2022 Research Leadership Award

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Crohn's and Colitis Canada
Crohn et Colite Canada

Integrating clinical care and research in paediatric IBD

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Integrating clinical care and research in paediatric IBD:

…….a philosophy and a plea

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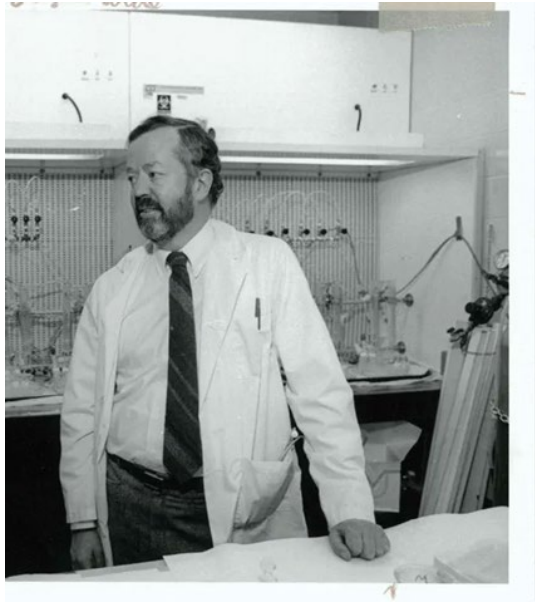
Conflict of Interest Disclosure
(over the past 24 months)

Commercial or Non-Profit Interest	Relationship
Abbvie, Amgen, Bristol/Myers/Squibb, Janssen, Lilly, Merck, Organon, Takeda	Advisory board or other consulting
Janssen, Abbvie, Takeda	Speaker fees
Abbvie	Investigator-initiated research support
Takeda, Janssen, Lilly	Industry-initiated clinical trial participation

What has made clinical care/research integration possible?

- **Centralized care in “IBD clinic”**

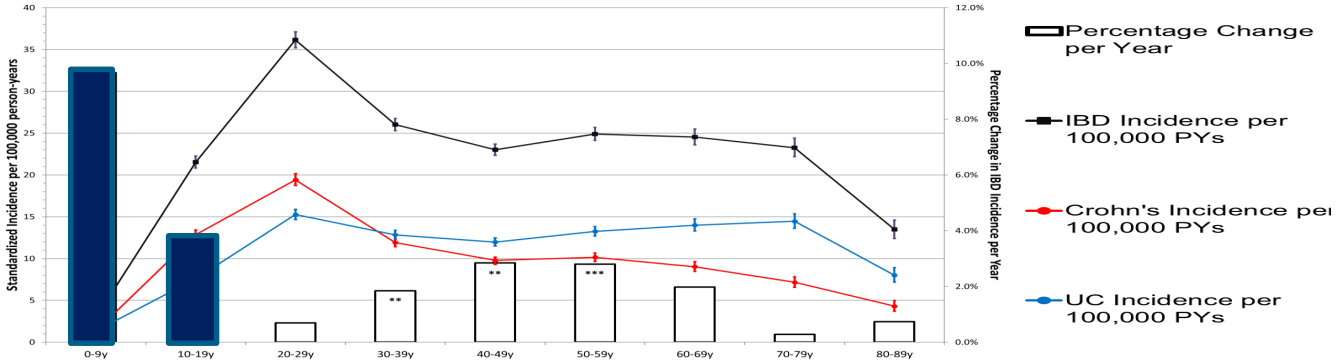
- **Paediatric GI fellowship program with a focus on preparation for investigative careers**

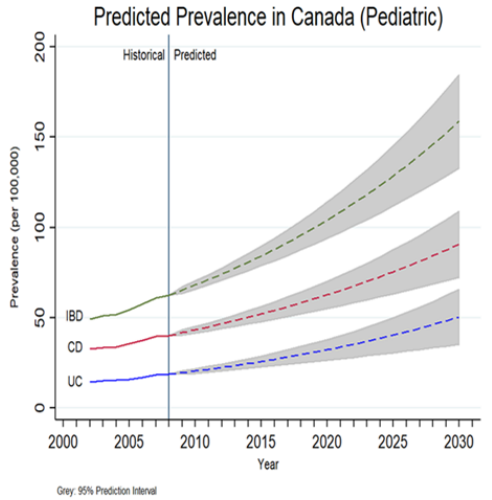


J. Richard Hamilton

Why is paediatric IBD important?

Incidence of paediatric-and adult-onset IBD in Canada (1999-2008)

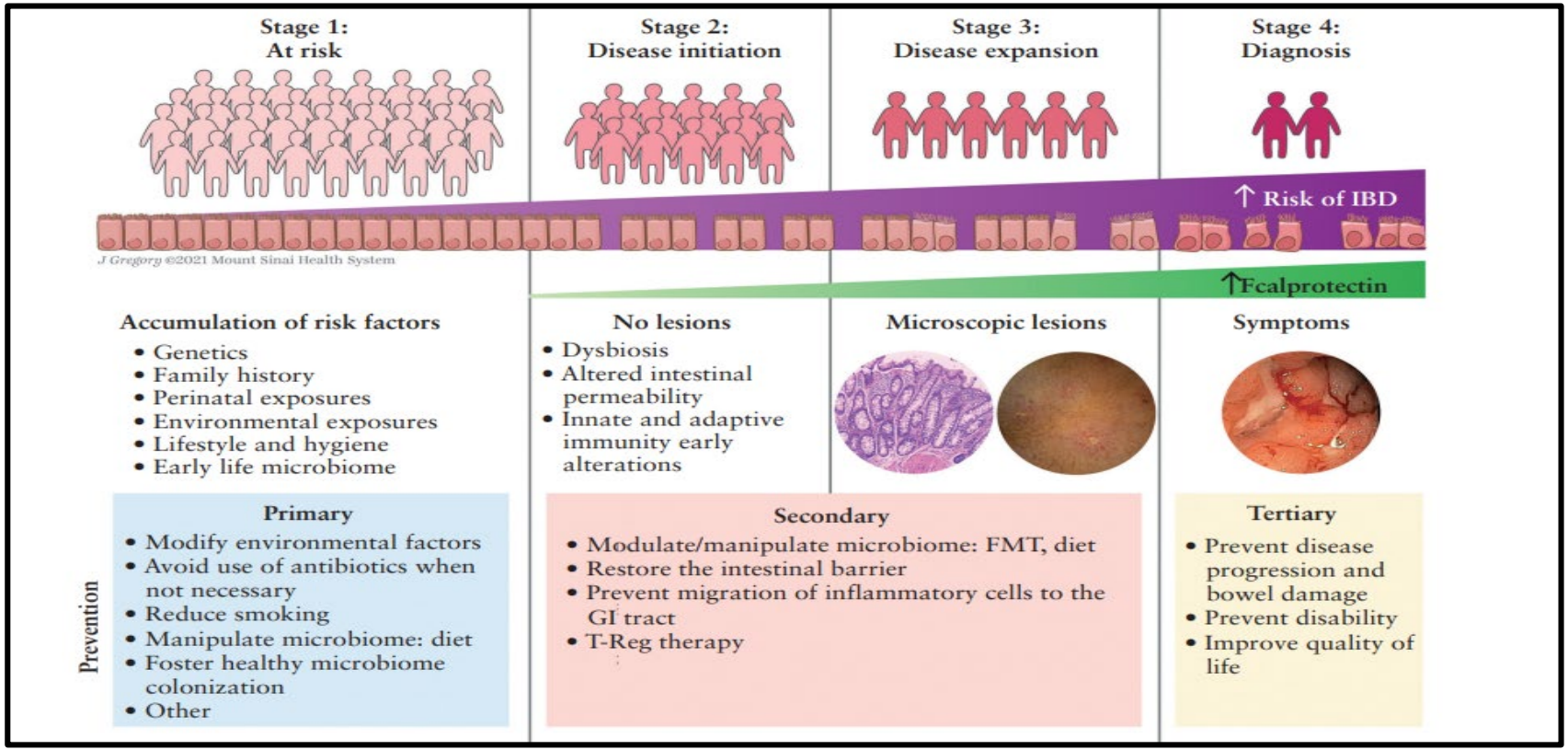




Benchimol and Kaplan

Benchimol et al, Inflamm Bowel Dis 2014; 20: 1761-9.

Proposed stages of Preclinical IBD



Torres J, et al ECCO workshop; JCC 2021; 1443-1454

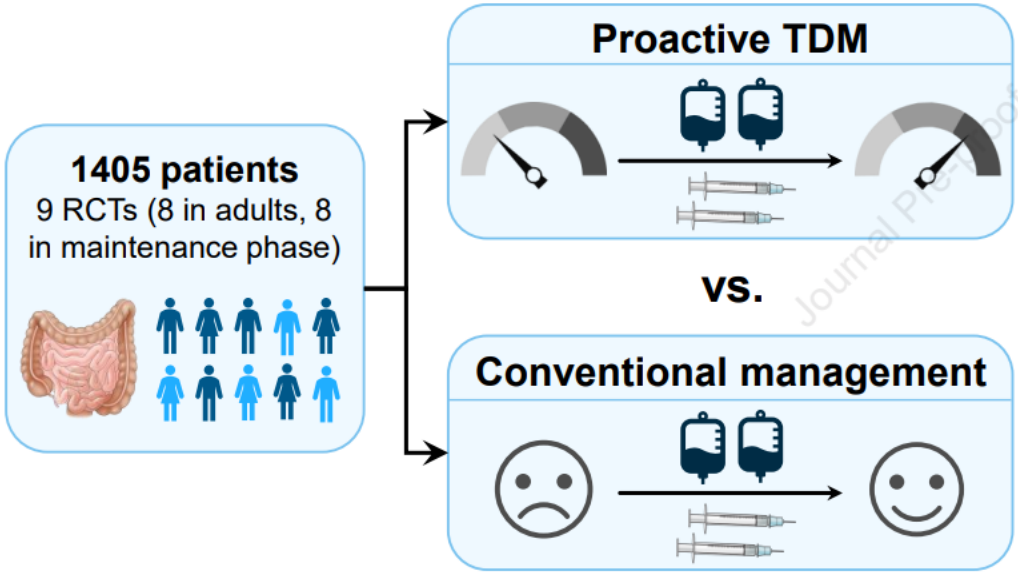
What are opportunities and responsibilities in paediatric IBD research?

- **Exploration of cause**

- **Evaluation and optimization of therapeutic strategies for children**
  - Canadian access to therapeutic drug monitoring

Systematic review and meta-analysis of RCT's of pro-active TDM

Proactive TDM vs. conventional management with TNFα antagonists in IBD



PRIMARY OUTCOME (AT 1 YEAR)	EVIDENCE
CLINICAL REMISSION	NO BENEFIT RR, 0.96; [0.81-1.13]
SECONDARY OUTCOMES	**EVIDENCE**
DOSE ESCALATION	HIGHER WITH TDM RR, 1.56 [1.25-1.94]
ANTI-DRUG ANTIBODIES	NO DIFFERENCE RR, 0.84 [0.58-1.22]

Gastroenterology

Nguyen NH et al, Gastroenterology on-line 19 June 2022

Paediatric CD adalimumab level-based optimization treatment

Enrolment: Week 4 responders to ADALIMUMAB

PAILOT

Proactive arm

TDM at week 4, 8 and every 8 weeks until week 72

TL measurement

- **Undetectable TL** (TL <0.3 µg/mL)
  - **ATA measurement**
    - **High ATA level**
      - **STOP**
- **TL <5 µg/mL**
  - **Interval decrease**
    - **Low ATA level**
      - **Interval decrease**
- **TL ≥5 µg/mL**
  - **No dose adaption**

TL >10 µg/ml interval increase

Reactive arm

TL measurement

LOR = PCDAI≥10 and/or CRP >0.5 mg/dL and/or FC >150µg/gr

TL exposure

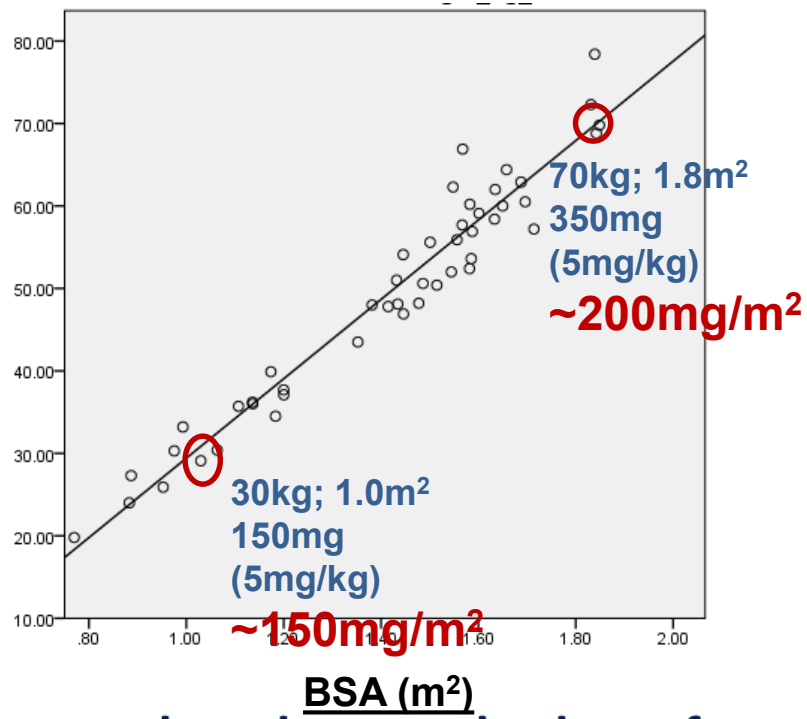
- **Undetectable TL** (TL <0.3 µg/mL)
  - **ATA measurement**
    - **High ATA level**
      - **STOP**
- **TL <5 µg/mL**
  - **Interval decrease**
    - **Low ATA level**
      - **Interval decrease**
- **TL ≥5 µg/mL**
  - **No dose adaption**

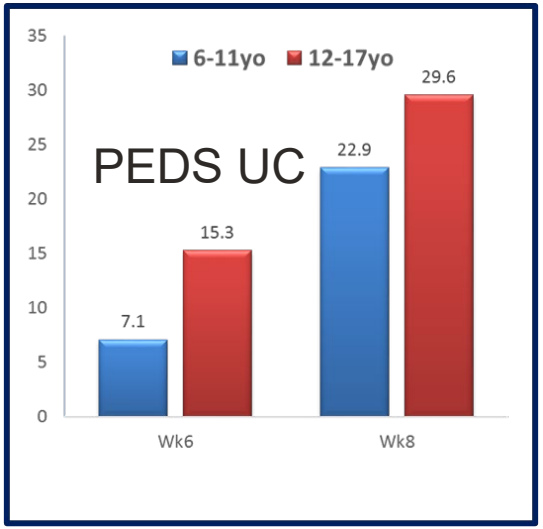
In patients receiving <40 mg, first escalation is dose increase to 40 mg

Assa A et al, Gastroenterology 2019; 157: 985-996

ATA, antibodies to adalimumab; CRP, C-reactive protein; FC, fecal calprotectin; LOR, loss of response; TL, trough level

Dosing of biologics in youngest children





Adedokun OJ et al.
IBD 2013;19:2753–2762

Weight-based dosing means less drug per body surface area for lighter children

Early pro-active therapeutic drug monitoring with infliximab

Week 0

3-dose Induction

Week 6

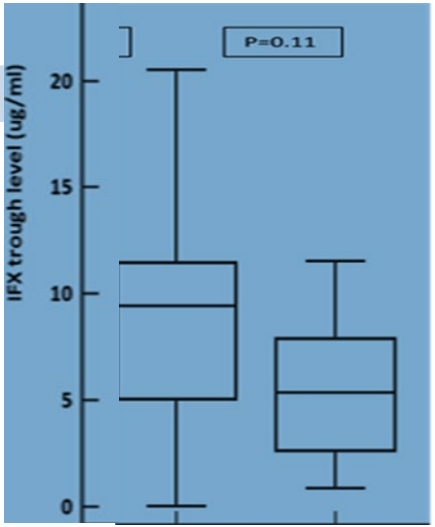
Week 2

Check trough level and infuse first maintenance dose early

Week 12

Week ?

Week ?



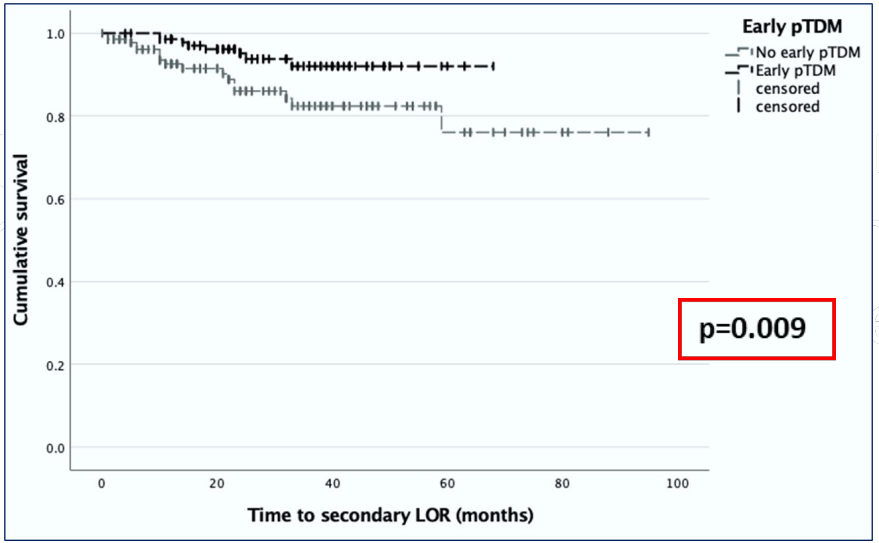
Week 12

Week 14

Use result to plan subsequent maintenance regimen

Early pro-active TDM is associated with greater durability of infliximab response

Luca Scarallo



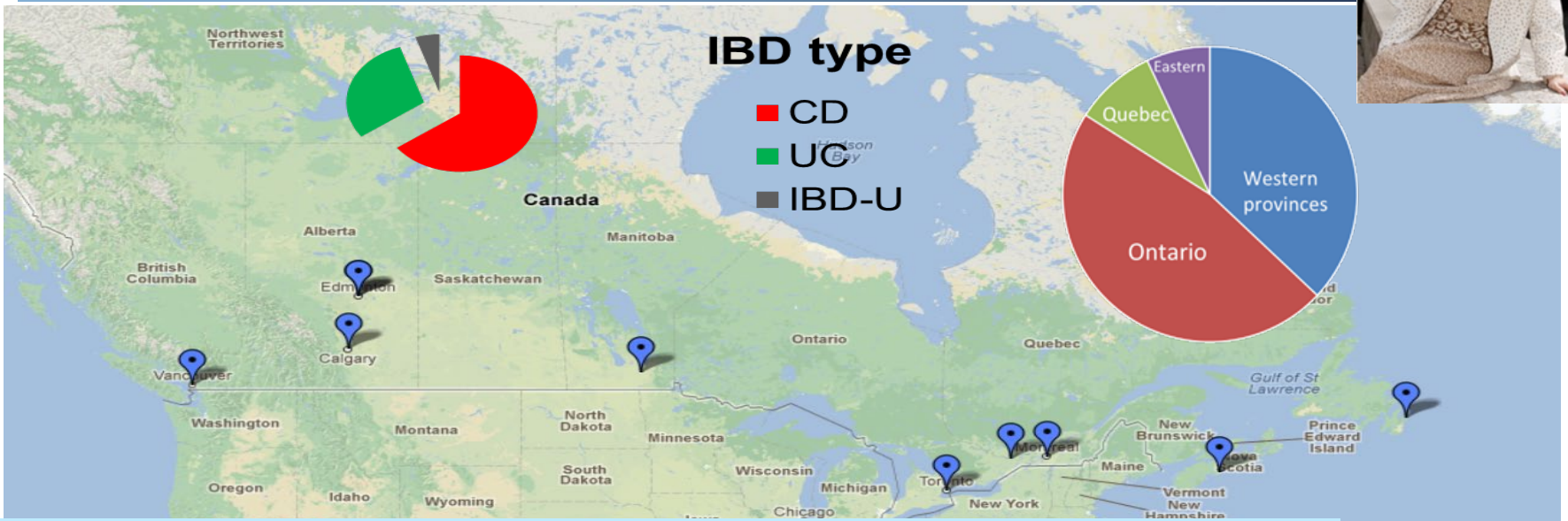
Retrospective single-centre

N=520 overall

N=312 in matched cohort (156 in each cohort)

Scarallo L, …….Church P, PIBD 2022

Canadian Children IBD Network: CIDsCANN ongoing inception cohort study (n=1493)



12 academic centres, where children at first assessed for suspected IBD

CHildren with Intestinal and Liver Disorders Foundation

Integration of research in prospective (inception) cohort

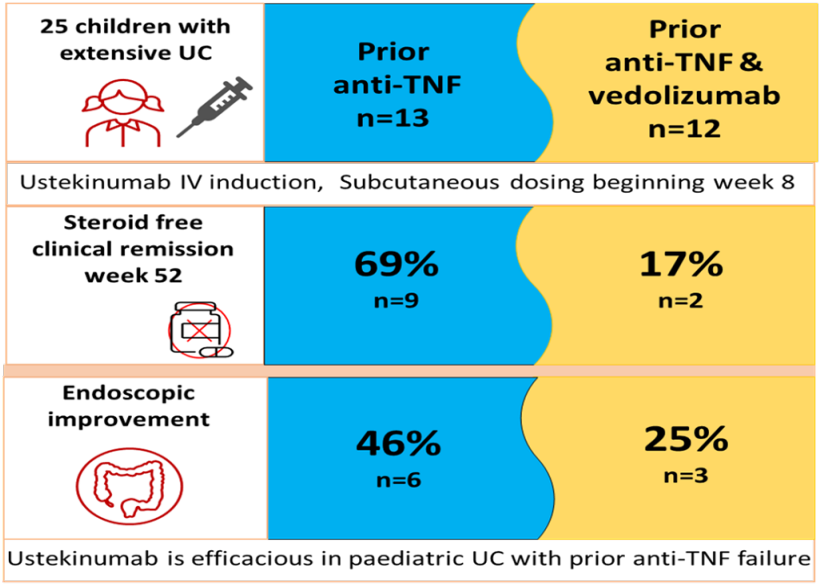
- **Physician/family choice of therapy** (recommended protocols for drug administration once selected)

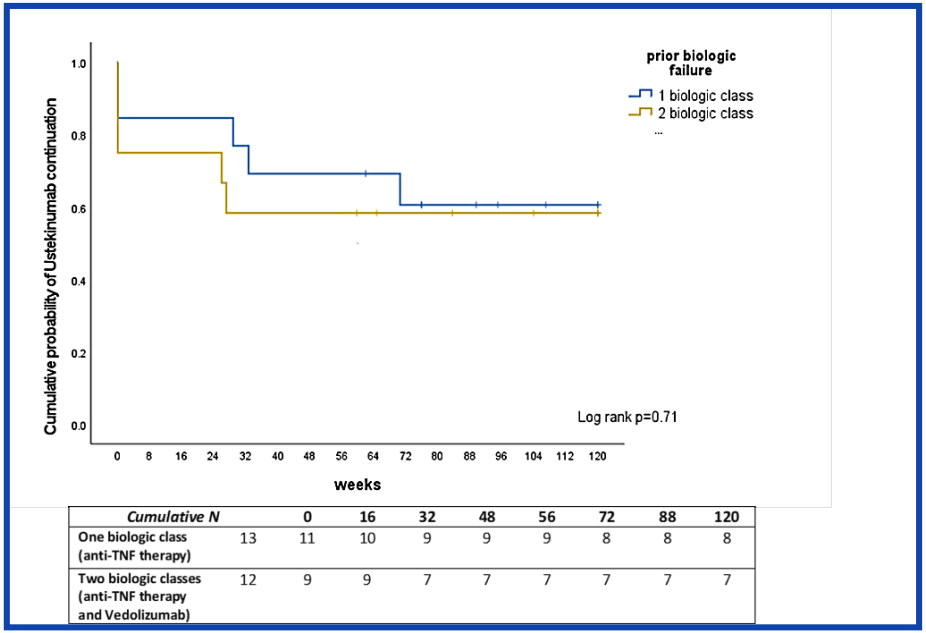
- **Rigorous phenotypic characterization** with pre-treatment biospecimen collection for research (serum, DNA, stool, urine, biopsies at 5 centres)

Thomas Walters

- **Prospective evaluation of outcomes** among phenotypically similar patients treated differently

Targeted cohort enrollment to evaluate emerging therapies



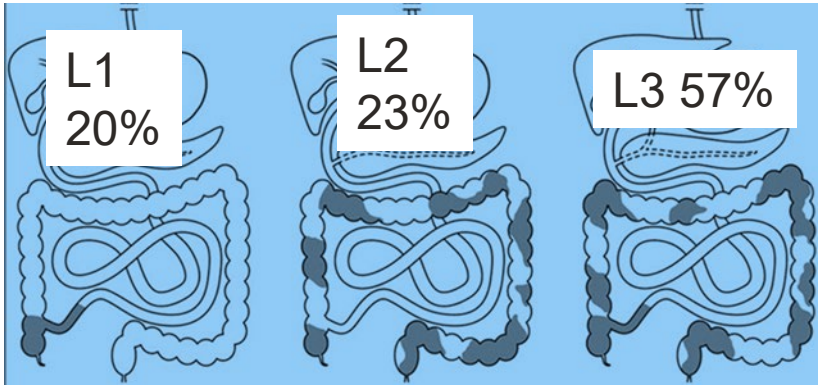


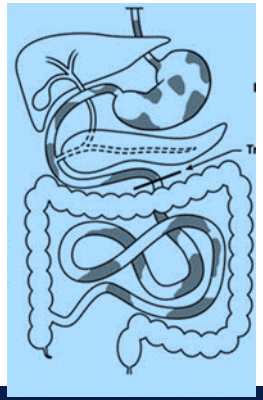
Cumulative N	0	16	32	48	56	72	88	120
One biologic class (anti-TNF therapy)	13	11	10	9	9	9	8	8	8
Two biologic classes (anti-TNF therapy and Vedolizumab)	12	9	9	7	7	7	7	7	7

CIDsCANN

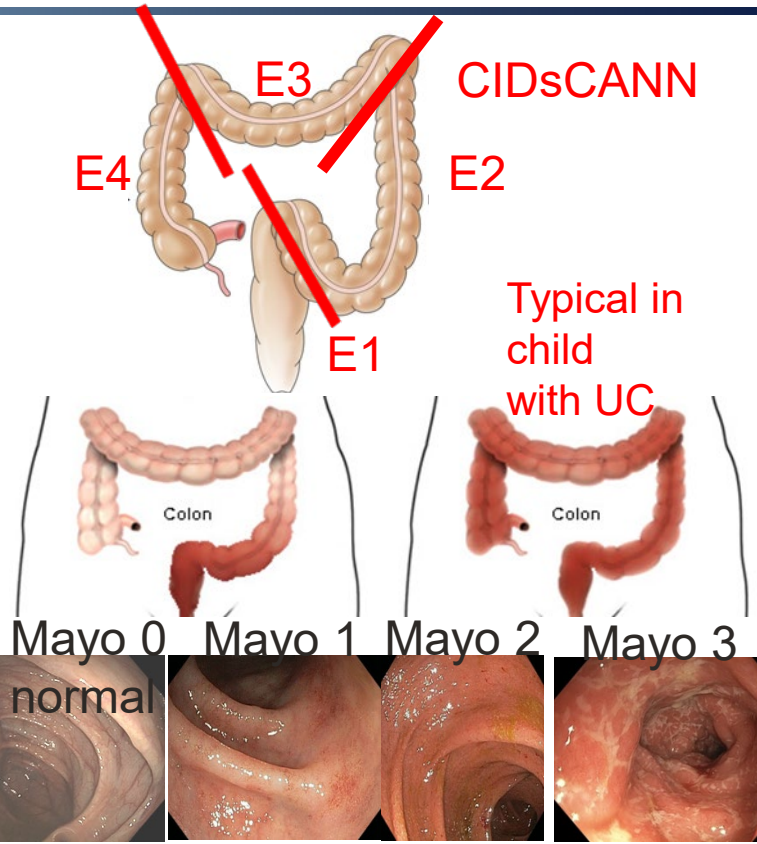
Dhaliwal J, McKay H, Deslandres C, et al Aliment Pharm Therapeutics 2021

Baseline phenotypic heterogeneity in new onset CD; consistency in UC





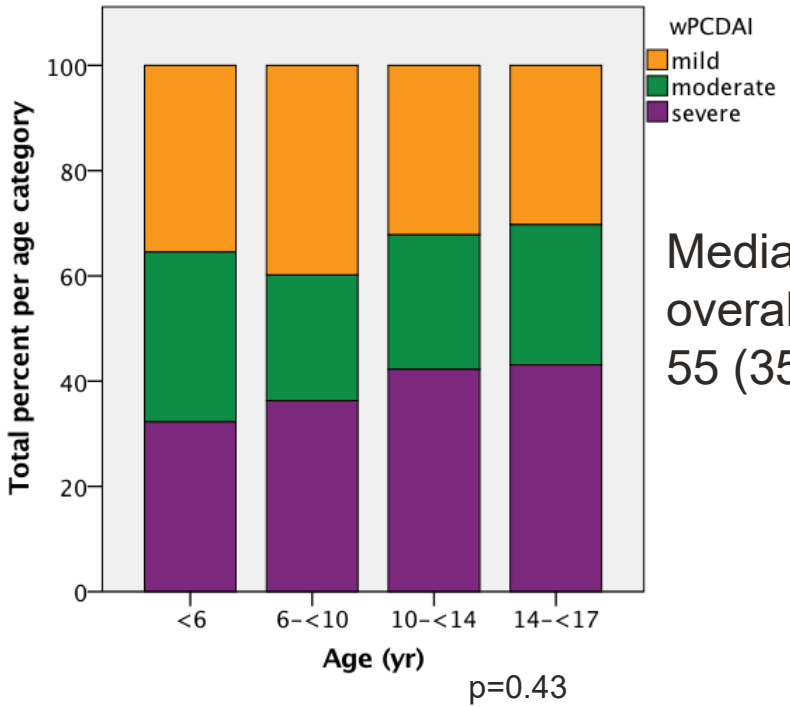
Additional
“upper tract”
L4a/L4b/L4ab
involvement
27%



Dhaliwal J et al, JCC 2020; 14:445-454

Spectrum of disease activity according to age

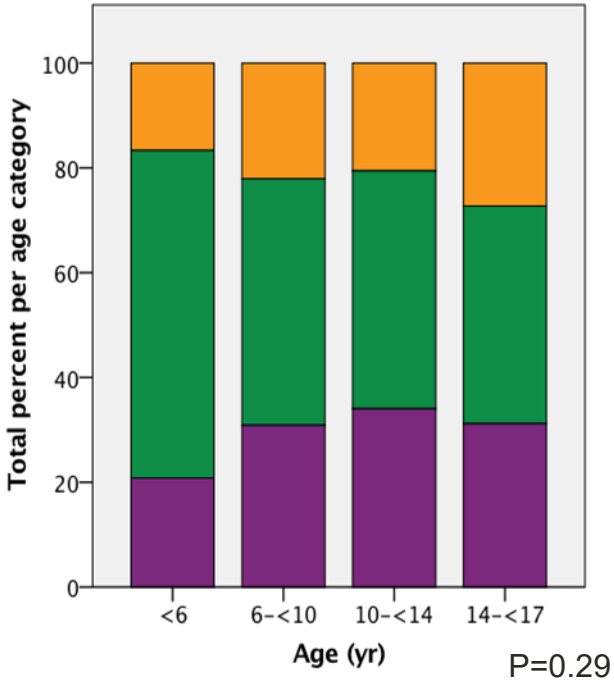
Crohn disease (wPCDAI)



Median overall 55 (35,75)

p=0.43

UC/IBD-U (PUCAI)



Median overall 50 (30, 65)

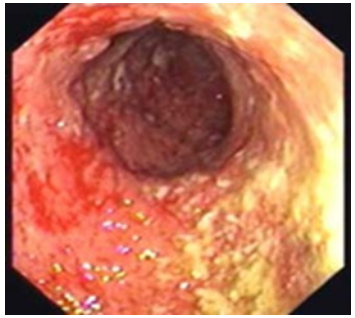
P=0.29

Children and Adolescents presenting with Ulcerative Colitis in Canadian Children IBD Network

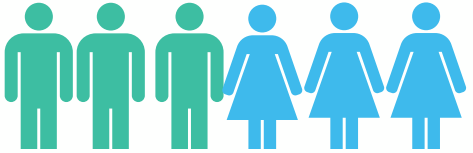
ACUTE SEVERE COLITIS N=105

- 14 (11-16) y
- PUCAI: 75 (70-80)
- E3: 13% E4:87%
- Albumin: 31 (25-35) g/L
- CRP: 14 (5-36) mg/L

CIDsCANN



MILD-MODERATE COLITIS N=274



- 13 (10-15) y
- PUCAI: 45 (30-55)
- E1:9% E2:8% E3/E4:83%
- Albumin:40 (35-43) g/L
- CRP: 5 (1-10) mg/L

Jazz Dhaliwal

105 children hospitalized with new onset ASUC (PUCAI≥65)
IV Corticosteroid treatment

Steroid refractory N=54

INFLIXIMAB induction n=54 (intensified)

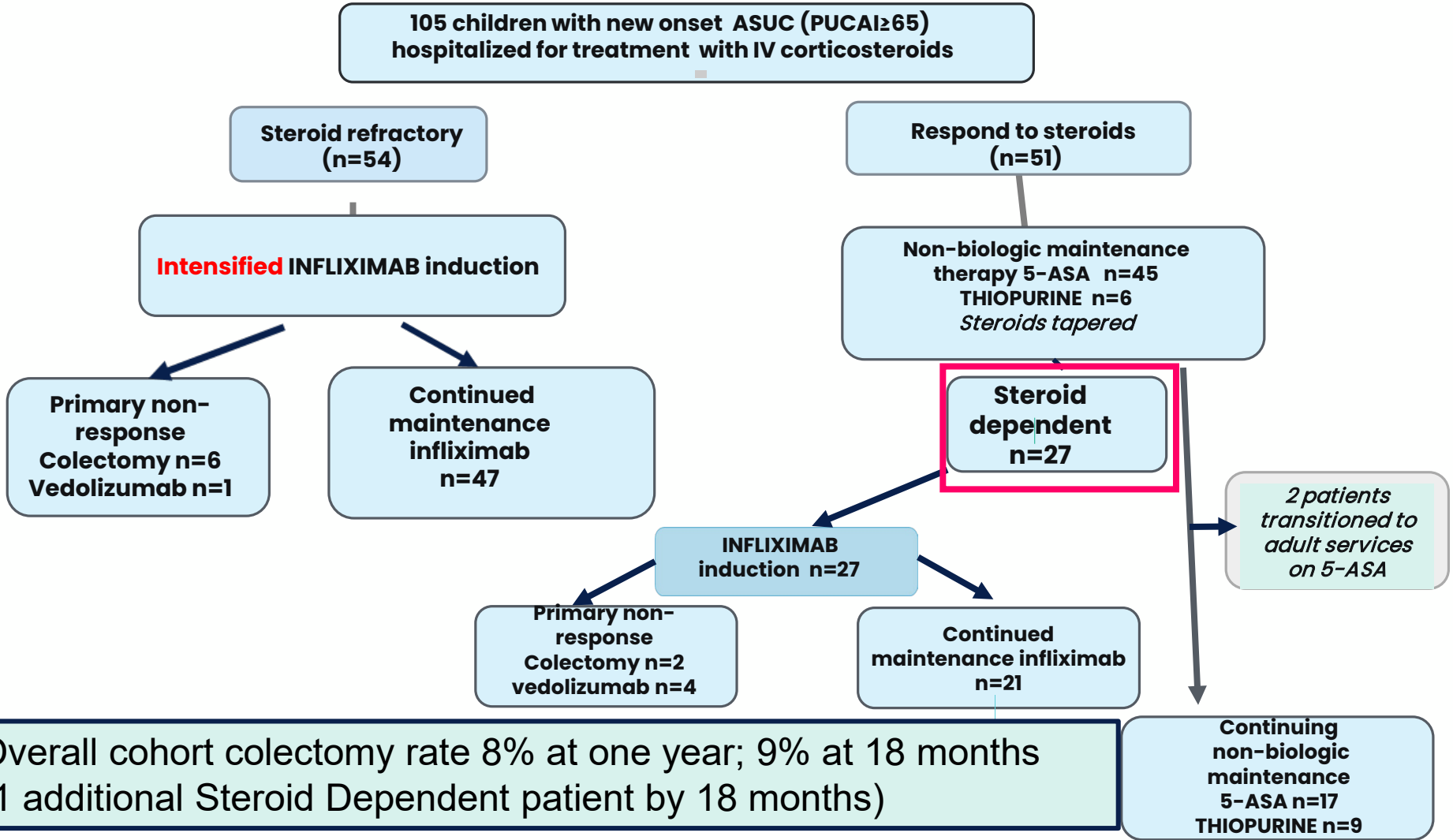
Steroid responsive n=51

Non-biologic maintenance therapy 5-ASA n=45
THIOPURINE n=6
Steroids tapered

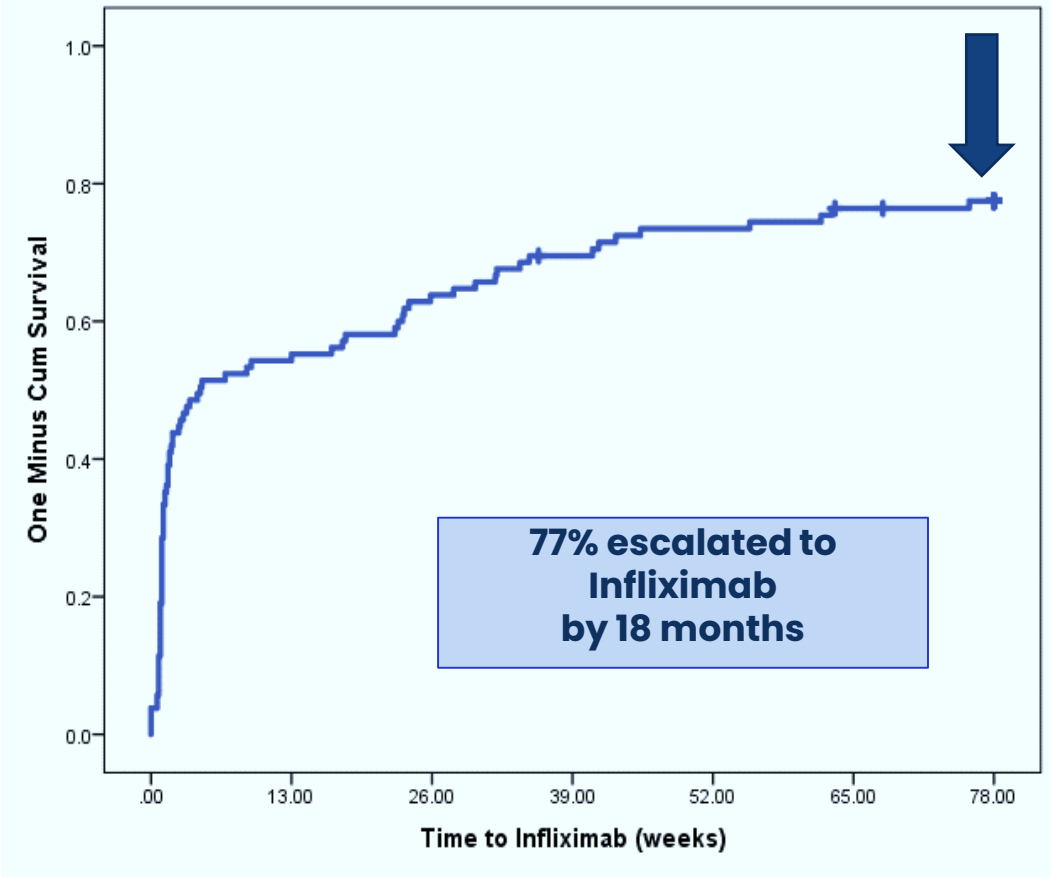
Overall 61% steroid-free clinical remission at 1 year

63% of initially steroid-refractory
All on biologics (33 IFX, 1 vedo)

54% of initially steroid responsive
13 5-ASA; 5 thiopurines;
7 IFX, 2 vedo; 1 ADA


105 children with new onset ASUC (PUCAI≥65) hospitalized for treatment with IV corticosteroids
Steroid refractory (n=54)
Respond to steroids (n=51)
Intensified INFLIXIMAB induction
Non-biologic maintenance therapy 5-ASA n=45
THIOPURINE n=6
Steroids tapered
Primary non-response Colectomy n=6 Vedolizumab n=1
Continued maintenance infliximab n=47
Steroid dependent n=27
2 patients transitioned to adult services on 5-ASA
INFLIXIMAB induction n=27
Primary non-response Colectomy n=2 vedolizumab n=4
Continued maintenance infliximab n=21
Continuing non-biologic maintenance 5-ASA n=17 THIOPURINE n=9
Overall cohort colectomy rate 8% at one year; 9% at 18 months
(1 additional Steroid Dependent patient by 18 months)

Time to infliximab: children with ASUC



- **Steroid refractory: 54 (67%)**
- **Steroid dependent: 27 (33%)**

- **Median (IQR) time to Infliximab 1.57 (0.93-20.3) weeks**

	2wk	4wk	3mo	6mo	9mo	12mo	18mo
N	46	5	7	9	6	4	4
Cum %	44%	49%	55%	64%	70%	73%	77%

~ equal use of Infliximab monotherapy versus + IM (usually MTX)

FACTORS ASSOCIATED with ESCALATION TO INFLIXIMAB

ALBUMIN

HR 0.93 (0.89–0.97)

AGE

HR 1.08 (1.01–1.16)

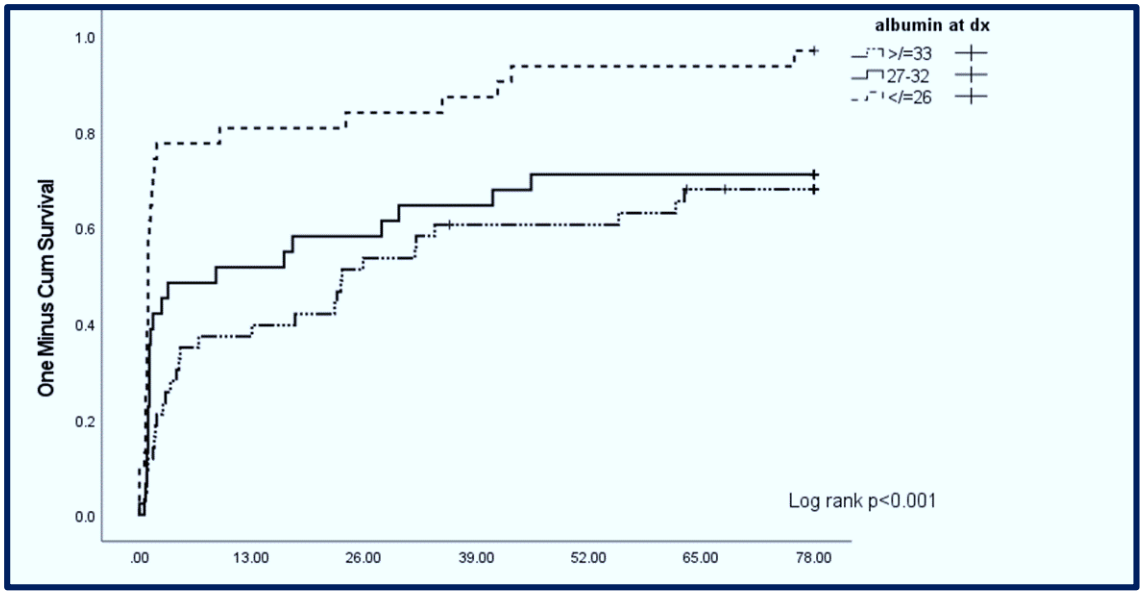
PUCAI

HR 1.04 (1.01–1.08)

MALE

HR 1.66 (1.06–2.60)

Acute severe colitis (ASUC) at first presentation



Albumin g/L	Hazard ratio (95%CI)	p-value
≤36	1.89 (1.01-3.53)	0.045
≤32	2.00 (1.25-3.18)	0.004
≤26	2.57 (1.60-4.11)	<0.001

Adjusted for PUCAI, age, sex

Children with serum albumin of ≤26g/L had greater than twice the chance of commencing infliximab, aHR of 2.57 (95% CI 1.6-4.1)

New onset paediatric UC: multicentre North American study

PROTECT
Predicting Response to Standardized Pediatric Colitis Therapy

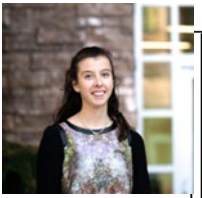
- N=423 patients with new onset UC; 33% mild (5-ASA induction); 67% moderate/severe (corticosteroids for induction)

12 month outcomes according to PUCAI at presentation

Baseline disease activity	Mild	Mod/Severe
CS Free Remission on 5-ASA only	49%	30%

Hyams JS et al Lancet Gastroenterol Hepatol 2017; 2: 855-68
Hyams JS et al, Lancet 2019: 1708-1720

Baseline gut microbiome differs in patients with ASUC and mild



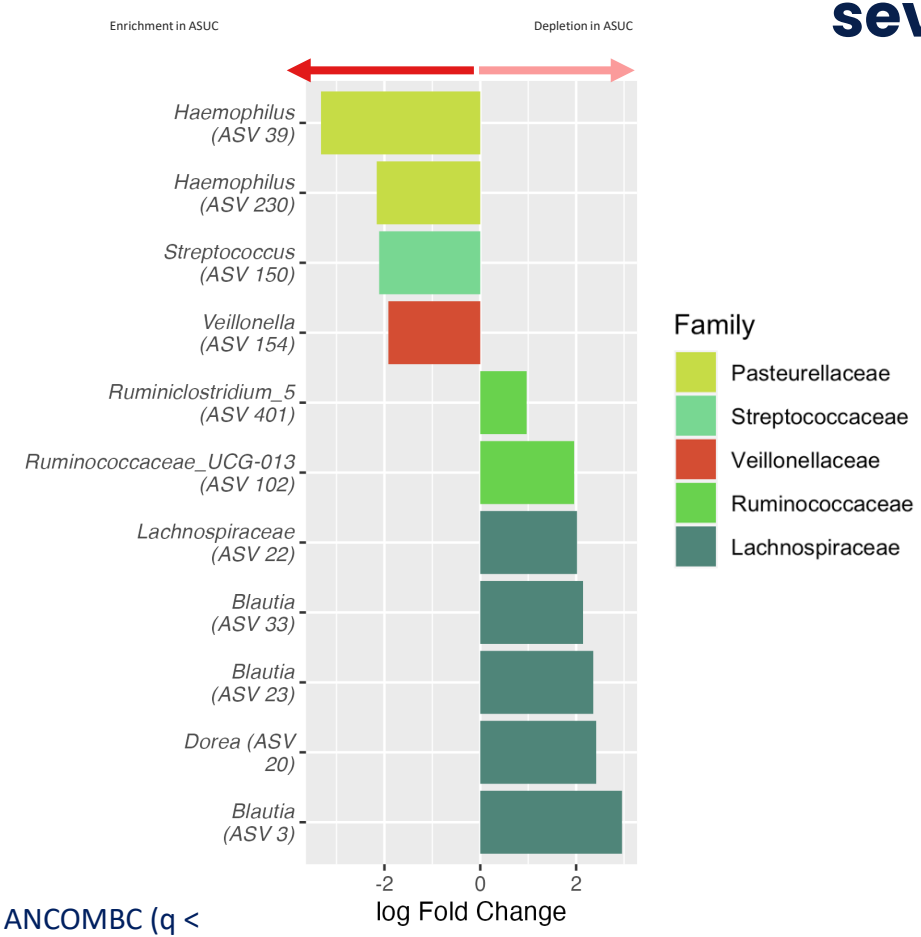
Dominique Tertigas

- **Beta diversity (Aitchison distance):** between sample diversity
- **Alpha diversity (Shannon diversity):** within sample diversity
  - Richness: # of species
  - Evenness: relative abundance

Adonis PERMANOVA ($p < 0.05$)

ANOVA ($*p < 0.05$)

Specific microbes are associated with UC severity



ANCOMBC (q <

- **Mild UC:** enrichment of some *Lachnospiraceae* and *Ruminococcaceae* members which are often described as short-chain fatty acid (SCFA) producers.
- **ASUC:** enrichment of oral microbes including *Haemophilus, Streptococcus,* and *Veilllonella.*
- Consistent with findings from the PROTECT study (Schirmer, M. et al. Cell Host Microbe (2018))

Extramural grants awarded using Network infrastructure/ collaboration/access to biospecimens

Network investigator	Agency; funding	Proposal
Bruce Vallance, PhD and Eytan Wine, MD, PhD	CIHR Microbiome Initiative Team Grant $2,000,000 (01/2020 – 12/2024)	Role of microbes in the pathogenesis of Pediatric IBD: From discovery, through causation, to novel treatments.
Eytan Wine, MD, PhD	CIHR project grant 2019-2024 $895,050 (+ $100,000 priority announcement)	Microbial Causes of Ulcerative Colitis: L Outside the Involved Region
Eric Benchimol, MD, PhD	Helmsley Charitable Trust via Crohn's and Colitis Canada $1,667,601 USD 2021-2024	"Implementing a Multimodal RCT Intervention to Improve the Transition of Patients with Crohn's disease from Pediatric to Adult Care.
Amanda Ricciuto, MD, PhD* (early career investigator)	Crohn's and Colitis Canada $375,000 2021-2024	Ascertaining Population-Based Long-Term Outcomes in Inflammatory Bowel Disease Patients with Primary Sclerosing Cholangitis

Extramural grants awarded using Network infrastructure/ collaboration/access to biospecimens

Network investigator	Agency; funding	Proposal
Amanda Ricciuto, MD, PhD*	Future Leaders in IBD (FLIBD). Pilot grant 2018-2019 $33,000	Serum Cytokine Profile for Predicting Anti-TNF Responsiveness in Pediatric IBD.
Amanda Ricciuto, MD, PhD*	CCFA PRO-KIDS New investigator grant. 2020-2021 219,966.80 USD.	Serum Cytokine Profiles to Predict Anti-TNF Response in Pediatric Inflammatory Bowel Disease.
Sara Ahola Kohut, PhD*	Crohn's and Colitis Canada $362,037.52 CAD (07/2017-06/2020)	iPeer2Peer program for youth with inflammatory bowel disease: a randomized controlled trial.

*** = Early career investigator**

We are in Phase 2

The Canadian Children Inflammatory Bowel Disease Network:

A Partnership with the Ch.I.L.D Foundation

CIDsCaNN

child

Assessment of **M**ucosal **B**iochemical and clinical response to **I**nterleukin-12/23 or **T**NF **I**nhibit**O**rs in biologic-**N**aïve **C**rohn's **D**isease (**AMBITION-CD**)

- Prospective non-randomized cohort study in luminal inflammatory Crohn's disease
- Comparison of outcomes (clinical, endoscopic, MR/IUS) with ustekinumab versus anti-TNF **as first biologic**
- Enrollment at diagnosis of patients where early biologic use is anticipated (facilitating pre-treatment biospecimen collection)
- Treatment regimens and monitoring (including TDM and FCAL) agreed upon by consensus

In Phase 2

- Process of leadership renewal
  - Co-chair elect: Eytan Wine
  - Co-chairs: Dave Mack, Jen Debruyn
- Broad engagement
- Roadmap for investigator-initiated proposals
- Making plans for sustainability

Integrating clinical care and research in paediatric IBD: