Natural History and Predictors of Course in Pediatric and Adult Ulcerative Colitis

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Disclosures

- **Janssen Biotech: consultant, Advisory Board, research support**
- **Abbvie: Advisory Board, consultant**
- **Takeda: consultant**
- **Soligenix: consultant**
- **UCB: consultant**
- **Celgene: consultant**
- **Lilly: consultant**
- **Receptos: consultant**
- **Boehringer Ingelheim: consultant**

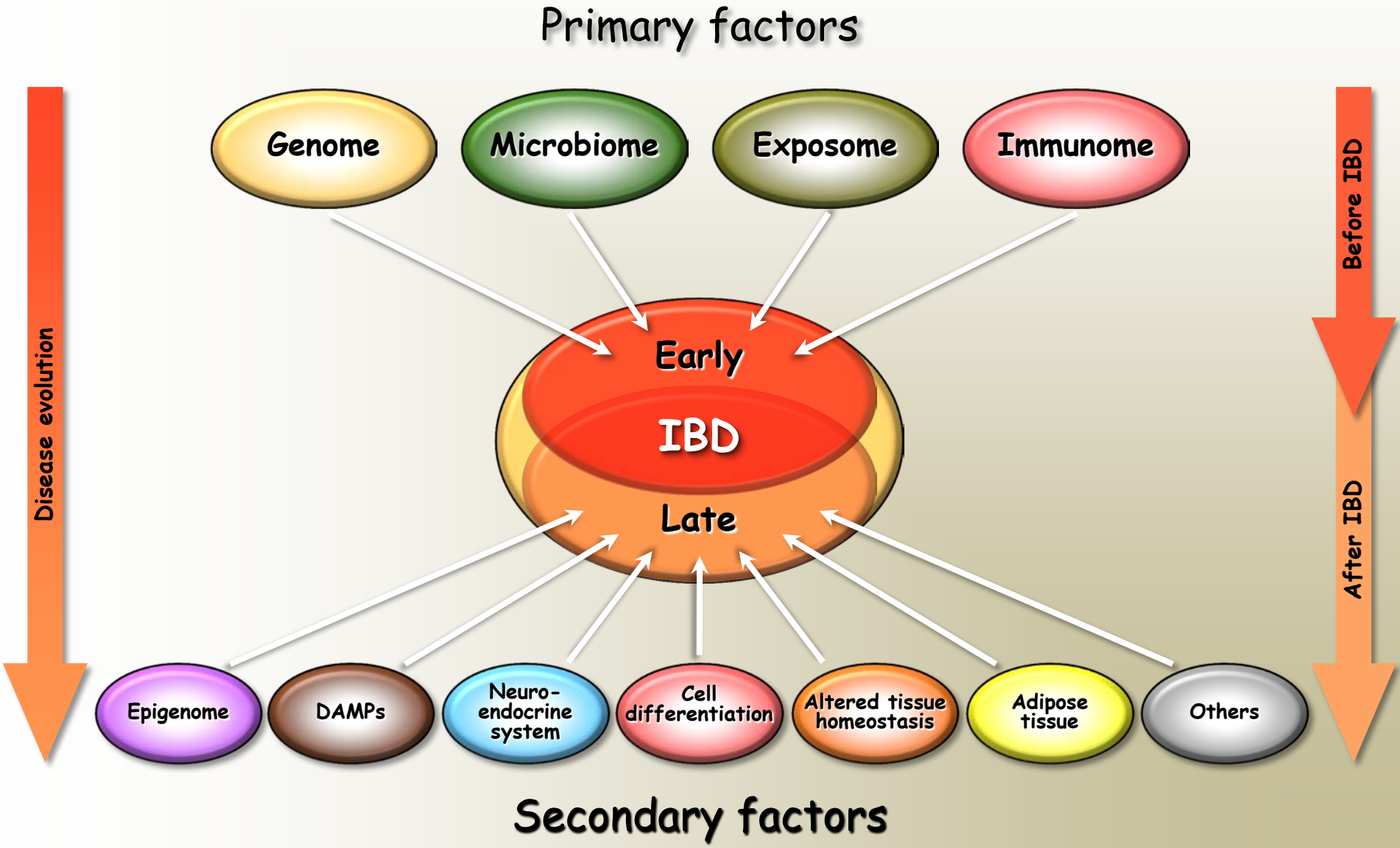
Outline

- Pathophysiology, Epidemiology
- Clinical expression: Adults vs. Children
- Standard of Care: Adults vs. Children
- Therapies and Natural history: Adults vs. children
- Predictors of course
- Age: How low can you go?
- Is UC a disease for which partial extrapolation is reasonable?

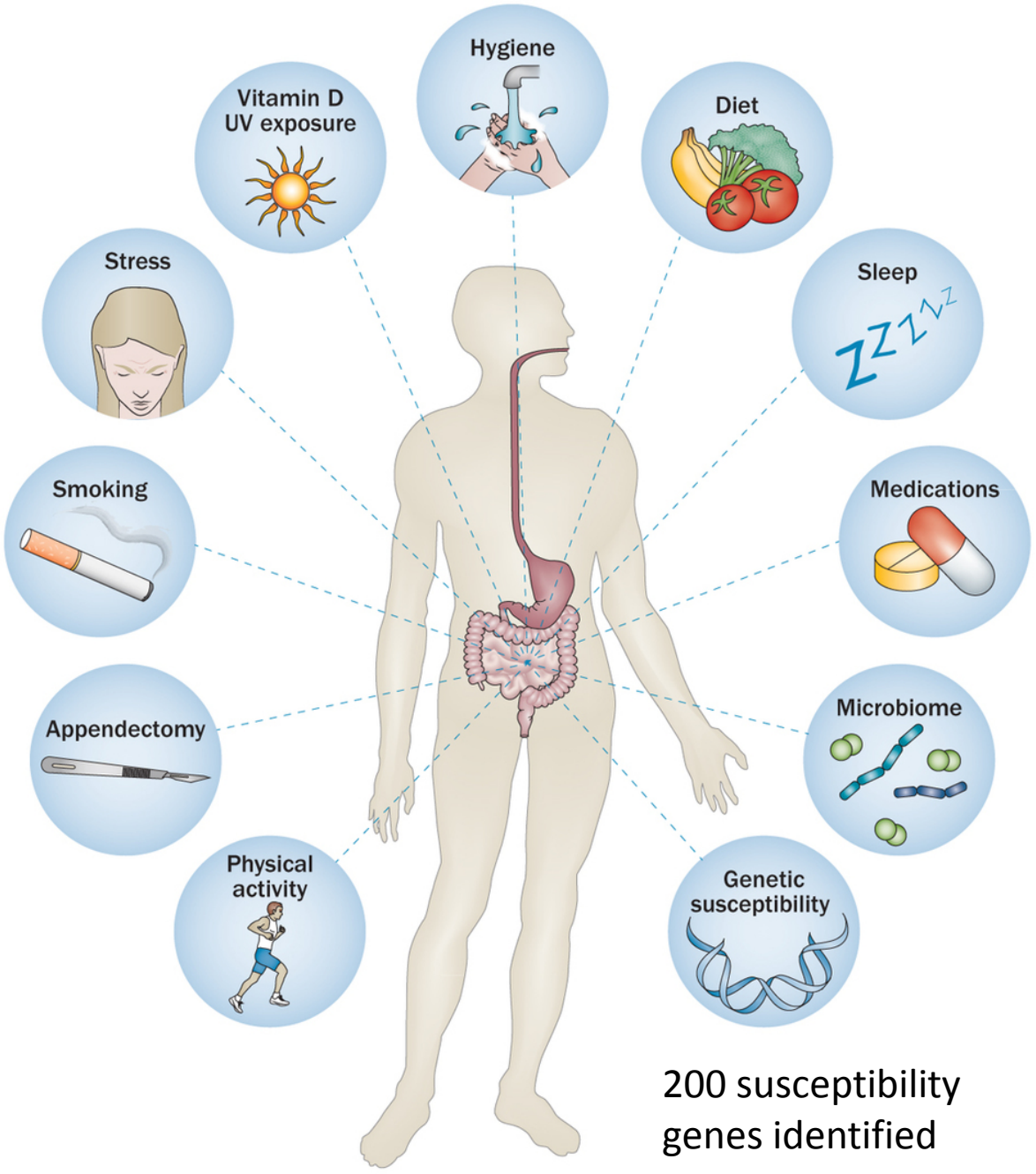
Ulcerative Colitis-Pathophysiology

A chronic inflammatory disorder of the colon that results from an inappropriate activation of the mucosal immune system by antigens derived from both the host epithelium and enteric flora in genetically susceptible individuals

IBD Pathogenesis

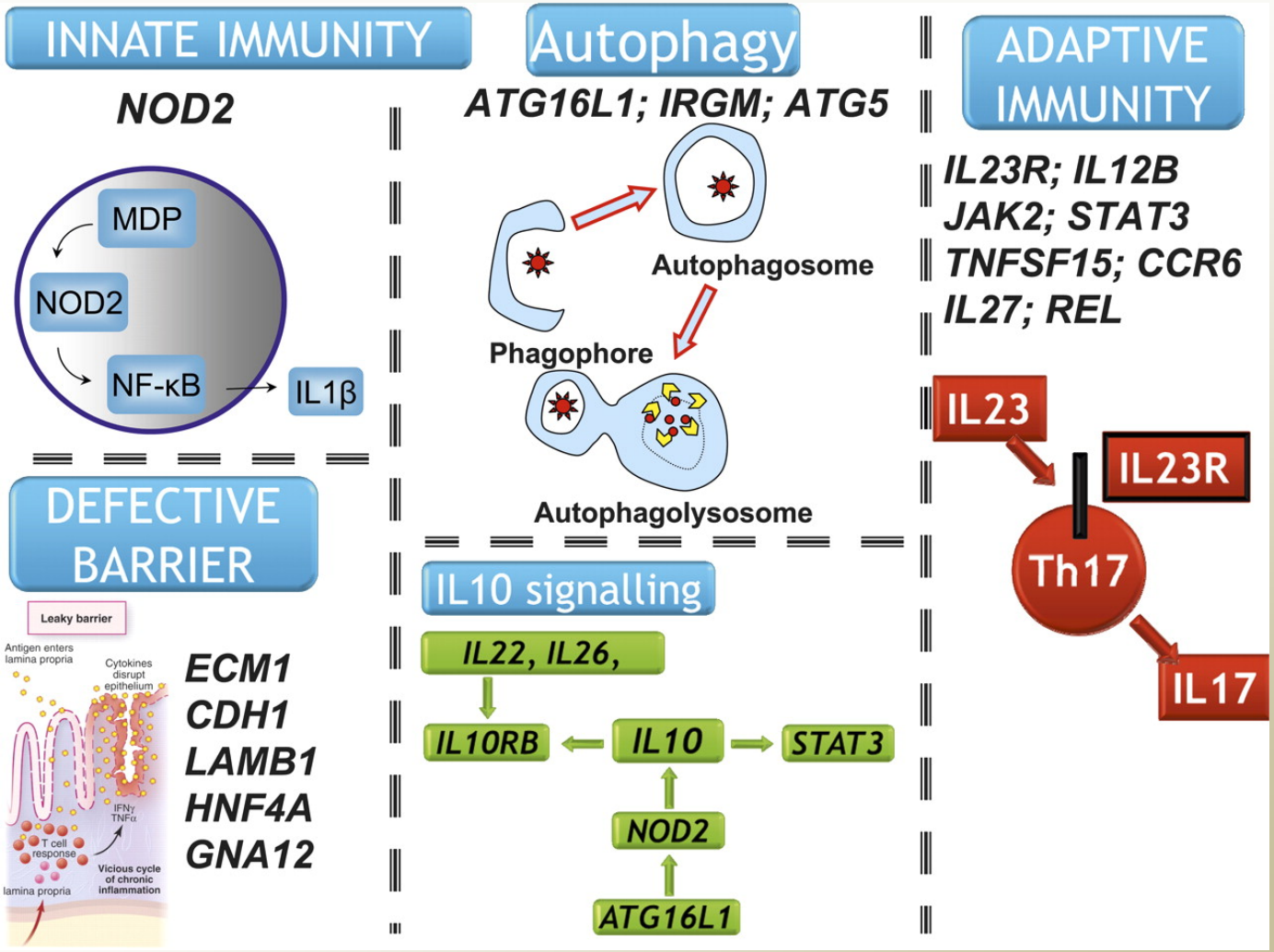


Courtesy of Claudio Fiocchi, MD



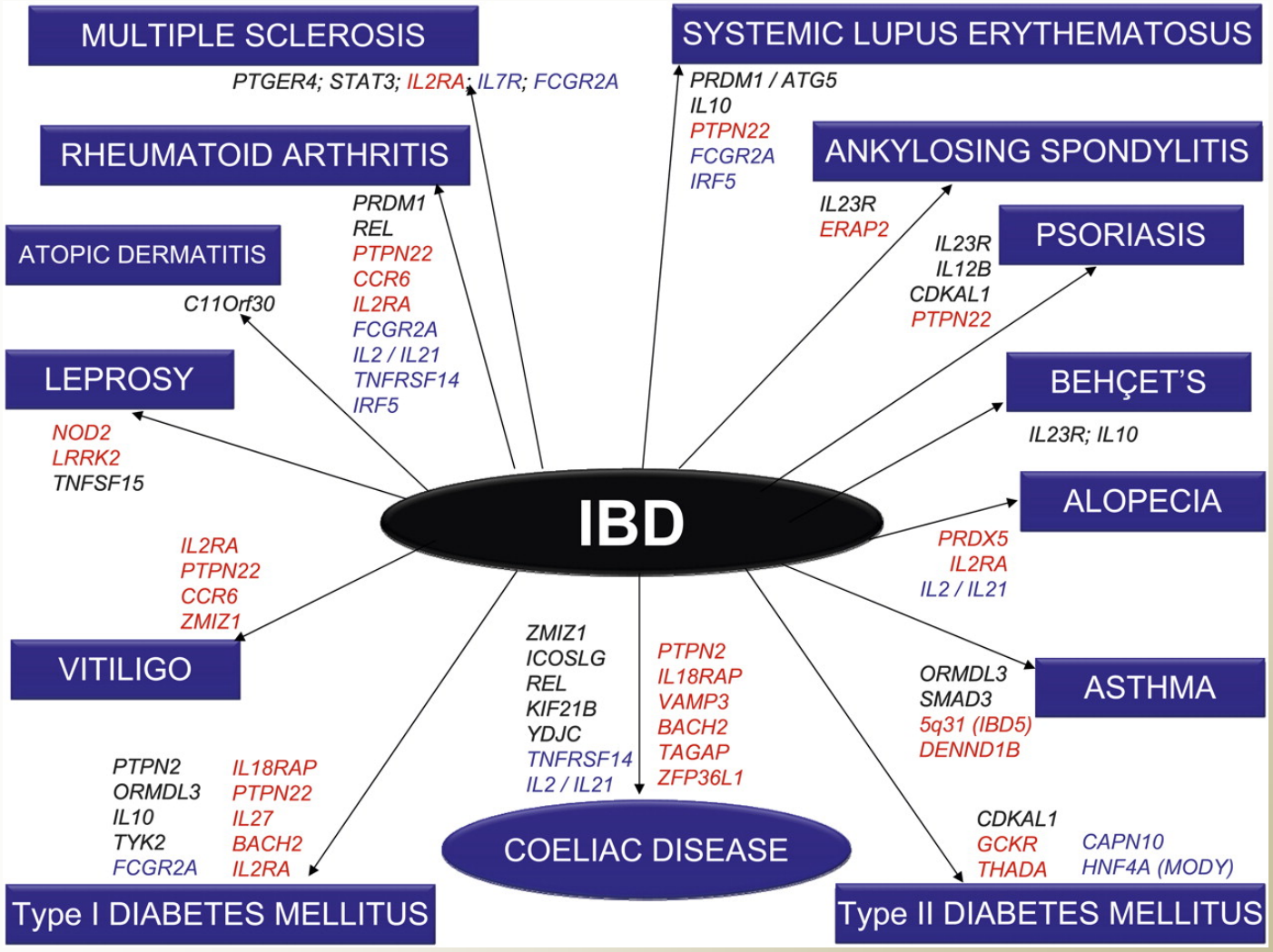
200 susceptibility genes identified

Key pathways arising from gene discovery in Crohn's disease and ulcerative colitis.



C W Lees et al. Gut 2011;60:1739-1753

Shared Genes With Other Immune Mediated Disorders



C W Lees et al. Gut 2011;60:1739-1753. Black: all IBD, Red: UC, Blue: CD

GUT

Global Map of Inflammatory Bowel Disease

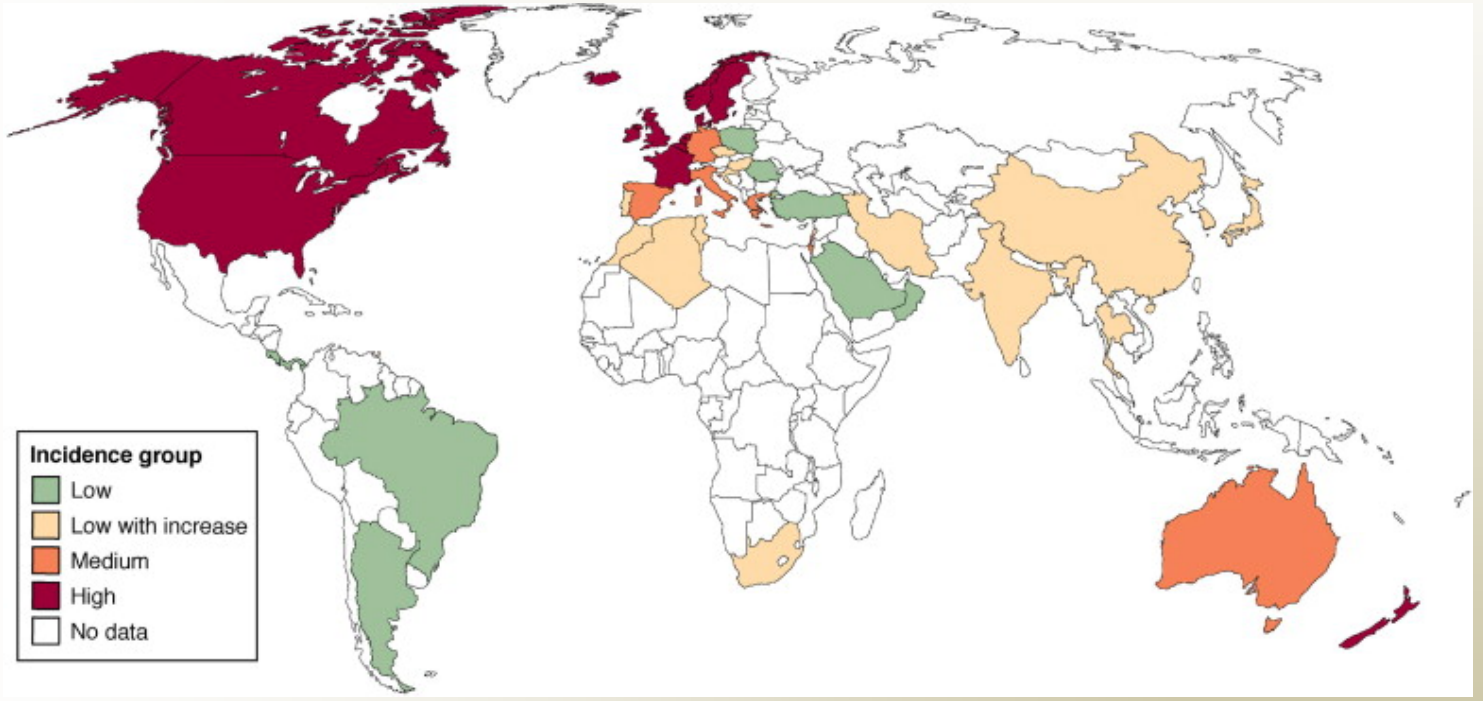


Figure 1. The global map of inflammatory bowel disease: red refers to annual incidence greater than 10/105, orange to incidence of 5–10/105, green to incidence less than 4/105, yellow to low incidence that is continuously increasing. Absence of color indicates...

Jacques Cosnes, Corinne Gower–Rousseau, Philippe Seksik, Antoine Cortot

Gastroenterology, Volume 140, Issue 6, 2011, 1785–1794.e4

Age Distribution

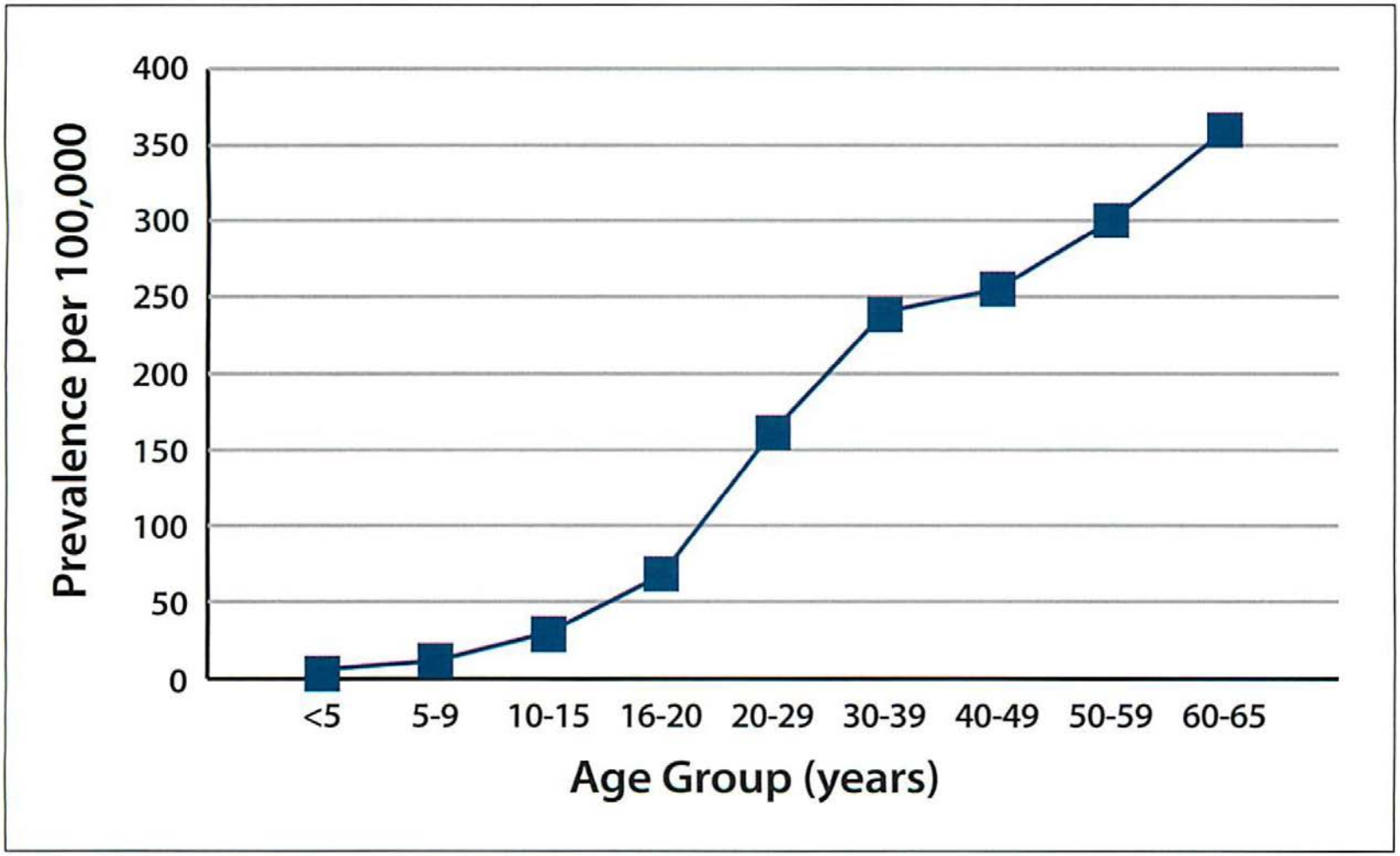


Figure 2. Age-specific prevalence of ulcerative colitis in the United States.

Adapted from Kappelman MD et al. *Dig Dis Sci.* 2013;58(2):519-525.[3]

Clinical Expression: The Same in Children and Adults

Feature	Adults	Children
Diarrhea	XXXX	XXXX
Bleeding	XXXX	XXXX
Abdominal Pain	XXXX	XXXX
Arthritis	XX	XX
Axial spondyloarthropathy	X	X
Liver disease	X	X
Other: pyoderma gangrenosum, erythema nodosum, uveitis, episcleritis	X	X

Disease Extent: Generally more extensive in children

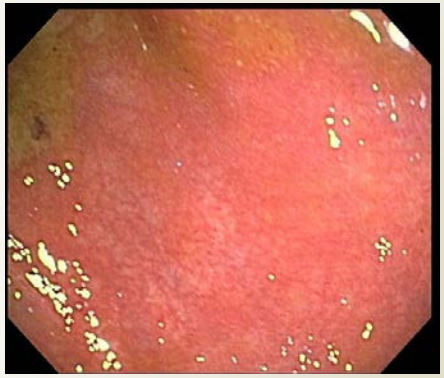
Anatomy of Large Intestine

Disease extent	Adults[1]	Adults[2]	Children[3]	Children[4]
Distal	12%	22%	5%	8%
Left sided	38%	37%	20%	23%
Extensive	48%	42%	75%	69%

[1]Lancet 2016;387:156, [2] APT 2015;43:540, [3]Gastroenterology 2008;135:1114, [4] PROTECT Study

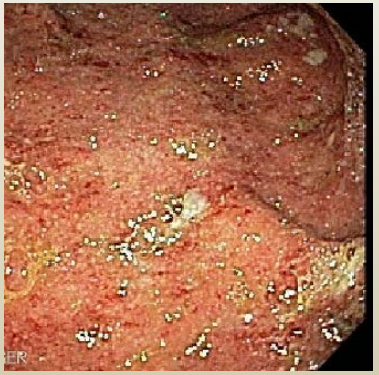
Endoscopic and Histologic Appearance of Disease Is the Same in Adults and Children

Mayo 0

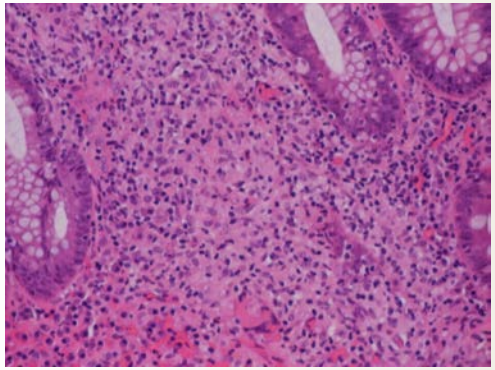


Mayo 1

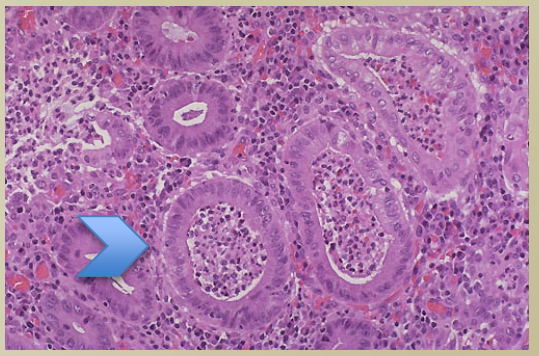
Mayo 2



Mayo 3



Infiltration of lamina propria with inflammatory cells, crypt abscesses, architectural distortion, basal plasmacytosis



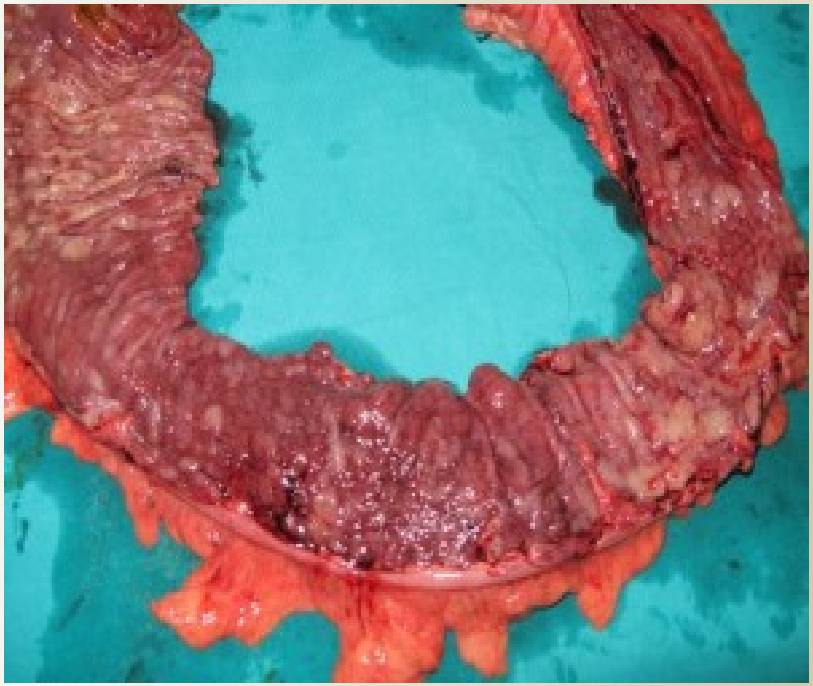
Natural History Is What Happens When There are No Good Therapies

Author	Year	Study cohort	Outcome
Hardy[1]	1933	95 adults	75% mortality at 1 year
Truelove/Witts[2]	1955	Adult UC treated with HC	6% HC and 15% control pts died within 6 months
Goel[3]	1973	25 hospitalized children with UC	20% died (post-colectomy), 19 had chronic disease
Michener[4]	1979	336 children	35% colectomy, 5% died (cancer); 69% chronically ill
Langholz[5]	1994	1161 adults	30% colectomy by 15 years

[1]BMJ 1933;2:812; [2]BMJ 1955;4947:1041; [3]Arch Dis Child 1973;48:337; [4]J Clin Gastroenterol 1979;1:301; [5]Gastroenterology 1994;107:3

The Natural History We Want To Avoid

- **Ulcerative colitis – poor quality of life; uncontrolled inflammation requiring colectomy; cancer**

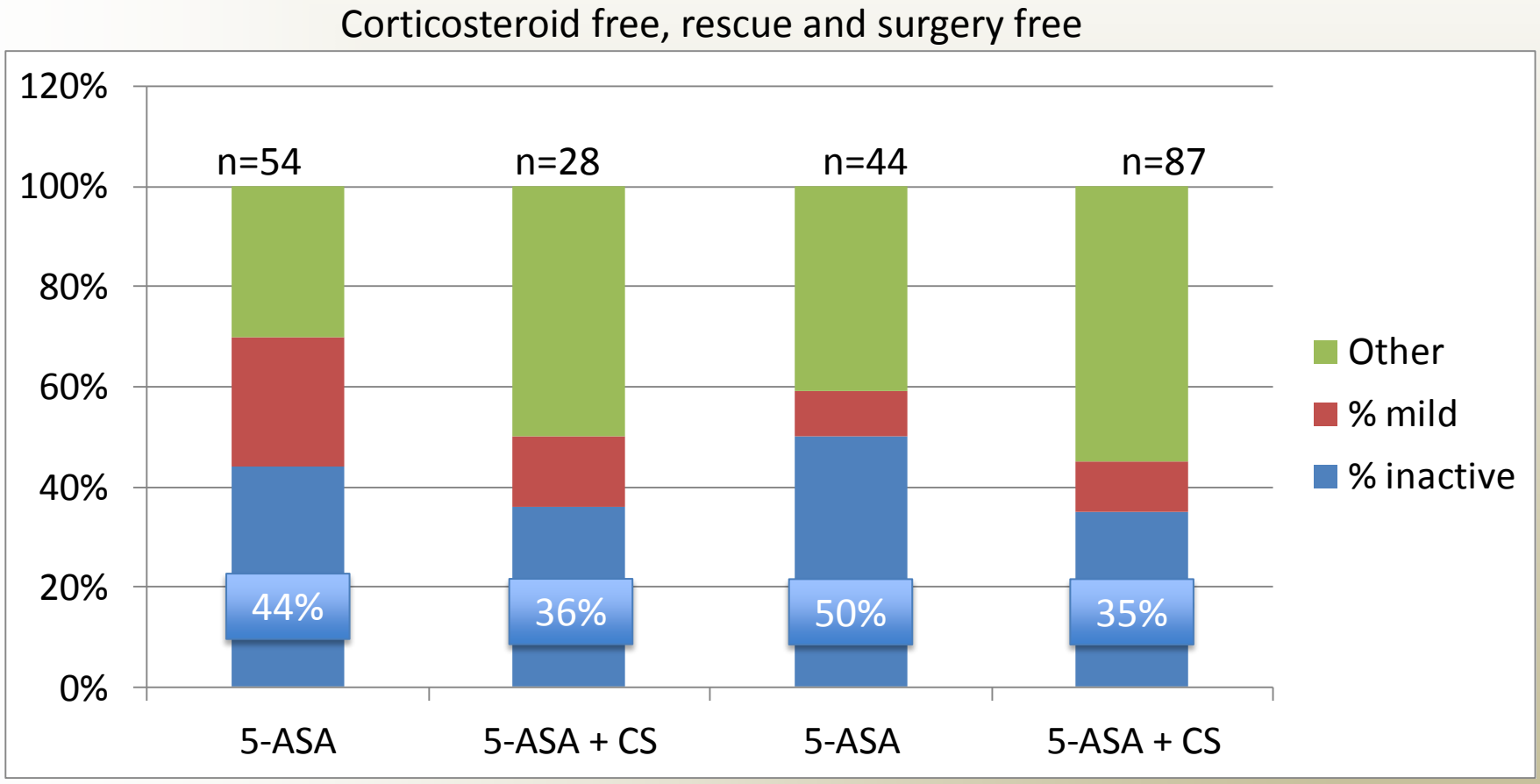


Standard of Care Non-biologic Therapies for Ulcerative Colitis: Adult vs. Child

- **The mainstay of therapy for pediatric or adult ulcerative colitis are aminosalicylates**
  - **Effective for both induction and maintenance of remission for mild to moderate disease**
- **Abundance of adult trials, paucity of pediatric trials for efficacy and safety. Most pediatric data are from observational studies**
- **Adult success rates around 50%[1]**
- **Cautiously note overall similarity in efficacy though <u>many</u> methodologic confounders**
- **Non-adherence a big issue in both populations**

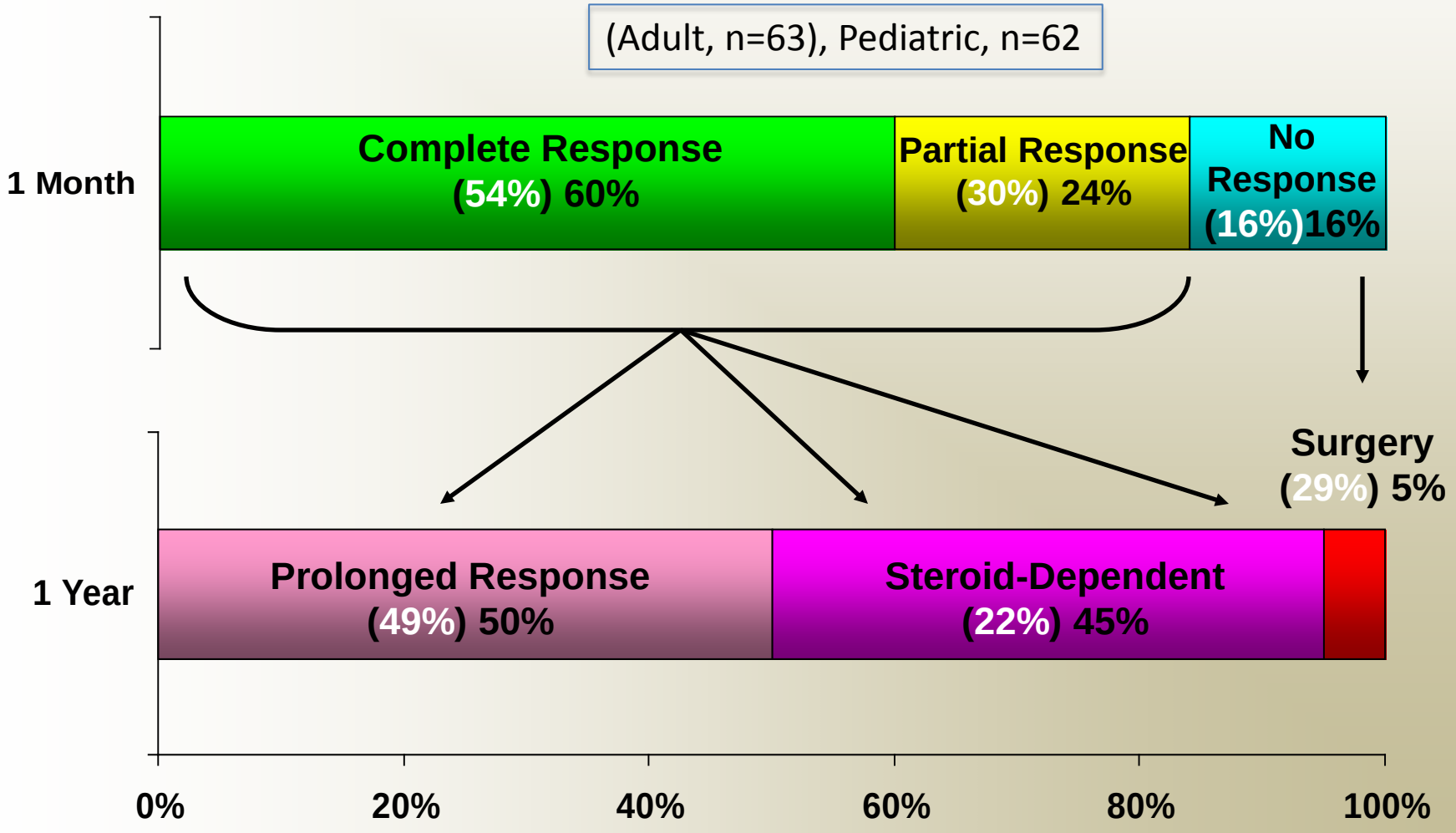
Ford et al. Am J Gastroenterol 2011;106:601

Outcome at 1 Year Children with Ulcerative Colitis Treated With 5-ASA±CS in First 30 Days (n=213)



Zeisler et al. JPGN 2013;56:12

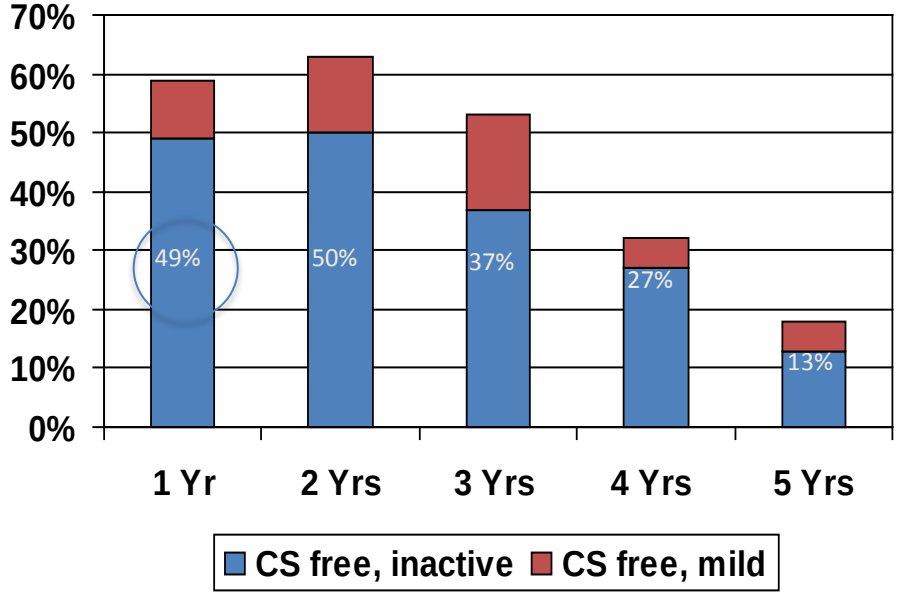
Immediate and Long-Term Outcomes of Corticosteroid Therapy in Ulcerative Colitis

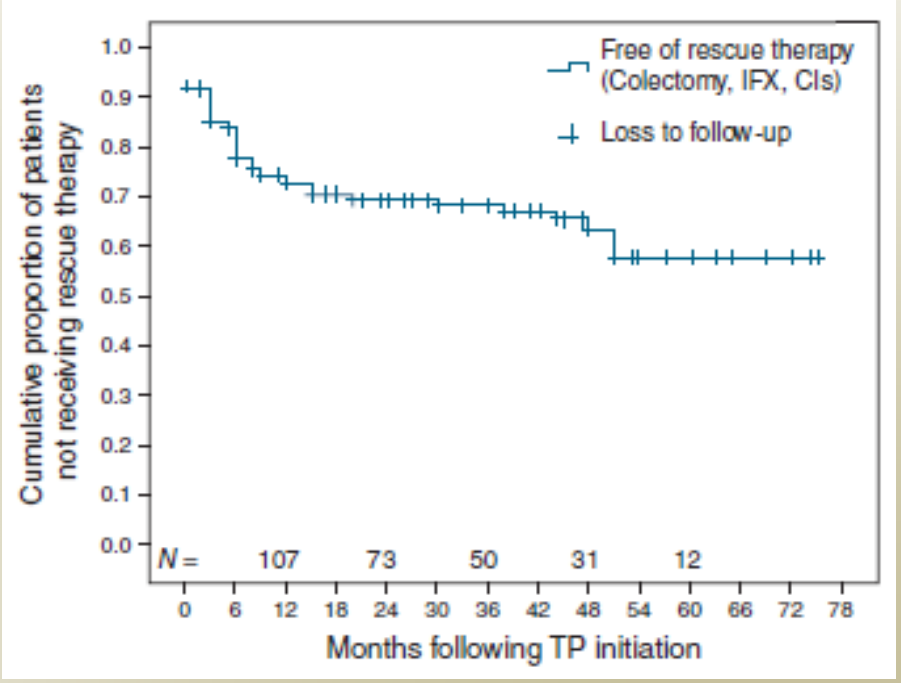


Hyams J et al. Clin Gastroenterol Hepatol 2006;4:1118, Faubion et al. Gastroenterology 2001;121:255

Thiopurine Treatment in Pediatric UC

133 children treated with 6-MP/azathioprine without concomitant biologic or previous calcineurin Rx

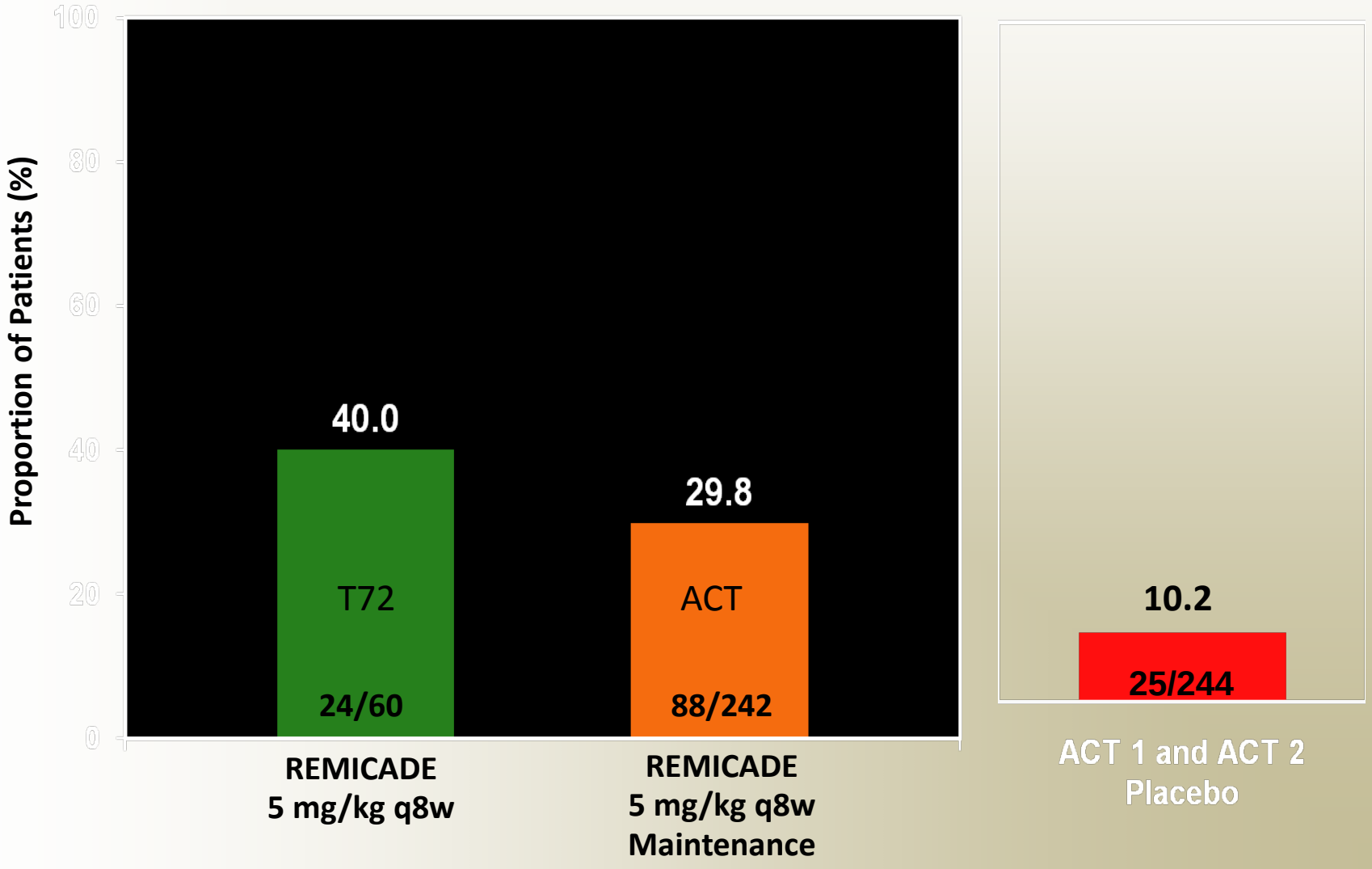




Adult data: 6 m – 1 yr, range 53%-63%
Ardizzone et al. Gut 2006;55:47, Adler et al. Am J Gastro 1990;85:717, Fraser et al. Gut 2002;50:485

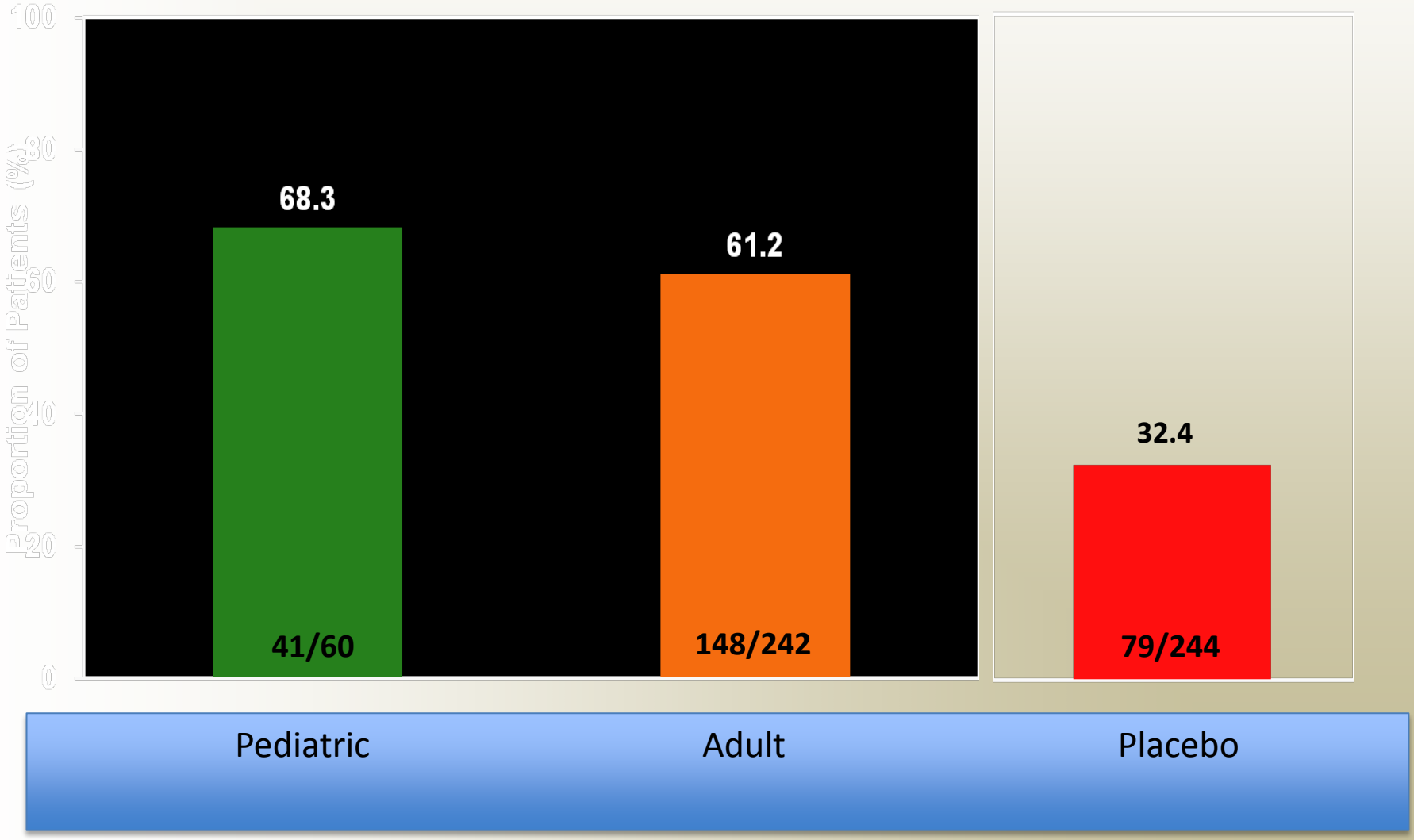
Hyams et al., Am J Gastroenterol 2011;106:981

Clinical Remission at Week 8: Infliximab Pediatric Trial (T72) Compared to ACT 1 and ACT 2



Hyams et al. Clin Gastro Hepatol 2012:10:391, Rutgeerts et al. NEJM 2005;353:2462

Mucosal Healing at Week 8: Infliximab Clinical Trial (T72) Compared to ACT1 and ACT2

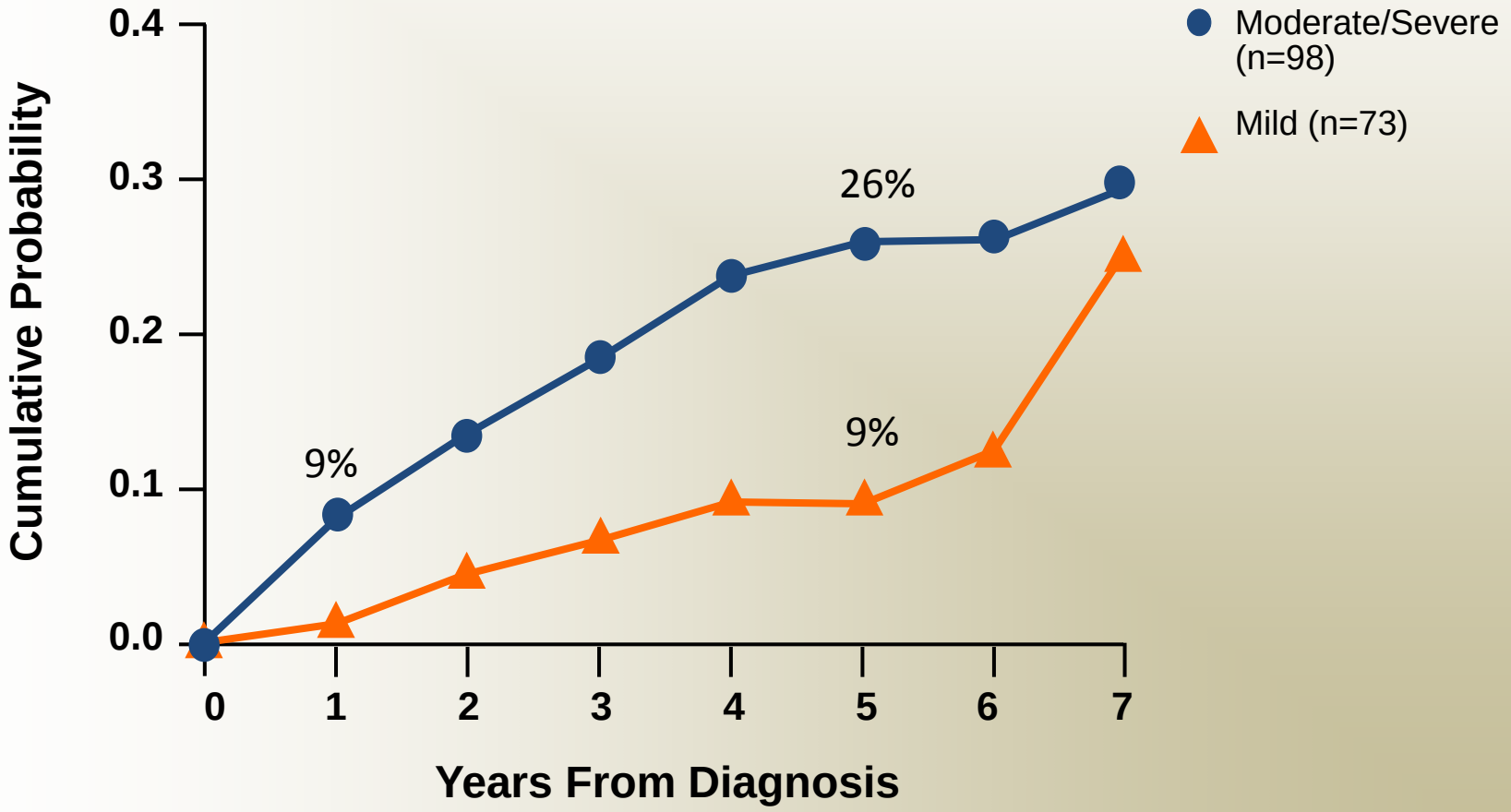


Hyams et al. Clin Gastro Hepatol 2012:10:391, Rutgeerts et al. NEJM 2005;353:2462.

Colectomy: The last choice natural history

- Often great resistance
- Medically refractory severe disease-life threatening, no choice
- Chronic disease –poorly responsive to medical therapy, impaired quality of life; medication toxicity, somewhat elective
- Dysplasia
- Improved use of current therapies and emerging therapies changing likelihood

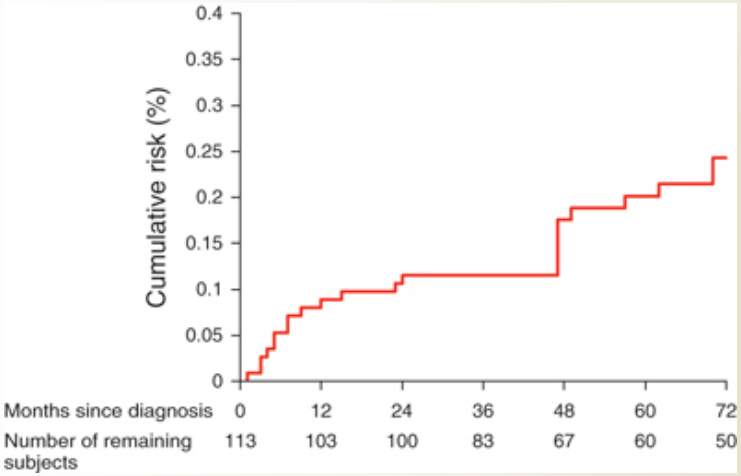
Cumulative Probability of Colectomy by Disease Activity at Diagnosis (1975-1995): Children, Pre-biologic era



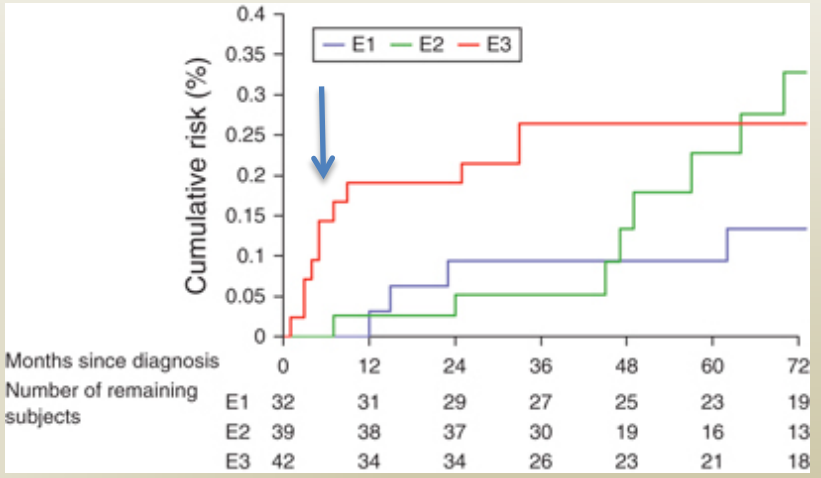
Mild vs moderate/severe, *P*<0.03, * 2 IBD centers

Hyams JS et al. *J Pediatr*. 1996;129:81.

Cumulative Probability of Colectomy, Pediatric Center 1988-2002



Overall rate of colectomy
5 years: 20%



Rate of colectomy by disease extent
29% for extensive disease

1st year high risk for extensive disease

Gower-Rousseau et al. Am J Gastroenterol 2009;104:2080

Cumulative Probability of Colectomy: Manitoba, 1987-2008

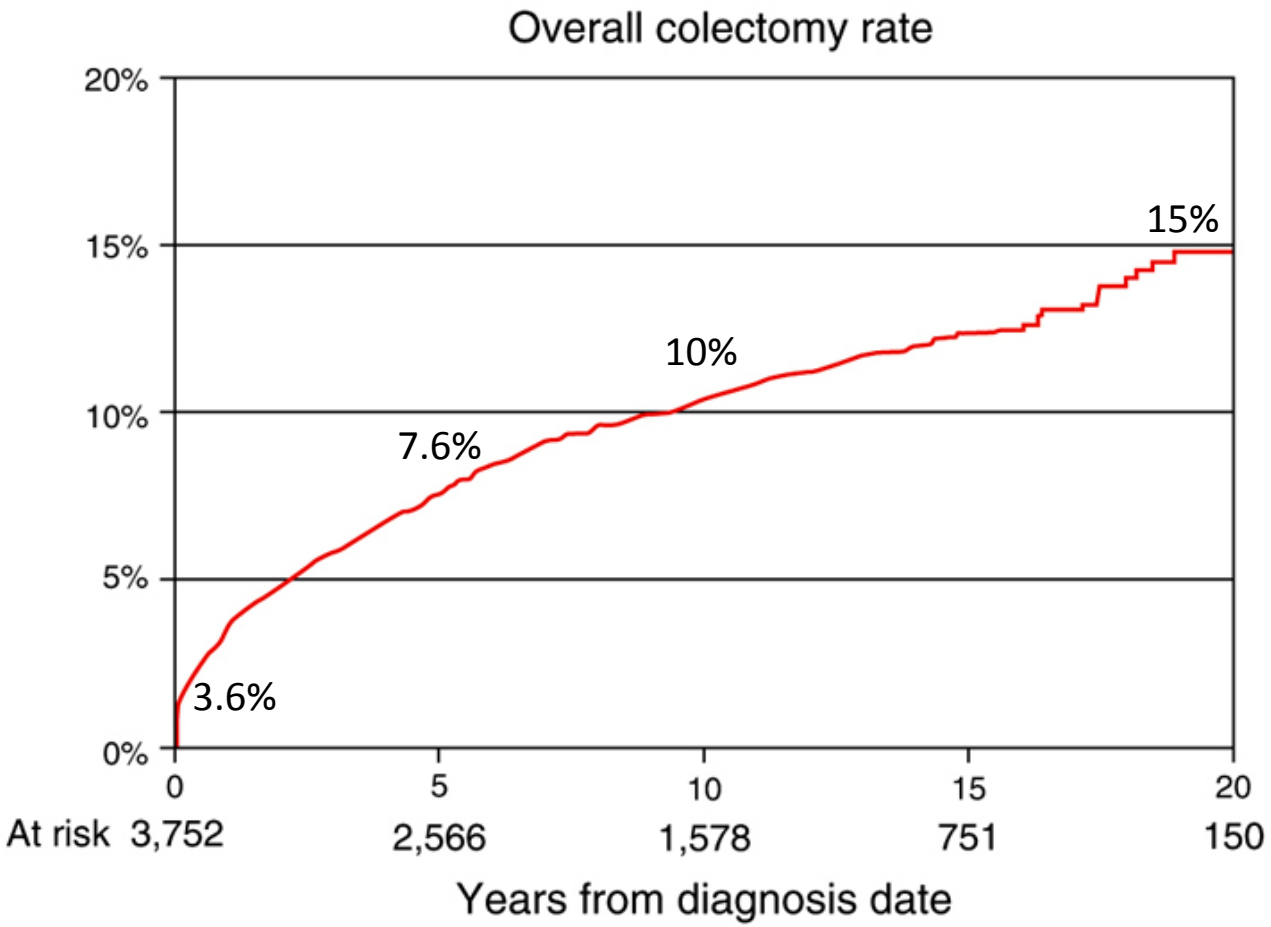
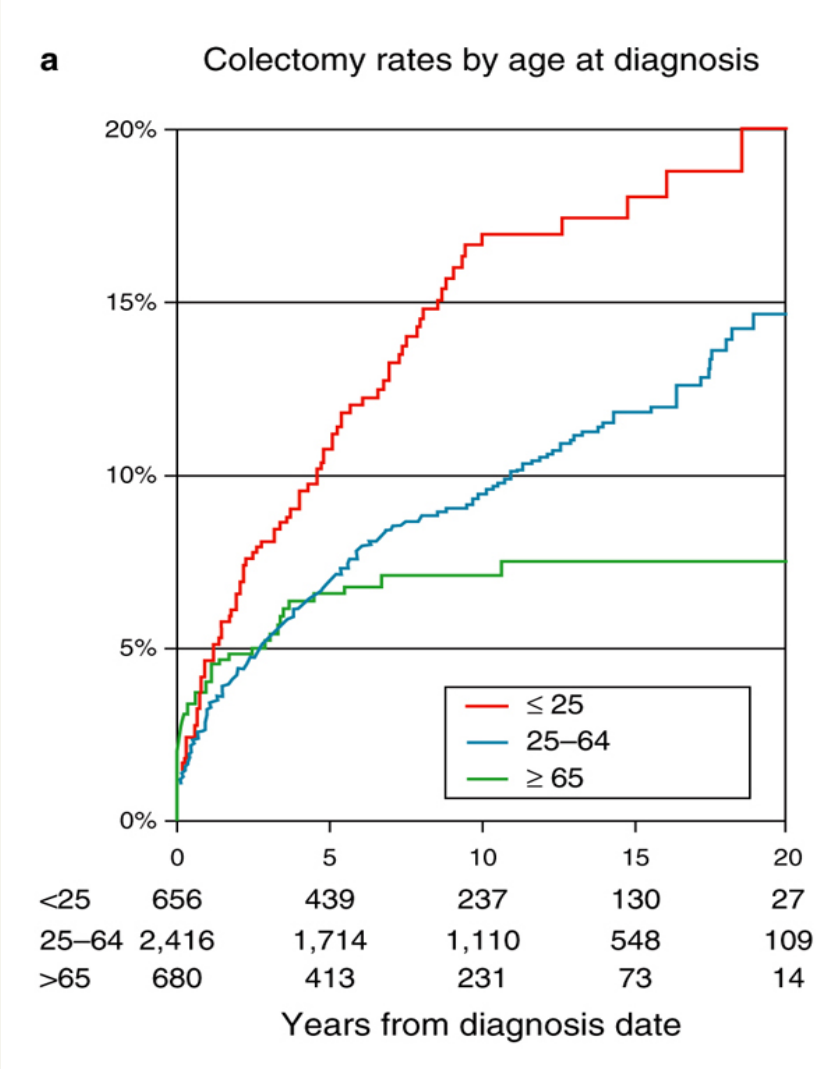


Figure 1. Overall colectomy rate.

367 colectomies

Targownik et al. Am J Gastroenterol 2012;107:1228

Cumulative Probability of Colectomy, Manitoba, by Age dx



Targownik et al. Am J Gastroenterol 2012;107:1228

Factors Associated with Poor Outcomes: Adults

Factor	Result
Age at diagnosis	Younger age associated with more severe disease, higher relapse, and higher risk of colectomy
Smoking status	Non-smokers and ex-smokers do worse than current smokers
Sex	Conflicting, though some evidence that males do worse; many confounders
Genetic factors	Conflicting, though ; CLEC7A, MDR, HLA DRB1, hMLH1 associated with refractory disease
Disease extent	Extensive disease ,worse outcomes
Histopathologic severity	More severe, worse outcomes
Early hospitalization	Markedly worse outcomes
Elevated acute phase reactants	Increased CRP, ESR associated with worse outcomes
Other labs	Anemia, hypoalbuminemia associated with worse outcomes

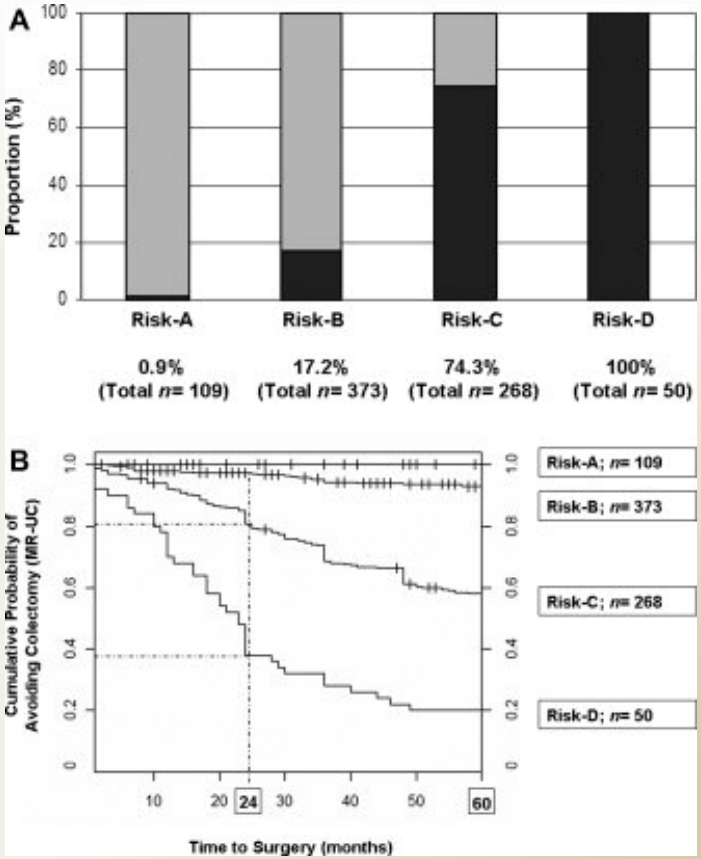
Reinisch et al. Clin Gastroenterol Hepatol 2015;13:635

Factors Associated with Poor Outcomes: Children

Factors	Result
Disease extent	Extensive, worse outcomes
Extension of disease	Limited becoming extensive, worse outcomes
Extraintestinal manifestations	Worse outcome
Family history	Associated with disease extension
Active disease at 3 months after dx	Associated with worse outcomes
Serum albumin	Hypoalbuminemia at diagnosis associated with worse outcome
Endoscopic severity	Associated with worse outcomes

Schechter et al. Gut 2015;64:580

Genetic predictors of medically refractory ulcerative colitis



A GWAS comparing 324 MR-UC patients with 537 non-MR-UC patients was analyzed using logistic regression and Cox proportional hazards methods. In addition, the MR-UC patients were compared with 2601 healthy controls.

Inflammatory Bowel Diseases
Volume 16, Issue 11, pages 1830-1840, 18 MAY 2010 DOI: 10.1002/ibd.21293
http://onlinelibrary.wiley.com/doi/10.1002/ibd.21293/full#fig2

nature genetics

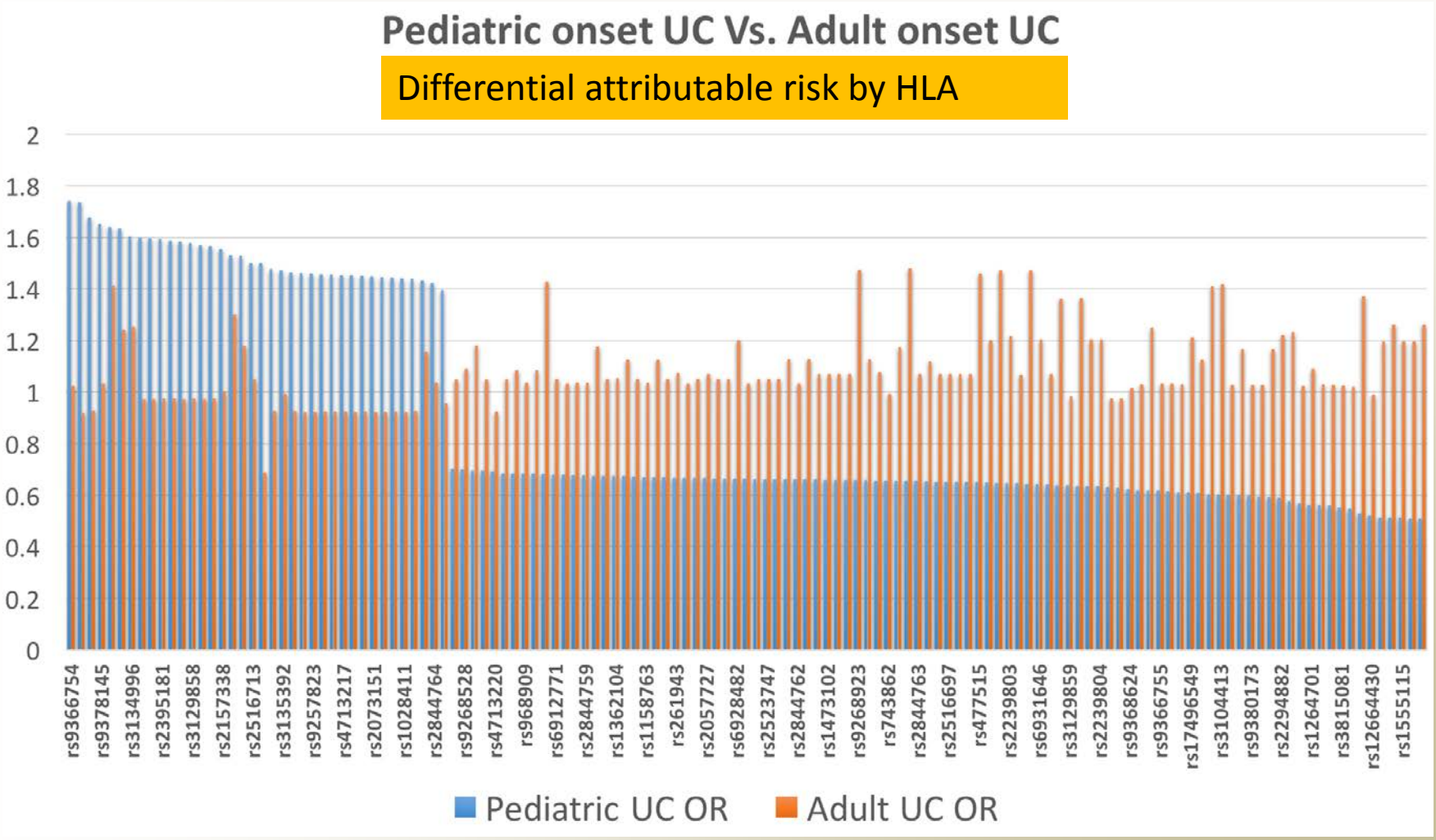
Pediatric vs. Adult HLA for UC

High-density mapping of the MHC identifies a shared role for HLA-DRB1*01:03 in inflammatory bowel diseases and heterozygous advantage in ulcerative colitis

Philippe Goyette[1,30], Gabrielle Boucher[1,30], Dermot Mallon[2,3], Eva Ellinghaus[4], Luke Jostins[5,6], Hailiang Huang[7,8], Stephan Ripke[7,8], Elena S Gusareva[9,10], Vito Annese[11,12], Stephen L Hauser[13], Jorge R Oksenberg[13], Ingo Thomsen[4], Stephen Leslie[14,15], International Inflammatory Bowel Disease Genetics Consortium[16], Mark J Daly[7,8], Kristel Van Steen[9,10], Richard H Duerr[17,18], Jeffrey C Barrett[19], Dermot P B McGovern[20], L Philip Schumm[21], James A Traherne[22,23], Mary N Carrington[24,25], Vasilis Kosmoliaptsis[2,3], Tom H Karlsen[26–28,31], Andre Franke[4,31]& John D Rioux[1,29,31]

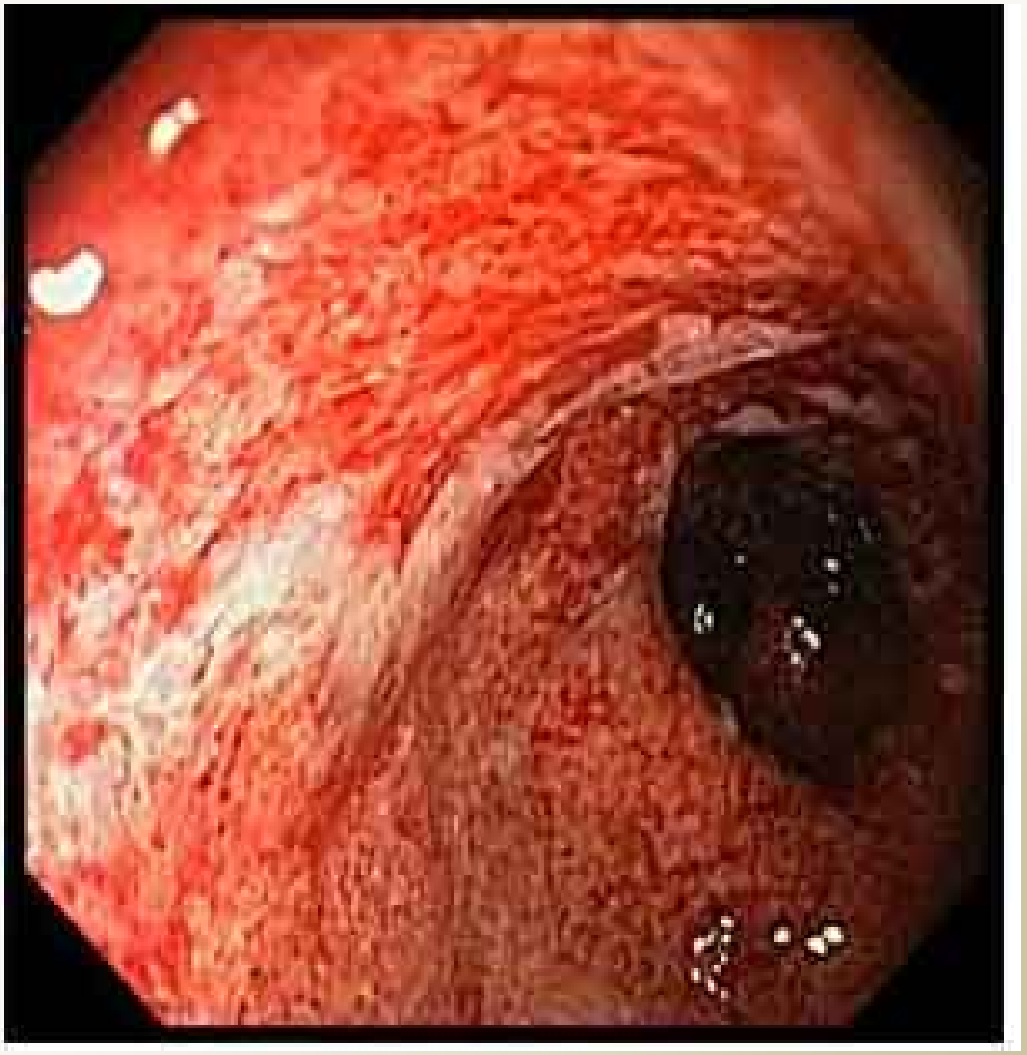
- **969 MHC region were reported from 14308 UC cases and 34241 controls.**
- **135 common SNPs were found between Pediatric vs. Adult UC**

OR comparison between Pediatric and Adult UC



Unpublished data, PROTECT Study, U01DK095745

Acute Severe Colitis: Worse Outcomes, Child and Adult

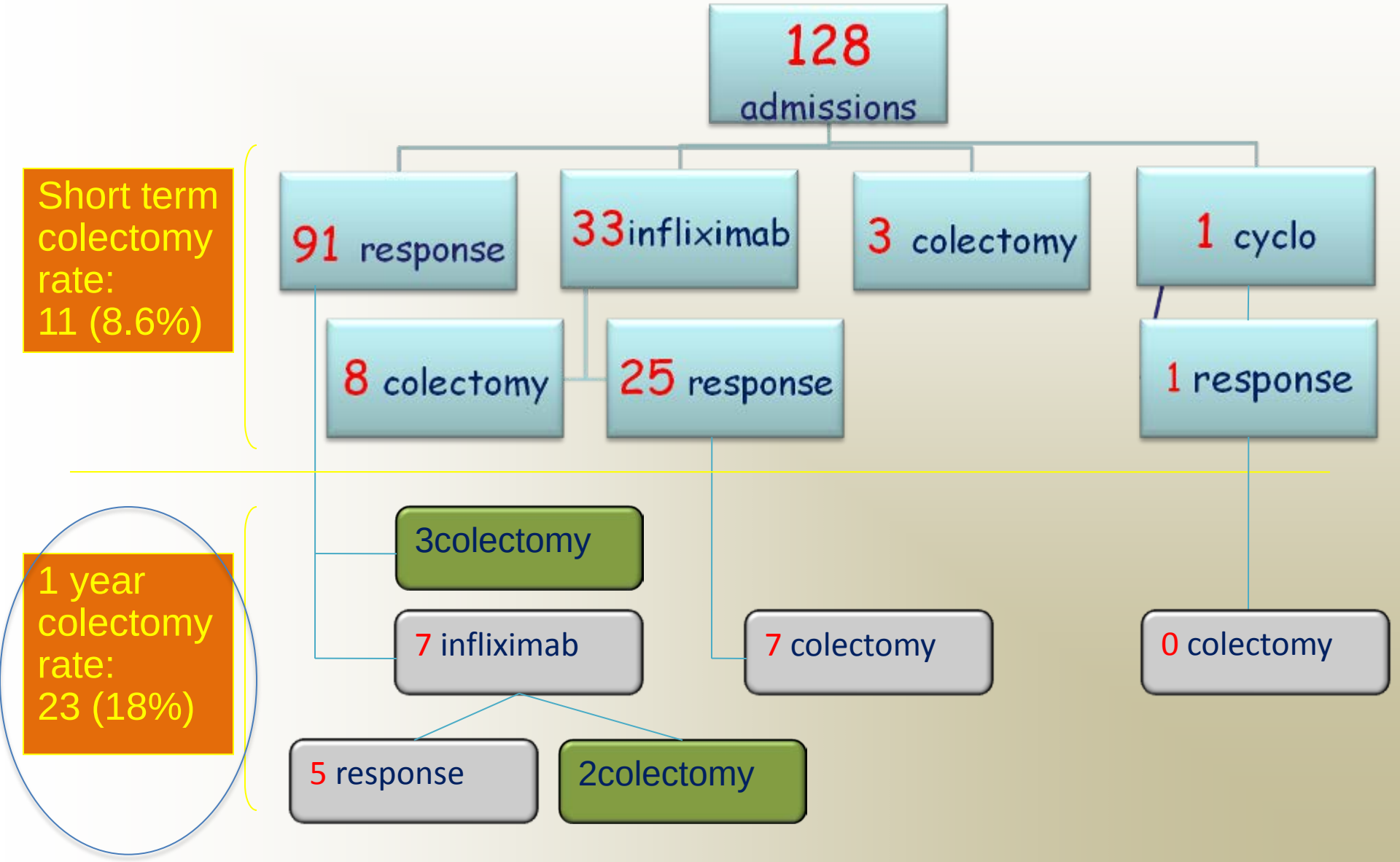


Criteria for Acute Severe Colitis

- **Hospitalized**
- **≥5 bloody stools daily**
- **Anemia**
- **Fever**
- **Hypoalbuminemia**
- **Elevated acute phase reactants**

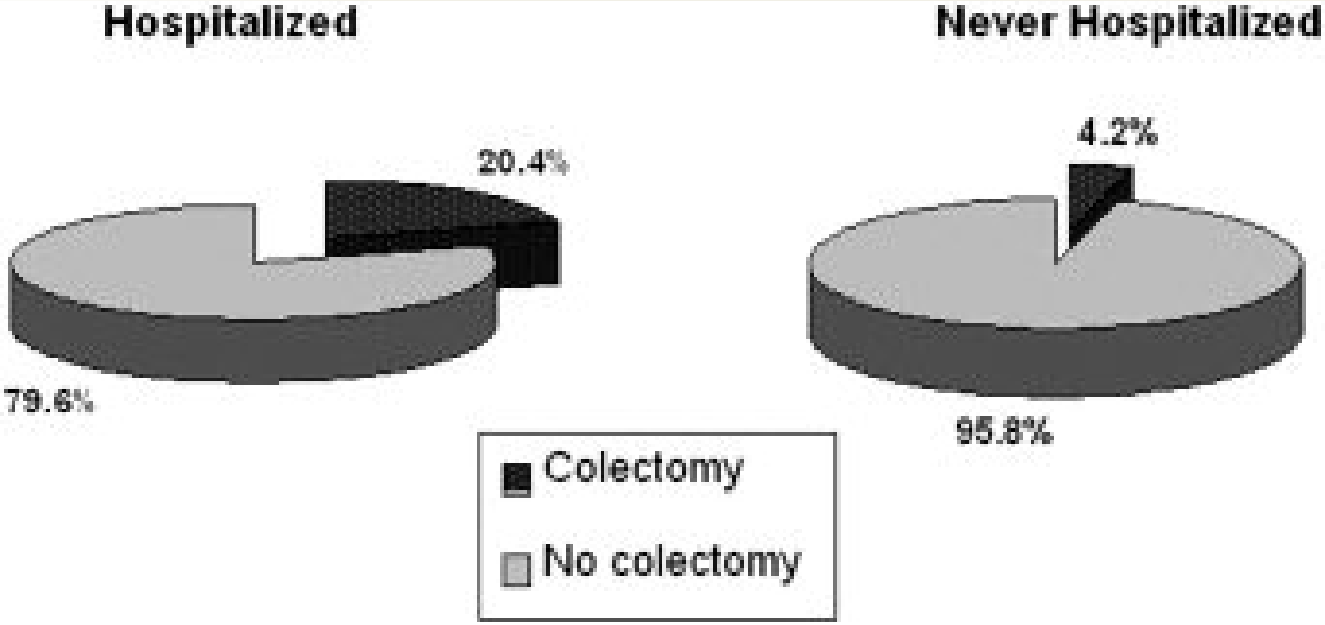
A small but disproportionately bad outcome group. Likely more common in children

One Year Outcomes: OSCI Study



Turner D et al, Gastroenterology 2010; 138: 2282 -2291

History of medical hospitalization predicts future need for colectomy in patients with ulcerative colitis



Inflammatory Bowel Diseases
Volume 15, Issue 2, pages 176-181, 4 AUG 2008 DOI: 10.1002/ibd.20639
http://onlinelibrary.wiley.com/doi/10.1002/ibd.20639/full#fig1

Caution in Very Young Children

- **Great care must be taken for very young children (≤2 yrs) where autosomal recessive disorders affecting the immune system may be causative of IBD-like illness- IL-10, IL-10R, XIAP, etc.**
- **Important that these children not be entered in clinical trials**
- **Very young children with "wild type" IBD invariably present with a colitis like phenotype making differentiation between Crohn's disease and ulcerative colitis difficult**

Summary

- Ulcerative colitis in adults and children have virtually identical clinical, endoscopic, and histologic features
- In general children have a higher likelihood of corticosteroid, immunomodulator, and biologic exposure than adults, i.e., a more severe phenotype
- However, response to these interventions is similar in adults and children

Fundamental Assumptions For Extrapolation of Drug Trials from Adults to Children: Similarities In…

- Disease pathogenesis
- Pathophysiologic, histopathologic, and pathobiological characteristics
- Criteria for disease definition
- Clinical classification
- Response to intervention
- Disease progression
- Measures of disease progression

Summary

- ***The use of partial extrapolation to enhance the speed of availability of IBD therapies found to be safe and effective in adults to children appears reasonable***
- ***Dosing and safety cannot be extrapolated***