RISING STAR AWARD
CROHN'S AND COLITIS CANADA

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OUTLINE

PSC-IBD

- Unique gut phenotype
- Symptoms underestimate inflammatory burden
- Oral vancomycin for PSC-IBD
- COMING SOON – PSC-IBD health services research study

Precision med in pediatric IBD

- Ongoing study examining predictors of anti-TNF response
- Pilot data – serum proteomics

PSC-IBD

PRIMARY SCLEROSING CHOLANGITIS (PSC)

Progressive fibro-inflammatory disease of the biliary tree

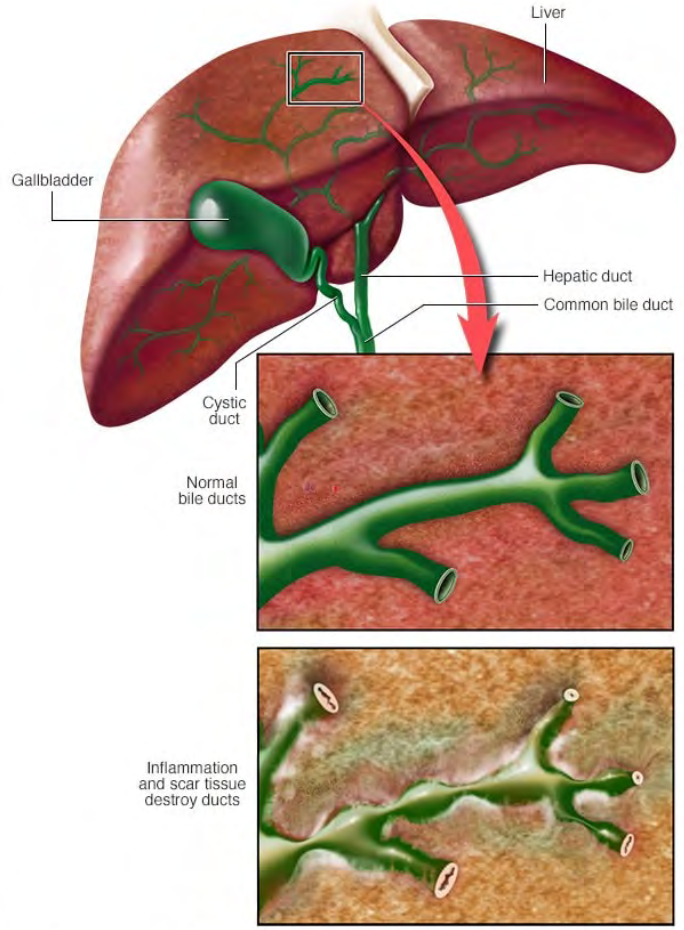
60-80% of people with PSC have IBD

Up to 8% of people with IBD have PSC

Etiology unclear – gut-liver axis*

Leading cause of M&M in IBD patients

- 30% of children require a LTx by 10 y post Dx
- Median LTx-free S in adults – 14 y
- **Up to 20% lifetime risk of colorectal cancer** (4x higher than UC) **and cholangiocarcinoma**
- No effective medical Rx



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Jiang X, Karlsen TH. Nature Reviews Gastroenterology & Hepatology 2017;14:279-295.

Lunder AK, et al. Gastroenterology 2016;151:660-669.e4; Deneau MR, et al. Hepatology 2017;66:518-527; Weismuller TJ, et al. Gastroenterology 2017;152:1975-1984.e8; Fung BM, et al. World Journal of Gastroenterology 2019;25:659-671.

PEDIATRIC PSC-IBD PHENOTYPE

Aim: To characterize the IBD phenotype in children with concomitant PSC

Design, setting & population:

- Single-centre retrospective cohort study – SickKids
- Children with PSC + colitis Dx 2000-2018 matched to 2 colitis controls (sex, DOB, IBD Dx date)

Analyses:

- Recorded data from each hospital encounter
- Mixed effects analysis, survival analysis, adjusting for covariates including time-dependent meds

Ricciuto A, et al. Clin Gastroenterol Hepatol 2020;18:1509-1517.e7.

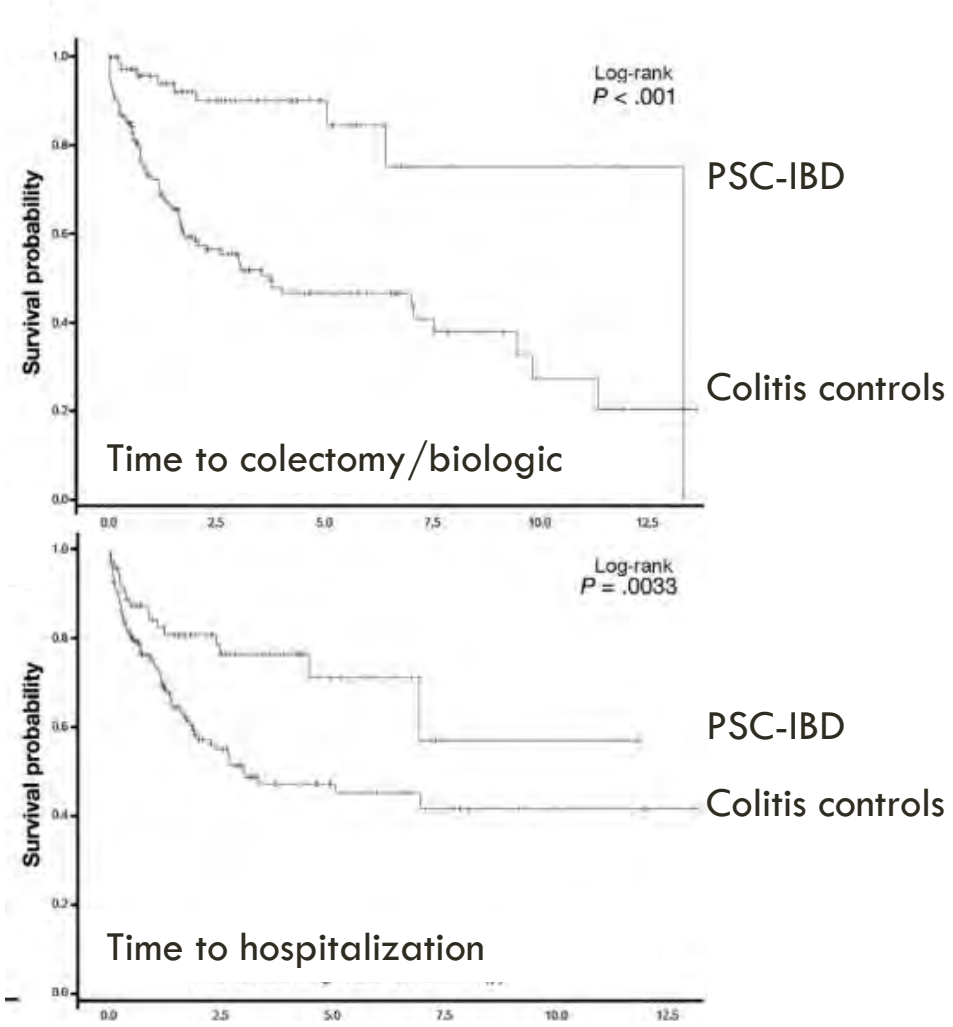
CHILDREN WITH PSC-IBD HAVE A UNIQUE MACROSCOPIC GUT PHENOTYPE

Median (IQR) or N (%)	PSC-IBD (N=74)	Colitis Controls (N=148)	P
Male	52 (70%)	104 (70%)	NS
Age at IBD Dx (y)	13.1 (10.6-15.1)	12.7 (9.9-14.8)	NS
Age at PSC Dx (y)	13.6 (11.3-15.4)	-	-
Relative Dx timing IBD/PSC concurrently IBD first PSC first	 45 (61%) 16 (22%) 13 (18%)	-	-
Backwash ileitis	34/52 (65%)	24/84 (28%)	**<0.001**
Rectal sparing	25/68 (37%)	22/145 (15%)	**<0.001**
Rt colon more inflamed	20/59 (34%)	8/118 (7%)	**<0.001**
Pancolitis (E4)	53/64 (83%)	75/121 (62%)	**0.004**

Confirmed histologically
Courtesy of R. Little

CHILDREN WITH PSC-IBD DISPLAY MILDER CLINICAL ACTIVITY

	Adjusted OR (95% CI) Clinical Remission	P
PSC	**2.94 (1.78-4.87)**	**<0.001**
Time (y)	1.52 (1.31-1.76)	<0.001
Age at IBD Dx (y)	1.06 (1.00-1.13)	0.039
Male	1.57 (0.95-1.59)	0.078
Endo severity (baseline)	1.12 (0.62-1.72)	0.41
Pancolitis	1.04 (0.62-1.72)	0.89
Current steroids	1.35 (1.06-1.71)	0.014
Current immunomodulator	1.56 (1.06-2.30)	0.025
Current biologic	1.89 (1.37-2.62)	<0.001



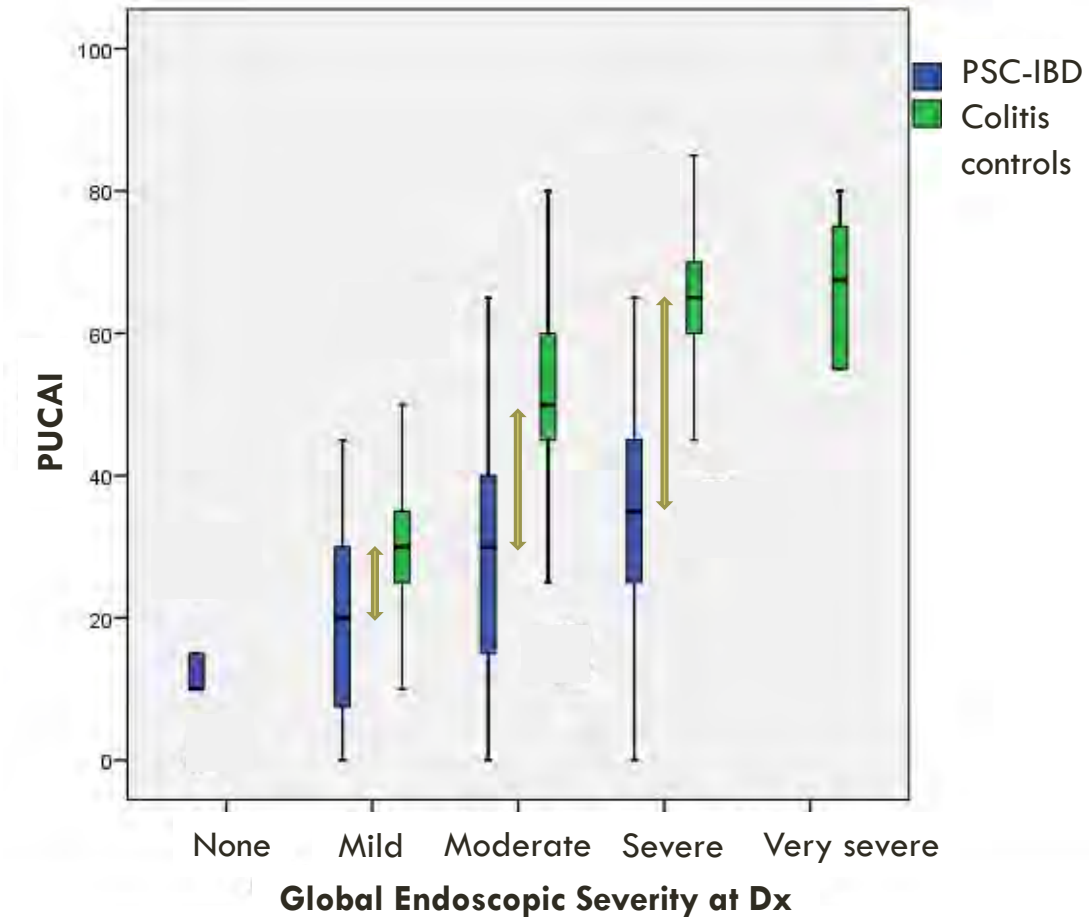
BUT CLINICAL ACTIVITY UNDERESTIMATES ENDOSCOPIC BURDEN IN PSC-IBD

Poor agreement between PUCAI and global endoscopic severity in PSC-IBD

Spearman Correlation	PSC-IBD	Colitis Controls
Dx	0.38	0.73
Over F/U	0.54	0.81

Among patients in clin remission, PSC-IBD patients less likely to be in endo remission:

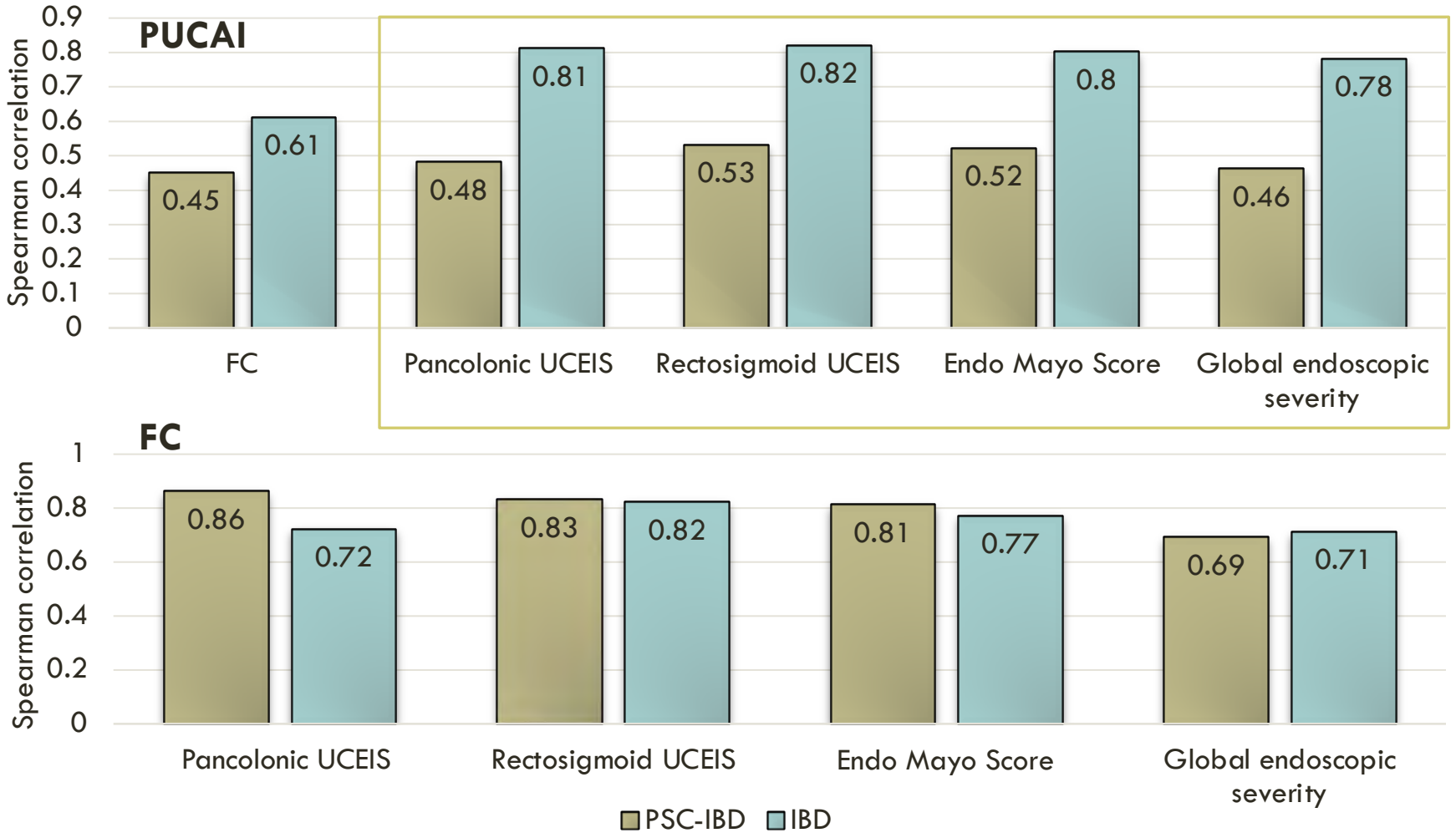
OR 0.44 (95% CI 0.20-0.96)



N=37 PSC-IBD; 47 colitis controls

PUCAI correlates **poorly** with endo activity in **PSC-IBD**; worse than colitis controls

FC correlates **well** with endo activity in **PSC-IBD**; just as well as colitis controls



Amongst patients in clin remission, PSC-IBD patients have more active endo disease:

Median (IQR)	PSC-IBD (N=20)	Colitis Controls (N=25)	P
UCEIS	2 (0-3)	0 (0-1.5)	**0.03**
Pancolonic UCEIS	1.2 (0.5-2.5)	0 (0-0.9)	**0.007**

Ricciuto A, et al. Clin Gastroenterol Hepatol 2018;16:1098-1105.e1; **Ricciuto A**, Carman N, et al. Am J Gastroenterol 2021;116:2052-2059.

FC OUTPERFORMS PUCAI AS A MARKER OF ENDOSCOPIC HEALING IN PSC-IBD

Optimal cut-point = 92 mcg/g

Sensitivity = 89%, specificity = 100%

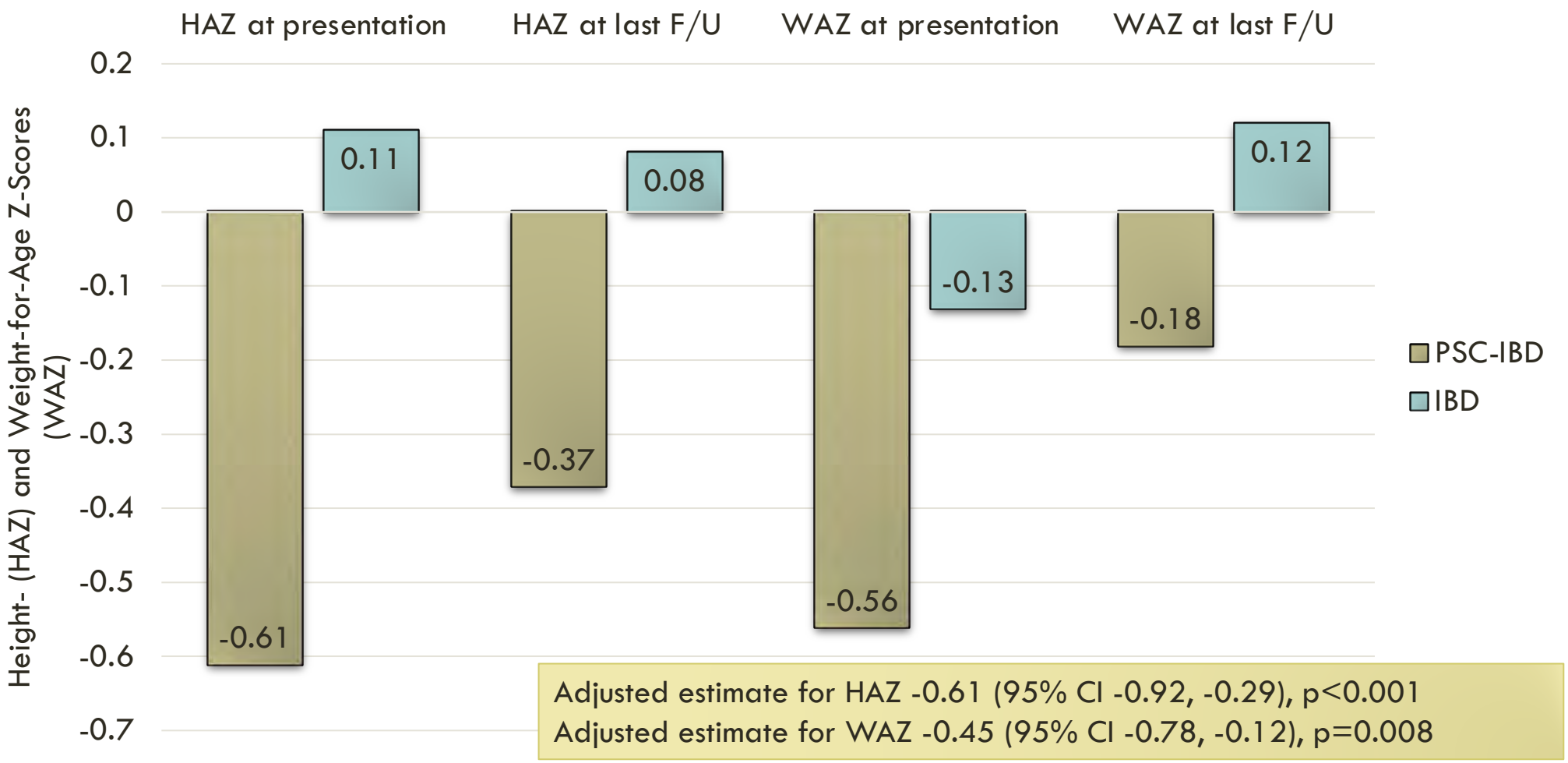
AUC:

FC = 0.93 (95% CI 0.82-1)

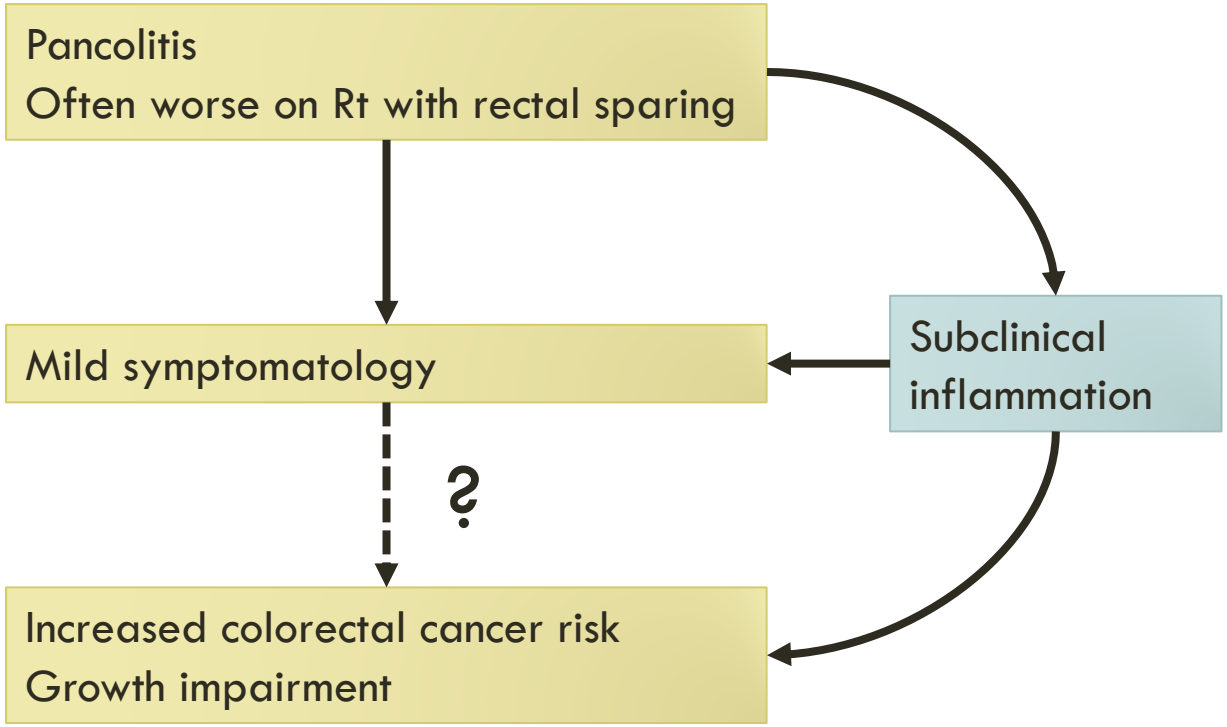
PUCAI = 0.56 (95% CI 0.30-0.81)

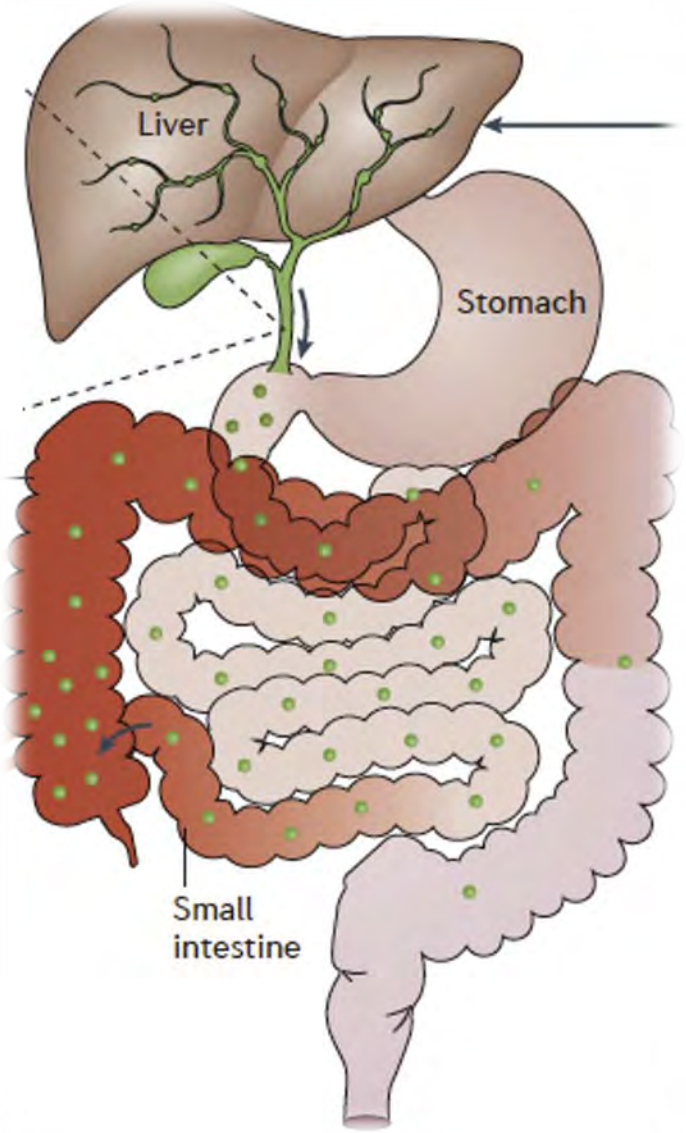
- P = 0.007

CHILDREN WITH PSC-IBD ARE SHORTER AND LOWER WEIGHT



PSC-IBD PHENOTYPE: PUTTING IT ALL TOGETHER





Jiang X, Karlsen TH. Nature Reviews Gastroenterology & Hepatology 2017;14:279-295.

VANCOMYCIN FOR PSC-IBD

Aim: To examine the clinical effectiveness of OVT for IBD in children with concomitant PSC

Design, Setting & Population:

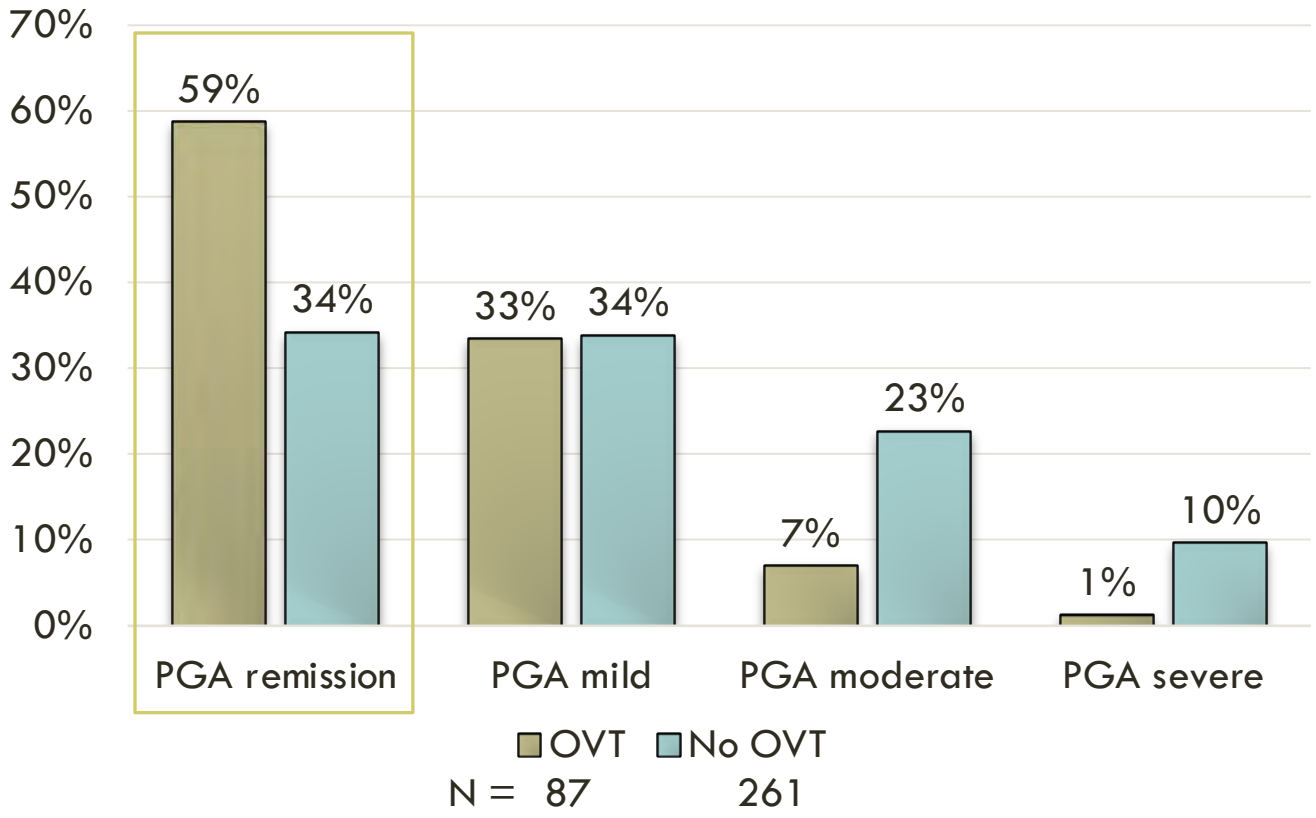
- Pediatric PSC Consortium – international retrospective registry – N = 1360
- Children with PSC + IBD, OVT x min 3 months

Analyses:

- IBD activity – PGA
- 3:1 untreated : treated cohort, matched on IBD duration at PGA assessment
- Multivariable logistic regression – 1ry outcome: clinical remission (PGA none) at 1 y
- Multivariable linear regression – 2ry outcome: labs at 1 y

Ricciuto A, Liu K, et al. Gastroenterology 2021;160:S-88-S-88. (Abstract)

OVT GROUP MORE LIKELY TO BE IN PGA CLINICAL REMISSION AT 1 YEAR



In multivariable linear regression, OVT associated with lower CRP (p=0.018) and higher albumin (p=0.008)

Variable	Adjusted OR (95% CI)	P
OVT	**2.72 (1.48-5.01)**	**0.001**
Age at IBD Dx (y)	0.99 (0.92-1.07)	0.80
Male	0.88 (0.46-1.69)	0.71
UC/IBD-U (vs. CD)	1.52 (0.70-3.31)	0.29
PGA at Dx		
None	Reference	
Mild	0.23 (0.04-1.42)	0.11
Moderate	0.24 (0.04-1.41)	0.12
Severe	0.29 (0.04-1.84)	0.19
Steroids (ever)	0.67 (0.34-1.31)	0.24
Anti-TNF (ever)	0.29 (0.10-0.82)	0.02
Steroids (at PGA)	1.10 (0.40-3.06)	0.85
Anti-TNF (at PGA)	1.75 (0.52-5.87)	0.37
Thiopurine (at PGA)	1.30 (0.62-2.76)	0.49
PSC-AIH overlap	0.69 (0.32-1.52)	0.36
GGT at PSC Dx	1.00 (0.998-1.001)	0.54
Ursodiol (ever)	0.76 (0.35-1.66)	0.49

ASCERTAINING POPULATION-BASED OUTCOMES IN PSC-IBD (COMING SOON!)

Aims:

- Derive/validate a case finding algorithm for PSC-IBD
- Delineate outcomes (surgery, cancer, death, LTx), health care usage in PSC-IBD vs. IBD-only
- Identify prognostic features and markers

Design, Setting & Population:

- Retrospective multi-centre study, pediatric/adult centres in ON, AB, MB, NS
- PSC-IBD Dx 2002-2017 identified locally -> linkage to HAD
- IBD-only identified from validated provincial HAD cohorts (e.g., OCCC)

CanGIEC (co-PIs: Eric Benchimol, Sanjay Murthy), **funding – CCC GIA**

PRECISION MEDICINE IN PEDIATRIC IBD

BIOMARK-IBD

Aim: To identify baseline biological and clinical predictors, and early markers of, IFX response in pediatric luminal IBD

Design, setting & population:

- Prospective multi-centre study (CIDsCaNN sites) -> children with colitis or (ileo)colonic CD initiating IFX

	Pre-IFX #1	Pre-IFX #2	Pre-IFX #3	Pre-IFX #4	6 months	12 months	Loss of response
Colonoscopy (central review) Bx – RNAseq, proteomics	X					X	
Serum – proteomics	X	X	X	X	X	X	X
Blood – RNAseq	X	X	X	X	X	X	X
Blood – DNA/WES	X						
Clinical assessment	X	X	X	X	X	X	X
Fecal calprotectin	X	X	X	X	X	X	X
Therapeutic drug monitoring			X	X	X	X	X

PROGRESS & PLANNED ANALYSES

48 enrolled, target = 75

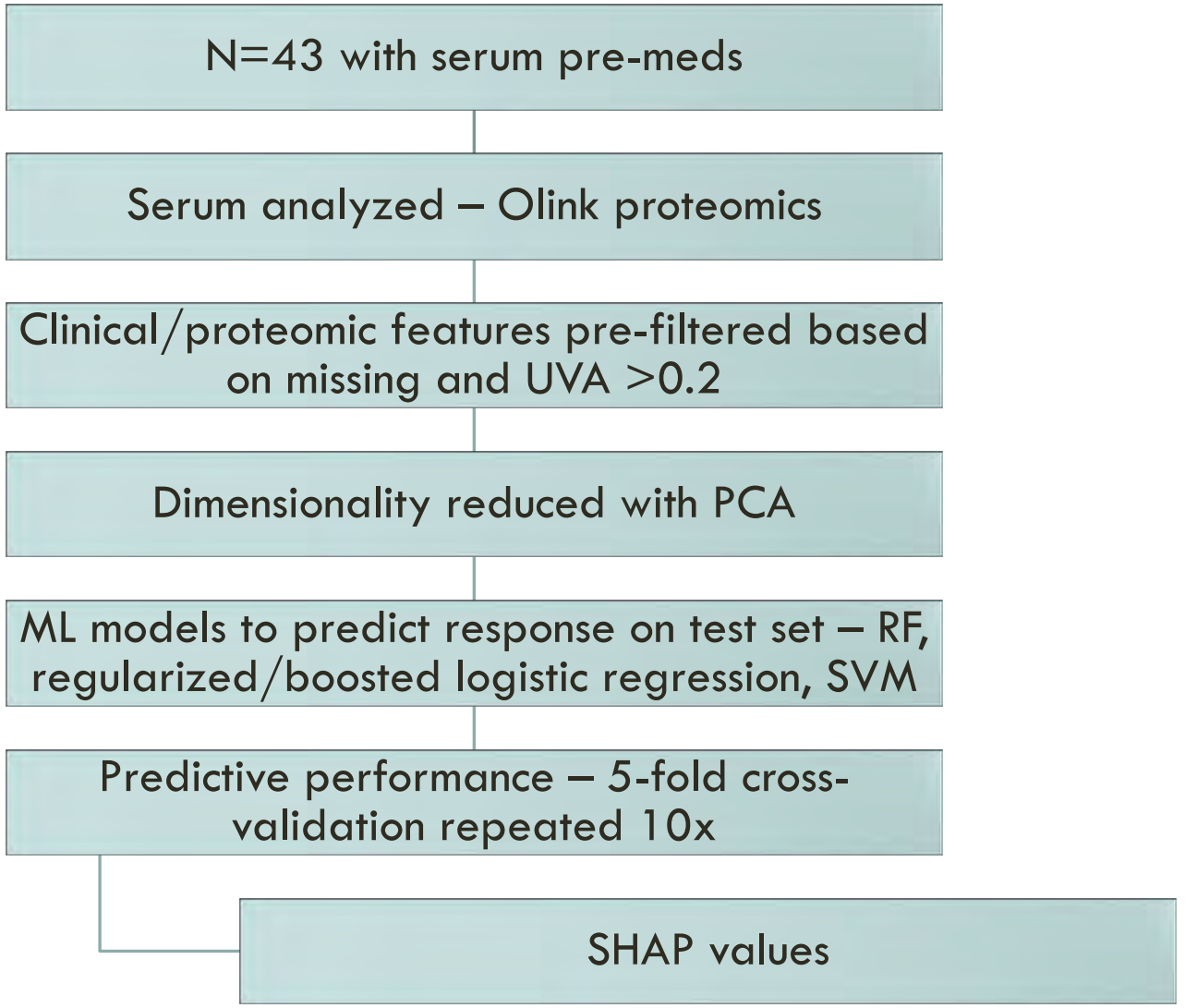
Planned analyses:

- Develop model using machine learning incorporating biological + clinical parameters to predict IFX response – collab with SickKids Centre for Computational Medicine
- Identify early changes/markers of response

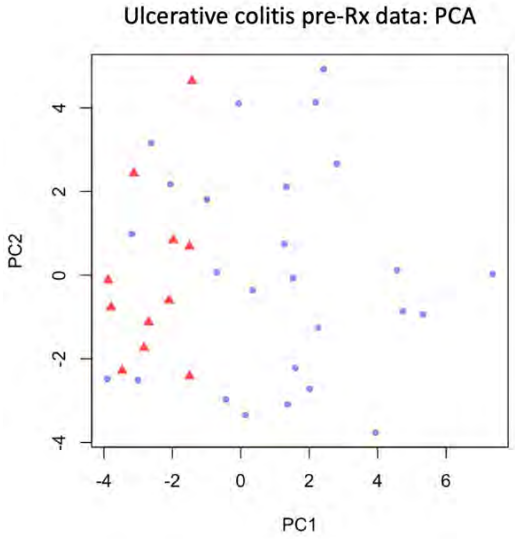
PILOT DATA: SERUM PROTEIN CYTOKINES TO PREDICT IFX RESPONSE IN PEDIATRIC UC

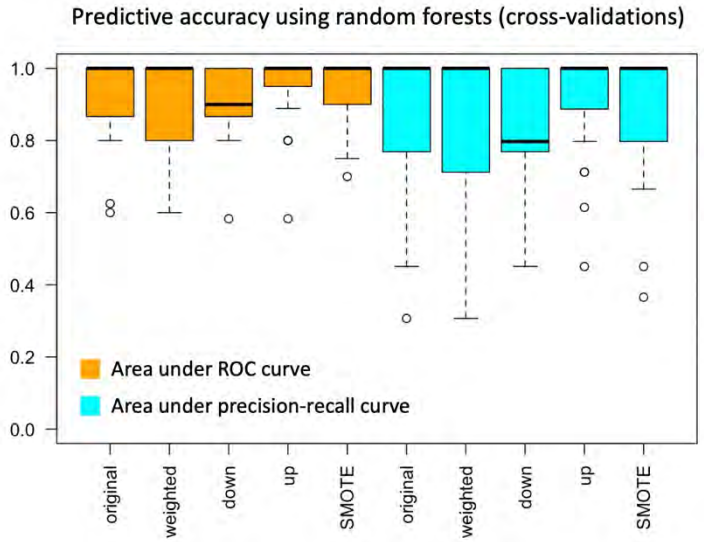
Median (IQR) or N (%)	Non-Responders (N=24)	Responders (N=48)	P
Age at IFX (y)	11.4 (9.3-15.0)	14.8 (12.9-16.2)	0.014
Male	46%	48%	0.87
PUCAI	55 (7.5-75)	48 (20-75)	0.83
Endo Mayo Score	2 (2-3)	2 (2-3)	0.41
Fecal calprotectin	1721 (1077-2924)	1801 (981-4716)	0.76
Steroid dependent	54%	33%	0.089
[IFX] pre-dose 3	**20.9 (9.1-28.8)**	**14.9 (13.0-23.5)**	**0.77**
[IFX] pre-dose 4	**12.4 (7.5-18.3)**	**12.2 (6.8-16.6)**	**0.83**

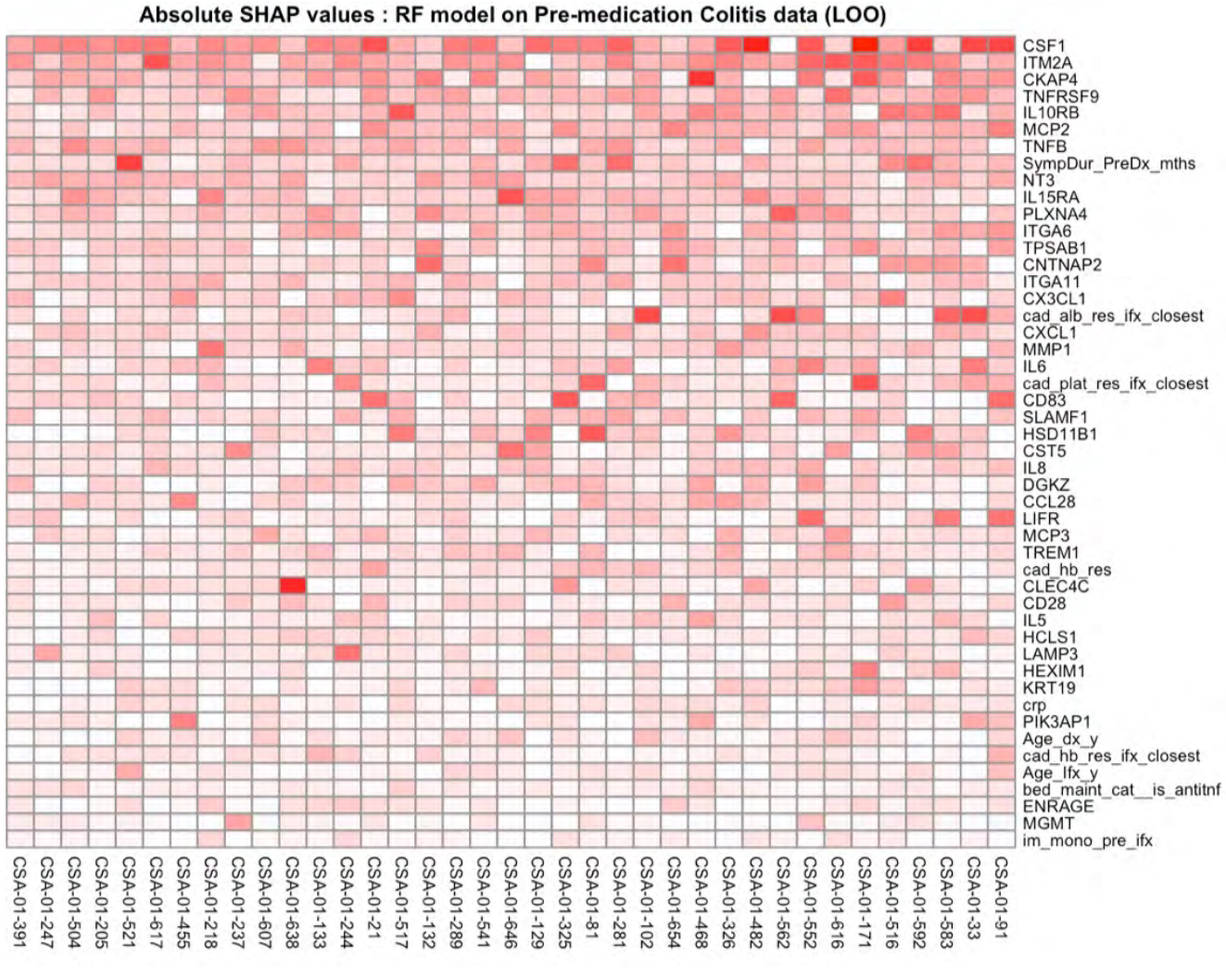
PREDICTIVE MODELS



PRELIMINARY RESULTS







TAKE-HOMES

PSC-IBD represents an important IBD population in need of additional attention/research

The emerging field of precision IBD holds great promise to improve treatment and outcomes for IBD patients

ACKNOWLEDGEMENTS

Crohn's and Colitis Canada

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