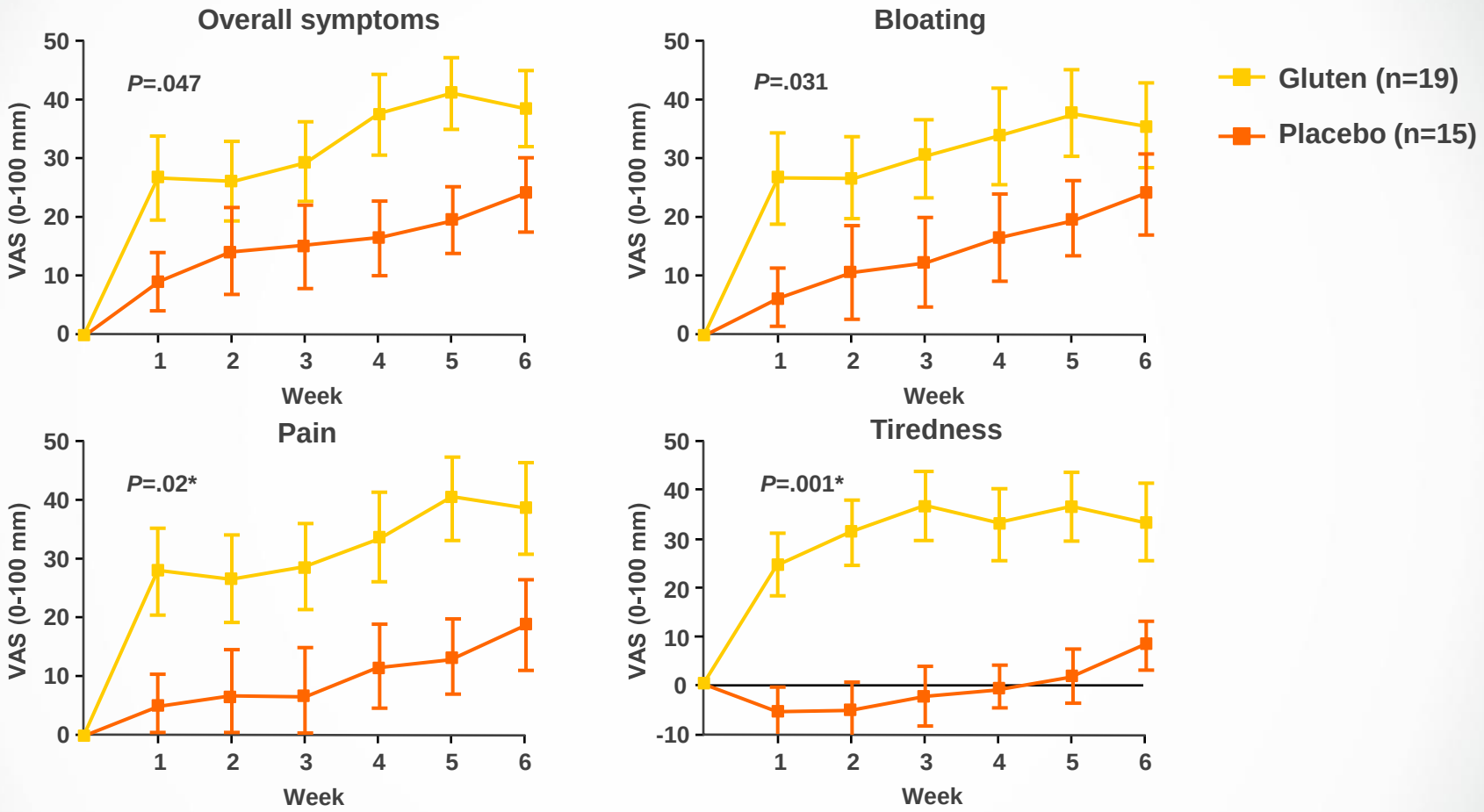
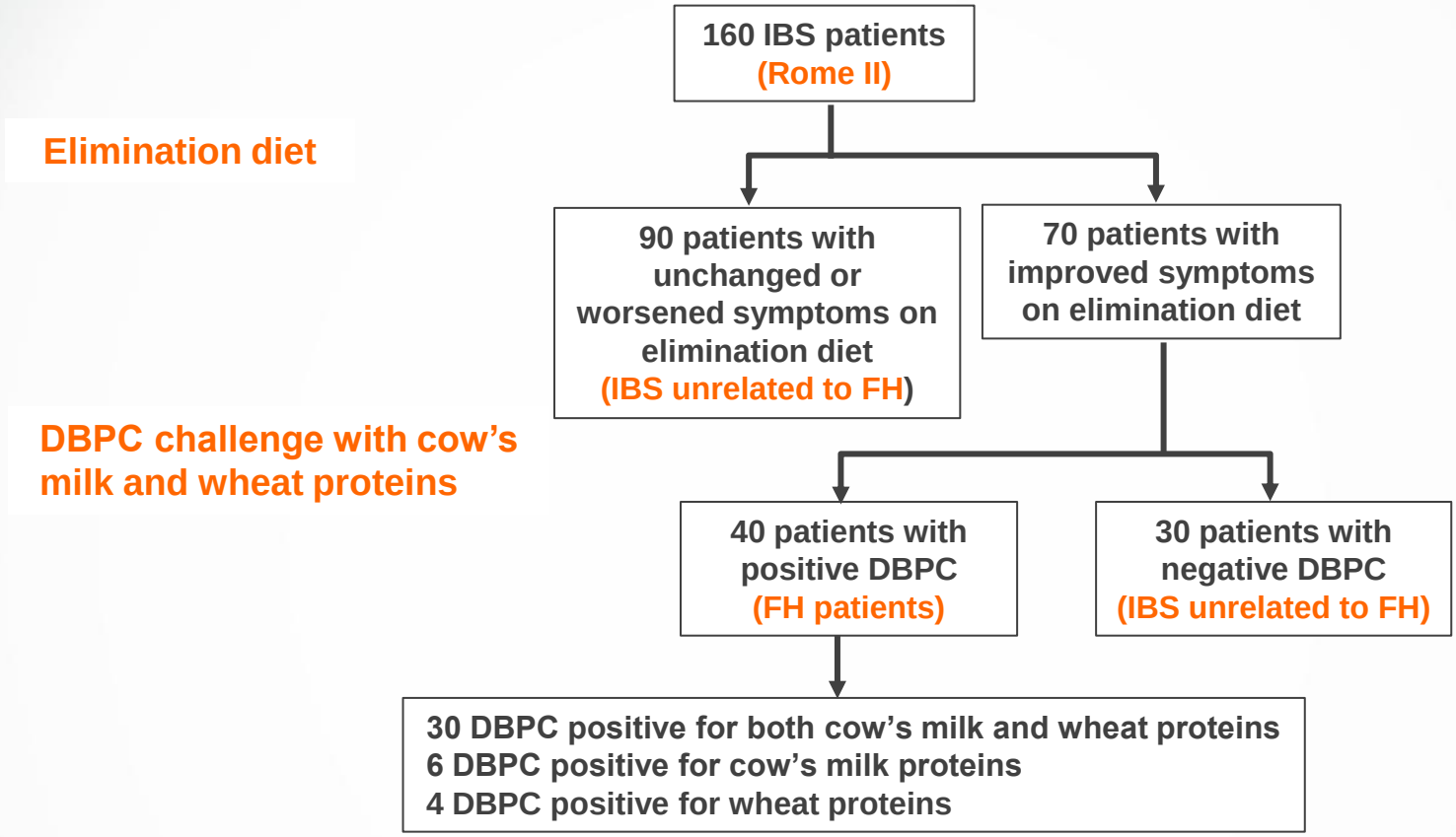


*P-value for analyses at Week 1 and entire study period.

Adapted from Biesiekierski JR, et al. *Am J Gastroenterol*. 2011;106:508-514.

Outcomes of IBS Patients after 4 Weeks of an Elimination Diet and Double Blind Food Challenge

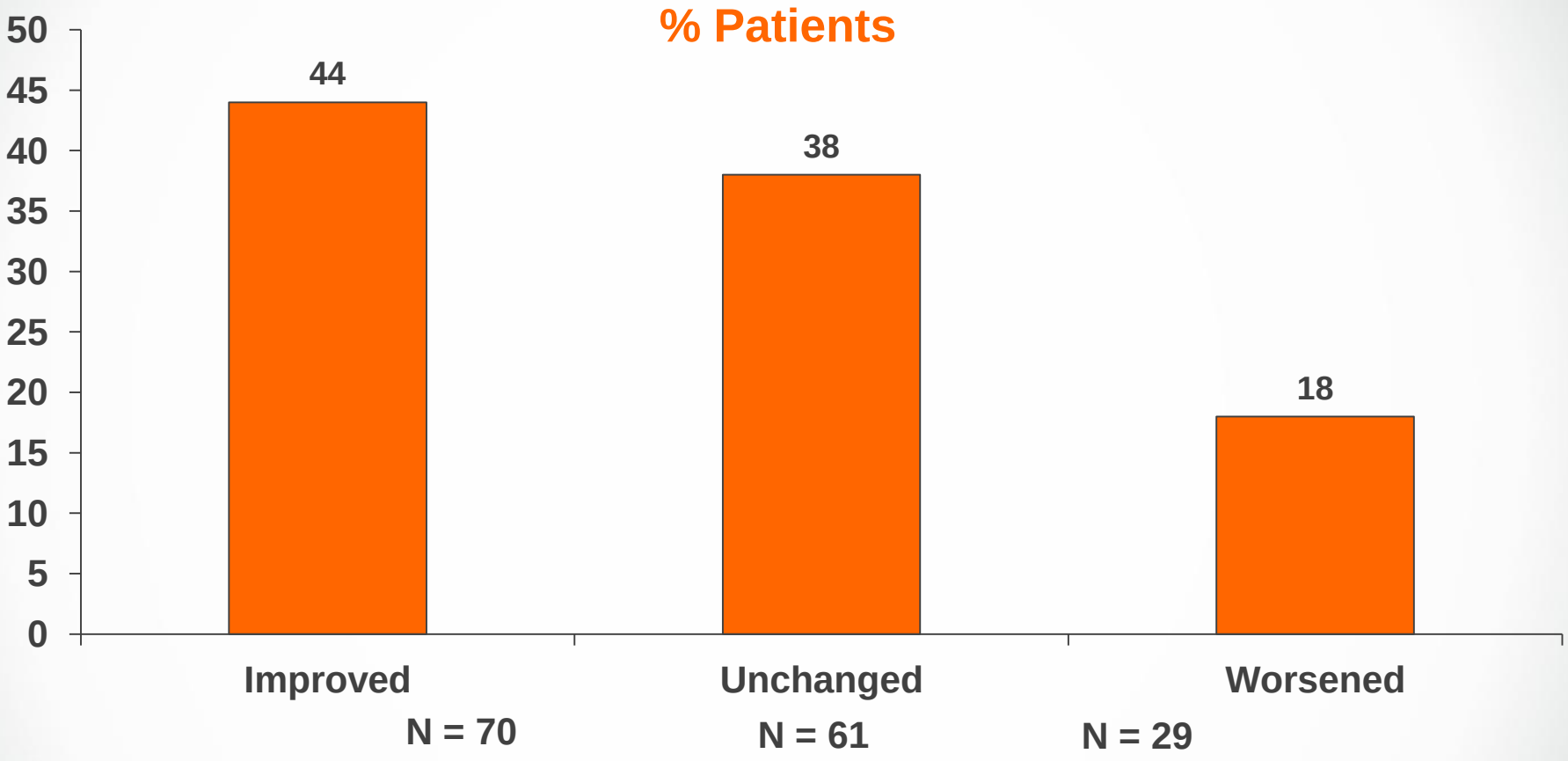


4 week Elimination Diet: cow's milk, wheat, egg, tomato, and chocolate
DBPC challenge: 2 wks of cow's milk or wheat proteins

DBPC=double-blind, placebo-controlled; FH=food hypersensitivity

Carroccio A et al. *Clin Gastroenterol Hepatol.* 2011;9:965-971.

Outcomes of IBS Patients After 4 Weeks of an Open Elimination Diet



Open elimination diet: cow's milk, wheat, egg, tomato, and chocolate

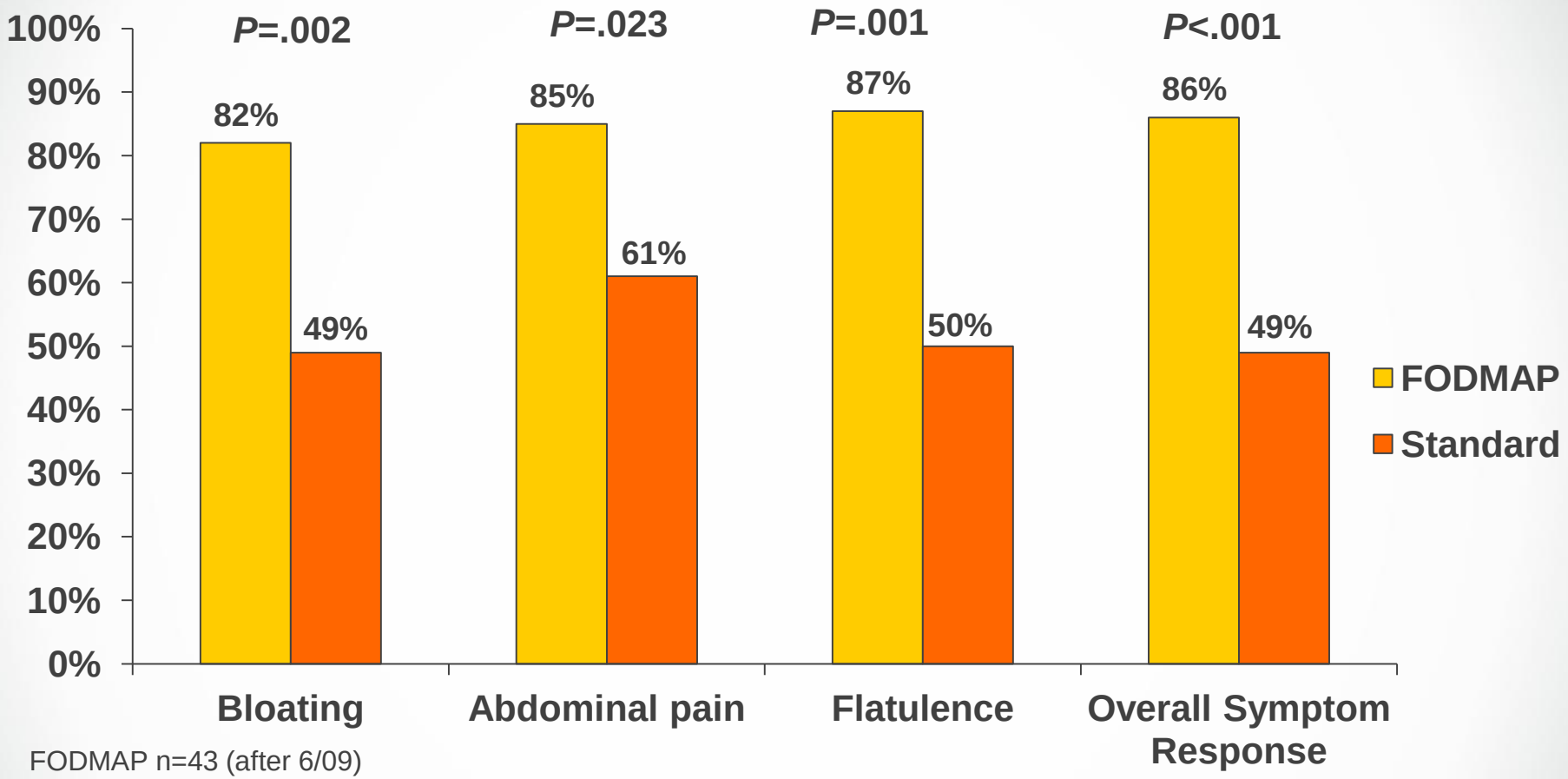
Carroccio A et al. *Clin Gastroenterol Hepatol.* 2011;9:965-971.

What are FODMAPs?

- Fermentable oligo-, di-, monosaccharides and polyols
- Fruits with fructose exceeding glucose
  - Apples, pears, watermelon
- Fructan-containing vegetables
  - Onions, leeks, asparagus, artichokes
- Wheat-based products
  - Bread, pasta, cereal, cake, biscuits
- Sorbitol- and lactose-containing foods
- Raffinose-containing foods
  - Legumes, lentils, cabbage, brussels sprouts

Shepherd SJ et al *Clin Gastro Hepatol.* 2008;6:765-771; Gibson PR, Shepherd SJ. *J Gastroenterol Hepatol* 2010;25:252-258.

Low FODMAP vs. Standard Diet for IBS



FODMAP n=43 (after 6/09)
Standard diet n=39 (before 6/09)
Consecutive IBS pts (NICE) from London

Staudacher HM et al. *J Hum Nutr Diet.* 2011;24:487-495.

Summary

- Patients with IBS-D/M should be screened for celiac disease
  - Expected US prevalence in IBS patients is ≤1% but likely varies based upon population genetics
- Non-celiac gluten sensitivity is a symptom-based disorder of heterogeneous pathogenesis
- NCGS is likely to be much more common than celiac disease
- Nomenclature, diagnostic criteria and biomarkers are needed
- Mounting evidence suggests that a gluten-free diet may offer benefits to patients with IBS symptoms

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