Similarities and discrepancies between adult and paediatric disease and differential drug effects

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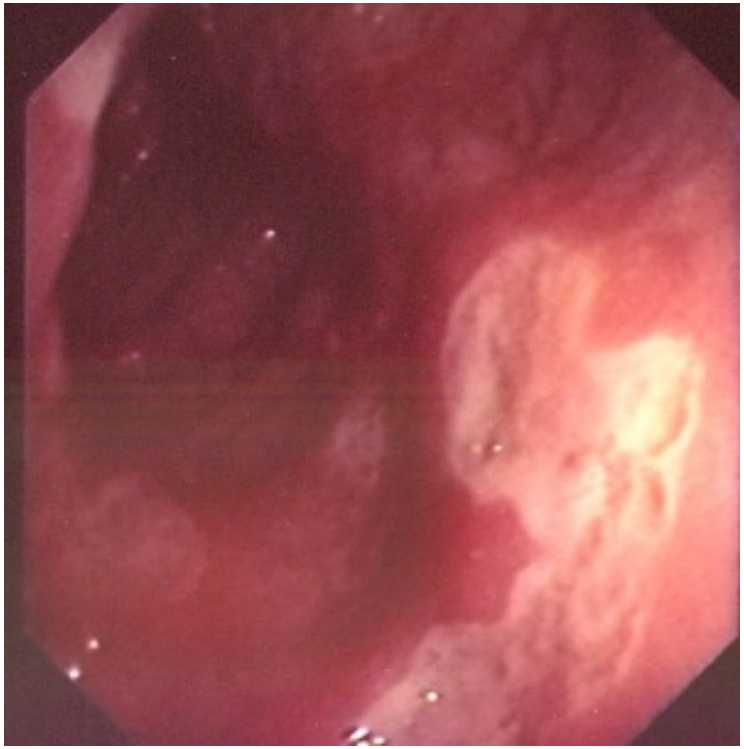
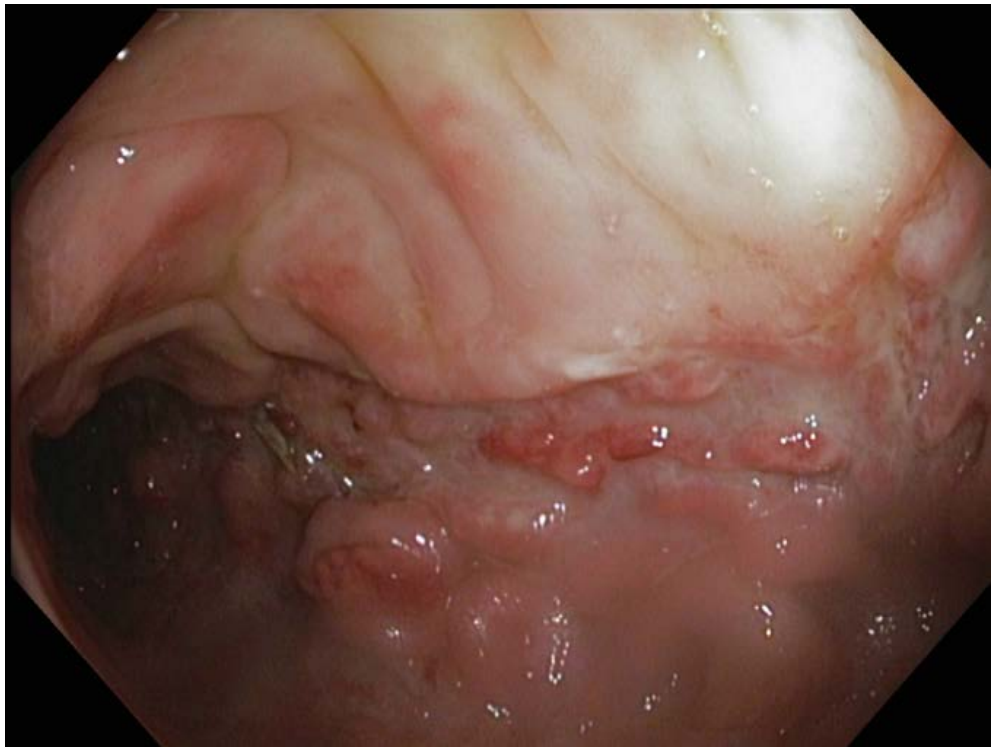
CONFLICT OF INTEREST

NONE for this report

But Research Funding and Speaker fees
from AbbVie, Celegen, Centocor,
Danone, Ferring, J&J, Mead Johnson,
MSD, Nestlé, Shering-Plough

Paediatric or adult-onset IBD ?





What signifies starting IBD 10-20 years earlier ?

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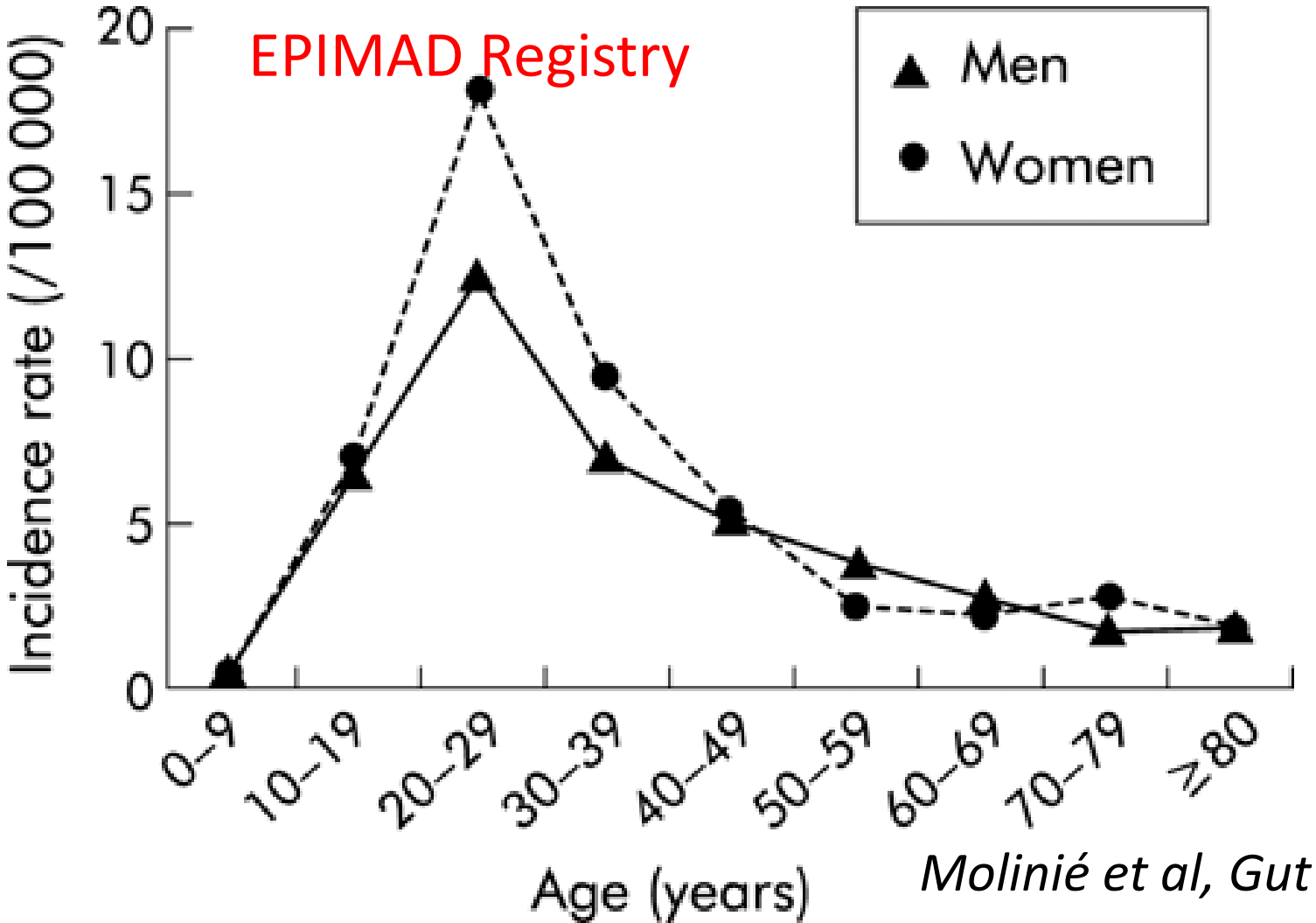

Molinié et al, Gut 2004

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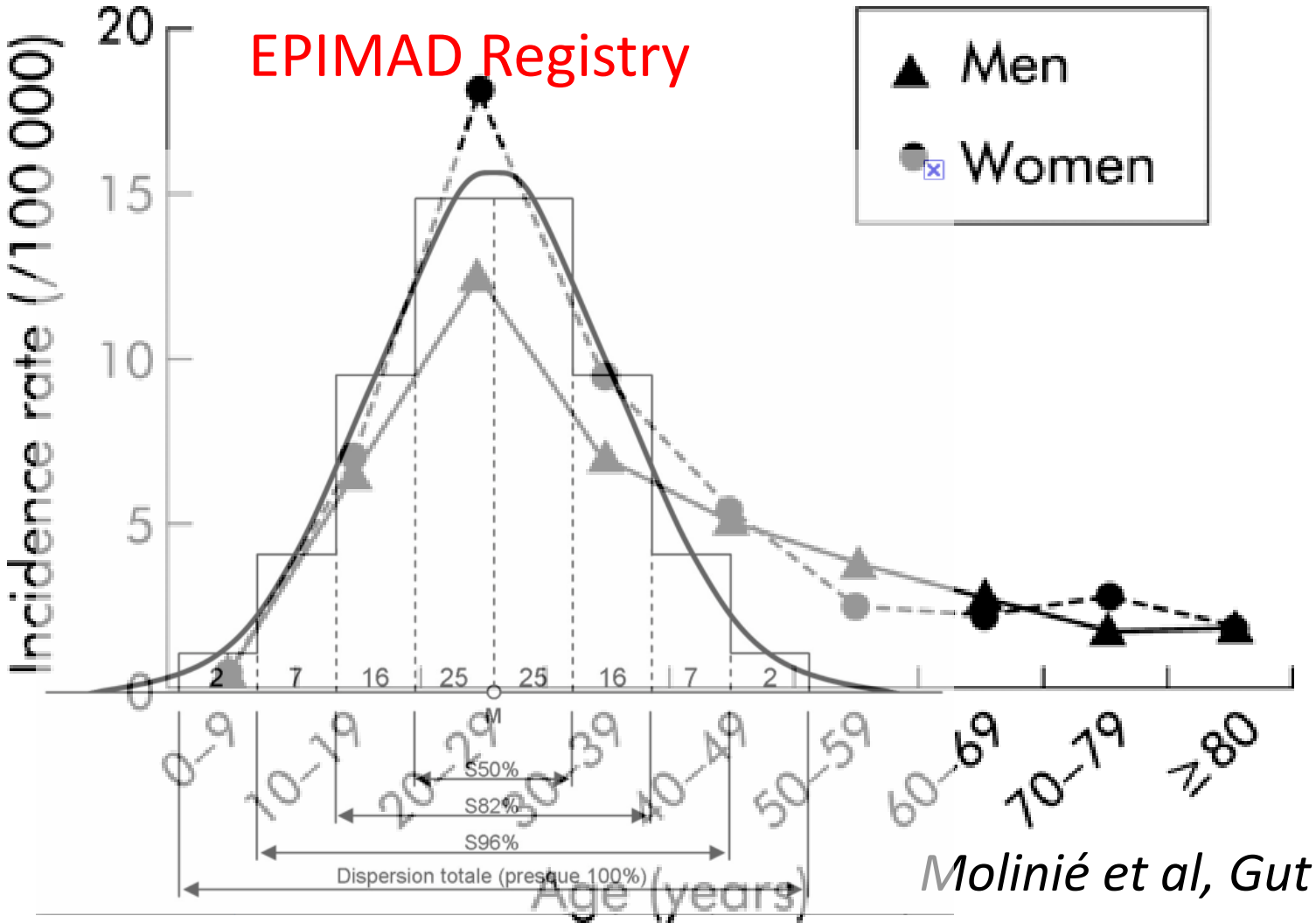

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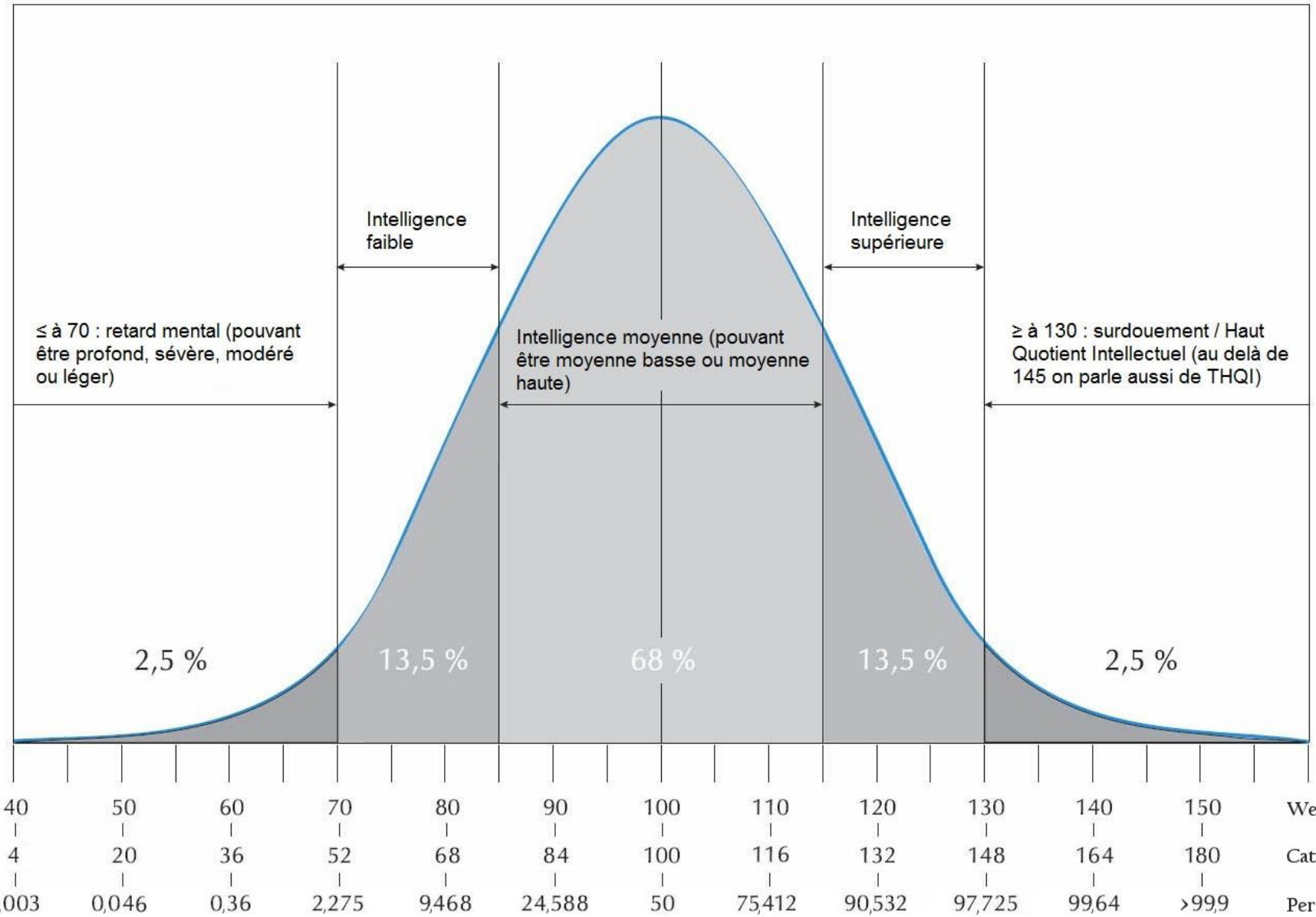

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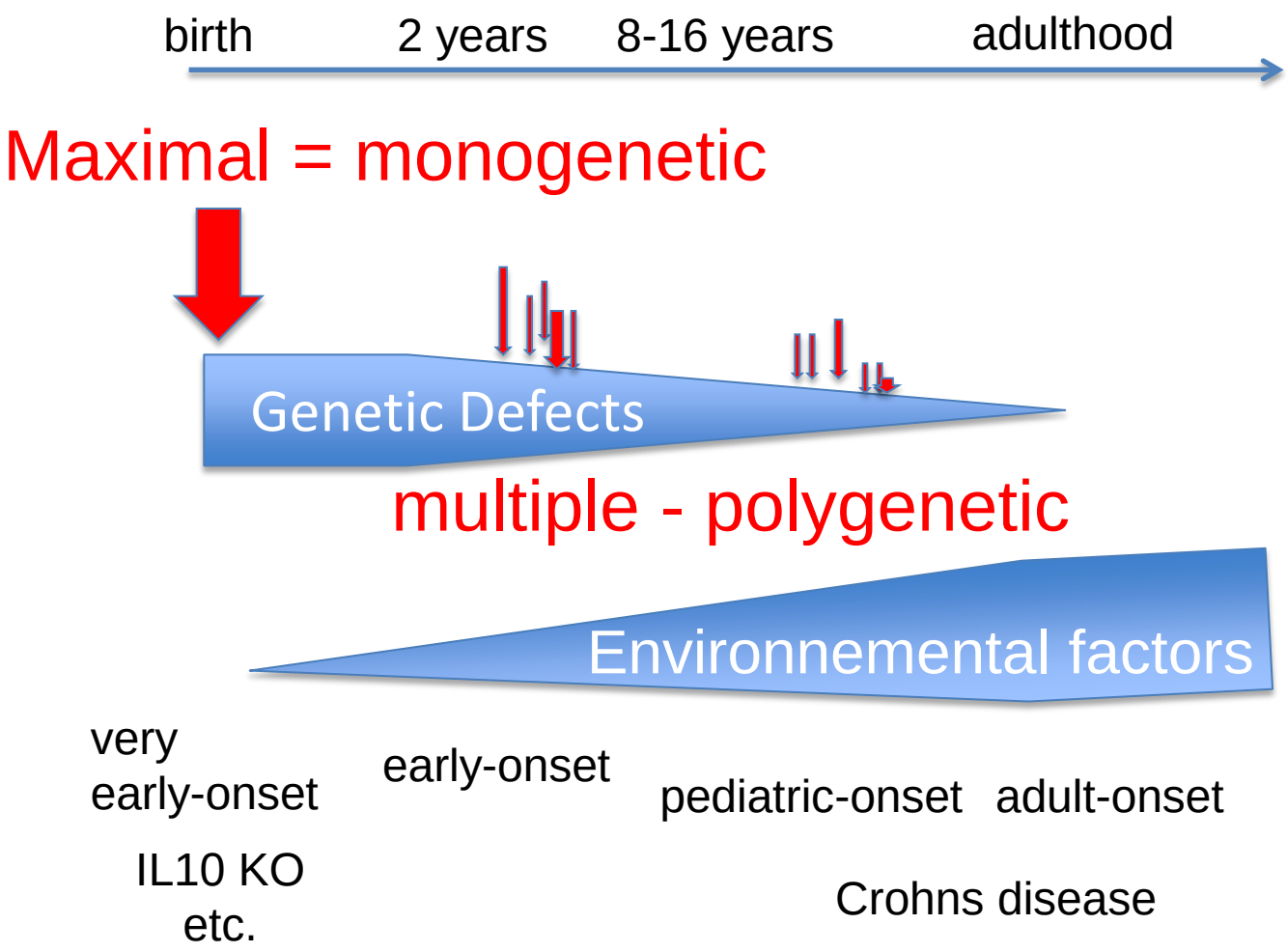
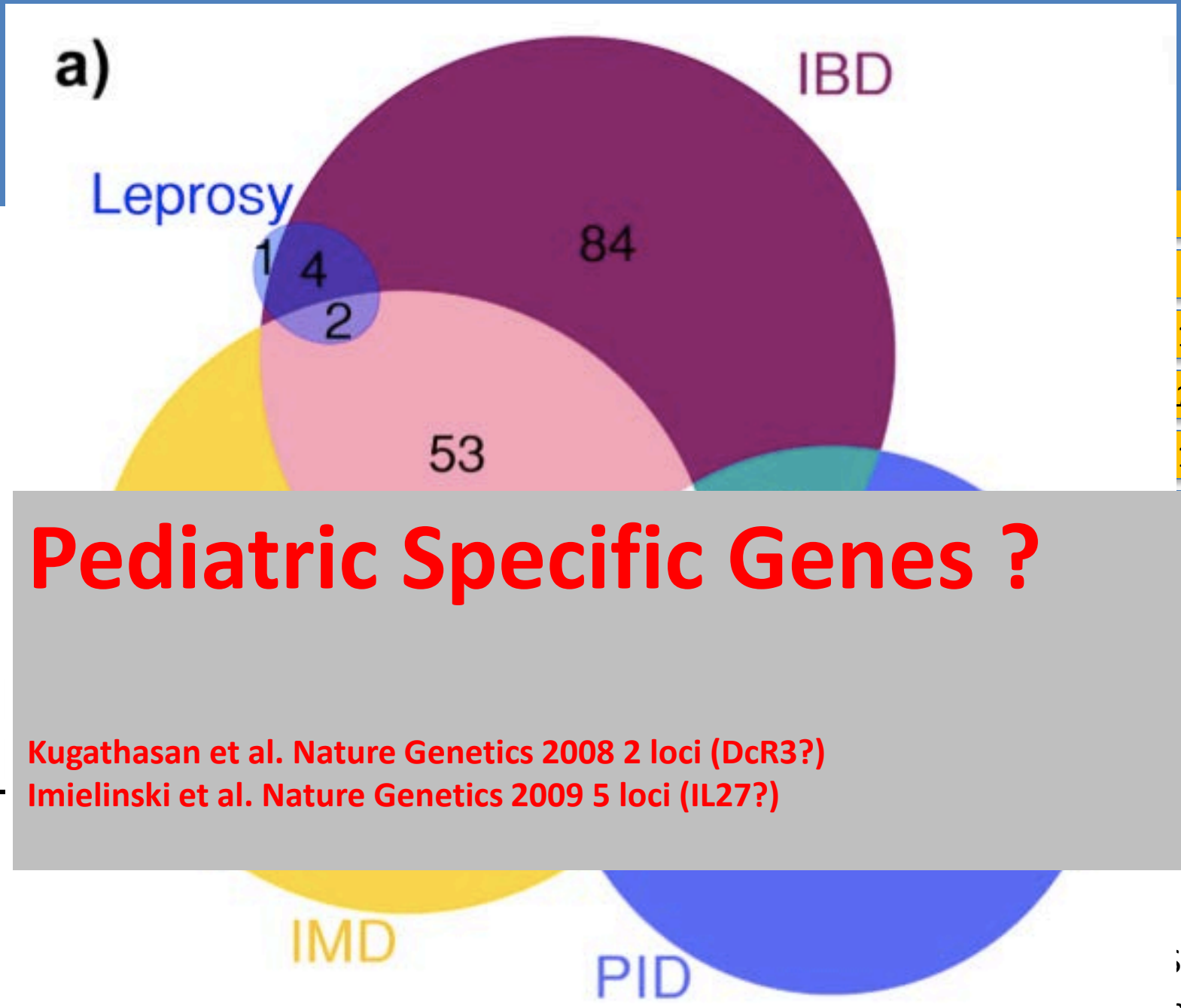




8q24

9p24

10p11

11orf30

12q12

Pediatric Specific Genes ?

Kugathasan et al. Nature Genetics 2008 2 loci (DcR3?)
Imielinski et al. Nature Genetics 2009 5 loci (IL27?)

alysis

Genetic background and IBD

No !

Genetic susceptibility is not different between pediatric and adult-onset IBD

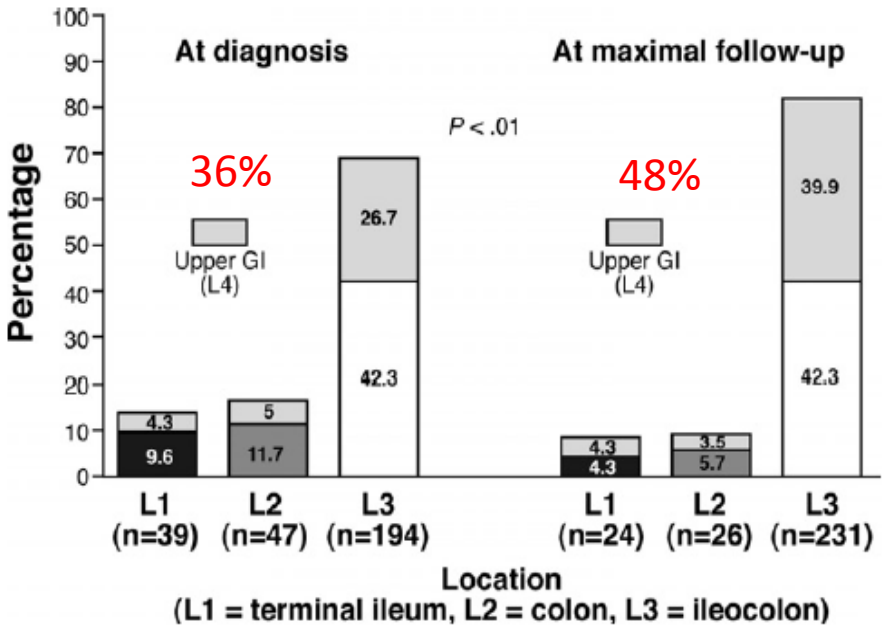
Genetic background and IBD

Pediatric versus adult-onset IBD

Pediatric IBD

Is it just a matter of size ??

Disease presentation at diagnosis



	Scottish childhood-onset IBD	Scottish adult-onset IBD
n	416	1297
	At last follow-up (*n* = 273)	At last follow-up (*n* = 507)
CD phenotype: Location*		
L1	7 (2.6%)	160 (31.5%)
L2	41 (15.0%)	183 (36.1%)
L3	52 (19.0%)	99 (19.5%)
L1 + L4	5 (1.8%)	21 (4.1%)
L2 + L4	43 (15.8%)	8 (1.6%)
L3 + L4	118 (43.2%)	16 (3.2%)
L4	2 (0.7%)	13 (2.6%)
P	60% <.001	10%
	At 5 years (*n* = 136)	At 5 years (*n* = 377)
CD phenotype: Behavior		
B1 (±p)	99 (72.7%)	249 (66.0%)
B2 (±p)	20 (14.7%)	54 (14.3%)
B3 (±p)	17 (12.6%)	74 (19.7%)
P	.17	
	At last follow-up (*n* = 73)	At last follow-up (*n* = 569)
UC phenotype		
E3	60 (82.2%)	271 (47.6%)
E2	12 (16.4%)	201 (35.3%)
E1	1 (1.4%)	97 (17.0%)
P	<.001	

Vernier-Massouille et al Gastro 2008
Van Limbergen J et al. Gastro 2008

Disease presentation

	Montreal	Paris
Age at Diagnosis	A1: below 17 y	A1a: 0–<10y
	A2: 17-40 y	A1b: 10–<17 y
	A3: Above 40 y	A2: 17–40 y
		A3: >40 y
Location	L1:terminal ileal± limited cecal disease	L1: distal 1/3 ileum ± limited cecal disease
	L2: colonic	L2: colonic
	L3: ileocolonic	L3: ileocolonic
	L4: Isolated upper disease*	L4a: upper disease proximal to Ligament of Treitz*
		L4b: upper disease distal to ligament of Treitz and proximal to distal 1/3 ileum*

Disease presentation at diagnosis

TABLE 2. Associations Between Ileocolonic Disease Location and Upper Gastrointestinal Disease, Disease Behavior, and Perianal Disease in 582 Pediatric Crohn's Disease Patients Who Underwent a Complete Diagnostic Workup According to the Porto Criteria[16]

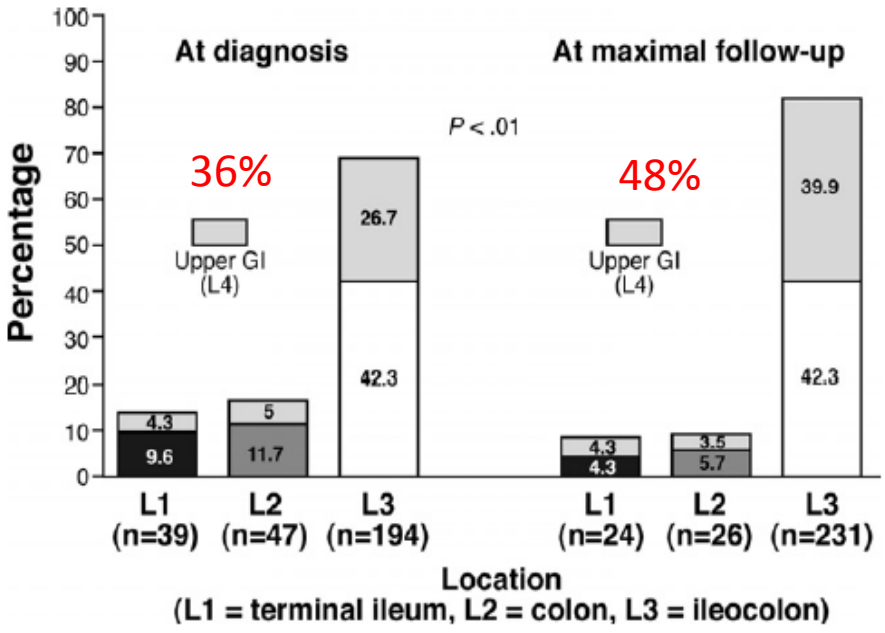
	Disease Location According to the Paris Classification				
	L1	L2	L3	L4	P[a]
L4A	29/95 (31%)[b]	31/159 (20%)	108/307 (35%)[b]	NA	0.002
L4B	28/95 (30%)[b]	29/159 (18%)	63/307 (21%)	NA	0.092
Stricturing disease behavior	20/95 (21%)[b]	9/155 (6%)	45/306 (15%)[b]	3/21 (14%)	0.005
Penetrating disease behavior	5/94 (5%)	6/153 (4%)	17/302 (6%)	0/21 (0%)	0.62
Perianal disease	2/95 (2%)[c]	13/156 (8%)	32/305 (11%)	1/21 (5%)	0.070

Table 1. Characteristics of CD Patients at 1 Year From Diagnosis

Population	Overall (n = 451), n (%)	A1 (n = 115), n (%)	A2 (n = 259), n (%)	A3 (n = 77), n (%)
Male	243 (53.9)	55 (47.8)	142 (54.8)	46 (60.0)
Age				
A1	115 (25.5)			
A2	259 (57.4)			
A3	77 (17.1)			
Location				
L1[a]	200 (45.8)	41 (36.3)	127 (49.2)	32 (43.8)
L2	121 (27.7)	26 (23.0)	67 (26.0)	27 (37.0)
L3[b,c]	112 (25.6)	45 (39.8)	54 (20.9)	14 (19.2)
L4	4 (0.9)	1 (0.9)	3 (1.2)	0
UGI involvement[a,c]	49 (11.0)	21 (18.4)	26 (10.2)	2 (2.7)

De Bie C IBD 2013, Israeli et al CGH 2014

Disease presentation at diagnosis



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Vernier-Massouille et al Gastro 2008
Van Limbergen J et al. Gastro 2008

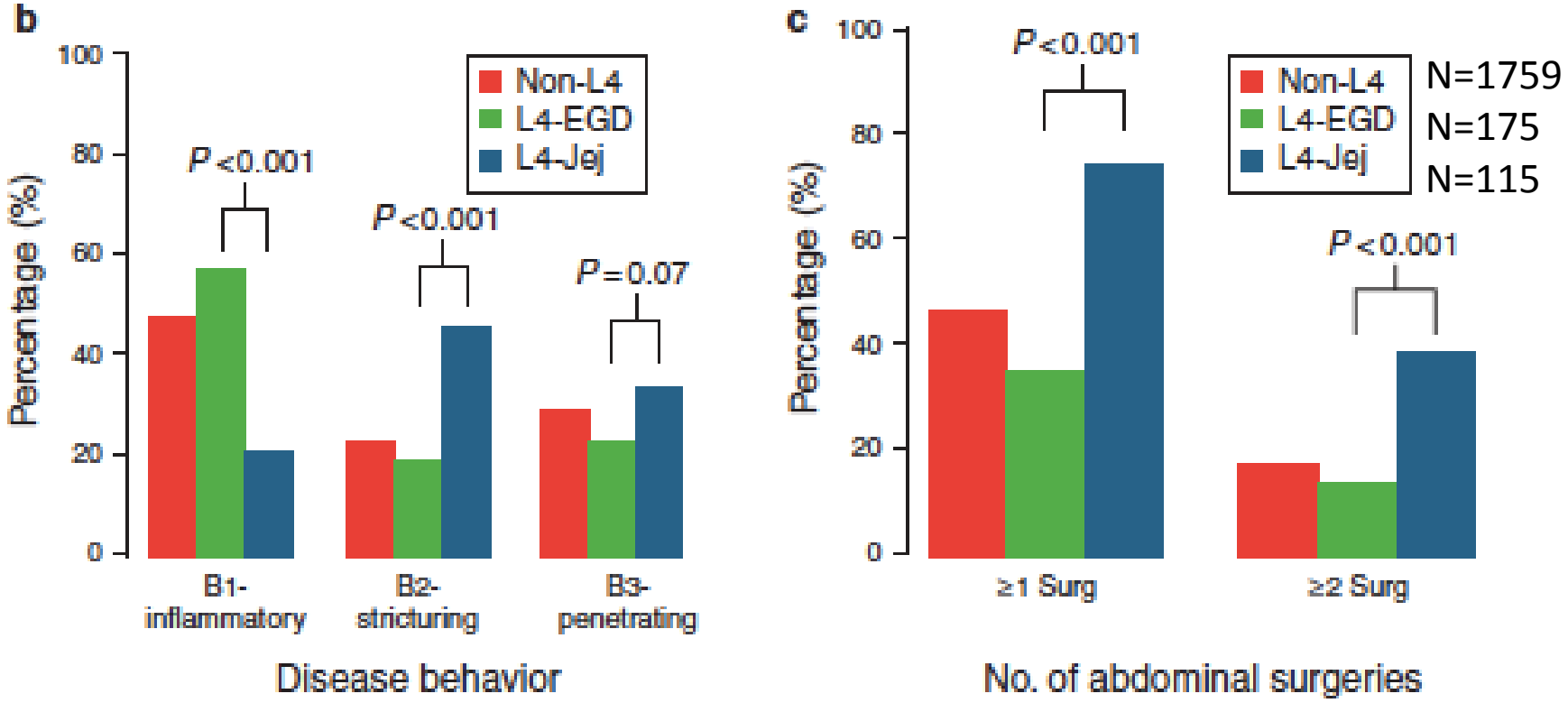
Disease presentation at diagnosis

Yes and No!

Disease presentation is not different between pediatric and adult onset IBD but there is a trend to a more frequent panenteric presentation in children

Disease presentation at diagnosis

Predictors for severe disease evolution



Lazarev M et al Am J Gastro 2013

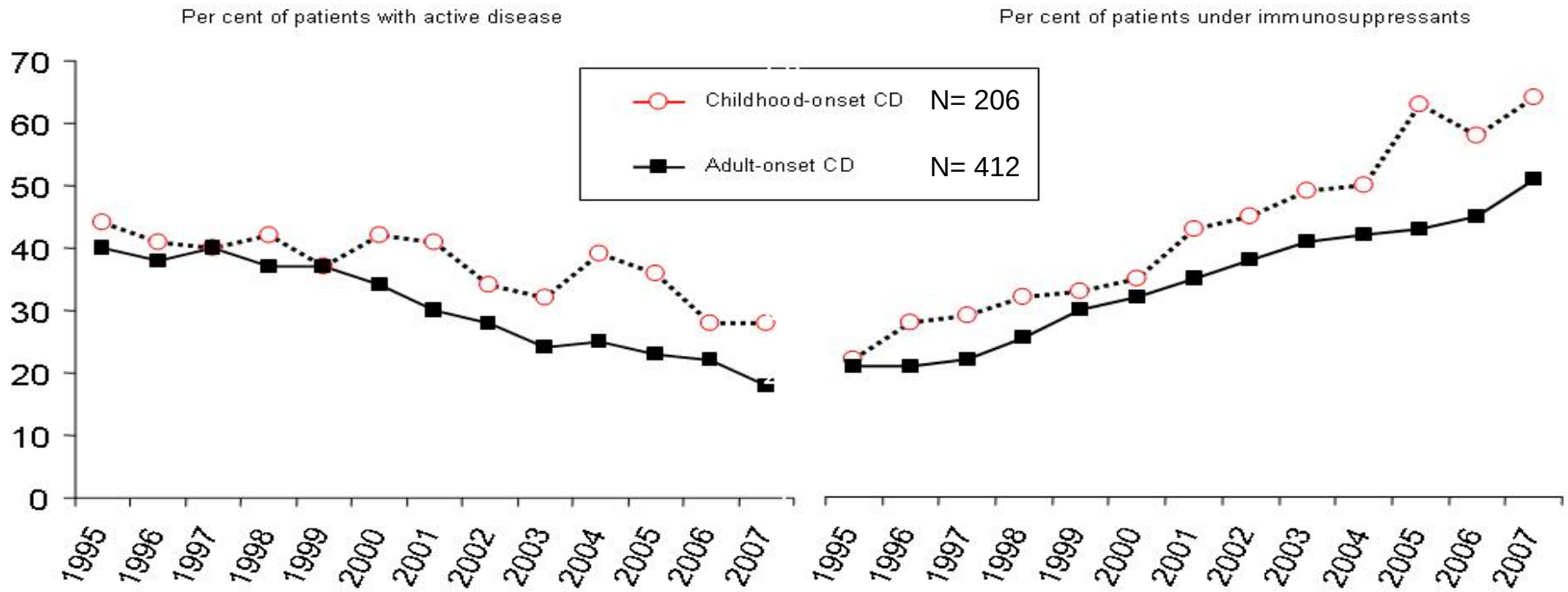
Predictors for severe disease evolution

Table 4. Stepwise Multivariable Cox Model of Variables Associated With Risk of Surgery in 394 Pediatric Patients With CD

	Hazards ratio	95% CI	*P* value
Behavior			
B1	1		
B2	2.54	1.58–4.01	<.01
B3	1.28	0.33–4.89	.72
Medications			
Corticosteroids	2.98	1.64–5.41	<.01
Azathioprine	0.51	0.33–0.78	<.01

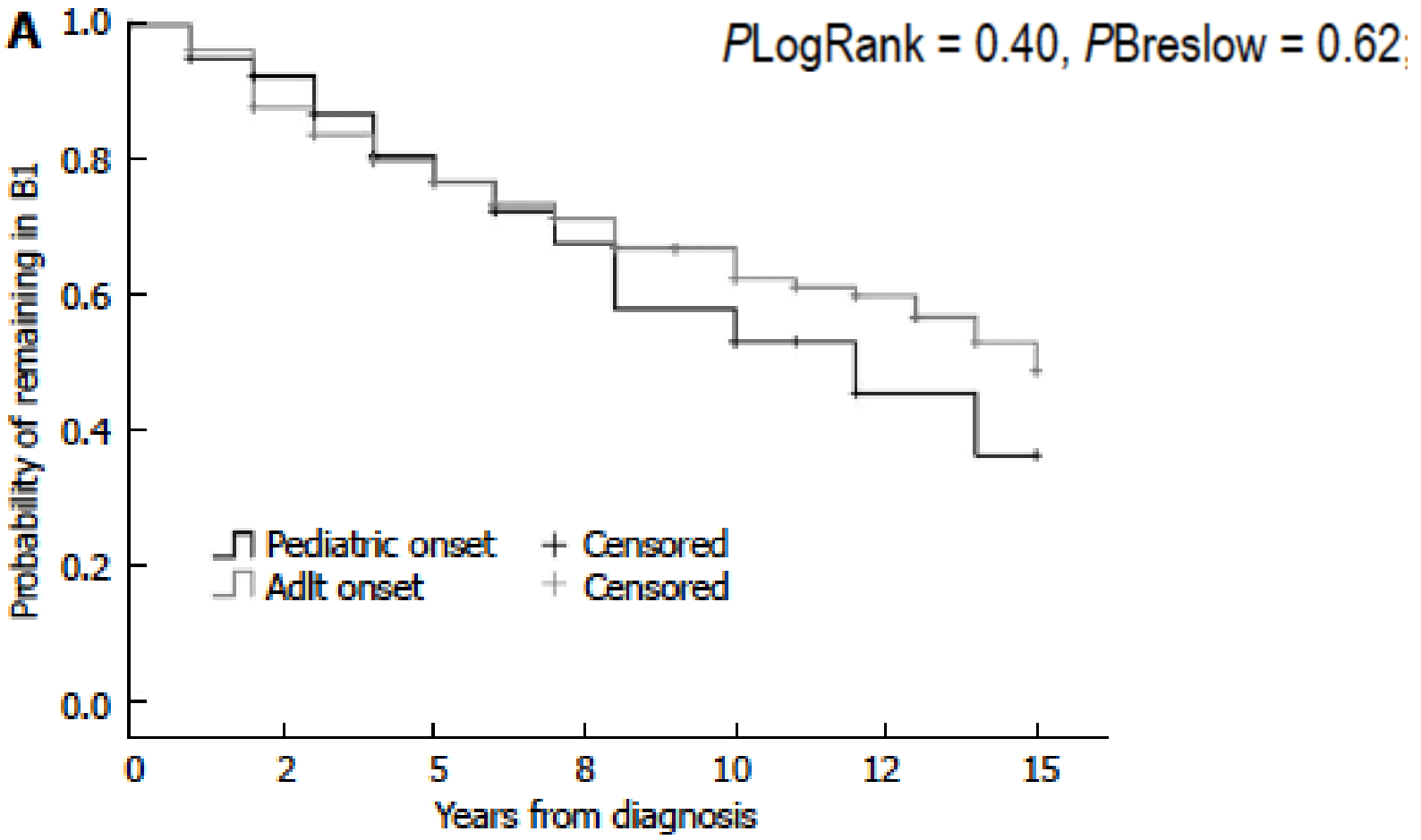
Vernier-Massouille et al Gastro 2008

Disease Evolution



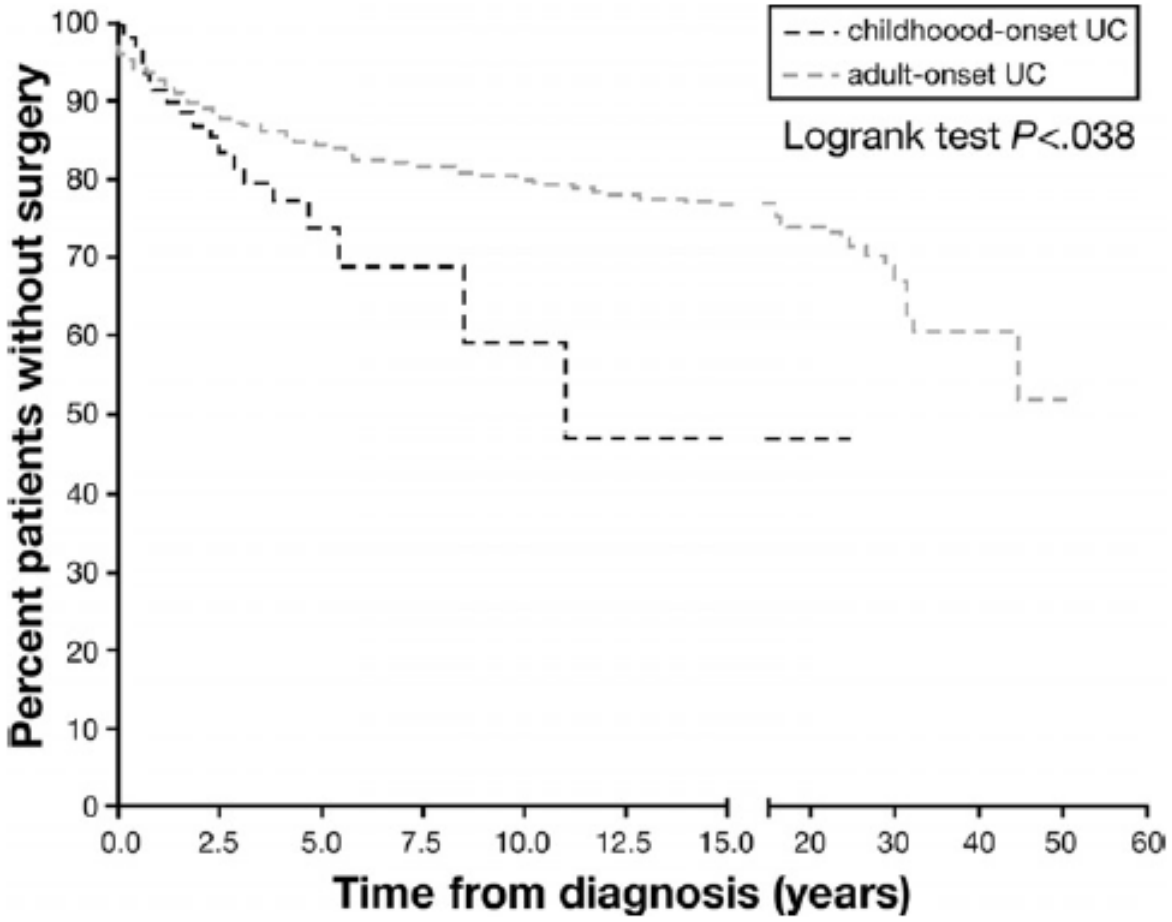
Pigneur et al IBD 2009

Disease Evolution



Lovasz B et al WJG 2013

Disease Evolution



Van Limbergen J et al Gastro 2008

Disease Evolution

Yes and No!

Several studies indicate a more severe disease evolution in pediatric versus adult onset IBD, but not all

Disease Evolution

Efficacy and Effectiveness data

Clinical trial

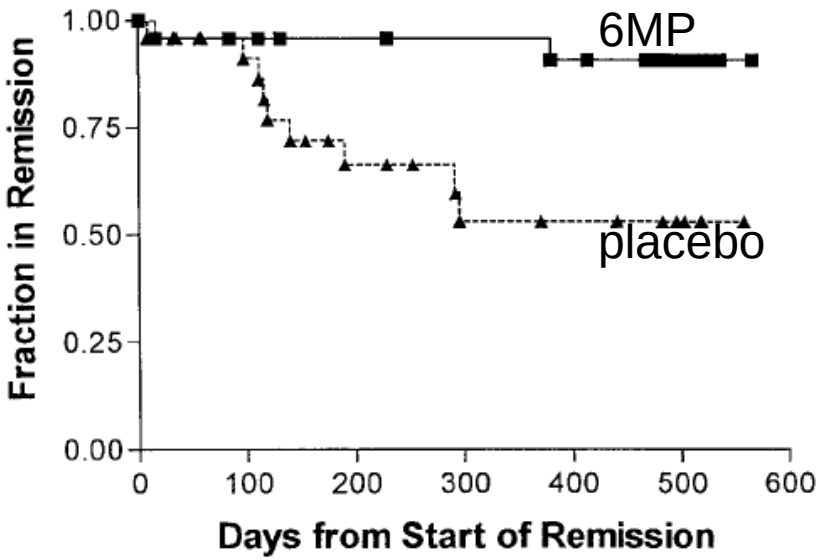
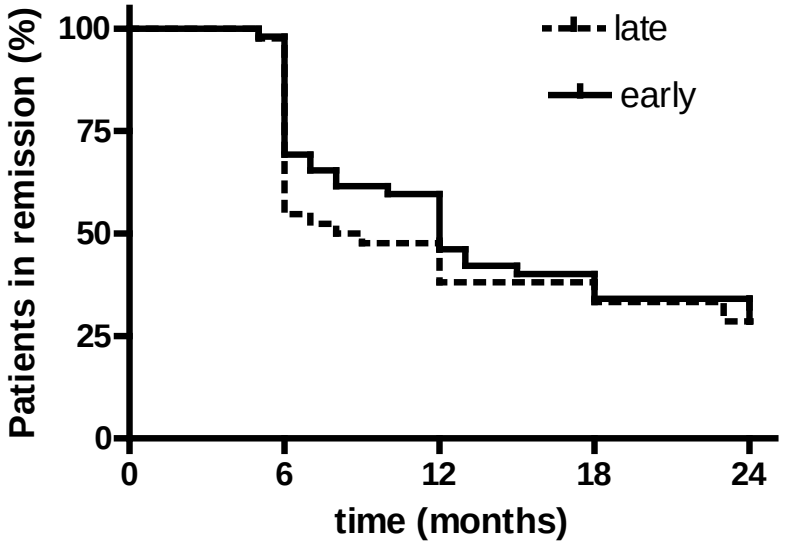


Figure 4. Kaplan–Meier survival curve of relapse-free duration of remission. ■, 6-MP; ▲, controls. $P < 0.007$.

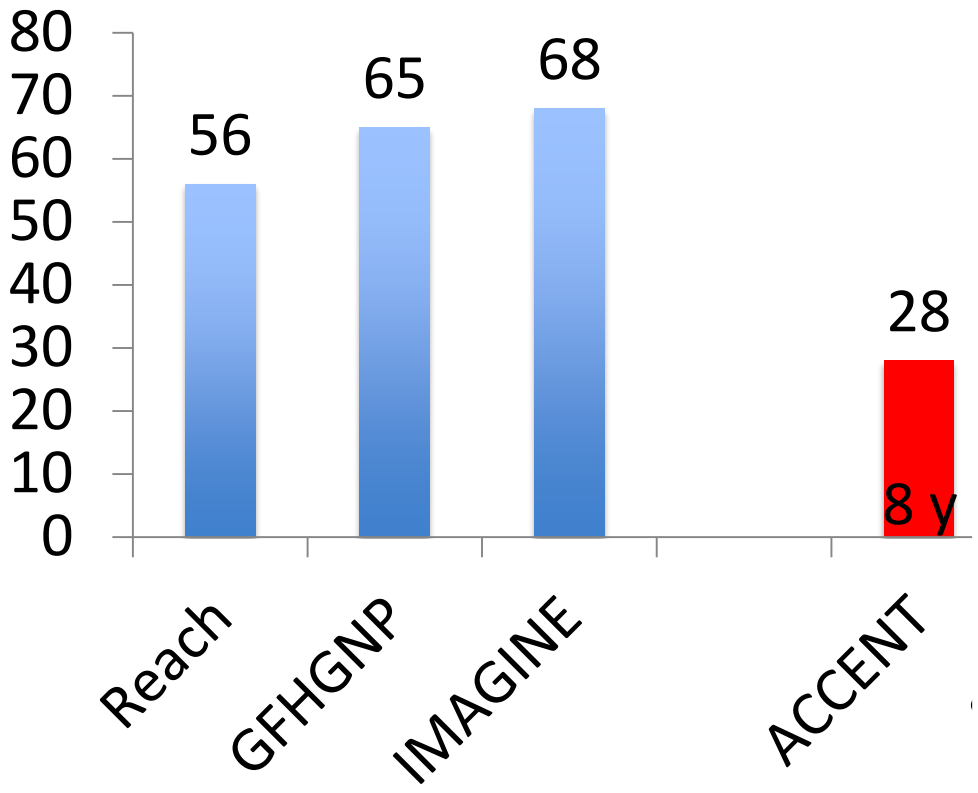
Markowitz J et al., Gastroenterology 2000

Cohort data



Riello et al. IBD 2011

Efficacy and Effectiveness data



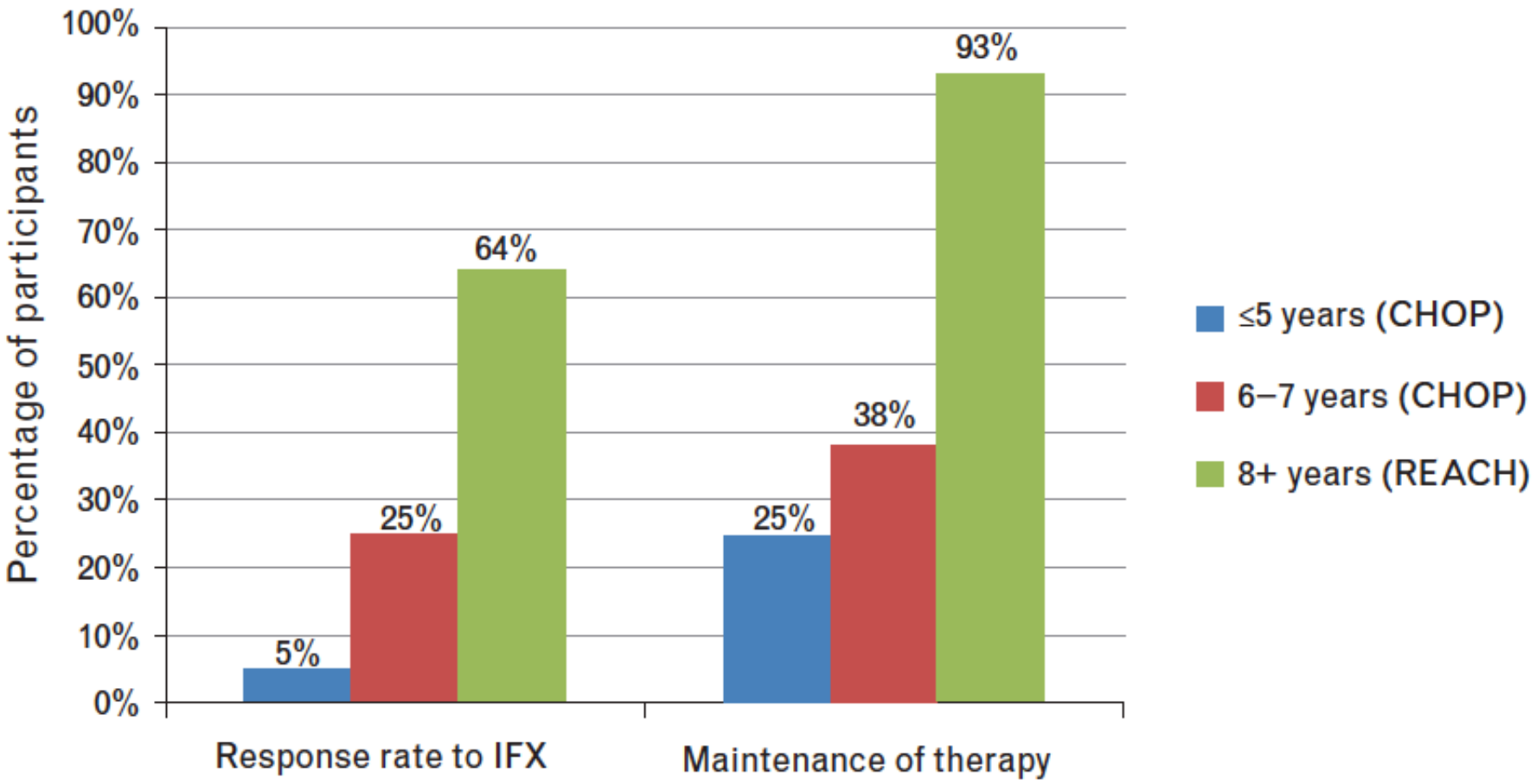
Efficacy/effectiveness

No!

No difference in clinical trials nor real-world cohorts for the drug responses between child- or adulthood onset IBD

Efficacy/effectiveness

PK/PD?



Kelsen JR et al. JPGN 2014

PK/PD?

ORIGINAL ARTICLE

Pharmacokinetics of Infliximab in Children with Moderate-to-Severe Ulcerative Colitis: Results from a Randomized, Multicenter, Open-label, Phase 3 Study

Omoniyi J. Adedokun, MS, RPh, Zhenhua Xu, PhD,* Lakshmi Padgett, PhD,† Marion Blank, PhD,‡ Jewel Johanns, PhD,§ Anne Griffiths, MD,¶ Joyce Ford, MS,‖ Honghui Zhou, PhD,* Cynthia Guzzo, MD,‡ Hugh M. Davis, PhD,‖ and Jeffrey Hyams, MD***

Results: Infliximab pharmacokinetics were not influenced by age (6–11 yr versus 12–17 yr), baseline immunomodulator use, or the extent of UC. At week 8, higher serum infliximab concentrations (≥41.1 μg/mL) were associated with greater proportions of patients achieving efficacy endpoints (clinical response, 92.9%; mucosal healing, 92.9%; and clinical remission, 64.3%) versus those with lower serum concentrations (<18.1 μg/mL; 53.9%, 53.9%,

TABLE 2. Summary of Median Serum Infliximab Concentrations (μg/mL) Through Week 8 by Patient Age Group Among Pediatric Patients With UC

	Infliximab 5 mg/kg	
Patient age, yr	6–11	12–17
Assessment time point		
Week 0		
1-h postinfusion	98.52 (n = 14)	96.13 (n = 41)
Week 2		
Preinfusion	18.21 (n = 14)	19.30 (n = 44)
1-h postinfusion	97.76 (n = 14)	118.51 (n = 37)
Week 6		
Preinfusion	7.08 (n = 13)	15.29 (n = 36)
1-h postinfusion	98.56 (n = 10)	107.00 (n = 30)
Week 8	22.89 (n = 11)	29.57 (n = 33)

PK/PD

Side effects/safety

Imagine 1 vs Classic 1

	Double-blind maintenance			
	Low-dose adalimumab 20 mg or 10 mg eow		High-dose adalimumab 40 mg or 20 mg eow	
	n = 95 n (%)	PYs = 47.5 Events (E/100PY)	n = 93 n (%)	PYs = 54.1 Events (E/100PY)
Any adverse event	81 (85.3)	464 (976.8)	86 (92.5)	507 (937.2)
At least possibly drug related[a]	37 (38.9)	110 (231.6)	39 (41.9)	111 (205.2)
Severe adverse event	11 (11.6)	14 (29.5)	19 (20.4)	27 (49.9)
Serious adverse event	19 (20.0)	20 (42.1)	22 (23.7)	24 (44.4)
Leading to discontinuation of study drug	12 (12.6)	13 (27.4)	15 (16.1)	20 (37.0)
At least possibly drug-related serious adverse event[a]	2 (2.1)	2 (4.2)	1 (1.1)	1 (1.8)
Infectious adverse event	47 (49.5)	101 (212.6)	56 (60.2)	98 (181.1)
Serious infections	3 (3.2)[b]	3 (6.3)	5 (5.4)[c]	5 (9.2)
Any malignancies	0	0	0	0
Lymphomas	0	0	0	0

Table 4. Infections and Serious Adverse Events

Variable	Placebo (n = 74)	Adalimumab 40 mg/20 mg (n = 74)	Adalimumab 80 mg/40 mg (n = 75)	Adalimumab 160 mg/80 mg (n = 76)
Infections, no. of patients (%)	12 (16)	8 (10)	13 (17)	16 (21)
Serious adverse events, no. of patients (%)	3 (4)	0 (0)	1 (1)	3 (4)
Serious infections, no. of patients (%)	0 (0)	0 (0)	0 (0)	2 (3)
Specific types of serious infections				
Perianal abscess	0 (0)	0 (0)	0 (0)	1 (1)
Pneumonia	0 (0)	0 (0)	0 (0)	1 (1)

Hyams Gastro 2012, Hanauer Gastro 2006

Side effects/safety

CHARM

Variable	Induction: Adalimumab 80/40 mg (N = 854)	Double-blind period: Placebo (n = 261)	Double-blind period: Adalimumab 40 mg every other week (n = 260)	Double-blind period: Adalimumab 40 mg weekly (n = 257)
Adverse events	507 (59.4)	221 (84.7)	231 (88.8)	220 (85.6)
Adverse events leading to discontinuation of study drug	54 (6.3)	35 (13.4)	18 (6.9)[a]	12 (4.7)[a]
Select adverse events occurring at a frequency of at least 5% in either the adalimumab or placebo groups[b]				
CD		84 (32.2)	51 (19.6)[c]	48 (18.7)[c]
Arthralgia		23 (8.8)	27 (10.4)	34 (13.2)
Nasopharyngitis		18 (6.9)	29 (11.2)	31 (12.1)
Headache	51 (6.0)	15 (5.7)	25 (9.6)	30 (11.7)[a]
Nausea	45 (5.3)	16 (6.1)	19 (7.3)	22 (8.6)
Fatigue		6 (2.3)	11 (4.2)	20 (7.8)[d]
Abdominal pain		17 (6.5)	20 (7.7)	19 (7.4)
Pyrexia		14 (5.4)	14 (5.4)	17 (6.6)
Upper respiratory tract infection		16 (6.1)	12 (4.6)	16 (6.2)
Injection site reaction		1 (0.4)	11 (4.2)[d]	15 (5.8)[c]
Urinary tract infection		4 (1.5)	11 (4.2)	15 (5.8)[d]
Influenza		13 (5.0)	14 (5.4)	13 (5.1)
Diarrhea		15 (5.7)	10 (3.8)	12 (4.7)
Pharyngolaryngeal pain		14 (5.4)	11 (4.2)	7 (2.7)
Serious adverse events	45 (5.3)	40 (15.3)	24 (9.2)[a]	21 (8.2)[a]
Infectious adverse events	130 (15.2)	96 (36.8)	120 (46.2)[a]	114 (44.4)
Serious infectious adverse events	10 (1.2)	9 (3.4)	7 (2.7)	7 (2.7)

Colombel et al Gastro 2007

Side effects/safety

Table 3. Summary of Safety Findings for All Patients (n = 112) Through Week 54

REACH vs ACCENT

Safety parameter	Patients not randomized at week 10	Patients randomized at week 10: Infliximab 5 mg/kg every 8 weeks	Patients randomized at week 10: Infliximab 5 mg/kg every 12 weeks	Patients randomized at week 10: Combined	Total patients
Patients treated	9	53	50	103	112
Average weeks of:					
Follow-up	8.8	51.5	49.6	50.6	47.2
Exposure	3.9	44.0	40.6	42.3	39.2
Infliximab exposure over 54 weeks (mean/patient)					
No. of infusions	21	409	319	29	31
Total mg/kg	11.0	40.0	31.1	40.0	39.9

	Group I (n=188)*	Group II (n=193)	Group III (n=192)	Total (n=573)
Infliximab exposure over 54 weeks, mean (SD)				
Number of infusions	2·2 (1·5)	6·7 (1·9)	6·8 (2·1)	5·3 (2·9)
Total dose (mg/kg)	10·7 (7·6)	36·0 (11·1)	55·5 (21·1)	34·3 (23·3)
Adverse events leading to discontinuation of study agent	5 (3%)	29 (15%)	16 (8%)	50 (9%)
Serious adverse events				
All events	55 (29%)	54 (28%)	43 (22%)	152 (27%)
Reasonably related	13 (7%)	15 (8%)	11 (6%)	39 (7%)
Infections				
Infection requiring antimicrobial treatment	70 (37%)	64 (33%)	52 (27%)	186 (32%)
Serious infection	8 (4%)	8 (4%)	6 (3%)	22 (4%)
Intestinal stenosis	6 (3%)	3 (2%)	5 (3%)	14 (2%)
Infusion reactions†	17 (9%)	44 (23%)	36 (19%)	97 (17%)
Serum-sickness-like reactions‡	3 (2%)	5 (3%)	6 (3%)	14 (2%)

Side effects/safety:HSTCL

- Reporting period: August 1998 – June 2011

HSTL cases, N	Deaths due to HSTL, n/N	Underlying pathology	Exposure to AZA or 6-MP, n/N	Exposure to biologic, n/N
31	26/31	CD – 25/31 UC – 4/31 IC – 1/31 Unknown – 1/31	30/31 (Unknown – 1/31)	IFX – 23/31 Other anti-TNFα – 6/31 Natalizumab – 1/31 Unknown – 1/31

- Infliximab treatment duration ranged from < 6 months to more than 5 years of therapy
- 87% (27/31 cases) were in males and 67% (20/30 known cases) were ≤ 30 years

Data on file, Centocor (*PSUR 24*, July 2011) See also: Mackey AC, et al. *J Pediatr Gastroenterol Nutr.* 2007;44:265-267; Rosh JR, et al. *IBD.* 2007;13:1024-1030; Shale M, et al. *Gut.* 2008;57: 1639-1641; Cucchiara S, et al. *J Pediatr Gastroenterol Nutr.* 2009;48:257-267.

Side Effects/Safety

No doubt !

There is a clear difference between paediatric and adult-onset IBD

Side Effects/Safety

Score 5:3

Conclusion

Pediatric and adult-onset IBD are to > 90% the same diseases, but

- **Children probably have a more extensive and more aggressive disease**

Urgent need for efficient medication

Conclusion

Data from RCT in adult IBD cohorts

- **Can easily be extrapolated to children with IBD**
- **Should help to design appropriate paediatric IBD trials**
  - **Addressing PK/PD issues**
  - **Safety issues**


Thank you !
SORBONNE PARIS CITÉ
RECHERCHE ENSEIGNEMENT SUPÉRIEUR
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