What's New in Medicine 2019

Evaluating the Patient with Diarrhea
&
IBD Primer for Internal Medicine

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Disclosures

- AbbVie – speaker
- Arena - advisor
- Janssen - speaker
- Medtronic - speaker
- Pfizer – advisor/speaker
- Takeda - speaker
- Prometheus Labs

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Objectives

- Define diarrhea and understand various pathophysiologic mechanisms
- Learn a 5-step approach to facilitate the evaluation of diarrhea
- Understand standards, modalities and exceptions for diagnosing inflammatory bowel diseases
- Review the differences between IBD and other GI disorders with similar presentation

Definition of Diarrhea

- Frequency >3/day
- Consistency
- Volume >200 g (200 mL)/24 h

- **Patients** main complaint: liquid stools
  - Urgency has biggest impact on QOL
- **Physicians** primarily consider frequency

Acute vs. Chronic Diarrhea

- <2 weeks = acute
  - Mostly infectious
  - Food poisoning
    - *Sudden onset*
- >4 weeks = chronic
  - Most chronic diarrhea start as acute
    - *Gradual onset*

Pathophysiology of Diarrhea

- Excess fecal water
  - Stool contains ≈ 70% water
- 10 L of water/day enter the small bowel
  - 99% absorbed in the SB + colon
    - 1% reduction in absorption □ diarrhea
    - Extremely difficult to elicit diarrhea by drinking water
      - Virtually all water is absorbed and eliminated in urine

Donowitz et al. – NEJM '95; Schiller et al. – Sleisenger & Fordtran GI & Liver Dis '10

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Pathophysiology of Diarrhea

- **3 main mechanisms**
  - **Decreased absorption**
    - Most common mechanism
  - **Secretory** – very rare in pure form (cholera)
    - Most secretory diarrhea is the result of impaired absorption of electrolytes
      - Named “secretory” based on stool electrolytes
  - **Osmotic**
    - Poorly absorbed substance w osmotic activity retains water

Fordtran et al. – Clin Gastroenterol ‘86

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Pathophysiology of Diarrhea

- **2 secondary mechanisms**
  - Increased **motility**
    - Impaired absorption (IBS)
  - **Inflammatory**
    - Intestinal damage
    - Combination of mechanisms

Fordtran et al. – Clin Gastroenterol '86

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Case Presentation #1

- 50 BM with T2D presenting with 6 months history of diarrhea
  - 6-8 explosive stools daily
  - No pain, no blood
  - Labs normal
    - Celiac serologies (-)
  - Stool studies normal
  - Colonoscopy normal

Case Presentation #2

- 35 Asian F presenting w intermittent diarrhea, bloating, gassiness for 4 years
  - Mild cramps preceding stools
  - No bleeding, no wt loss
  - No international travel
  - No medications
  - Labs normal
  - Colonoscopy elsewhere negative

A Simplified 5-Step Approach to Diarrhea

1. Does the patient really have diarrhea?
2. Rule out medications, lactose intolerance and bile acid diarrhea
3. Distinguish acute vs. chronic
4. Categorize in watery, inflammatory, fatty
5. Consider fictitious diarrhea

1. Does the Patient Have Diarrhea?

- **Fecal incontinence**
  - Commonly reported as “diarrhea”
  - Clarified by history and rectal exam
- **Fecal impaction**
  - Large stool bolus (fecaloma) in the rectum
    - Rectal distension relaxes internal sphincter
    - Causes overflow diarrhea (around the impaction)

2a. Rule Out Medications

- Temporal association
- Common offenders:
  - Magnesium (in “natural” supplements)
  - Antibiotics
  - “Herbal supplements” – cascara, sennosides
    - Frequently advertised as immune stimulators, wt control
  - Diabetes drugs (metformin, acarbose)
    - Metformin-induced diarrhea can start years after initiating the drug
  - Immunomodulators:
    - Mycophenolate mofetil
  - Other:
    - Quinine
    - chemotherapy

Refractory Diarrhea in a 67-Year-Old Female

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2b. Rule out Lactose Intolerance

- Lactose malabsorption extremely common in adults
    - 60% Caucasians
    - 80% Hispanics
    - 90-100% Asians
  - History provides clues
  - Elimination diet very effective
    - May re-challenge

Bayless et al. – Curr Gastroenterol Rep ’17; Scrimshaw et al. – Am J Clin Nutr ‘88

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2c. R/o Bile Acid Diarrhea

- Excess bile acid in the colon (following cholecystectomy) cause increased secretion of water + lytes
  - Post-prandial
  - Generally mild
  - Responds to fasting & *cholestyramine*
- US performs 3x more choly than other developed countries
  - Choly for GB w/o stones increased 3.5x since '95
    - 80% likely unnecessary

Fromm et al. – Clin Gastroenterol '86; Legorreta et al. – JAMA '93; Weiss et al - https://www.hcup-us.ahrq.gov/reports/statbriefs/sb170-Operating-Room-Procedures-United-States-2011.pdf

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3. Acute or Chronic Diarrhea

- Acute diarrhea (<2 weeks)
  - Infectious, food poisoning
  - Self-limited
  - Investigate only if alarm features present
    - Bleeding, fever, ↑ WBC, old age, immunosuppressed
- Chronic diarrhea
  - Broad differential
  - Usually needs investigations

4. Characterize Diarrhea

a. **Watery**
    a. Secretory or osmotic
b. **Fatty** (steatorrhea)
c. **Inflammatory**

4a. Watery Diarrhea

- Most common form (secretory, osmotic)
  - Osmotic diarrhea resolves with fasting
- Lab distinction by the *fecal osmotic gap*:

  = 290 - (Na + K)x2

    - >50 = osmotic diarrhea
- DO NOT measure stool osmolarity
  - Unless you suspect surreptitious laxatives

Causes of Osmotic Diarrhea

- **Ions**
  - Magnesium
  - Sulfate, phosphate
- **Carbohydrates**:
  - Lactose, fructose, mannose
  - Sugar alcohols (sorbitol)
    - 10 g (4-5 sugar-free mints) can cause diarrhea

Causes of Secretory Diarrhea

- Infectious (acute)
- Bile acid malabsorption (choly, TI resection)
- Stimulant laxatives
- Inflammation (Crohn's, UC, microscopic colitis)
- Autonomic (vagotomy, diabetes)
- Secretagogue peptides (VIP, gastrin, glucagon)
- Neoplasia (v. rare)
- Idiopathic

4b. Fatty Diarrhea (Steatorrhea)

- Bulky, greasy stools, difficult to flush
  - Floating stools indicate gas = carbohydrate malabsorption NOT steatorrhea
- Oil droplets
- Weight loss
- If accompanied by abdominal pain, indicative of pancreatic disease

4b. Fatty Diarrhea (Steatorrhea)

Two entities:

- **Maldigestion**
  - Pancreatic exocrine insufficiency
  - Bile acid deficiency (cholestasis, SIBO)
- **Malabsorption**
  - Loss of mucosal real estate
    - *Celiac disease*, short gut, bypass
      - Usually accompanied by anemia, low Ca, Mg

4b. Fatty Diarrhea (Steatorrhea)

Testing:

- **Qualitative** fat (Sudan)
  - Very easy
  - Fairly reliable
- **Quantitative** fat
  - >7g/24 h (on 100 g fat diet!)
  - Accurate
  - Information about stool volume

4c. Inflammatory Diarrhea

- Frequent stools, blood, pain, tenesmus
- ***Nocturnal stools***
- ↑ calprotectin or lactoferrin
- ↑ CRP, ESR, ↓ Albumin

Causes of Inflammatory Diarrhea

Acute:

- Infections (bacterial, CMV, Entamoeba)

Chronic:

- Radiation, ischemia, medications
- Immune-mediated
  - Crohn's disease
  - Ulcerative colitis
  - Microscopic colitis
- Most appropriate indication for colonoscopy, imaging

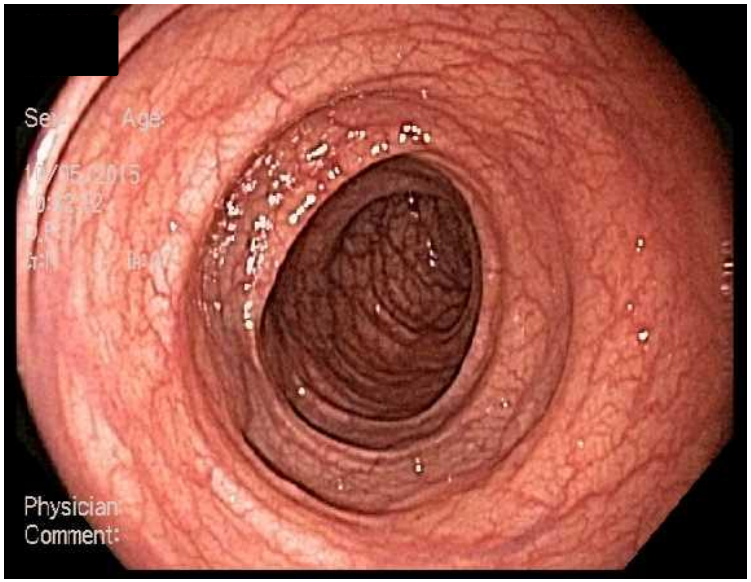
5. R/o Factitious Diarrhea

- Intentional use of laxatives
- 15% of patients referred to gastroenterologists for chronic diarrhea
- Diagnosis of exclusion
  - History of multiple consultations/specialties
  - Frequent hospitalizations
- Diagnostic tests:
  - Stool osmolarity (low/high)
  - Urine laxative screening
  - Colonoscopy (melanosis)

Bytzer et al. – Gut '89

Melanosis coli

Melanosis



Normal

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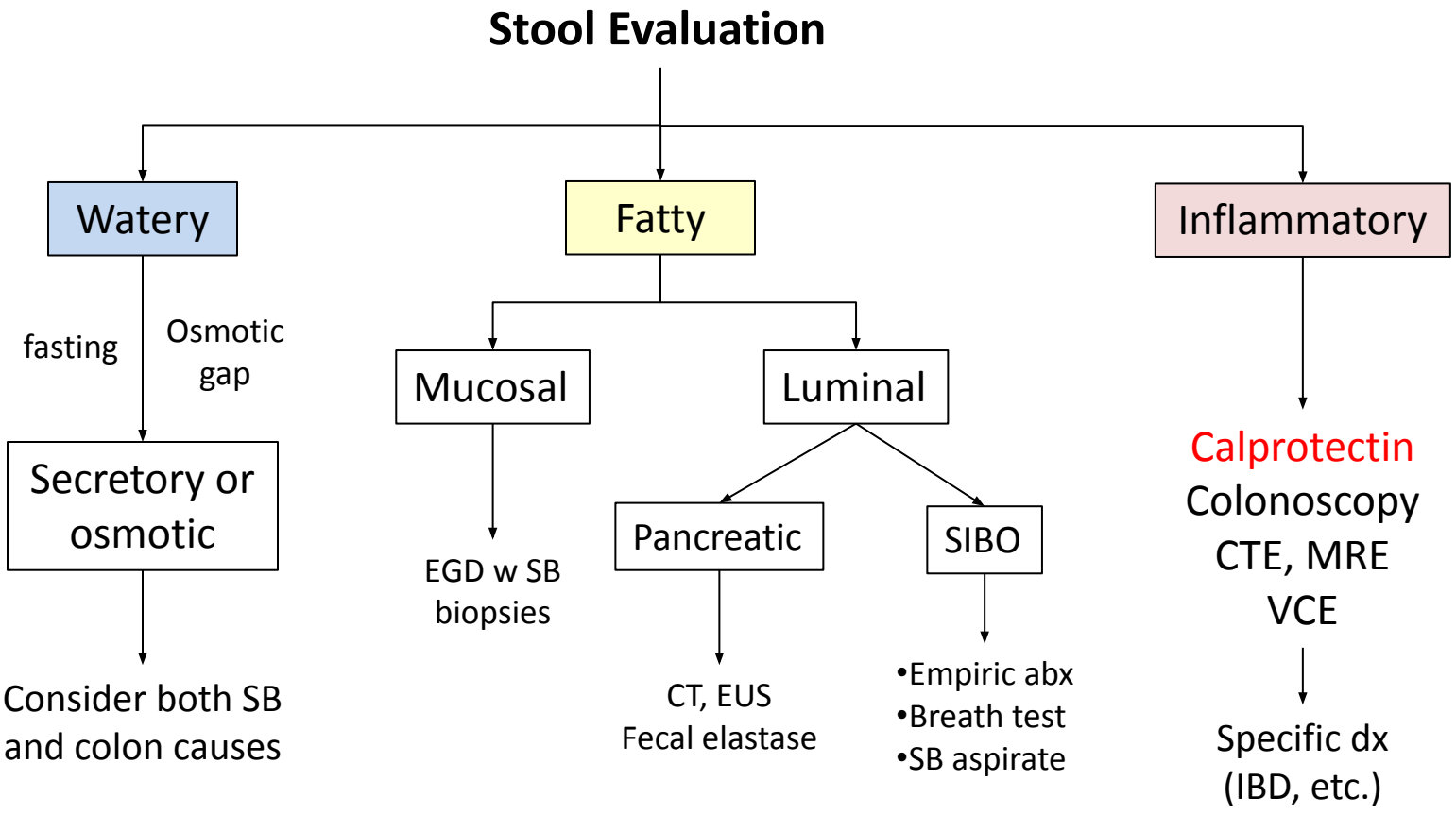
Categorizing Diarrhea



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The “6 Pattern” Classification of Chronic Diarrhea

A. Stool weight <200 g/24 h

- No diarrhea (incontinence)
- Hyperdefecation (hyperthyroidism)
- Soft consistency
- Osmotic gap (malabsorption, magnesium)
- Steatorrhea

B. Secretory diarrhea w/o steatorrhea (>200 g/24 h; no osmotic gap)

- Likely colonic origin (microscopic colitis)

Steffer et al. – Gastroenterol Clin North Am ‘12

The “6 Pattern” Classification of Chronic Diarrhea

C. Carbohydrate malabsorption without steatorrhea (osmotic gap)

- Dietary (lactose, fructose)

D. Steatorrhea with or without carbohydrate malabsorption

- Mild (<10% fat): small bowel disease
- Severe (>10% fat): pancreatic exocrine

E. Osmotic diarrhea due to laxatives

F. Unclassified (>200 g/24 h)

Steffer et al. – Gastroenterol Clin North Am ‘12

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Summary

- Differentiate acute (infectious) from chronic diarrhea
- R/o most common etiologies first
  - Drugs, lactose, cholecystectomy – bile acids, C diff
- Classify in watery/fatty/inflammatory
  - Stool osmotic gap
  - Stool qualitative fat
  - Fecal calprotectin
- If alarm features check for inflammation or pancreatic disease
- Remember mimickers (incontinence, laxatives)
- Celiac disease is not uncommon (1:200) but non-celiac gluten sensitivity (NCGS) is far more common (3%)

Case Presentation #1

- 50 BM with T2D presenting with 6 months history of diarrhea
  - 6-8 explosive stools daily
  - Normal exam, labs, scopes

Answer: Metformin-induced diarrhea

  - Resolved w drug interruption
  - Re-challenge □ recurrence □ loperamide

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Case Presentation #2

- 35 Asian F presenting w intermittent diarrhea, bloating, gassiness for 4 years
  - Mild cramps
  - Normal labs, colonoscopy

Answer: lactose malabsorption (intolerance)

  - Very common in Asians

IBD Primer for Internists

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Why Is IBD such a Big Deal?

- Prevalence of IBD is ≈1% in North America, W Europe and Australia
- Incidence of Crohn's disease is still increasing
- Rapid increases in the incidence of IBD are now being observed in Asia-Pacific region
- IBD may emerge as a worldwide epidemic in the coming years

Molodecky NA, et al. Gastroenterology 2012;142:46–54

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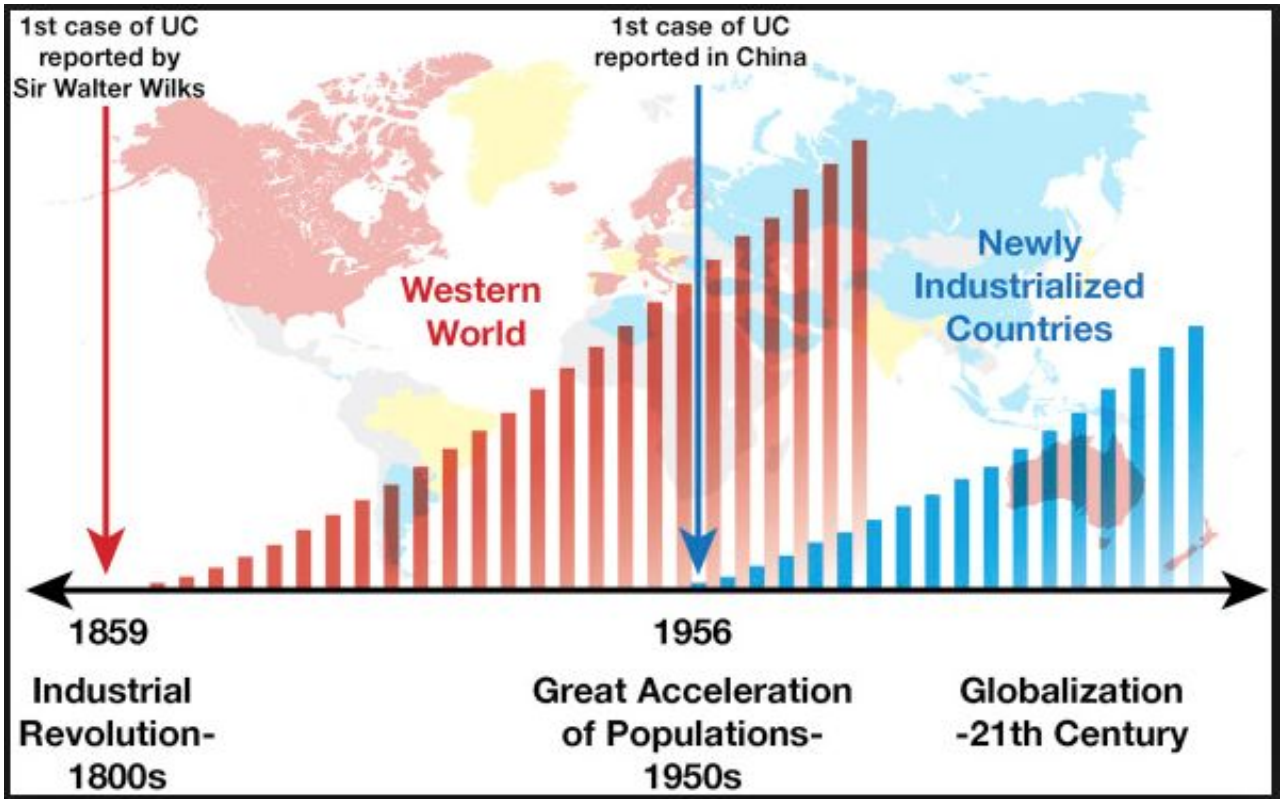
Temporal Trends in IBD Worldwide



Kaplan G, et al. Gastroenterology 2017;152:313–321

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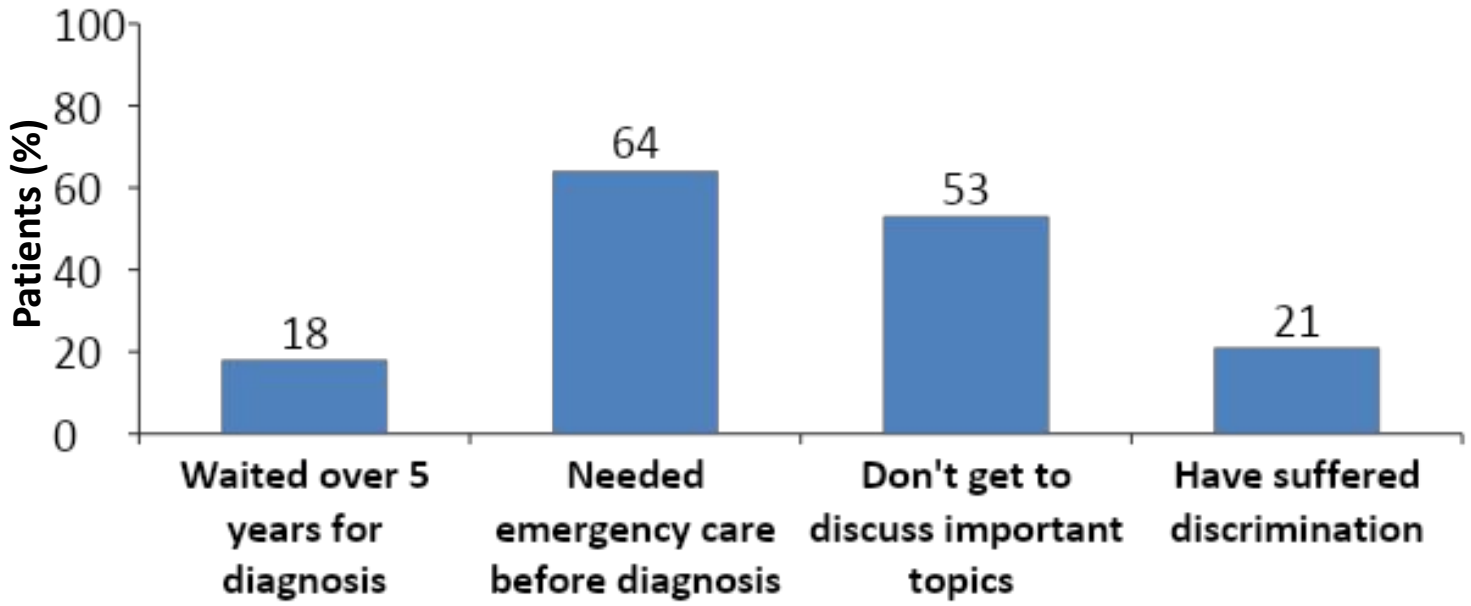
What do Patients Think? The IMPACT survey

- 4,990 IBD surveys analyzed in 24 EU countries
- Most (68%) respondents were aged 19–44 years



Data from IMPACT. http://efcca.org/media/files/press-Join Fight/3.PRESS_KIT_IBD_IMPACT_REPORT_BCN.pdf

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Diagnosing IBD Like an Expert

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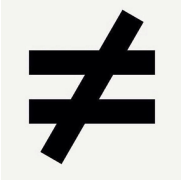
Avoid the Common Confusion

- **Inflammatory Bowel Disease (IBD)**
  - Chronic or relapsing immune activation and inflammation damage in the GI tract



- **Irritable Bowel Syndrome (IBS)**
  - Overactive/oversensitive bowel (functional)
  - No damage

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NIDDK IBD Genetics Consortium Diagnostic Criteria for IBD

- **Symptoms:** one or more of
  - Diarrhea
  - Rectal bleeding
  - Abdominal pain
  - Fever
  - Perianal fistulas
  - Extraintestinal manifestations
  - Weight loss

AND

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NIDDK IBD Genetics Consortium Diagnostic Criteria for IBD

- Objective evidence on 1 or more of **endoscopy**, **radiology**, or **histology**

- IBD *"serologies"* are not part of the diagnosis

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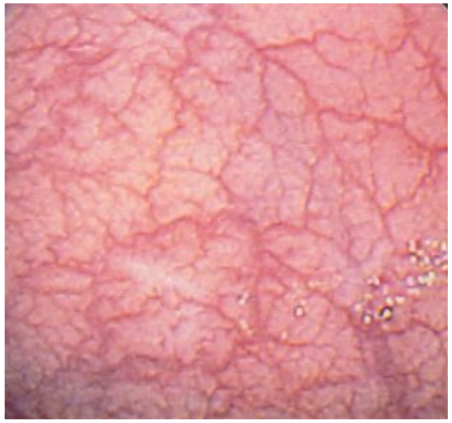
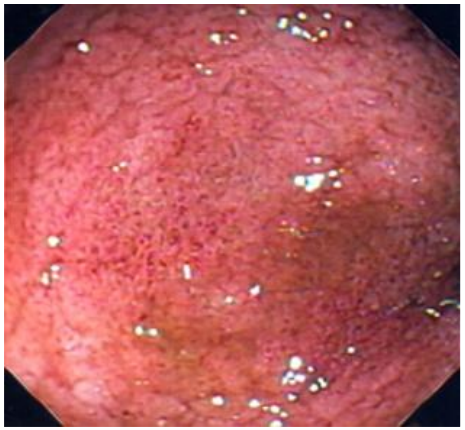
Endoscopic Appearance in UC: Modified Baron Score

0 = NORMAL

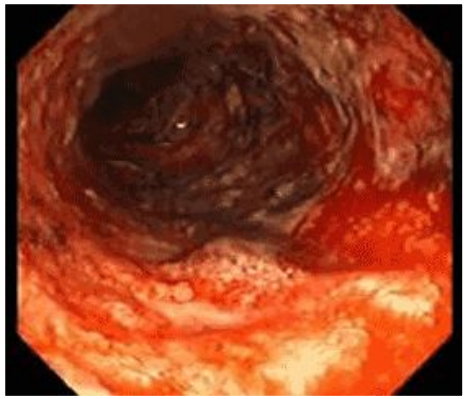


1 = MILD



2 = MODERATE

3 = SEVERE



Colombel JF, et al. Gastroenterology. 2011.

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“Rake ulcers” in Crohn’s disease

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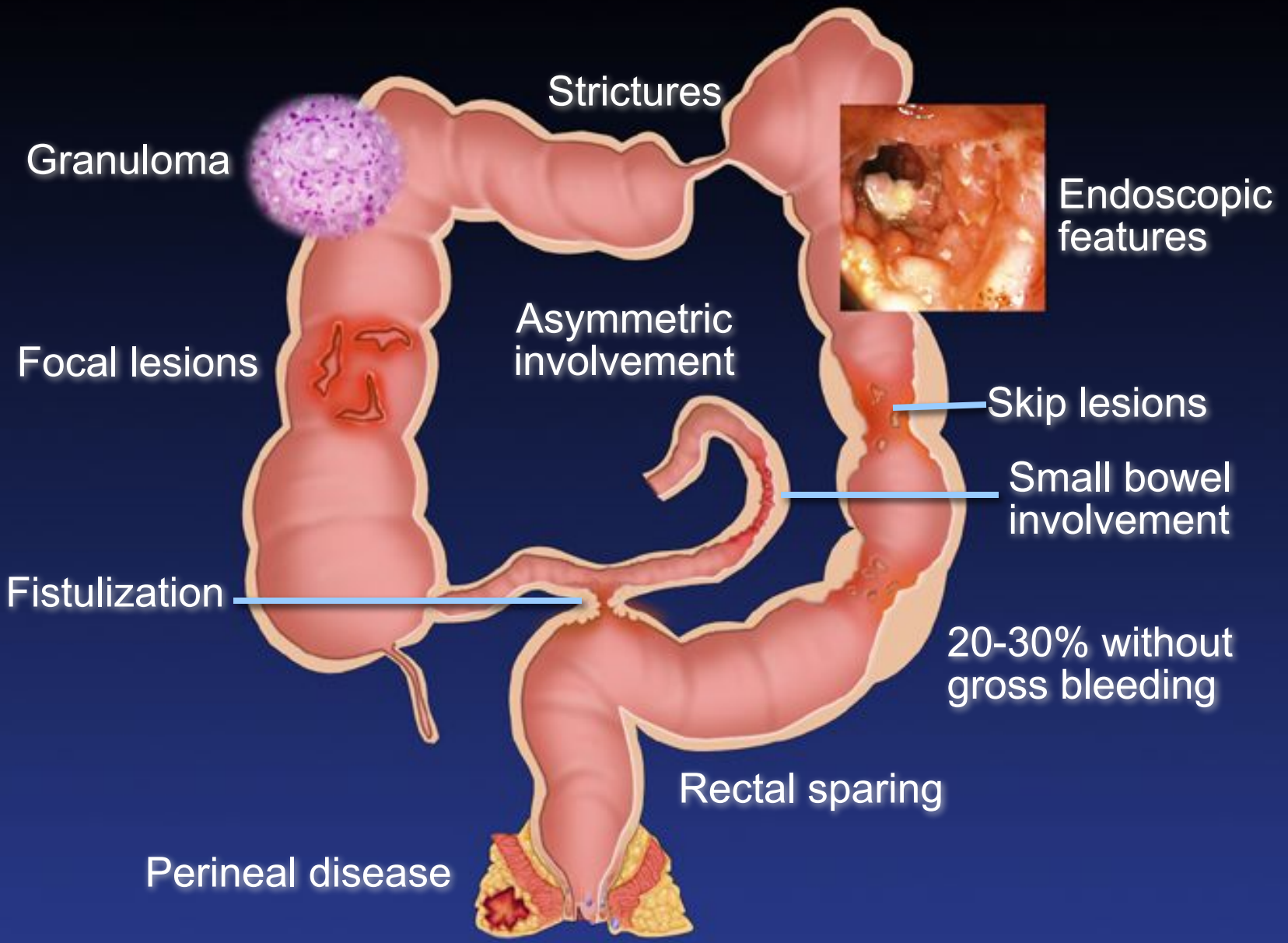
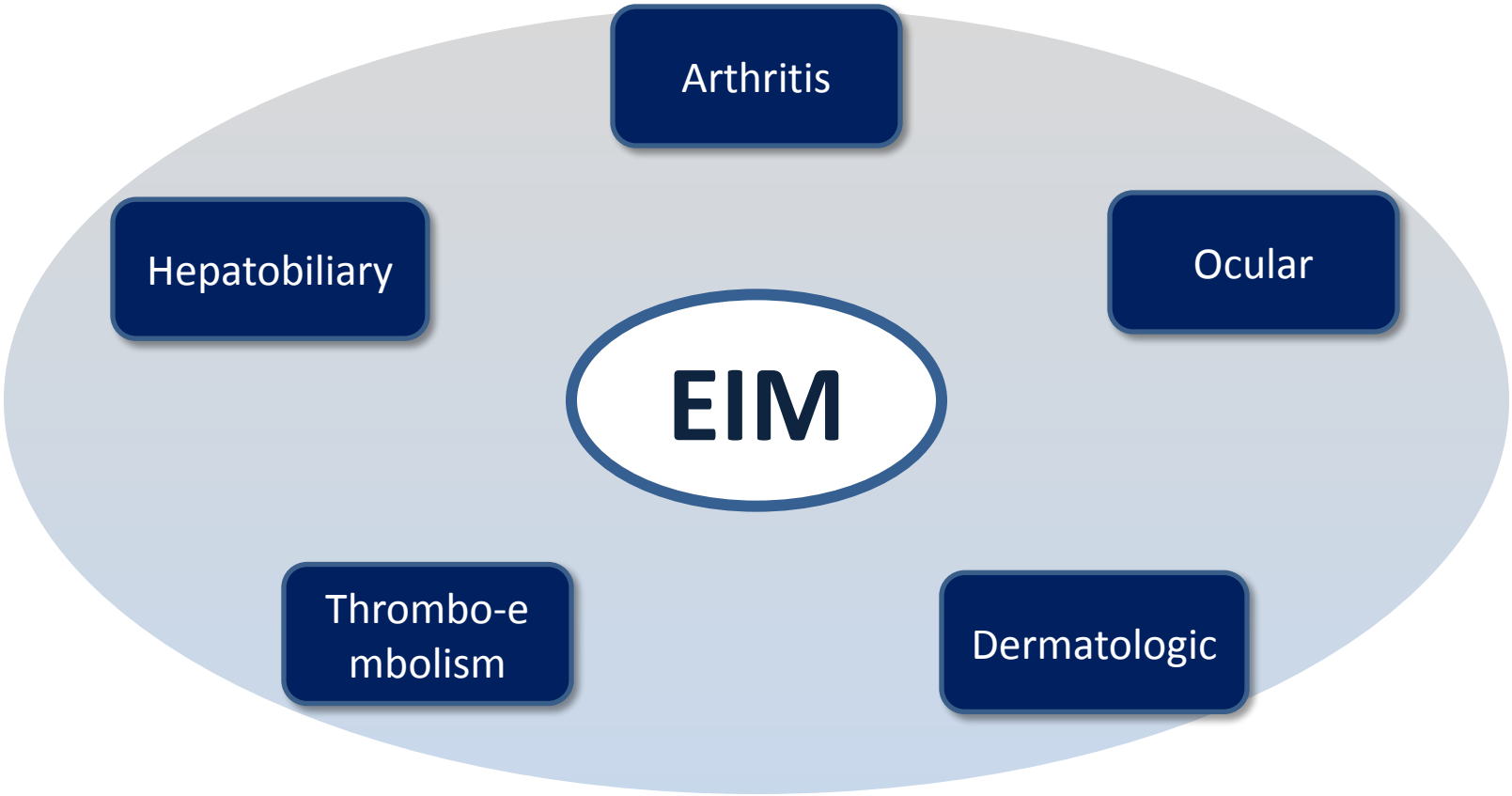
Crohn's Disease - Distinguishing Features



Extraintestinal Manifestations of IBD



EIM are present in 30% of IBD patients and may affect multiple systems

Larsen et al. – Ann Med '10; Vavricka et al. – IBD '15

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Extraintestinal Manifestations

	Parallels bowel disease activity	Independent from bowel disease activity
Joints	Peripheral arthritis	Axial arthritis (sacroiliitis, ankylosing spondylitis)
Skin	Erythema nodosum	Pyoderma gangrenosum
Ocular	Episcleritis, scleritis	Uveitis
Hepatobiliary		PSC (primary sclerosing cholangitis)

Larsen et al. – Ann Med '10

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Dermatological Manifestations

Erythema Nodosum

Pyoderma Gangrenosum

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Spondyloarthropathy in IBD

- **Prevalence**: 20%-40% (higher in Crohn's)
  - May predate IBD diagnosis in 25%
- **Pattern**:
  - *Axial* (AS): does not parallel IBD activity
  - *Peripheral*
    - Pauciarticular - asymmetric, transient, nonerosive
    - Polyarticular (small joints, "RA like") - independent
- **Soft tissue**: enthesopathy, clubbing

Oliveri et al. – Autoimm Rev '14; Vavricka et al. – IBD '15

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Differentiating IBD from Unusual Manifestations of Other Forms of Colitis

- Acute self-limited colitis
- Infectious colitis (C Difficile, TB)
- NSAID-induced colitis
- Neoplasia
- Ischemia
- Diverticular disease associated colitis (SCAD syndrome)
- Diversion colitis

Symptoms are Unreliable

- Patients with irritable bowel syndrome (IBS) and other GI disorder can have symptoms that are indistinguishable from mild-moderate IBD
- Symptoms correlate poorly with objective markers of disease activity
- *Abdominal pain by itself is NOT an indicator of active IBD*

Signs and Symptoms of IBD and Other GI Conditions May Overlap

	Celiac Disease	IBS	IBD	SIBO
Abdominal pain		X	X	X
Diarrhea	X	X	X	X
Hematochezia			X	
Anemia	X		X	X
Anorexia			X	
Weight Loss	X		X	
Fever			X	
Diarrhea ↔ constipation		X		X
Bloating, gas	X	X	X	X
Mucus		X	X	X

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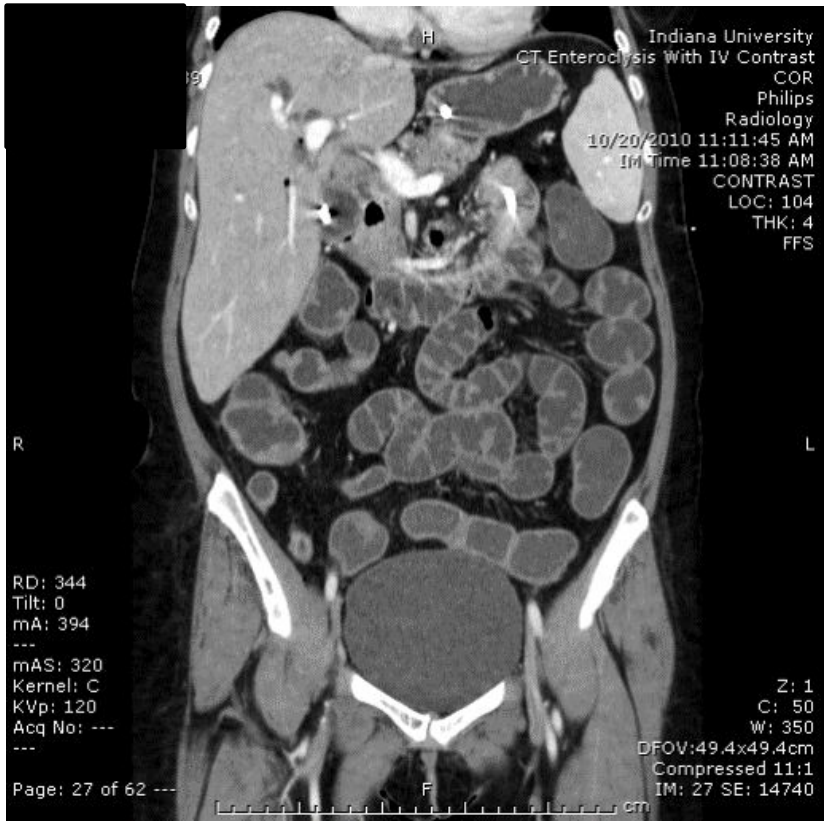
Automatic Imputation in IBD

- In a patient with IBD, all (abdominal) symptoms are attributed to IBD
- Reason IBD is liable for automatic imputation:
  - Uncommon
  - Immune-mediated
  - Poorly understood
  - Multi-systemic

Automatic Imputation in IBD

- 40 WM s/p SB resection for Crohn's
- In remission on treatment with methotrexate



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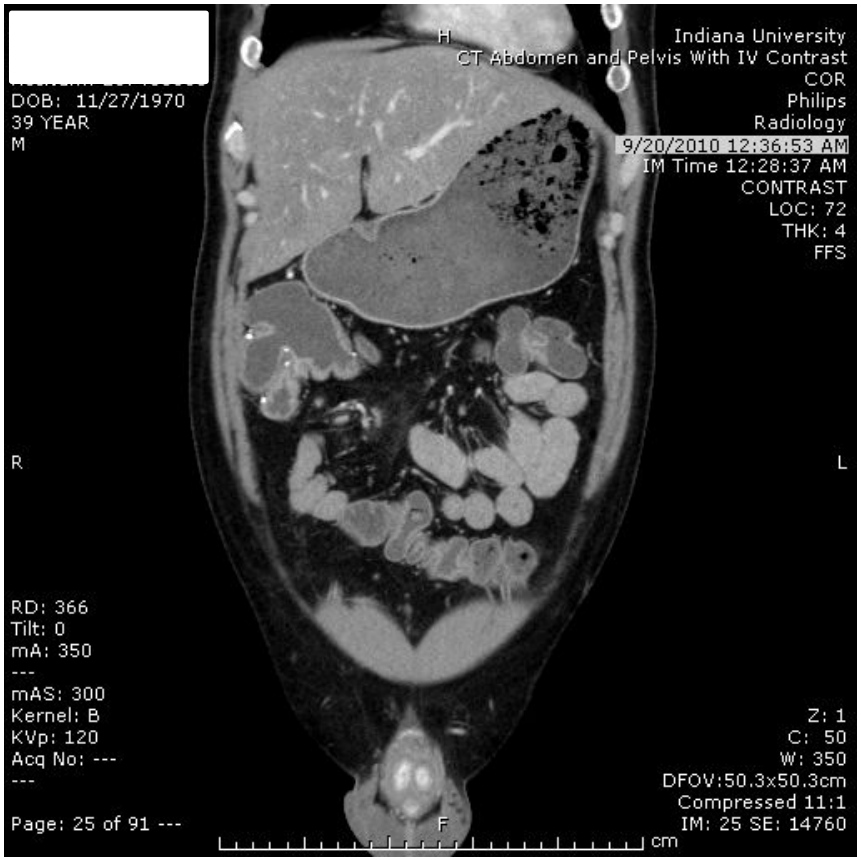
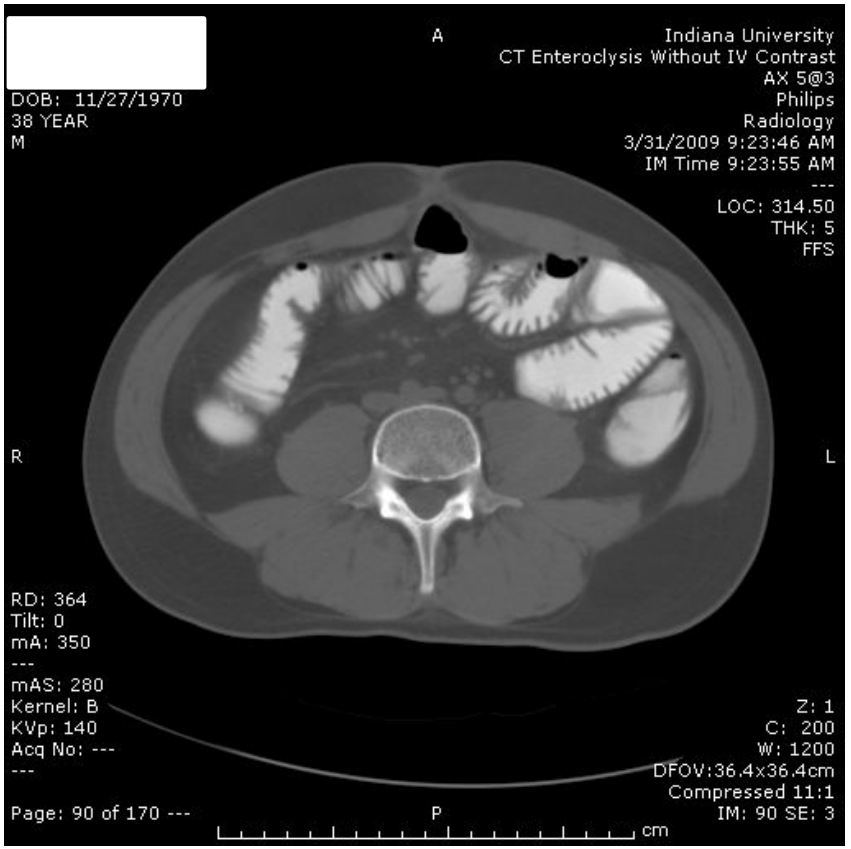
No Evidence of Radiological Disease





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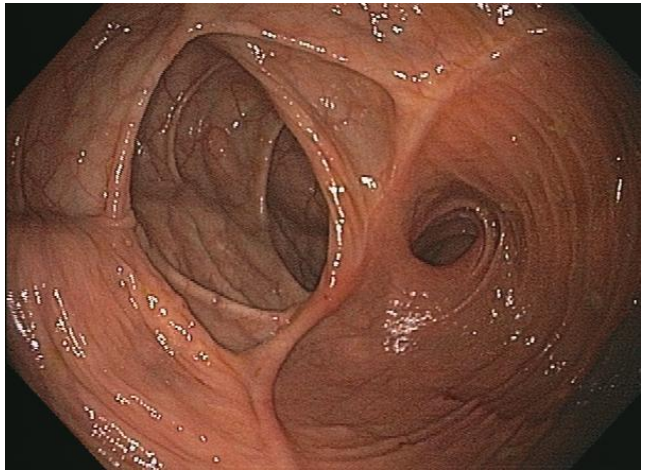
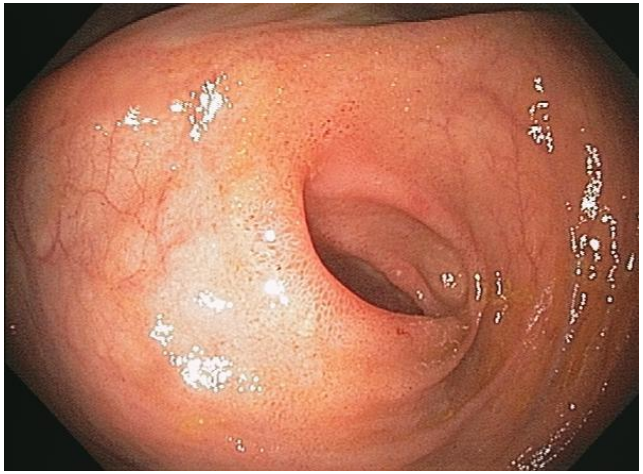
No Evidence of Endoscopic Disease





Yet …

- 13 CT scans in 2 years
- 4 ER visits
  - Normal labs
- 2 hospitalizations for pain
  - Each time started on systemic steroids for "Crohn's flare"

So How Can We Distinguish IBD From Other Conditions?

CRP and ESR in Inflammatory Bowel Disease vs Functional Bowel Disease

	ESR ≥10mm/hr	CRP ≥ 6mg/L	ESR ≥ 10mm/hr & CRP ≥ 6mg/L
Sensitivity, %	79	77	50
Specificity, %	67	70	84
PPV, %	42	42	50
NPV, %	91	91	84

Dolwani et al. Aliment Pharmacol Ther 2004; 20: 615–621

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Fecal Inflammatory Biomarkers in IBD Diagnosis

- Have replaced fecal WBC
- **Calprotectin**
  - Abundant in neutrophil cytoplasm
  - Stable at room temp
- **Lactoferrin**
  - Found in neutrophil granules
  - Unstable

Lewis J – Gastro '11

Accuracy of Fecal Calprotectin for IBD Diagnosis

- Suspected IBD (pre-test probability 40%)
  - *sensitivity 93%*
  - *specificity 96%*
- Conclusions:
  - Use of calprotectin would prevent 30 colonoscopies
  - Delayed diagnosis may occur in 6% of patients

- Von Roon – Am J Gastro ’07; Van Rheenan et. al. BMJ 2010; 341:c3369.

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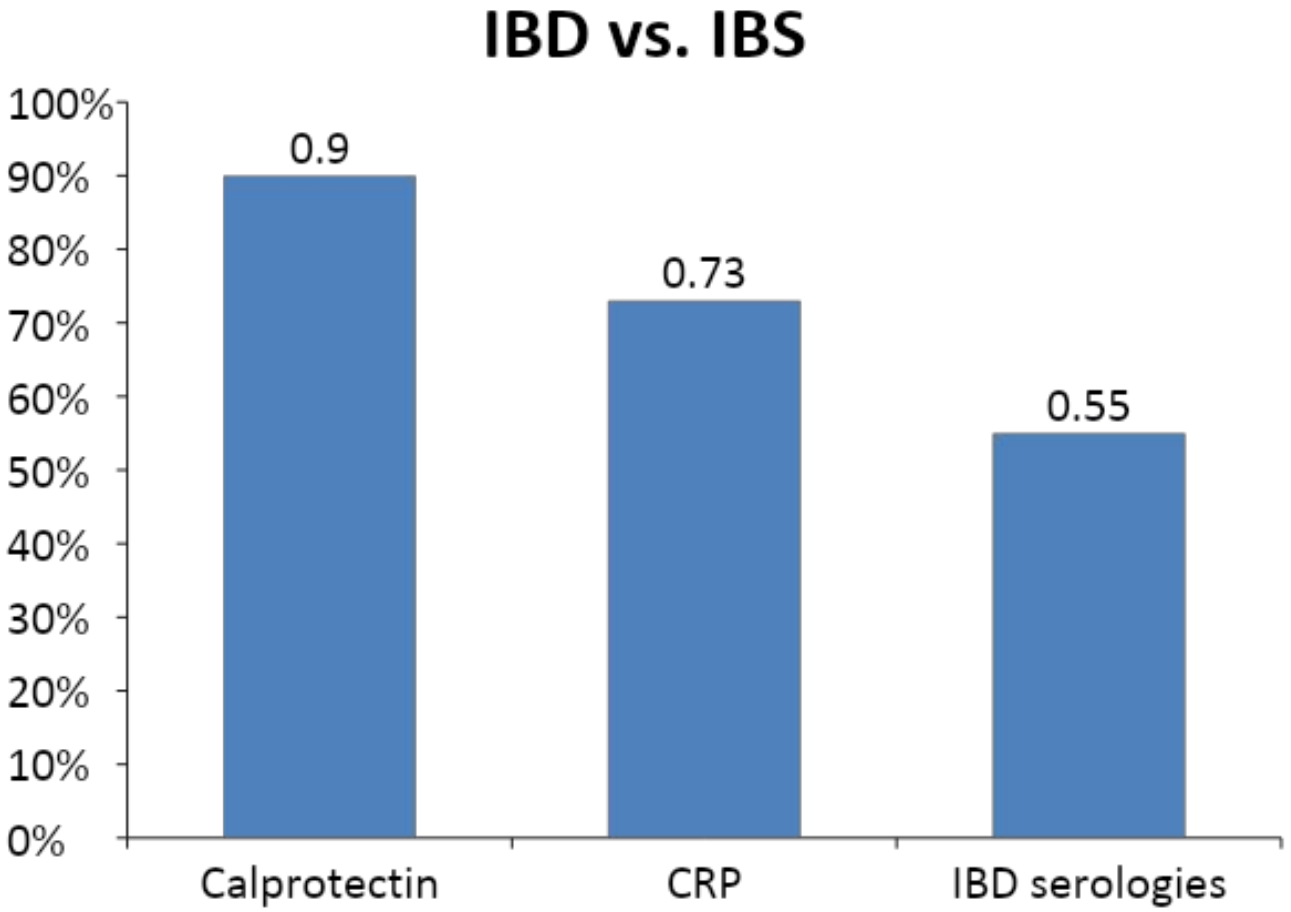
Accuracy of Biomarkers for IBD



Schoepfer et. al. Inflamm Bowel Dis 2008;14:32-39

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Fecal Calprotectin is Cost-Effective

- Screening with FC saves $ 417/patient with suspected IBD against direct endoscopic evaluation*
  - 1/16 false negative – delay in diagnosis

*2012 Medicare costs

Yang et al. – Clin Gastro Hepatol '14

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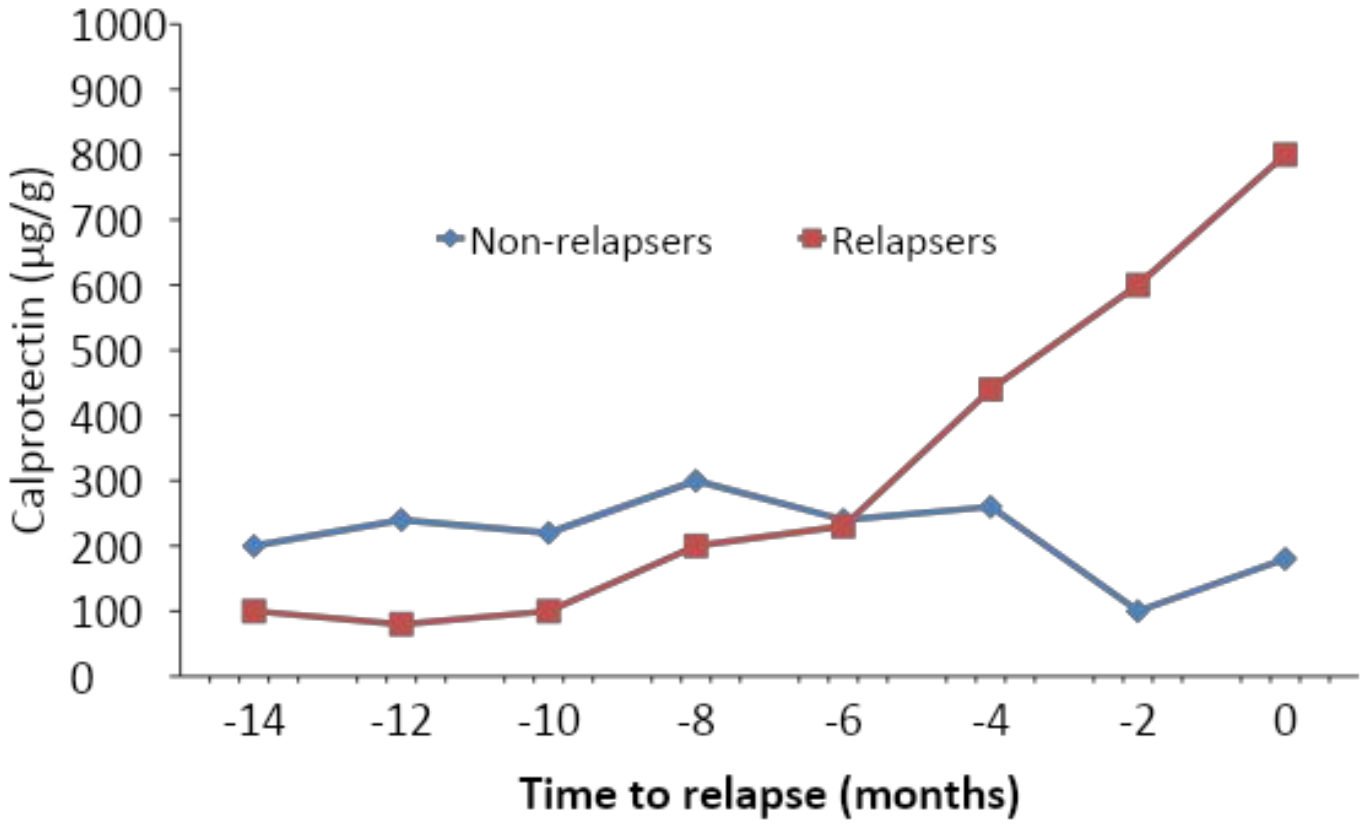
Calprotectin can Predict Relapse in Patients with Crohn's Disease in Remission (STORI)



De Suray et al. – DDW '12: A864

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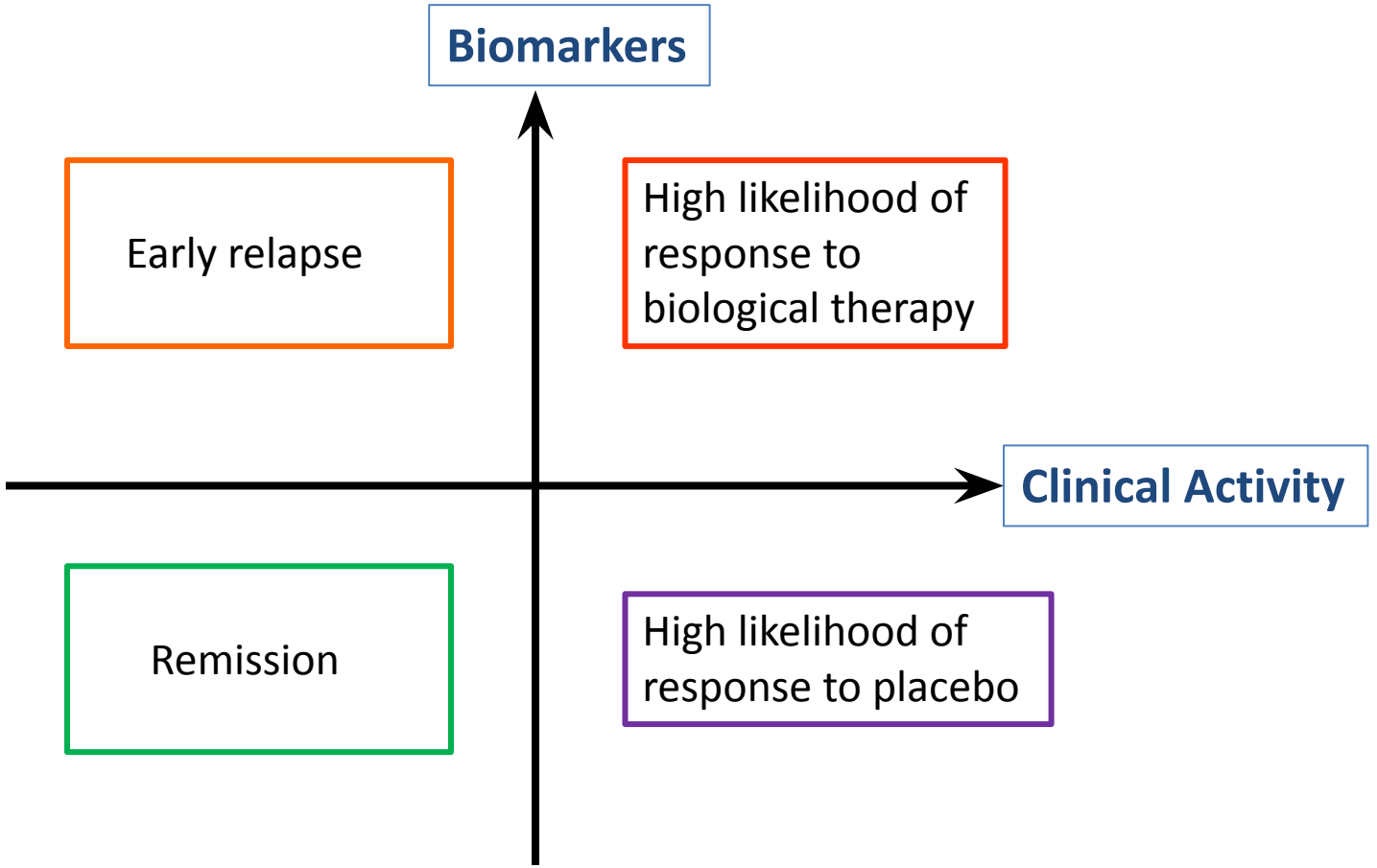
Using Biomarkers to Predict Patient Outcomes in IBD



*Take home message

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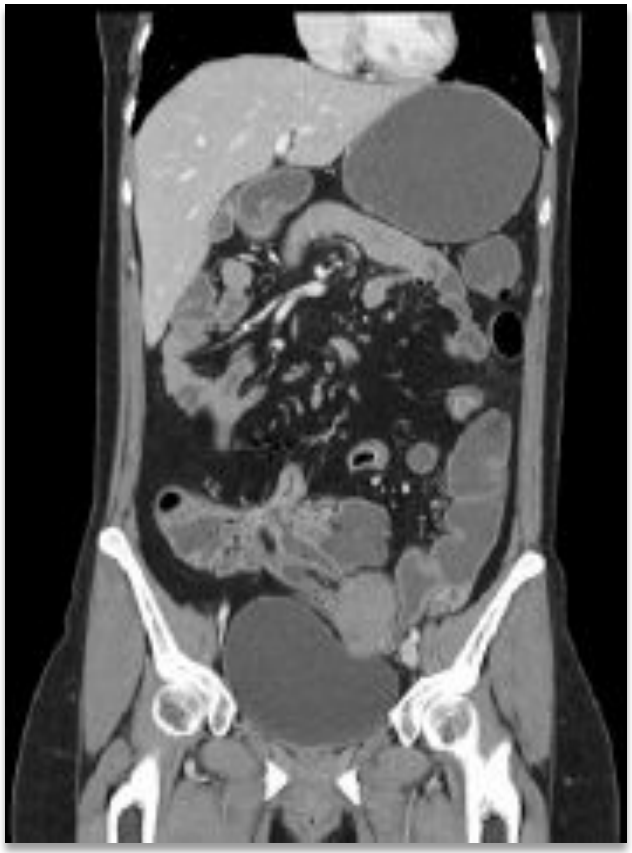
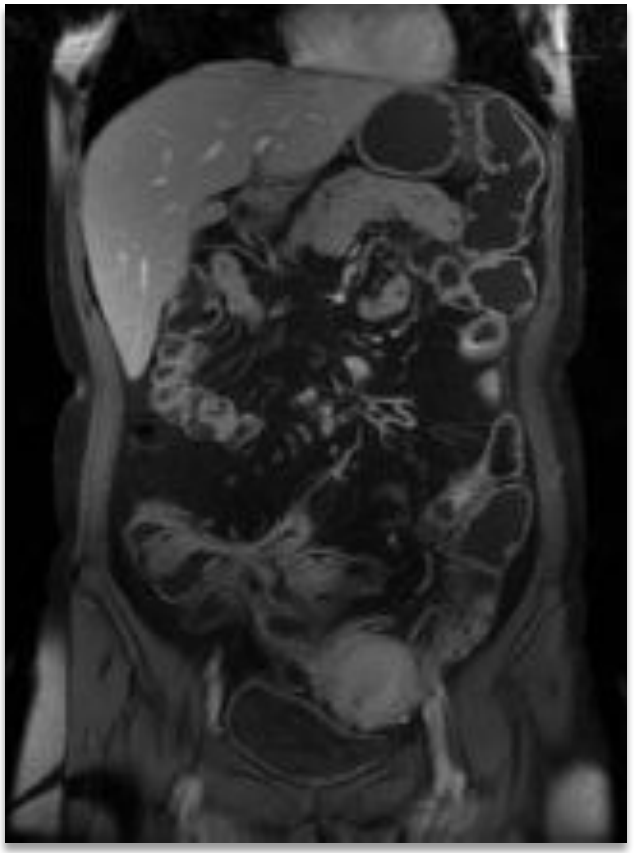
Role of Imaging Studies in IBD

- Initial diagnosis
  - Extent
  - Severity
  - Behavior
- Diagnosis of complications:
  - Strictures
  - Penetrating disease (fistula, abscess)
- Monitor Crohn's disease progression
- Monitor response to therapy in CD

CTE and MRE have similar performance for detecting active Crohn's disease



CTE



MRE

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CT vs. MR Enterography in Crohn's Disease

CTE Advantages

- Lower inter-observer variability
- Wider access
- Faster
- Lower cost
- Higher image quality
- Easier to interpret

MRE Advantages

- No radiation
- "*functional*" imaging (diffusion-weighted)
- Superior for pelvis (perianal fistula)
- Pregnancy

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IBD Diagnosis Summary

- There is no “gold-standard” IBD diagnosis
- Inflammatory Bowel Disease is not IBS
- NIDDK criteria include clinical, laboratory, endoscopic ± radiologic
- **Calprotectin** can be used for initial diagnosis and monitoring disease activity
- Imaging studies are probably overutilized
- Avoid “automatic imputation”