

Controversies in perianal fistulizing Crohn's disease

Debunking the myths

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Disclosures

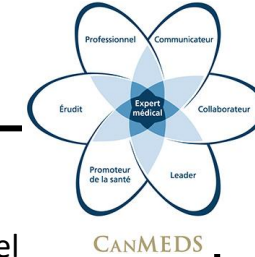
Advisory board honorarium:

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

Speaker honorarium:

AbbVie, J&J, Ferring, Pfizer

Compétences CanMEDS



	Expert médical (En tant qu'experts médicaux, les médecins assument tous les rôles CanMEDS et s'appuient sur leur savoir médical, leurs compétences cliniques et leurs attitudes professionnelles pour dispenser des soins de grande qualité et sécuritaires centrés sur les besoins du patient. Pivotal du référentiel CanMEDS, le rôle d'expert médical définit le champ de pratique clinique des médecins .)
	Communicateur (En tant que communicateurs, les médecins développent des relations professionnelles avec le patient et ses proches ce qui permet l'échange d'informations essentielles à la prestation de soins de qualité.)
	Collaborateur (En tant que collaborateurs, les médecins travaillent efficacement avec d'autres professionnels de la santé pour prodiguer des soins sécuritaires et de grande qualité centrés sur les besoins du patient.)
	Leader (En tant que leaders, les médecins veillent à assurer l'excellence des soins, à titre de cliniciens, d'administrateurs, d'érudits ou d'enseignants et contribuent ainsi, avec d'autres intervenants, à l'évolution d'un système de santé de grande qualité.)
	Promoteur de santé (En tant que promoteurs de la santé, les médecins mettent à profit leur expertise et leur influence en oeuvrant avec des collectivités ou des populations de patients en vue d'améliorer la santé. Ils collaborent avec ceux qu'ils servent afin d'établir et de comprendre leurs besoins, d'être si nécessaire leur porte-parole, et de soutenir l'allocation des ressources permettant de procéder à un changement.)
	Érudit (En tant qu'érudits, les médecins font preuve d'un engagement constant envers l'excellence dans la pratique médicale par un processus de formation continue, en enseignant à des tiers, en évaluant les données probantes et en contribuant à l'avancement de la science.)
	Professionnel (En tant que professionnels, les médecins ont le devoir de promouvoir et de protéger la santé et le bien-être d'autrui, tant sur le plan individuel que collectif. Ils doivent exercer leur profession selon les normes médicales actuelles, en respectant les codes de conduite quant aux comportements qui sont exigés d'eux, tout en étant responsables envers la profession et la société. De plus, les médecins contribuent à l'autoréglementation de la profession et voient au maintien de leur santé.)

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?

Case 1

45 y/o male presents to the ED with a perianal abscess.

Similar episode 1 year ago requiring I&D.
Normal ileocolonoscopy

PMHx: smoker

Meds: None (no NSAIDs)

FMHx: Father with CD and MS



Case 1 continue:

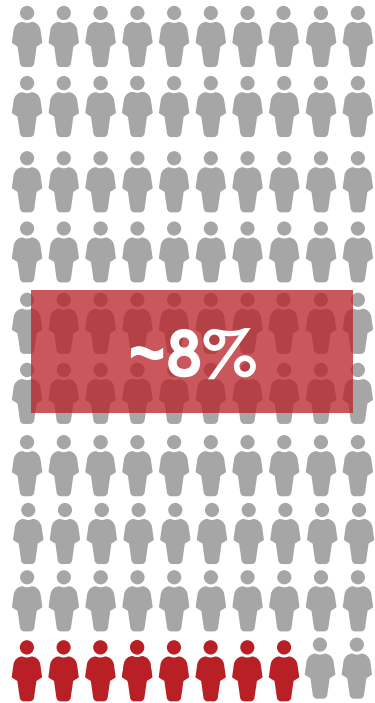
- Repeat I&D procedure

What is the diagnosis

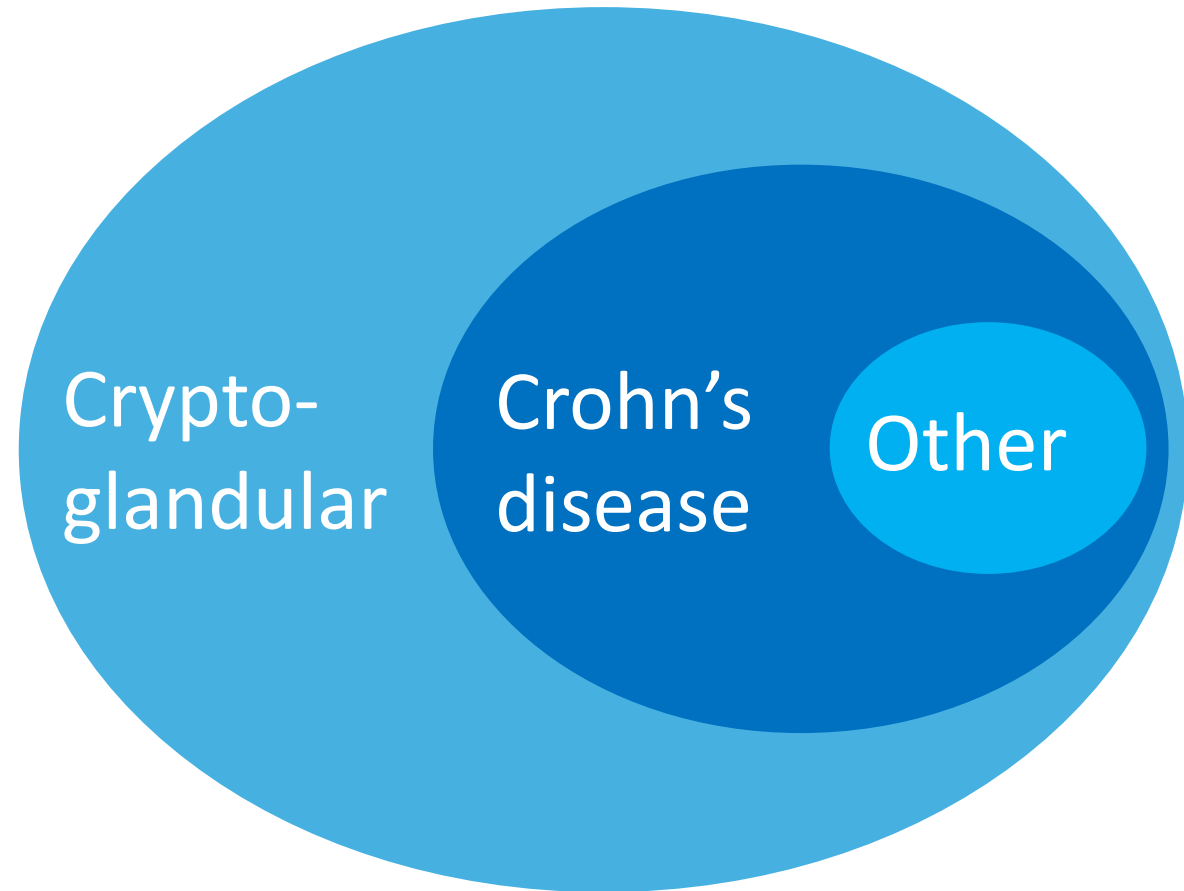
Controversy 1:

Does PFCD require the presence of luminal inflammation?

Isolated perianal fistulas:



Proportion of patients
with PF as their first
manifestation of CD



VCE for isolated perianal fistulas

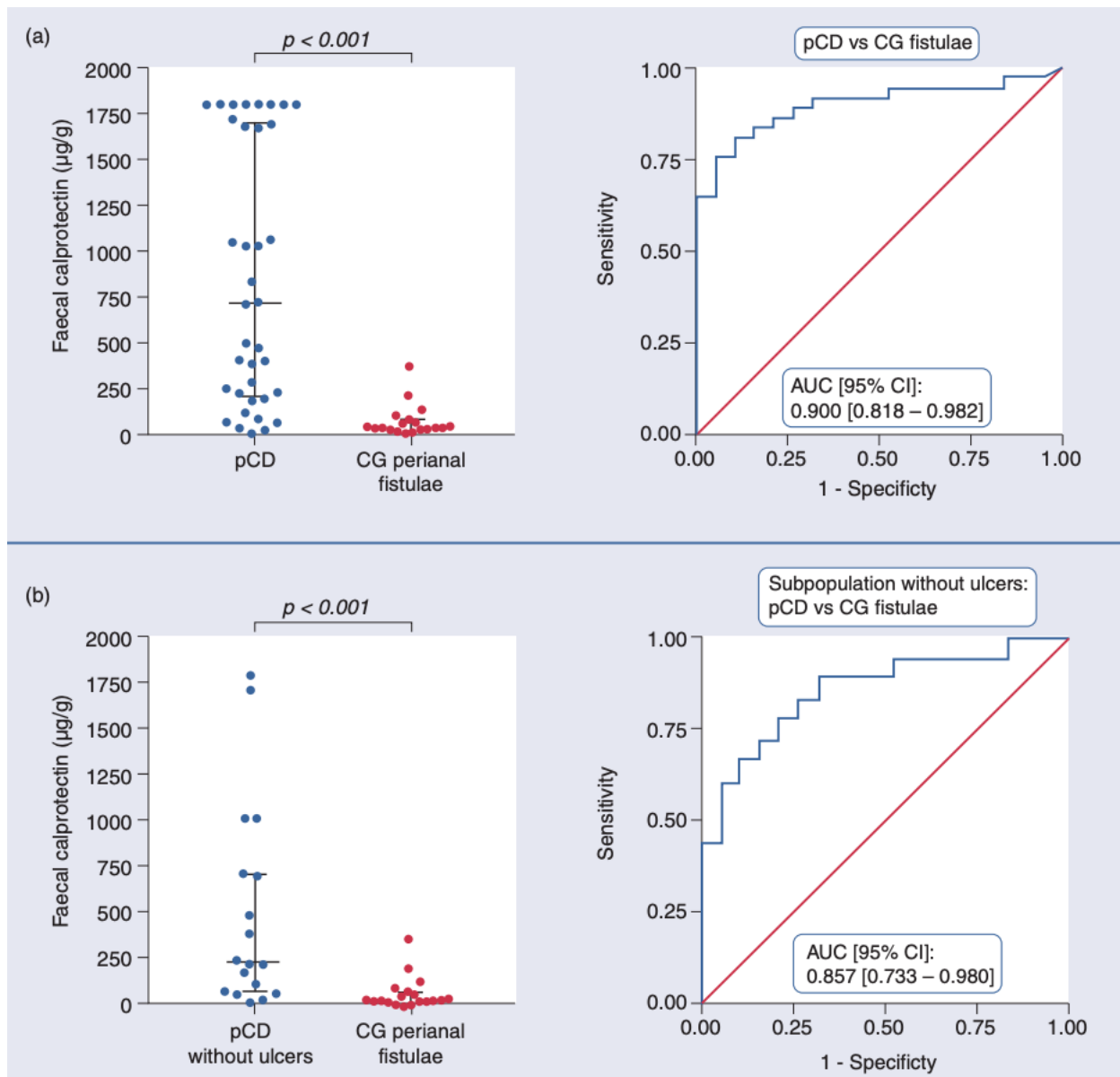


Fecal Calprotectin

CD n=37

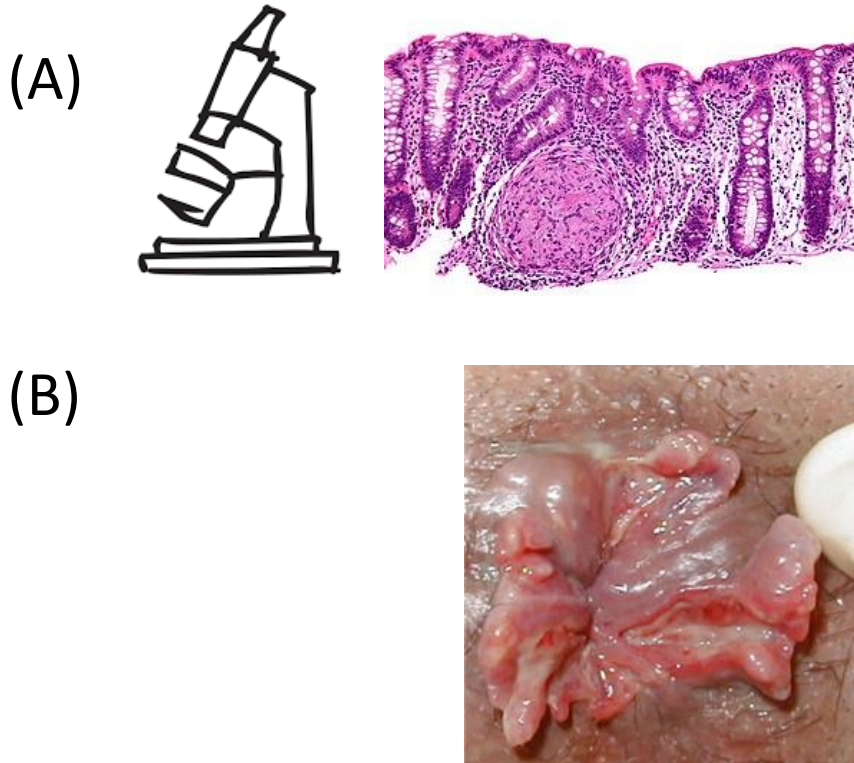
CG n=19

FCP >150 $\mu\text{g/g}$
sen 81%,
spec 89%



TopClass criteria for isolated PFCD

Independent Criteria



Composite Criteria (score ≥ 5)

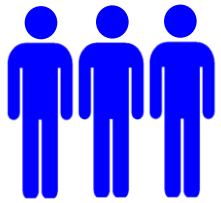
Major: (scores 3)

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

Minor: (scores 1)

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

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

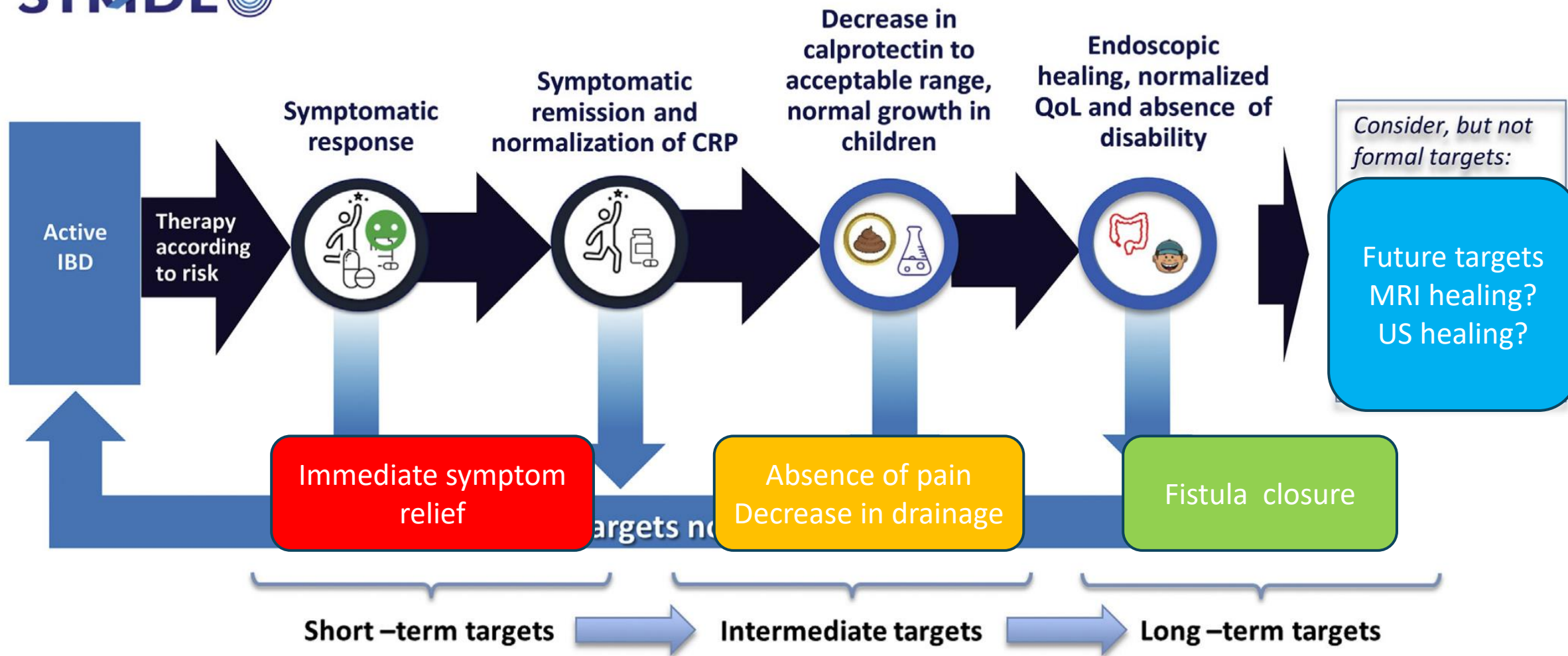


Perianal surgery HR 1.40
[95% CI 1.18-1.68]

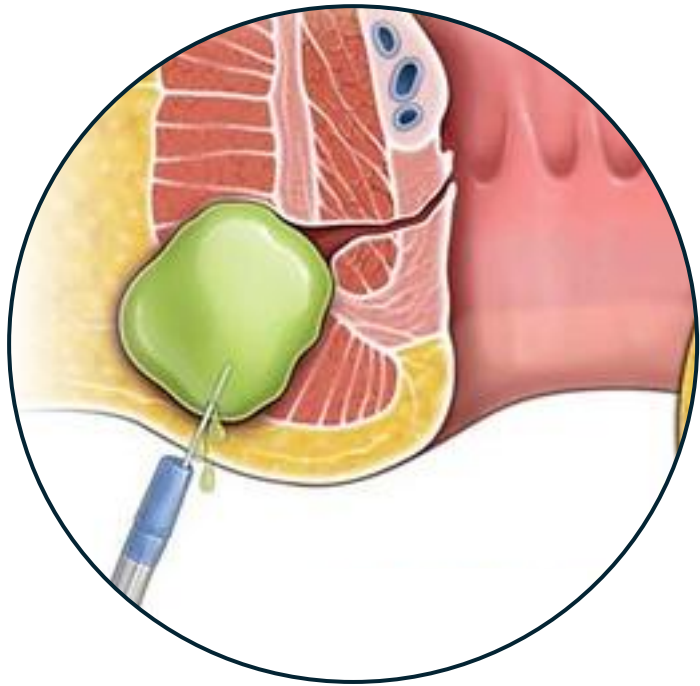
Case 1 continue:

- Video capsule endoscopy reveals multiple SB ulcers suggestive of CD
- FCP is elevated 320 mcg/g
- O/E: external fistula opening, no obvious abscess
- MRI: complex, transsphincteric fistula with branching, hyper enhancing tracts and no residual abscess

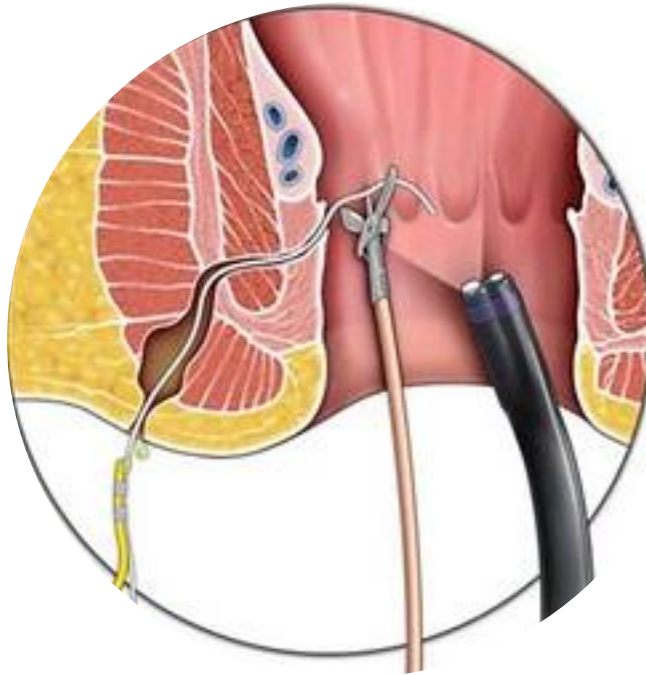




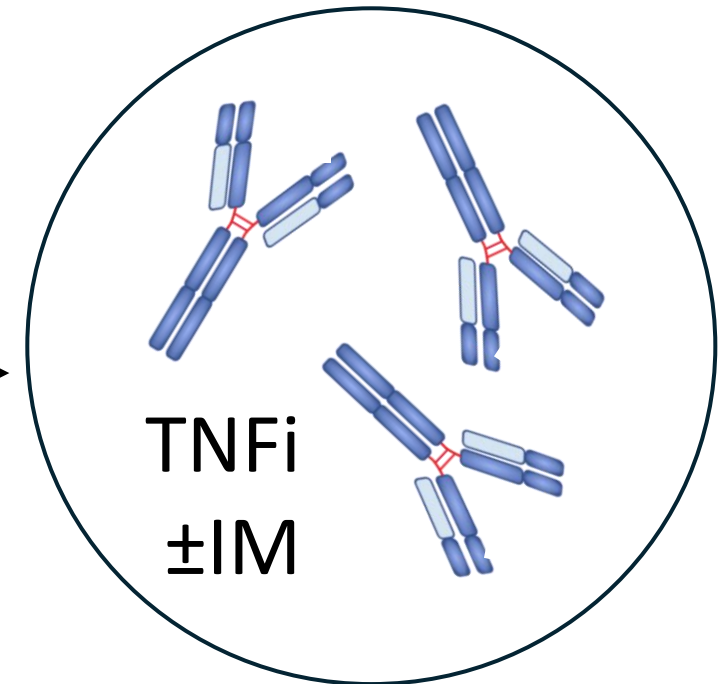
EUA+/- drainage



Seton placement



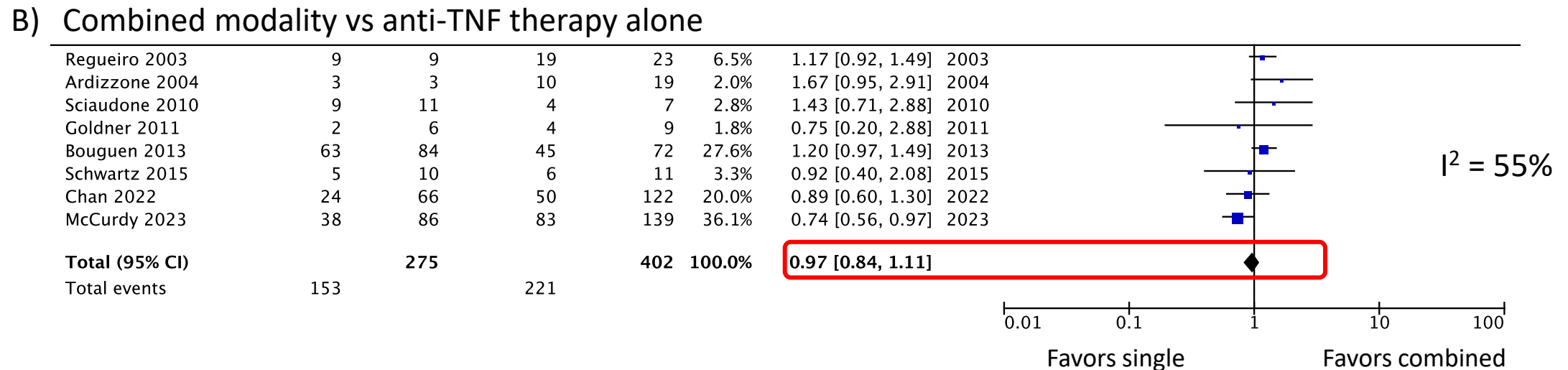
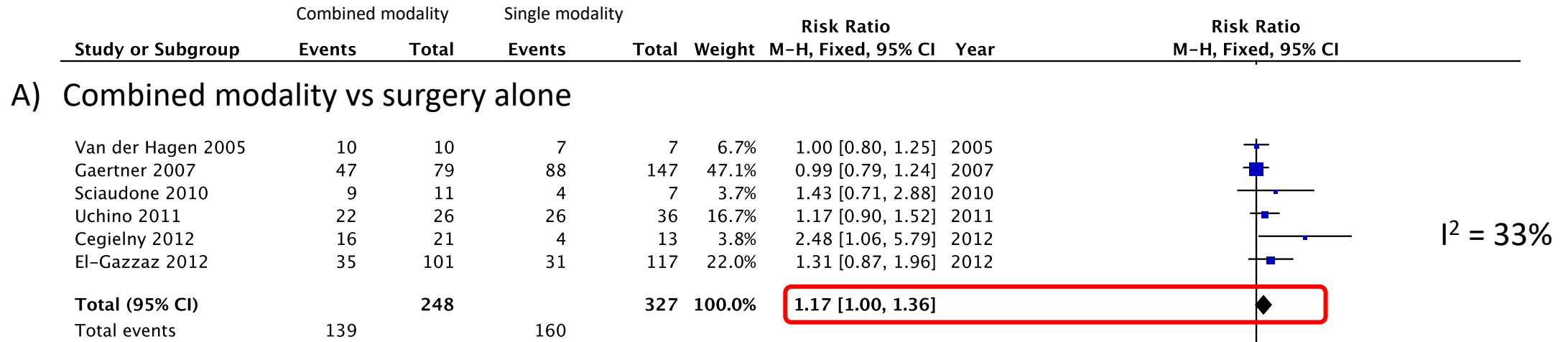
Medical therapy



Controversy 2:

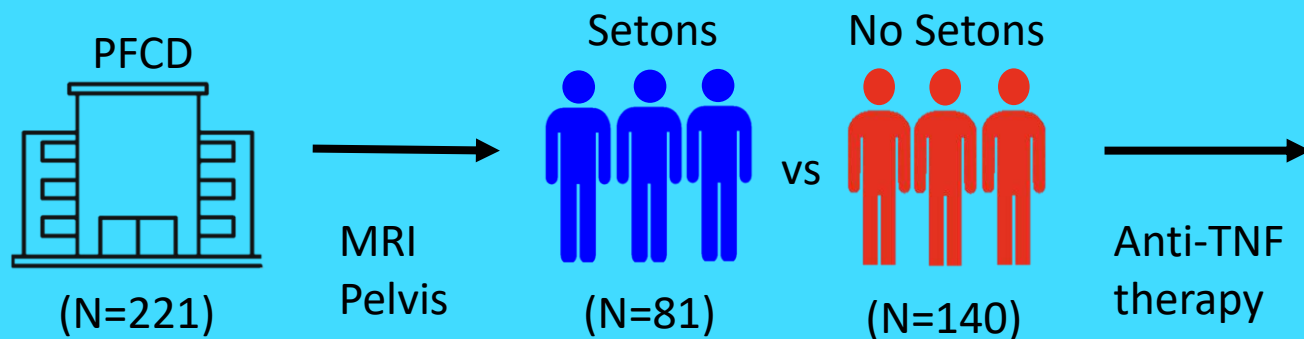
EUA + setons are required for all patients with PFCD?

Does combined therapy improve remission?



Impact of setons on perianal fistula outcomes

Multicenter, retrospective observational study



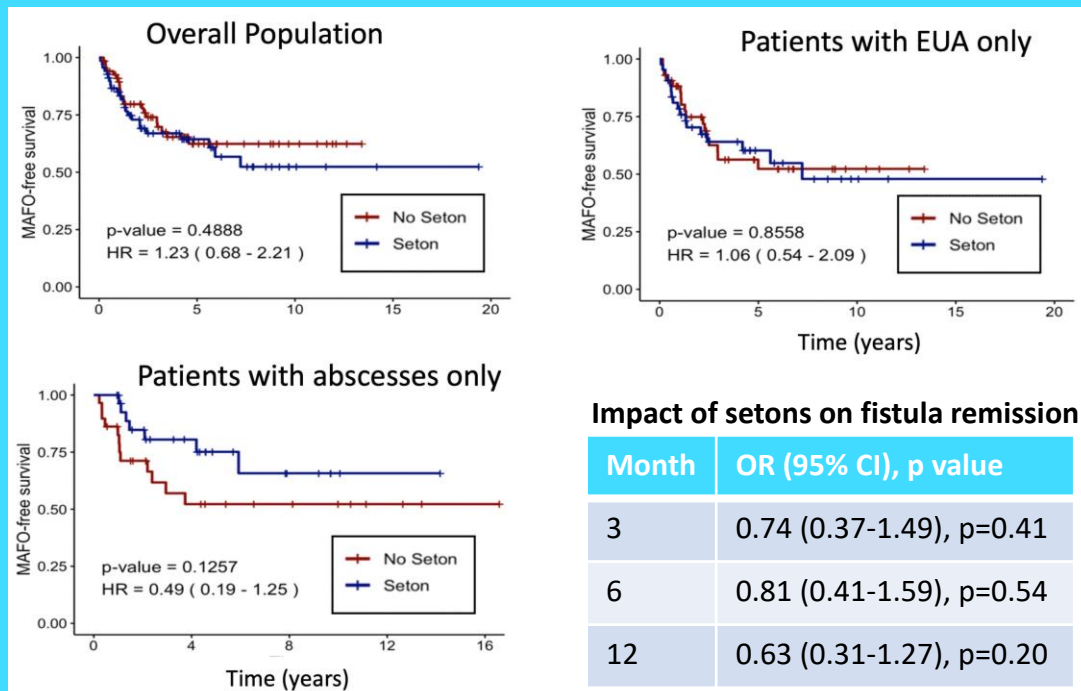
Population

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)*



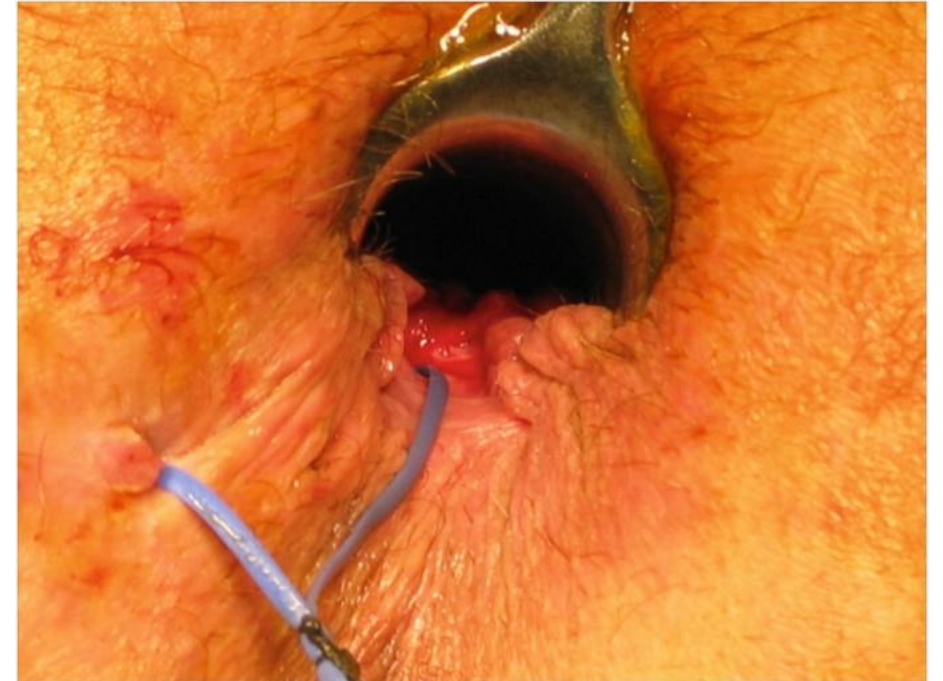
Impact of setons on fistula remission

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

Case 1 continue...

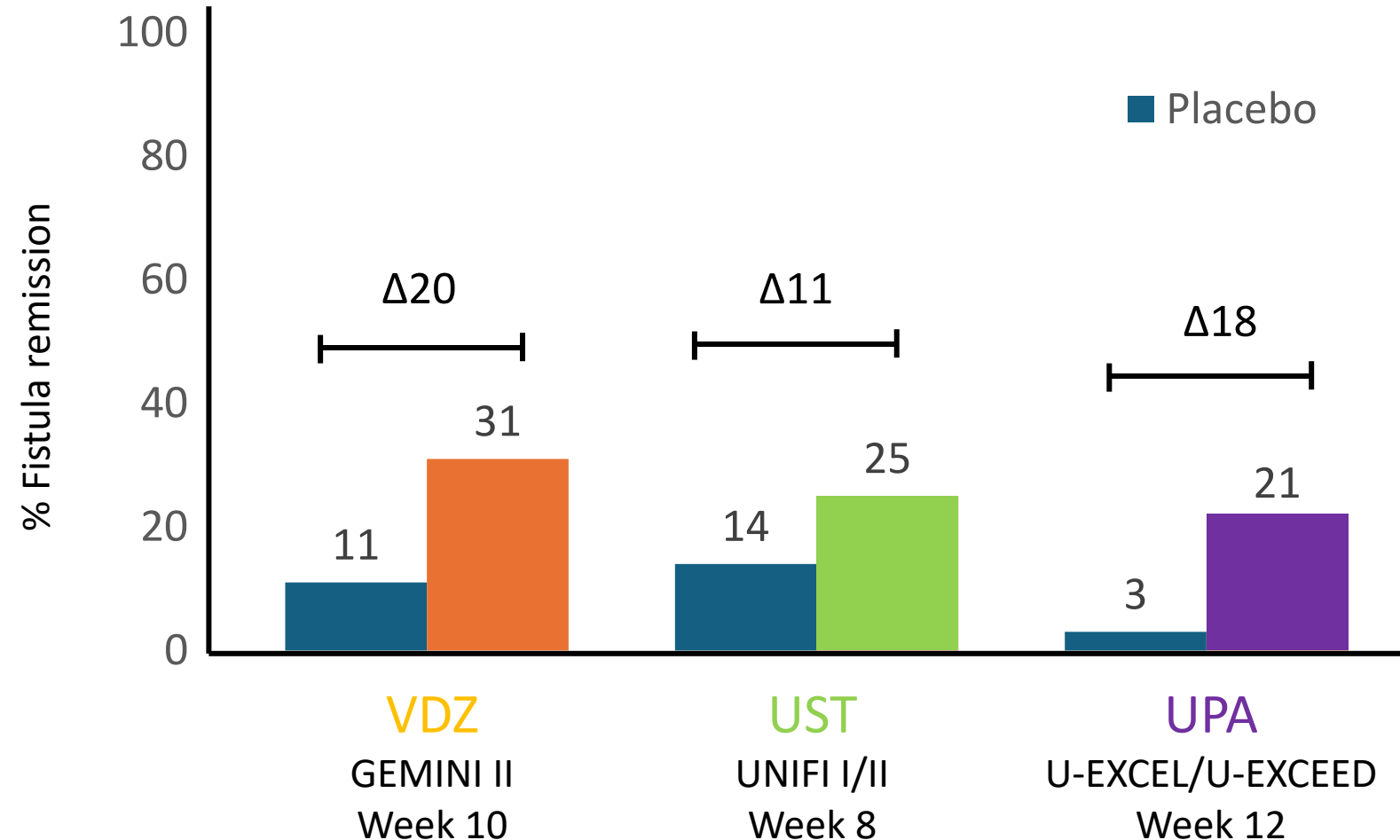
- EUA + single, non-cutting seton
- Antibiotics
- He is concerned with anti-TNF therapy given his family history of MS and would like to know if there are alternate treatment options



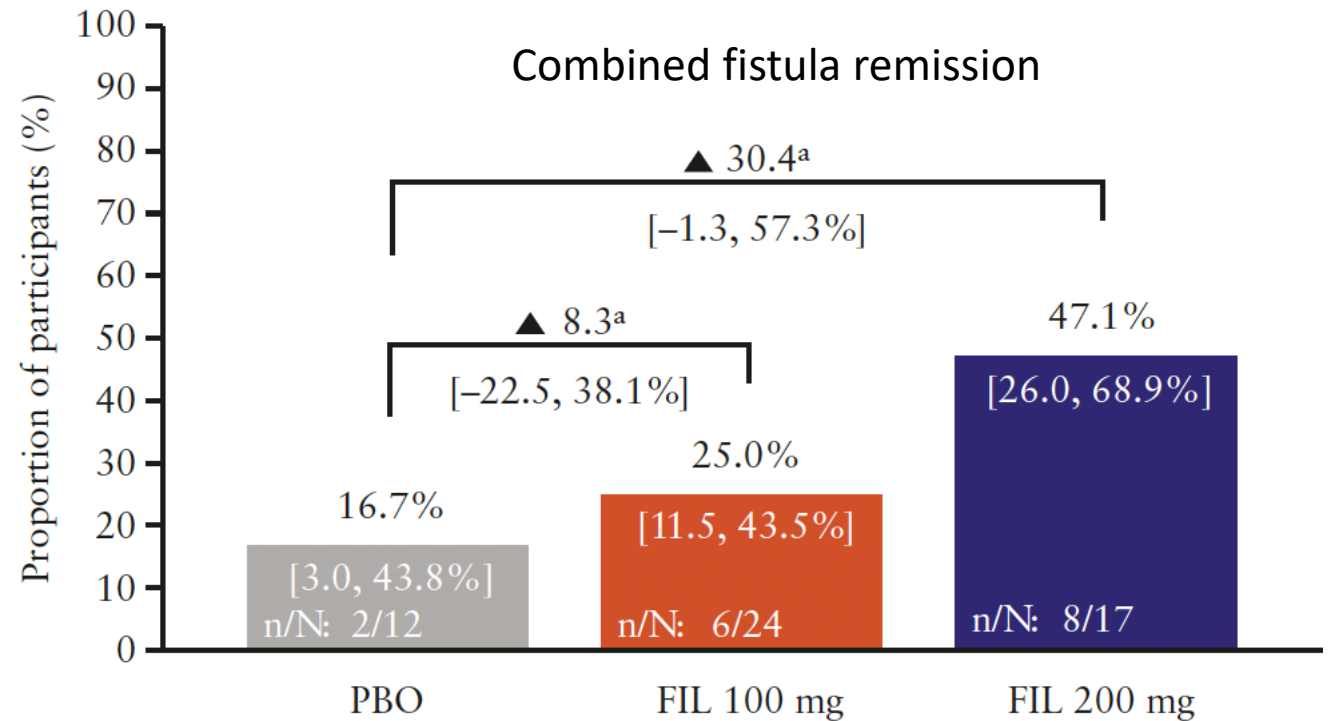
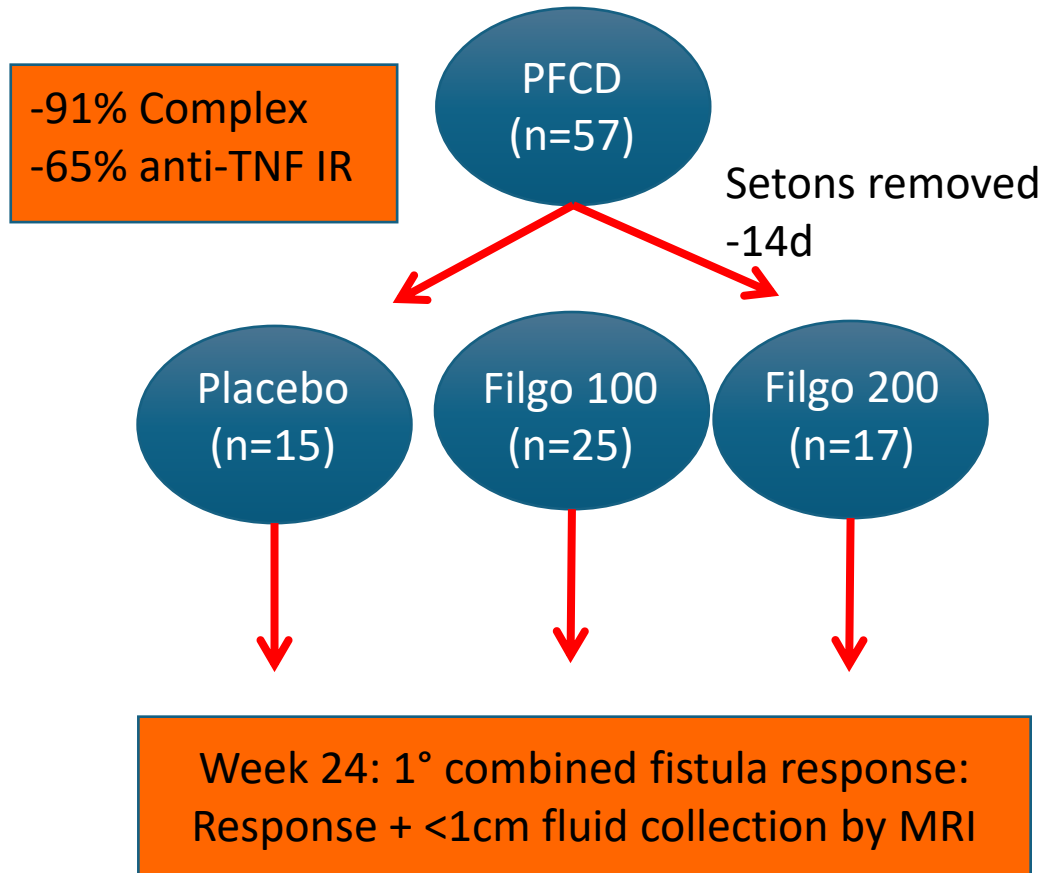
Controversy 3:

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

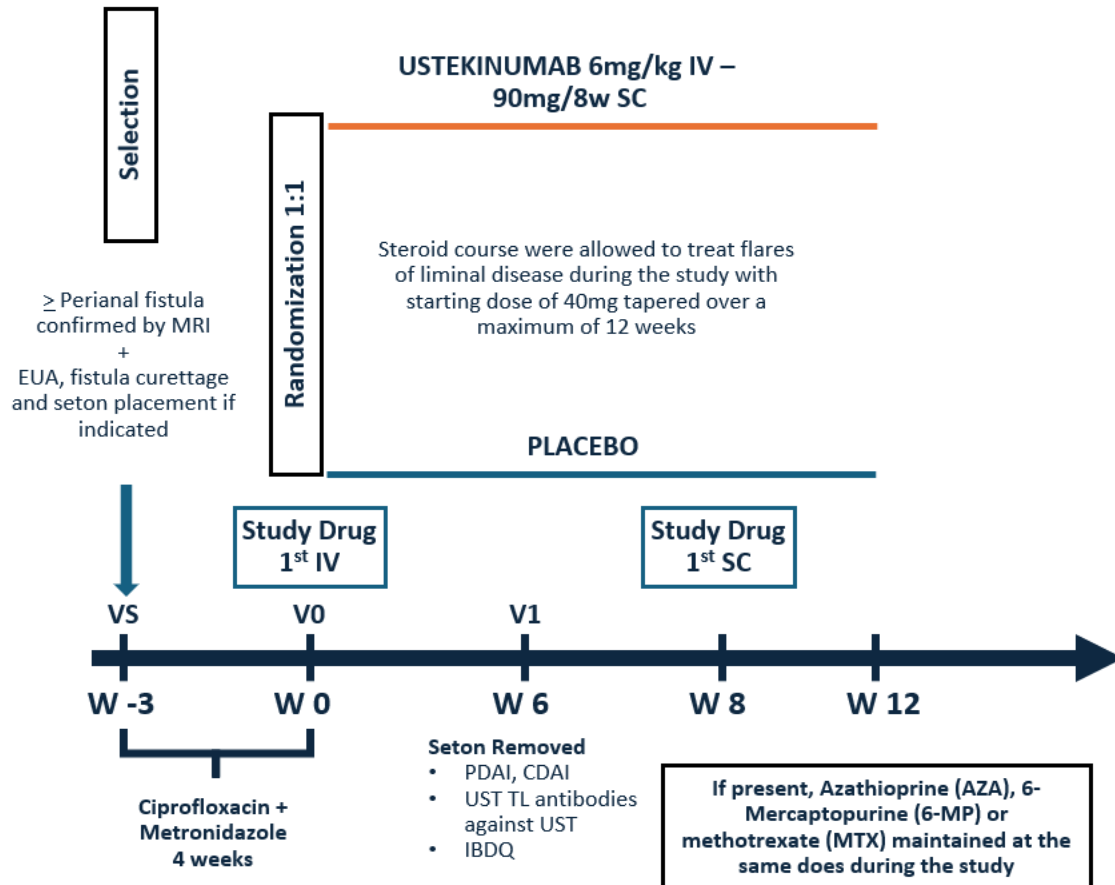
Post-hoc analyses of advanced therapies



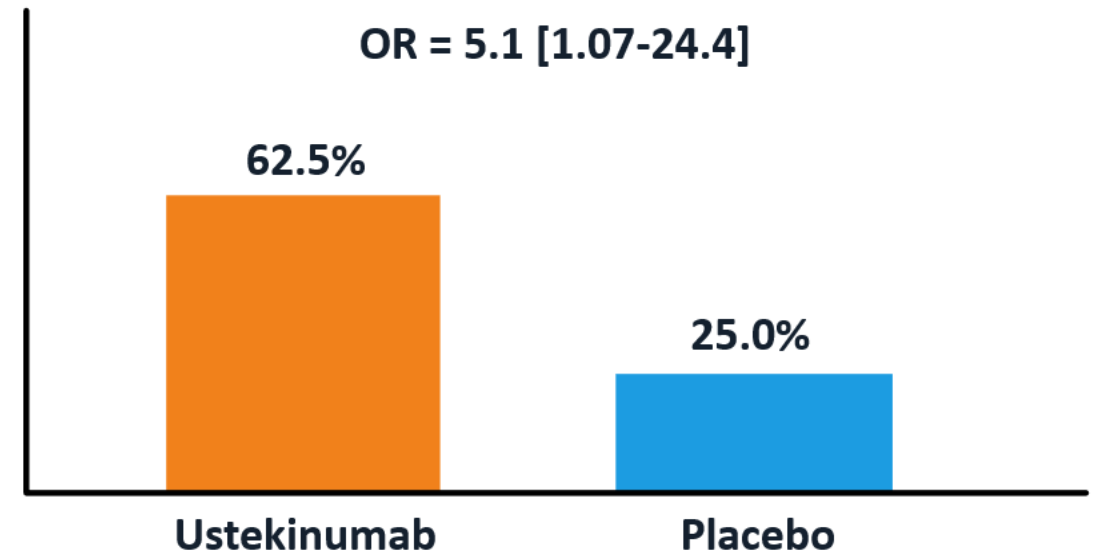
DIVERGENCE-II Trial (Filgotinib)



USTAP Trial (Ustekinumab)



Combined remission at week 12 (Clinical + MRI)



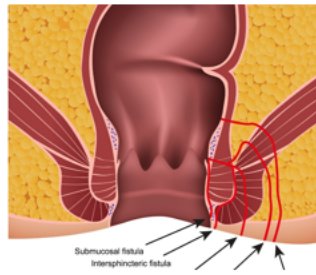
Comparative effectiveness of biologics

Risk of penetrating disease

LPD



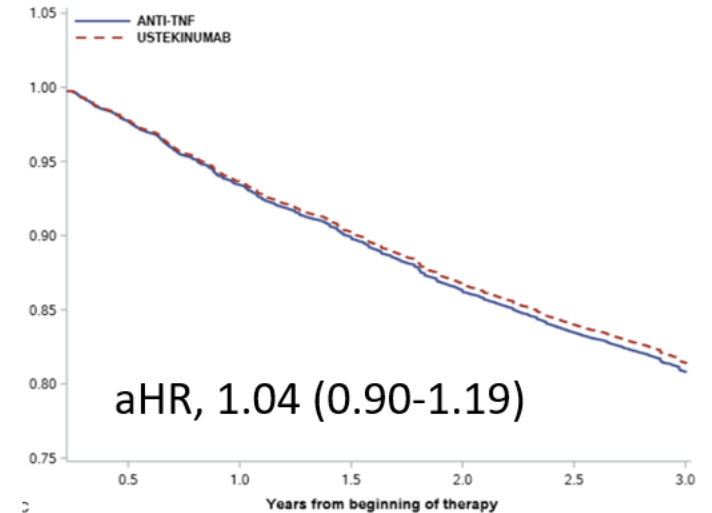
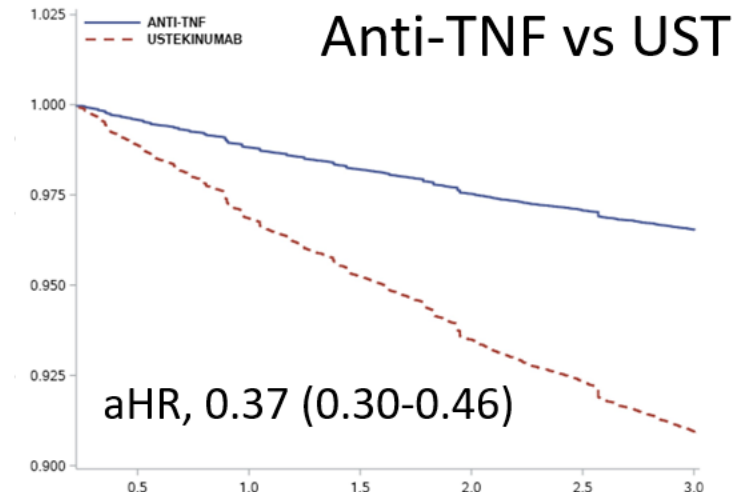
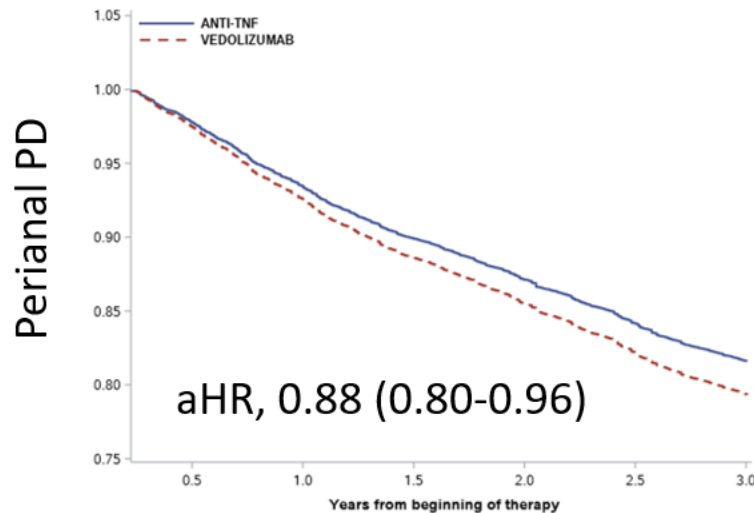
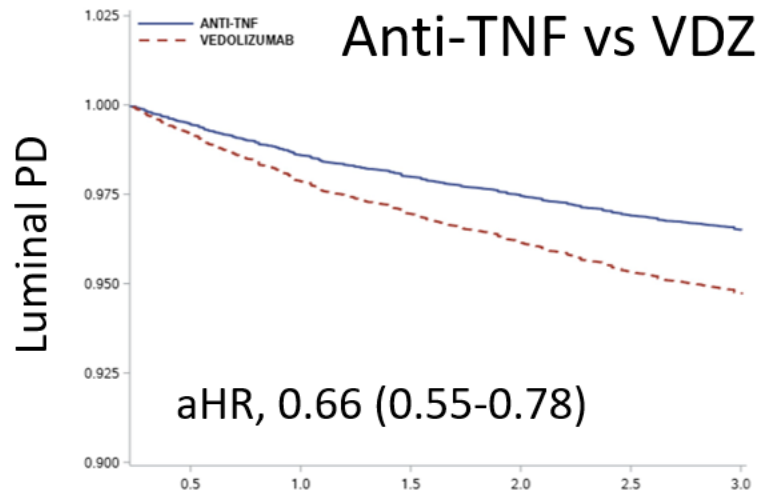
PPD



(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



Case 1 continue...

Treatments

- IFX (5 mg/kg IV every 8 weeks)
- Methotrexate (15 mg PO weekly)

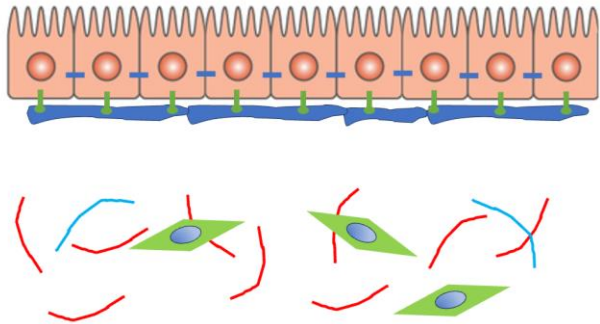
6 months later - perianal symptoms persist with mild discomfort and moderate daily drainage requiring frequent changing of pads

Controversy 4:

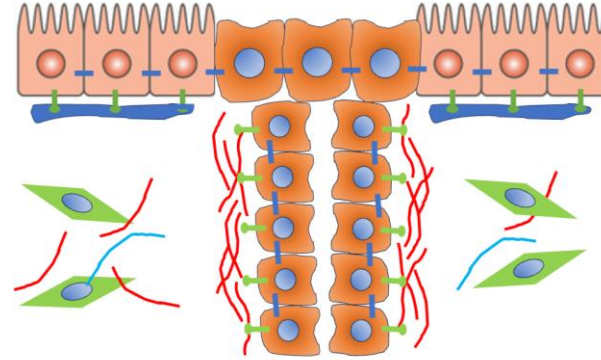
Can fistula healing be reliably determined clinically?

Closed

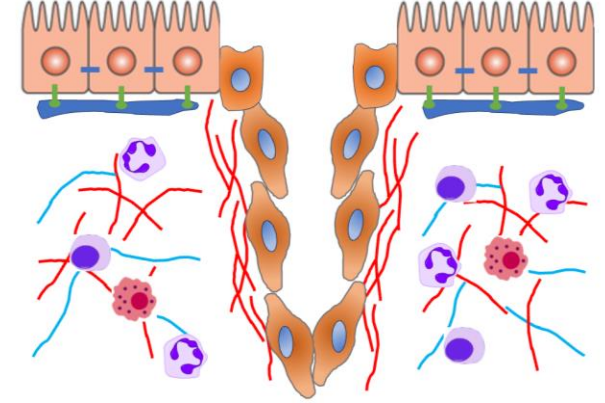
Type A (restitution)



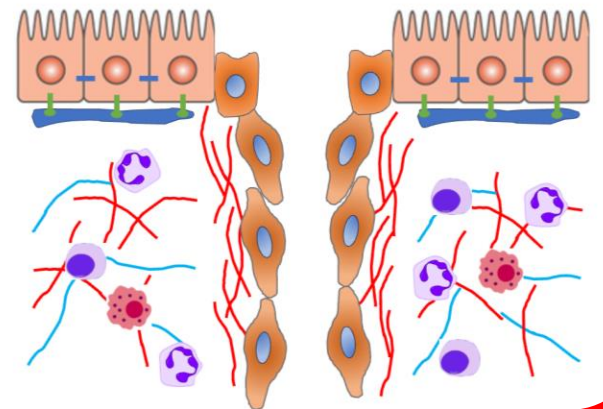
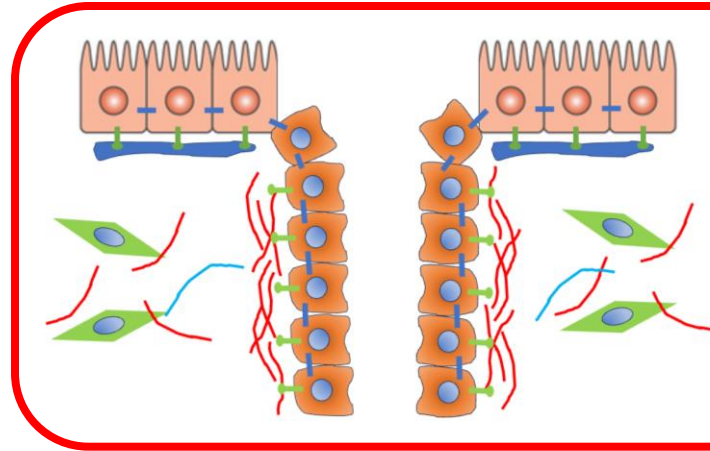
Type B (epithelialization)



Type C (chronic wounds)

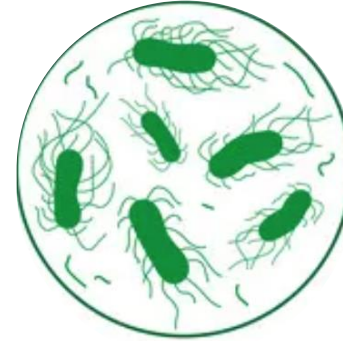


Open



Mechanisms preventing healing/closure

Dysregulated
inflammation



Microbiologic

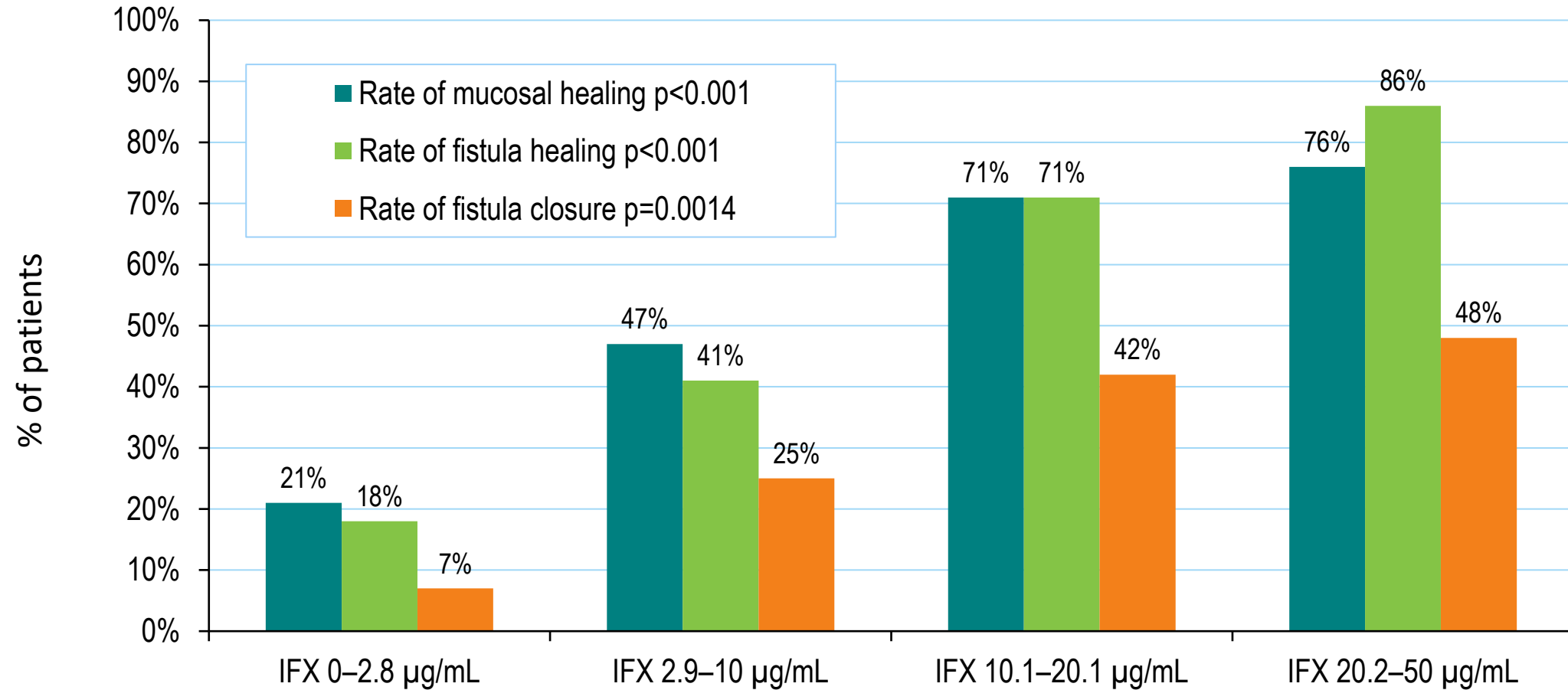
Anatomic

Complexity/
“High pressure
zone”

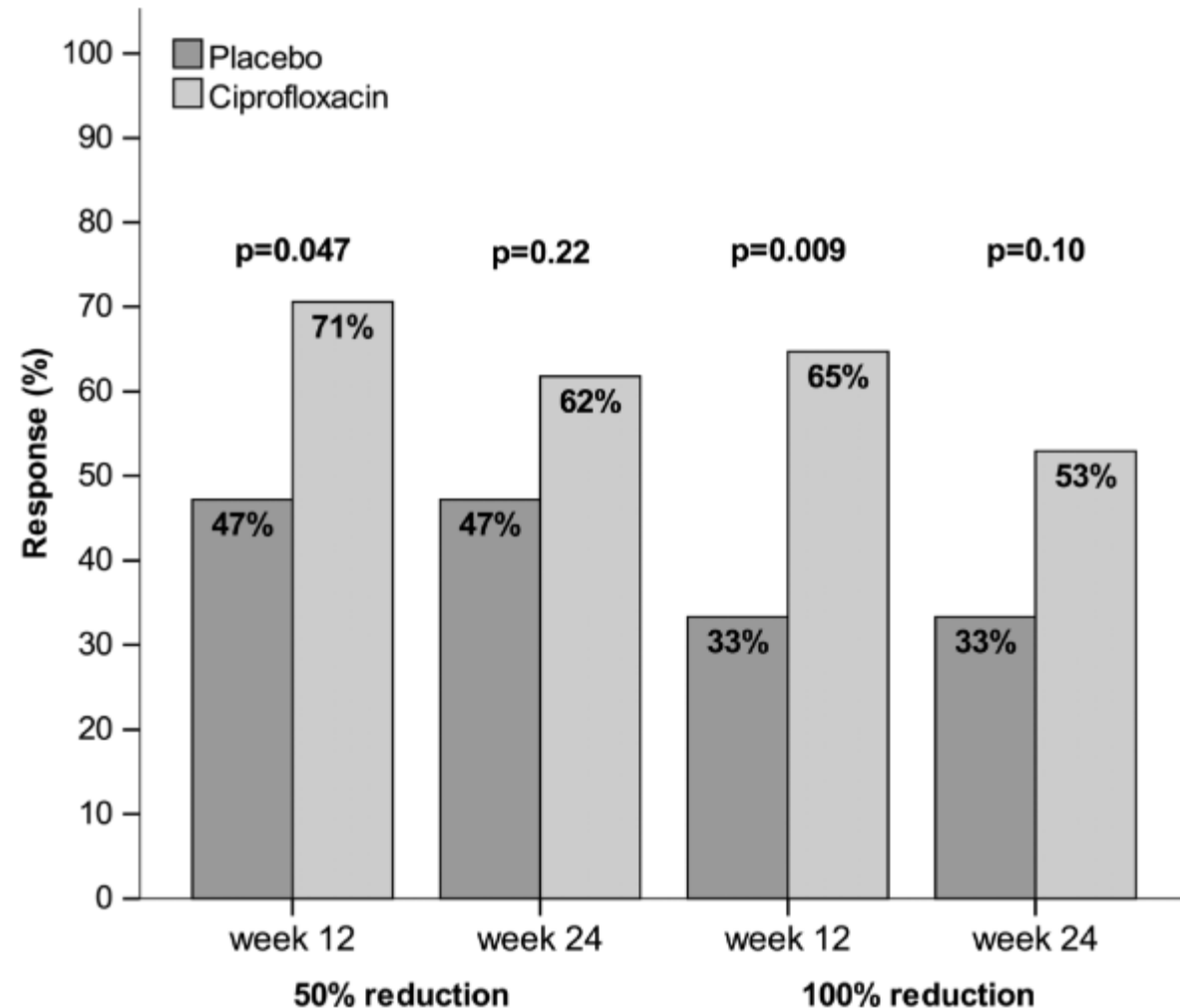
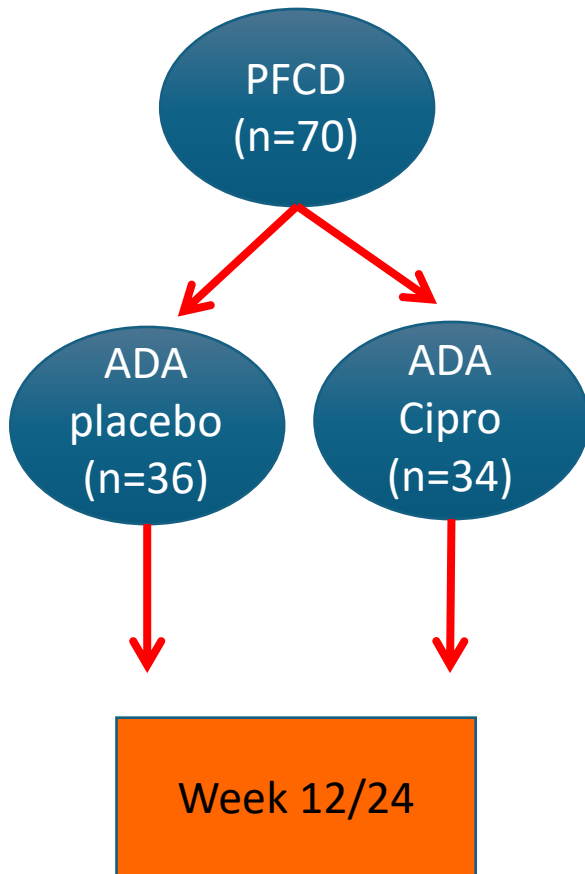


Aberrant
Healing

Higher IFX concentrations & healing

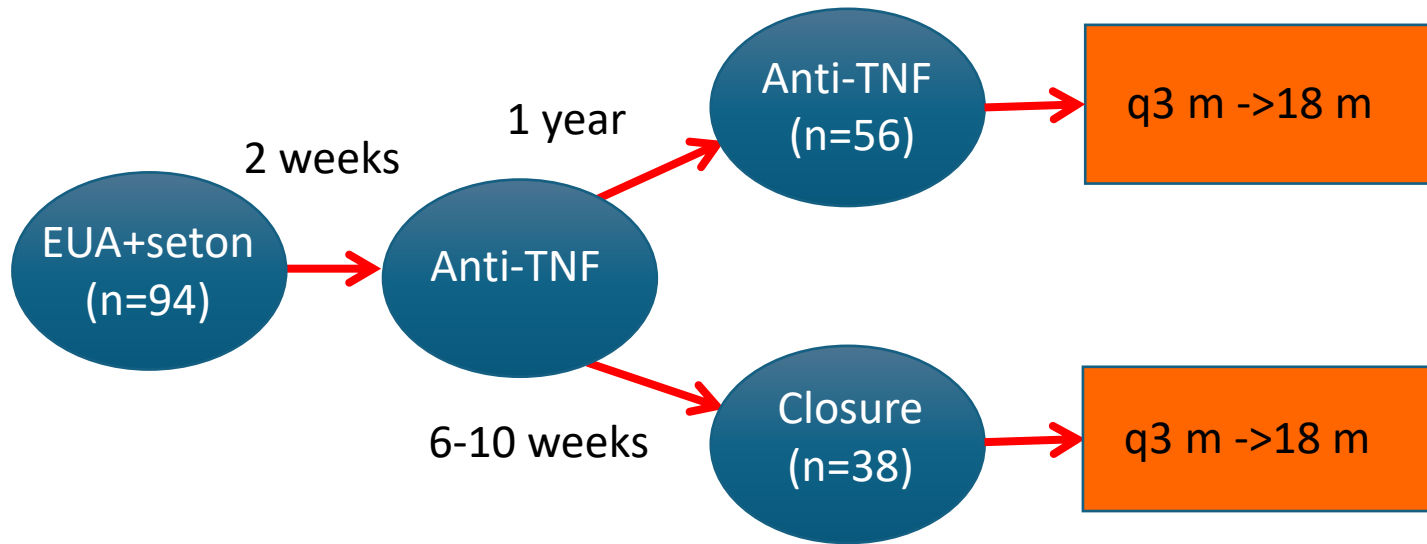


Abx may improve anti-TNF efficacy



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

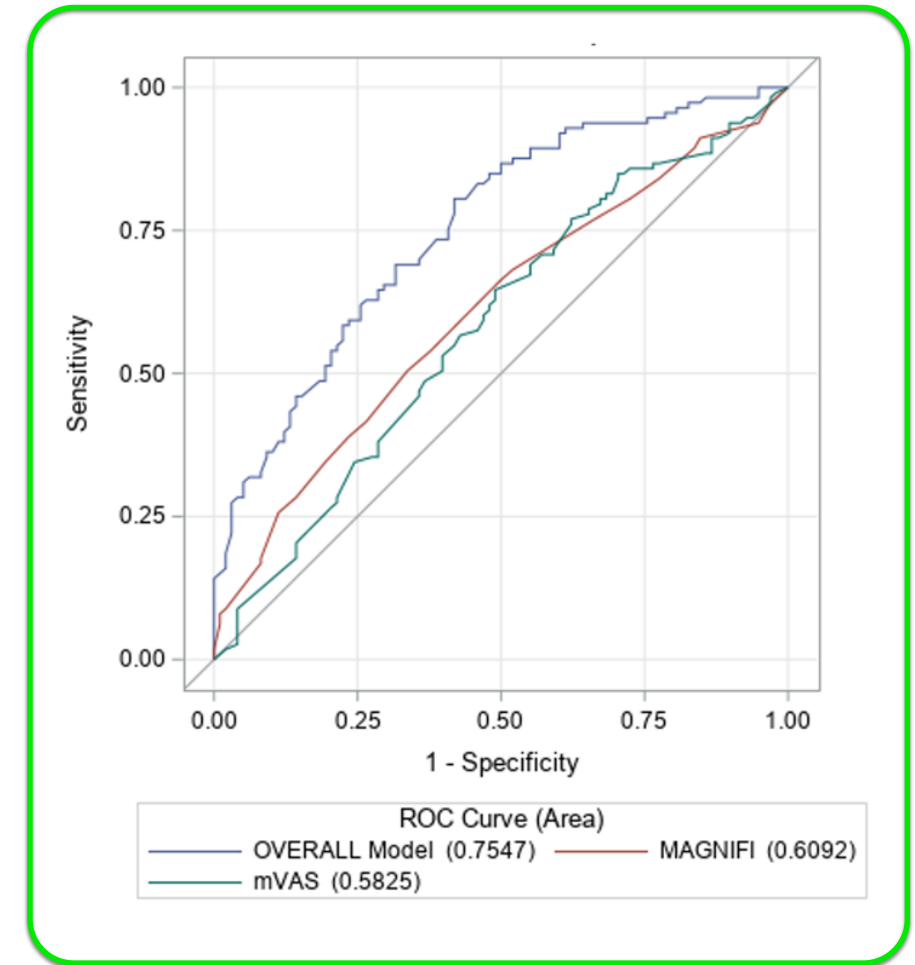
-SC: 4/14 (29%)

-Anti-TNF: 5/31 (16%)

HR 1.17
(0.32–4.37)
p=0.81

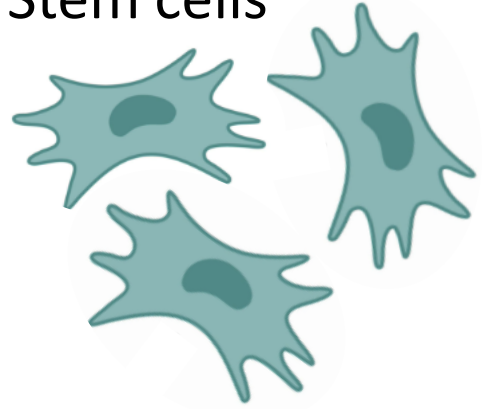
Predicting treatment failure

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



Are there emerging treatment strategies?

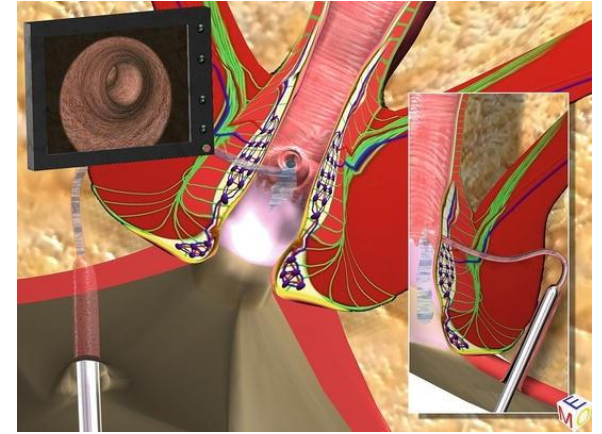
Mesenchymal
Stem cells



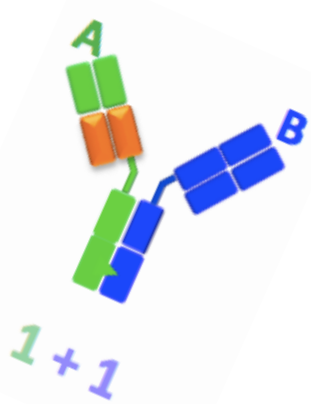
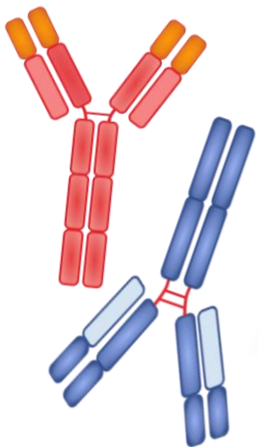
HBOT



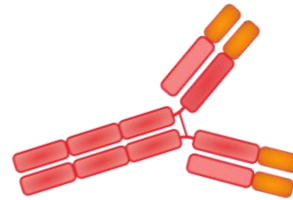
VAFT



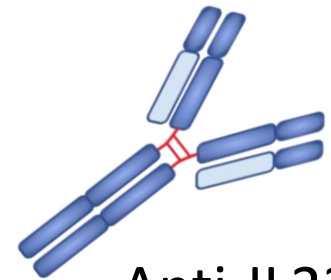
What does the
future hold?



Dual targets

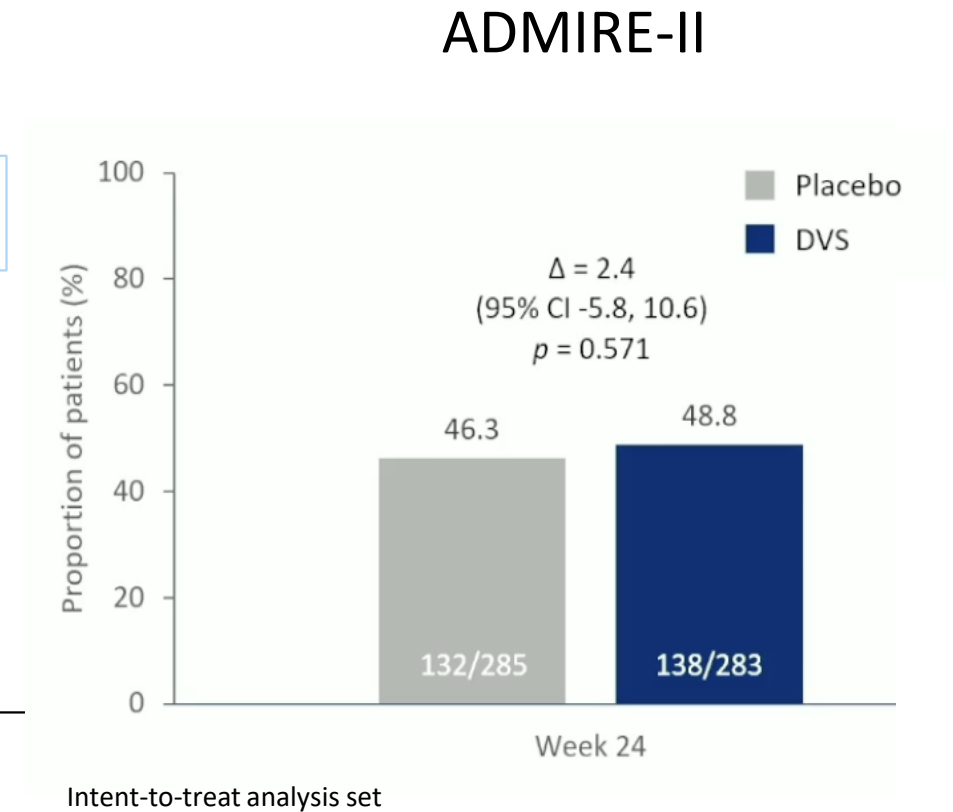
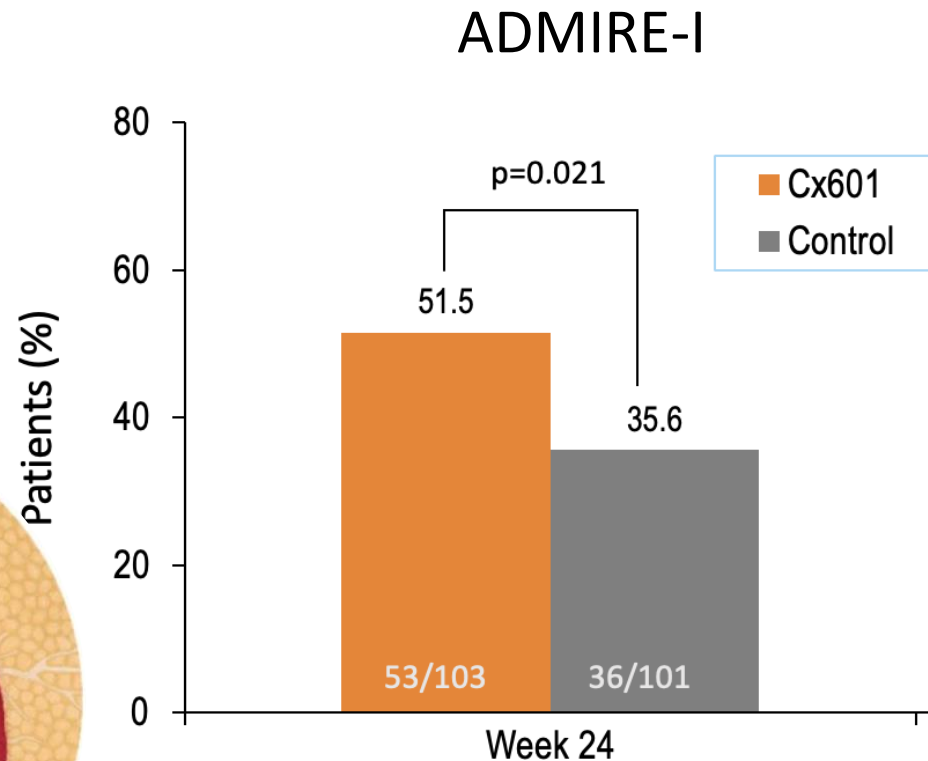
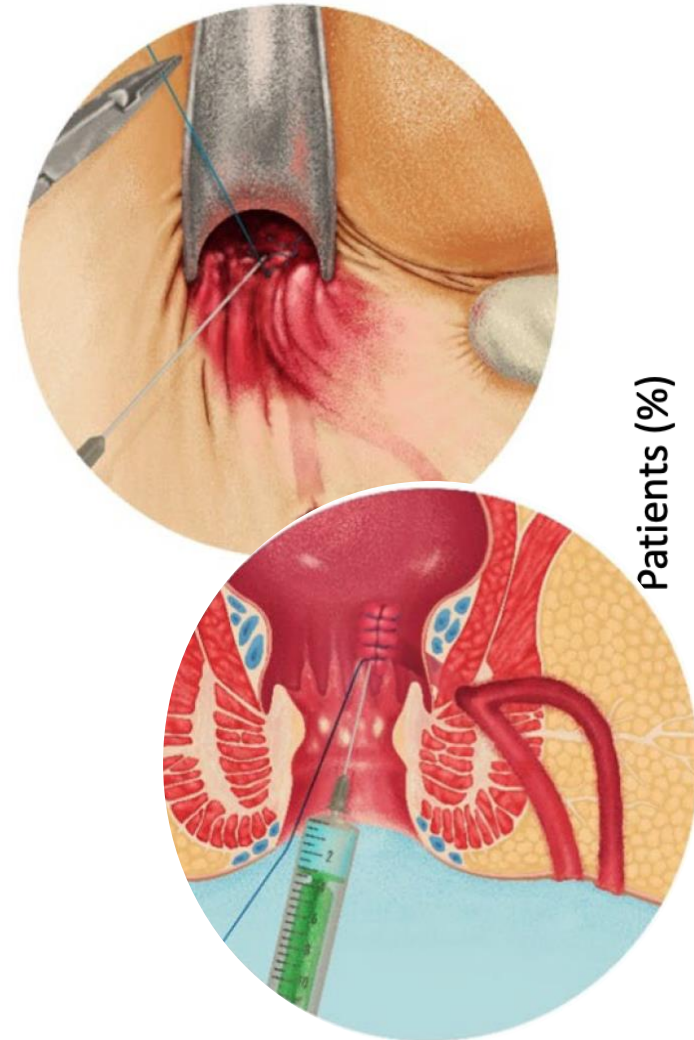


Novel targets



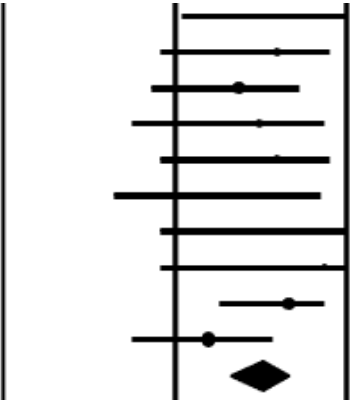
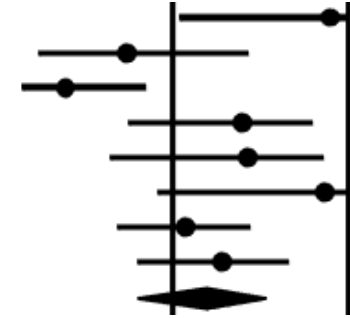
Anti-IL23

ADMIRE Trials: MSC therapy for PFCD



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	

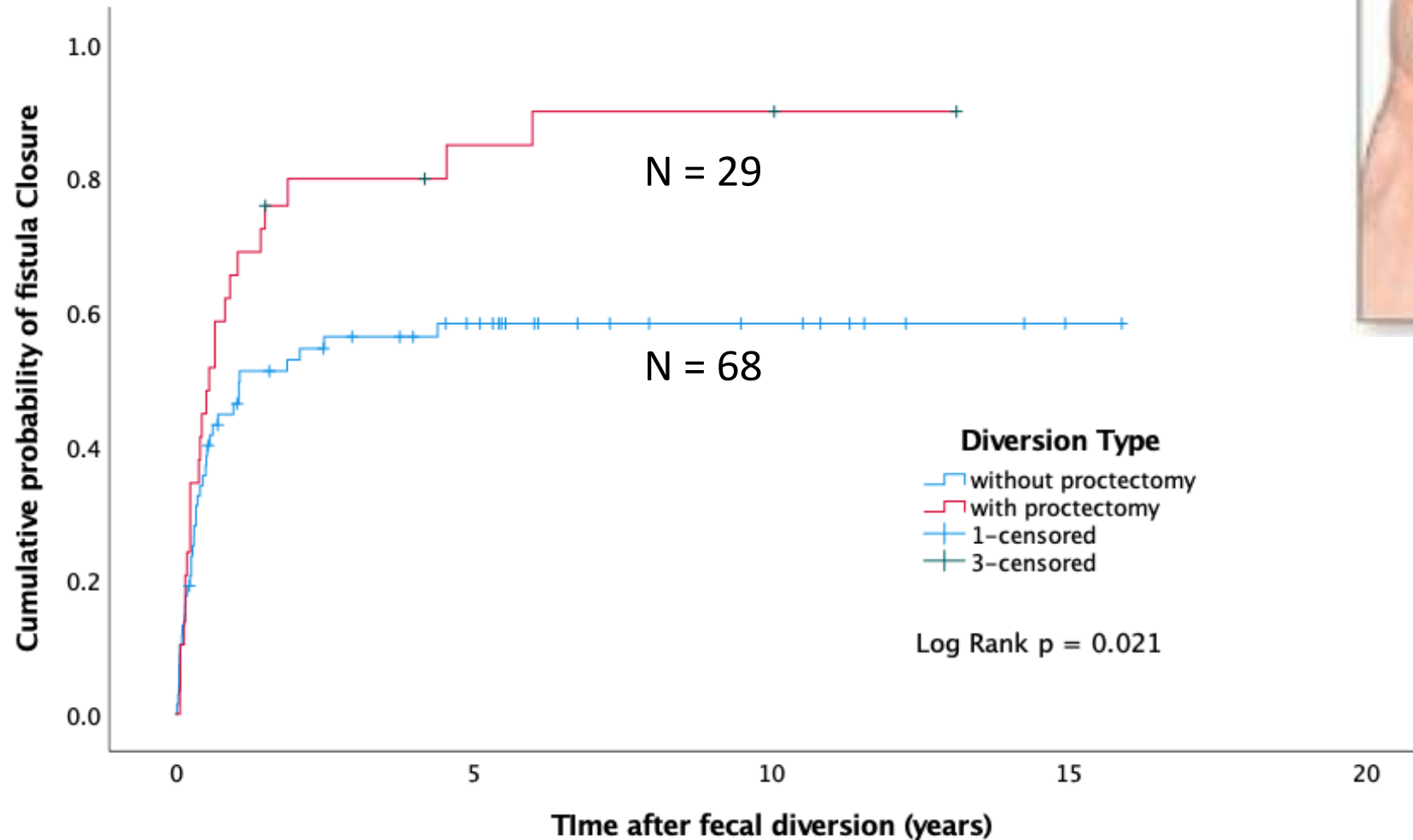
Case 1 continue...

- 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

Controversy 5:

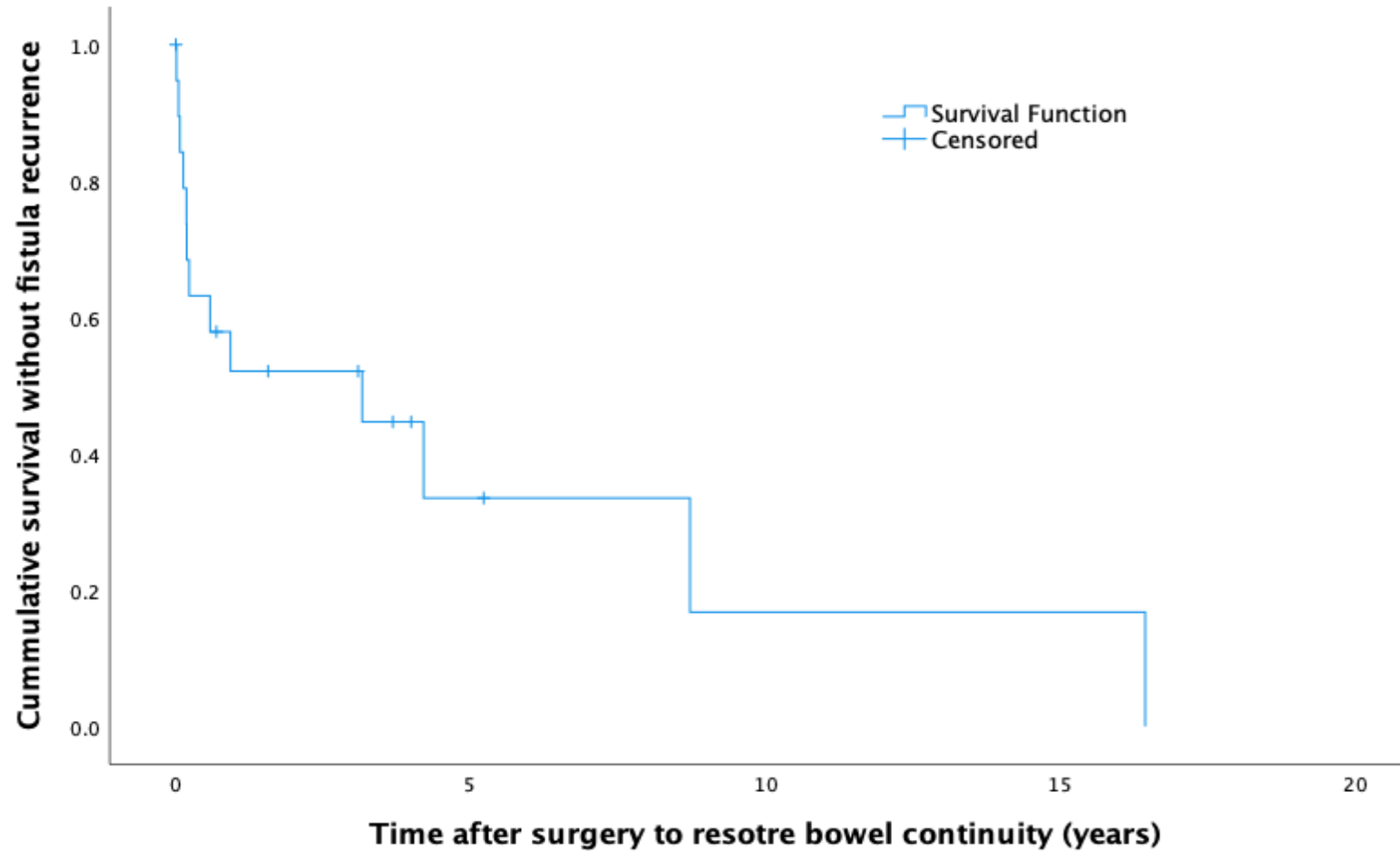
Can fecal diversion be used as an effective temporizing measure?

Impact of fecal diversion



Diverting ostomy
82 patients
97 fecal diversions

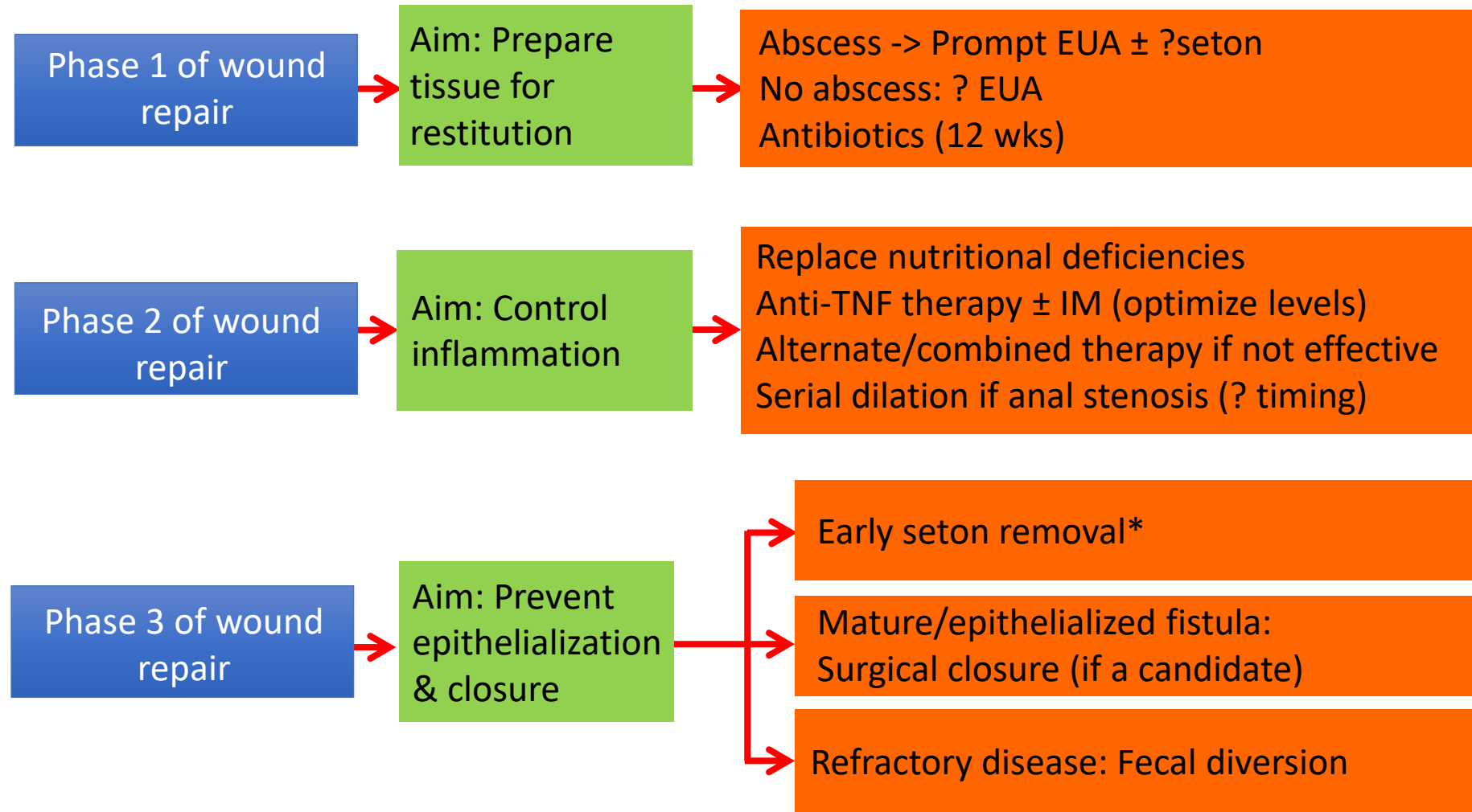
Success of bowel restoration



Bowel restoration
n=21

Putting everything together

Management of PFCD



Conclusions

- 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
- Multiple mechanisms exist for treatment failure
- Fecal diversion while effective is often permanent

IBD CLINICAL CARE PATHWAYS

Helps to improve **quality of care** and **health outcomes** for people with IBD

Available in
French and English



For more info, contact
research@crohnsandcolitis.ca

17 IBD pathways

Providing evidence-based best practices when treating people with IBD

Informed

By the most current evidence available, best practices, and expert opinions

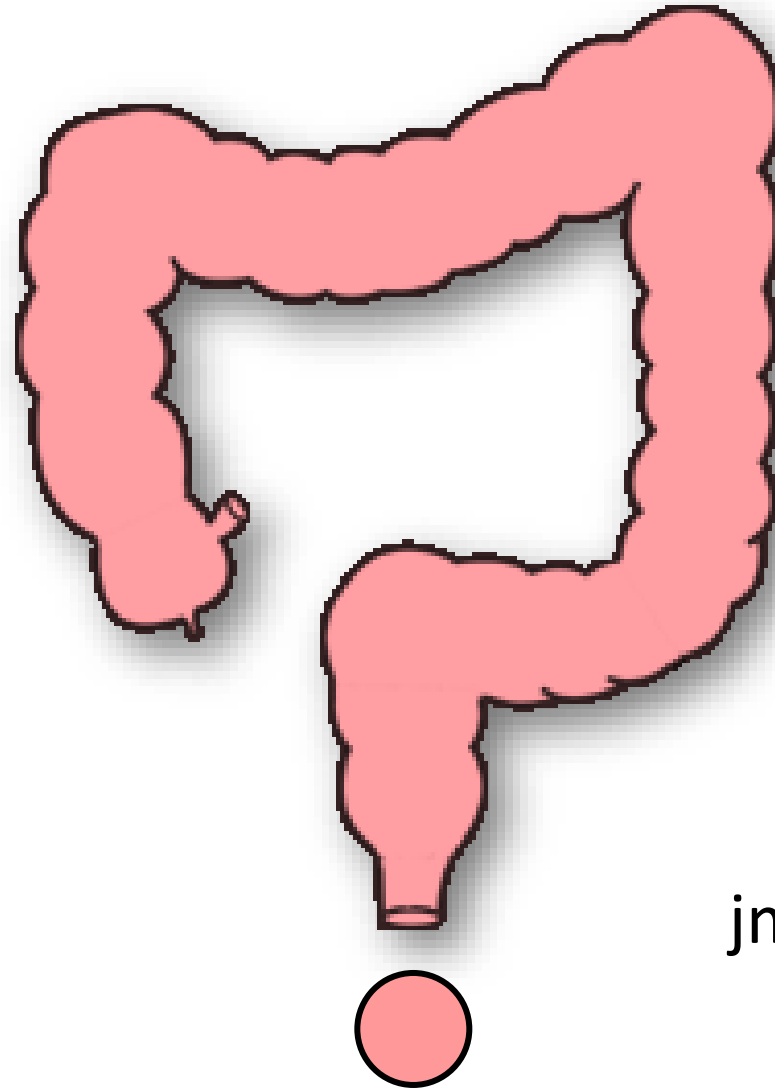
Reviewed

By a multi-disciplinary group of IBD clinical and community practitioners, and patient partners

Interactive versions

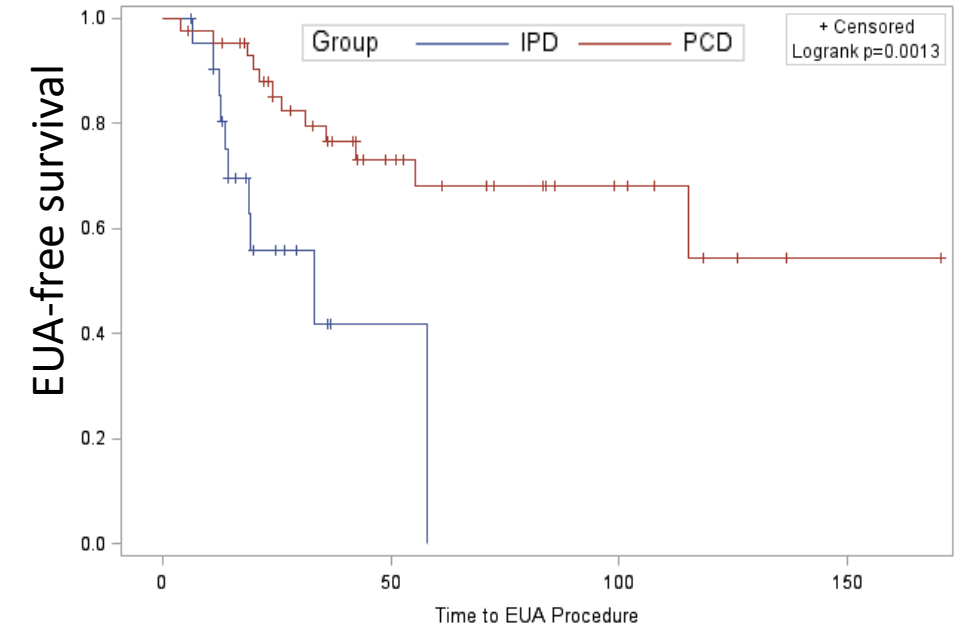
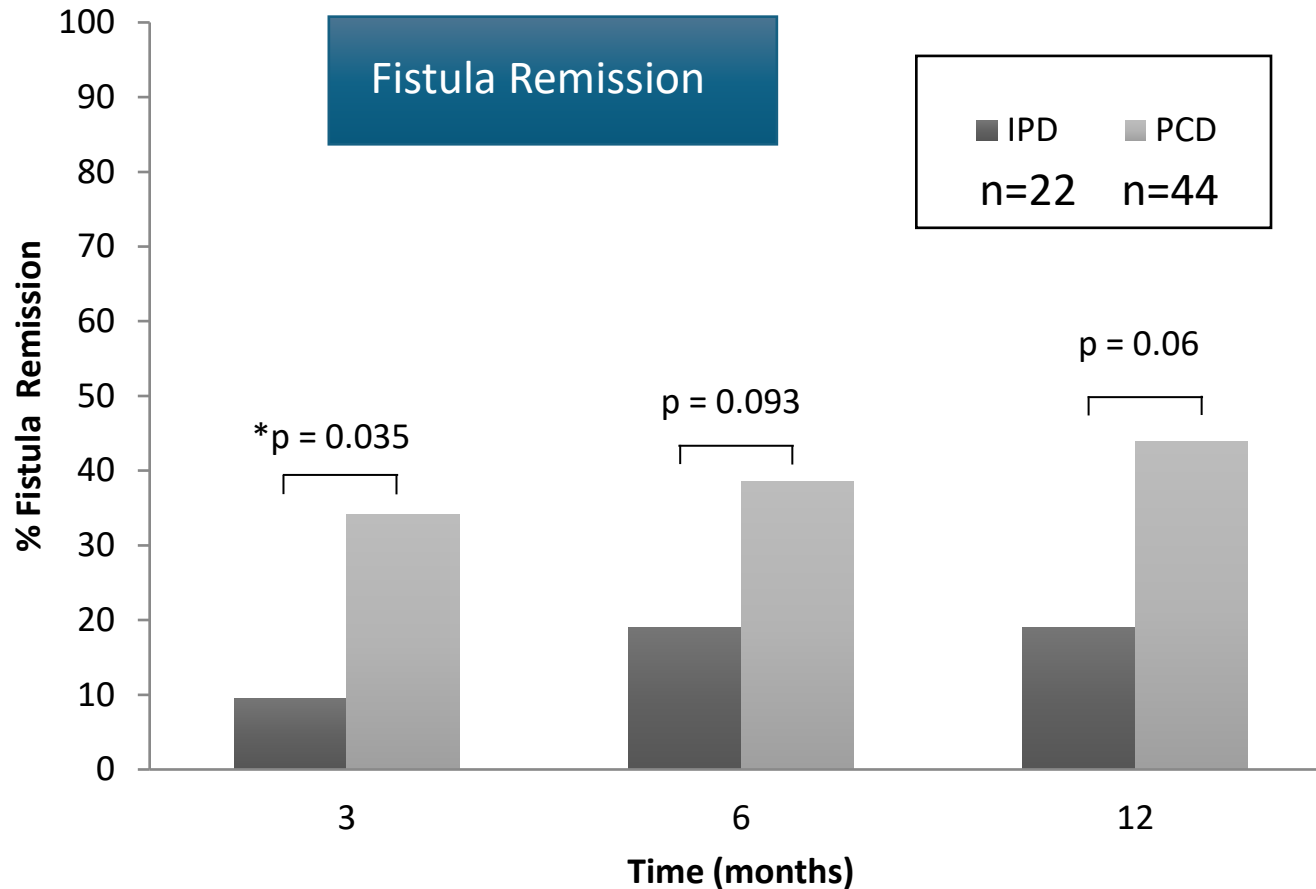
Available for select pathways

Thank you



jmccurdy@toh.ca

Anti-TNF for isolated PFD?



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)

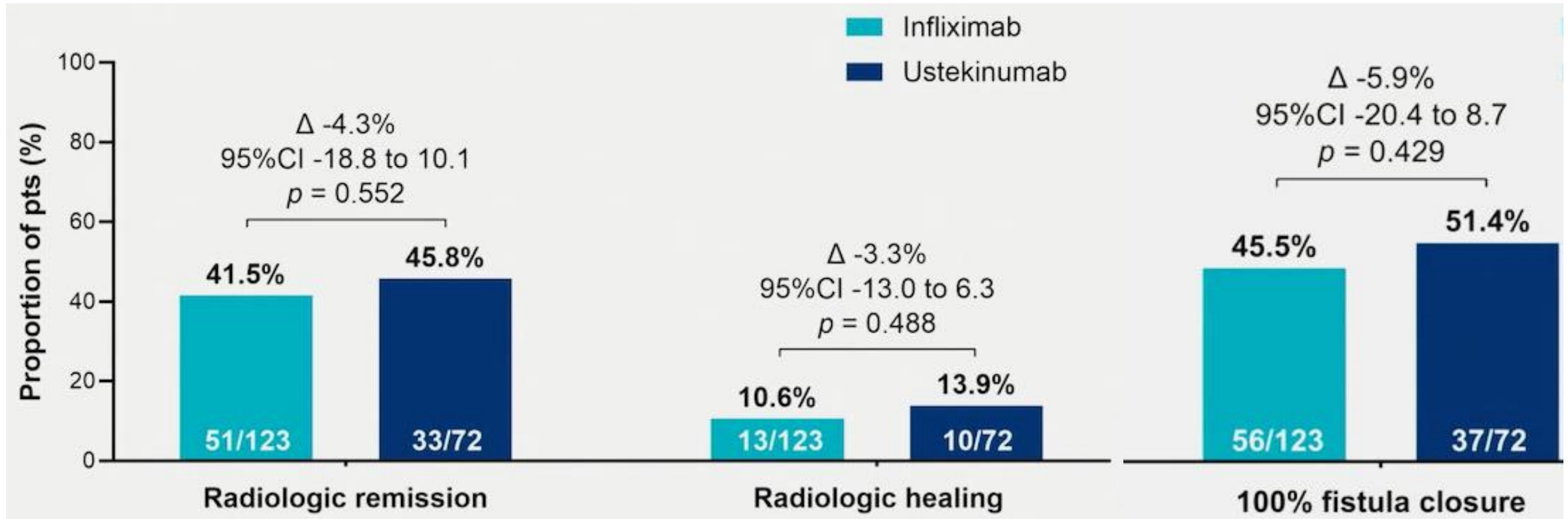
Clinical suspicion*

- 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

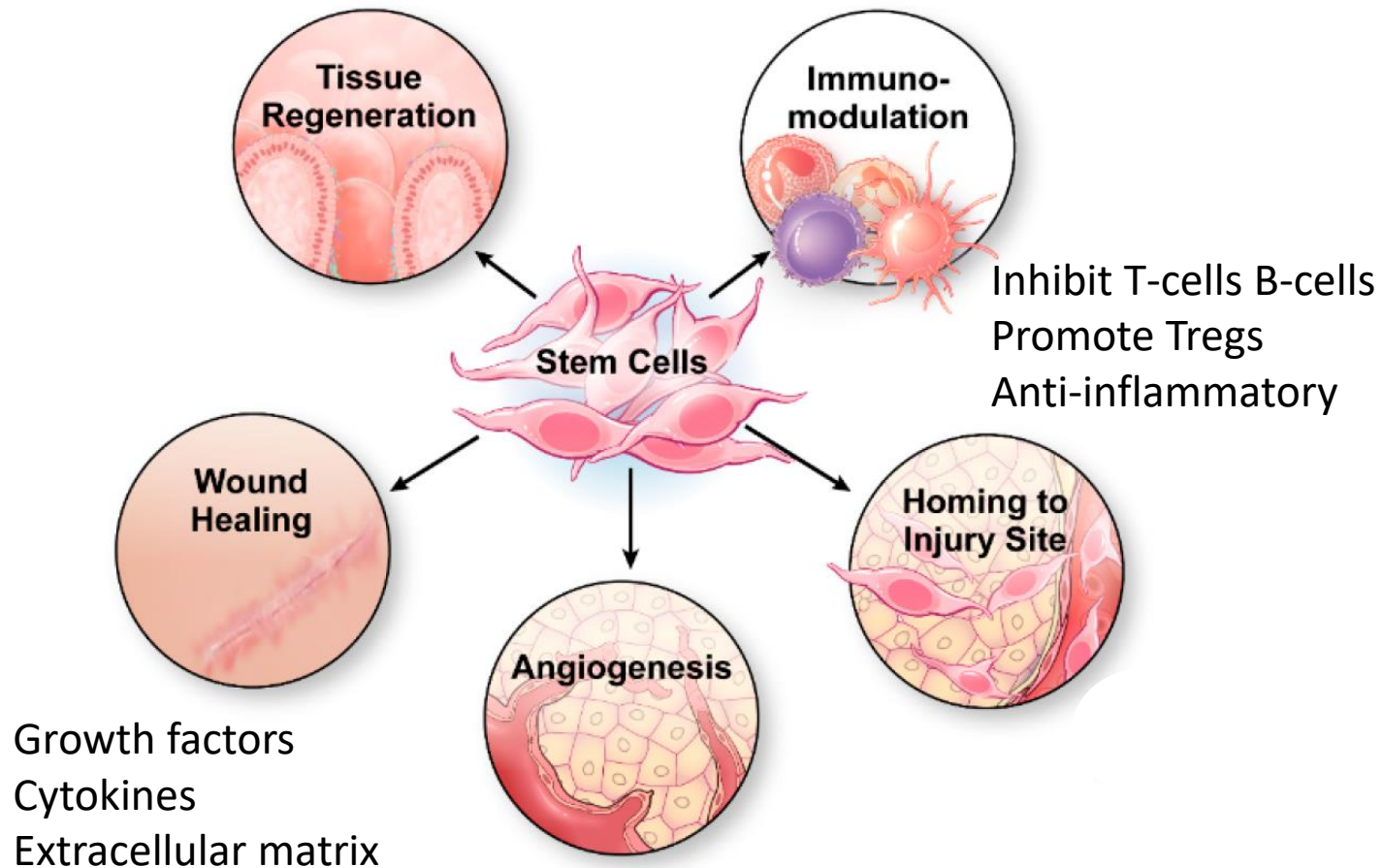
Criteria for consideration of early colonoscopy in patients with perianal fistula

Comparative effectiveness of IFX vs UST



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

Targeting aberrant healing



- ↓ Inflammation
- ↑ Growth factors
- ↑ Stem cell
- ↑ Antimicrobial