Controversies in perianal fistulizing Crohn's disease

Debunking the myths

Jeffrey McCurdy MD PhD FRCPC
Assistant Professor of Medicine
University of Ottawa

Disclosures

Advisory board honorarium:
AbbVie, Amgen, Celltrion, Eli Lilly, Ferring, Fresenius Kabi, J&J, Pendopharm, Merck, Pfizer and Takeda

Speaker honorarium:
AbbVie, J&J, Ferring, Pfizer

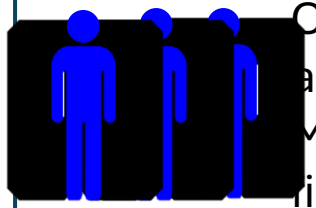
Objectives

- How to screen for PFCD?
- How to determine cause of isolated perianal fistulas?
- Is combine medical and surgical therapy required?
- Are non-anti-TNF therapies effective?
- Is assessing for healing clinically sufficient?

Controversy 1:

Is a clinical exam sufficient to rule out PFCD?

Subclinical PFCD in patients with CD



Consecutive Korean adults undergoing MRE for CD w/out fistula clinically

37/290 [13%] with PFCD → Symptomatic PFCD aHR, 3.45 [95% CI, 0.70-17]

Consecutive children with new diagnosis of CD (2018-2023)

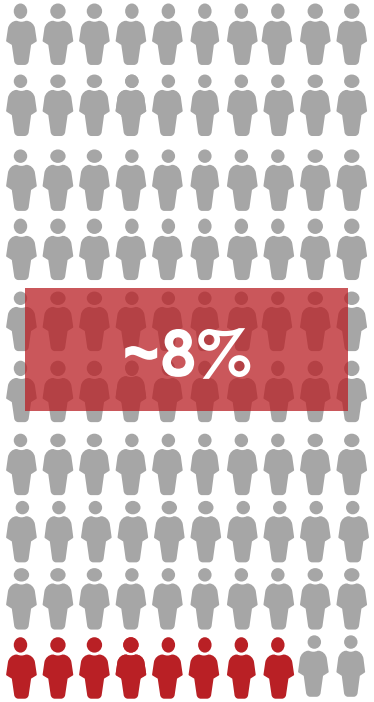
17/86 [20%] with PFCD → Perianal surgery HR 1.40 [95% CI 1.18-1.68]

Hwa Kim et al., CGH 2020
Antanya and Hudson et al., AJG 2025

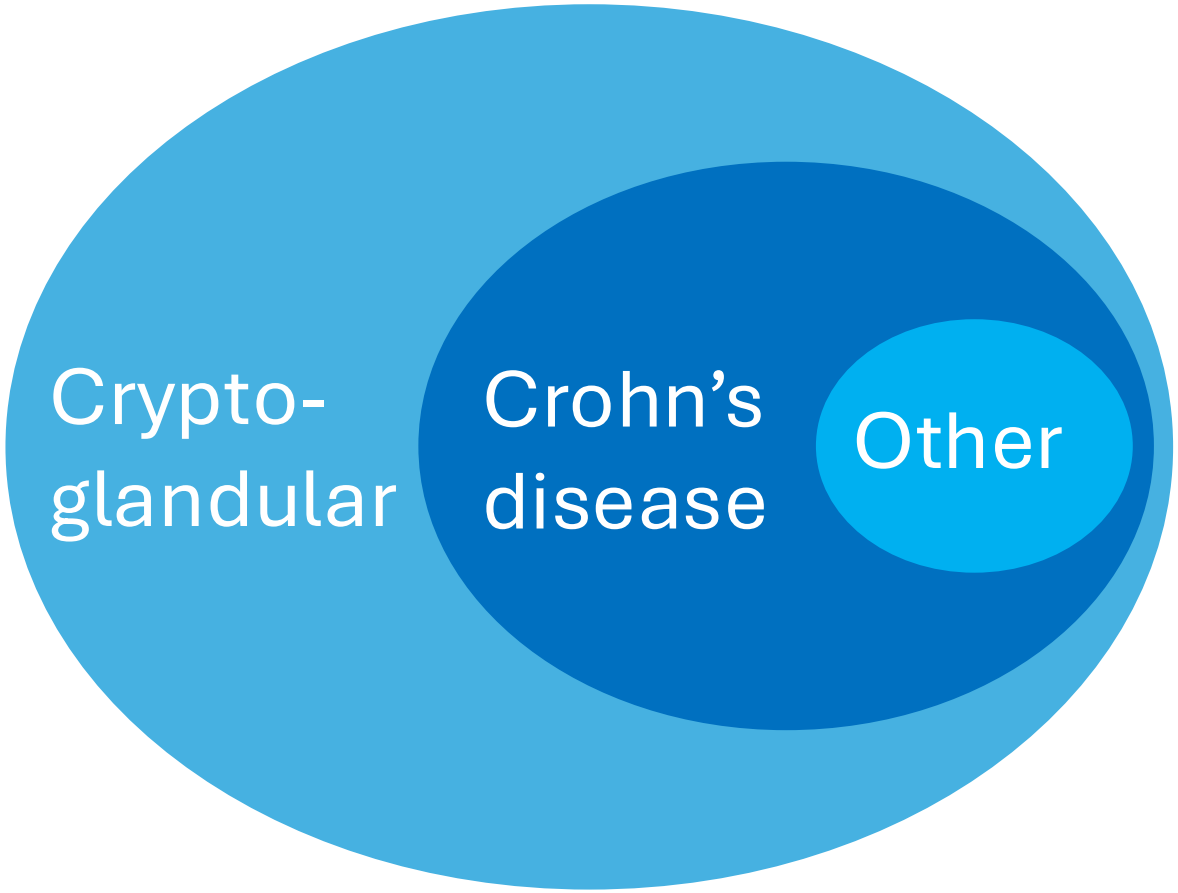
Controversy 2:

Does PFCD require the presence of luminal inflammation?

Isolated perianal fistulas:



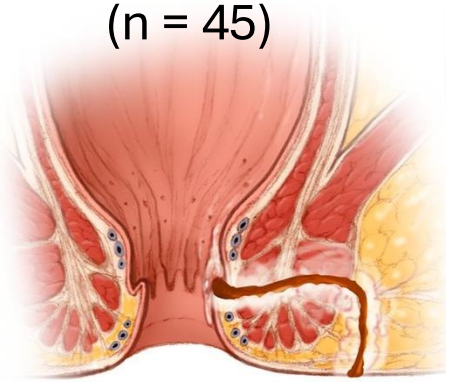
Proportion of patients with PF as their first manifestation of CD



Tsai et al., IBDJ, 2022

VCE for isolated perianal fistulas

Isolated PAF
(n = 45)



Capsule positive
n = 12 (26%)

Matched Controls
(n = 90)

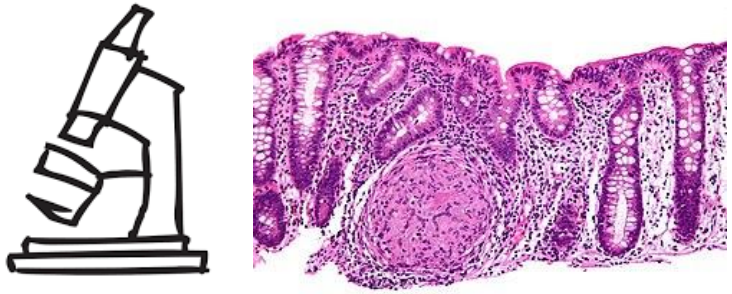
Capsule positive
n = 3 (3%)

McCurdy, et al., JCC 2023

TopClass criteria for isolated PFCD

Independent Criteria

(A)



(B)

Composite Criteria (score ≥ 5)

Major: (scores 3)

- Complex anatomy
- Family history IBD
- Confirmed EIM/orofacial granulomatosis

Minor: (scores 1)

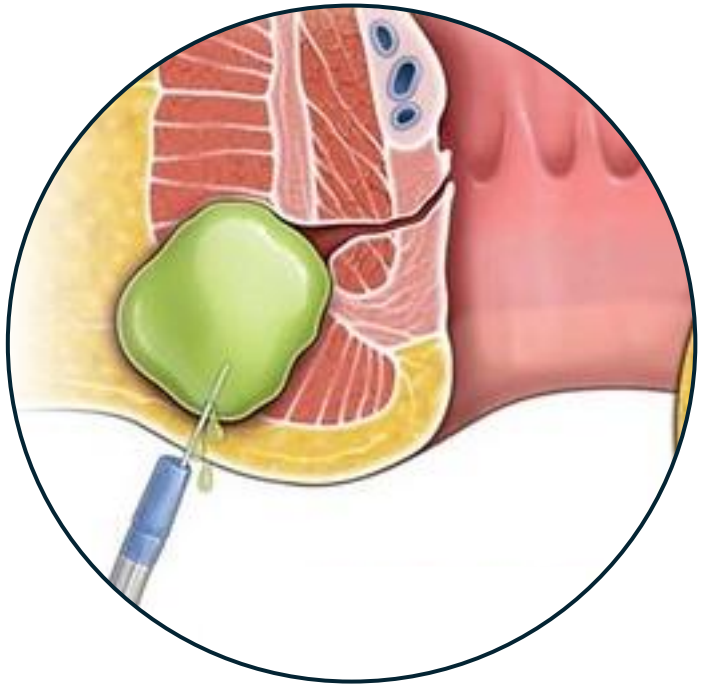
- Potential EIM
- Suspected genital CD
- Coexisting HS
- Recurrence following repair

Hanna, et al. Lancet Gastro Hep 2025

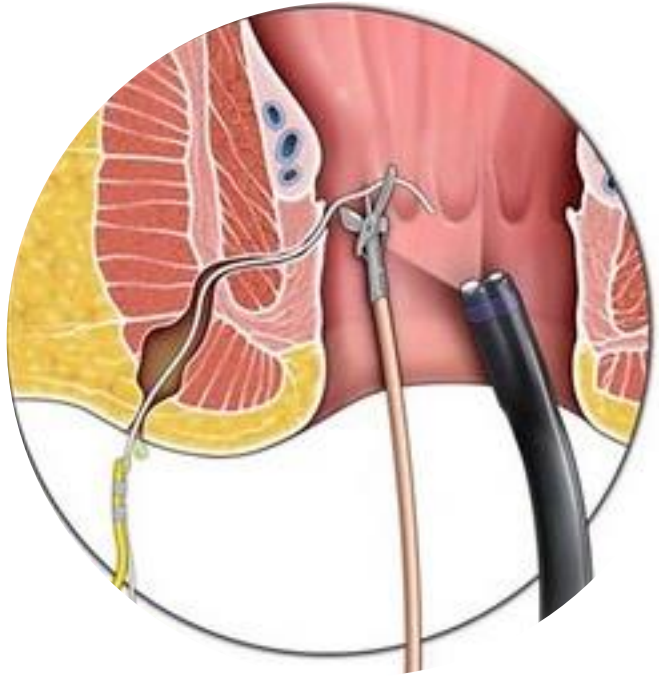
Controversy 3:

EUA + setons are required for all patients with PFCD?

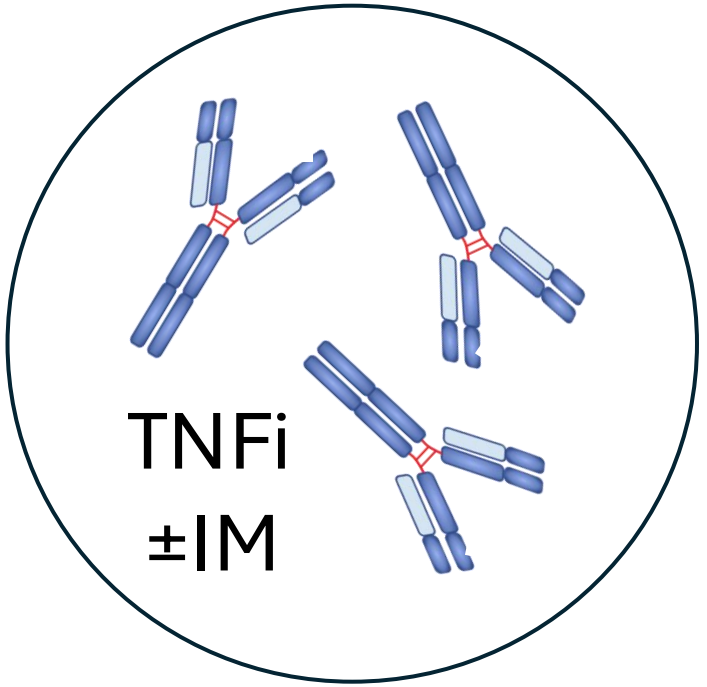
EUA+/- drainage



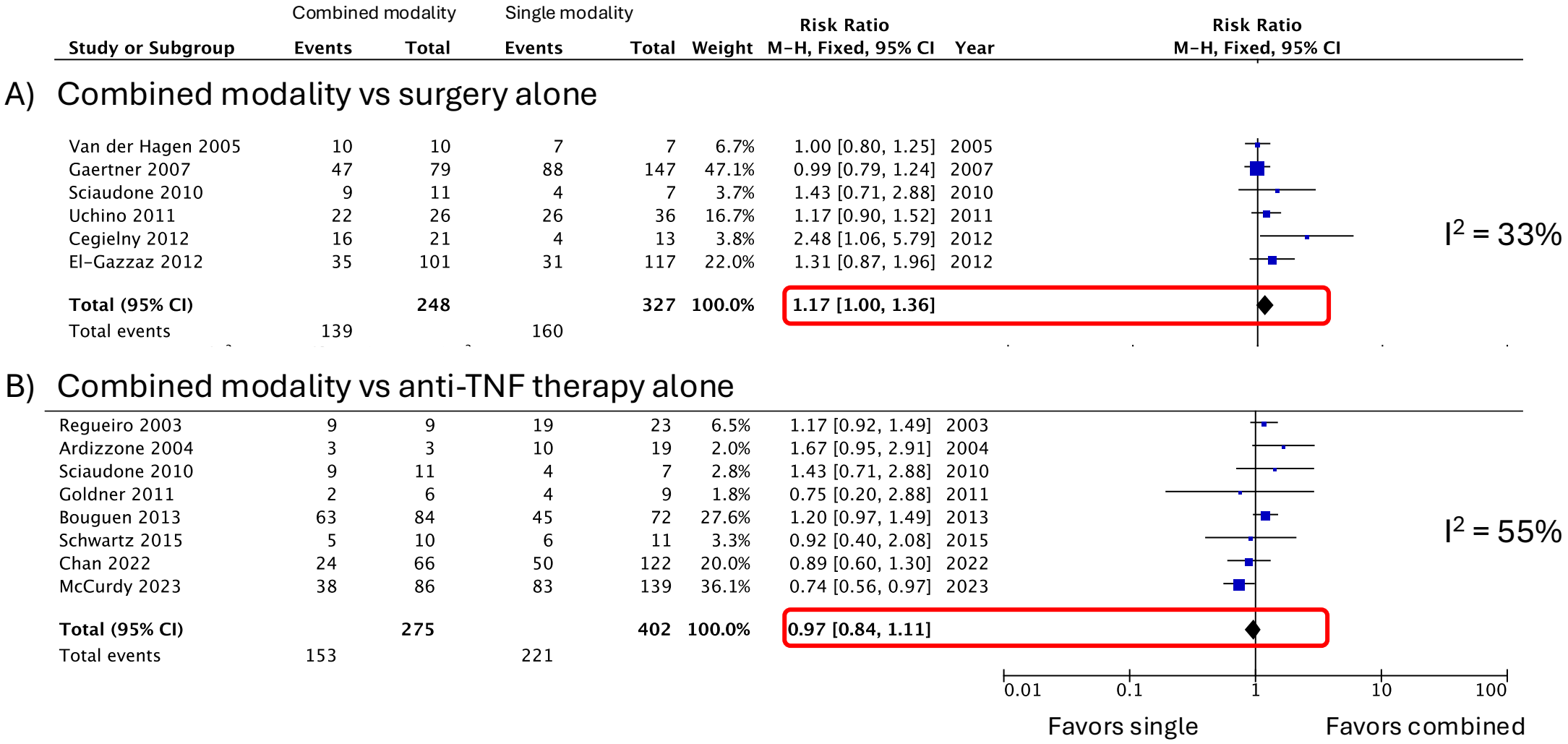
Seton placement



Medical therapy



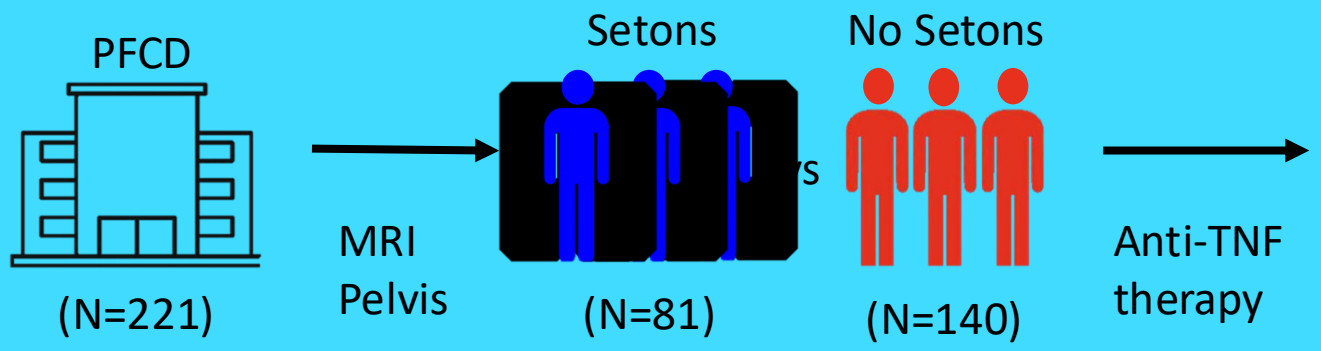
Does combined therapy improve remission?



Fung et al., JCC 2024

Impact of setons on perianal fistula outcomes

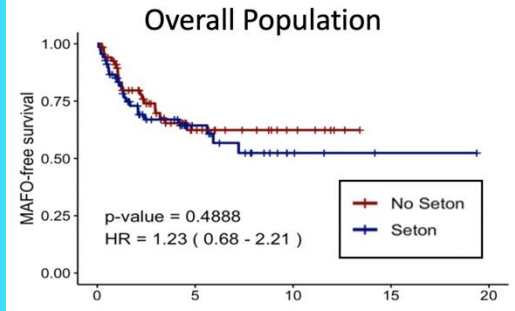
Multicenter, retrospective observational study

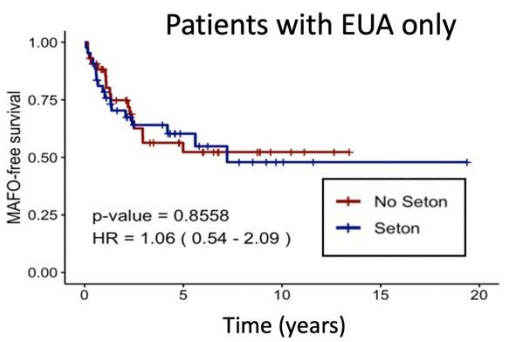


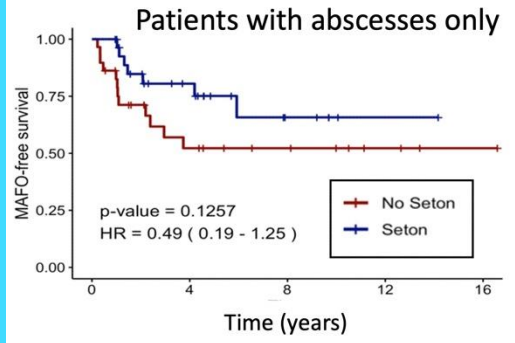
Population
PFCD (n=221) from 6 NA centers
Pre-treatment MRI pelvis
Treated with first anti-TNF therapy

Methods
Seton vs no seton groups balanced by cardinality matching and IPTW based on clinical, treatment and MRI characteristics

Impact of setons on major adverse fistula outcomes (MAFO)*







Impact of setons on fistula remission

Month	OR (95% CI), p value
3	0.74 (0.37-1.49), p=0.41
6	0.81 (0.41-1.59), p=0.54
12	0.63 (0.31-1.27), p=0.20

***composite of EUA, hospitalization or fecal diversion for PFCD**

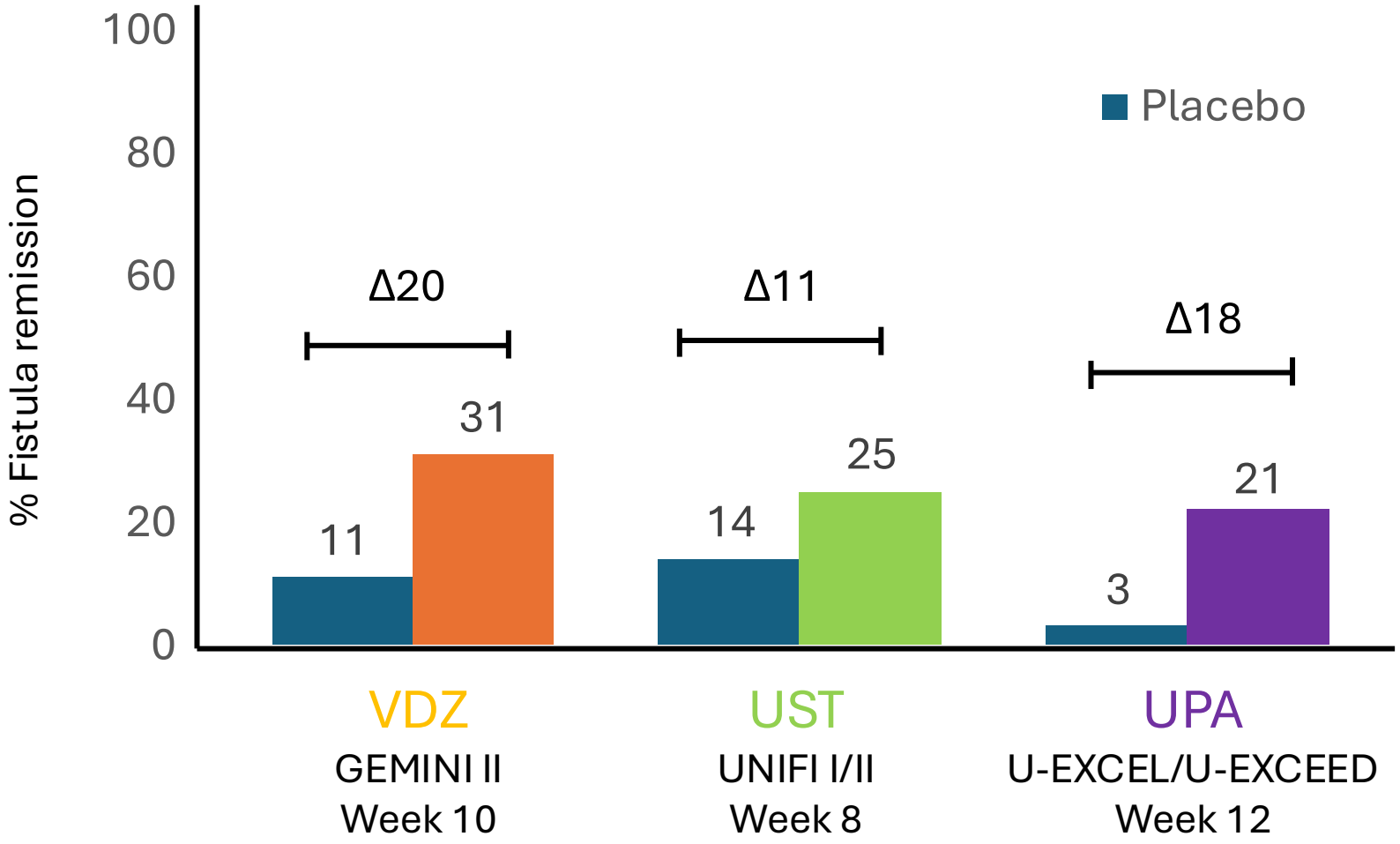
McCurdy, et al. *Aliment. Pharmacol. Ther.*

AP&T

Controversy 4:

Is anti-TNF the only effective medical therapy for PFCD?

Post-hoc analyses of advanced therapies



Sands DDW 2017
Sandborn NEJM 2013
Colombel DDW 2023

DIVERGENCE-II Trial (Filgotinib)

-91% Complex
-65% anti-TNF IR

PFCD (n=57)

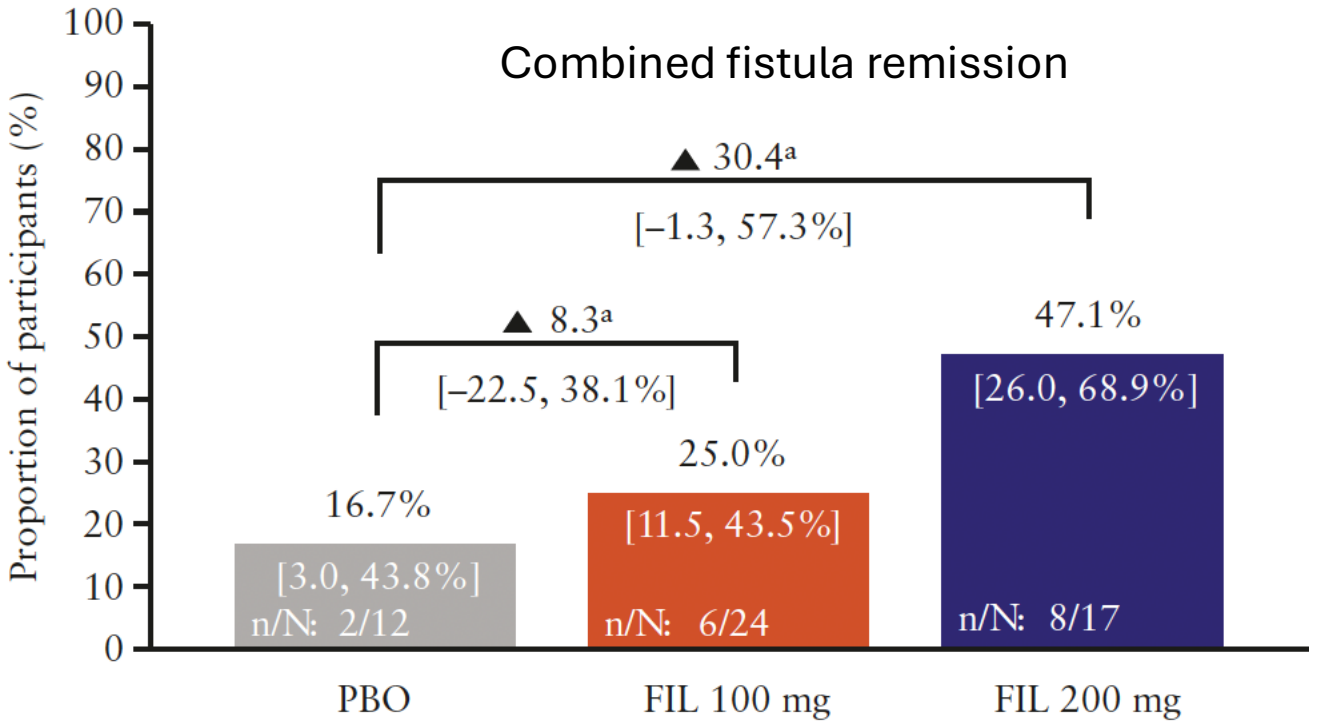
Setons removed -14d

Placebo (n=15)

Filgo 100 (n=25)

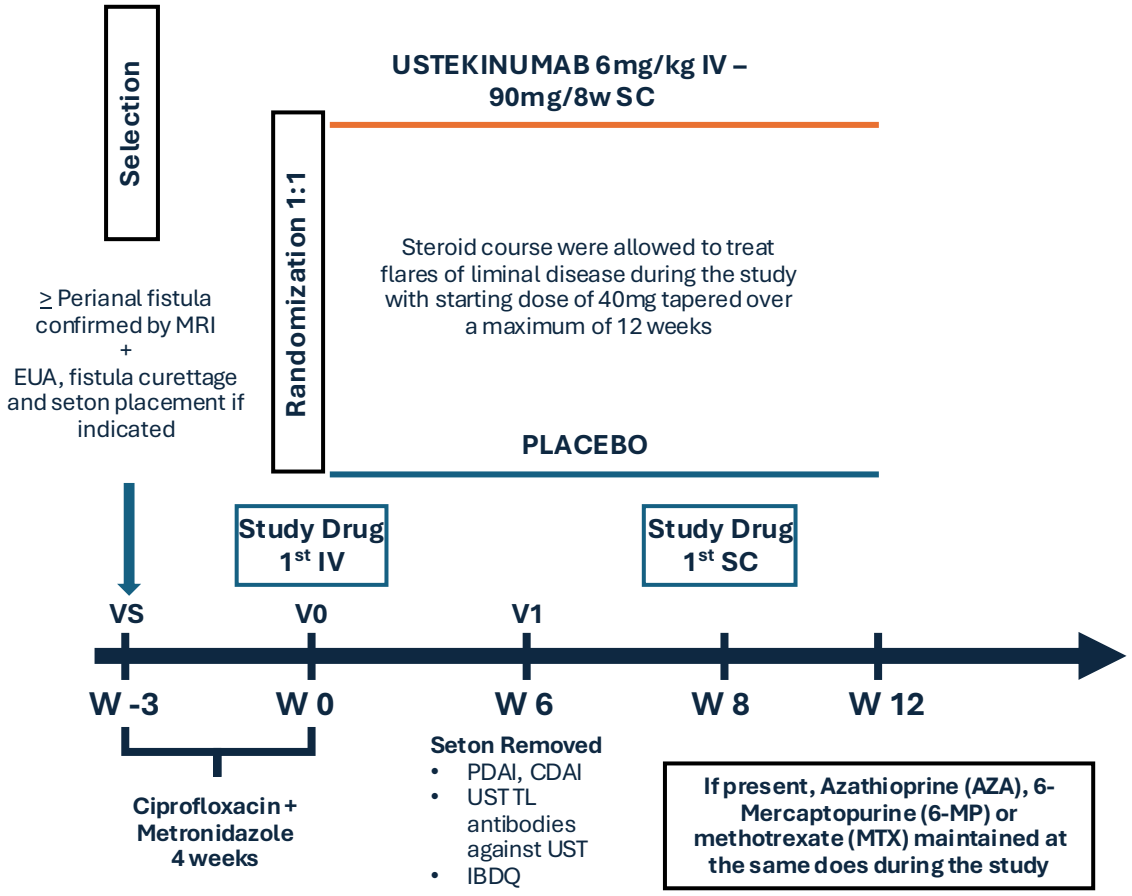
Filgo 200 (n=17)

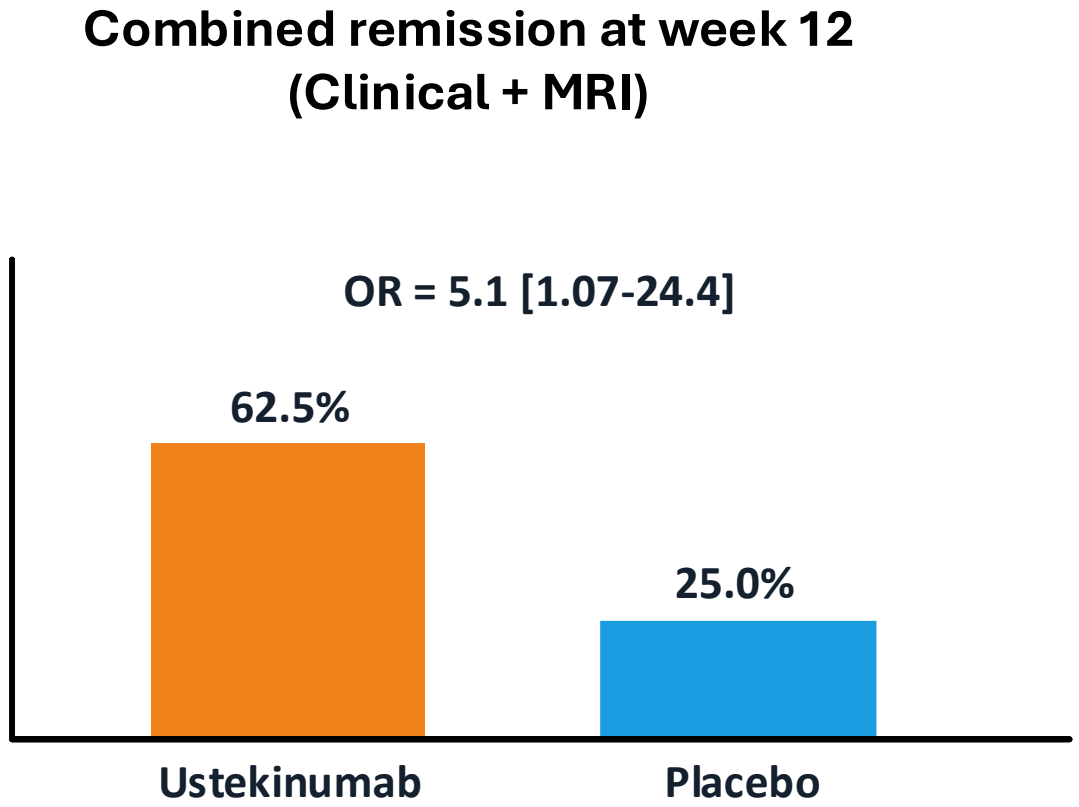
Week 24: 1° combined fistula response: Response + <1cm fluid collection by MRI



Reinisch et al., JCC 2024

USTAP Trial (Ustekinumab)



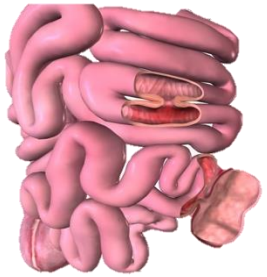


Wils et al., UEGW 2025

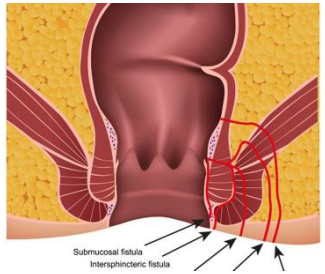
Comparative effectiveness of biologics

Risk of penetrating disease

LPD



PPD



(Merivate™ database)

Cohort: N = 40,693: (93%) anti-TNF, (3%) UST & (4%) VDZ

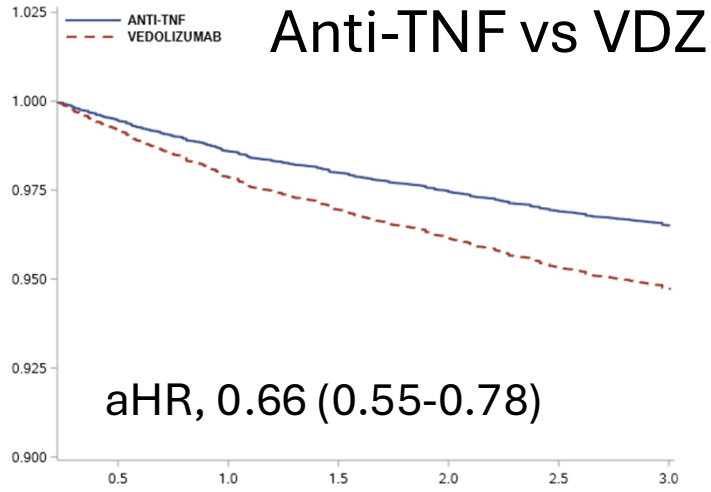
Outcome: PD 8,567 (21%) overall: 2,204 (5%) LPD; 7,474 (18%) PPD

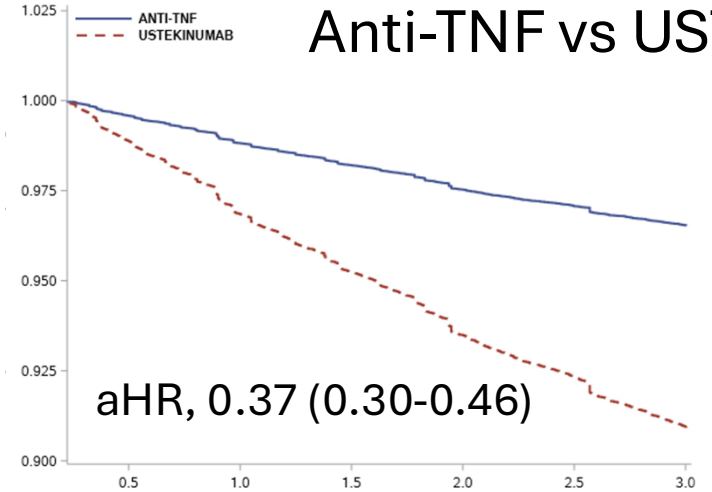
McCurdy et al., CGH 2023

Anti-TNF vs VDZ

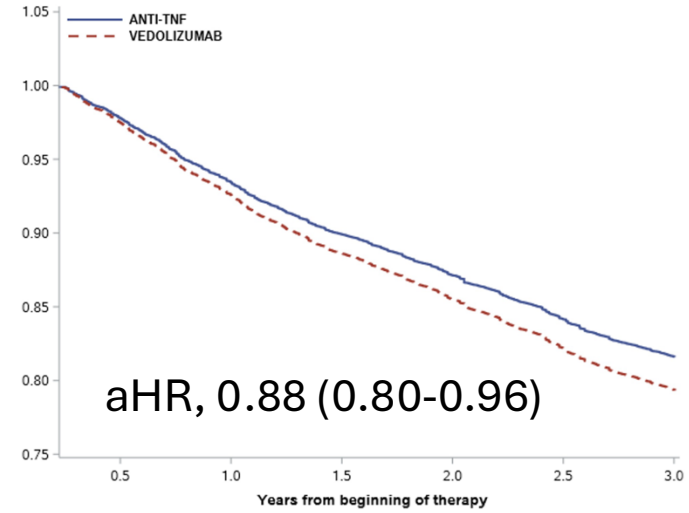
Anti-TNF vs UST

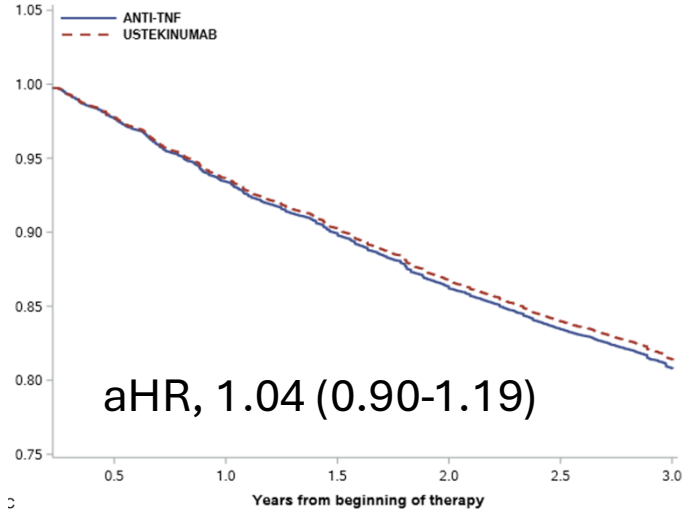
Luminal PD



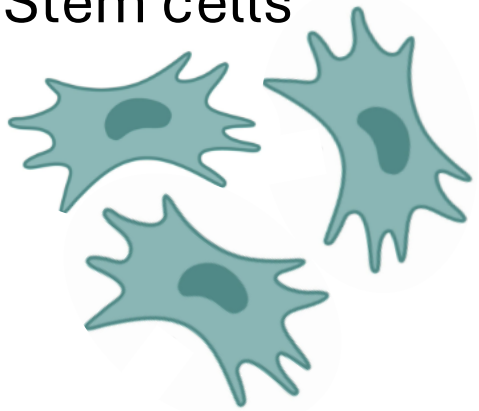


Perianal PD



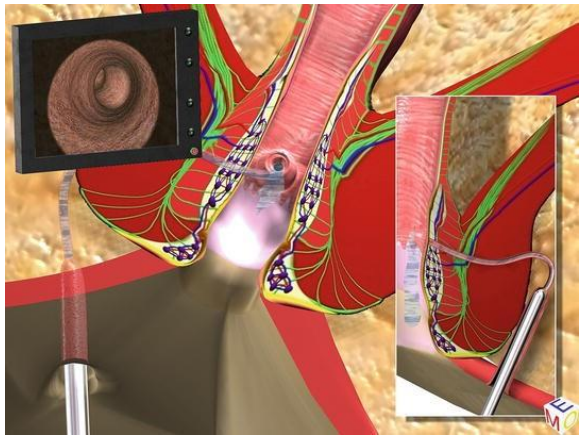


Mesenchymal Stem cells

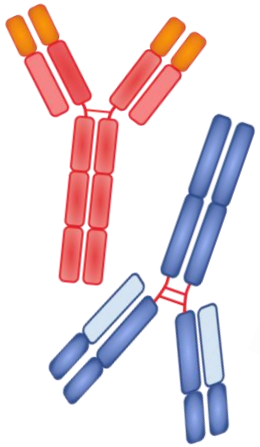


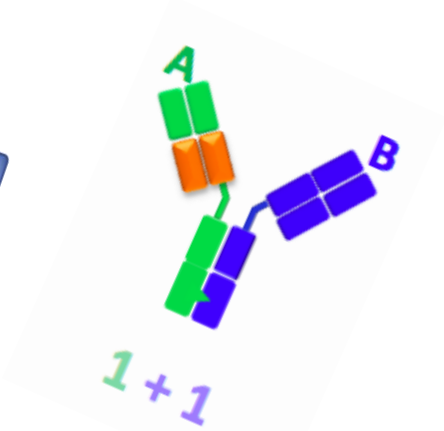
HBOT

VAFT

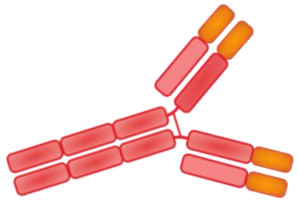


What does the future hold?

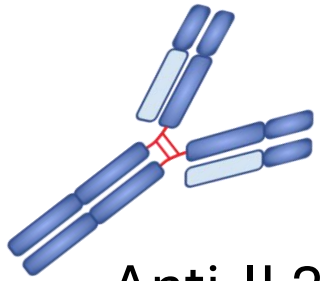




Dual targets



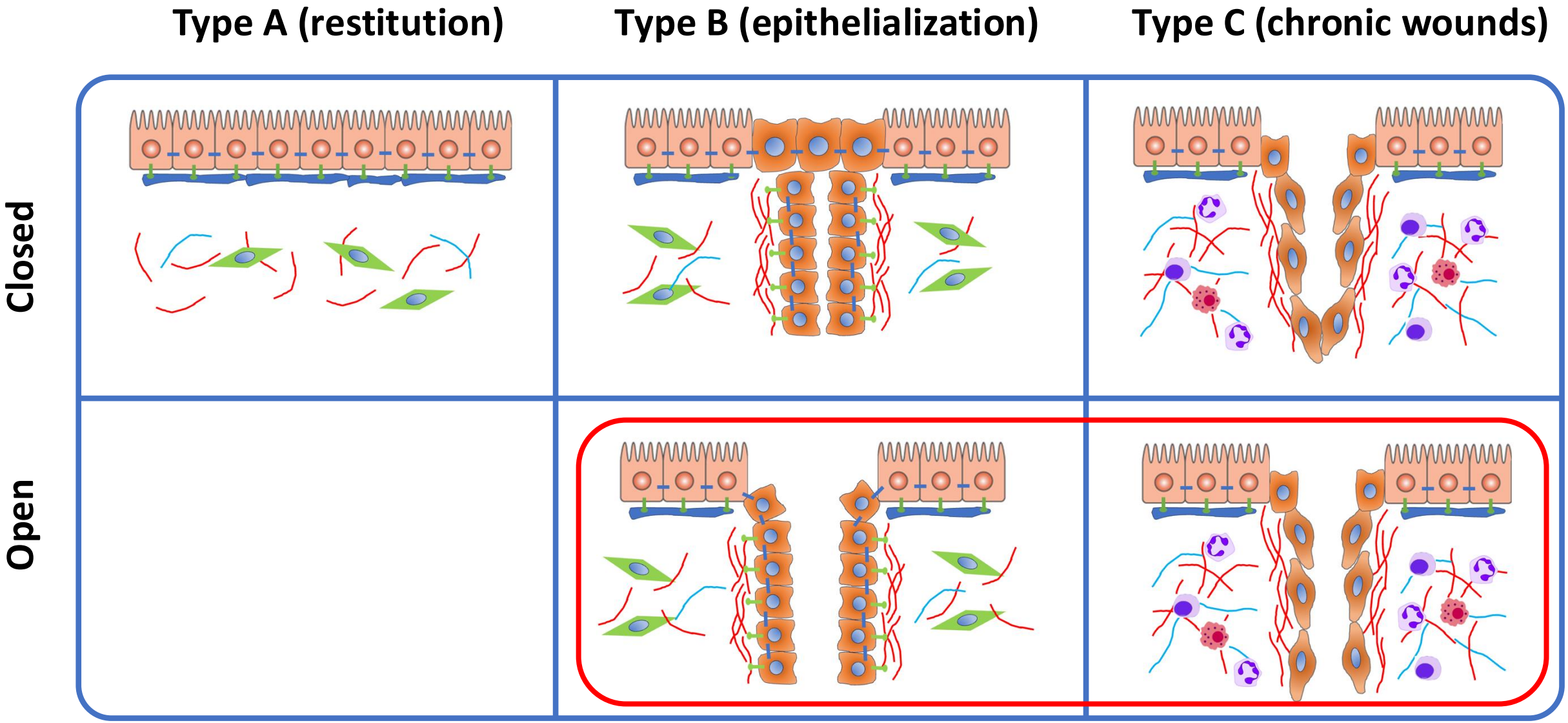
Novel targets



Anti-IL23

Controversy 5:

Can fistula healing be reliably determined clinically?



McCurdy et al., AP&T 2025

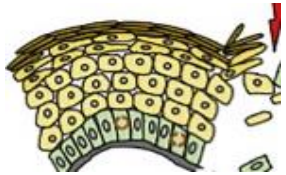
Mechanisms preventing healing/closure

Dysregulated inflammation

Anatomic

PK/PD

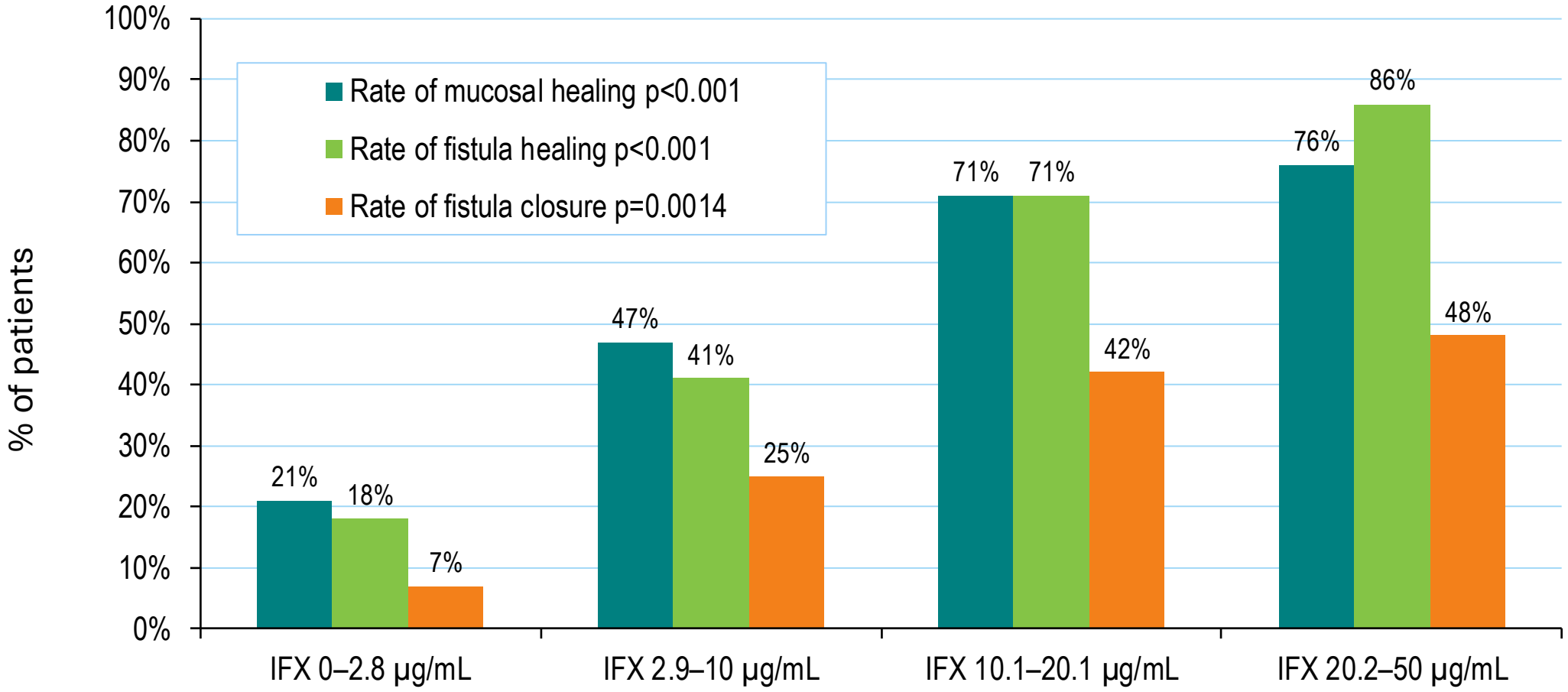
Complexity/ “High pressure zone”



Microbiologic

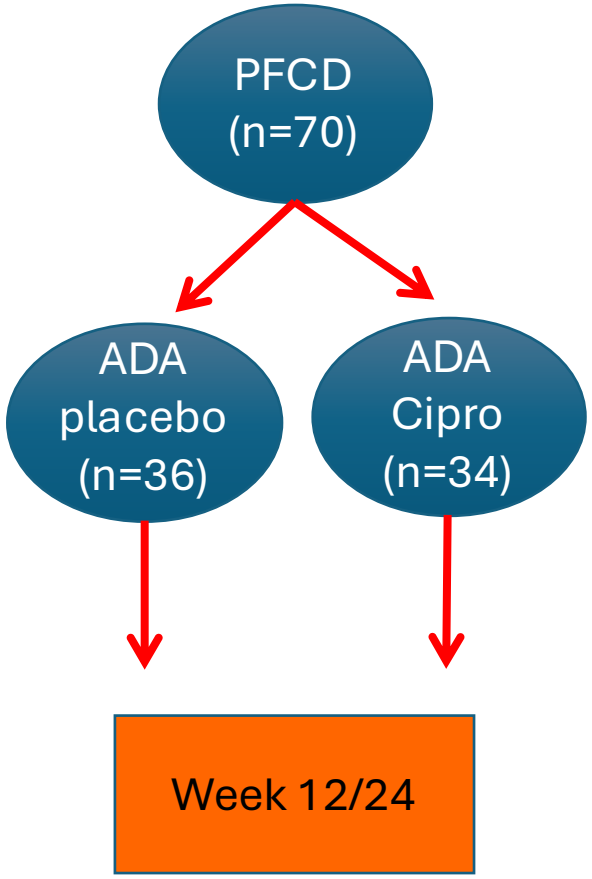
Aberrant Healing

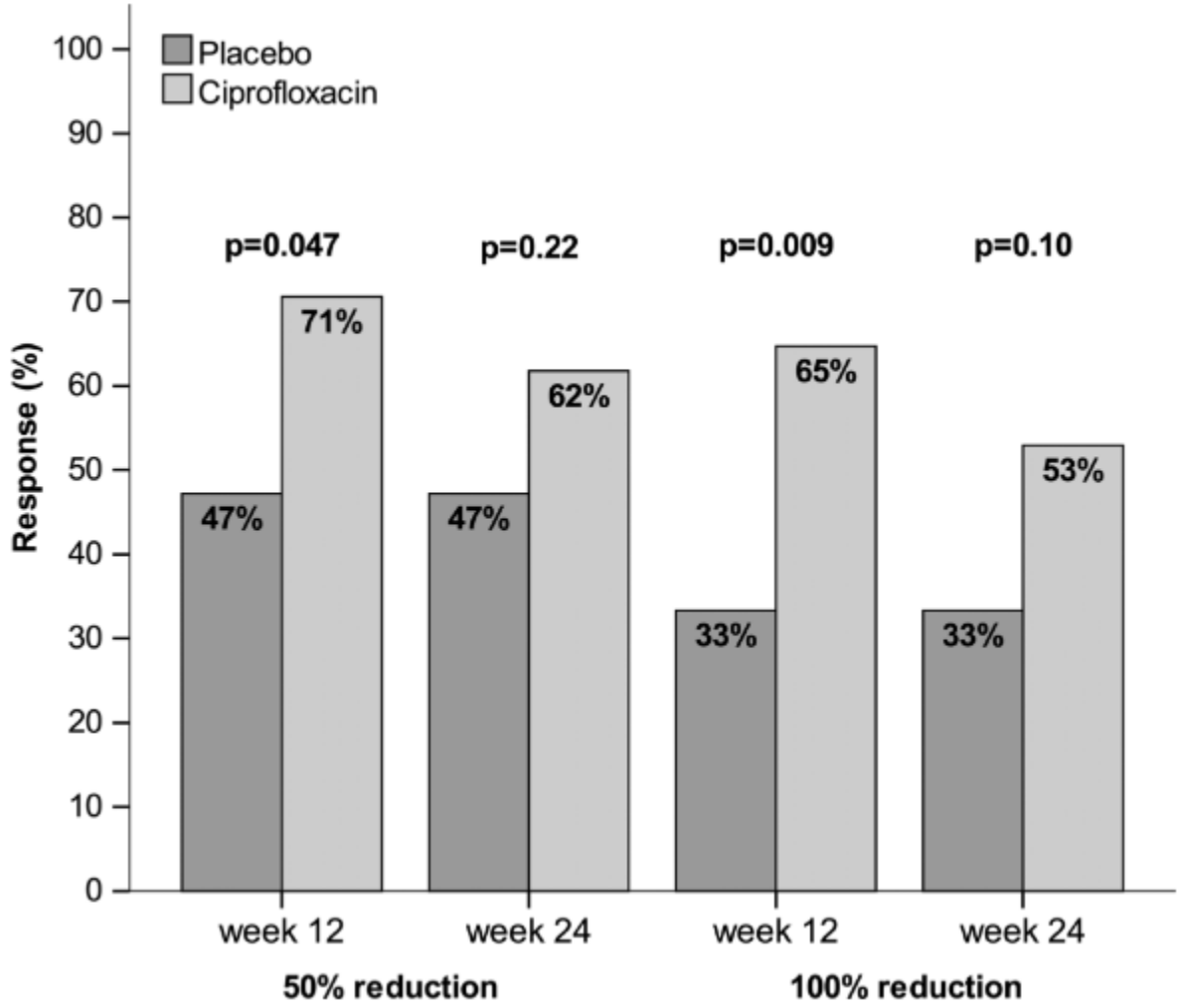
Higher IFX concentrations & healing



Andres Yarur et al., DDW 2016

Abx may improve anti-TNF efficacy

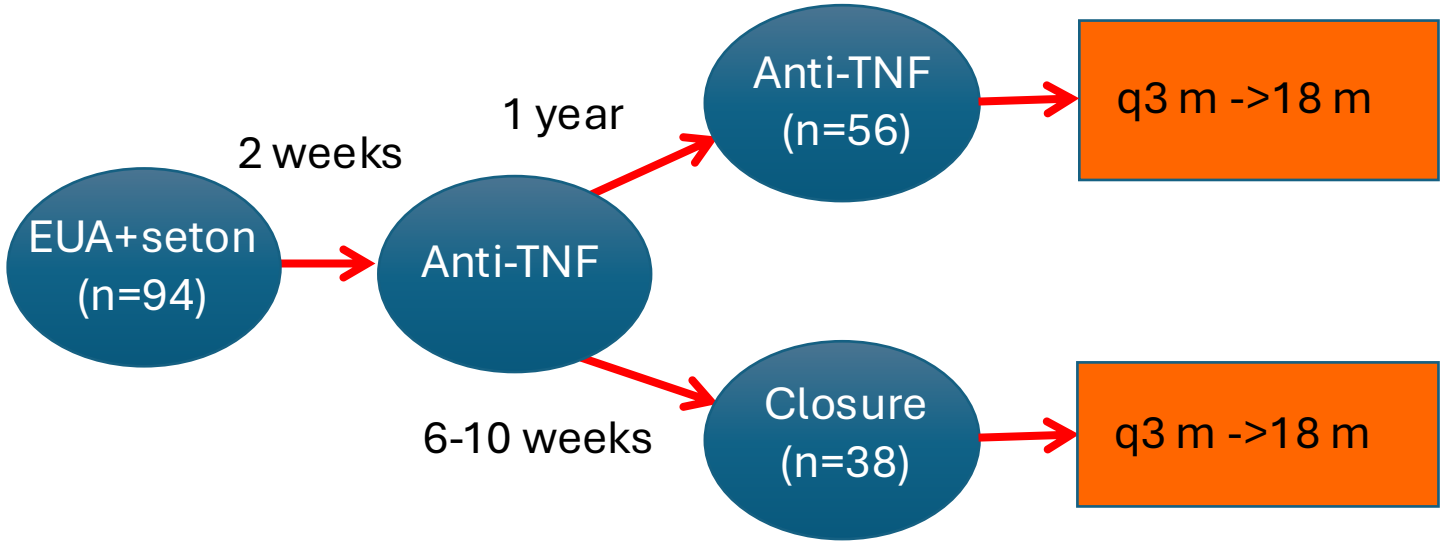




Dewint et al., Gut 2013

Combined anti-TNF + surgical closure

PISA II: Patient preference RCT



*Setons removal
-6 weeks after insertion (anti-TNF arm)
-8-12 weeks after insertion (closure arm)

Radiologic healing
-SC: 12/38 (32%)
-Anti-TNF: 5/56 (9%)
P = 0.005

Clinical closure (ITT)
-SC: 26/38 (68%)
-Anti-TNF: 29/56 (52%)
P = 0.076

Clinical closure (PP)
-SC: 32/45 (71%)
-Anti-TNF: 22/44 (50%)
P = 0.016

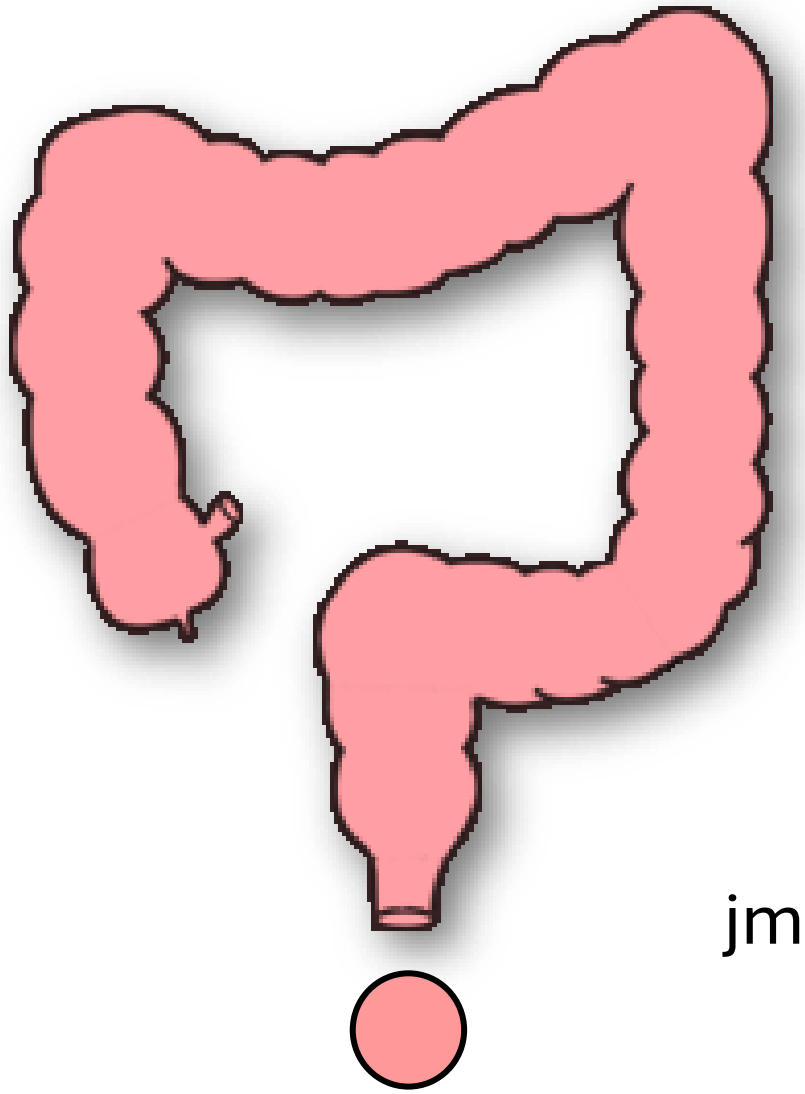
Recurrence rates
-SC: 4/14 (29%)
-Anti-TNF: 5/31 (16)%
HR 1.17
(0.32–4.37)
p=0·81

Meima-van Praag et al., Lancet 2022

Conclusions

- Physical exam may not be sufficient to exclude PFCD or determine fistula healing
- New guidelines can help determine etiology of isolated PAF
- Setons may not be required for all patients with PFCD
- Anti-TNF therapy (IFX) remains first line advanced therapy

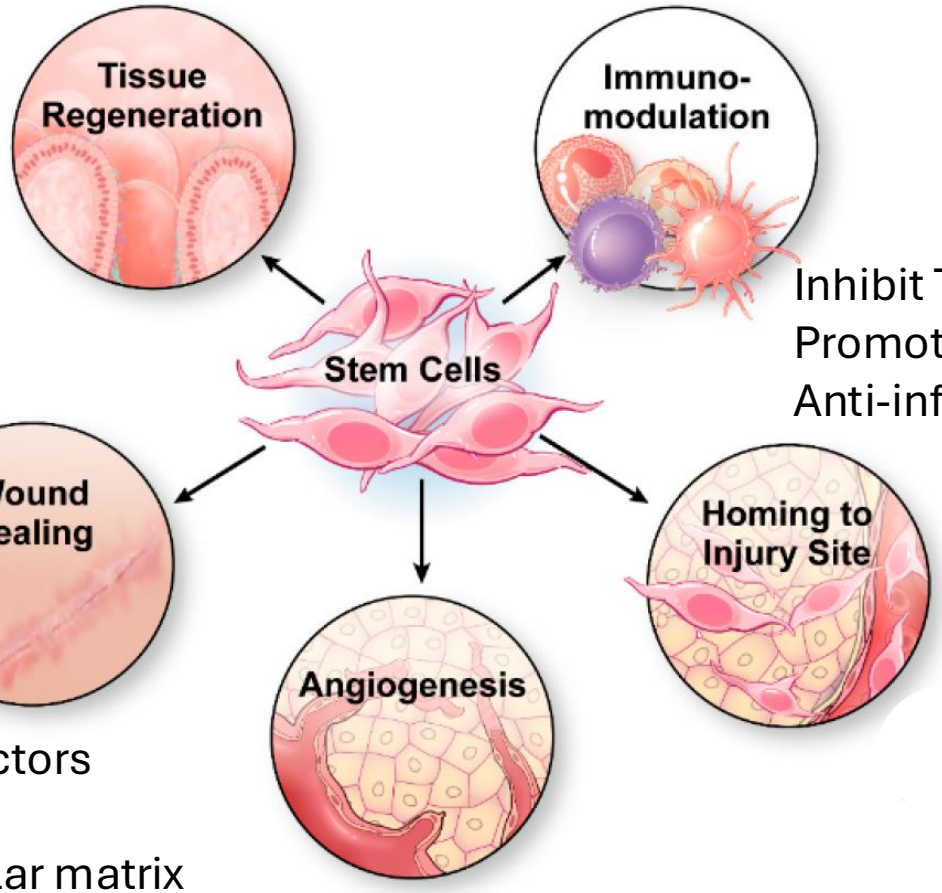
Thank you



jmccurdy@toh.ca

Are there emerging treatment strategies?

Targeting aberrant healing



Inhibit T-cells B-cells
Promote Tregs
Anti-inflammatory

Growth factors
Cytokines
Extracellular matrix

↓ Inflammation

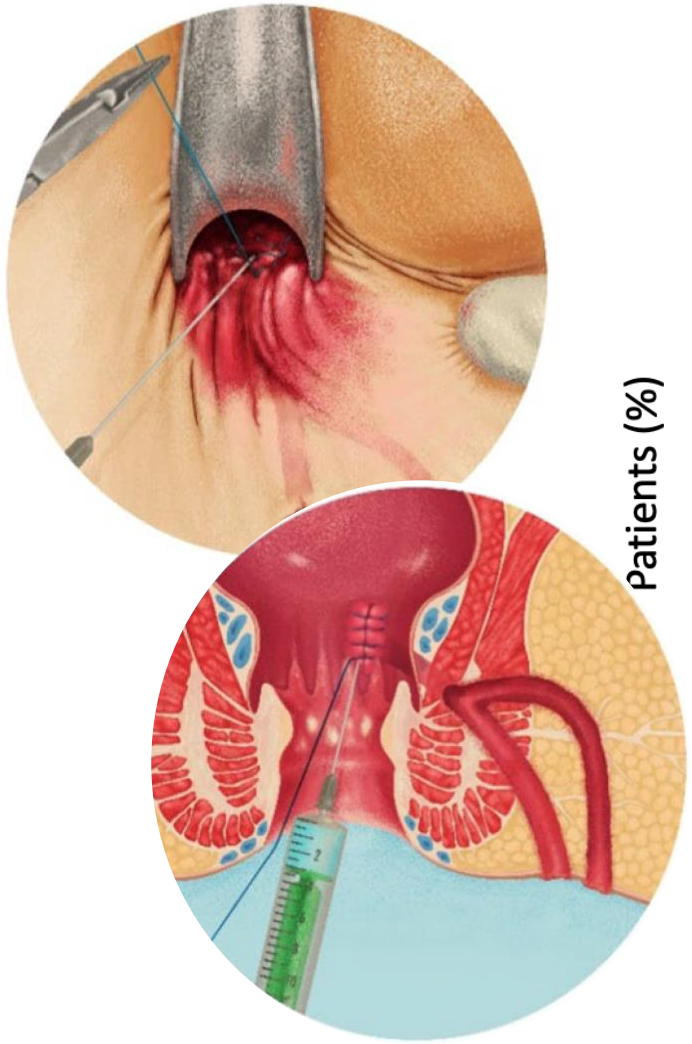
↑ Growth factors

↑ Stem cell

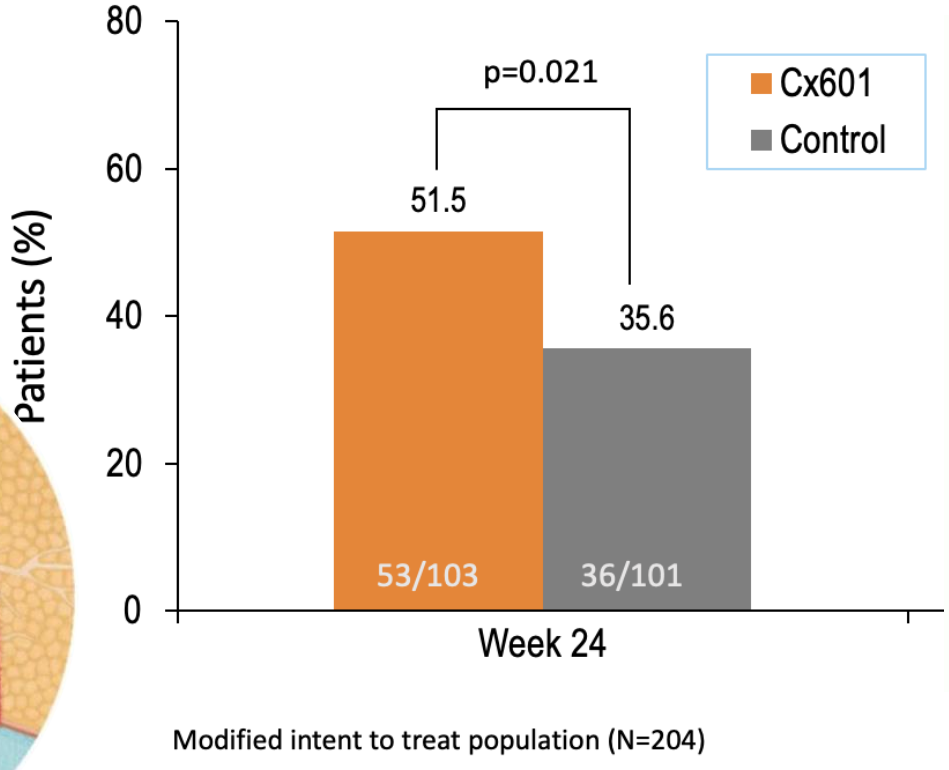
↑ Antimicrobial

Carvello et al., Cells 2019

ADMIRE Trials: MSC therapy for PFCD

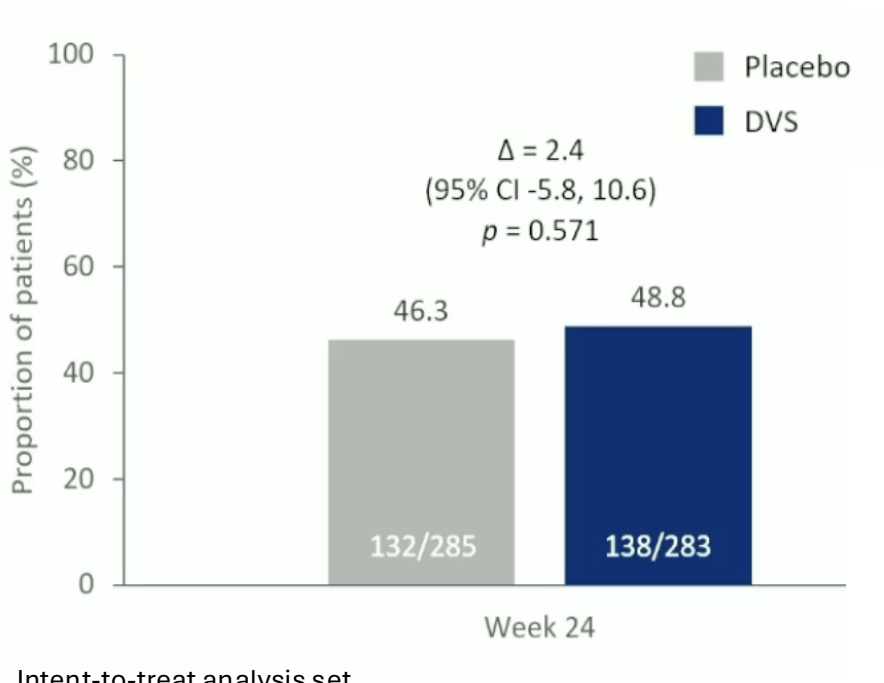


ADMIRE-I



Modified intent to treat population (N=204)

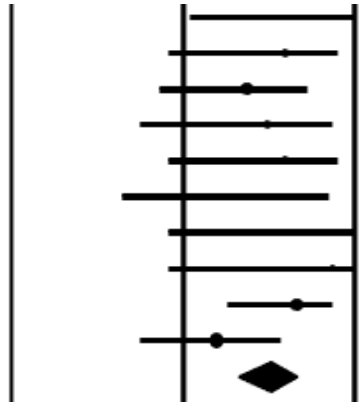
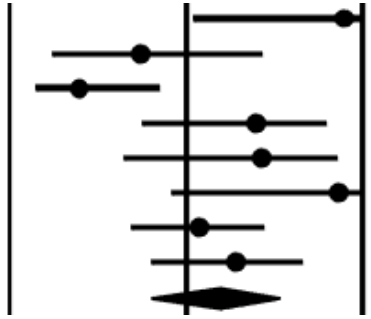
ADMIRE-II



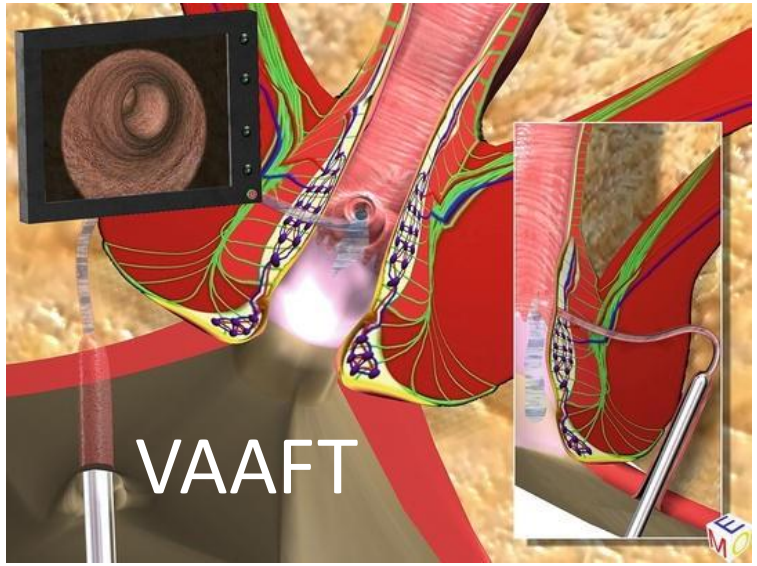
Intent-to-treat analysis set

Panes et al., Lancet 2016
Serclova et al., ECCO 2024

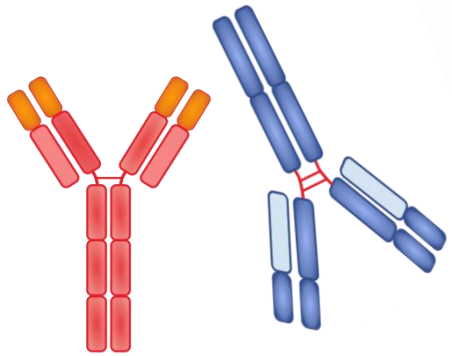
HBOT: effectiveness in PFCD

Phenotype	Study name				Events/Total	Event rate & 95% CI
Perianal fistulas (Response)	Agrawal, 2015	0.95	0.53	1.00	9 / 9	
	Iezzi, 2011	0.80	0.46	0.95	8 / 10	
	Feitosa, 2016	0.69	0.43	0.86	11 / 16	
	Colombel, 1991	0.75	0.38	0.94	6 / 8	
	Lavy, 1994	0.80	0.46	0.95	8 / 10	
	Piotrowicz, 2017	0.71	0.33	0.93	5 / 7	
	Weisz, 1997	0.94	0.46	1.00	7 / 7	
	Fahad, 2020	0.94	0.46	1.00	7 / 7	
	Hasan, 2020	0.83	0.63	0.94	20 / 24	
	Lansdorp, 2020	0.60	0.38	0.79	12 / 20	
		0.75	**0.66**	**0.83**	**93 / 118**	
Perianal fistulas (Remission)	Agrawal, 2015	0.950	0.525	0.997	9 / 9	
	Colombel, 1991	0.375	0.125	0.715	3 / 8	
	Lansdorp, 2020	0.200	0.077	0.428	4 / 20	
	Lavy, 1994	0.700	0.376	0.900	7 / 10	
	Weisz, 1997	0.714	0.327	0.928	5 / 7	
	Fahad, 2020	0.938	0.461	0.996	7 / 7	
	Hasan, 2020	0.542	0.346	0.725	13 / 24	
	Feitosa, 2016	0.647	0.404	0.832	11 / 17	
		0.595	**0.403**	**0.762**	**59 / 102**	

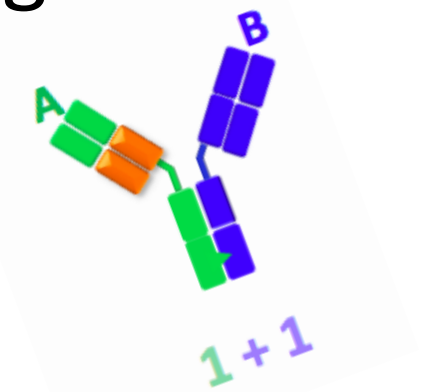
Siw et al., IBDJ 2021



Dual targets

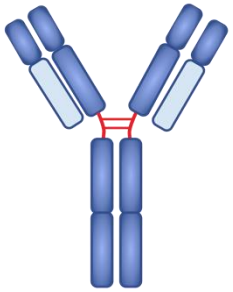


Combined Abs

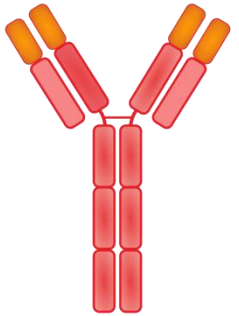


Bispecific Abs

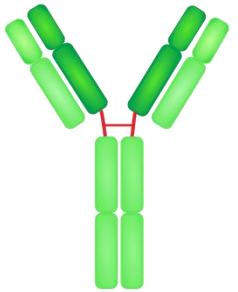
Novel targets



Anti-IL-13



Anti-MMP
Anti-B6



Anti-fibrotics

TopClass criteria for isolated PFCD

Independently diagnostic criteria:

Histological diagnosis
- Epithelioid granulomata in fistula or surrounding perianal tissue
  - ↳ excluding cryptolytic and foreign-body type granuloma

or

Macroscopic (Crohn's perineum) diagnosis
- Anorectal stricturing or ≥1 inflammatory fissure(s) or ulcer(s) evident on examination
  - ↳ ie, significant perianal lesions in the absence of another cause (eg, medication, anastomosis)

If either are present, then consider an isolated perianal Crohn's disease diagnosis

Major criteria: (scores 3)

- **Advanced fistula complexity**
  >1 internal opening, >1 discrete fistula, or organ fistulation (without an alternative provoked or iatrogenic cause)
- **Family history of IBD**
  First or second degree relative
- **Confirmed diagnosis of classic EIM of IBD or orofacial granulomatosis**

Minor criteria: (scores 1)

- **Potential, current, or previous EIM of IBD**
  (diagnosis unconfirmed)
- **Suspected oral Crohn's disease**
- **Suspected genital Crohn's disease**
- **Coexistent hidradenitis suppurativa**
- **Minor associated perianal disease***
- **Recurrence following fistula repair or lay-open with curative intent**

If major and minor score ≥5, then consider isolated perianal Crohn's disease diagnosis

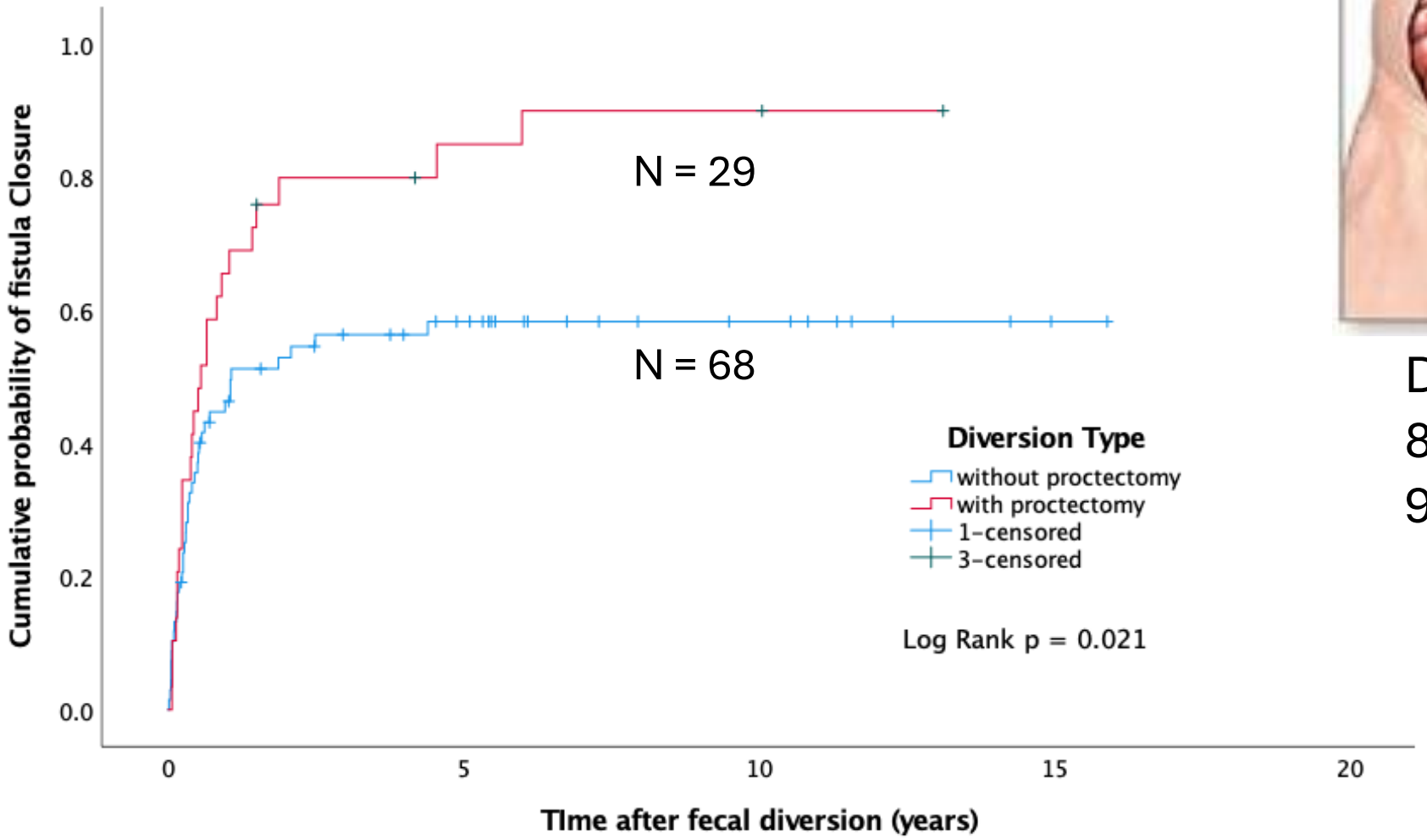
Hanna, et al. Lancet Gastro Hep 2025

Case presentation cont: 12 months later…

- Anti-TNF therapy optimized (TDM = 25mcg/ml)
- Anal canal stricture serially dilated
- Symptoms persist with substantial impact on QoL
- Not a candidate for advanced surgical closure

Can fecal diversion be used as an effective temporizing measure?

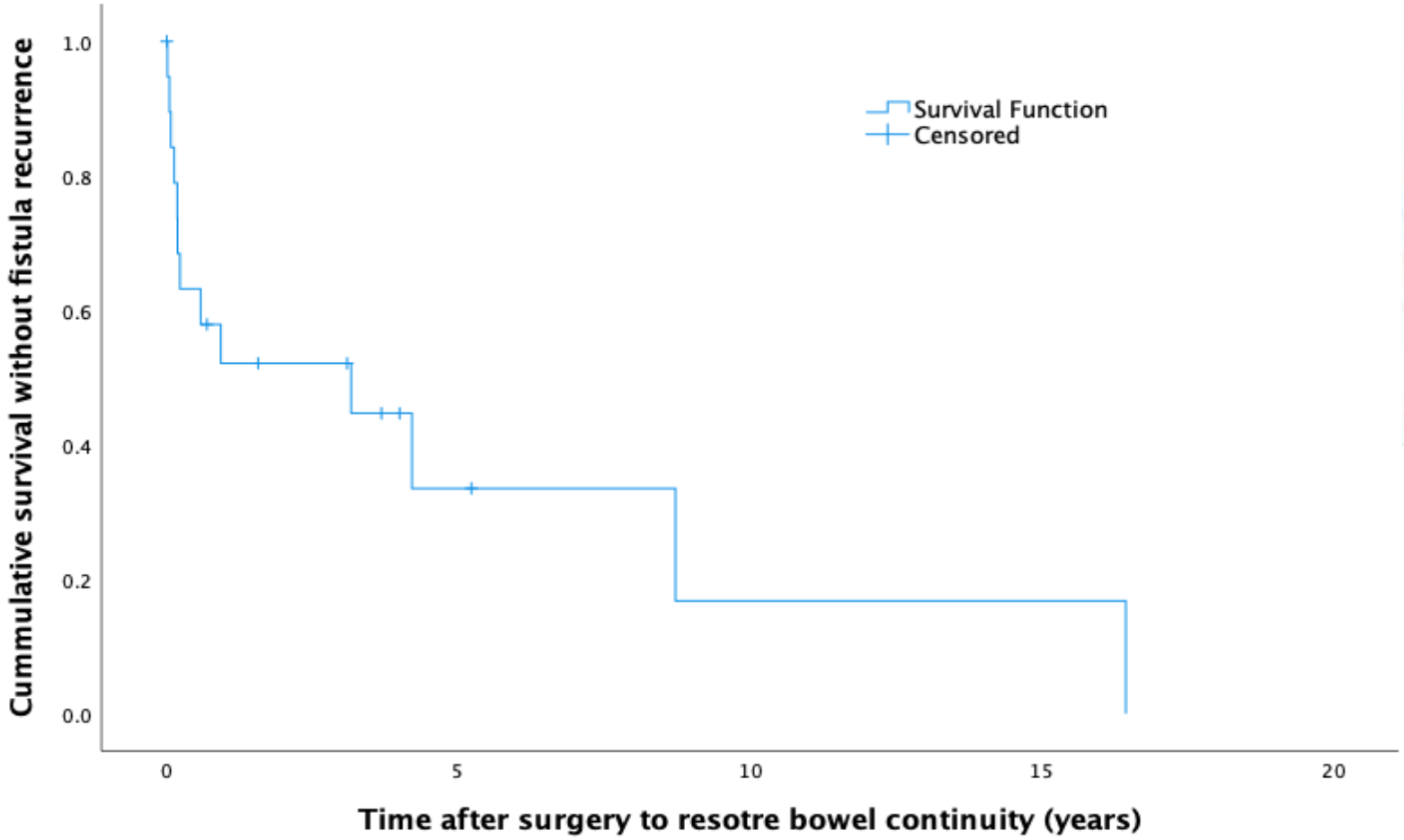
Impact of fecal diversion



Diverting ostomy
82 patients
97 fecal diversions

McCurdy, et al. IBDJ 2022

Success of bowel restoration



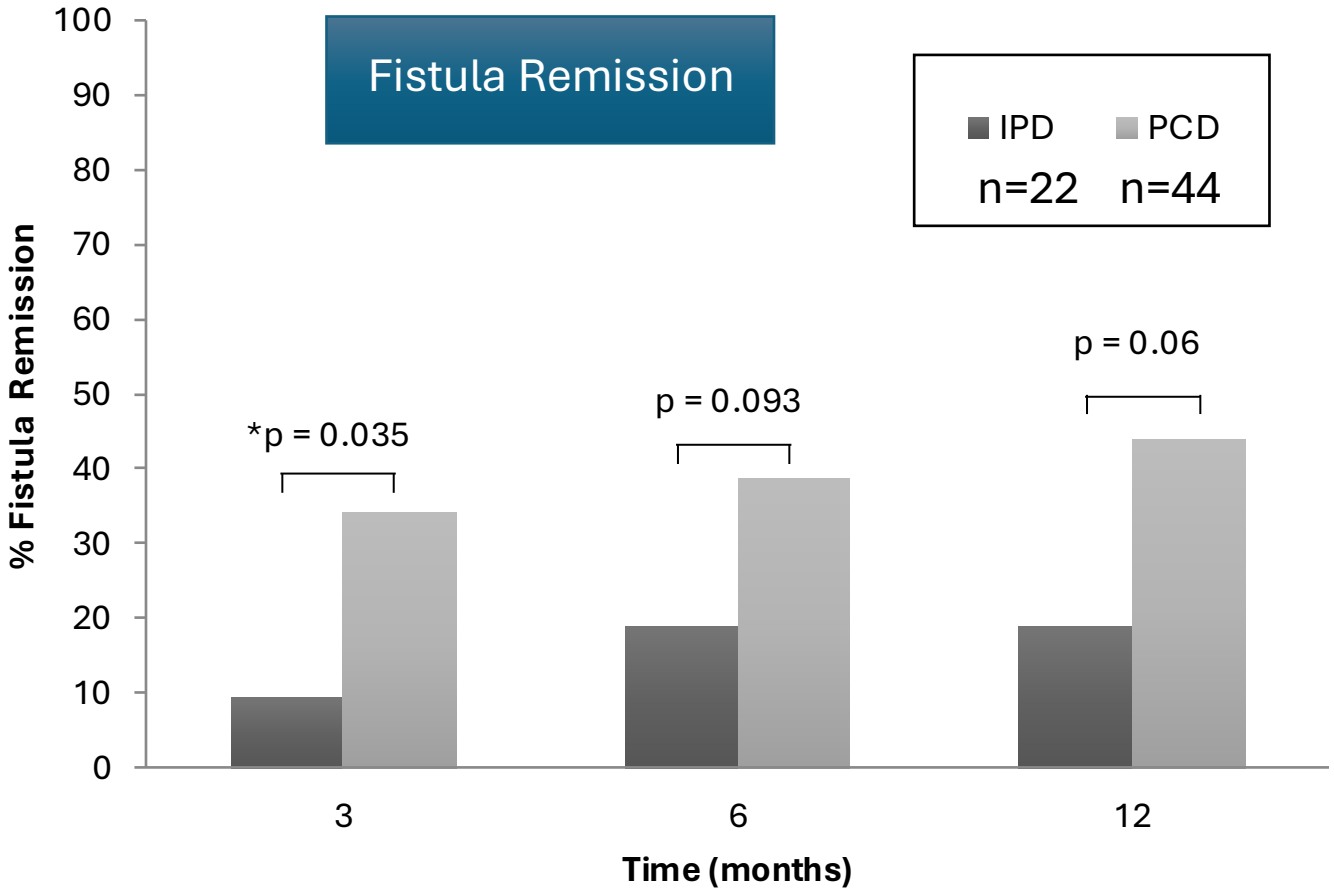
Bowel restoration
n=21

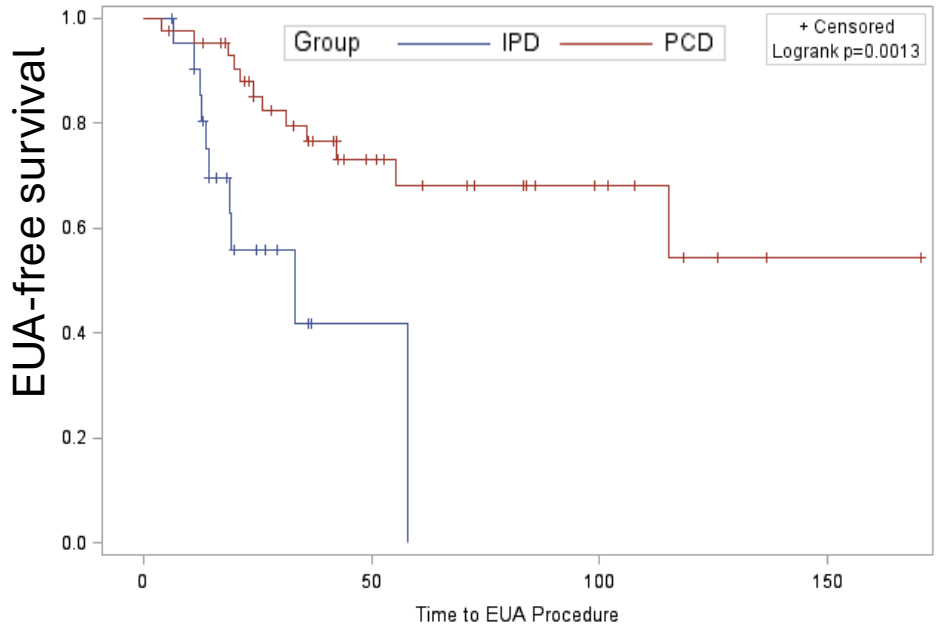
McCurdy, et al. IBDJ 2022

What to do with patients with isolated perianal fistulas?

Putting everything together

Anti-TNF for isolated PFD?





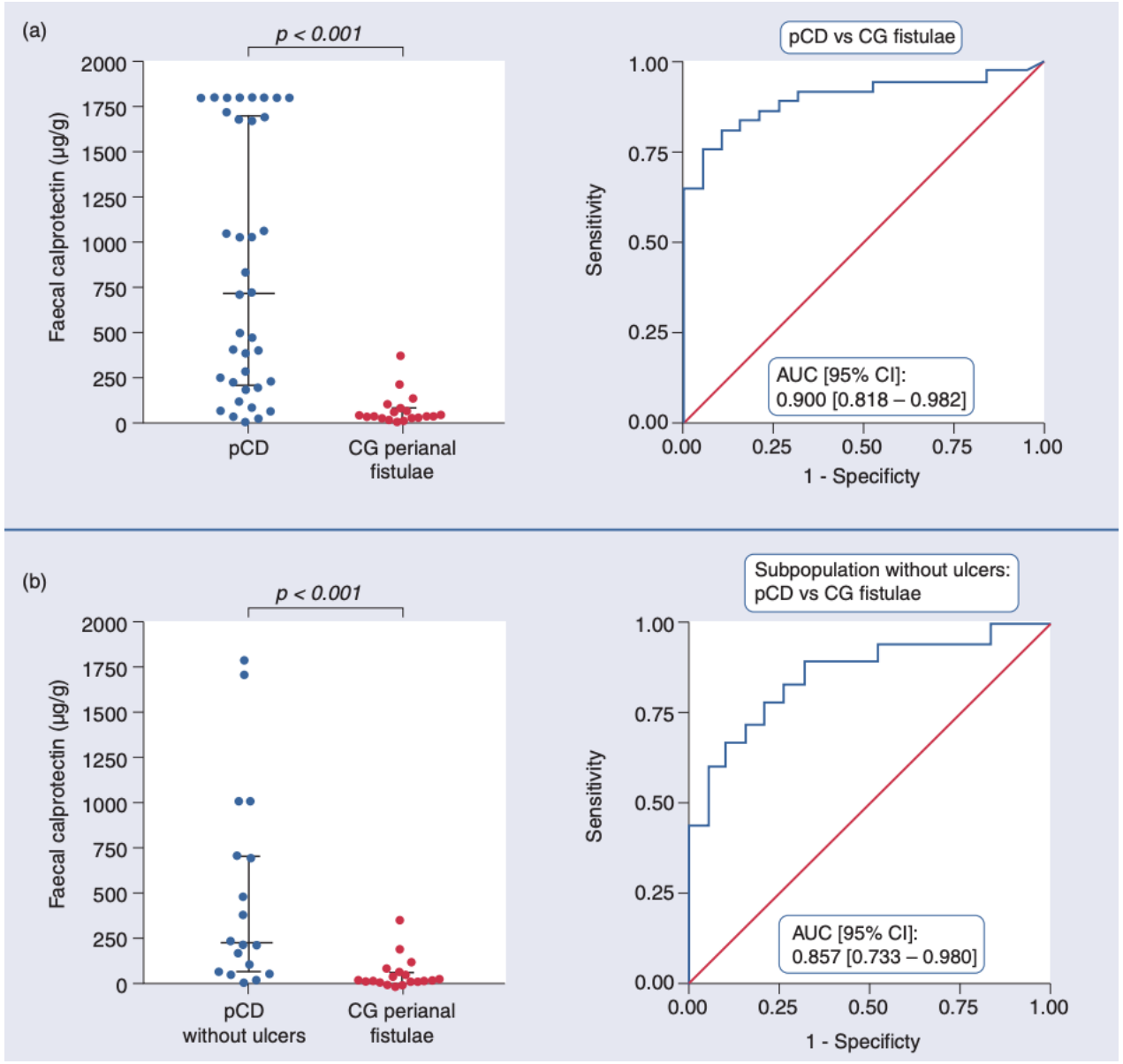
McCurdy *et al.*, DDS 2019

Fecal Calprotectin

CD n=37

CG n=19

FCP >150 µg/g
sen 81%, spec 89%



Stevens et al., Eur Gastroenterol J. 2019

PREFAB: TopClass Delphi consensus

A screening colonoscopy for early identification of Crohn's disease should be performed in PAF patients with:

Major criteria:

Biological suspicion
- Elevated FCP level (≥150 mcg/g)

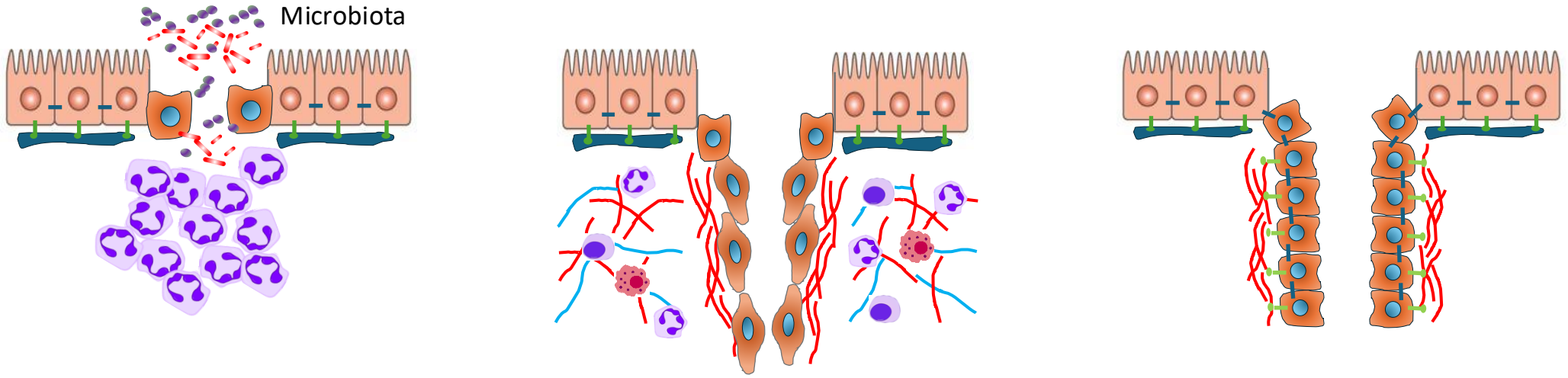
Clinical suspicion*
- Unintentional weight loss
- Unexplained diarrhea
- Primary Sclerosing Cholangitis
- Ulcerative Colitis
- >1 internal fistula openings
- Fistula involving other organs (vagina/bladder)
- Recurrent fistulation (after initial healing)
- Proctitis
- Anal stenosis

In case of ≥1 major criteria:
refer patient for screening colonoscopy
* and/or suspicion on MRI/US if already performed

Criteria for consideration of early colonoscopy in patients with perianal fistula

Munster et al., JCC 2025

Phases of wound repair



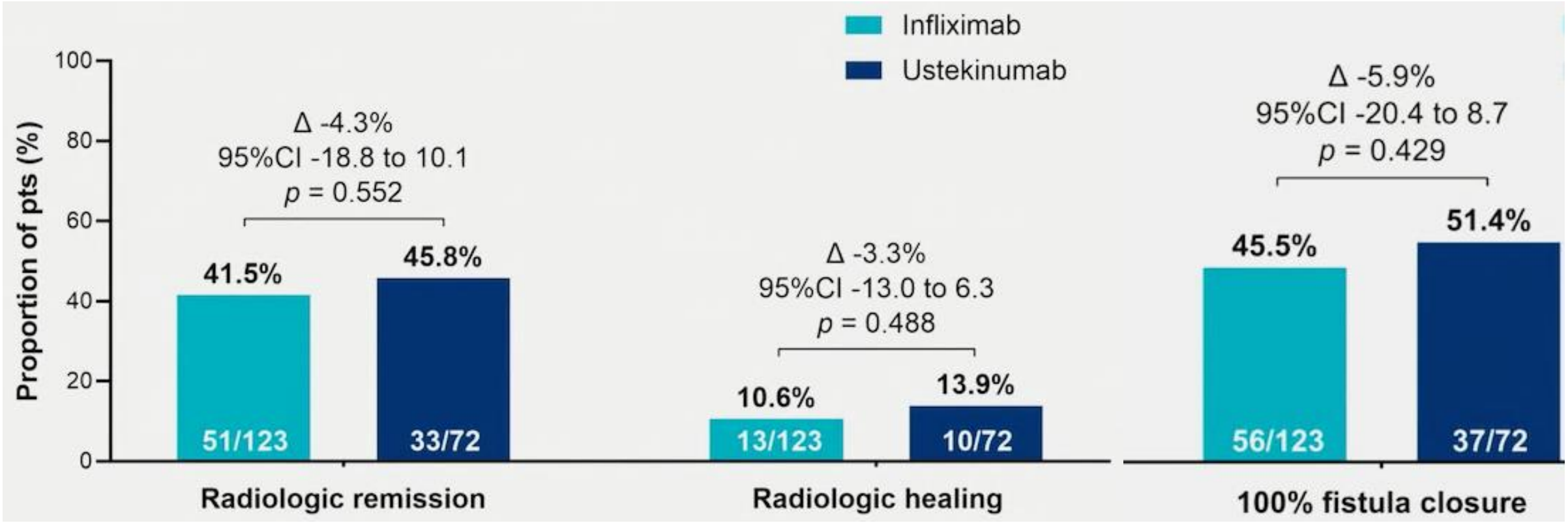
1) Inflammatory

2) Recruitment/differentiation

3) Remodeling

McCurdy et al., AP&T 2025

Comparative effectiveness of IFX vs UST

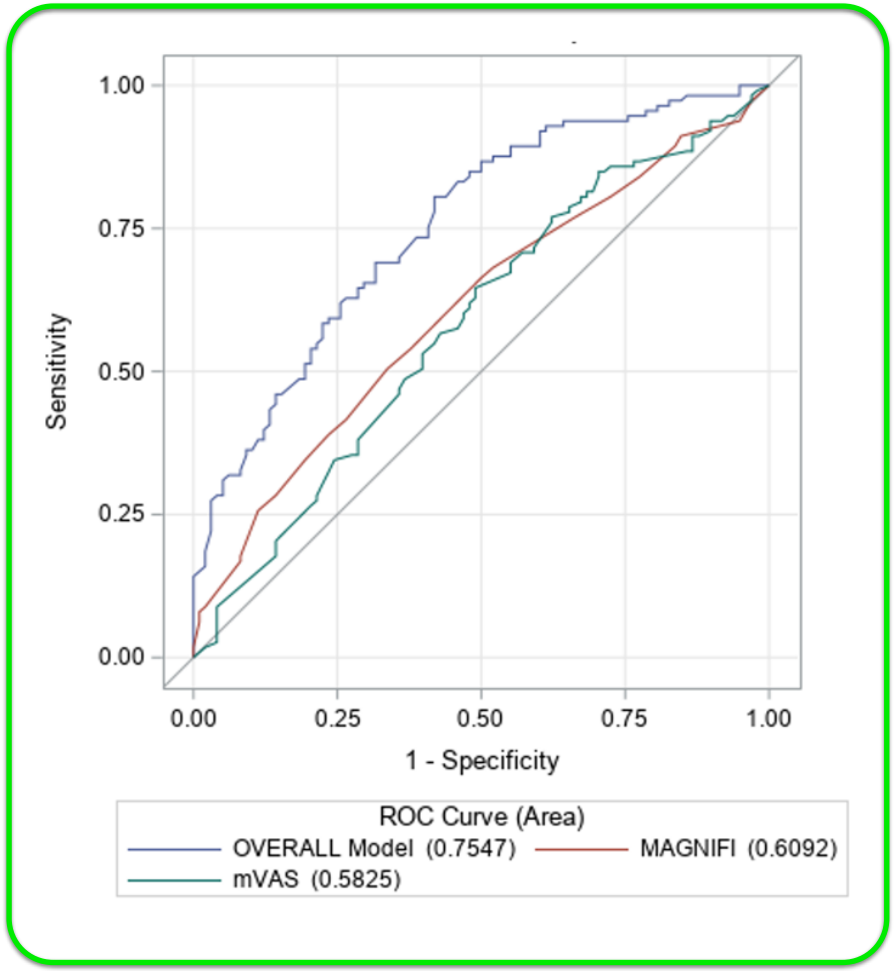


Similar baseline characteristics: complex fistulas, mVAI, CDAI and SES-CD

Huang et al., DDW 2025

Predicting treatment failure

Variables	OR (95% CI)	P value
Clinical Characteristics		
Age at fistula diagnosis (increase by 1 year)	1.03 (1.00-1.05)	0.011
Current smoking	2.98 (1.30-6.80)	0.010
Time to anti-TNF† >7 months	2.98 (1.30-6.80)	0.010
MRI Characteristics		
Supra/extrasphincteric (ref intersphincteric)	2.28 (0.97-5.35)	0.058
Horseshoe configuration	1.92 (1.08-3.43)	0.027
Primary tract length (increase by 1 cm)	1.13 (1.00-1.28)	0.048
>1 Primary (ref 0 or 1)	2.01 (1.10-3.69)	0.024
>1 Secondary tract (ref 0 or 1)	2.54 (1.38-4.67)	0.003
>1 external openings (ref 0 or 1)	6.52 (2.00-20.60)	0.002
T2 weighted hyperintensity		
Mild (ref absent)	2.90 (0.83-10.10)	0.094
Moderate/pronounced (ref absent)	3.88 (1.12-13.48)	0.032
Fluid collections > 1.3 cm (ref < 1.3 cm)	1.93 (0.98-3.79)	0.056



McCurdy et al., CGH 2024

Management by phase of wound repair