

# **Contemporary approaches to management of perianal fistulae in Crohn's Disease**

Tim Raine

Consultant Gastroenterologist & IBD lead, Addenbrooke's Hospital, Cambridge, UK

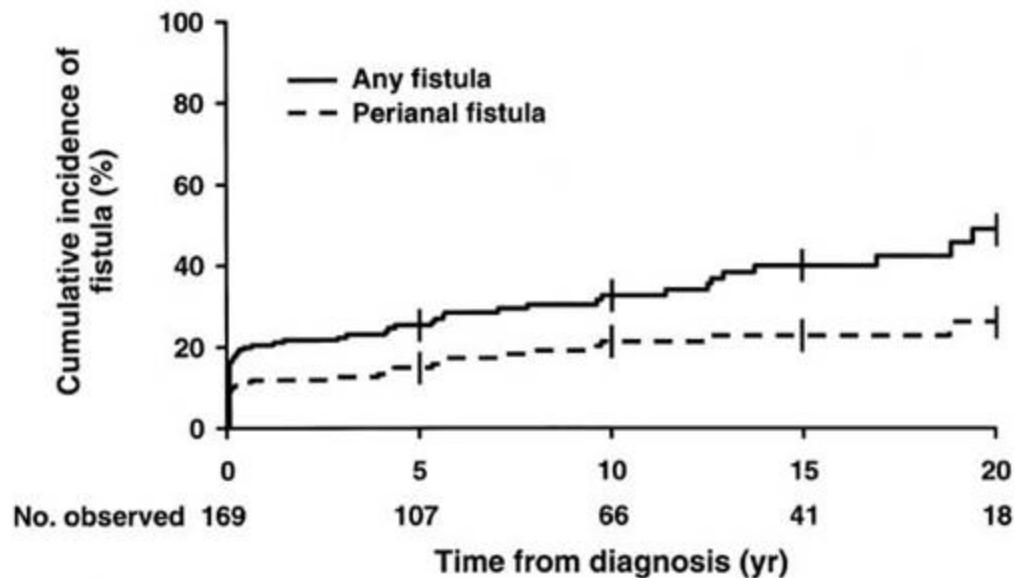
## Disclosures

### Tim Raine

Has received research/educational grants and/or speaker/consultation fees from:

- Abbvie, BMS, Celgene, Ferring, Gilead, GSK, LabGenius, Janssen, MSD, Novartis, Pfizer, Sandoz, Takeda and UCB

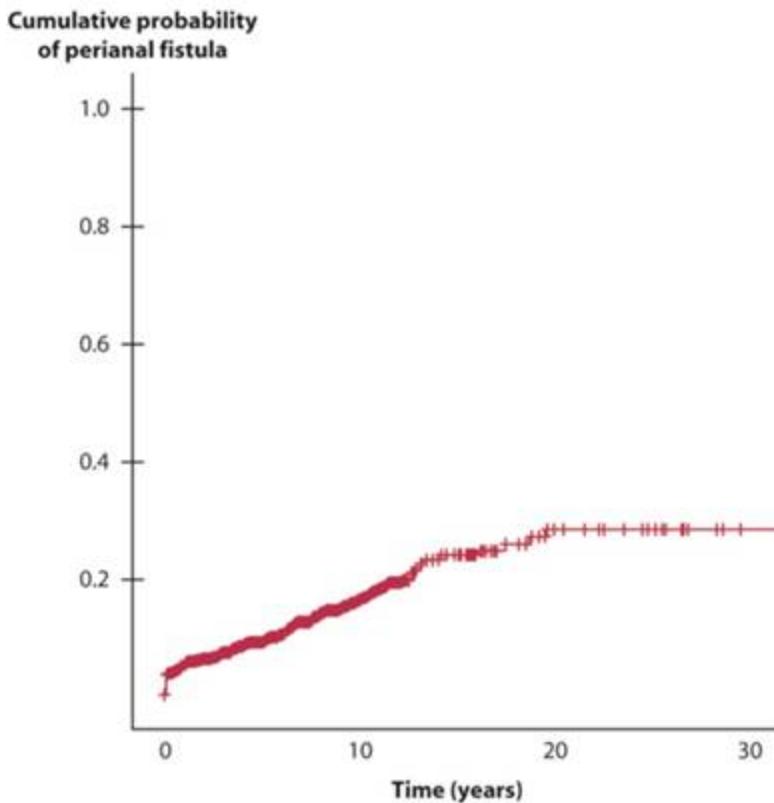
## Scale of the problem?



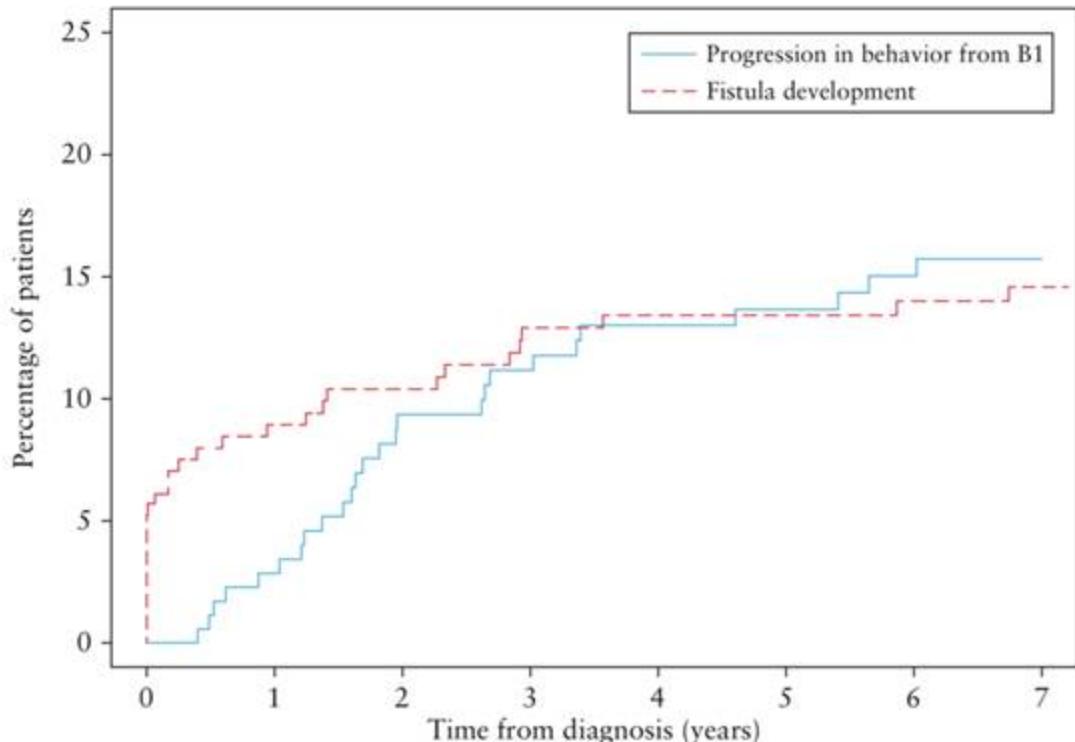
## Scale of the problem?

<i>Site of intestinal lesion</i>	<i>Patients (no.)</i>		
	<i>Total</i>	<i>With fistulae</i>	
		(No.)	(%)
Small intestine	339	40	12
Combined ileocolic	341	51	15
Large intestine			
No rectal involvement	68	28	41
With rectal involvement	71	65	92

## Scale of the problem?



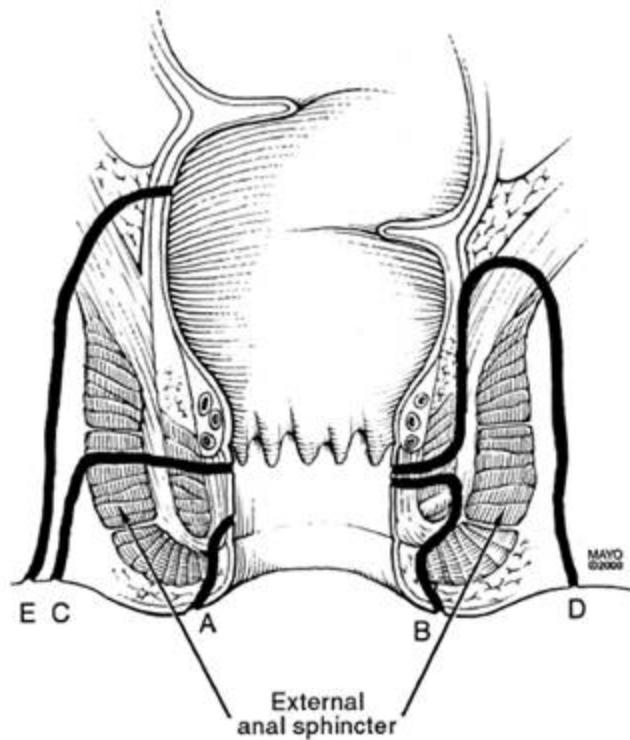
# Scale of the problem?



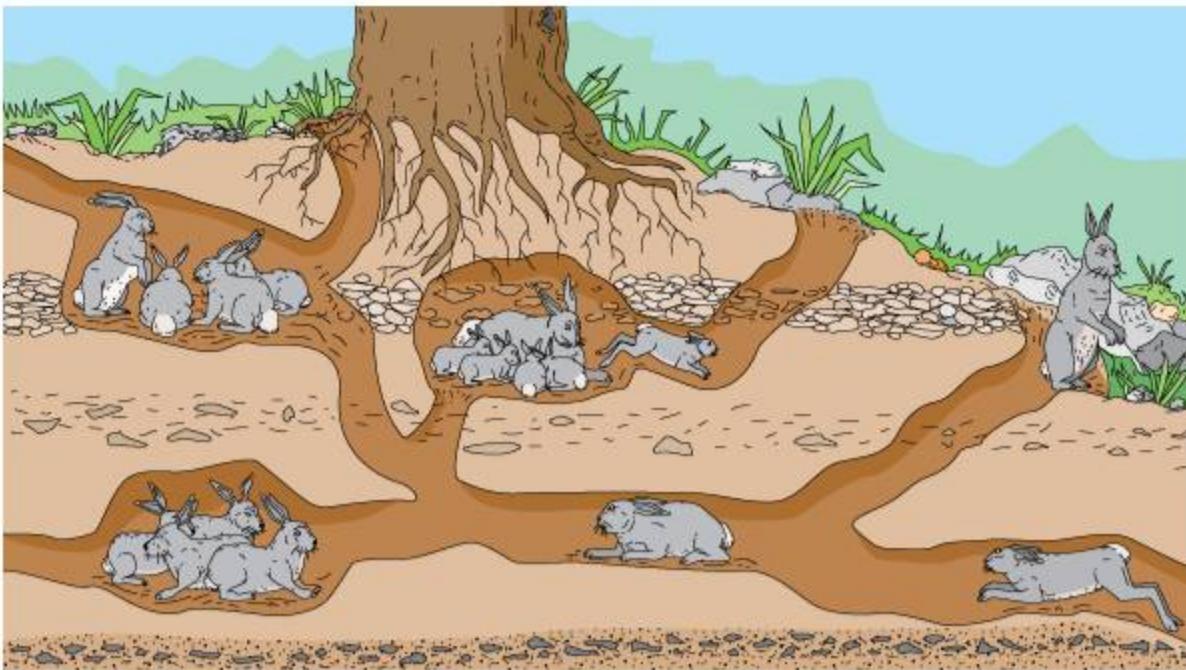
	Predictors
	Fistula development
Observations	204
Gender [male]	1.56 [0.64, 3.82]
Smoking status	
Former	0.28 [0.03, 2.26]
Never	1.15 [0.47, 2.81]
Current	[Ref]
Diagnostic delay	1.00 [1.00, 1.01]
Age group	
A3	1.34 [0.26, 6.94]
A2	1.82 [0.39, 8.38]
A1	[Ref]
Behaviour at diagnosis	
B3	5.14** [1.77, 14.89]
B2	1.4 [0.26, 7.56]
B1	[Ref]
Location at diagnosis	
L4	2.38 [0.36, 15.72]
L3	4.03 [0.86, 19.01]
L2	3.91 [0.92, 16.56]
L1	[Ref]
Change in location	1.88 [0.63, 5.58]
Medical treatment	
5-aminosalicylates	1.84 [0.51, 6.54]
Corticosteroids	0.24* [0.06, 0.87]
Immunomodulators	1.87 [0.57, 6.17]
Biologics	2.76* [1.04, 7.34]

Zhao M et al. *Inflammatory Bowel Diseases* 2019

## Anatomical classification of perianal fistulae



## In complex Crohn's the challenge is the multiple tracts



## Empiric classification of perianal disease

- Physical examination
  - Skin tags, fissures, perianal fistulae, rectovaginal fistulae, suspected abscesses, anorectal strictures
- Endoscopic examination
  - Proctitis?

Simple?

- *Superficial/low intersphincteric/low transphincteric*
- *Single opening*
- *No evidence of abscess or stricture*

## Empiric classification of perianal disease

- Physical examination
  - Skin tags, fissures, perianal fistulae, rectovaginal fistulae, suspected abscesses, anorectal strictures
- Endoscopic examination
  - Proctitis?

Complex?

- *High origin*
- *Multiple external openings – signifies multiple tracts*
- *Pain, fluctuance, stricture*
- *Rectovaginal involvement*

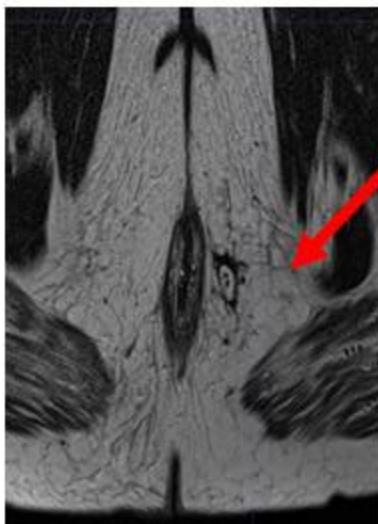
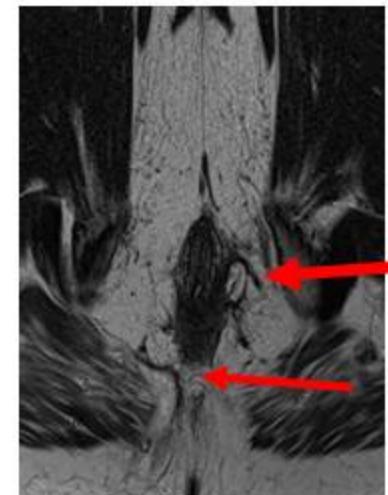
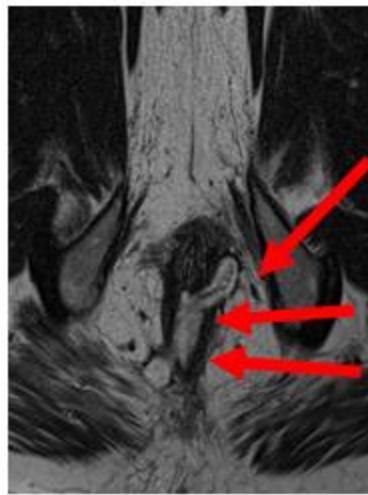
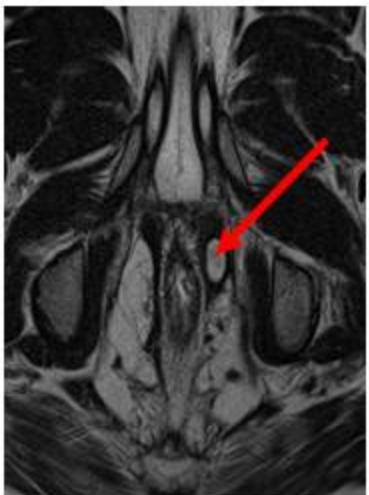
## Further evaluation of complex fistulae

- Examination under anaesthetic



- Imaging
  - What is the best approach?
  - When is the best time to image?
  - What questions do we need from imaging?





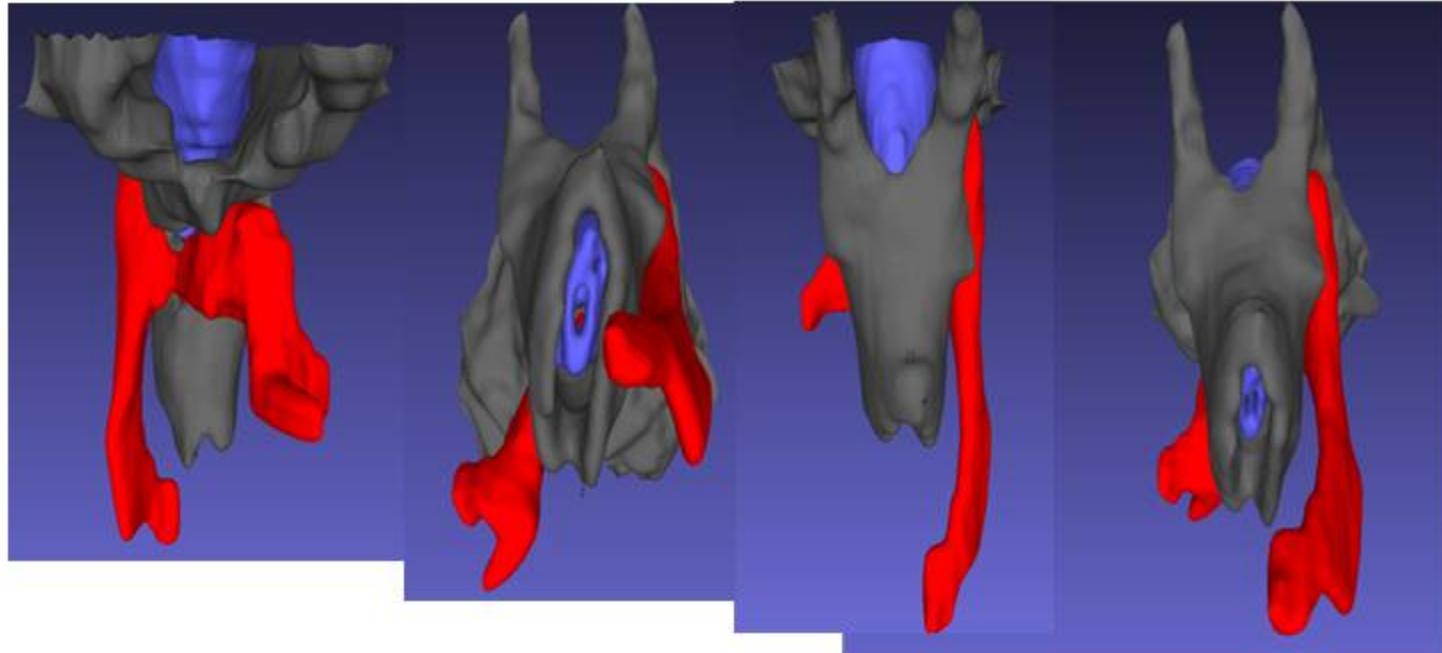
Images courtesy of Janindra Warusavitarne

PA/2245/2019/UK

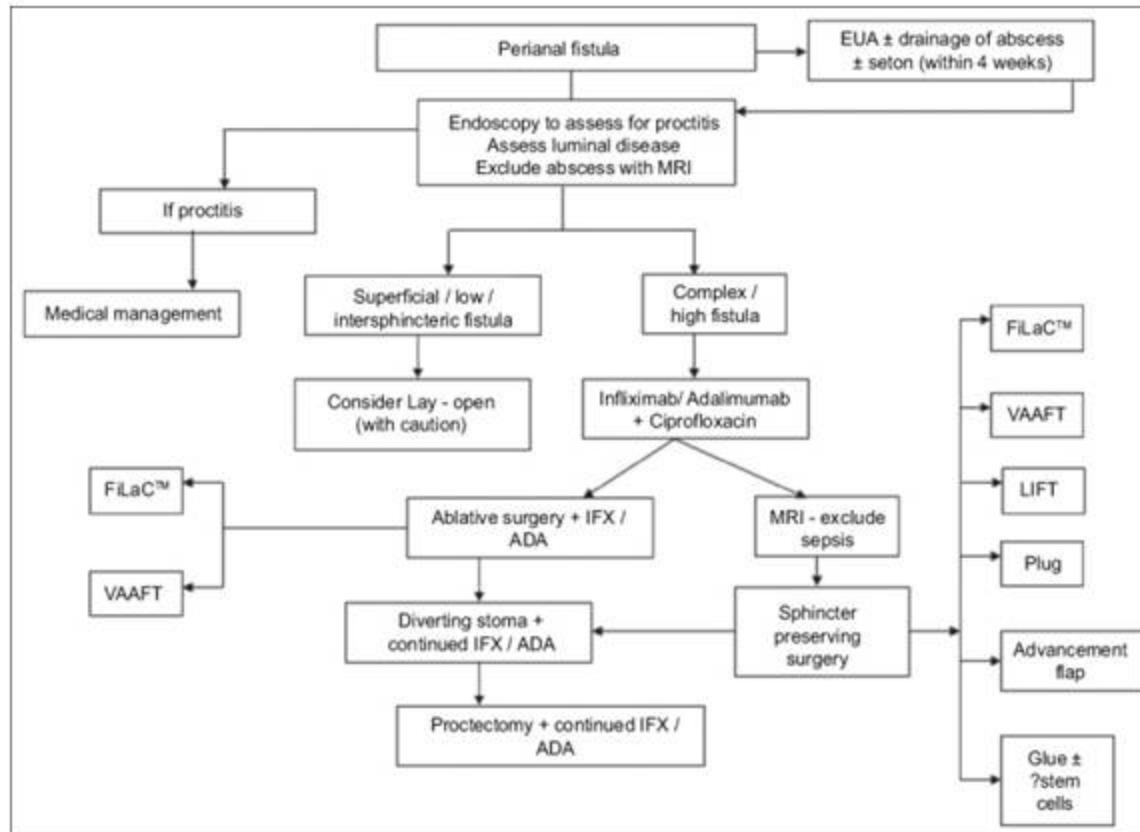
September 2019

Author	Type of Study	Patients (CD)	Imaging	Gold Standard	FISTULAS			ABSCESSSES		
					Sensitivity	Specificity	Accuracy	Sensitivity	Specificity	Accuracy
Lummis, P.J. 1992	Prospective	16 (n.r.)	1) MRI	EUA	n.r.	n.r.	1) 78%	n.r.	n.r.	n.r.
Spencer, J.A. 1996	Prospective	42 (2)	1) MRI	EUA	1) 97%	1) 67%	1) 88%	n.r.	n.r.	n.r.
Stoker, J. 1998	Prospective	20 (n.r.)	1) MRI	EUA	1) 86%	1) 100%	n.r.	n.r.	n.r.	n.r.
Orsoni, P. 1999	Prospective	22 (22)	1) EUS 2) MRI	EUA	1) 100% 2) 77%	1) 66% 2) 80%	1) 82% 2) 50%	1) 100% 2) 55%	1) 77% 2) 77%	1) 86% 2) 59%
Beets-Tan, R.G. 2001	Prospective	56 (15)	1) MRI	EUA	1) 100%	1) 86%	n.r.	1) 96%	2) 97%	n.r.
Schwartz, D. 2001	Prospective	33 (33)	1) EUS 2) MRI 3) EUA	consensus after EUS, MRI, EUA	n.r.	n.r.	1) 91% 2) 87% 3) 91%	n.r.	n.r.	1) 91% 2) 83% 3) 91%
Maier, A.G. 2001	Prospective	39 (17)	1) EUS 2) MRI	EUA	1) 60% 2) 84%	1) 21% 2) 68%	n.r.	n.r.	n.r.	n.r.
Buchanan, G. 2004	Prospective	104 (9)	1) EUS 2) MRI 3) EUA	consensus after EUS, MRI, EUA	n.r.	n.r.	1) 81% 2) 90% 3) 61%	n.r.	n.r.	1) 75% 2) 85% 3) 33%
Wedemeyer, J. 2004	Prospective	25 (25)	1) TPUS 2) MRI	n.r.	1) 88% 2) 91%	n.r.	n.r.	n.r.	n.r.	n.r.
Dwarkasing, S. 2004	Retrospective	20 (n.r.)	1) MR endoanal coil	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.	n.r.
Maconi, G. 2007	Prospective	46 (46)	1) TPUS	EUS	1) 84,9%	n.r.	n.r.	n.r.	n.r.	n.r.
Losco, A. 2009	Prospective	62 (62)	1) CA-EUS 2) FDA 3) PDAI	n.r.	n.r.	n.r.	1) 81% 2) 77% 3) 87%	n.r.	n.r.	n.r.
Villa, C. 2011	Prospective	50 (50)	1) MRI	PDAI and FDA	1) 93,8%	1) 71,4%	n.r.	n.r.	n.r.	n.r.

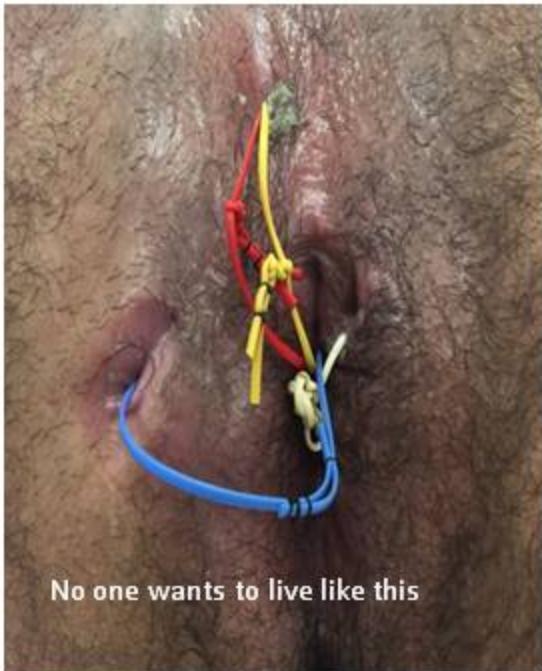
## 3D reconstruction for the surgeon



## Management?



# Setons



## Medical therapy of fistulae



## Medical Treatments – in a nutshell

Drug	Level of evidence
Antibiotics	Small case series – short term benefit 1 small negative RCT; 1 positive RCT as add-on
Thiopurines	Secondary outcomes of small RCT; Meta-analysis no benefit
Ciclosporin	Case series
Tacrolimus	Case series and small RCT
Infliximab	RCT (ACCENT II)
Adalimumab*	Secondary outcome of RCT (CHARM)
Vedolizumab*	Exploratory endpoint of RCT (GEMINI 2)
Ustekinumab*	Post-hoc analysis of pooled RCT (CERTIFI/UNITI)

\*Adalimumab, Vedolizumab and Ustekinumab not specifically licensed for the treatment of perianal fistulae in Crohn's disease.  
Infliximab is the only biologic with a specific licence to treat fistulising Crohn's disease.

# Measuring fistula outcomes

Common outcome measure	Definition given in paper
'Healed'/'healing'/'complication healed' (n = 4)	No discharge on history or examination, with healing of the external opening [24]
	Complete closure of fistulae without sign of activity or pain for at least a month [37]
	Complete healing or successful dilation of anal stenosis, after surgical intervention [30]
	Non-defined [27]
Response (n = 3)	≥50% reduction in fistulas [31]
	Maintained fistulae healing; PDAI $2.8 \pm 2.4$ [29]
	Absence of fistulae drainage, even after compression for at least 4 weeks [33]
Complete response (n = 4)	The complete cessation of drainage from all fistulas despite gentle finger compression [26]
	Absence of any draining fistulas [23]
	Absence of any drainage fistulas despite gentle finger compression [28]
	PDAI $0.8 \pm 1.0$ fistulae closure or absence of any draining fistulas despite gentle finger compression [29]
Partial response (n = 2)	At least 50% reduction from baseline in the number of fistulas or drainage for at least 4 consecutive weeks after the discontinuation of drug infusions [26]
	Reduction of 50% or more from baseline in the number of draining fistulas [28]
Recurrence (n = 4)	Presence of fistulae openings among patient who experienced fistulae closure [32]
	Reopening of a former track or presence of new fistulae after primary response [34]
	Reappearance of active perianal fistulas or associated abscesses after prior inactivation or healing [37]
	Recurrence of the same or different complication after a period of complete healing [30]

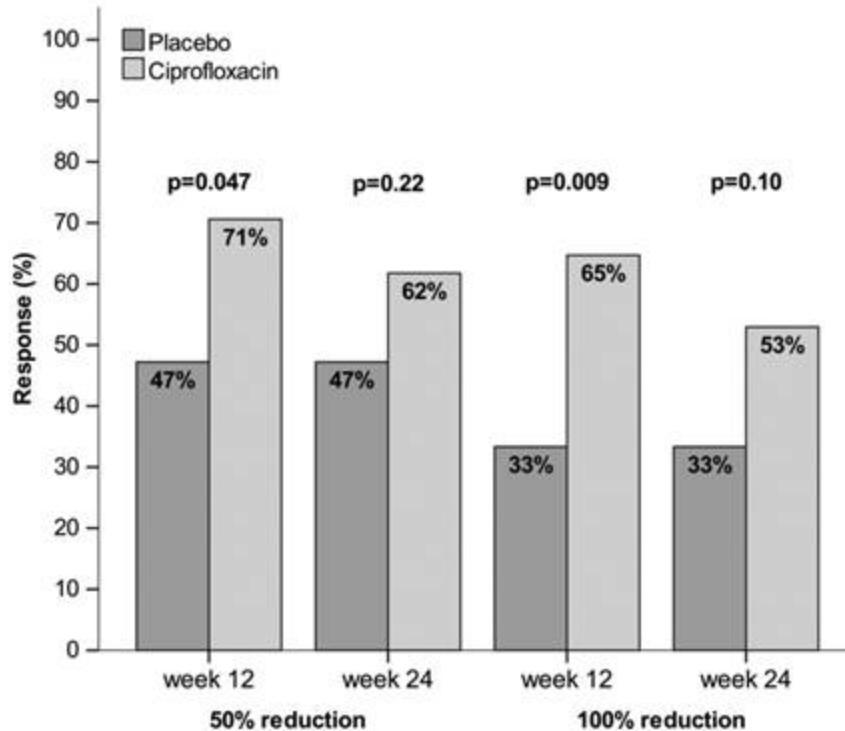
## Measuring fistula outcomes

**Table 4** The most commonly outcome measures reported

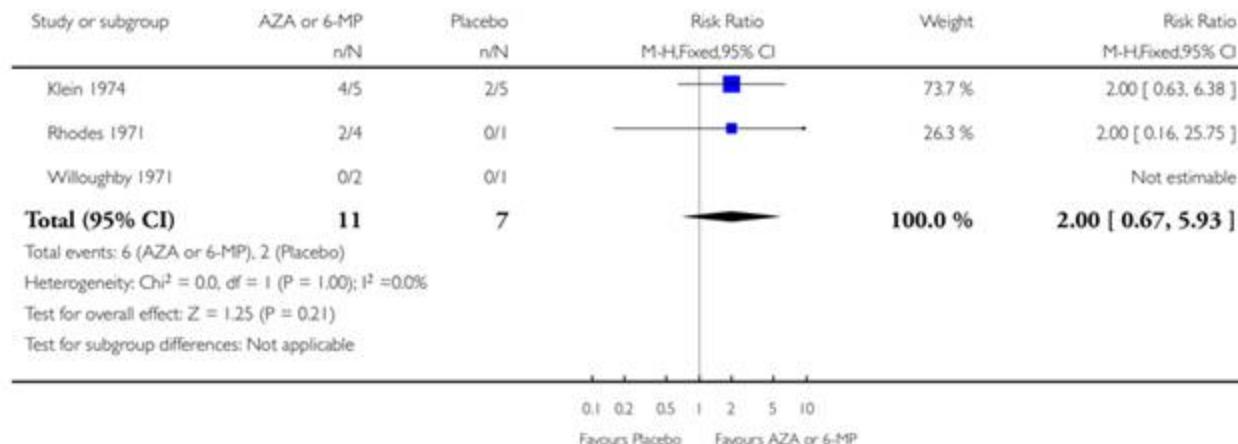
Outcome measures in the included studies	Number of studies
≥50% tracts not draining on clinical examination	22
Perianal Disease Activity Index	20
Crohn's Disease Activity Index	19
Closure of external opening	17
No drainage either spontaneously or on gentle finger pressure	12

## Antibiotics

- Frequently used; control of sepsis
- 1 small (negative) RCT
- Add-on therapy – short term gain?
- Not recommended (alone)



## Thiopurines



Present et al. NEJM 1980

40 fistulas were observed in 36 patients

9 of 29 fistulas (31 per cent) closed completely during treatment with 6-MP

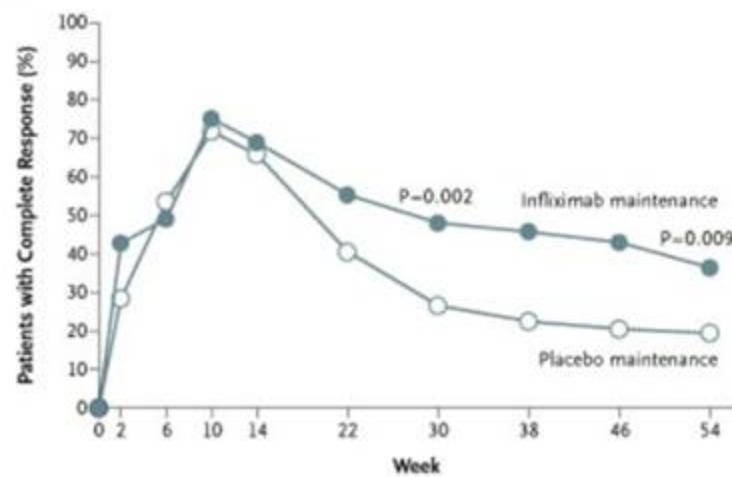
1 of 17 (6 per cent) closed completely during administration of placebo

*Recommendations & role?*

# Fistulising CD: Infliximab

**TABLE 2.** OUTCOME OF TREATMENT, ACCORDING TO STUDY GROUP.

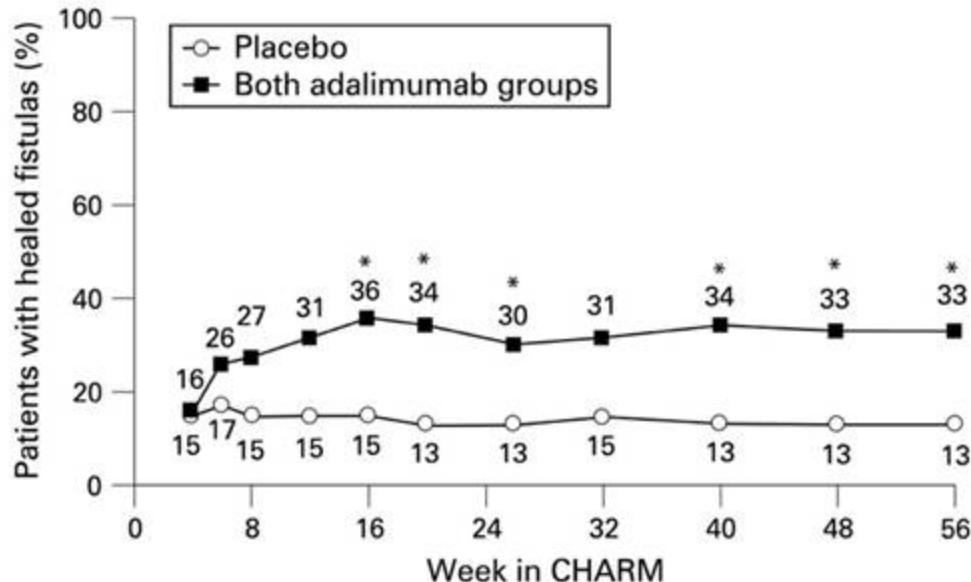
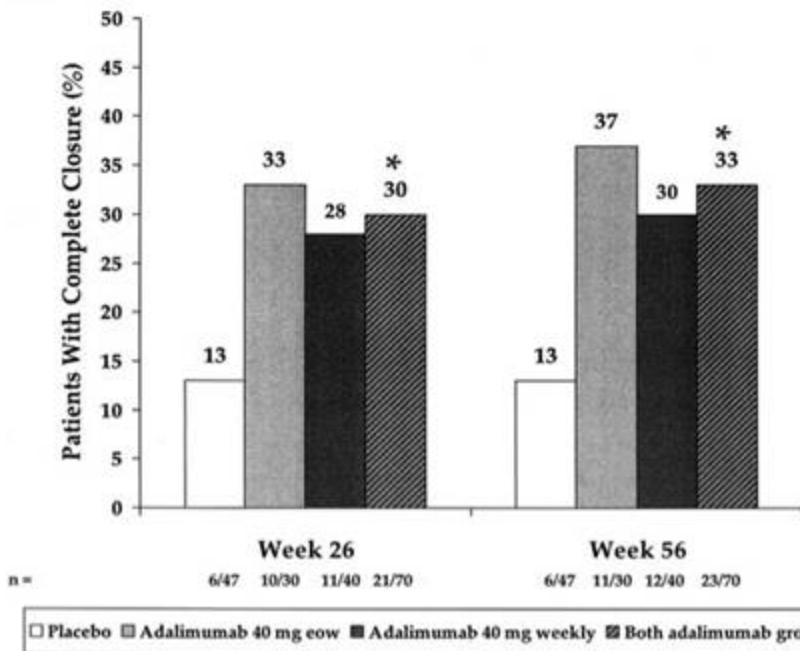
VARIABLE	PLACEBO		INFILIXIMAB	
	5 mg/kg	10 mg/kg	5 OR 10 mg/kg	10 mg/kg
<b>End points</b>				
Primary end point — no./total no. (%)*	8/31 (26)	21/31 (68)	18/32 (56)	39/63 (62)
P value vs. placebo	—	0.002	0.02	0.002
Complete response — no./total no. (%)†	4/31 (13)	17/31 (55)	12/32 (38)	29/63 (46)
P value vs. placebo	—	0.001	0.04	0.001
Time to onset of response (days)‡				
Median	42	14	14	14
Interquartile range	15–72	14–42	14–42	14–42
Duration of response (days)‡				
Median	86	84	99	86
Interquartile range	56–104	31–113	86–113	57–113



1. Present DH et al. *N Engl J Med* 1999;340:1398-1405. 2. Sands et al. *N Engl J Med* 2004;350:876-85

## Fistulising CD: Adalimumab\*

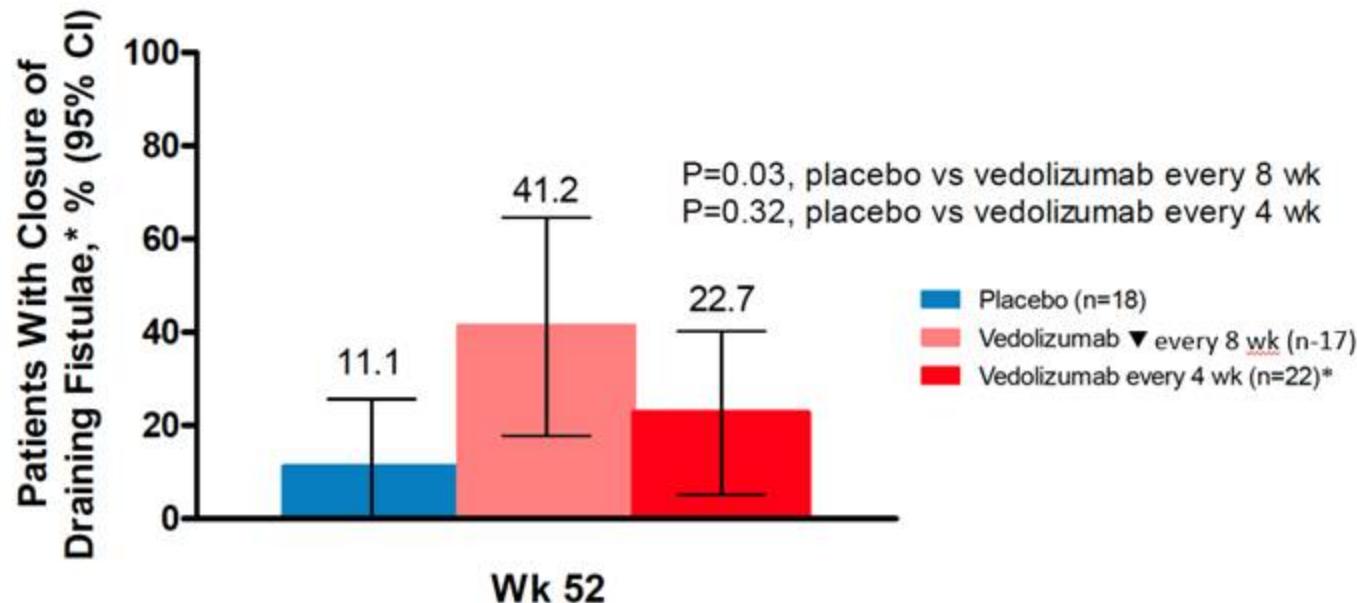
A



\* Adalimumab not specifically licensed for the treatment of perianal fistulae in Crohn's disease

## Fistulising CD: Vedolizumab\*

Results from sub-analysis of GEMINI 2 patient with draining fistulae at baseline

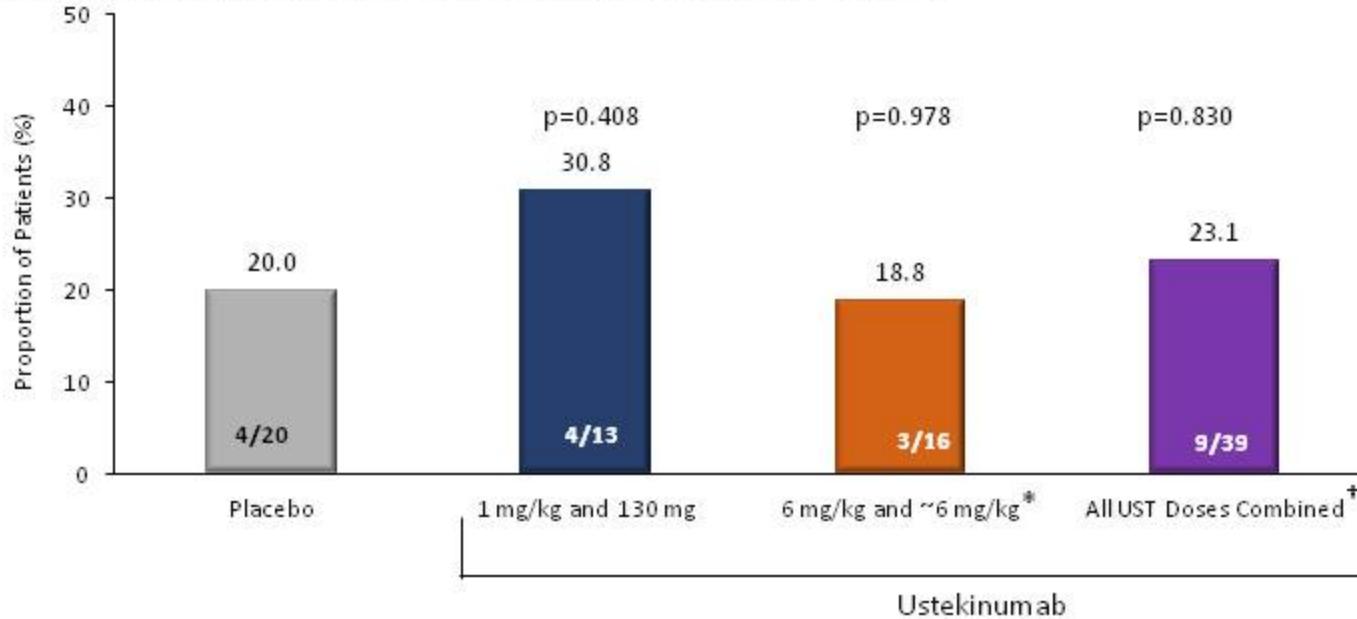


\*Vedolizumab is not licensed for the treatment of perianal fistulas

# Fistulising CD: Ustekinumab\*

Fistula Response ( $\geq 50\%$  Reduction) at Week 8 Among Randomized Patients with Multiple Open, Draining Fistulas at Baseline in Pooled data from CERTIFI, UNITI-1 and UNITI-2

\*Ustekinumab is not licensed for the treatment of perianal fistulas

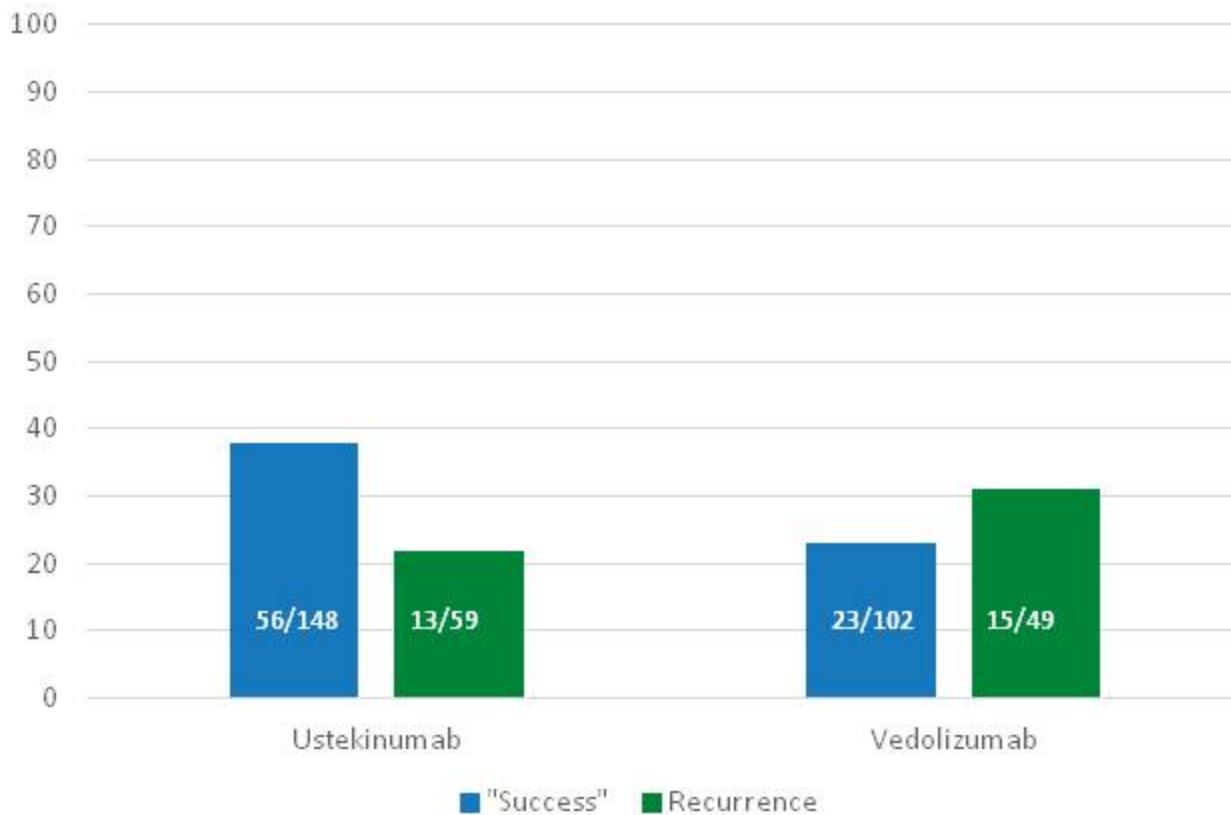


\* 6 mg/kg group includes 6 mg/kg group in CERTIFI and weight-range based ustekinumab doses approximating 6 mg/kg group:

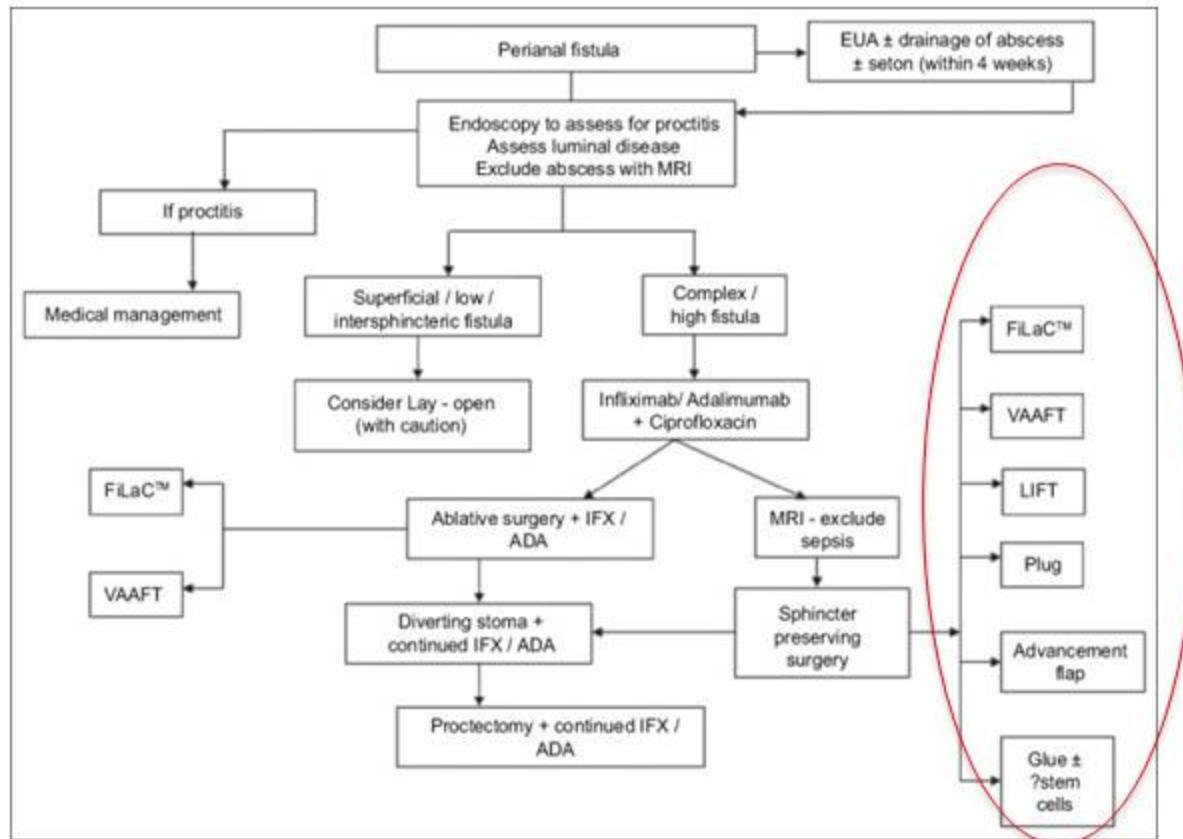
260 mg (weight  $\leq 55$  kg), 390 mg (weight  $> 55$  kg and  $\leq 85$  kg), 520 mg (weight  $> 85$  kg) in UNITI-1 and UNITI-2

<sup>†</sup>Combined treatment group includes 1 mg/kg group, 3 mg/kg group, 6 mg/kg group, and 130 mg group.

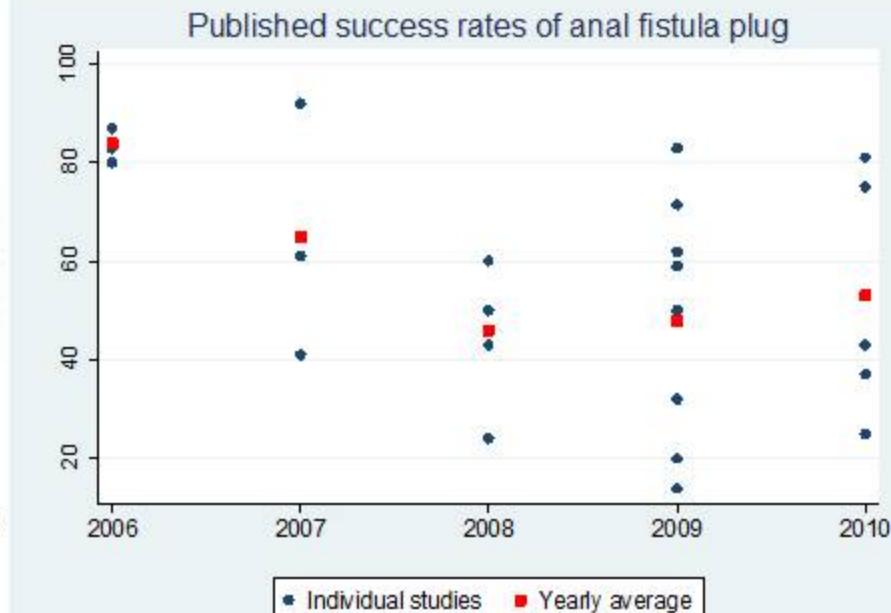
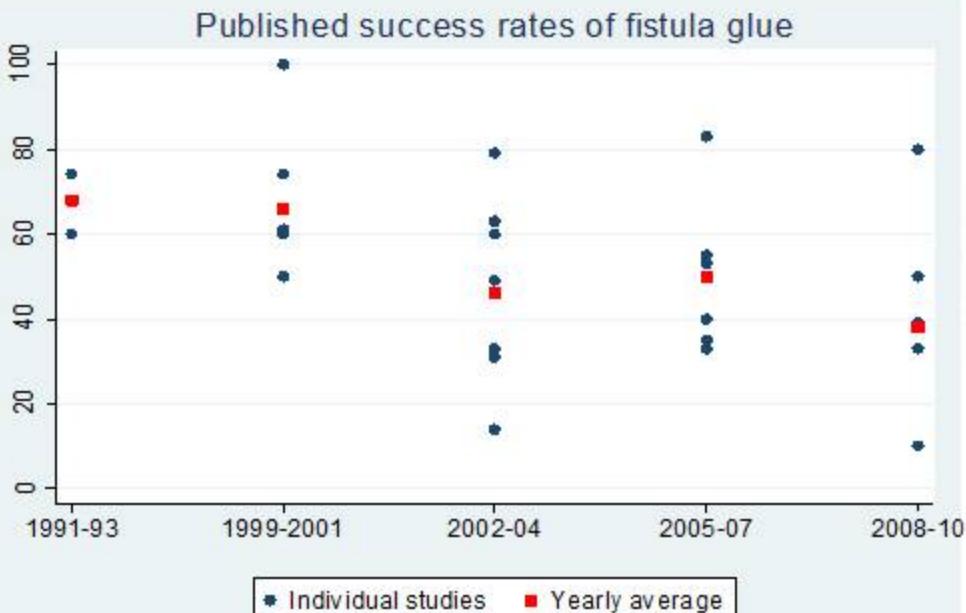
## Bio-LAP: Real world UST or VDZ?



## Can't the surgeons just fix it all?



## Surgical tales and regression to the mean?



# Stem cells?

## Efficacy of Injection of Freshly Collected Autologous Adipose Tissue Into Perianal Fistulas (PF) in Patients With Crohn's Disease(CD)

### 21 CD Patients w/ PF

- 13 transsphincteric
- 7 anovaginal
- 1 intersphincteric

Repeated injections

Two injections: 9 pt.

Three injections: 4 pt.

Injection(s) with  
autologous adipose tissue



### Results 6 months after

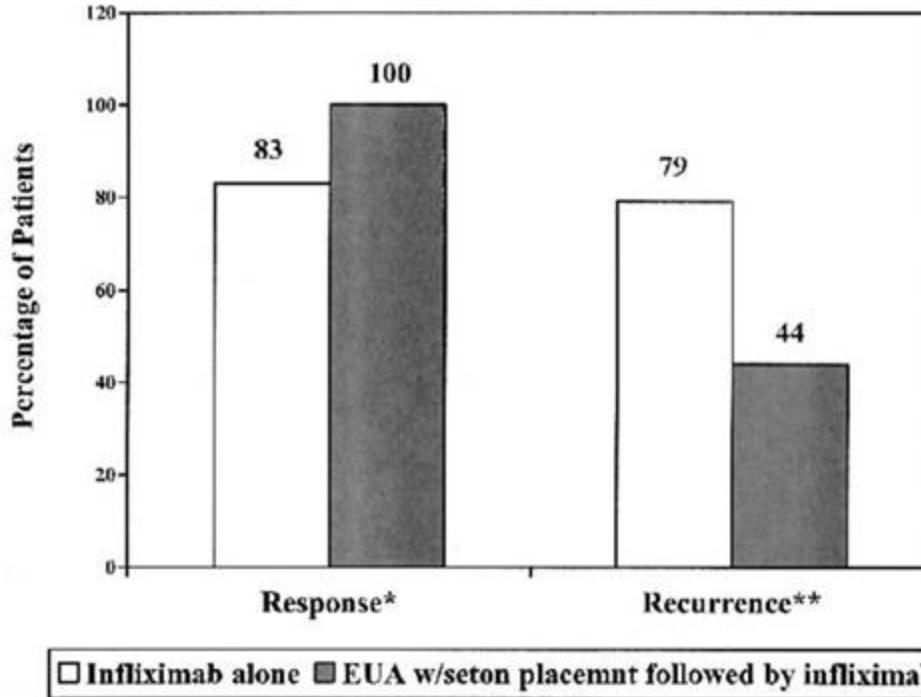
- Overall response in 76%
- Fistula healing in 57%
- Ceased secretion in 14%
- Reduced secretion in 5%

### Complications

Abscess ( $n=2$ ), postoperative urinary retention ( $n=1$ ), proctalgia ( $n=4$ ), bleeding ( $n=1$ )

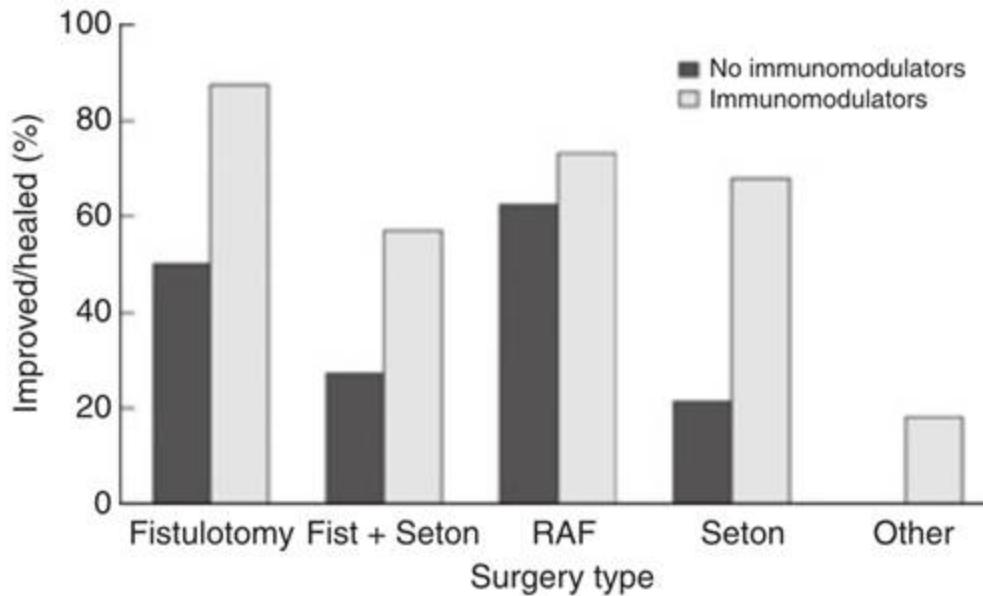
Gastroenterology

## Should we be tackling these in isolation?



\* $p = 0.014$  \*\*  $p = 0.001$

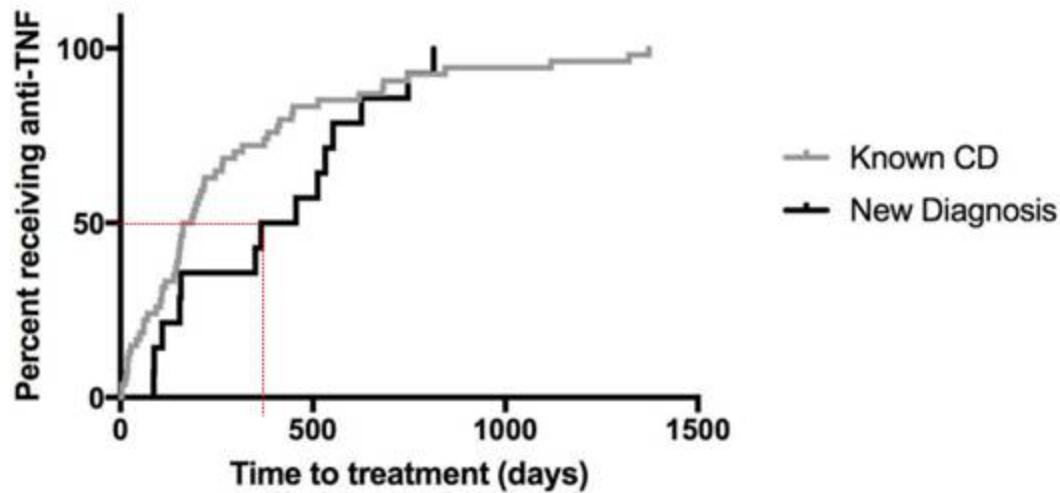
## Should we be tackling these in isolation?



## Should we be tackling these in isolation?

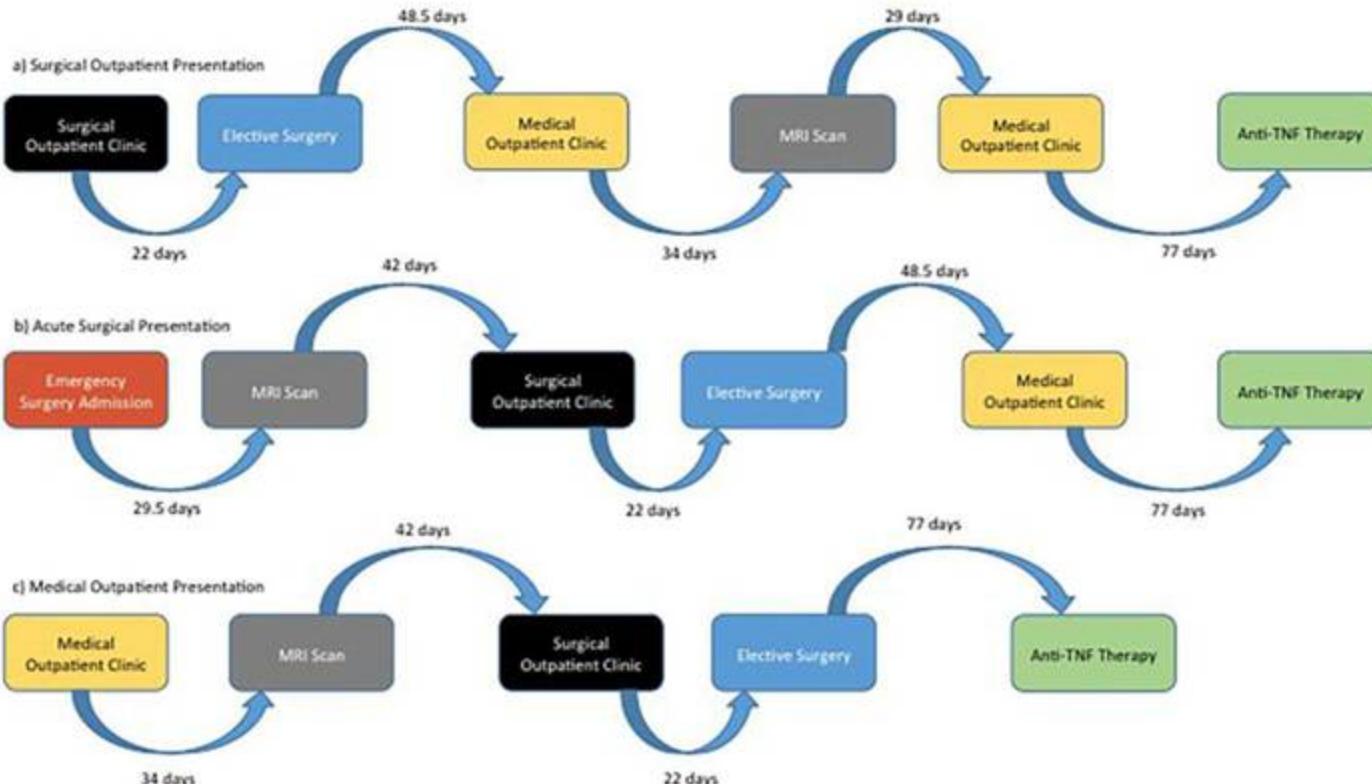
Author	Single therapy group						Combined therapy group							
	Total n	No response		Partial response		Complete remission		Total n	No response		Partial response		Complete remission	
		n	%	n	%	n	%		n	%	n	%	n	%
Regueiro (2003)	23	4	17	19	83	0	0	9	0	0	9	100	—	—
van der Hagen (2005)	7	0	0	—	—	7	100	10	0	0	—	—	10	100
Gaertner (2007)	147	21	14	38	26	88	60	79	15	19	17	22	47	60
Sciaudone (2010)	21	2	10	5	24	14	67	14	1	7	2	14	11	79
Gaertner (2011)	25	14	56	5	20	6	24	26	10	39	4	15	12	46
Uchino (2011)	36	10	28	26	72	0	0	26	4	15	22	85	0	0
El-Gazzaz (2012)	117	75	64	11	9	31	27	101	29	29	35	35	37	37
Bouguen (2013)	72	27	38	—	—	45	63	84	21	25	—	—	63	75
Total	448	153	34	104	23	191	43	349	80	23	86	25	180	52

## Not so shared care after all?



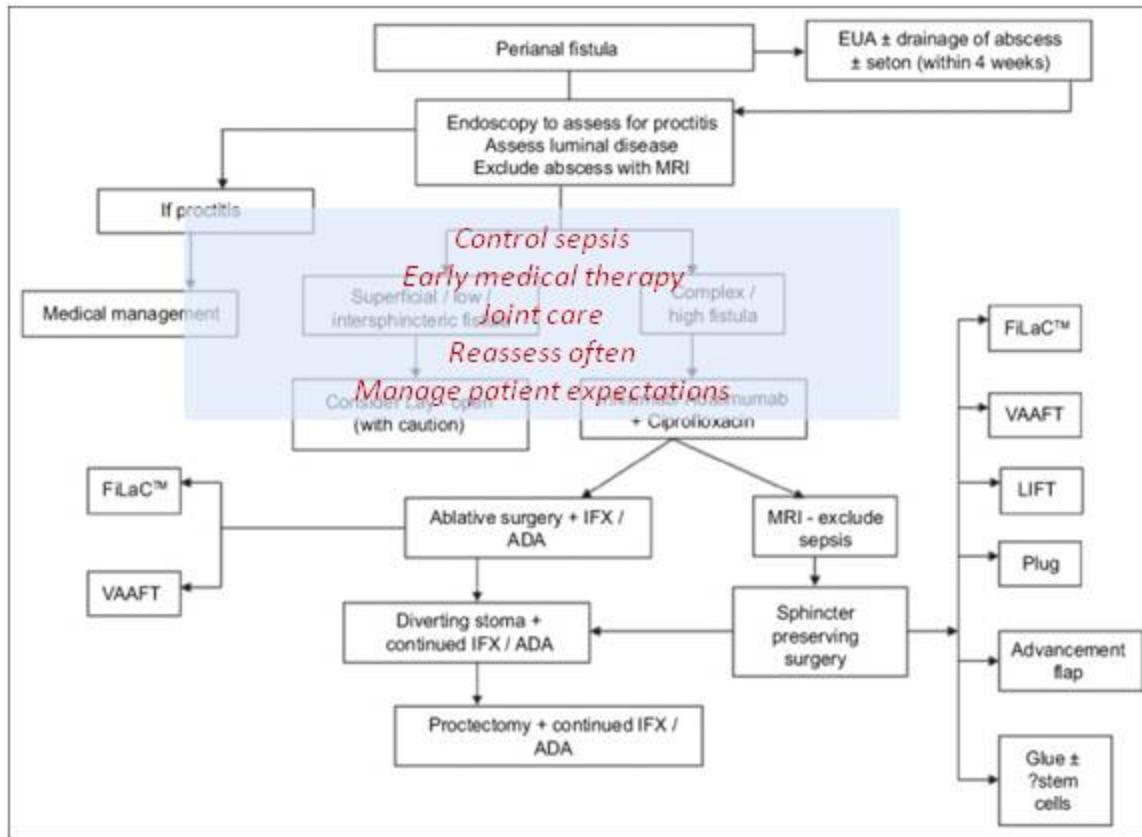
Median time to anti-TNF 204d  
New diagnosis? 365d

# Not so shared care after all?





# Conclusions



## How do we define success



*"I say, if at first you don't succeed, redefine success."*

## Backup slides

## Direct injection of biologics

Study	Numbers	Median follow-up in months (range)	Outcomes
Lichtiger S. 2001 [9] (USA)	9	1	44% (4/9) demonstrated complete and 33% (3/9) partial response
Poggioli et al. 2005 [12] (Ita)	15	18.2 (3–30)	67% (10/15) demonstrated complete response
Asteria et al. 2006 [11] (Ita)	11	10.5 (7–18)	36% (4/11) demonstrated complete and 36% (4/11) partial response
Alessandroni et al. 2011 [10] (Ita)	12	35 (19–43)	62.5% (5/8) demonstrated complete response
Laureti et al. 2012 [14] (Ita)	33	11 (7–14)	40% demonstrated complete response
Tonelli et al. 2012 [13] (Ita)	12	17.5 (5–30)	75% (9/12) demonstrated complete and 25% (3/12) partial response