Clinical trials in pediatric IBD – Is there hope on the therapeutic horizon?

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Schulich MEDICINE & DENTISTRY

Western

Disclosures

I have the following financial relationships to disclose:

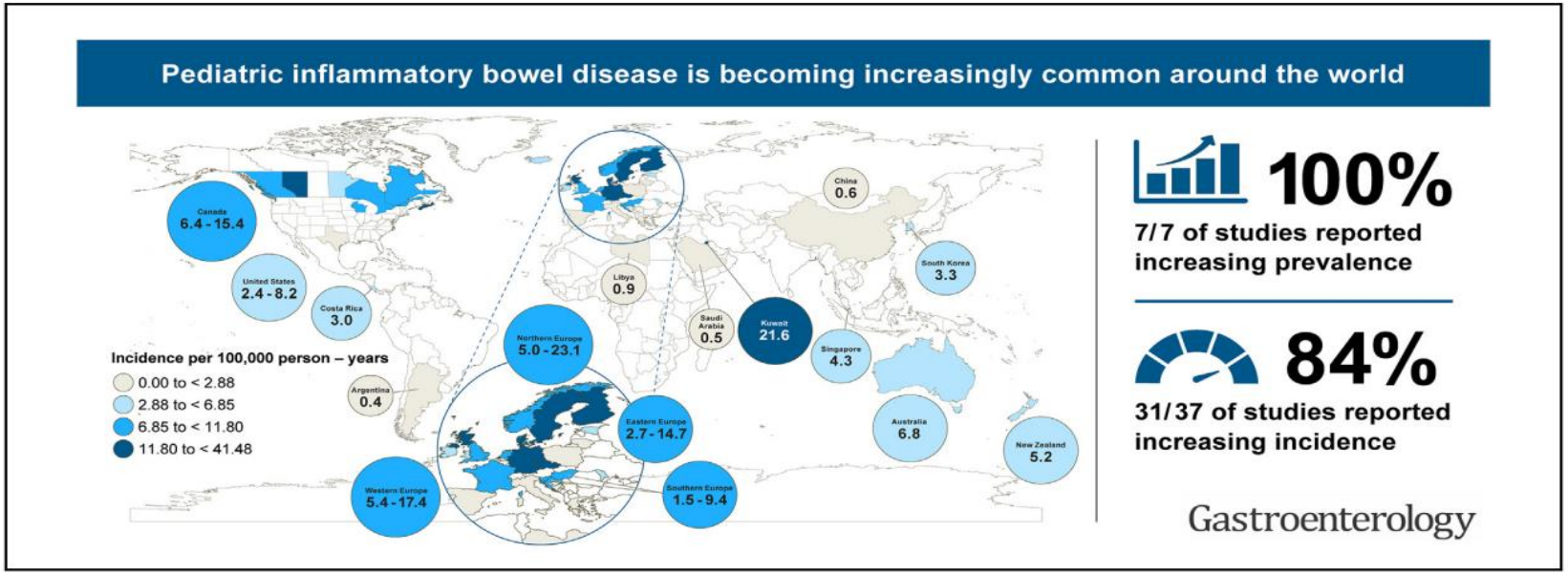
- Advisory board, consultant - Sanofi, Abbvie, Alimentiv Inc.
- Educational grant - Pfizer

Background

- Over **7000 children** under 18 years old living with IBD in Canada, and **600 to 650 young children** (under 16 years) diagnosed every year.
- By 2035, number of Canadians with IBD is expected to rise to **1.1% of the population**.
- Across Canada, the incidence rate in younger children is increasing by **7% per year**.
- Epidemiologic data suggest that the prevalence of childhood-onset IBD is increasing.

Kaplan et al, JCAG 2019; Coward et al. JCAG 2023;
Benchimol et al. Gastroenterology 2014; Am. J Gastroenterology 2017.

Background



Kuenzig, Benchimol et al. Gastroenterology, 2022

Objectives

Past

- 1. Explore efforts by regulatory agencies to facilitate drug approval in pediatric clinical trials.

Present

- 2. Understand the current landscape for clinical trials in the pediatric setting.

Future

- 3. Consider future directions to accelerate drug approvals in pediatric IBD (pIBD).

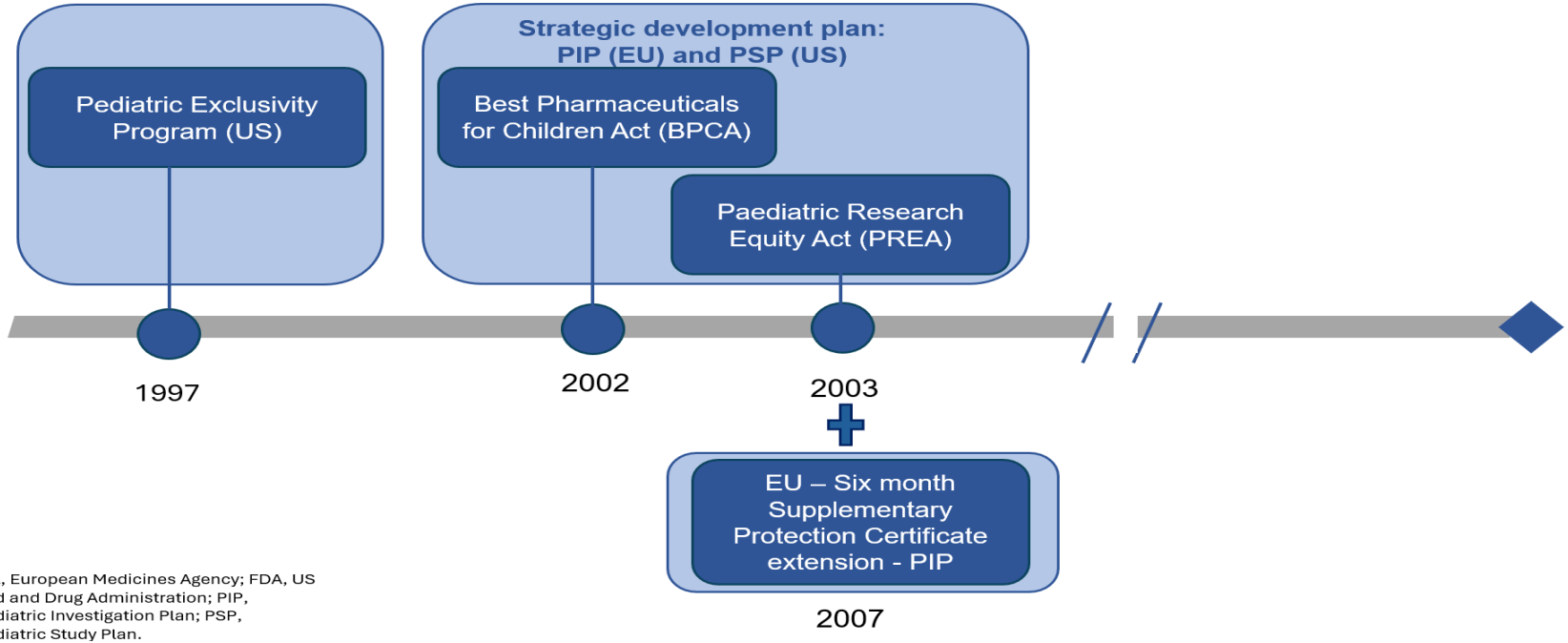
Past - What efforts have been made to facilitate drug approvals in pediatric patients?

Drug Approval Pathways for pIBD

- Children have a right to receive the **highest standards** of health care.
- The **European Medicines Agency (EMA)** and the **Food and Drug Administration (FDA)** are the 2 largest global regulators setting standards.
- Policies governing the development, approval, and reimbursement of medicines are, overall, designed for **adult populations**.
- **Efficient approaches** to drug development and inclusion of pediatric patients in clinical trials are critical to reduce the time between adult and pediatric drug approval.
- These delays lead to reduced access to new drugs and their extensive off-label use in children, often without clear guidance on dosing.

Gilpin et al. CMAJ May 16, 2022

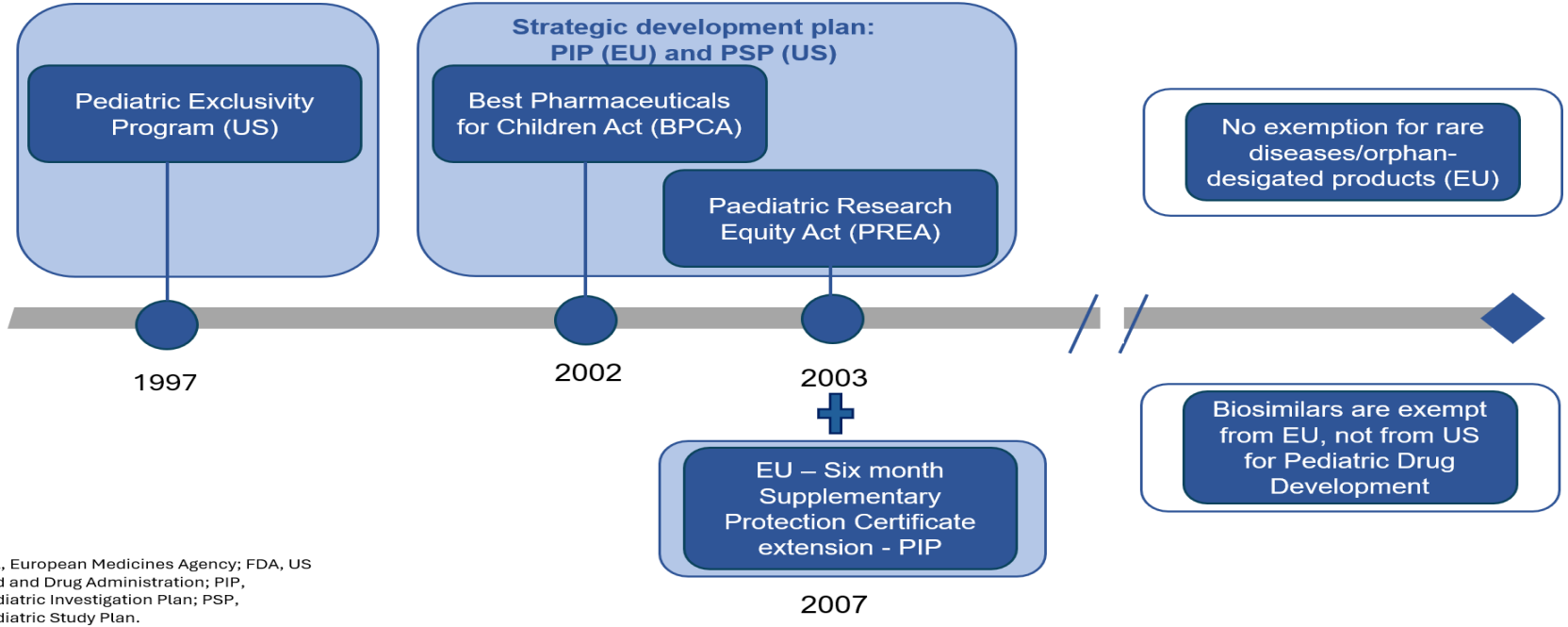
Impact of Drug Approval Pathways for pIBD



EMA, European Medicines Agency; FDA, US Food and Drug Administration; PIP, Paediatric Investigation Plan; PSP, Paediatric Study Plan.

Crowley E, Jairath V et al. JCC 2022

Impact of Drug Approval Pathways for pIBD



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Crowley E, Jairath V et al. JCC 2022

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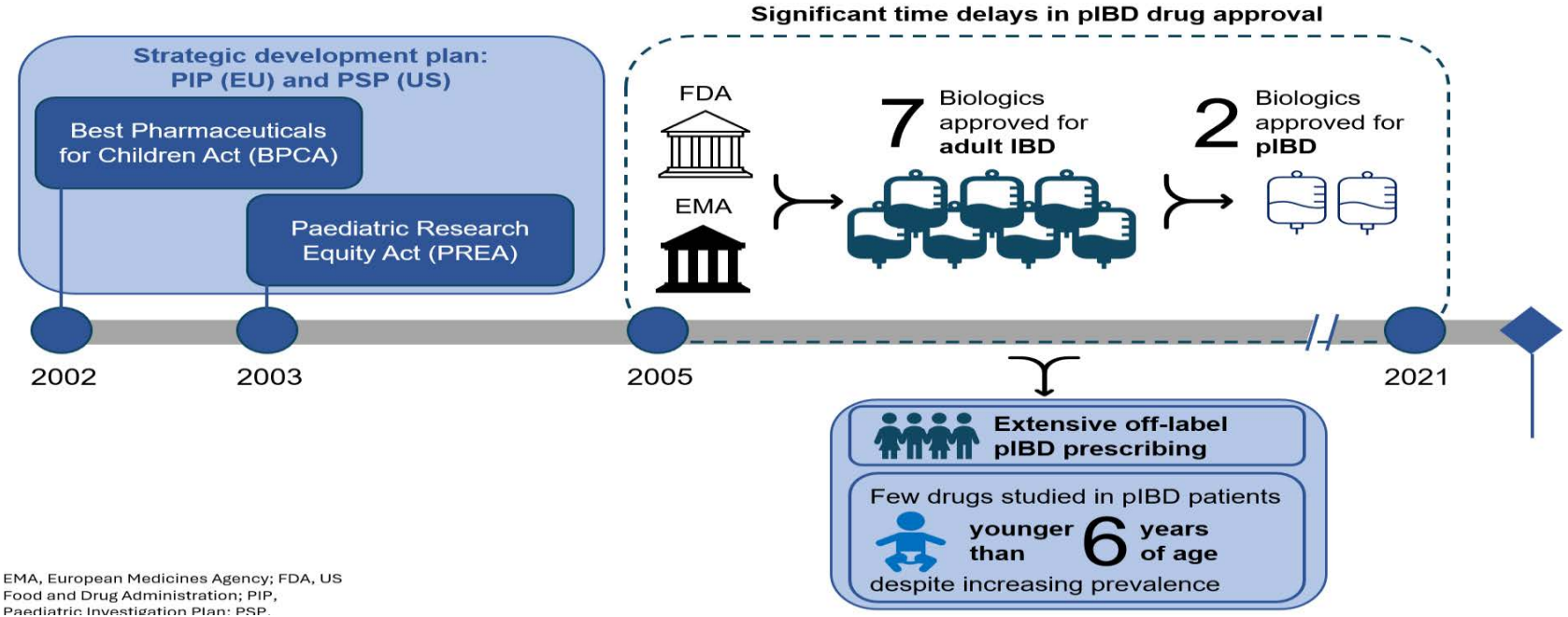

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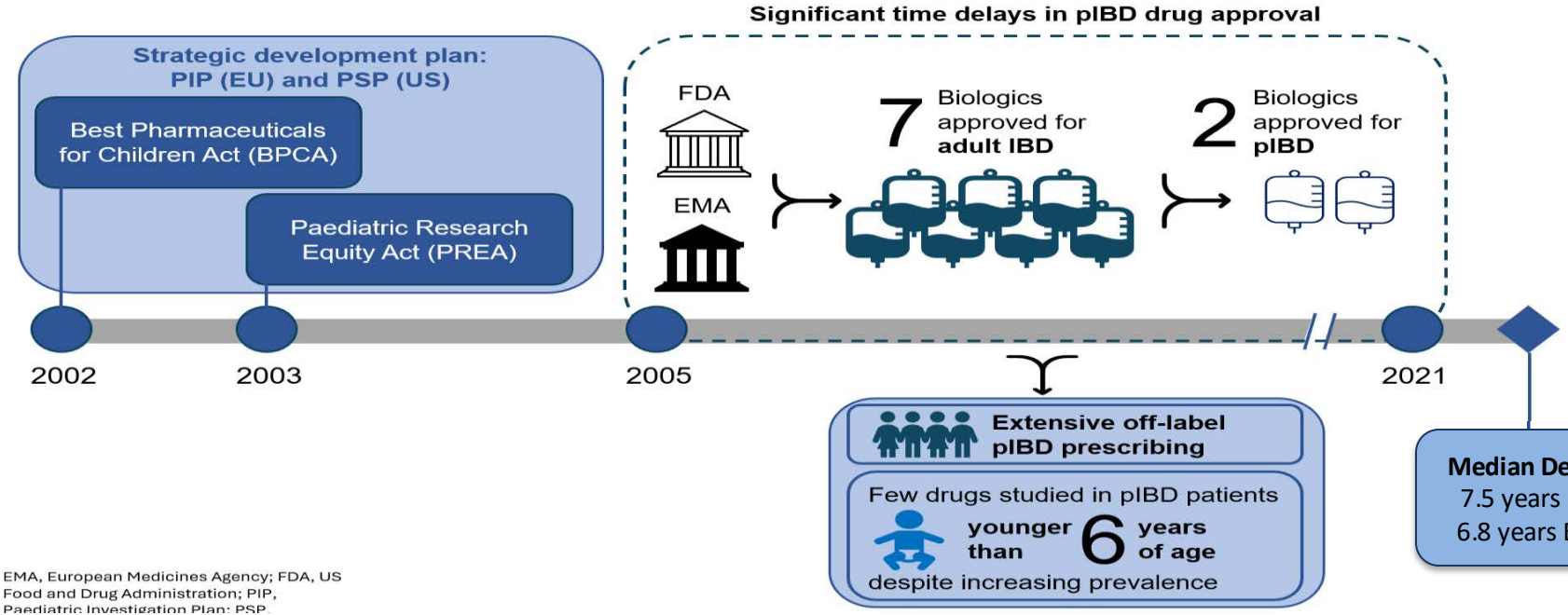


EMA, European Medicines Agency; FDA, US Food and Drug Administration; PIP, Paediatric Investigation Plan; PSP,

Crowley E, Jairath V et al. JCC 2022

PIBDnet commentary

- First consensus process of pediatric IBD experts on how to optimize clinical drug trial designs.
- Clinical drug trials are more difficult to perform in children. Barriers to enrollment include –
  - Long washout and screening periods
  - Use of placebo
  - Multiple study visits
  - Colonoscopies
  - Venipunctures
- Extrapolation from adult trials with PK/PD studies
- Attention to dosing studies for younger children (<30kg)
- Feasibility is a major criterion for a successful RCT

Turner, Griffiths, et al. Gut 2020

Outcome measures for clinical trials in pIBD

- **P-ECCO** committee established an international expert panel to determine the best outcomes measures in pIBD.
- Panel defined **steroid-free MH** as the primary outcome measure for all drugs of a new category.
- Trials could use pediatric-specific disease activity scores as primary outcome (PCDAI, PUCAI).
- Secondary outcomes should include safety, MRE assessment, inflammatory scores, fecal calprotectin, quality of life scales and a patient-reported outcome.


Outcome measures for clinical trials in paediatric IBD: an evidence-based, expert-driven practical statement paper of the paediatric ECCO committee

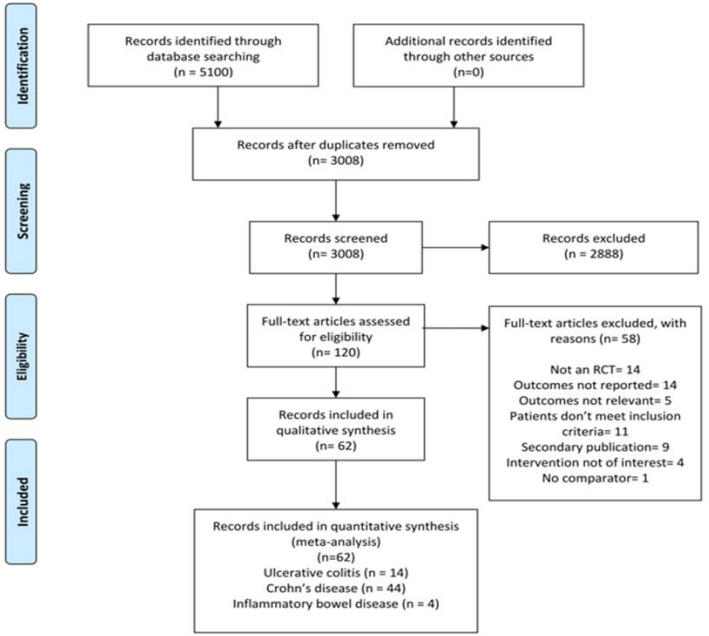
Frank M Ruemmele [1, 2, 3], Jeffrey S Hyams [4], Anthony Otley [5], Anne Griffiths [6], Kaija-Leena Kolho [7], Jorge Amil Dias [8], Arie Levine [9], Johanna C Escher [10], Jan Taminiau [11], Gabor Veres [12], Jean-Frederic Colombel [13], Séverine Vermeire [14], David C Wilson [15], Dan Turner [16]

Ruemmele F. et al. Gut 2014

Clinical Trial Endpoints

- Currently, the **regulatory guidance for IBD therapeutic agents does not include any pIBD indices.**

- We conducted a systematic review to summarize efficacy and safety endpoints that have been evaluated in pIBD randomized controlled trials (RCTs).



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement.* PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Crowley E., Jairath V. et al. Gastroenterology. 2022

Clinical Trial Endpoints

- ***Clinical efficacy outcomes and definitions***
  - There were **26 unique definitions** for clinical remission or response, 20 for CD and 6 for UC.
  - Most common definition of clinical remission:
    CD: PCDAI score ≤ 10; UC: PUCAI score ≤ 10
  - Thresholds for defining clinical response by PCDAI varied. Clinical response in UC was most commonly defined by a drop in PUCAI of ≥ 20.

- ***Other outcome measures:***
  - Patient reported outcomes (PRO) were reported in 13% of trials.
  - 16% of CD trials included endoscopic response, whereas 57% of UC trials reported the same.
  - Serum or fecal biomarkers were reported in 65% of maintenance trials and in 41% of induction + maintenance trials
  - 36 trials reported adverse events. Serious adverse events were reported in 24% of induction trials and 39% of maintenance trials.

- ***Considerable heterogeneity was identified in both outcome reporting and definitions of response and remission in RCTs of pIBD***

Crowley E., Jairath V. et al. Gastroenterology. 2022

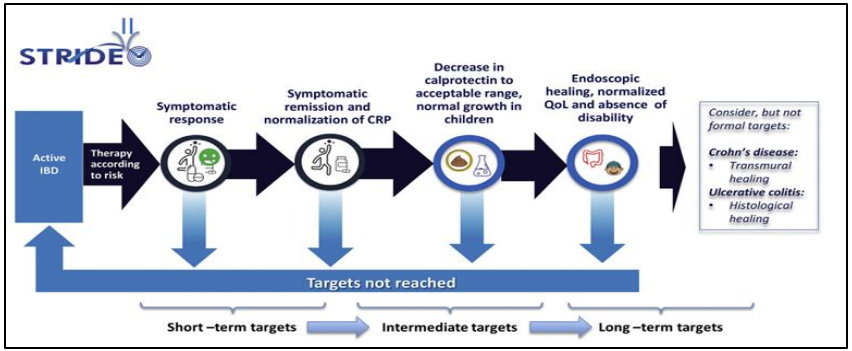
Future endpoints in pIBD

	Crohn's Disease		Ulcerative Colitis	
Clinical Trial	Short-term Induction	Long-term Maintenance	Short-term Induction	Long-term Maintenance
Disease activity endpoint	Steroid free clinical remission	Sustained steroid free remission	Steroid free clinical remission	Sustained steroid free remission
Clinical endpoint	•SFCResp – Drop >17.5 wPCDAI or >12.5 PCDAI. •SFCRem – PCDAI <10 or wPCDAI <12.5	PCDAI or wPCDAI remission measured at ≥2 timepoints.	•SFCResp – Drop ≥ 20 points PUCAI •SFCRem – PUCAI<10	PUCAI remission measured at ≥2 discrete timepoints.
Linear growth	n/a	Height velocity (cm/year)	n/a	Height velocity (cm/year)
Endoscopic endpoint	SES-CD (<3 points; >50% decrease) or CDEIS (<6;>50% decrease) MINI index in visits without endoscopy	SES-CD (<3 points; >50% decrease) or CDEIS (<6;>50% decrease) MINI index in visits without endoscopy	Mayo Endoscopic Subscores of 0-3 Remission subscore = 0	Mayo Endoscopic Subscores of 0-3 Remission subscore = 0
Composite – Disease activity + biomarker (where endoscopy is not possible)	Fecal calprotectin <200-300 + SFCRem - PCDAI <10 or wPCDAI <12.5	Fecal calprotectin <200-300 + SFCRem - PCDAI <10 or wPCDAI <12.5	Fecal calprotectin <200-300 + SFCRem - PUCAI<10	Fecal calprotectin <200-300 + SFCRem - PUCAI<10
Imaging endpoint	*IUS ^MRE - PICMI PEMPAC - pCD	*IUS ^MRE - PICMI PEMPAC - pCD	*IUS	*IUS
PRO	˚TUMMY-CD	˚TUMMY-CD	TUMMY-UC	TUMMY-UC
HRQOL	IMPACT-III	IMPACT-III	IMPACT-III	IMPACT-III

*Table adapted from PIBDNet guidance

To define these endpoints further…

- **STRIDE II** has stratified targets throughout the disease course, validated reliable indices are needed at each of these time points as the disease evolves.
- In 2005, Griffiths et al. conducted the first review that assessed the operating properties of existing disease activity indices in young patients with CD.



Turner D, Ricciuto A et al. Gastro 2021
Griffiths AM et al. IBD 2005
Colman R, Crowley E. et al. IBD 2024

Operating Properties of Disease Activity Indices in pIBD

- Operating Properties of pIBD clinical trial end points **vary widely**.

- Crohn's disease:
  - Pediatric Crohn's disease activity index (**PCDAI**) – varies widely in terms of validity and reliability, less feasible.
  - Mucosal Inflammation Noninvasive Index (**MINI**) – better operating properties than the PCDAI.
  - Simplified Endoscopic Mucosal Assessment (**SEMA**) of CD – more feasible with similar operating properties than the longer **SES-CD**.

- Ulcerative Colitis:
  - Pediatric Ulcerative Colitis Activity Index (**PUCAI**) – feasible, valid and reliable – but responsiveness needs to be evaluated further.

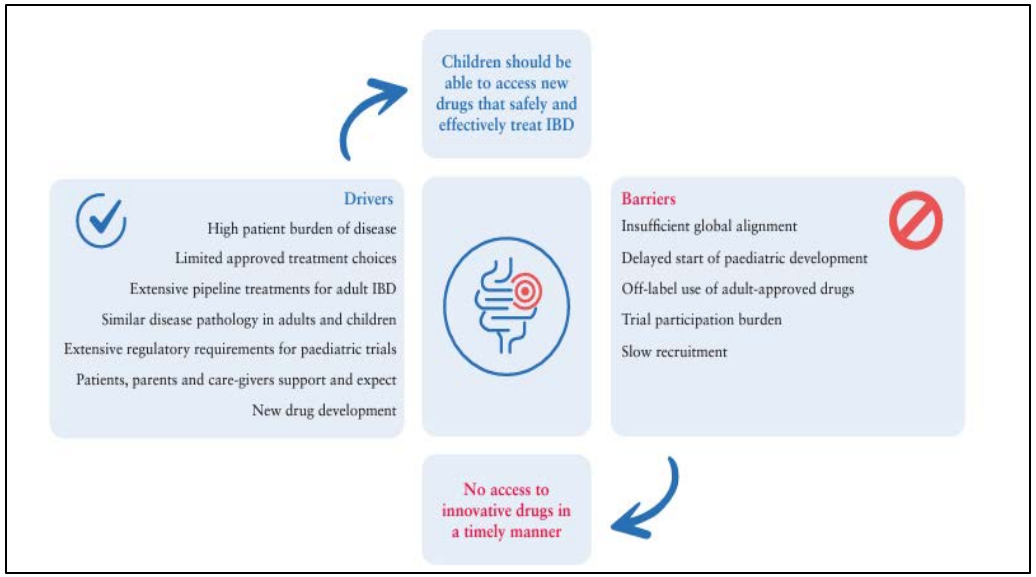
- Imaging and quality of life indices need further evaluation.

- Results highlight need for **further validation** of robust pediatric indices to accelerate the pediatric drug approval process for IBD

Colman R, Crowley E. et al. IBD 2024

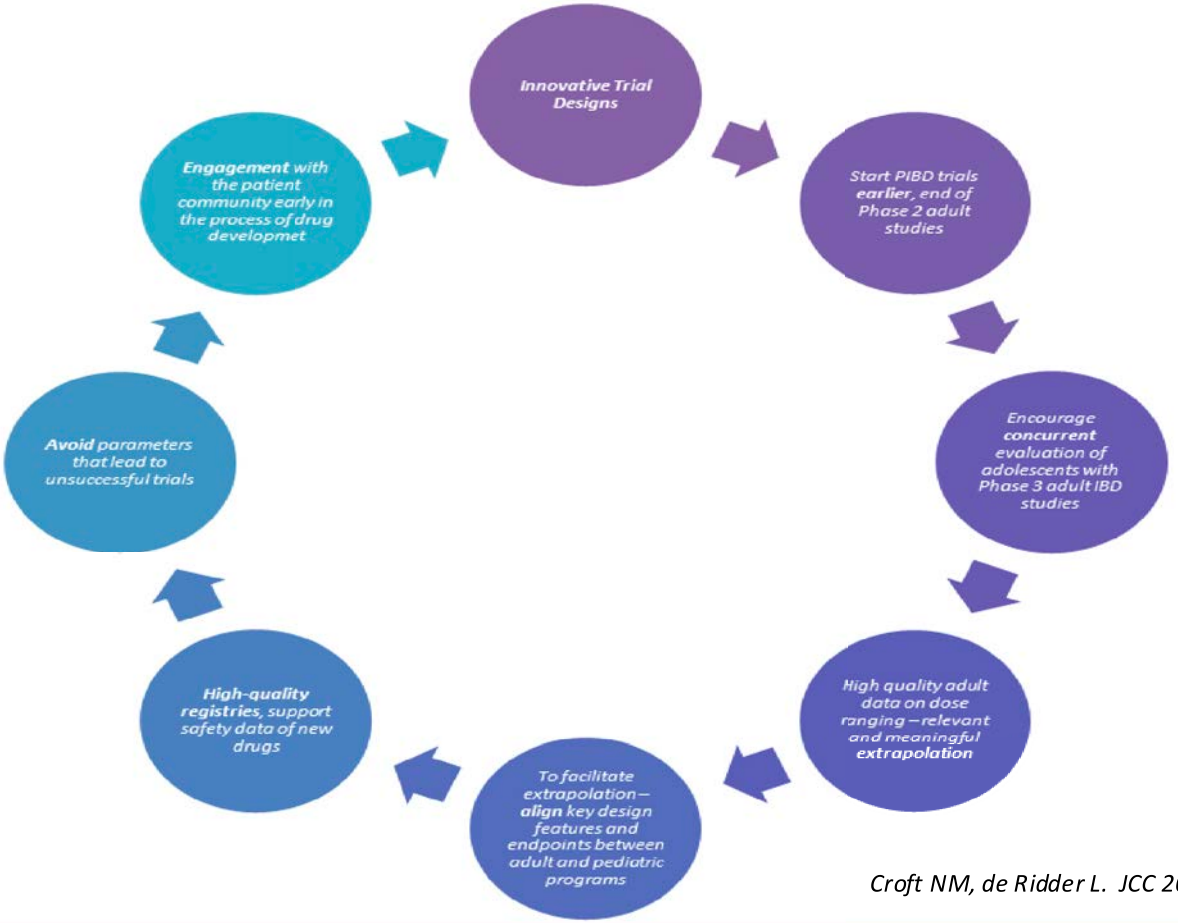
Present – Where do we stand?

Issues leading to delayed pediatric approvals of innovative drugs being developed for adults with IBD



Croft NM, de Ridder L. JCC 2023

Actions for accelerating development of new drugs for PIBD



Croft NM, de Ridder L. JCC 2023

FDA

Pediatric Inflammatory Bowel Disease: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-inflammatory-bowel-disease-developing-drugs-treatment

International pIBD Responses

1. **Efficacy Extrapolation:** "In general, the pathophysiology, disease characteristics, and response to treatment of UC or CD are sufficiently similar between adult and pediatric patients to support extrapolation of efficacy from adequate and well-controlled trials in adult subjects for the same indication".
2. **Early weaning of corticosteroids**.
3. **Shortening washout periods**, even if a previous failed biologic still has measurable blood levels of the drug. This will reduce risk for children from uncontrolled disease progression.
4. **Avoiding placebo arms**.
5. **Embracing Bayesian approaches** to analyses.

Hyams et al. IBD 2024
Wine E, de Bruyn J, Crowley E, Griffiths AM on behalf of CIDsCaNN. JCAG 2024
Turner D., Pediatric IBD Porto Group of ESPGHAN – accepted JPGN 2024.

International pIBD Responses

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- **Frequency of Ileocolonoscopies**: We oppose the requirement for three bowel cleanouts (AKA full ileocolonoscopies) in one year, particularly two within three months before and after induction, in both CD and UC.
- **Efficacy Extrapolation**: Given this, we should question the added value of full ileocolonoscopy post-induction in CD when non-invasive measures show general trends. In UC, the added benefit of a full ileocolonoscopy over a sigmoidoscopy is not established and the huge burden of three cleanouts on children outweighs the potential benefits.
- **Dosing Considerations**: Only fully effective doses should be tested, avoiding doses that are shown to be inferior in adults.

Hyams et al. IBD 2024
Wine E, de Bruyn J, Crowley E, Griffiths AM on behalf of CIDsCaNN. JCAG 2024
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International pIBD Responses

Recommendations

- **Full extrapolation of findings** from adult studies (focus on PK/PD & dosing in younger children).
- Use of **surrogate markers** – MINI index, fecal calprotectin, IUS, most especially post induction, would allow restriction of colonoscopy to baseline and end of study.
- Oppose the use of ‘half placebo’- avoid **suboptimal dosing** in children.

Hyams et al. IBD 2024
Wine E, de Bruyn J, Crowley E, Griffiths AM on behalf of CIDsCaNN. JCAG 2024
Turner D., Pediatric IBD Porto Group of ESPGHAN – accepted JPGN 2024.

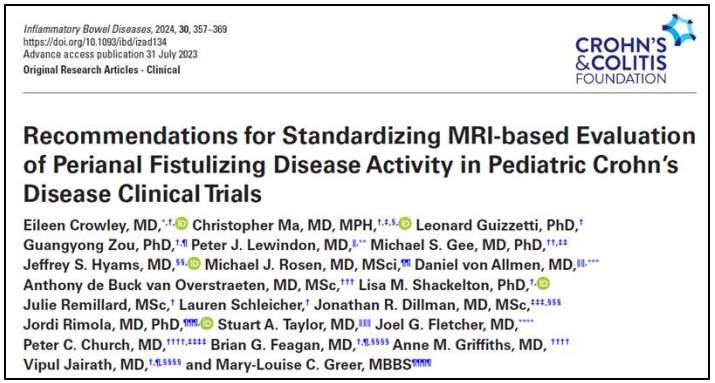
‘At risk’ phenotypes in pIBD

- Exclusion criteria often prevent those with distinct phenotypes of pIBD to enroll in clinical trials –

1. Pediatric Perianal Fistulizing Crohn’s Disease (pfCD)
2. Very early-onset IBD (VEO-IBD)
3. Immune Mediated Inflammatory Disease (IMID)

MRI-based evaluation of pfCD in clinical trials

- Canadian multicenter inception cohort study (CIDsCaNN), pfCD was present at diagnosis in 16% of CD.
- A validated imaging assessment tool for quantification of perianal disease severity needed to evaluate treatment response.
- We aimed to identify (MRI)-based measures of perianal fistulizing disease activity appropriate for pediatric patients.
- An international RAND panel (N=15) of gastroenterologists, radiologists, and surgeons rated statement appropriateness.


Inflammatory Bowel Diseases, 2024, 30, 357–369
https://doi.org/10.1093/ibd/izad134
Advance access publication 31 July 2023
Original Research Articles - Clinical

CROHN'S & COLITIS FOUNDATION

Recommendations for Standardizing MRI-based Evaluation of Perianal Fistulizing Disease Activity in Pediatric Crohn's Disease Clinical Trials

Eileen Crowley, MD, Christopher Ma, MD, MPH, Leonard Guizzetti, PhD, Guangyong Zou, PhD, Peter J. Lewindon, MD, Michael S. Gee, MD, PhD, Jeffrey S. Hyams, MD, Michael J. Rosen, MD, MSci, Daniel von Allmen, MD, Anthony de Buck van Overstraeten, MD, MSc, Lisa M. Shackelton, PhD, Julie Remillard, MSc, Lauren Schleicher, Jonathan R. Dillman, MD, MSc, Jordi Rimola, MD, PhD, Stuart A. Taylor, MD, Joel G. Fletcher, MD, Peter C. Church, MD, Brian G. Feagan, MD, Anne M. Griffiths, MD, Vipul Jairath, MD, and Mary-Louise C. Greer, MBBS

Crowley E, Greer MLC et al. IBD 2024

MRI-based evaluation of pfCD in clinical trials

- The modified Van-Asche Index (**mVAI**) and the Magnetic Resonance Novel Index for Fistula Imaging in CD (**MAGNIFI-CD**) were deemed appropriate disease activity indices for use in pediatric pfCD disease clinical trials.
- Although there was concern regarding the use of intravascular contrast material, its use was deemed appropriate in clinical trials.
- Appropriate trial inclusion criteria included a clinically evident fistula tract and radiologic disease defined as at least one fistula or abscess on pelvic MRI.
- A **co-primary clinical and radiologic endpoint** and inclusion of a patient-reported outcome were also considered appropriate.
- Efforts are ongoing to assess the reliability of these indices in a pediatric cohort with pfCD

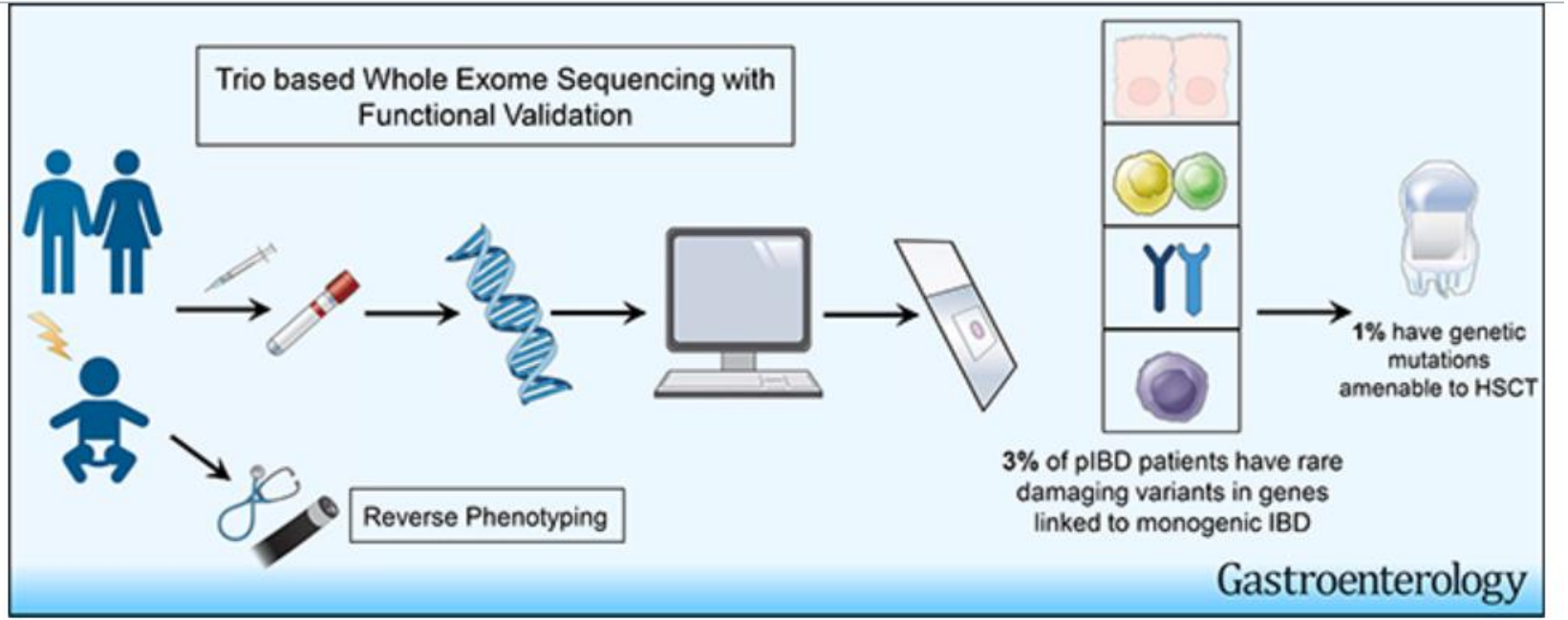
Crowley E, Greer MLC et al. IBD 2024

VEO-IBD

- Few drug studies are performed in children <6 years, despite the increasing incidence.
- International efforts to gather and report real world evidence on the efficacy and durability of medications.
- Data to support that traditional weight based dosing results in inadequate drug exposure in these younger children.
- Move towards Precision Medicine to help advance therapies in this space.

Keunzig ME, Benchimol E et al. Gastro 2022
Kerur B, Crowley E, Muise A, Benchimol E et al. JPGN 2022
Stallard L, Muise A, Ricciuto A et al. Gastro Hep 2024
Uhlig et al Gastroenterology 2014

Moving towards Precision Medicine in pIBD



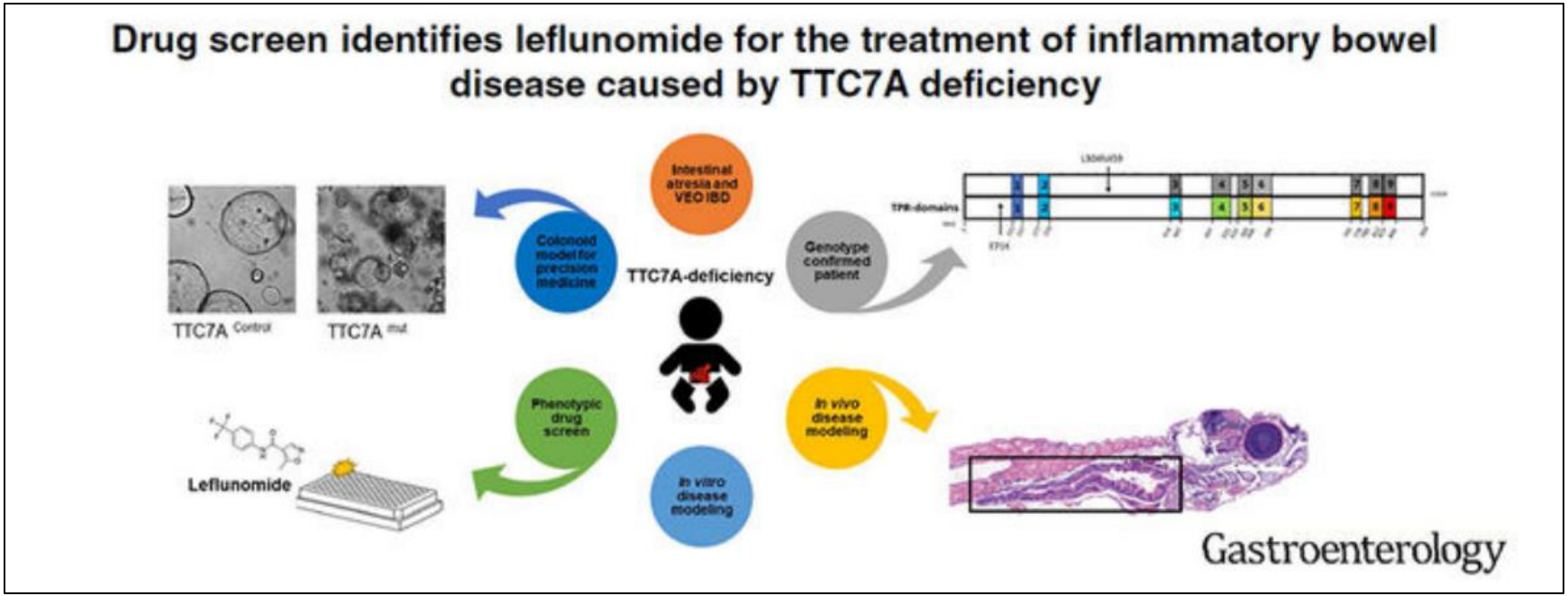
Crowley, Muise et al. Gastro 2020

Moving towards Precision Medicine in pIBD

Gene defect:	Potential therapeutic approach:	Contraindications to therapy:
IL10 & IL 10 receptor	HSCT likely curative	
FOXP3, IL2RA, CTLA4, MALT1.	HSCT likely curative	
XIAP	HSCT likely curative	
SH2D1A	HSCT likely curative	
DCLRE1C	HSCT likely curative	
ZAP70	HSCT likely curative	
WAS	HSCT likely curative	
CGD **CYBB, CYBA, NCF1, NCF2, NCF4**	HSCT likely curative Leukine antibiotics, IL1 receptor antagonist (Anakinra), possible use to bridge to HSCT or if HSCT not available	Anti-TNF contraindicated – increase risk of severe infections, maybe fatal
EPCAM		HSCT not helpful
TTC7A		HSCT not helpful
Mevalonate kinase deficiency, NLRC4 gene defects, IL-10 R deficiency	IL-1 targets	
NLRC4	IL-18, ILR inhibition	
LRBA deficiency	CTLA4 fusion protein – Abatacept, (possible use to bridge to HSCT).	
STAT1	HSCT or Janus kinase inhibitor Ruxolitinib.	

Crowley, Muise et al, Gastro Clinics 2018

Drug Discovery Workflow



Jardine, Muise et al. Gastroenterology 2020

Future – Is there hope on the therapeutic horizon?

Novel therapeutics in pIBD

The therapeutic landscape for IBD has advanced considerably over the past two decades.

However, only one advanced therapy class is approved for children with IBD.

Long delays exist following adult approval, with a median delay of over seven years to pediatric approval.

We conducted a cross-sectional review to identify investigational therapeutic agents treatment of pIBD.

Gupte D, Crowley E et al. Unpublished data

Novel therapeutics in pIBD

116 completed trials included in the review

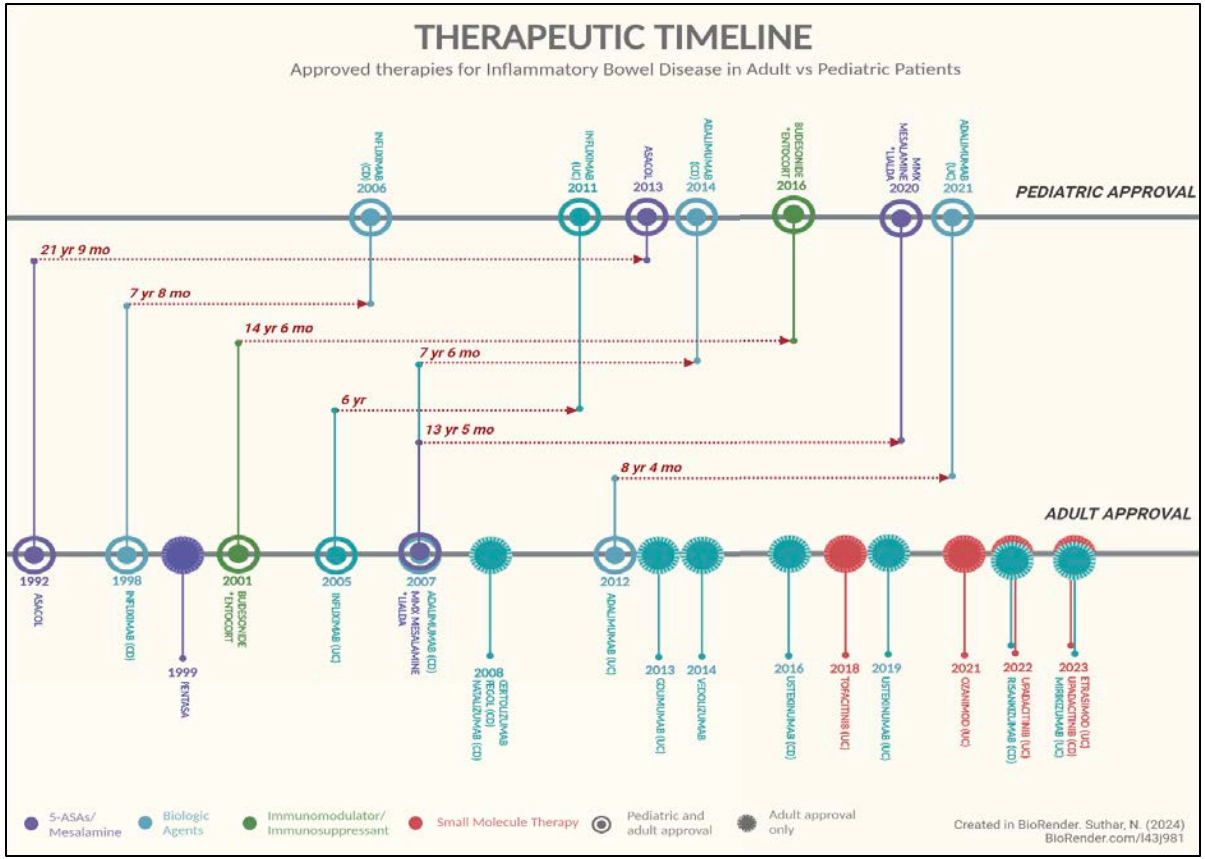
- 34 studies focused on biologic agents (29%)
- Novel small molecule agents - 7 studies (6%)

118 IBD trials are actively recruiting pediatric patients.

- 17 trials are exploring the use of approved biologic agents in children
- 34 trials are focusing on novel oral small molecule agents

Gupte D, Crowley E et al. Unpublished data

FDA Approved therapies for IBD in Adult versus Paediatric Patients



Gupte D, Ma C, Feagan B, Jairath V, Crowley et al. Unpublished data

Pharmacoequity in pIBD

Efforts to hasten approvals paramount to ensure **timely access** to effective medications.

Consideration for **innovative trial designs** and **collaboration** between research networks.

Adopting a **multi-omic approach** to those with distinct phenotypes, to identify therapeutic targets.

Continued **engagement** with regulatory bodies and the international pIBD community offers a **critical opportunity** to advance drug approvals in children with IBD.

Acknowledgements

Mentors
- Aleixo Muise
- Anne Griffiths
- Vip Jairath
- Brian Feagan

IBD Clinical Team
- Melanie Watson
- Kevin Bax
- Ashok Dhandapani
- Chris Medeiros

IBD Research Team
- Nidhi Rashmikant Suthar
- Lindsey McLeish
- Julia Sawicka

VEO-IBD team
- Ashley Geerlinks
- Maha Saleh
- Sam Colaiacovo

Precision Medicine team
- Richard Kim
- Aze Wilson

IMID team
- Andreanne Zizzo
- Roberta Berard
- Sarah Wells

CIDsCaNN
- Eytan Wine
- Jennifer de Bruyn
- Eric Benchimol

*On behalf of the Network

Muise Lab
- Neil Warner
- Karoline Fiedler
- Karen Frost
- Jie Pan
- Sasha Jardine

Brudno Lab
- Sam Khalouei
- Justin Foong
- Arun Ramani
- Michael Brudno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