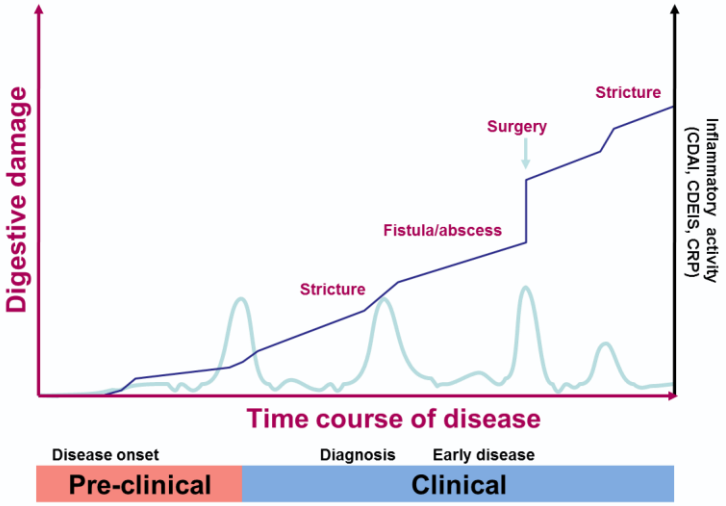
מה חדש - מחלות מעי דלקתיות וגסטרואנטרולוגיה

ד״ר מתי וטרמן
מנהל, השירות למחלות מעי דלקתיות
רמב״ם- הקריה הרפואית לבריאות האדם, חיפה

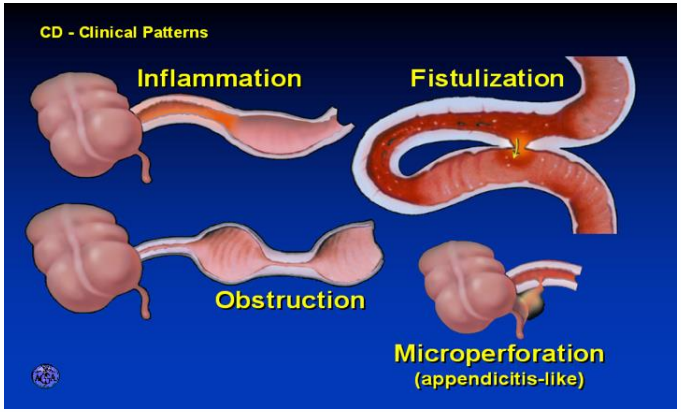
RAMBAM
Health Care Campus

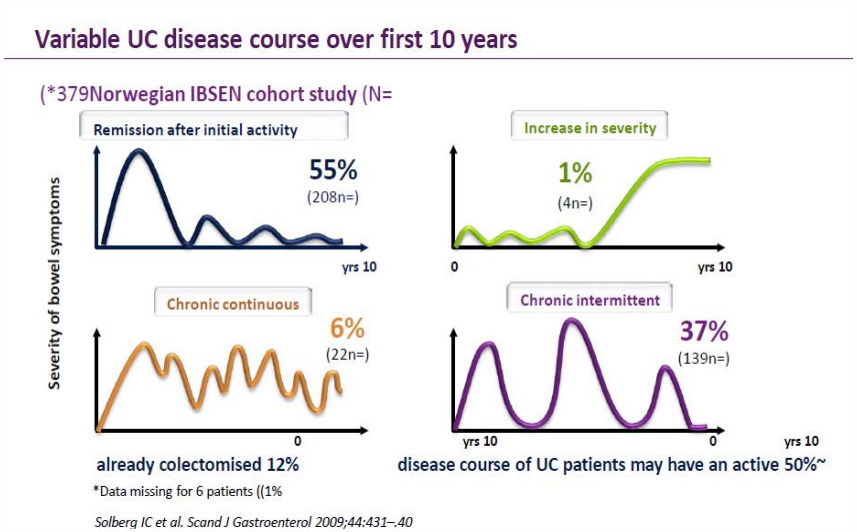
AN EXCELLENT
ACADEMIC
MEDICAL CENTER

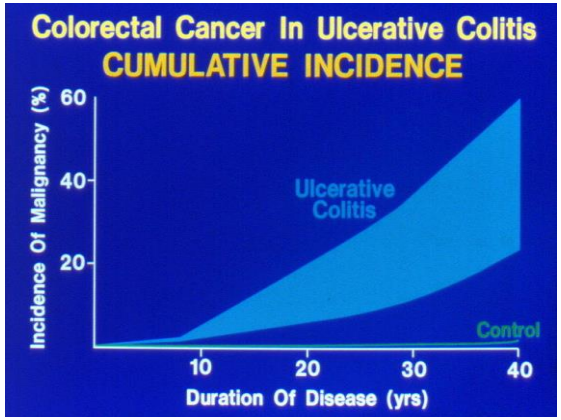
Accumulation of damage in IBD



Adapted from: 1. Pariente B, *et al*. Inflamm Bowel Dis. 2011;17:1415–1422.







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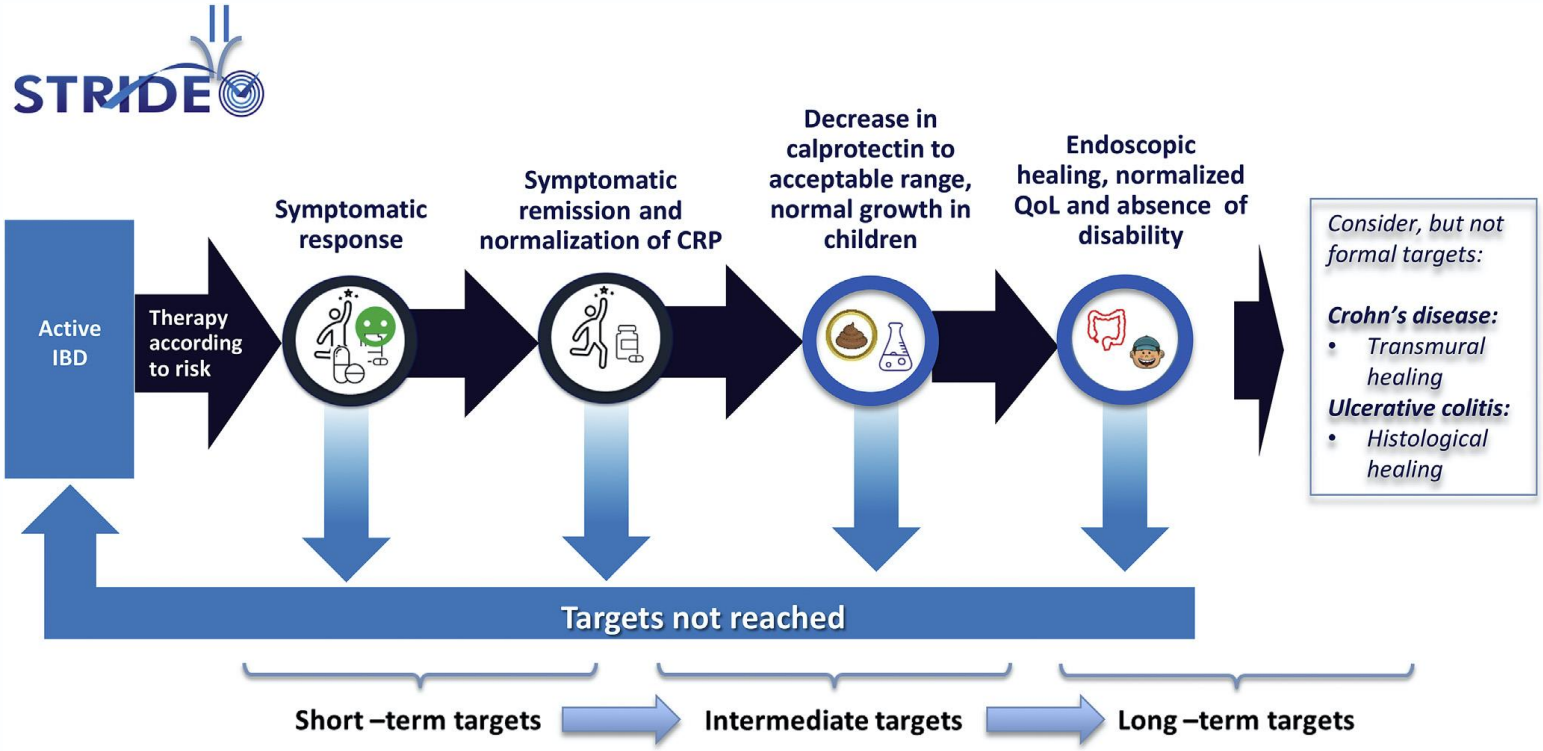
Treatment targets in IBD



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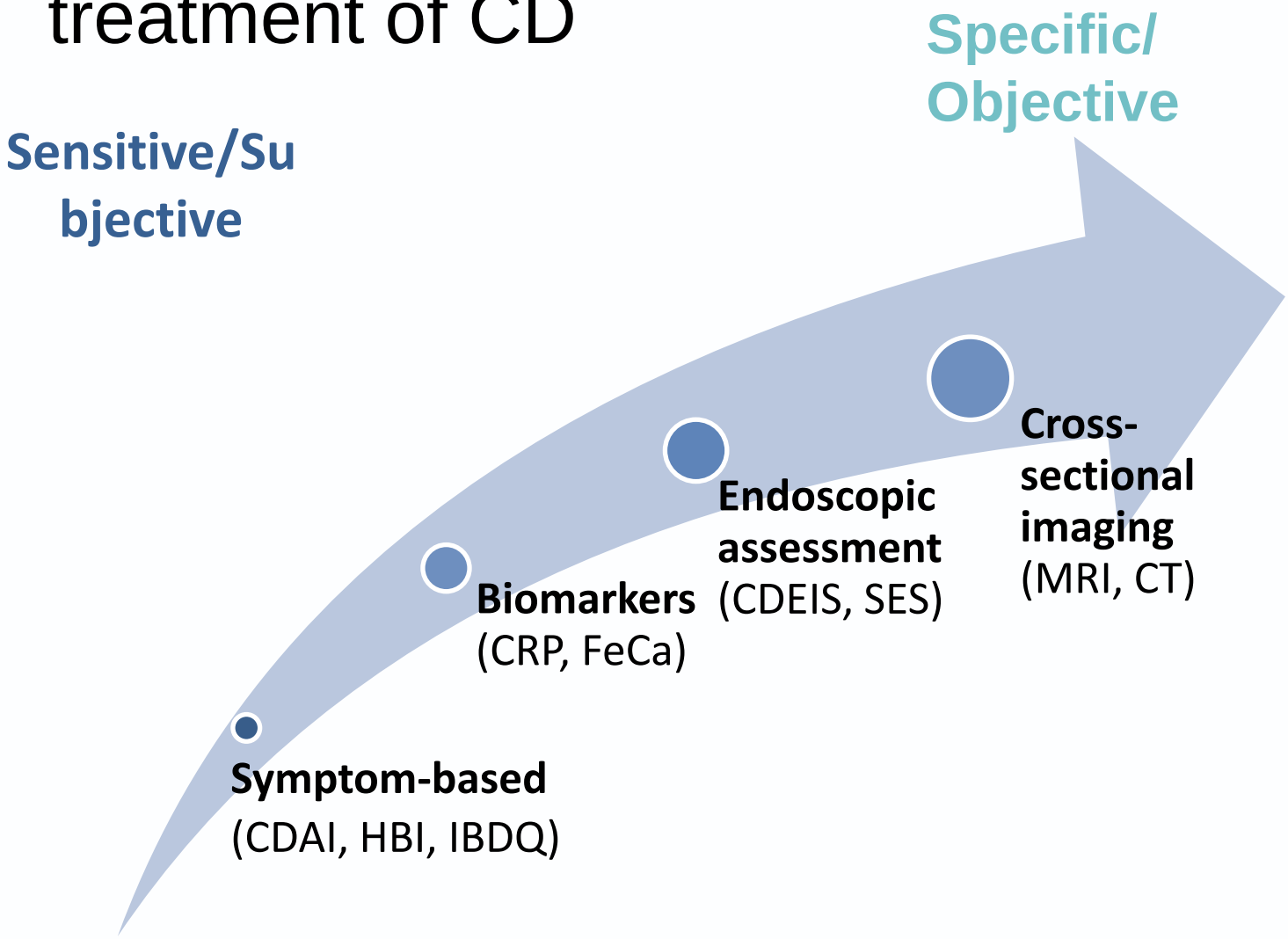
Turner D. et al. Gastroenterol 2021;160:1570-83

Monitoring tools for decision making in treatment of CD



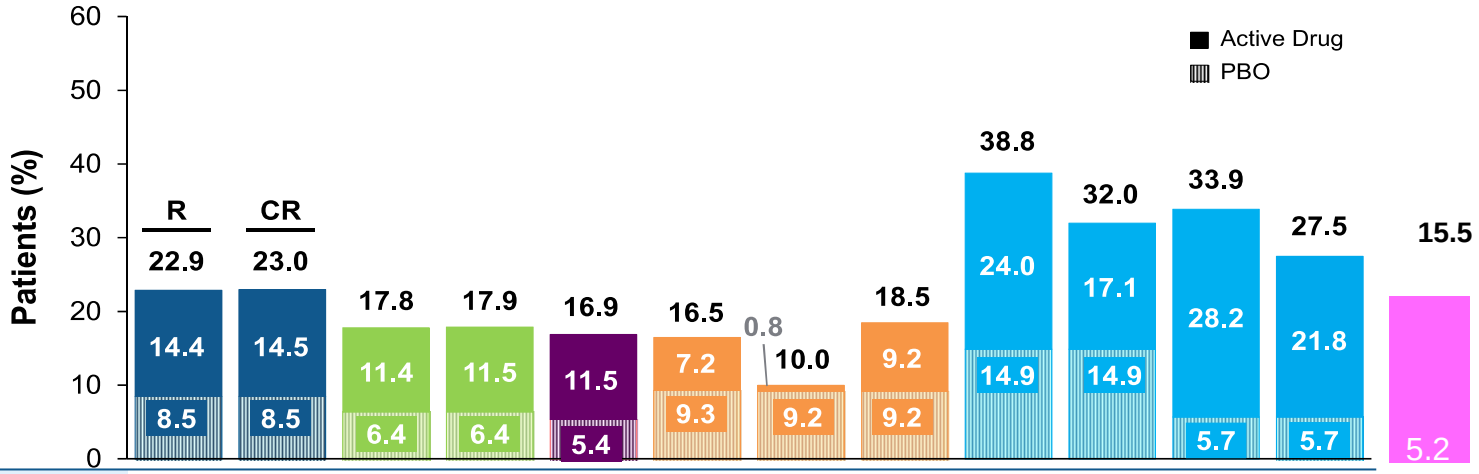
"Mind the Gap"

- Approximately, 40% to 60% of patients will **not** benefit from the available treatments, indicating a considerable unmet need for new, more effective therapies.

Many medications but mediocre efficacy– Ulcerative colitis

Treatment Effects in Clinical Remission* (Tofacitinib and Approved Biologics)

Data are derived from published randomized controlled trials and do not represent a head-to-head comparison.



Drug	Tofa† (2015)[1]	Tofa (2015)[1]	Gol (2014)[2]	Gol (2014)[2]	Vedo (2013)[3]	Ada (2012)[4]	Ada (2010)[5]	Ada (2010)[5]	IFX (2005)[6]	IFX (2005)[6]	IFX (2005)[6]	IFX (2005)[6]	UST (2019)
Dosages	10 mg BID	10 mg BID	400/200 mg	400/200 mg	300 mg	160/80/ 40 mg	80/40 mg	160/80/ 40 mg	5 mg/kg	10 mg/kg	5 mg/kg	10 mg/kg	6 mg/kg
Time point	8 wk	8 wk	6 wk	6 wk	6 wk	8 wk	8 wk	8 wk	8 wk	8 wk	8 wk	8 wk	8 wk
Prior TNFi, %	54	54	0	0	48	40‡	0	0	0	0	0	0	
N, drug	905	905	257	257	225	248	130	130	121	122	121	120	
N, PBO	234	234	251	251	149	246	130	130	121	121	123	123	
P value vs PBO	<0.0001	<0.0001	<0.001	<0.001	0.001	0.019	0.833	0.031	<0.001	0.002	<0.001	<0.001	

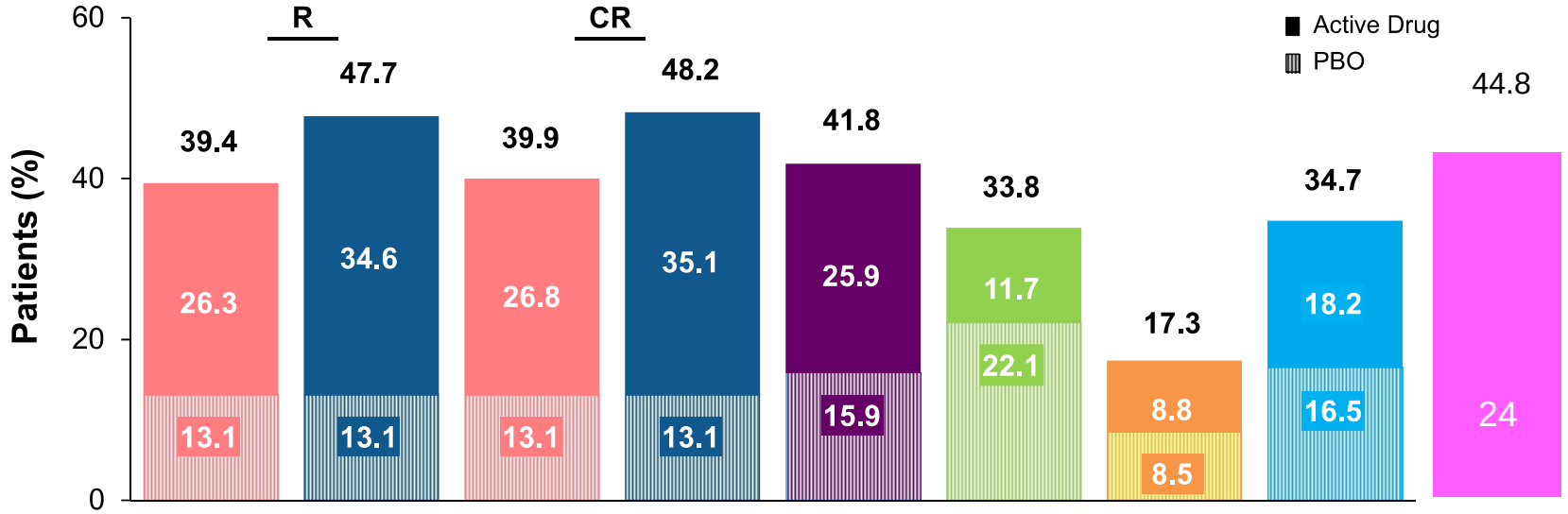
*Data on clinical remission, defined as total Mayo score ≤2 points, with no individual subscore >1 point, are shown. Data are based on local read. †Data on remission, defined as clinical remission *and* a rectal bleeding subscore of 0, are shown (local read). ‡Primary TNFi nonresponders were excluded.
Ada=adalimumab; BID=twice daily; CR=clinical remission; Gol=golimumab; IFX=infliximab; TNFi=tumor necrosis factor inhibitor; PBO=placebo; R=remission; Tofa=tofacitinib; Vedo=vedolizumab.

1. A3921094 and A3921095 Pooled Study Report Output; Tables 14.2.2.3.p and 14.2.4.3.p. Data as of July 2015. 2. Sandborn WJ et al. Gastroenterology. 2014;146:85-95. 3. Feagan BG et al. N Engl J Med. 2013;369:699-710. 4. Sandborn WJ et al. Gastroenterology. 2012;142:257-265. 5. Reinisch W et al. Gut. 2011;60:780-787. 6. Rutgeerts P et al. N Engl J Med. 2005;353:2462-2476. 7. Sands BE et al. N Engl J Med. 2019;381:1201-1214

Many medications but mediocre efficacy– Ulcerative colitis

Maintenance Treatment Effects in Clinical Remission* (Tofacitinib and Approved Biologics)

Data are derived from published randomized controlled trials and do not represent a head-to-head comparison.



Drug	Tofa†[1]		Tofa[1]		Vedo[2]	Gol[3]	Ada‡[4]	IFX‡[5]
Dosages	5 mg PO BID	10 mg PO BID	5 mg PO BID	10 mg PO BID	300 mg IV Q8W	100 mg SQ Q4W	40 mg SQ Q2W	5 mg/kg IV Q8W
Time point	52 wk	52 wk	52 wk	52 wk	52 wk§	54 wk	52 wk§	54 wk§
N, drug	198	197	198	197	122	151	248	121
N, PBO	198	198	198	198	126	154	246	121
P value vs PBO	<0.0001	<0.0001	<0.0001	<0.0001	<0.001	0.011	0.004	0.001

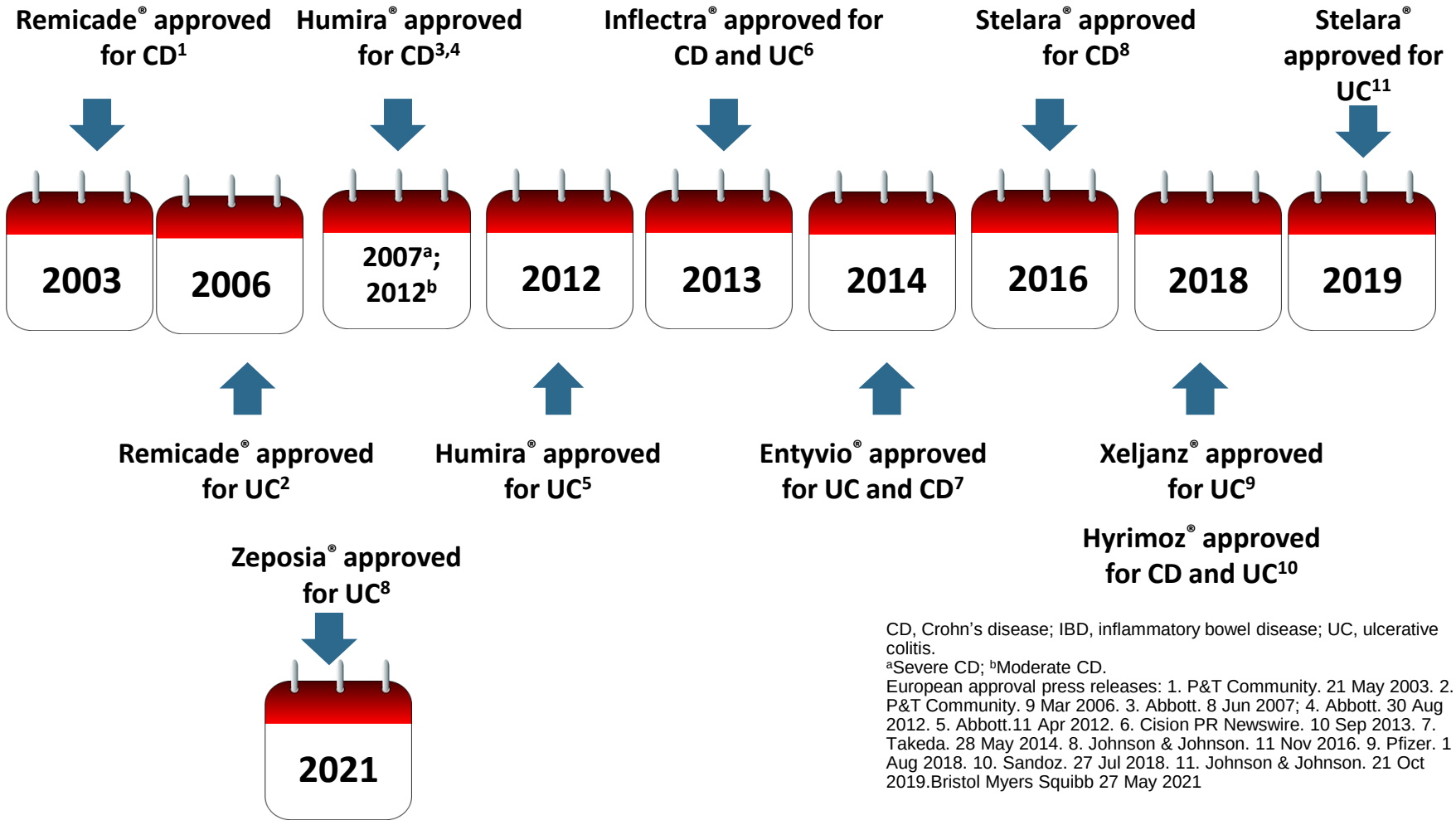
UST (2019) 90 mg Q8W 44 wk

1. A3921094 and A3921095 Pooled Study Report Output; Tables 14.2.2.3.p and 14.2.4.3.p. Data as of July 2015. 2. Sandborn WJ et al. Gastroenterology. 2014;146:85-95. 3. Feagan BG et al. N Engl J Med. 2013;369:699-710. 4. Sandborn WJ et al. Gastroenterology. 2012;142:257-265. 5. Reinisch W et al. Gut. 2011;60:780-787. 6. Rutgeerts P et al. N Engl J Med. 2005;353:2462-2476. 7. Sands BE et al. N Engl J Med. 2019;381:1201-1214

MANAGING THE THERAPEUTIC GAP

We now have several strategies that can help us choose the right treatment for the patient and thereby bridge the therapeutic gap that currently exists in our daily reality.

The evolution of biologic therapies in IBD



CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis.
[a]Severe CD; [b]Moderate CD.

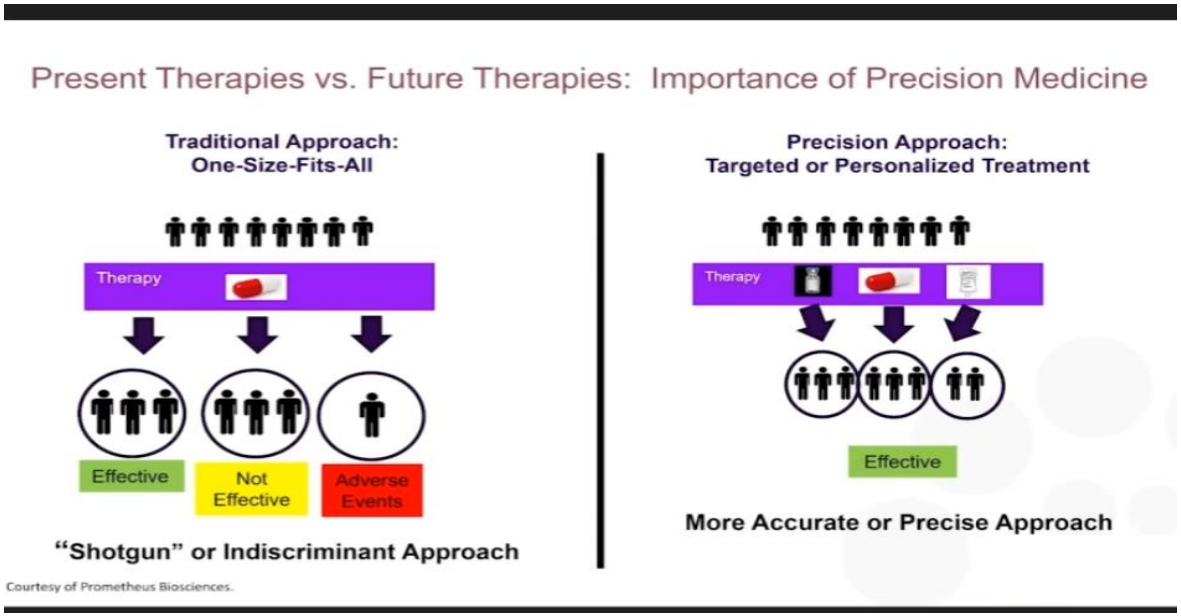
European approval press releases: 1. P&T Community. 21 May 2003. 2. P&T Community. 9 Mar 2006. 3. Abbott. 8 Jun 2007; 4. Abbott. 30 Aug 2012. 5. Abbott.11 Apr 2012. 6. Cision PR Newswire. 10 Sep 2013. 7. Takeda. 28 May 2014. 8. Johnson & Johnson. 11 Nov 2016. 9. Pfizer. 1 Aug 2018. 10. Sandoz. 27 Jul 2018. 11. Johnson & Johnson. 21 Oct 2019.Bristol Myers Squibb 27 May 2021

This is what we all want!

PRECISION MEDICINE

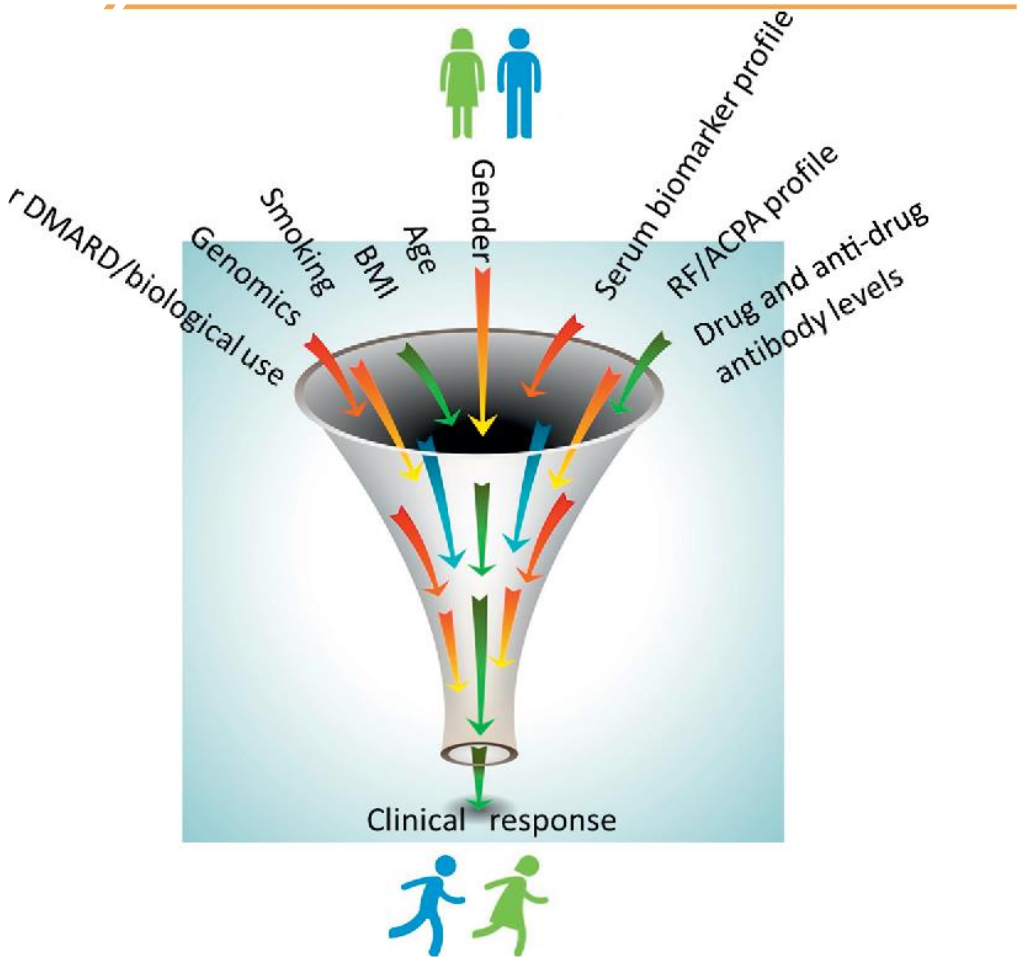
where treatment strategies are tailored to the individual patient

- Allows for shifting the emphasis in medicine *from reaction to prevention.*
- Medical decisions, practices, interventions and/or products tailored to the individual patient based on their predicted response or risk of disease



Predicating response to treatment

- Clinical predictors
- Biochemical predictors
- Genetics and epigenetics predictors

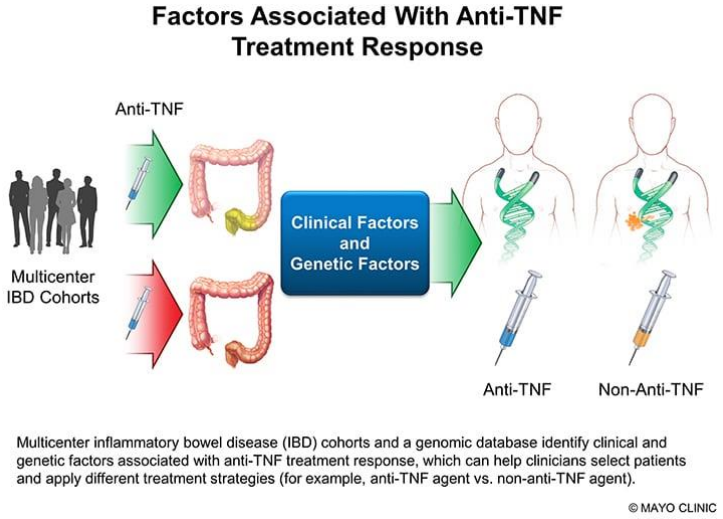


PREDICTORS FOR TREATMENT RESPONSE-CLINICAL

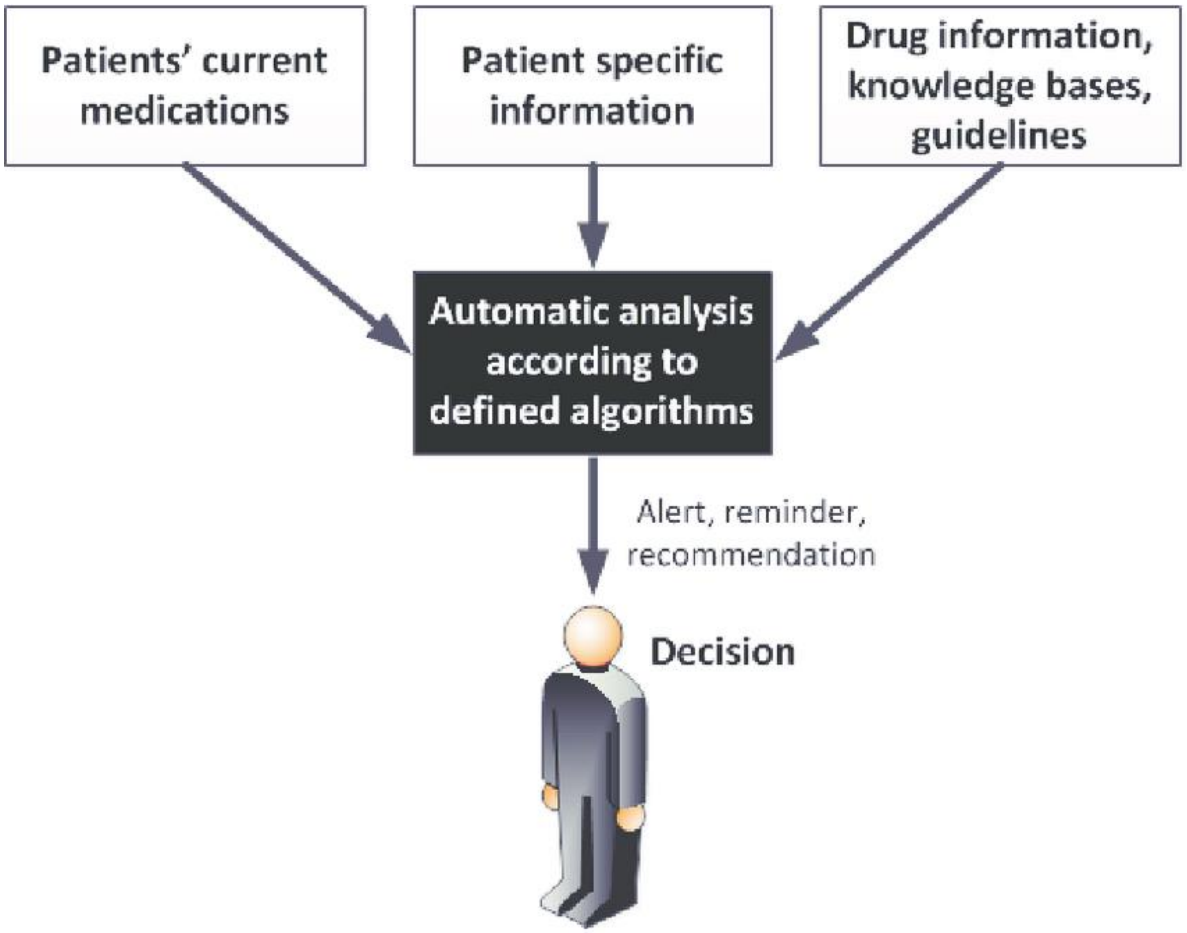
Zampeli E *et al*. Anti-TNF treatment for ulcerative colitis

Table 1 Prognostic indicators of response to anti-tumor necrosis factor treatment in ulcerative colitis

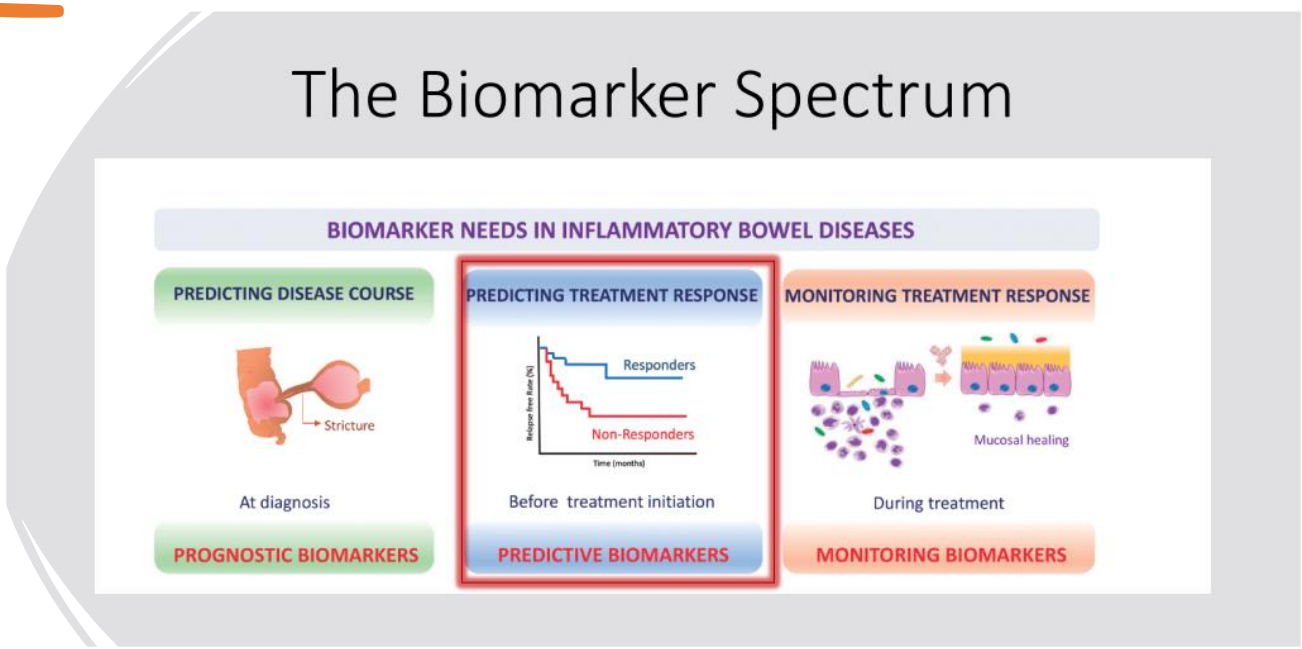
At initiation of treatment	During treatment
Clinical and epidemiological parameters	
Severity of the disease	Early clinical response
Younger age	
Duration of colitis < 3 yr	
Extensive colitis	
Laboratory indicators	
CRP	Low CRP at week 12
Hemoglobin	Drop of serum CRP
Serum albumin	Fecal calprotectin
Immunological and genetic markers	
p-ANCA	Gene expression profiling
Pre-treatment mucosal TNF-α expression	Percentages of regulatory T cells
Mucosal expression of IL-17 and IFN-γ	
Genetic polymorphisms	
Endoscopic findings	
	Mucosal healing
Treatment-related factors	
Pharmacological history	Number of IFX infusions
Exposure to immunosuppressants	Co-administration of immunosuppressants
Response to prior treatment with infliximab	Escalation of anti-TNF therapy
	IFX trough levels
	Antibodies against anti-TNF



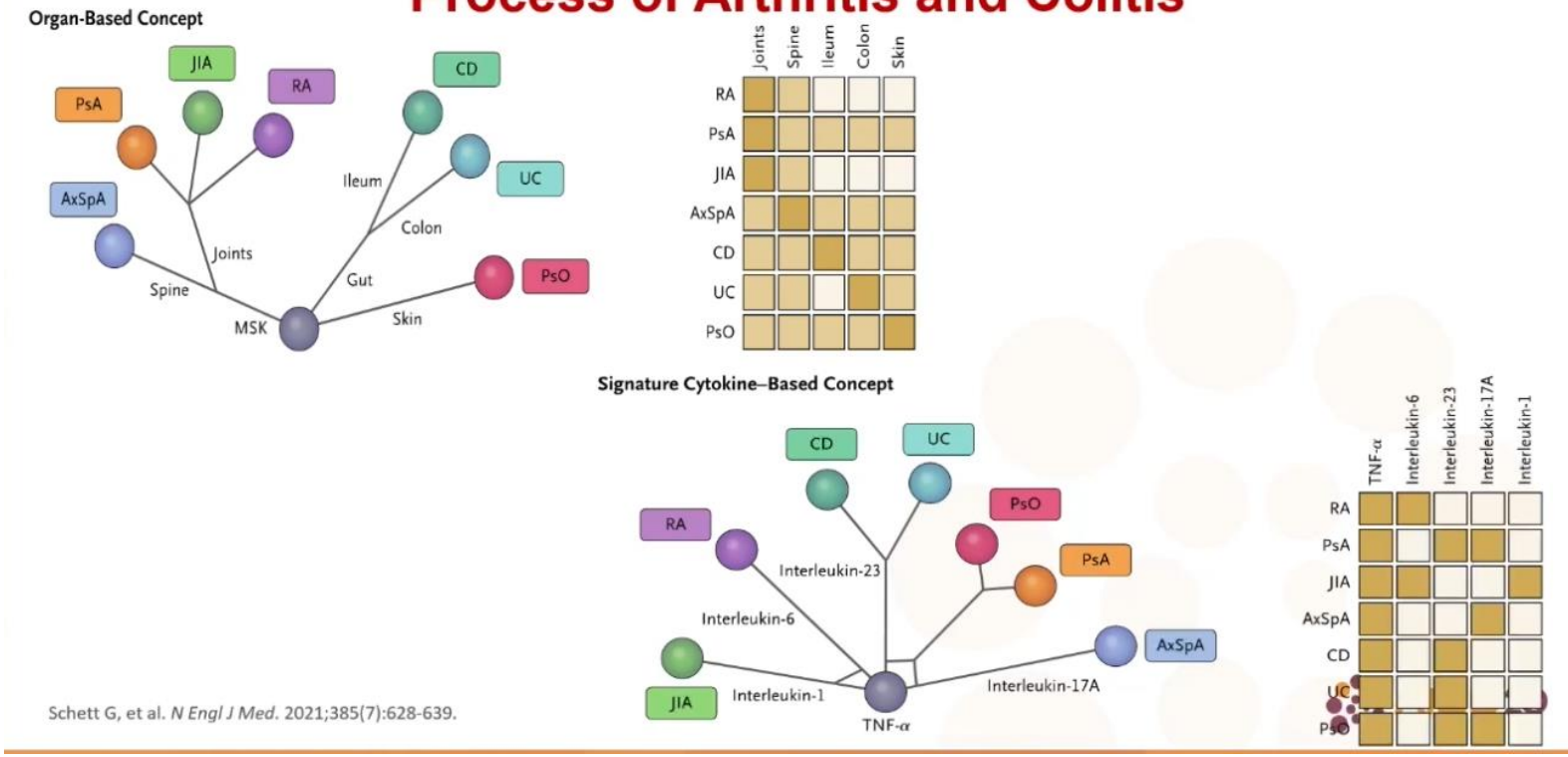
clinical decision support tools (CDSTs)



The use of biochemical biomarkers



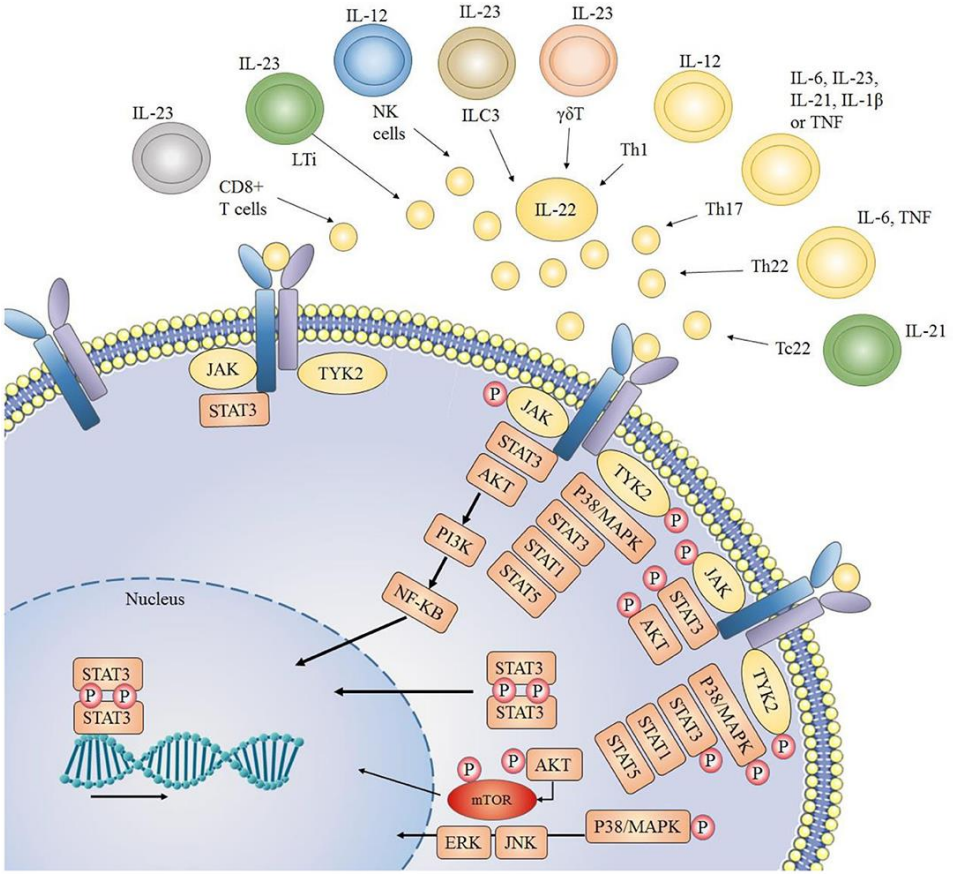
Signature Cytokines and Their Functions in the Inflammatory Process of Arthritis and Colitis



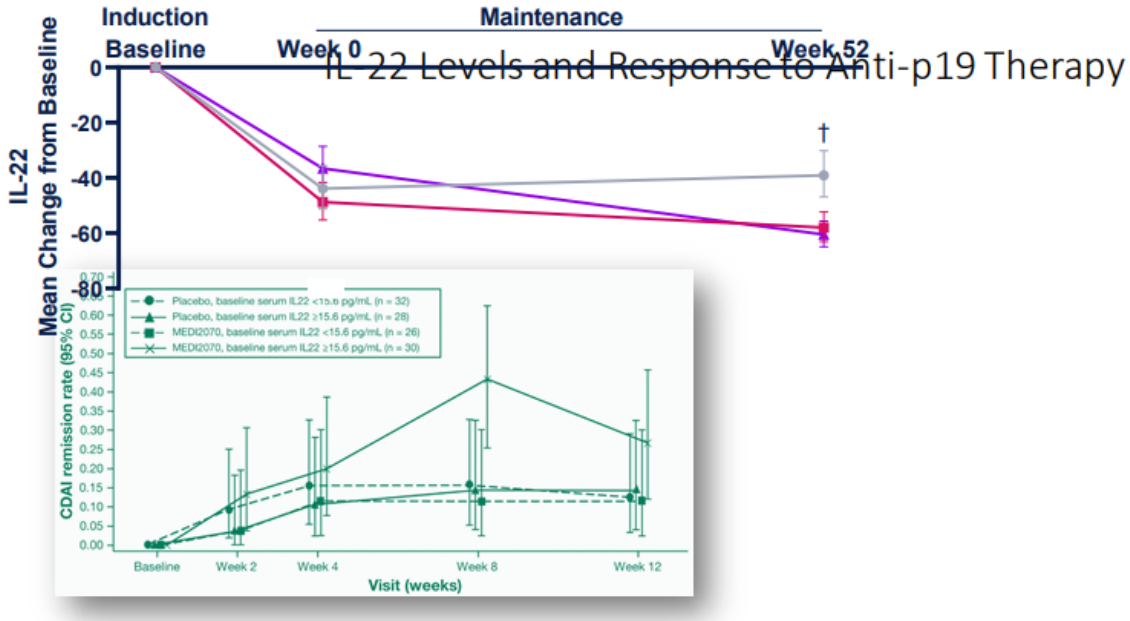
Schett G, et al. *N Engl J Med*. 2021;385(7):628-639.

Predicating response to treatment-biochemical

- **Pre-and post-treatment levels of IL-22** and post-treatment levels of IL-17 have been identified as potential molecular **predictors of response to therapy** in several studies *Gottlieb ZS, Sands BE. Personalized Medicine with IL-23 Blockers: Myth or Reality? J Crohns Colitis. 2021*



IL-22 Levels and Response to Anti-p19 Therapy

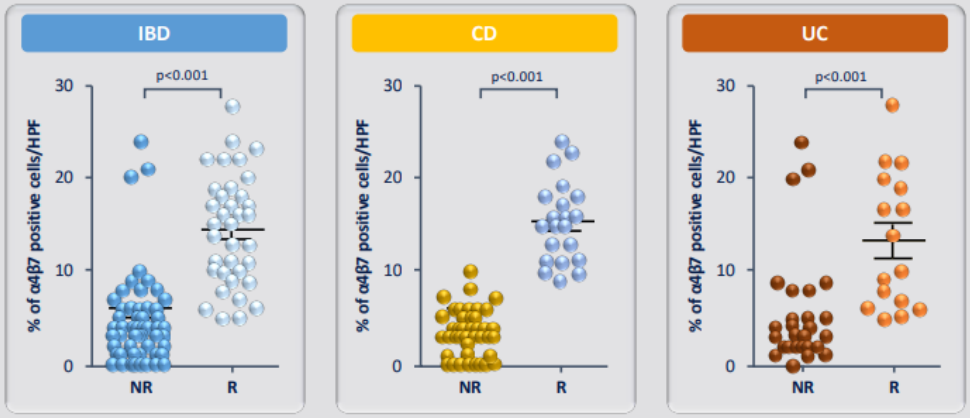


Ferrante M et al ACG 2021/UEGW 2021

Sands B et al Gastroenterology 2017

Predicating response to treatment- biochemical

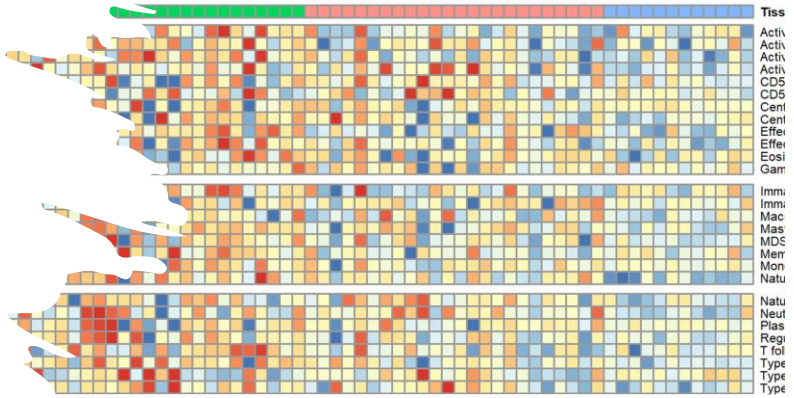
Intestinal α4β7 expression predicts therapeutic response to VDZ

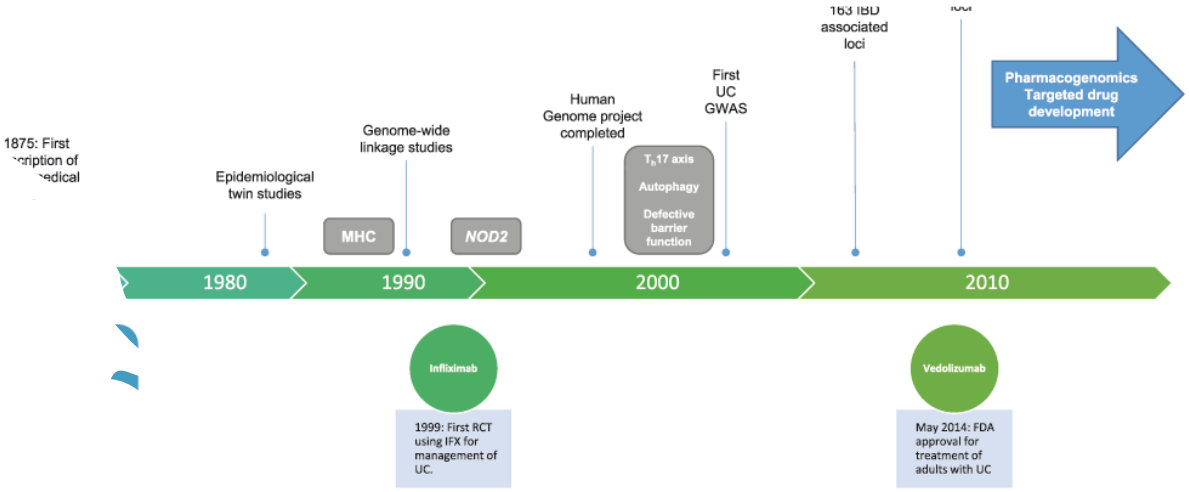


CD, Crohn's disease; HPF, high power field; IBD, inflammatory bowel disease; NR, non-remitters; R, remitters; UC, ulcerative colitis

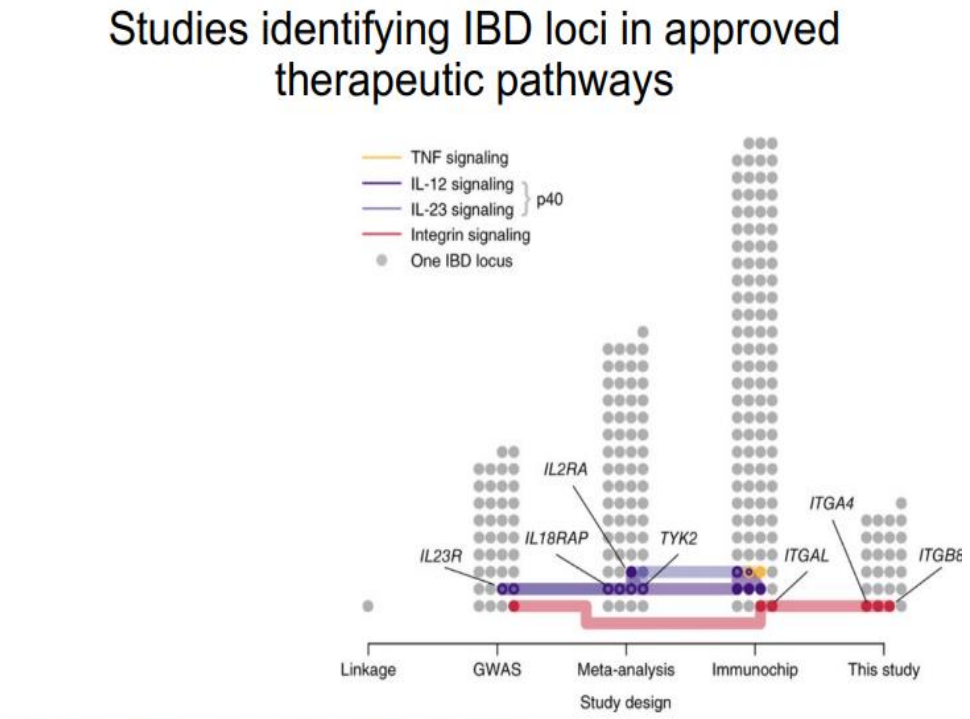
PREDICTORS FOR TREATMENT RESPONSE

- Mucosal **gene signatures and epigenetics** to predict response to treatment:



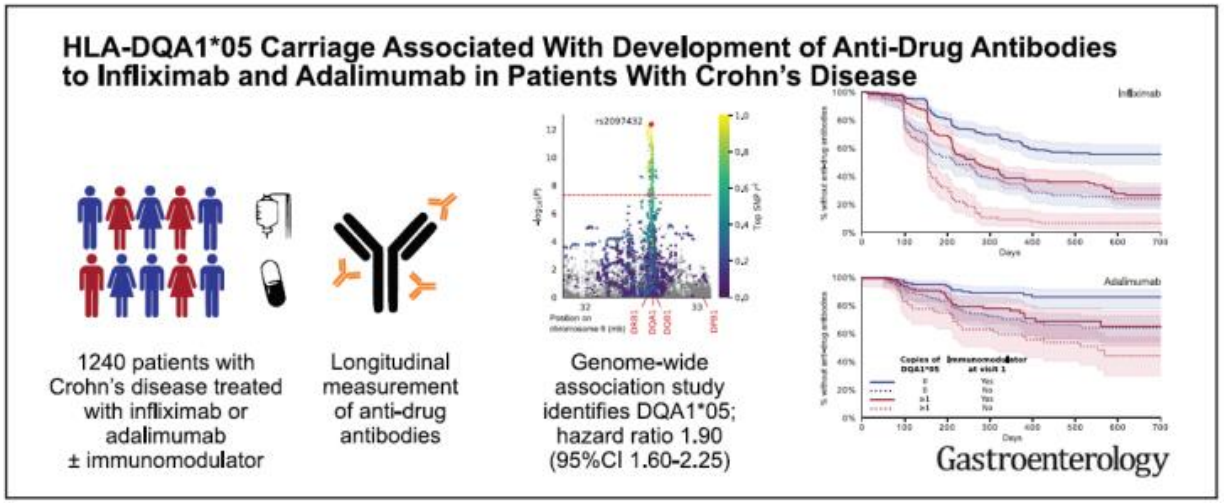


Mucosal **gene signatures and epigenetics** to predict response to treatment:

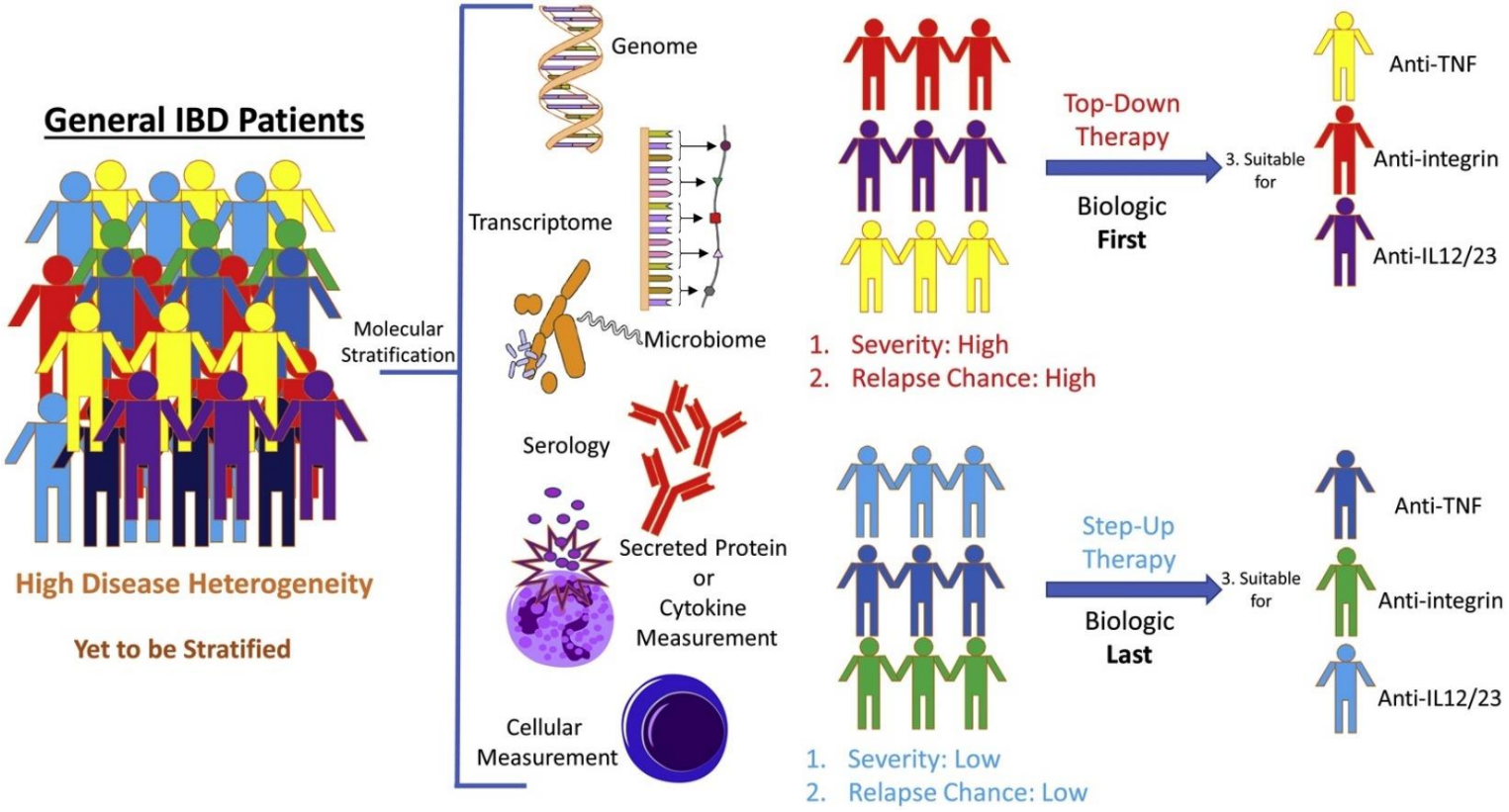


de Lange, K., Moutsianas, L., Lee, J. et al. Nat Genet (2017).

HLA-DQA1*05 Carriage Predicts Anti-TNF Antibody Formation in CD



- In order to advance our therapy we need new predictive tools, based on – Omics, Serologic Markers, Serum and Fecal Biomarkers



Ongoing Studies with Potential to Yield Data Relevant to Precision Care

In the Pipeline….

Study	Description & Aim(s)
Genetic	
PANTS (NCT03088449)	A prospective, uncontrolled cohort study of 1610 patients with IBD started on anti-TNF therapy; recruitment to this study has been completed and is now in the follow-up phase; aiming to provide novel insights into anti-TNF response and non-response
IBD BioResource	An observational study across the UK that is seeking to recruit 50 000 cases of IBD; aiming to further understand the functional effect of IBD-associated gene variants
Transcriptomic	
PROFILE (ISRCTN 11808228)	A biomarker-stratified trial in Crohn's disease seeking to recruit 400 patients to determine whether clinical outcomes can be optimized from diagnosis by using a blood-based prognostic biomarker to stratify therapy
RISK (NCT00790543)	An observational prospective study of treatment-naive, newly diagnosed pediatric Crohn's disease; 913 cases of Crohn's disease and 887 controls have been recruited and are currently undergoing clinical follow-up; seeking to determine novel genetic, transcriptomic, and microbial biomarkers associated with outcomes
Microbiomic/Metabolomic	
PREdICCt (ISRCTN 11808228)	An observational study aiming to recruit 3100 patients with IBD in remission, seeking to determine environmental factors—including contributions from dietary intake and the gut microbiome—to both remission and relapse of inflammation
IBD Multiomics database	An in-depth multiomic profiling project of 90 participants over the course of 1 year with data then made publicly available to allow the scientific community to gain increased understanding of the complex interplay in IBD
Proteomic	
IBD-Character	A proteomic biomarker discovery study of 400 patients with newly diagnosed, treatment-naive IBD, 200 symptomatic patients without evidence of IBD, and 200 healthy age-matched controls; seeking to identify proteomic markers associated with clinical outcomes
PREDICTS	A biorepository platform study of military personnel from the USA, with 2000 IBD cases (1000 with Crohn's disease and 1000 with ulcerative colitis) and 500 healthy controls; seeking novel proteomic biomarkers particularly before development of IBD

Noor NM, Lancet Gastroenterol Hepatol. 2020 Jan;5(1):80-92.

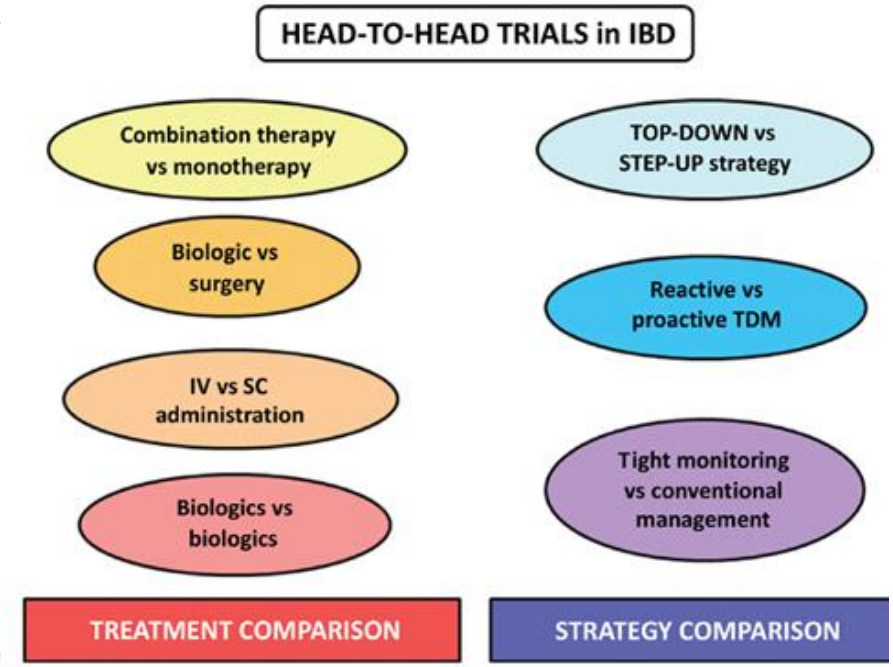
התלבטות אמיתית?

- בן 22 אובחן לפני 3 חודשים עם מחלת מעי דלקתית הגורמת לשלשולים ולכאבי בטן
- אין מחלות רקע ולא ידוע על סיבוכים מחוץ למעי
- חומרת המחלה קלינית ואנדוסקופית בינונית
- האבא (ה"טחון") מוכן לשלם לך כל סכום על מנת לקבל ממך המלצה חד-משמעית לכל טיפול שתמצאי לנכון
- מוכן לשלם כל סכום על מנת שבנו יקבל את הטיפול היעיל ביותר לטווח הקצר והארוך

COMPARING THERAPIES-

20 Years of Comparative Effectiveness Research (CER) in IBD

20 Years of Comparative Effectiveness Research (CER) in IBD

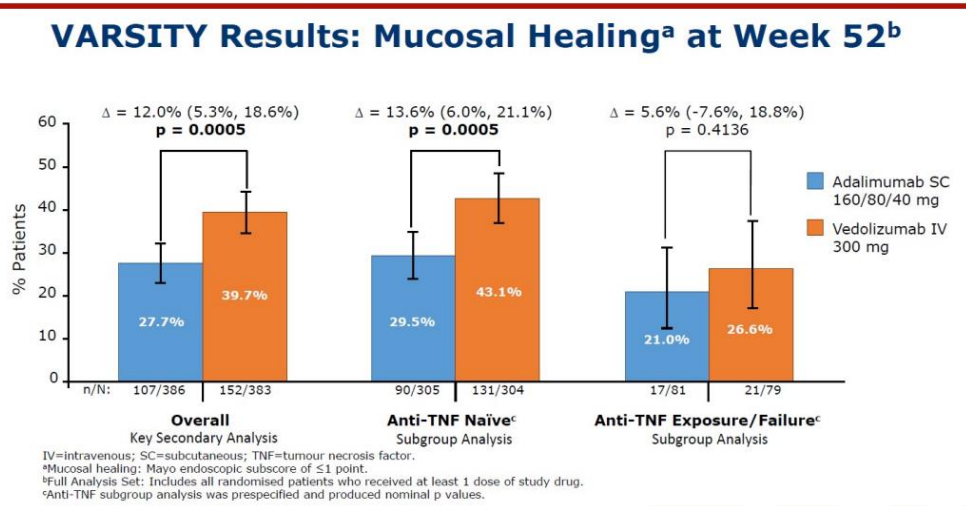


Head to head trials in IBD: treatment comparison *vs.* strategy comparis

HEAD TO HEAD-VARSITY

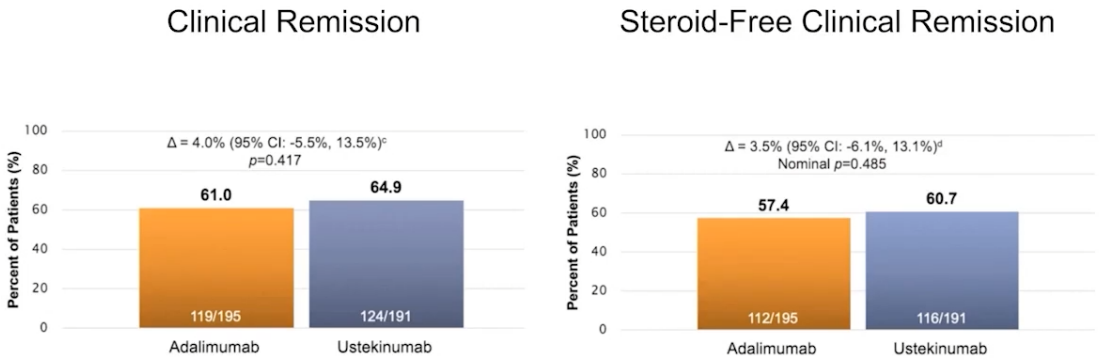
Head-to-head trials designed and powered to enable formal comparisons are the gold standard in comparative research

Varsity Trial: Mucosal Healing (2015-2019)



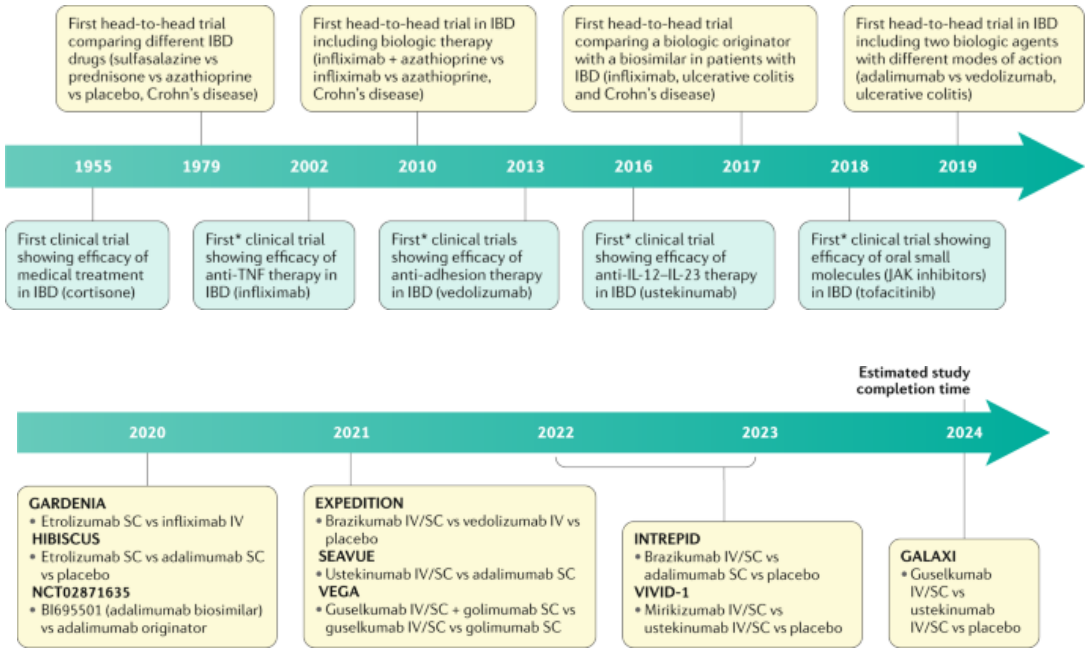
HEAD TO HEAD-SEAVUE

Clinical Remission and Steroid-Free Remission



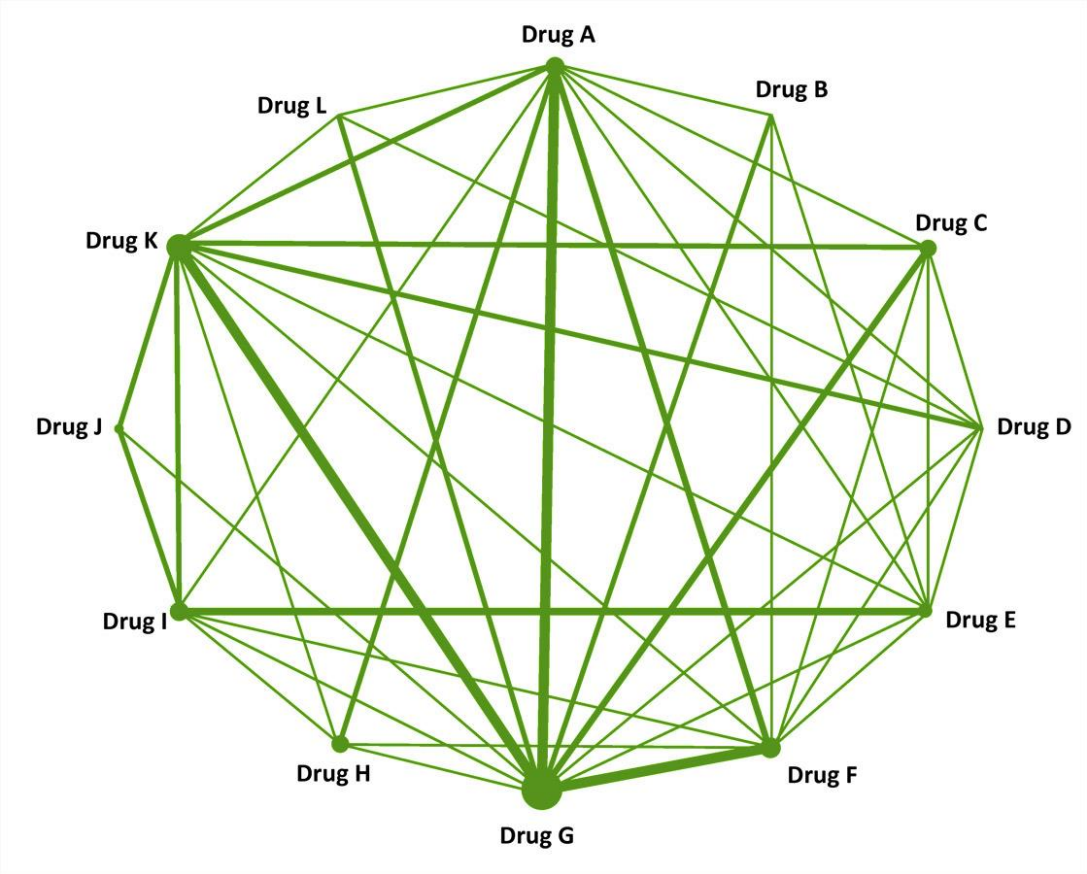
Sands BE, et al. Digestive Disease Week 2021, SEAVUE Study

- Head-to-head trials in inflammatory bowel disease: past, present and future

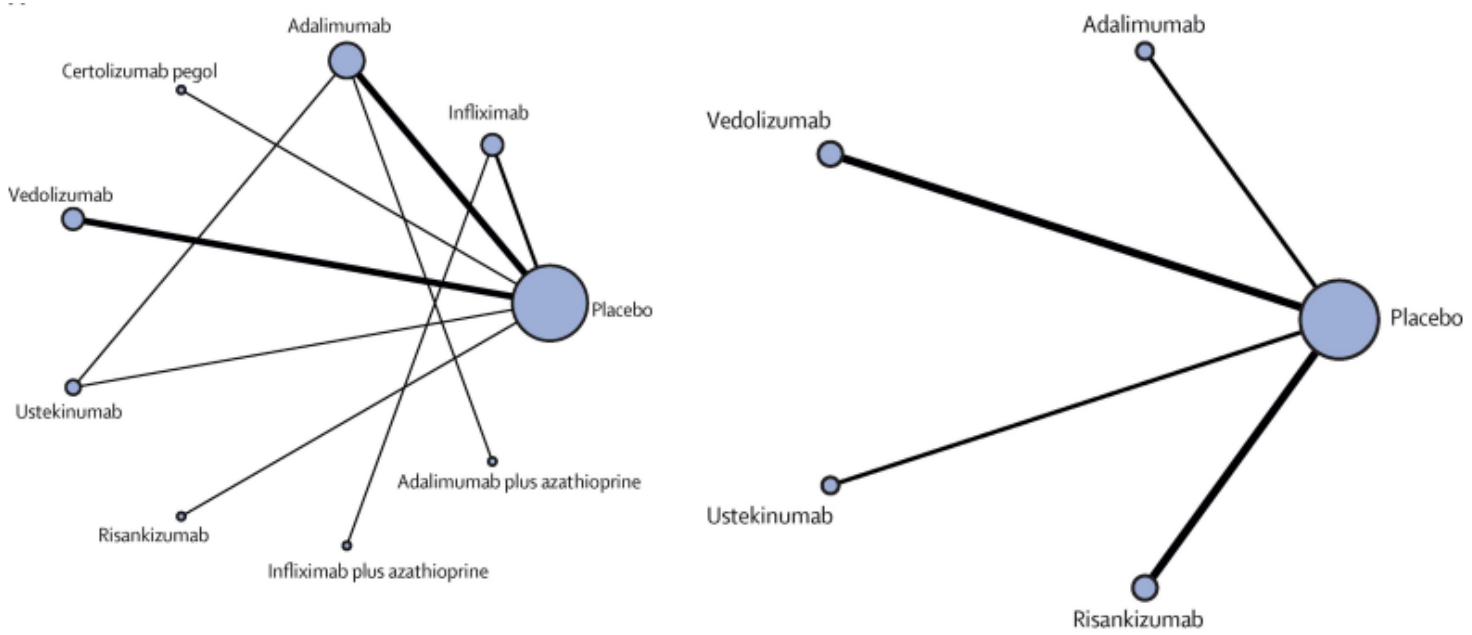


Comparative Effectiveness via Network Meta-Analysis

- Network meta-analysis is a meta-analysis in which multiple treatments (that is, three or more) are being compared using both **direct** comparisons of interventions within randomized controlled trials and **indirect** comparisons across trials based on a common comparator.



Network meta-analysis



Siddharth Singh, et al. ***Lancet Gastroenterol Hepatol* 2021; 6:1002–14**

Network meta-analysis of biologics in CD

- Biologic naïve

Induction of clinical response	Induction of clinical remission								
	Infliximab	0·61 (0·31–1·19)	1·50 (0·54–4·22)	2·65 (0·70–10·02)	1·72 (0·61–4·87)	2·07 (0·63–6·87)	2·28 (0·73–7·06)	**4·53 (1·49–13·79)**	**6·17 (2·54–15·01)**
	0·56 (0·36–0·87)	Infliximab plus thiopurines	2·49 (0·73–8·52)	4·38 (0·99–19·45)	2·85 (0·83–9·82)	3·43 (0·87–13·54)	**3·76 (1·01–14·03)**	**7·49 (2·04–27·49)**	**10·20 (3·34–31·10)**
	8·84 (1·95–40·03)	**15·88 (3·29–76·64)**	Adalimumab	1·76 (0·76–4·08)	1·15 (0·66–1·99)	1·38 (0·51–3·69)	1·51 (0·61–3·74)	**3·01 (1·25–7·27)**	**4·10 (2·31–7·27)**
	..	..	..	Adalimumab plus thiopurines	0·65 (0·24–1·77)	0·78 (0·21–2·85)	0·86 (0·25–2·95)	1·71 (0·51–5·77)	2·33 (0·84–6·43)
	7·90 (1·78–35·10)	**14·18 (2·99–67·26)**	0·89 (0·61–1·31)	..	Ustekinumab	0·83 (0·31–2·21)	1·32 (0·54–3·23)	**2·63 (1·10–6·28)**	**3·58 (2·05–6·25)**
	..	..	..	..	..	Risankizumab	1·10 (0·38–3·19)	2·19 (0·77–6·21)	**2·98 (1·33–6·64)**
	12·76 (2·76–59·08)	**22·91 (4·64–113·02)**	1·44 (0·75–2·80)	..	1·62 (0·87–3·00)	..	Vedolizumab	1·99 (0·75–5·26)	**2·71 (1·34–5·48)**
	15·08 (3·46–65·83)	**27·08 (5·81–126·25)**	**1·71 (1·02–2·84)**	..	**1·91 (1·21–3·00)**	..	1·18 (0·67–2·10)	Certolizumab pegol	1·36 (0·70–2·66)
	22·00 (5·17–93·56)	**39·49 (8·68–179·61)**	**2·49 (1·62–3·82)**	..	**2·79 (1·94–3·99)**	..	**1·72 (1·04–2·85)**	**1·46 (1·11–1·92)**	Placebo

Siddharth Singh, et al. ***Lancet Gastroenterol Hepatol* 2021; 6:1002–14**

Network meta-analysis of biologics in CD

- Biologic-exposed

	Induction of clinical remission				
Induction of clinical response	**Risankizumab**	1·34 (0·79–2·27)	0·74 (0·35–1·57)	**2·10 (1·12–3·92)**	**2·64 (1·89–3·68)**
	1·34 (0·62–2·90)	**Ustekinumab**	0·56 (0·25–1·22)	1·57 (0·80–3·06)	**1·97 (1·31–2·97)**
	1·51 (0·64–3·56)	1·13 (0·51–2·51)	**Adalimumab**	**2·82 (1·20–6·62)**	**3·55 (1·82–6·93)**
	1·87 (0·87–4·02)	1·40 (0·68–2·87)	1·24 (0·55–2·77)	**Vedolizumab**	1·26 (0·74–2·14)
	3·31 (1·86–5·90)	**2·47 (1·49–4·09)**	**2·19 (1·17–4·09)**	**1·77 (1·07–2·92)**	**Placebo**

Siddharth Singh, et al. ***Lancet Gastroenterol Hepatol* 2021; 6:1002–14**

Being a second drug always portend worse response rates

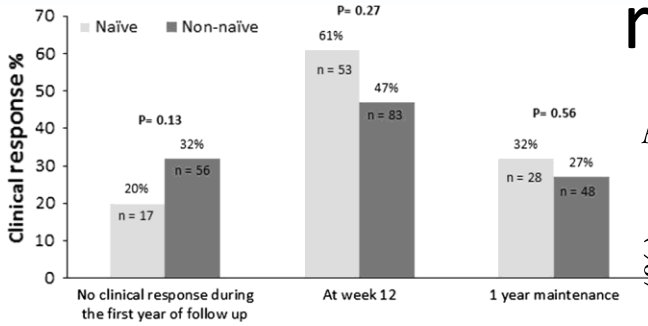
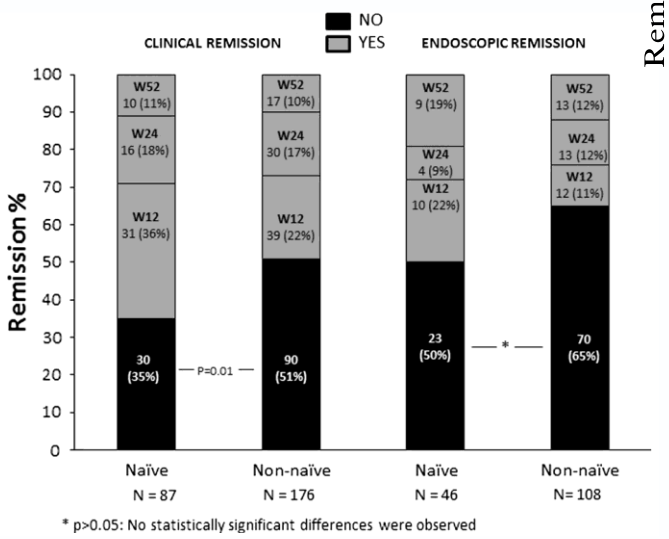
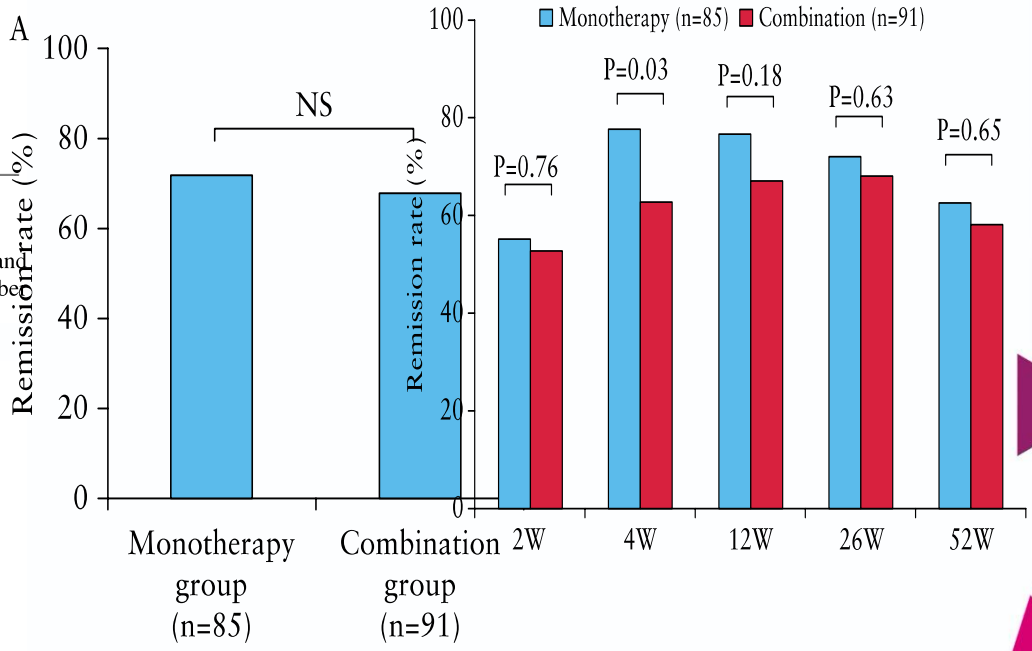


Fig. 1 Rate of short- and long-term clinical response in naïve and non-naïve patients. Results are expressed as absolute number (percentage)





UC patients
46-48% prior exposure to thiopurines

Diamond study - CD patients
0% prior exposure to thiopurines

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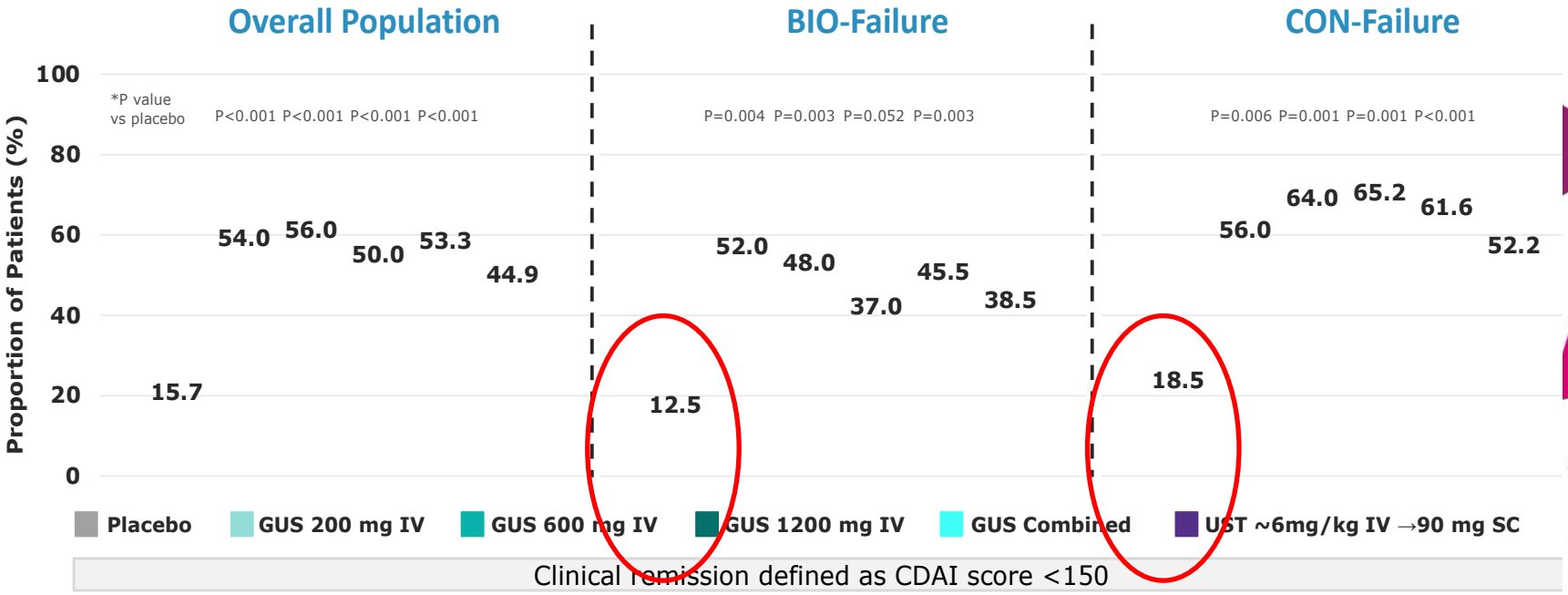
Matsumoto T et al. J Crohn's Colit 2016;10:1259–1266
Iborra M et al. J Gastroenterol 2017; 52:788–799

Being a second drug always portend worse remission rates – guselkumab and ustekinumab

Clinical (CDAI) Remission at Week 12



Sandborn WJ et al. UEGW Virtual 2020; 11–13 Oct 2020; OP089

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Conclusions – the first therapeutic agent is always more effective

- This effect is universal
- True for biologics and small molecules
- Probably through selection of less resistant disease
- Demonstrated also in the placebo
- Network (*and other types of*) meta-analyses unlikely to provide a definite answer

How Do We Put Together the Puzzle of Therapy Selection?

DRUG

Efficacy

Indication
Rapidity of onset
Durability
Pharmacokinetics/TDM
Combination vs. monotherapy
Positioning and sequence

Safety

Infection
Cancer
Specific concerns by agent or mechanism

PATIENT

Individual Characteristics

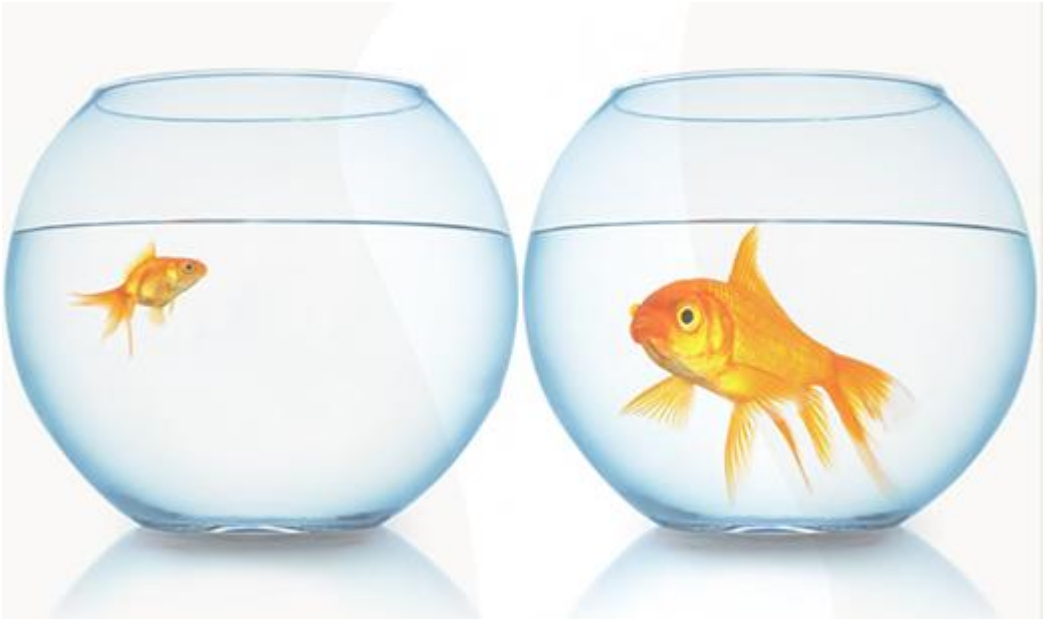
Age
Comorbidities
Preferences (IV/SQ/PO)
Insurance
Costs
Access to care

Disease Characteristics

CD vs. UC
Disease behavior/complication
Disease severity
Early vs. late
EIMs
Prior treatment success or failure

EIMs = extraintestinal manifestations; TDM = therapeutic drug monitoring

"The good physician treats the disease; the great physician treats the patient who has the disease" –
Sir William Osler, 1903



- **ONE SIZE DOES NOT FIT ALL**

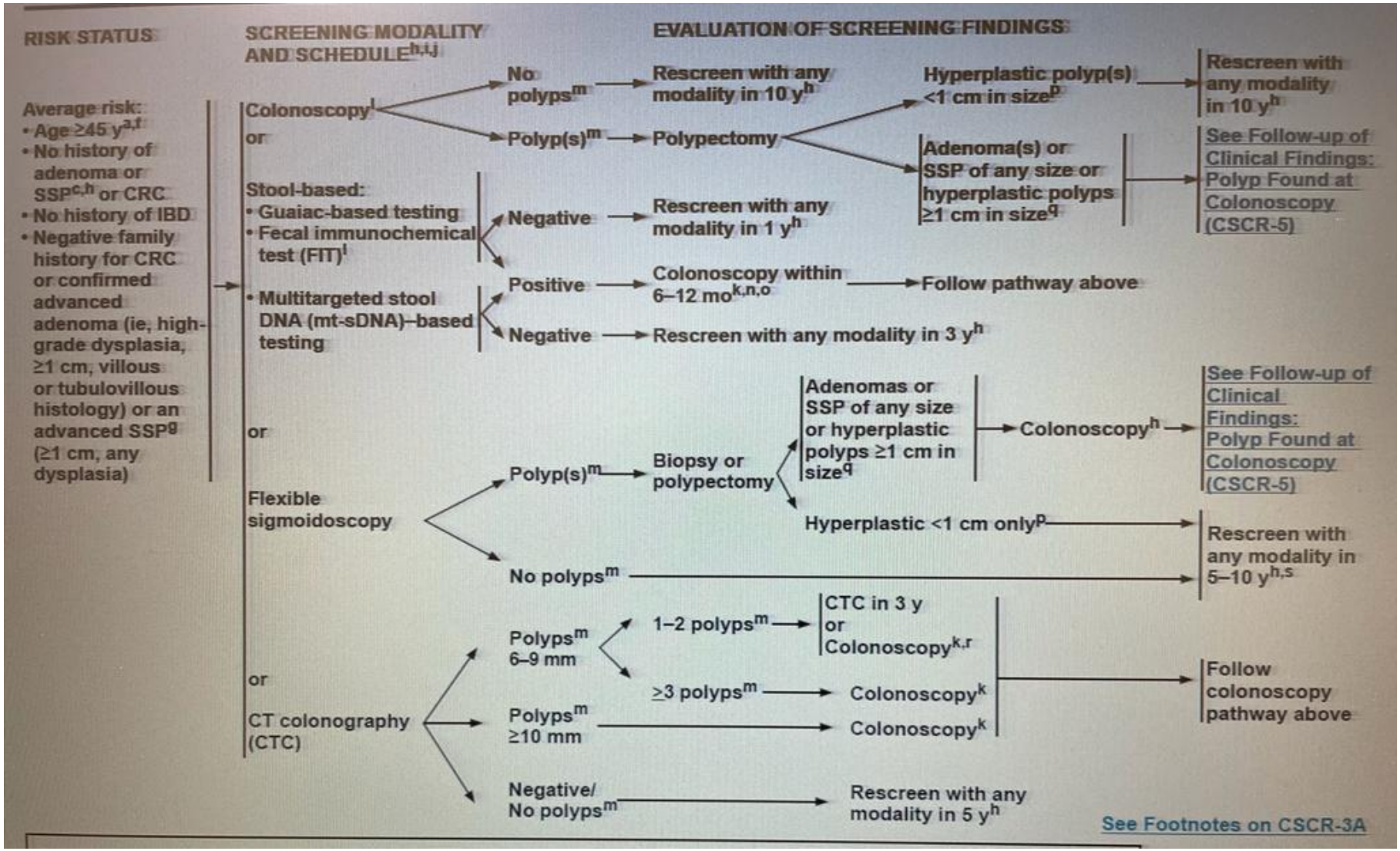
מסקנות

- בחירת טיפול אינה רשות אלא חובה!!
- בעתיד סביר שיהיו לנו אמצעים קליניים ומעבדתיים לבדוק מנבאי תגובה לטיפול על מנת ליישם רפואה מדוייקת
- בינתיים: חובה עלינו לדבוק בתכנית המוודאת שהטיפול שניתן יעיל ולהפסיק טיפול שאינו יעיל
- שיתוף הפעולה בין המטפלים למטופל הכרחי לטיפול

Colorectal cancer screening

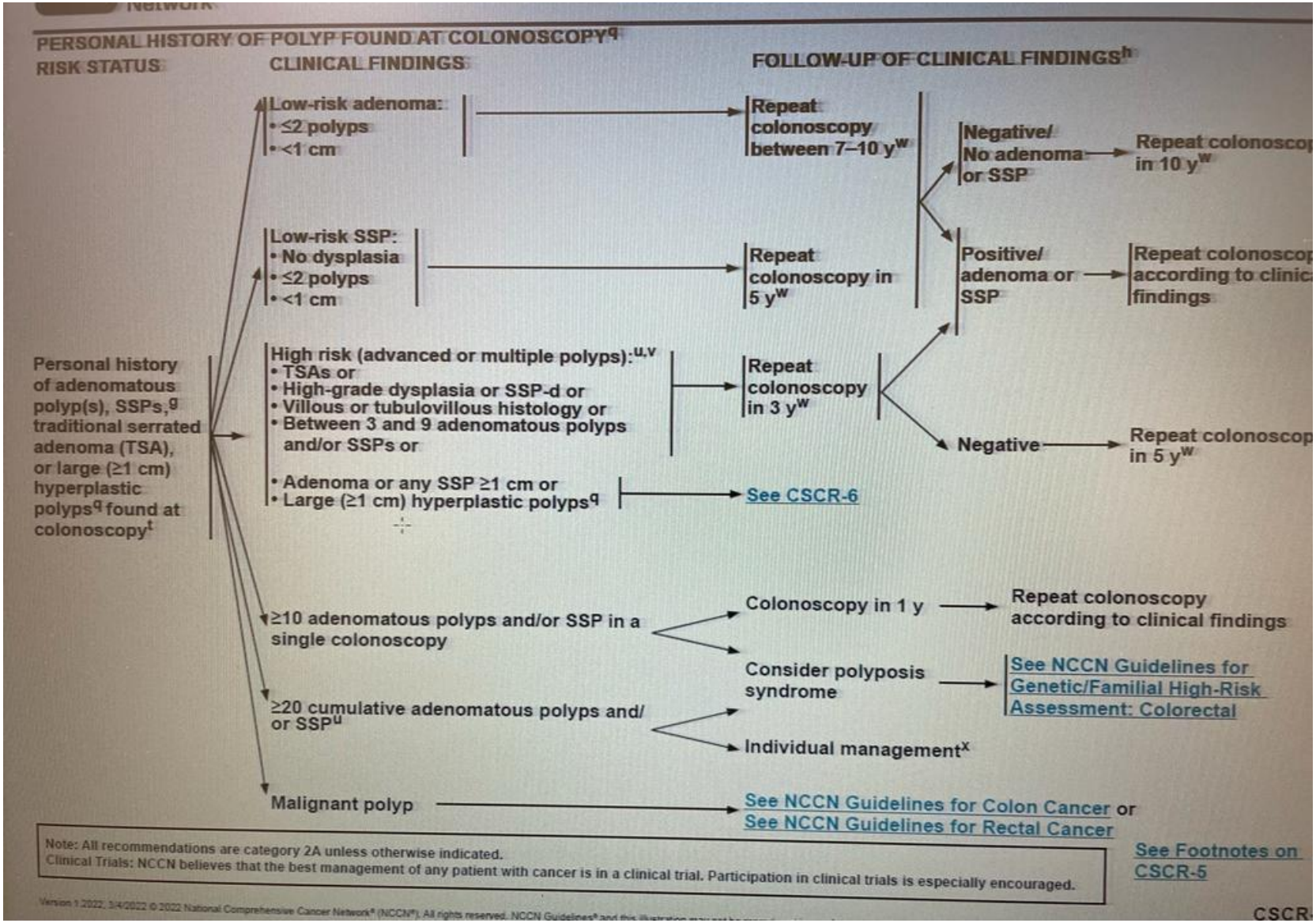
מה חדש?

סיכון ממוצע



NCCN guidelines version 1.2022

מעקב פוליפים



NCCN guidelines version 1.2022

ותודה לכל מי שמגלה עניין גם
בשעות מאוחרות כאלה של הערב