Risk Stratification in Pediatric Inflammatory Bowel Disease: Are we there yet?

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University of Connecticut School of Medicine

on behalf of many others

Inflammatory Bowel Diseases

- Disorders characterized by chronic intestinal inflammation from a dysregulated immune response to the enteric microbiome in a genetically predisposed host
- Today we label them as Crohn's disease and ulcerative colitis though we recognize they often have similar clinical features and large genetic homology
- Presenting symptoms range from mild to severe and clinical course is often unpredictable but may range from easily controlled to fulminant disease
- Short of finding a cure, or preventing these disorders, it would greatly aid patient care if we could….

Predict the Future and Match Our Therapy to Anticipated Course: Risk Stratify

Over treatment

Under treatment

What is Risk Stratification?

- **A statistical process to determine detectable characteristics associated with an increased chance of experiencing unwanted outcomes.**
- **By identifying factors before the occurrence of an event, it is possible to develop targeted interventions to mitigate their impact.**

What are the unwanted outcomes?

- **Continued active gastrointestinal and extraintestinal symptoms**
- **Growth failure**
- **Impaired quality of life**
- **Relentless progression of disease**
- **Cancer**
- **Surgery**

Progressive Bowel Damage in CD

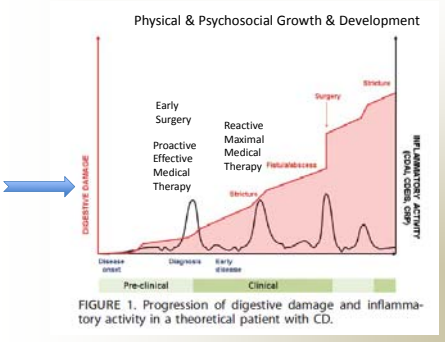
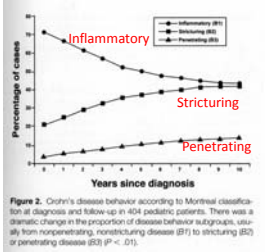


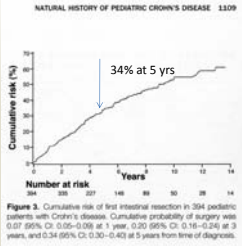
FIGURE 1. Progression of digestive damage and inflammatory activity in a theoretical patient with CD.

What you see on the outside does not always indicate what is going on inside

Pariente et al. Inflamm Bowel Dis 2011

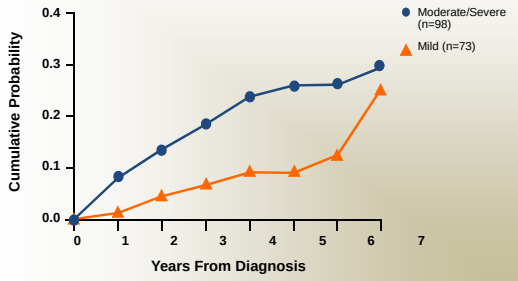
Crohn's Disease Progression in Children: Pre-Biologic Era:1988-2002





Vernier-Massouille et al. Gastroenterology 2008;135:1106

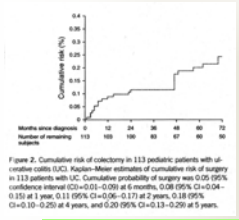
Cumulative Probability of Colectomy by Disease Activity at Diagnosis

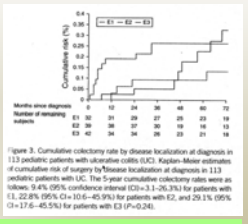


Mild vs moderate/severe, $P<0.03$

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

EPIMAD Study from Northern France





20% at 5 years

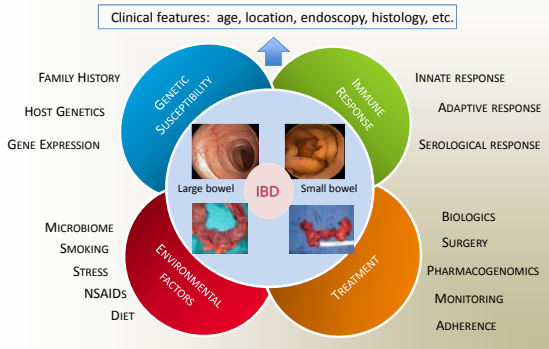
9% (E1), 23% (E2), 29% (E3)

Vernier-Massouille et al. Am J Gastroenterol 2009;104:2080

We Need To Do A Better Job Of Understanding Our Patients Before We Treat Them

One approach does not fit all patients

IBD patients may have unique signatures that predict complicated or treatment refractory disease



Exploding Head Syndrome

Exploding head syndrome is a condition that causes the sufferer to occasionally experience a tremendously loud noise as originating from within his or her own head, usually described as the sound of an explosion, roar, waves crashing against rocks, loud voices, or a ringing noise. Sufferers often feel a sense of fear and anxiety after an attack, accompanied by elevated heart rate. There may be a correlation with stress. Can occur at any time.


Crohn's disease

The Manhattan Project of Risk Stratification


Ulcerative colitis

Risk Study – CCFA 2008

- Subra Kugathasan
- Ted Denson
- Thomas Walters
- Yael Haberman
- Jeffrey Hyams
- Marla Dubinsky
- Robert Baldassano
- Michael Stephens
- James Markowitz
- Bruce Aronow
- Anne Griffiths
- MiDi Kim
- Francisco Sylvester
- David Mack
- James Markowitz
- Joel Rosh
- Neal Lesko
- Mel Heyman
- Wallace Crandall
- Stan Cohen
- Susan Baker
- Ashish Patel
- Dedrick Moulton
- Marian Pfefferkorn
- Steve Steiner
- Barbara Kirschner
- David Ziring
- Maria Oliva-Hemker
- David Kelju
- Anthony Otley
- David Mack
- Jon Evans
- Josh Noe
- Jonah Evans
- Scott Snapper
- Richard Kellermayer
- Steve Guthery
- Dirk Gevers
- Ramnik Xavier
- Curtis Huttenhower

PROTECT Study – NIDDK 2012

- Jeffrey Hyams
- Ted Denson
- Thomas Walters
- Subra Kugathasan
- Marla Dubinsky
- Francisco Sylvester
- Anne Griffiths
- Cary Sauer
- David Mack
- James Markowitz
- Joel Rosh
- Neal Lesako
- Mel Heyman
- Brendan Boyle
- Anthony Otley
- David Kelju
- Susan Baker
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- Steve Guthery
- Marian Pfefferkorn
- Jon Evans
- Ashish Patel
- Joshua Noe
- David Ziring
- Maria Oliva-Hemker
- Michael Kappelman
- Boris Sudel
- Keith Benkov
- Prateek Vasi
- Dedrick Moulton
- Jennifer Strogle
- Scott Snapper
- Paul Rufo
- Neera Gupta

- Collaborative Studies Coordinating Center (UNC)

Predictors of Disabling Crohn's

Referred cohort of 1128 CD patients

3 factors independently predictive disabling CD course within 5-year

- **Initial requirement for steroids**
  OR: 3.1 [95% CI: 2.2 – 4.4]
- **Age at diagnosis below 40**
  OR: 2.1[95% CI: 1.3 – 3.6]
- **Perianal disease at diagnosis**
  OR: 1.8[95% CI: 1.2 – 2.8]

Beaugerie L et al. Gastroenterology 2006;130:650-6

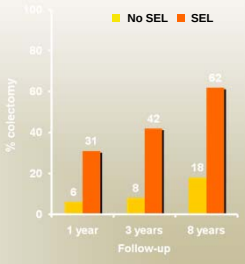
Consensus Predictors of Poor Outcome*

- **Deep colonic ulcerations on endoscopy**
- **Persistent severe disease despite adequate induction therapy**
- **Extensive (pan-enteric) disease**
- **Marked growth retardation (> -2.5 height Z scores),**
- **Severe osteoporosis**
- **Stricturing or penetrating disease (B2 and/or B3 disease behavior) at onset**
- **Severe perianal disease**

*Ruemmele et al. J Crohn's Colitis ECCO/ESPGHAN Working Group 2014;8:1179

Prognosis of CD Patients with Severe Endoscopic Ulcerations

- Retrospective cohort
- 102 adult patients with active CD
- Severe endoscopic lesions (SEL) defined as deep ulcerations >10% of mucosal area with at least one colonic segment
- Risk of colectomy associated with SELs
- All that developed penetrating disease had SELs
- This was not at diagnosis
- These are not pediatric data

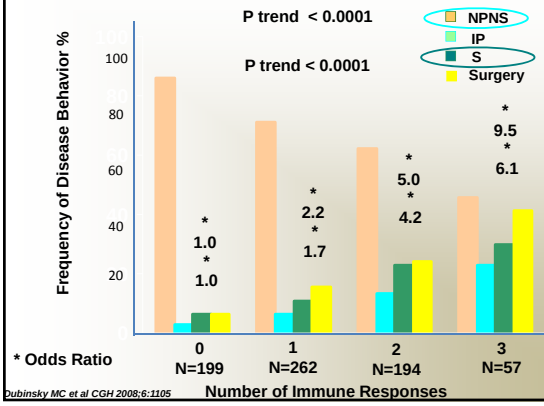


Allez et al. Am J Gastroenterology 2002;97:947

Anti-microbial Serologic Signature

ASCA, anti-omp C, anti-Cbir1

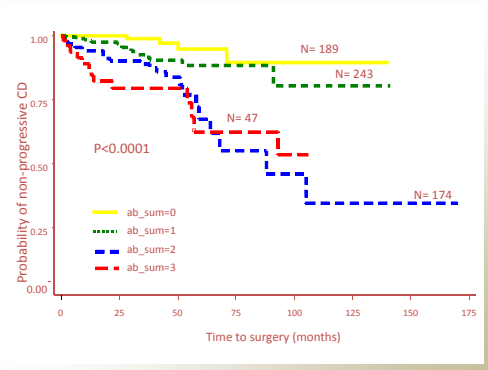
Antibody Sum and Disease Behavior



* Odds Ratio

Dubinsky MC et al CGH 2008;6:1105

Antibody Sum and Surgery



Dubinsky MC et al CGH 2008;6:1105

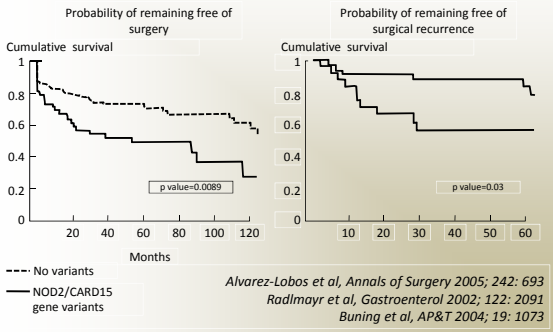
Host genetic signature & variable outcome

NOD2/CARD15

- ***NOD2*** **gene associated with an intracellular protein in the proinflammatory nuclear factor kappa B (NFkB) pathway, involved with a receptor for bacterial products**
- **This "defect" in the innate immune system may allow intracellular bacteria to escape the first-line defense of the immune system, thereby leading to an enhanced adaptive response**
- ***NOD2*** **acts as a negative regulator following bacterial stimulation of the cell surface receptor toll-like receptor-2, and CD-associated mutations result in a loss of this "brake" on the immune response leading to elevated NFkB**
- ***NOD2*** **mutations may lead to a reduction in the production of alpha-defensins (small antibacterial proteins) by Paneth cells located in the small bowel**
- **NOD2 may have some role in autophagy, a process that, among other things, deals with intracellular "debris," including bacterial products**

Ogura, Nature 2001;411:603, Watanable, Nature Immunol 2004;5:800, Wehkamp, Chem Immunol Allergy 2005:86:42, Cooney Nature Med 2010;16:90

NOD2/CARD15 and need for surgery



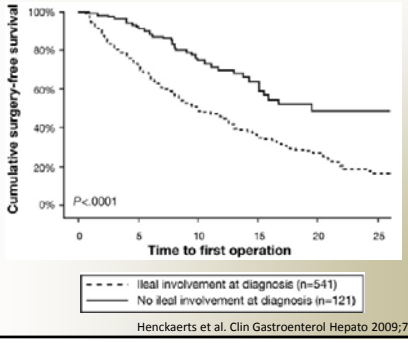
Alvarez-Lobos et al, Annals of Surgery 2005; 242: 693
Radlmayr et al, Gastroenterol 2002; 122: 2091
Buning et al, AP&T 2004; 19: 1073

But,

- **Only 1/3 of patients with Crohn's disease have polymorphisms of NOD2/CARD15[1]**
- **Having 2 mutations is much worse than having one mutation for RR of surgery[2]**
- **Virtually no Japanese patients with Crohn's disease have polymorphisms of NOD2/CARD15[3]**
- **Is it the gene or is it ileal location?**

[1]Niesse et al. Digestive Dis Sci 2012;57:879, [2]Adler et al. Am J Gastroenterol 2011;106:699, [3] Yamazaki et al. J Hum Genet 2002;47:469

Kaplan–Meier cumulative survival plots for time to first IBD-related operation: 682 adults with B1 disease



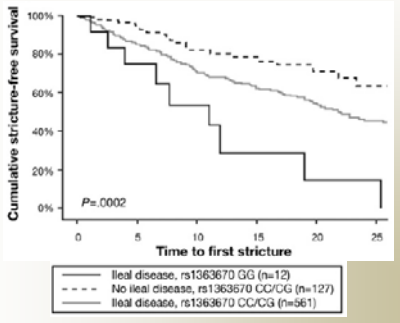
Henckaerts et al. Clin Gastroenterol Hepato 2009;7:972

What About Other Genes?

- ***IL*-23 is a cytokine that acts as a proinflammatory mediator of autoimmune and chronic inflammatory diseases.**
- **In association with *IL*-12, it is part of the T-helper 17 cell axis.**
- **The *IL-12B* gene, alternatively known as natural killer cell stimulatory factor 2, cytotoxic lymphocyte maturation factor 2, or p40, encodes the p40 subunit of IL-12B (ligand) and IL-23R (receptor), both of which are dimeric proteins.**
- **The *IL-12B* gene contains two major sites, both of which appear susceptible to variation and at which different alleles are associated with variable levels of gene expression**

Brand, Gut 2009;58:1152, van de Vosse, Microbes and Infection 2006;8:1167, Parham, J Immunol 2002;168:5699, Mangino, J Mol Med 2008;86:99

Kaplan–Meier cumulative survival plots for time to first stricture



Rs1363670 is gene linked to the *IL12B* LOCUS

So perhaps it is not all location, location, location

Small bowel

Large bowel

But what about our patients

We need pediatric specific data

CCFA Sponsored Clinical Research Network: PRO-KIIDS RISK Study

1100 children with Crohn's at diagnosis between 2008-2012

Follow-up to 2017

Study:

DNA

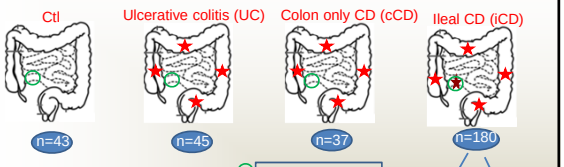
Fecal microbiome

Immune reactivity to bacteria, food, infections etc

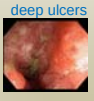
Environmental Exposures

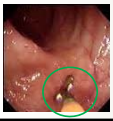
3 years → 160 – 200 patients with complication / surgery

RISK Study: Ileal biopsy at the initial endoscopy



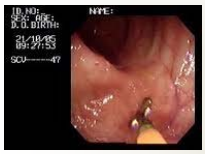
- Age, gender and ethnicity were not statistically different.
- CD groups - perianal involvement, BMI, PCDAI were not statistically different.





- DNA >>16s (Broad, Illumina MiSeq)
- RNA >> mRNA-seq (CCHMC, single end 50bp, Illumina HiSeq 2000)

RISK Study: Using Next Gen Sequencing to Classify the Intestinal Microbiome and Genome at Diagnosis



- Processed ~ 5300 intestinal biopsies from 950 CD, UC, IBDU patients and non-IBD controls
- DNA yield: 10,500 (8,468,12,670) ng
- RNA yield: 11,490 (9,351, 13,640) ng
- RNA quality sufficient for PCR or RNASeq in >95%
- Microbiome: 1000 ng DNA
- RNASeq: 1000 ng RNA

RISK Study: Gene prioritizing for further analysis

Top 5 up-regulated genes

	Gene	iCD-1 FC	iCD-2 FC
1	DUOXA2	43.6	50.2
2	MMP3	29.5	24.2
3	AQP9	29.4	35.0
4	IL8	23.5	26.0
5	DUOX2	14.3	24.1

Top 5 down-regulated genes

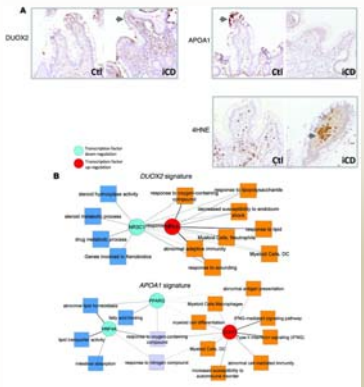
	Gene	iCD-1 FC	iCD-2 FC
1	APOA1	-8.6	-10.7
2	NAT8	-8.6	-9.8
3	AGXT2	-8.8	-9.5
4	CUBN	-9.0	-9.4
5	FAM151A	-10.4	-8.9

FC = fold change

Top upregulated genes, epithelial antimicrobial dual oxidase *DUOX2* *and its maturation* factor *DUOXA2. Top downregulated genes,* Anti-inflammatory HNF4α-dependent lipoprotein *APOA1*

Haberman et al. J Clin Invest 2014

RISK Study: A Core CD Ileal Gene Expression Signature Contains *DUOX2* and *APOA1* Co-expression Signatures

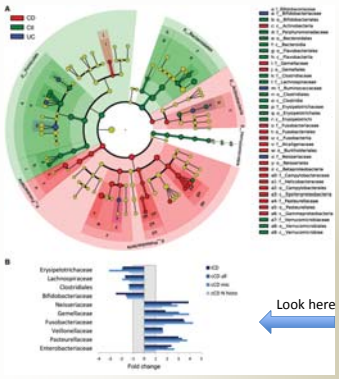


Haberman et al JCI 2014
PRO-KIIDS RISK Study

RISK Study: Microbial Profiling

- ***Ileal Firmicutes and Proteobacteria taxa abundance are associated with the APOA1 and DUOX2 gene coexpression signatures and clinical outcomes.***
- **70 significant associations between gene expression and microbial taxa and 34 significant associations between clinical parameters and microbial taxa**

Haberman et al. JCI 2014



Haberman et al.RISK Study, JCI 2014

So?

- **Gene expression, microbial profiling, and clinical data used to model outcome compared to clinical data alone**
- **Neither age at dx or clinical disease activity by PCDAI predicted 6 month SSFR**
- **Higher APOA1 expression and and certain microbial taxa including Blautia (worse) and Veilloneolla (better) were prognostic factors**

Haberman et al. RISK Study, JCI 2014

A multi'omic model is superior in predicting surgery and steroid free remission in comparison to clinical factors alone.

The relative goodness of fit of the models, *P* <0.0043		
	Clinical variables only	Clinical, expression and microbial
C statistics (AUC)	0.705	0.760

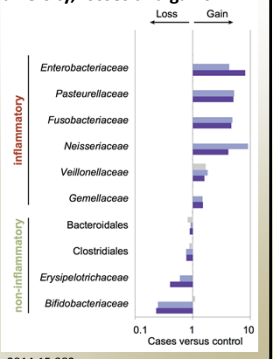
Multiple regression analysis including clinical, gene expression, and microbial variables.				
		p-value	OR	CI
Age≥10 vs. <10		0.8868	0.944	0.430, 2.075
Ileal DU vs. no DU	PCDAI>30	0.6244	0.771	0.271, 2.188
	PCDAI≤30	0.0029	4.713	1.701, 13.057
Anti-TNF therapy		0.0020	5.181	1.828, 14.706
APOA1 expression level > 80th percentile		0.0152	3.058	1.241, 7.576
Blautia Abundant (>70th percentile) vs non-abundant	Veillonella abundant	0.5183	1.634	0.368, 7.25
	Veillonella non-abundant	0.0028	0.231	0.089,0.604

Haberman et al JCI 2014
PRO-KIIDS RISK Study

Host microbiota signature & ? variable outcome

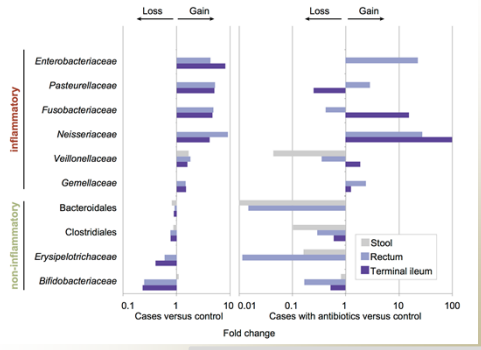
RISK Study: The Microbiome shifts in pediatric Crohn's disease: Decreased diversity, losses and gains

Microbiome was profiled in 800 RISK subjects enrolled at 28 pediatric centers in US/CAN
500 cases + 300 controls



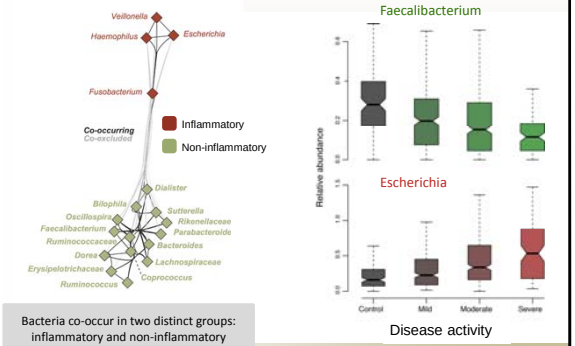
Gevers et al. Cell Host Micro 2014;15:382

RISK Study: The Microbiome shifts in pediatric Crohn's disease



Antibiotic exposure amplifies the microbial dysbiosis
Gevers et al. Cell Host Microbe 2014;15:382

RISK Study: The Microbiome shifts in pediatric Crohn's disease: ? cause versus association



Bacteria co-occur in two distinct groups: inflammatory and non-inflammatory

Gevers et al. Cell Host Microbe 2014;15:382

Determining the key players of microbial dysbiosis in new-onset pediatric CD

- Taxa identified as significant biomarkers for disease, including members of the Pasteurellaceae, Veillonellaceae, Neisseriaceae, and Fusobacteriaceae.
- Antibiotic exposure amplifies the microbial dysbiosis, by further loss of *Bacteroides*, *Clostridiales*, and *Erysipelotrichaceae*, and increase in *Fusobacteriaceae* and *Enterobacteriaceae*
- **Hypothesis: Does your flora help determine your outcome? Can manipulation of the bacterial flora change the outcome?**

Is it or is it not out of our hands?

By the time we see someone is it too late?

Is Outcome Determined At the Time of Diagnosis or Does Timing and Specificity of Treatment Matter?

(Does it matter what your genes or bugs are?)

Increased Effectiveness of Early Therapy With Anti–Tumor Necrosis Factor-α vs an Immunomodulator in Children With Crohn's Disease

Thomas D. Walters,[1,*] MiOk Kim,[2,*] Lee A. Denson,[3] Anne M. Griffiths,[1] Marla Dubinsky,[3] James Markowitz,[4] Robert Baldassano,[5] Wallace Crandall,[6] Joel Rosh,[7] Marian Pfefferkorn,[8] Anthony Otley,[9] Melvin B. Heyman,[10] Neal LeLeiko,[11] Susan Baker,[12] Stephen L. Guthery,[13] Jonathan Evans,[14] David Ziring,[15] Richard Kellermayer,[16] Michael Stephens,[17] David Mack,[18] Maria Oliva-Hemker,[19] Ashish S. Patel,[20] Barbara Kirschner,[21] Dedrick Moulton,[22] Stanley Cohen,[23] Sandra Kim,[24] Chunyan Liu,[2] Jonah Essers,[25] Subra Kugathasan,[26] and Jeffrey S. Hyams,[27] for the PRO-KIIDS Research Group

[1]Hospital for Sick Children, Toronto, Ontario, Canada; [2]Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; [3]Cedars Sinai Medical Center, Los Angeles, California; [4]Cohen Children's Medical Center, New Hyde Park, New York; [5]Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; [6]Nationwide Children's Hospital, Columbus, Ohio; [7]Goryeb Children's Hospital, Morristown, New Jersey; [8]Riley Children's Hospital, Indianapolis, Indiana; [9]IWK Health Centre, Halifax, Nova Scotia, Canada; [10]University of California, San Francisco, California; [11]Hasbro Children's Hospital, Providence, Rhode Island; [12]Children's Hospital of Buffalo, Buffalo, New York; [13]University of Utah and Primary Children's Medical Center, Salt Lake City, Utah; [14]Nemours Children's Clinic, Jacksonville, Florida; [15]Children's Hospital of Los Angeles, Los Angeles, California; [16]Baylor College of Medicine, Houston, Texas; [17]Children's Hospital of Wisconsin, Milwaukee, Wisconsin; [18]Children's Hospital of Eastern Ontario, Ottawa, Canada; [19]Johns Hopkins Medical Center, Baltimore, Maryland; [20]Texas Children's Hospital, Dallas, Texas; [21]University of Chicago, Chicago, Illinois; [22]Vanderbilt Children's Hospital, Nashville, Tennessee; [23]Children's Healthcare, Atlanta, Georgia; [24]University of North Carolina, Chapel Hill, North Carolina; [25]Children's Hospital, Boston, Massachusetts; [26]Emory University, Atlanta, Georgia; [27]Division of Digestive Diseases, Hepatology, and Nutrition, Connecticut Children's Medical Center, Hartford, Connecticut

Walters, Kim et al. RISK Study. Gastroenterology 2014;146:383

Table 2. Characteristics at Diagnosis of Propensity Score–Matched Sample (N = 204)

	Therapy in the first 3 months			
	Anti-TNFα[a] only (n = 68)	IM only[b] (n = 68)	No early immunotherapy (n = 68)	*P* value
Paris age, <10 y	9 (13%)	8 (12%)	7 (10%)	.87
Male	46 (68%)	34 (50%)	44 (65%)	.078
Tanner I-III	73%	71%	77%	.81
Paris classification				.21
L1	19 (28%)	10 (15%)	11 (16%)	
L2	17 (25%)	16 (24%)	16 (25%)	
L3	28 (41%)	41 (60%)	38 (56%)	
Small-bowel involvement	51 (75%)	52 (76%)	50 (74%)	.92
PCDAI, >30	42 (62%)	42 (62%)	41 (60%)	.98
Presence of perianal disease	16 (24%)	12 (18%)	12 (18%)	.61
Presence of deep ulceration	41 (60%)	41 (60%)	41 (60%)	1.0
Mean serum albumin level, g/L (SD)	3.5 (0.6)	3.3 (0.7)	3.5 (0.6)	.29
Median ESR, mm/h	39 (25–51)	36 (22–52)	33 (15–49)	.43
CRP level, ×ULN	5.09 (2.0–9.03)	5.85 (1.55–20.1)	6.0 (2.8–20.6)	.45
Platelet count	487 (307–554)	457 (371–578)	430 (305–531)	.82
Height z-score, <−1.65	9 (13%)	7 (10%)	8 (12%)	.87
Corticosteroid use in the first 3 months	41/68 (60%)	58/68 (85%)	49/68 (72%)	.006

ESR, erythrocyte sedimentation rate; ULN, upper limit of normal.
[a]Sixty-seven of 68 participants received infliximab therapy, 2 of 68 participants received adalimumab therapy.
[b]Fourteen of 68 participants received azathioprine therapy, 40 of 68 participants received 6-mercaptopurine therapy, and 14 of 68 participants received methotrexate therapy.
[c]Patients were not matched by sex or CS use within 3 months, and hence the matched sample is not balanced. Sex was not considered as a confounder and CS use is a postbaseline covariate.

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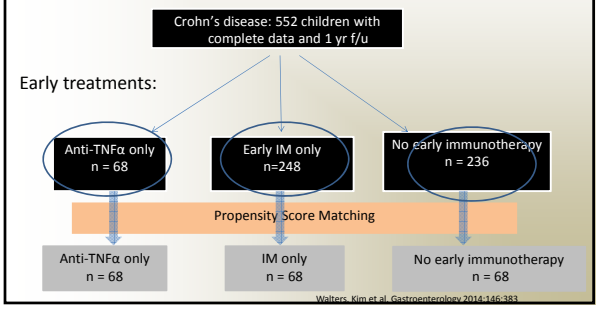
2008-2012: 552 children Newly Diagnosed with Crohn's Disease Enrolled in CCFA RISK Study



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12 Month Outcomes For The Three Early Therapy Approaches: PCDAI≤10 Without Resection

(n=204 for 68 propensity score matched triads)

CS-free, Surgery free

Treatment	Yes (n=136)	No (n=68)
Early anti-TNFα only (n=68)	58 (85%)	10 (15%)
Early IM only (n=68)	41 (60%)	27 (40%)
No early immunotherapy (n=68)	37 (54%)	31 (46%)

(p=0.0003)

No difference between early IM and no early IM

Walters, Kim et al. RISK Study Gastroenterology 2014;146:383

Relationship of Early Therapy to CRP at 12 months*

Early Treatment	Elevated CRP at 12 months given elevated CRP at baseline
Anti-TNFα only	24%
IM only	44%
No early immunotherapy	53%

81% of all patients had an elevated CRP at baseline, no difference between treatment groups

(p=0.007)

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Growth Parameters of Study Triads at Diagnosis

Early Therapy	Height z-score	Weight z-score	BMI z-score
Anti-TNFα only (n=68)	-0.16 (1.1)	-0.56 (1.4)	-0.79 (1.5)
IM only (n=68)	-0.29 (1.1)	-0.72 (1.3)	-0.81 (1.3)
No immuno-therapy (n=68)	-0.32 (1.1)	-0.67 (1.1)	-0.68 (1.1)
Difference between groups	P=0.6	P=0.8	P=0.8

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Growth Parameters of Study Triads at Diagnosis/One Year

Early Therapy	Height z-score	Weight z-score	BMI z-score
Anti-TNFα only (n=68)	-0.16 (1.1)	-0.56 (1.4) +0.85 (0.7)*	-0.79 (1.5) +1.1 (0.9)
IM only (n=68)	-0.29 (1.1)	-0.72 (1.3) +0.60 (0.7)*	-0.81 (1.3) +0.87 (0.97)
No immuno-therapy (n=68)	-0.32 (1.1)	-0.67 (1.1) +0.62 (0.5)*	-0.68 (1.1) +0.91 (0.87)
Difference between groups	P=0.6	P=0.8 P=0.044	P=0.8 P=0.3

*p<0.001 for all groups, diagnosis vs. 1 year

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Growth Parameters of Study Triads at Diagnosis

Early Therapy	Height z-score	Weight z-score	BMI z-score
Anti-TNFα only (n=68)	-0.16 (1.1)	-0.56 (1.4)	-0.79 (1.5)
IM only (n=68)	-0.29 (1.1)	-0.72 (1.3)	-0.81 (1.3)
No immuno-therapy (n=68)	-0.32 (1.1)	-0.67 (1.1)	-0.68 (1.1)
Difference between groups	P=0.6	P=0.8	P=0.8

Walters, Kim et al. RISK Study. Gastroenterology 2014;146:383

Growth Parameters of Study Triads at Diagnosis/One Year

Early Therapy	Height z-score	Weight z-score	BMI z-score
Anti-TNFα only (n=68)	-0.16 (1.1) +0.14 (0.4)*	-0.56 (1.4)	-0.79 (1.5)
IM only (n=68)	-0.29 (1.1) -0.02 (0.4)	-0.72 (1.3)	-0.81 (1.3)
No immuno-therapy (n=68)	-0.32 (1.1) -0.06 (1.1)	-0.67 (1.1)	-0.68 (1.1)
Difference between groups	P=0.6 P=0.039	P=0.8	P=0.8

*p=0.002, anti-TNFα group only

Walters, Kim et al. RISK Study Gastroenterology 2014;146:383

Table 3. Additional Therapies Beyond 3 Months for Study Triads

Therapy type	Started between 3 and 6 mo	Started between 6 and 12 mo	Total
Early anti-TNFα (n = 68)			
6-mercaptopurine	0	1	1
Methotrexate	4	2	6
Total additional IM	4	3	7
Early immunomodulators (n = 68)			
Adalimumab	0	1	1
Infliximab	6	13	19
Total additional anti-TNFα	6	14	20
No early immunotherapy (n = 68)			
6-mercaptopurine	9	1	10
Azathioprine only	2	2	4
Methotrexate only	8	5	13
Adalimumab only	1	1	2
Infliximab only	7	4	11
Adalimumab + IM	2	0	2
Infliximab + IM	1	4	5
Total additional IM or anti-TNFα therapy	30	17	47

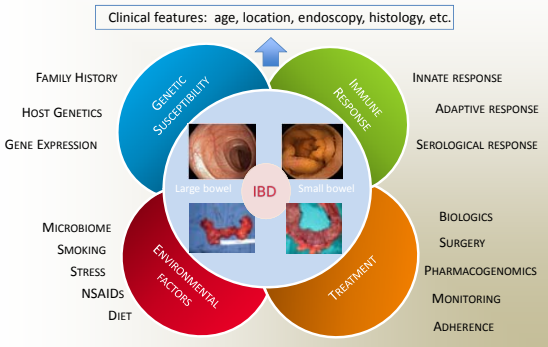
Walters, Kim et al. RISK Study. Gastroenterology 2014;146:383

So,

- In clinically similar populations of children with moderately to severely active Crohn's disease, early (<3 mon) therapy with anti-TNFα was superior to early IM or no early immunotherapy despite later addition of those agents
- But there was no particular clinical or laboratory characteristic that helped predict response or non-response to an initial therapeutic decision
- We need to better define further characteristics of patients, such as genetics, serology, microbiome, gene expression that help predict outcome

Risk Stratification

Treatment IBD patients have unique signatures that predict complicated or treatment refractory disease



But…
THINK about your patients

- Are there currently known risk factors for doing poorly?
- Am I using therapy that is unlikely to change the history of the disease?
- Am I using current therapies properly?
- What is the safety profile of therapies I am using?
- What is the risk of undertreated disease?

Ulcerative Colitis: Stay tuned

PROTECT

Predicting Response to Standardized Pediatric Colitis Therapy

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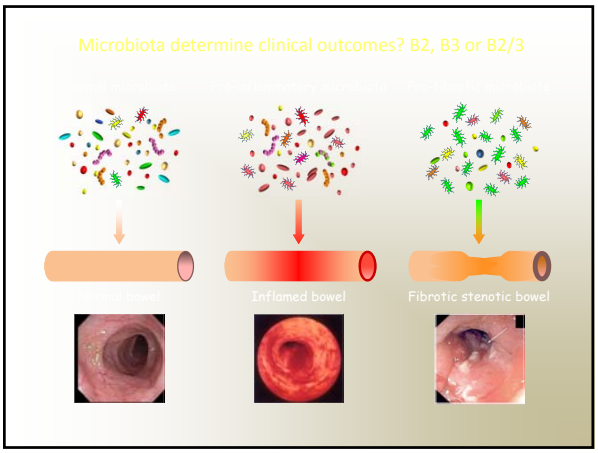

Antibiotics Associated with Increased Risk of New-Onset Crohn's Disease But Not Ulcerative Colitis: A meta-analysis

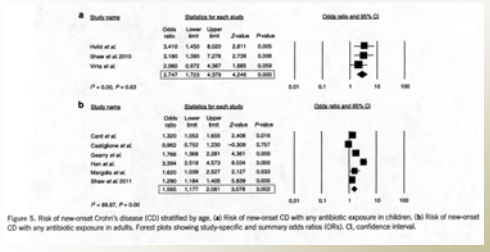

Figure 5. Risk of new-onset Crohn's disease (CD) stratified by age. (a) Risk of new-onset CD with any antibiotic exposure in children. (b) Risk of new-onset CD with any antibiotic exposure in adults. Forest plots showing study-specific and summary odds ratios (ORs). CI, confidence interval.

Ungaro et al. Am J Gastroenterol 2014