15η Πανελλήνια Εκπαιδευτική Συνάντηση ΕΛΙΓΑΣΤ

6-8 Μαρτίου 2020, Divani Caravel, Αθήνα

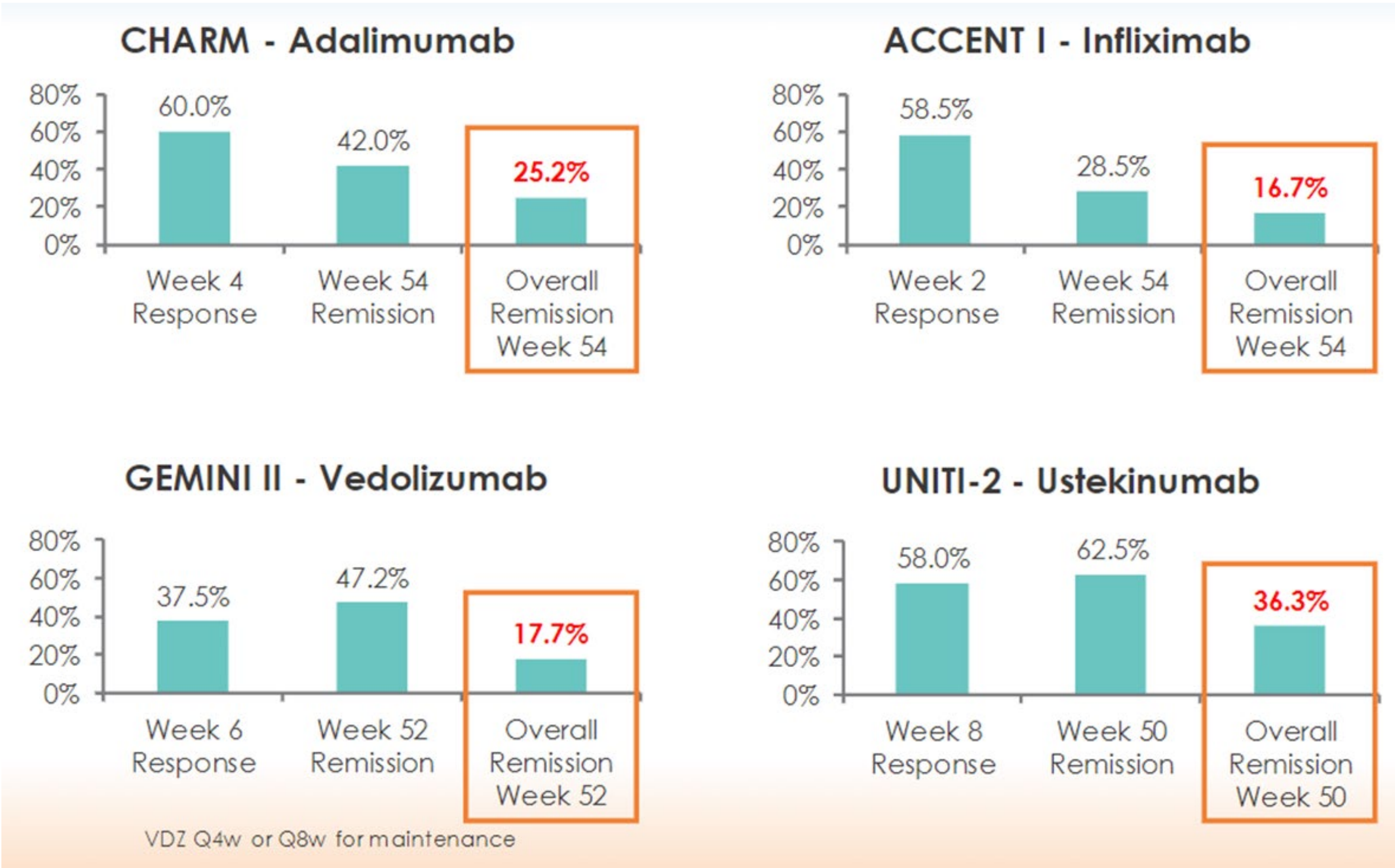
ΙΦΝΕ: Μπορούμε να προβλέψουμε την ανταπόκριση στη θεραπεία και πώς;

Κωνσταντίνος Σουφλέρης
Γαστρεντερολόγος,
Επιμελητής Α΄Ε.Σ.Υ.,
Γαστρεντερολογική Κλινική,
Θεαγένειο Α.Ν.Θ.
Θεσσαλονίκη

Δήλωση Σύγκρουσης Συμφερόντων

Abbvie
Amgen
Enorasis
Faran
Janssen
Merck
Mylan
Pfizer
Roche
Sandoz
Shire
Takeda
Vianex

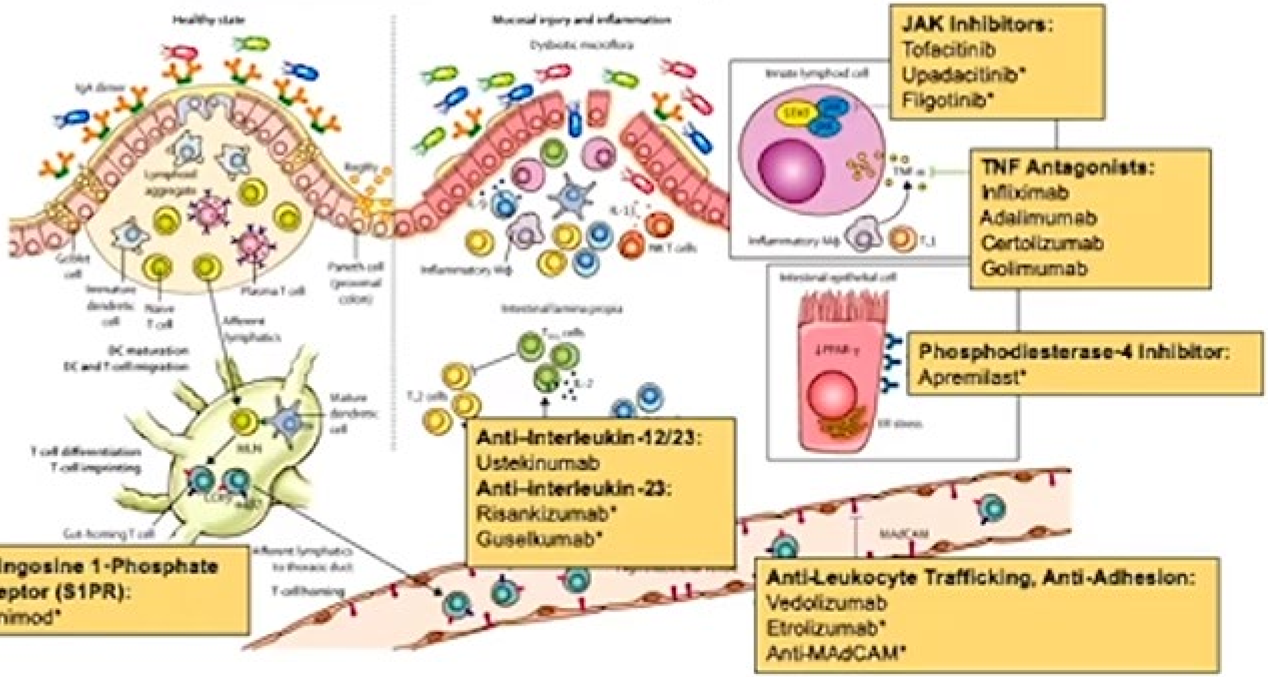
Approved Biologic Therapies in IBD: Efficacy, Clinical Trials



Από Fiocchi, ECCO 2018

Novel Biologic Therapies in IBD: Efficacy, Clinical Trials

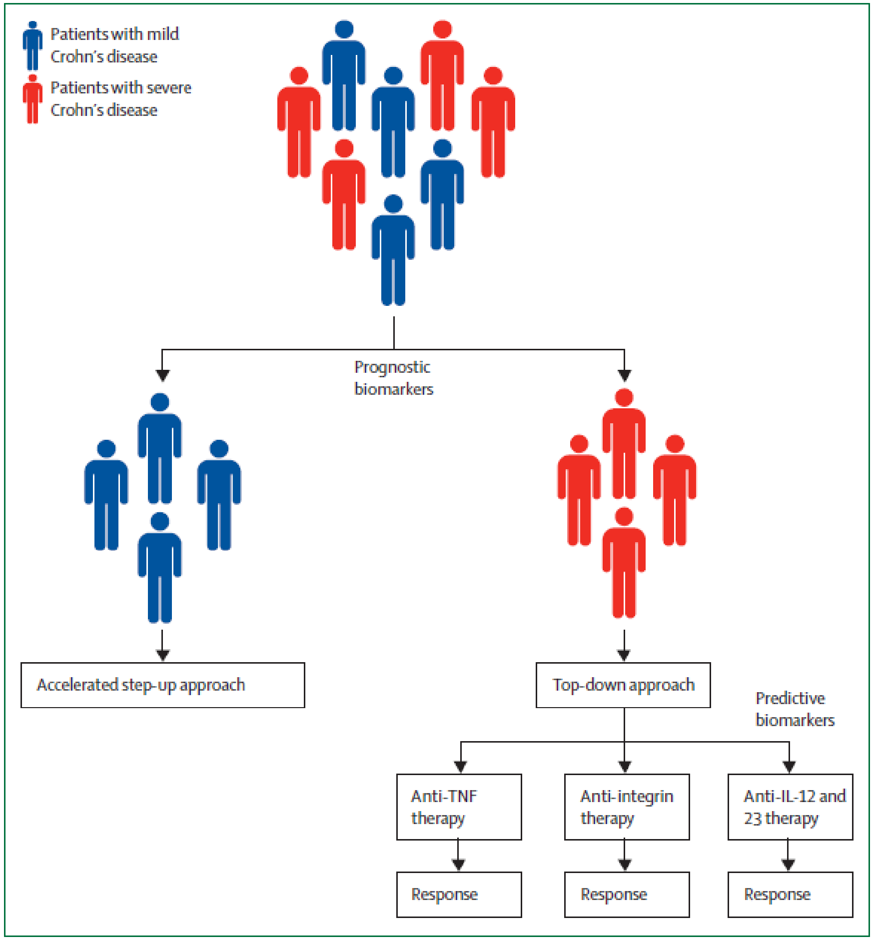
Novel Targets and Therapies in IBD
30:60 rule = 30% remission:60% response



*Not approved by the U.S. Food and Drug Administration (FDA) for the treatment of UC.
Ungaro R, et al. Lancet. 2017;389:1756-1770.

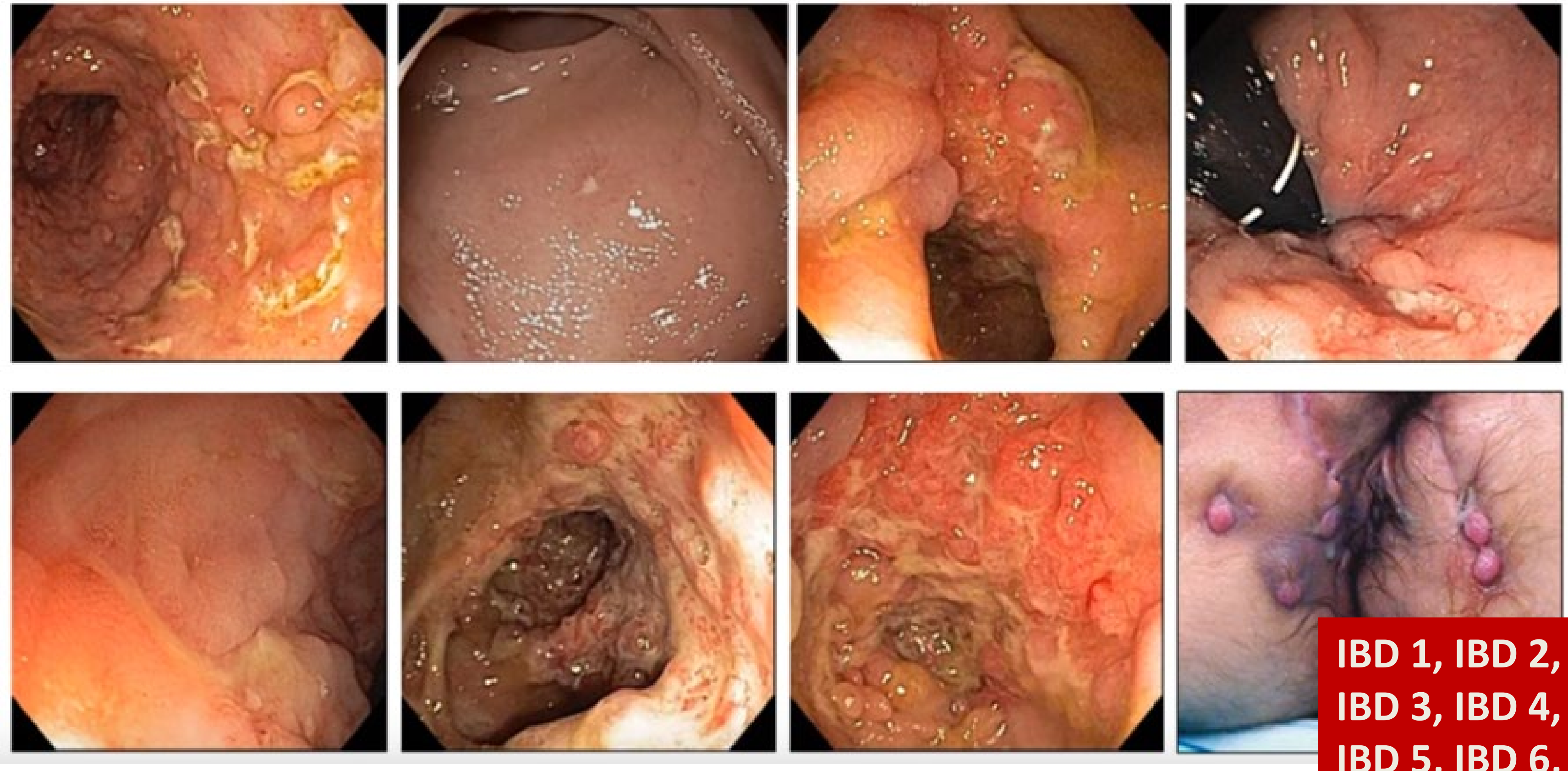
Από Regueiro, Personalized Approach to IBD: Treating to Target With New and Emerging Therapies, AIBD 2019

One Size fits all?



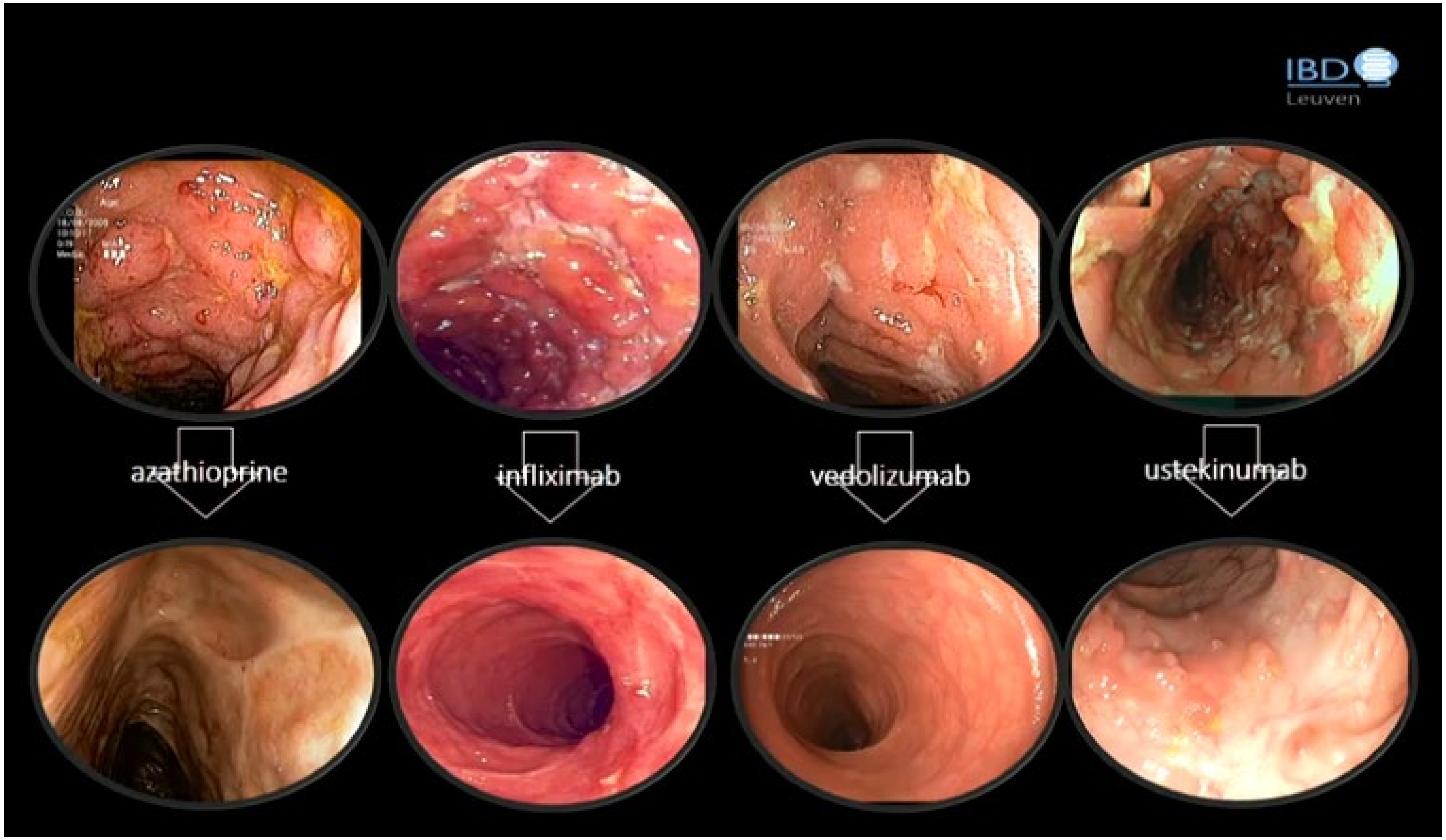
Noor, Lancet 2020

IBD Heterogeneity



IBD 1, IBD 2,
IBD 3, IBD 4,
IBD 5, IBD 6,
IBD 7, IBD 8…

IBD therapy 2020: Trial and Error



Από Vermeire, ECCO 2020

ΙΦΝΕ Θεραπεία 2020

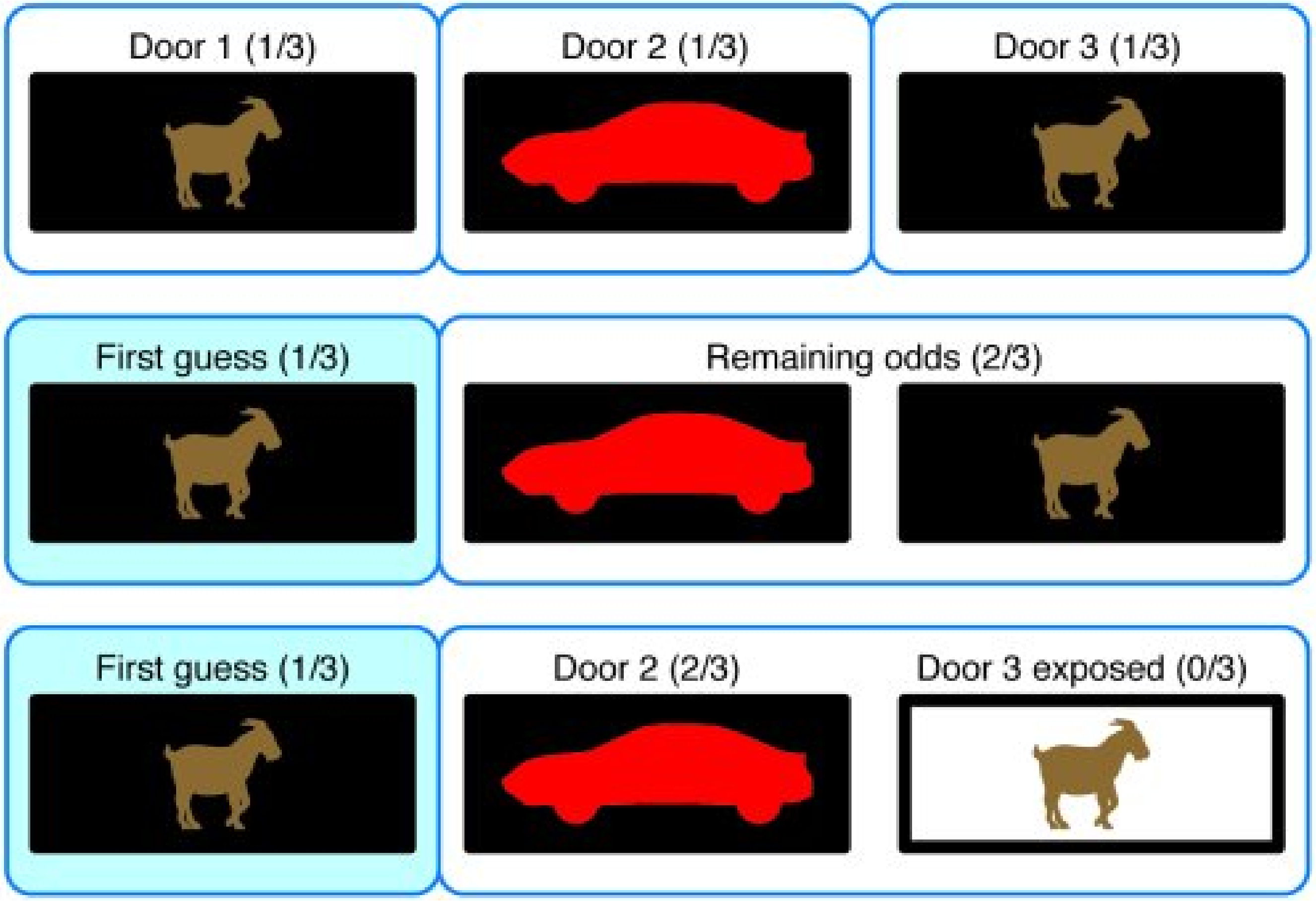
- Πολλαπλές θεραπευτικές επιλογές!
- Υπο-βέλτιστη Αποτελεσματικότητα:

-anti TNF primary non response 30%

-anti TNF secondary loss of response, immunogenicity

- Παρενέργειες…
- Κόστος…
- Ετερογένεια
- Undertreat aggressive disease…
- Overtreat mild disease…
- Diagnostics
- Stratification
- Prognosis
- **Prediction**

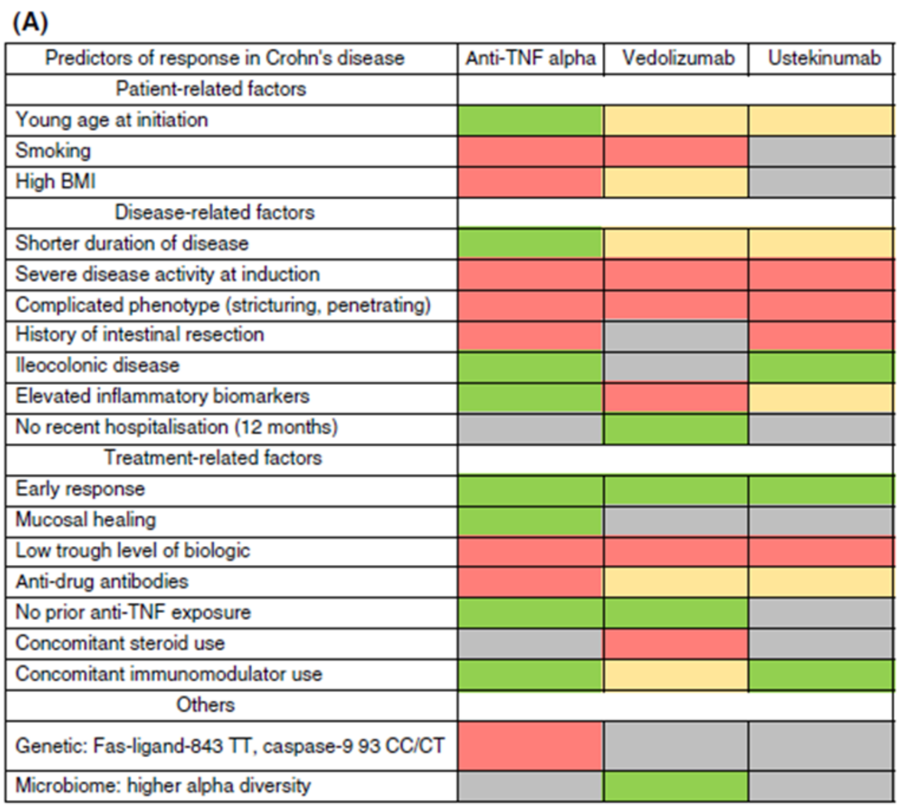
The Monty Hall Problem: Let's Make a Deal!

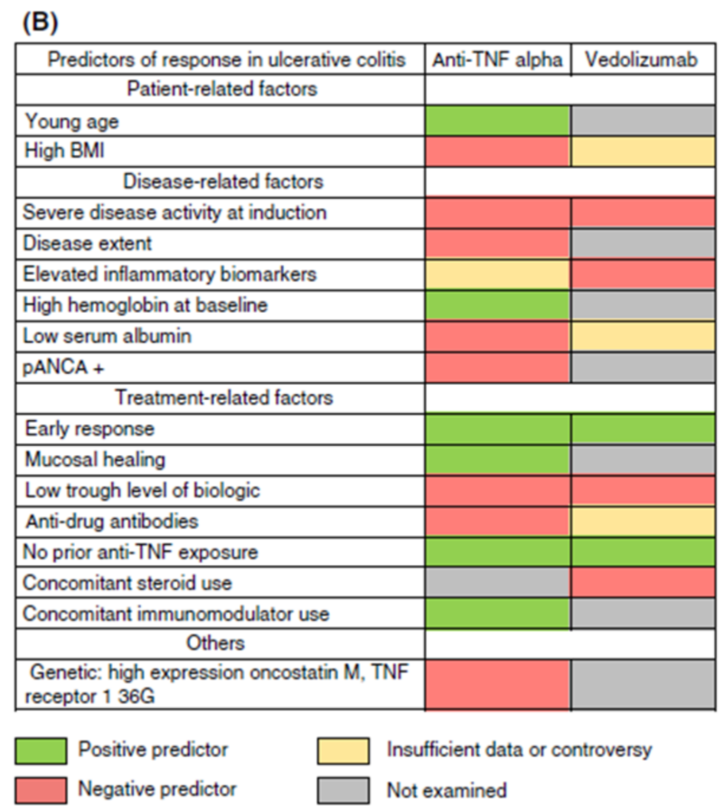


Friedman, JCI 2011

Κλινικά Προσανατολισμένες Θεραπευτικές Επιλογές

Predictors of Response:
Patient related, Disease related, “Others”…





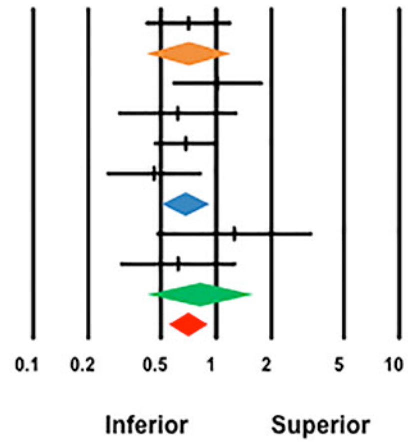
Barre, APT 2018

Νόσος του Crohn:
Η εντόπιση ως προβλεπτικός παράγοντας

Response to Different Biologic Agents - Ileal vs. Colonic CD

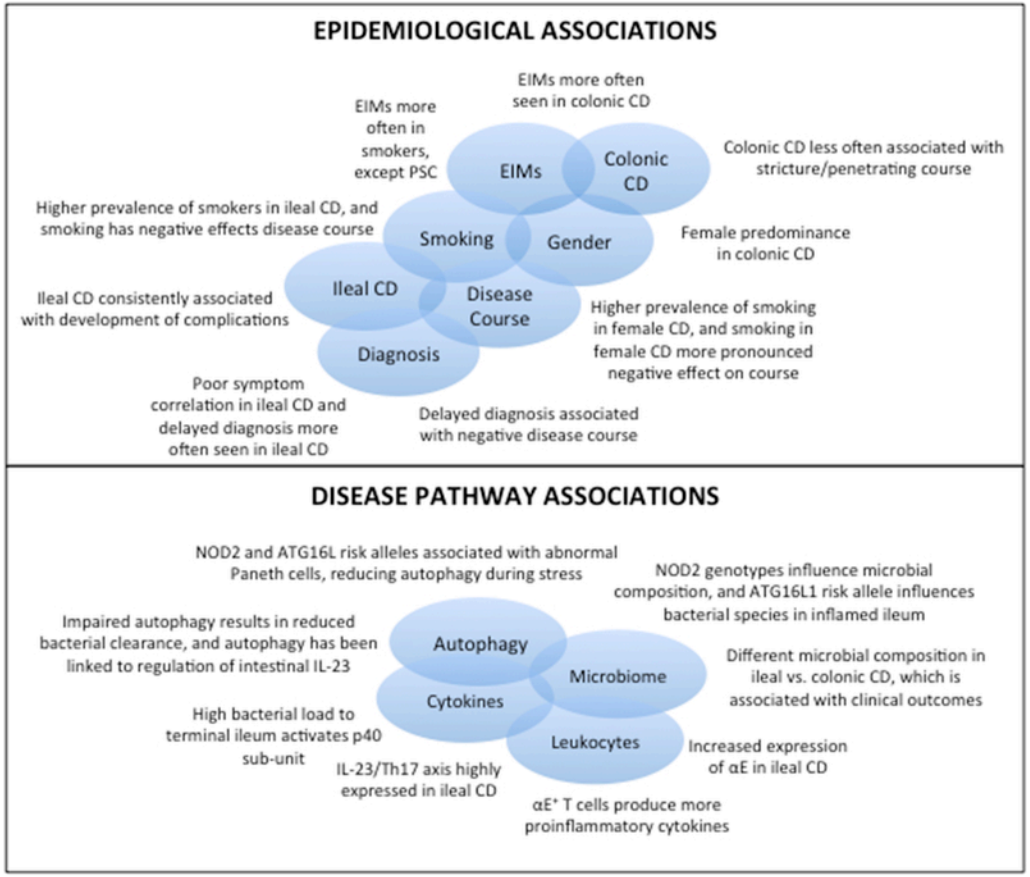
Group by Drug	Study name	Risk ratio	Lower limit	Upper limit	Events / Total: Ileal CD	Events / Total: Colonic CD
	Sandborn 2011	0.71	0.41	1.20	16 / 62	23 / 63
TNFi		0.71	0.41	1.20	16 / 62	23 / 63
	CERTIFI	1.02	0.58	1.78	15 / 34	13 / 30
	UNITI-1	0.62	0.29	1.30	8 / 37	14 / 40
	UNITI-2	0.68	0.46	1.02	21 / 49	27 / 43
	IM-UNITI	0.46	0.26	0.83	13 / 50	13 / 23
Ustekinumab		0.68	0.50	0.92	57 / 170	67 / 136
	GEMINI-II	1.26	0.47	3.34	6 / 37	8 / 62
	GEMINI-M	0.62	0.30	1.28	8 / 29	12 / 27
Vedolizumab		0.82	0.42	1.60	14 / 66	20 / 89
OVERALL		0.70	0.55	0.90	87 / 298	110 / 288

Risk ratio and 95% CI



Dulai, CGH 2019

Should We Divide Crohn's Disease into Ileum-Dominant and Isolated Colonic Diseases?

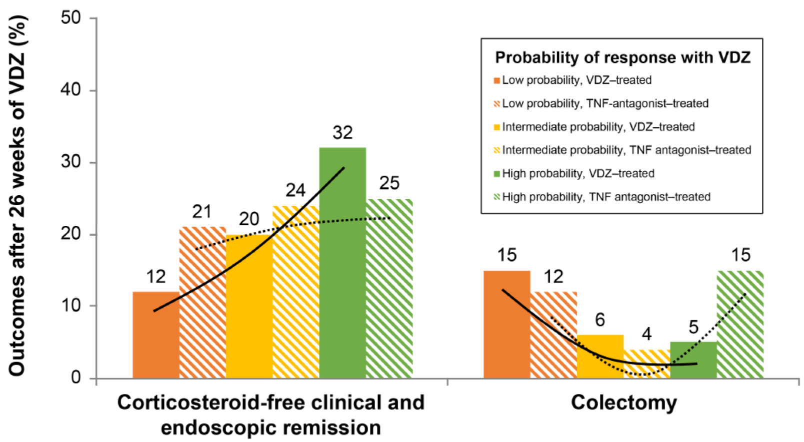


Dulai, CGH 2019

Development and Validation of Clinical Scoring Tool to Predict Outcomes of Treatment With Vedolizumab

Ulcerative Colitis

Disease duration ≥2 years	No prior TNF antagonist	Baseline endoscopy moderate activity	Baseline albumin concentration
+3 points	+3 points	+2 points	+0.65 points per unit (g/L)



Dulai, CGH 2020

Crohn's Disease

The CDST is calculated using the following five variables:

1. No prior bowel surgery (+2 points).
2. No prior TNF-antagonist therapy (+3 points).
3. No prior fistulising disease (+2 points).
4. Baseline albumin (+0.4 points per g/L).
5. Baseline C-reactive protein (−0.5 points if 3.0-10.0 mg/L; −3.0 points if >10 mg/L).

Patients with a score of 13 points or less are classified as low probability, >13 to 19 points as intermediate probability and >19 points as high probability.[13]

Dulai, APT 2020

IBD Holy Grail

The Bench to Bedside Abyss

No Association of response to Infliximab with -308 TNF Gene Polymorphism in Patients with Crohn's

Table III: *TNF-α levels (pg/ml) expressed as median and range before infliximab treatment according to response to treatment*

	Responders	Non-responders
Whole group of patients (109 responders/44 non-responders)	14 (10-314)	14 (10-90.9)
Luminal Crohn's disease (60 responders/25 non-responders)	15.2 (10-314)	10 (10-32.6)*
Fistulizing Crohn's disease (49 responders/19 non-responders)	13 (10-242)	21.6 (10-90.9)

*P=0.06.

Table IV: *Allelic and genotype frequencies (%) for -308 TNF gene polymorphism according to response to infliximab treatment*

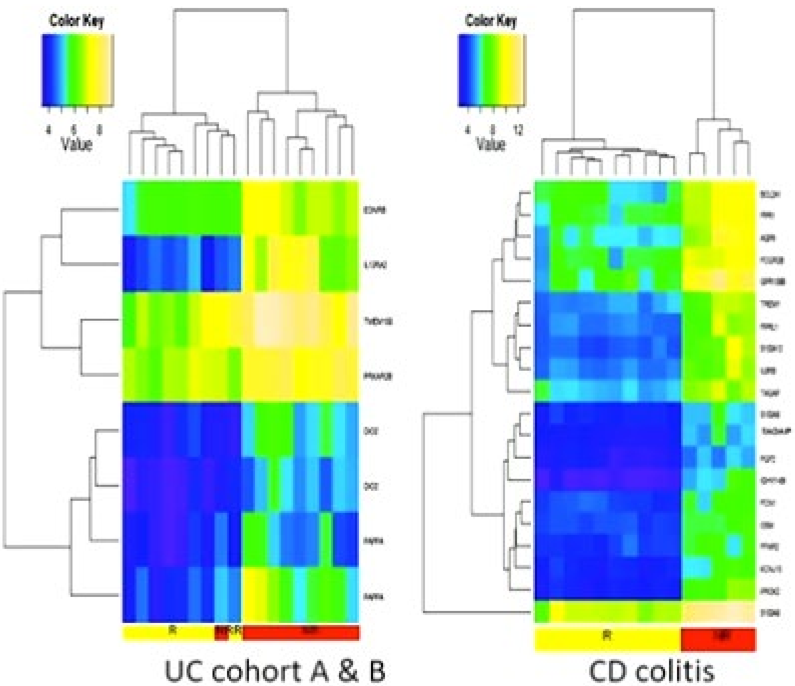
	TNF1	TNF2	TNF1/TNF1	TNF1/TNF2	TNF2/TNF2
Responders (n = 158)	85.8	14.2	73.4	24.7	1.9
Non-responders (n = 56)	78.6	21.4	62.5	32.1	5.4

Louis, Scand J Gastroenterol 2002

Predictive Gene Signature of Non Response to Infliximab in IBD Colitis

Mucosal gene expression to predicting response to infliximab

IBD Leuven

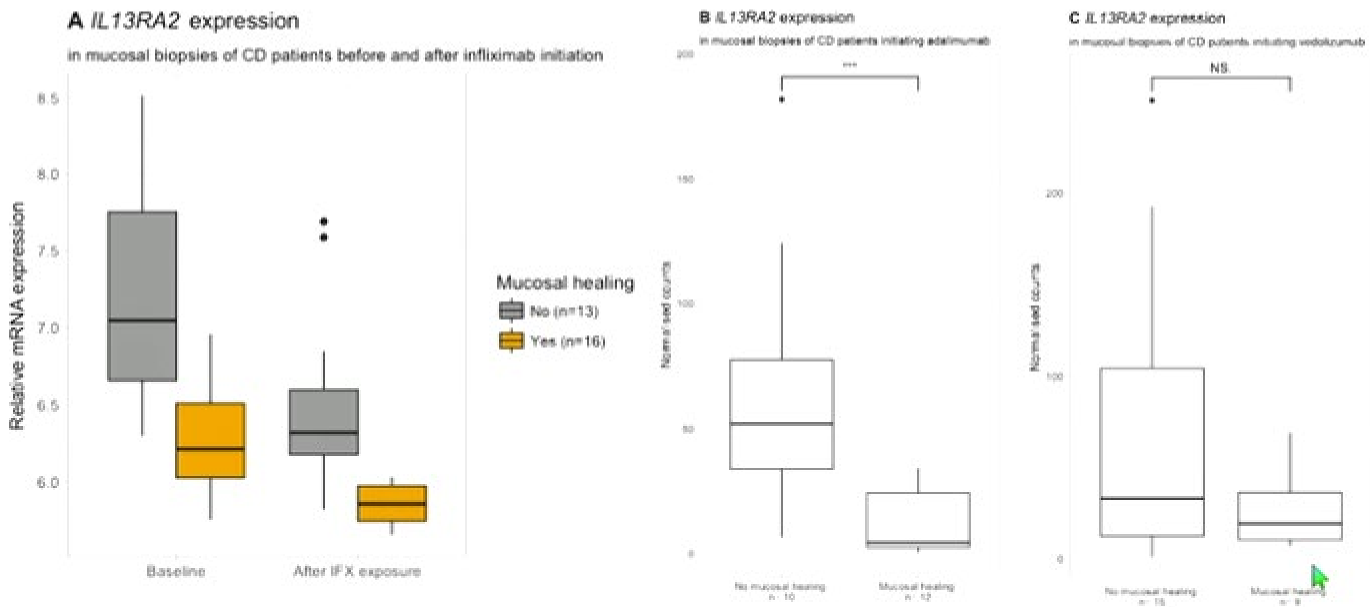


5-gene signature predicts (non)response to IFX in colitis

IL13Rα2
TNFAIP6
S100A8
IL11
G0S2
S100A9

Arijs I et al, Gut 2009;
Arijs I et al Inflamm Bowel Dis 2010;

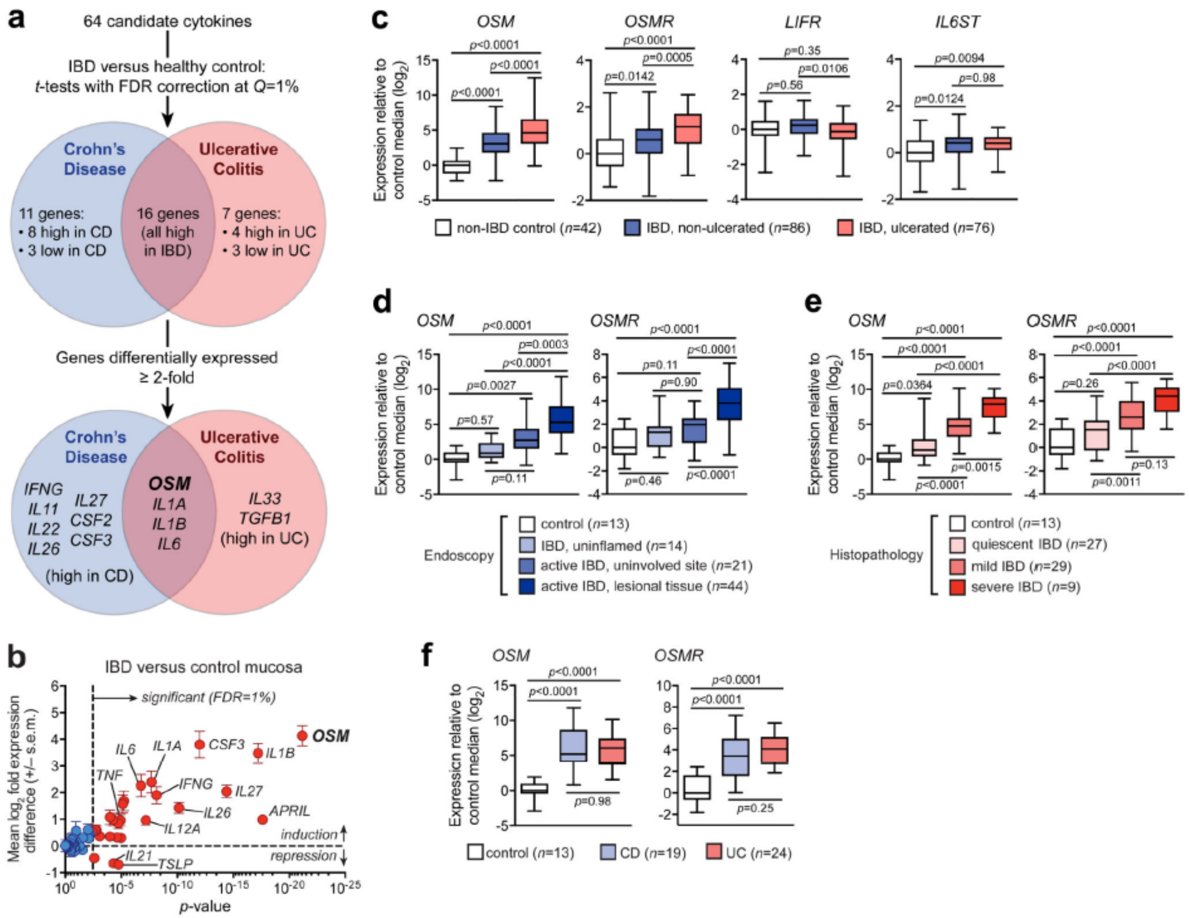
Mucosal IL13RA2 expression predicts nonresponse to anti-TNF therapy in Crohn's Disease



infliximab | adalimumab | vedolizumab

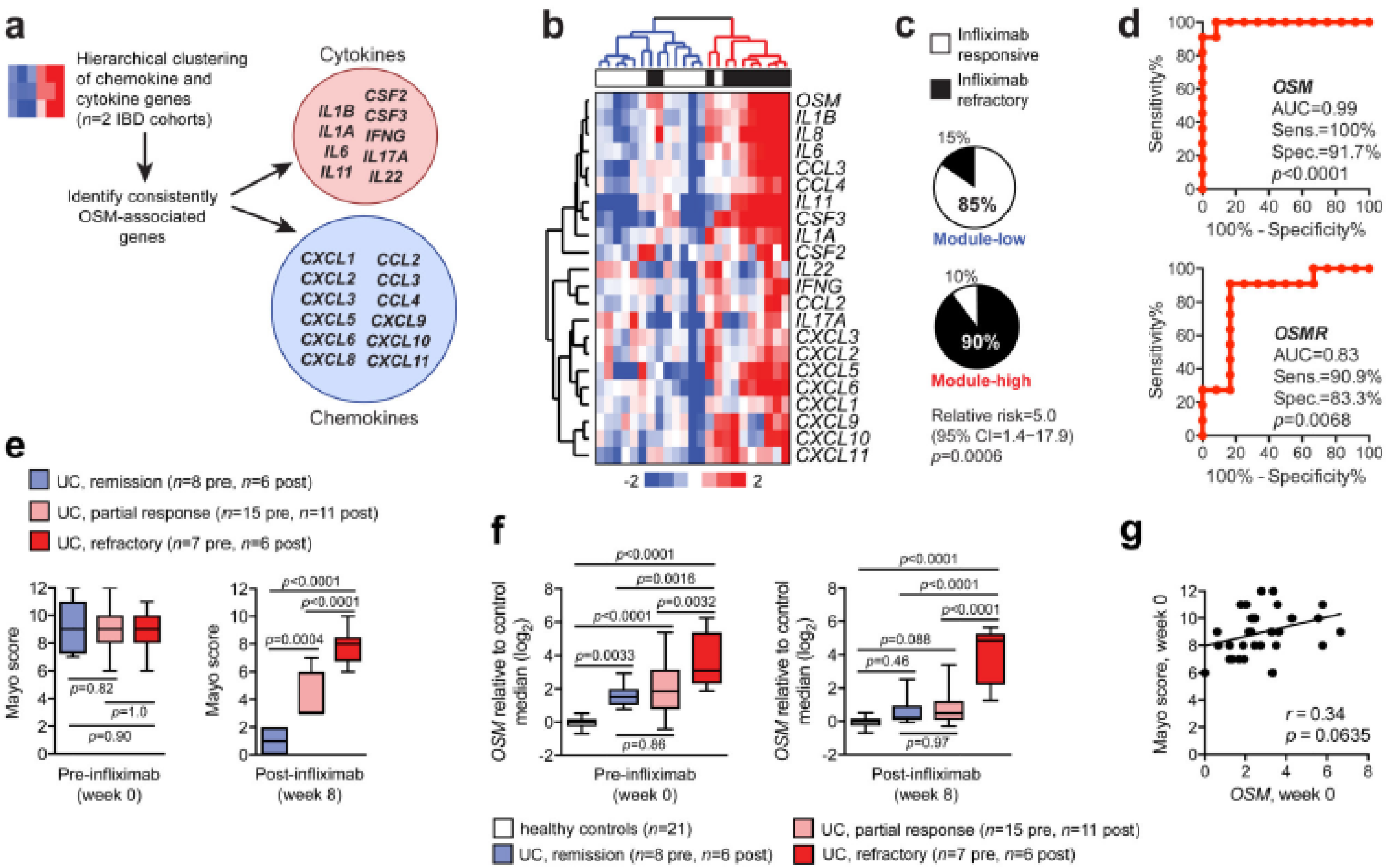
Verstockt B et al. AP&T 2019; 49: 572-81

High Mucosal Oncostatin M Predicts Primary Non Response to anti TNF Antibodies



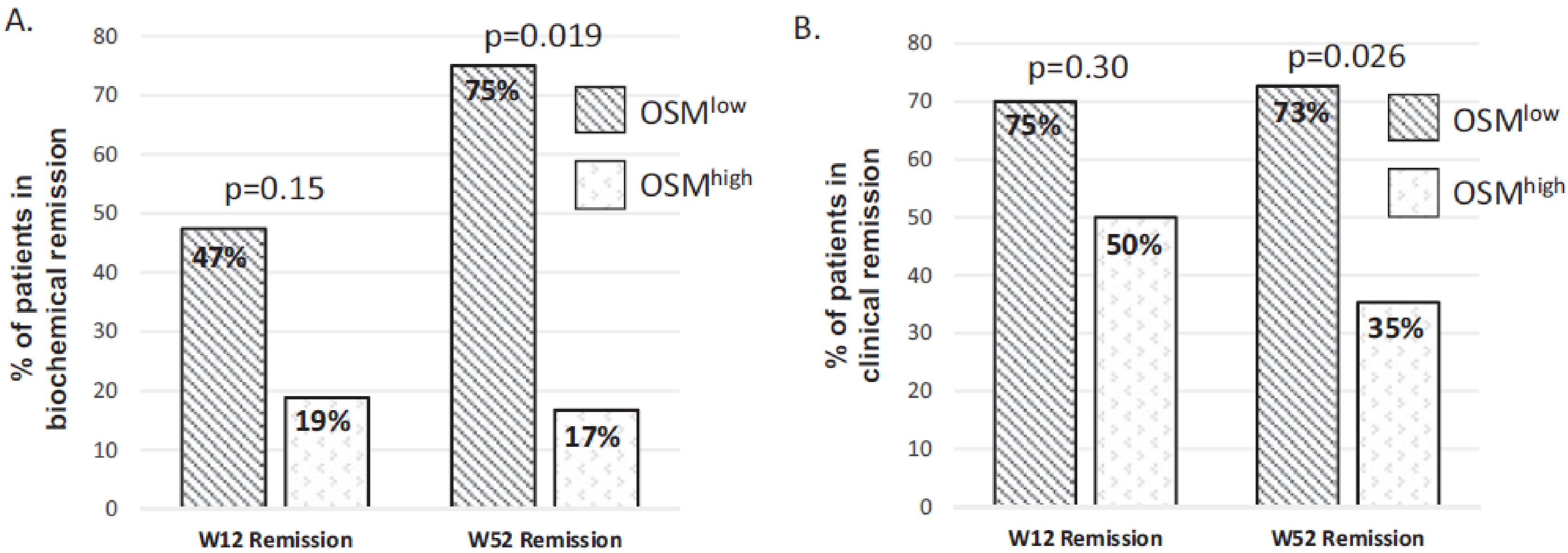
West, Nat Med 2017

High Mucosal Oncostatin M Predicts Primary Non Response to anti TNF Antibodies



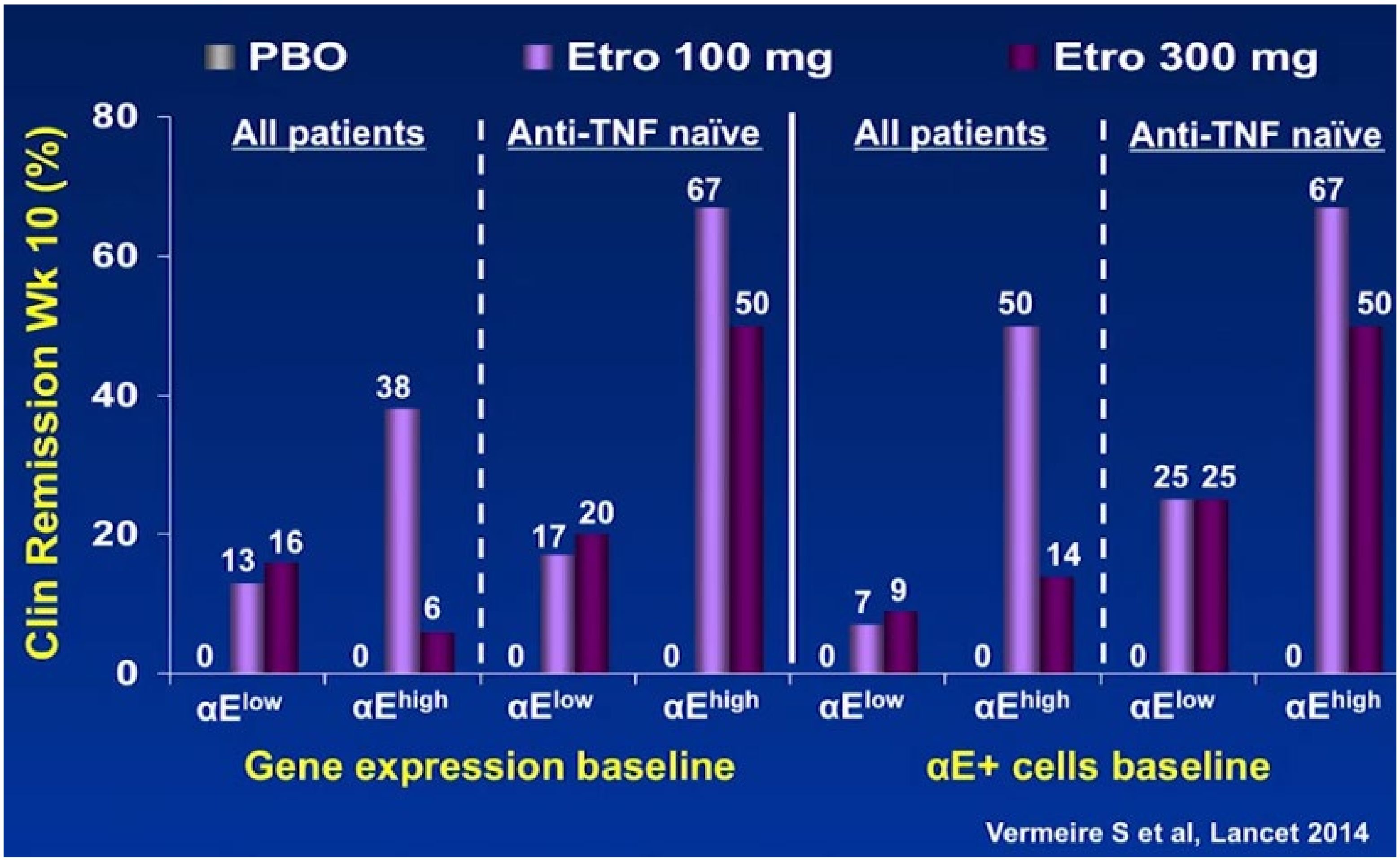
West, Nat Med 2017

Elevated Pretreatment Plasma Oncostatin M Is Associated With Poor Biochemical Response to Infliximab

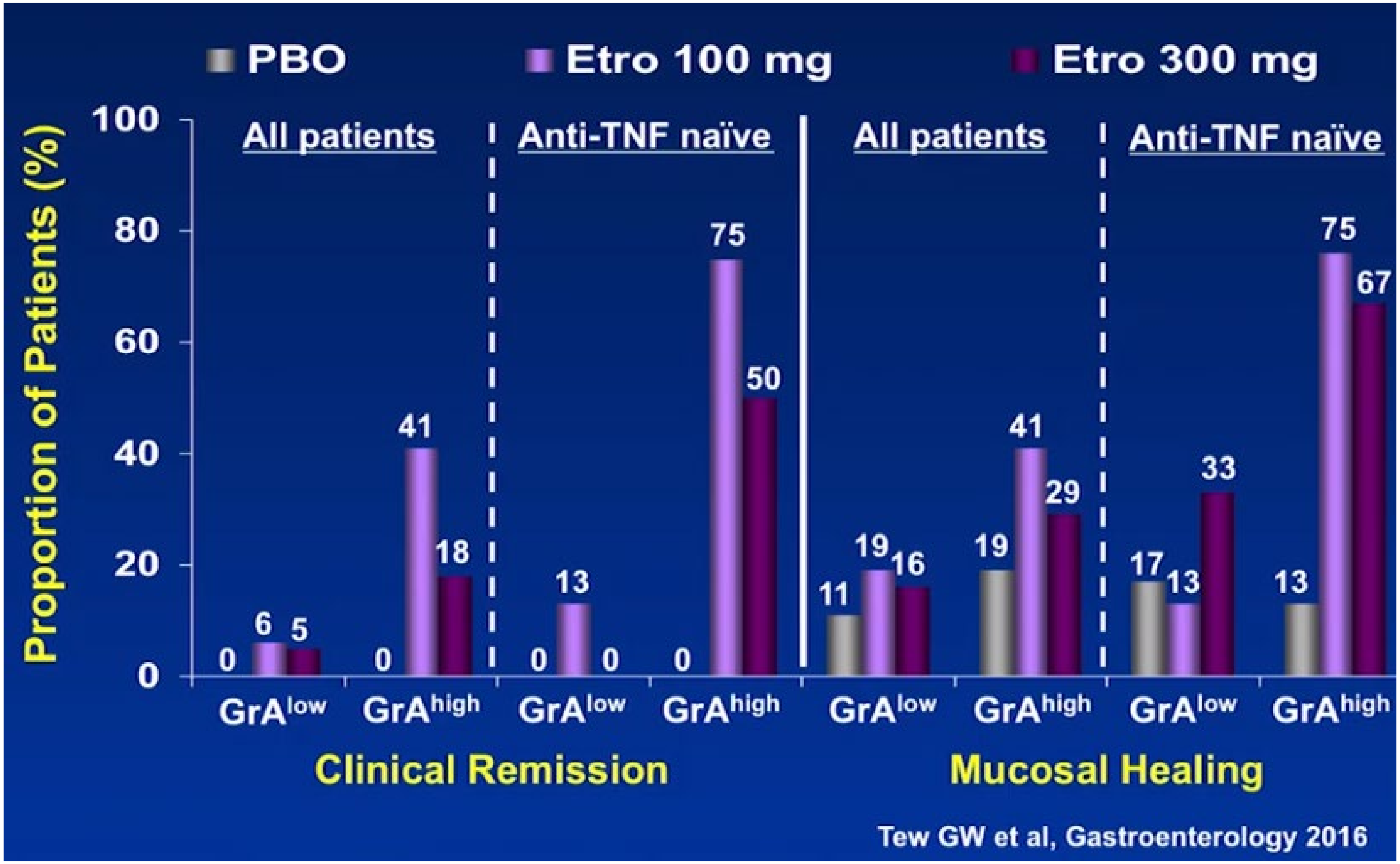


Minar, Crohn's and Colitis 360, 2019

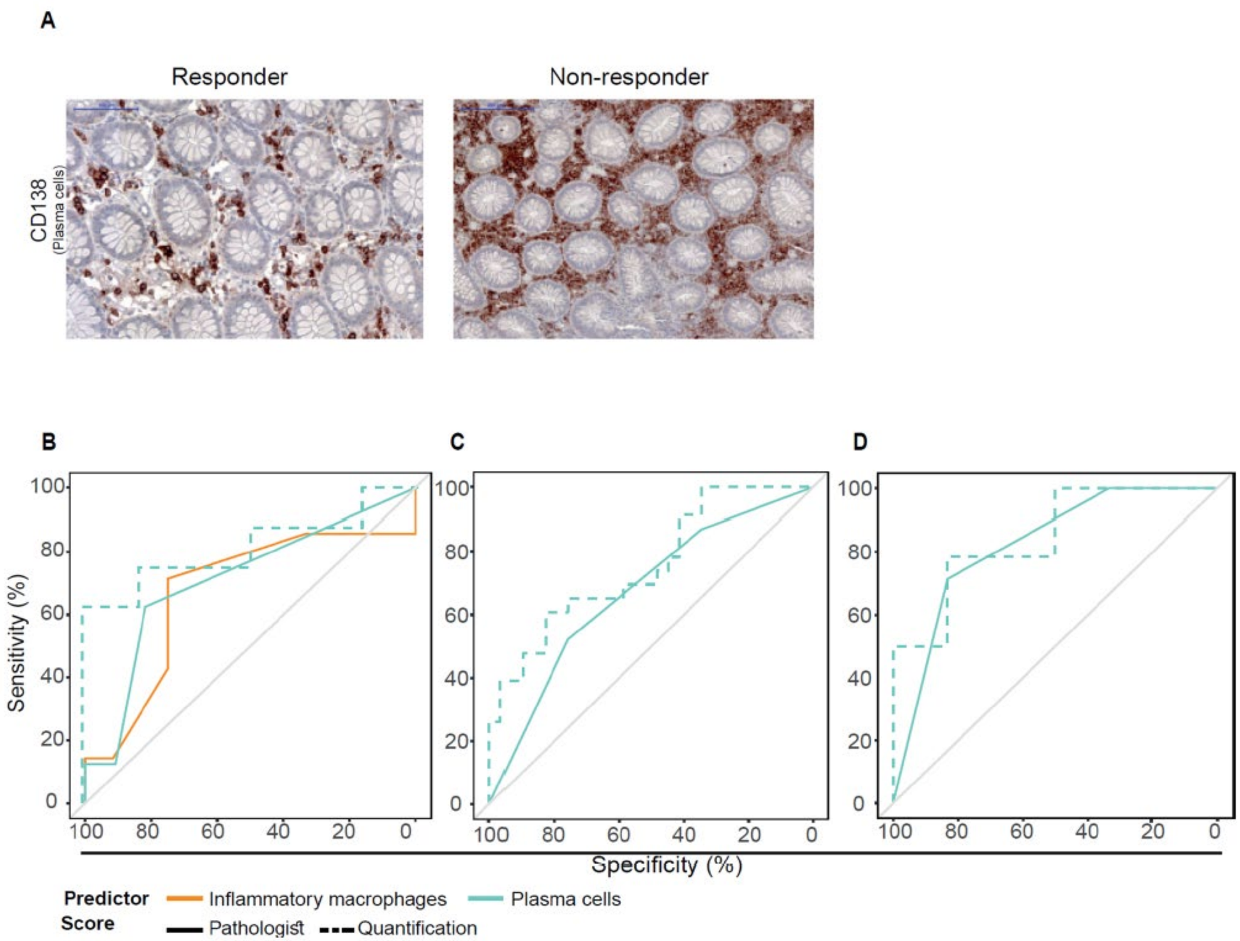
Phase II with Biomarkers: Etrolizumab



Phase II with Biomarkers: Etrolizumab

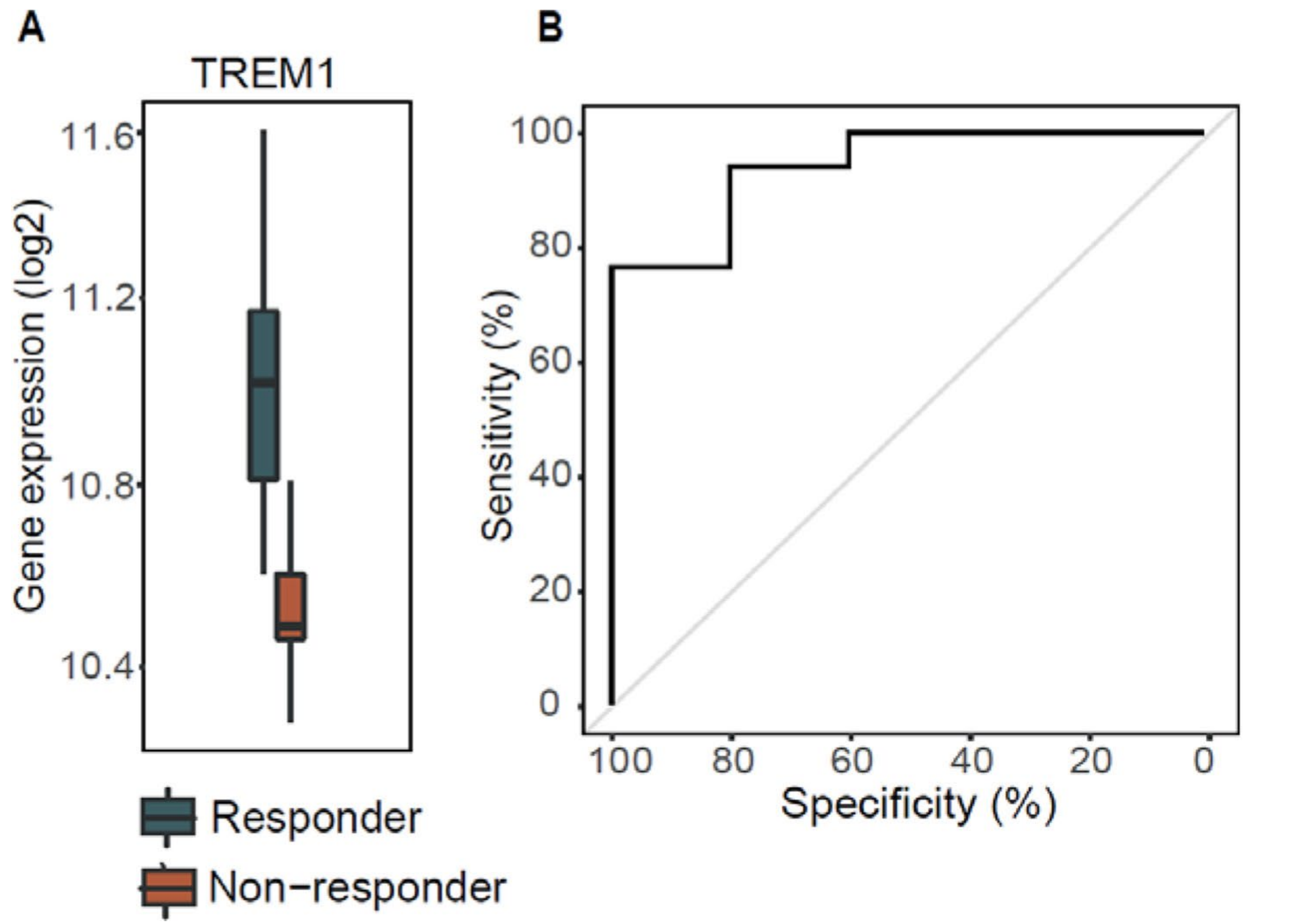


Baseline plasma cell proportions are predictive of anti-TNFα non-response



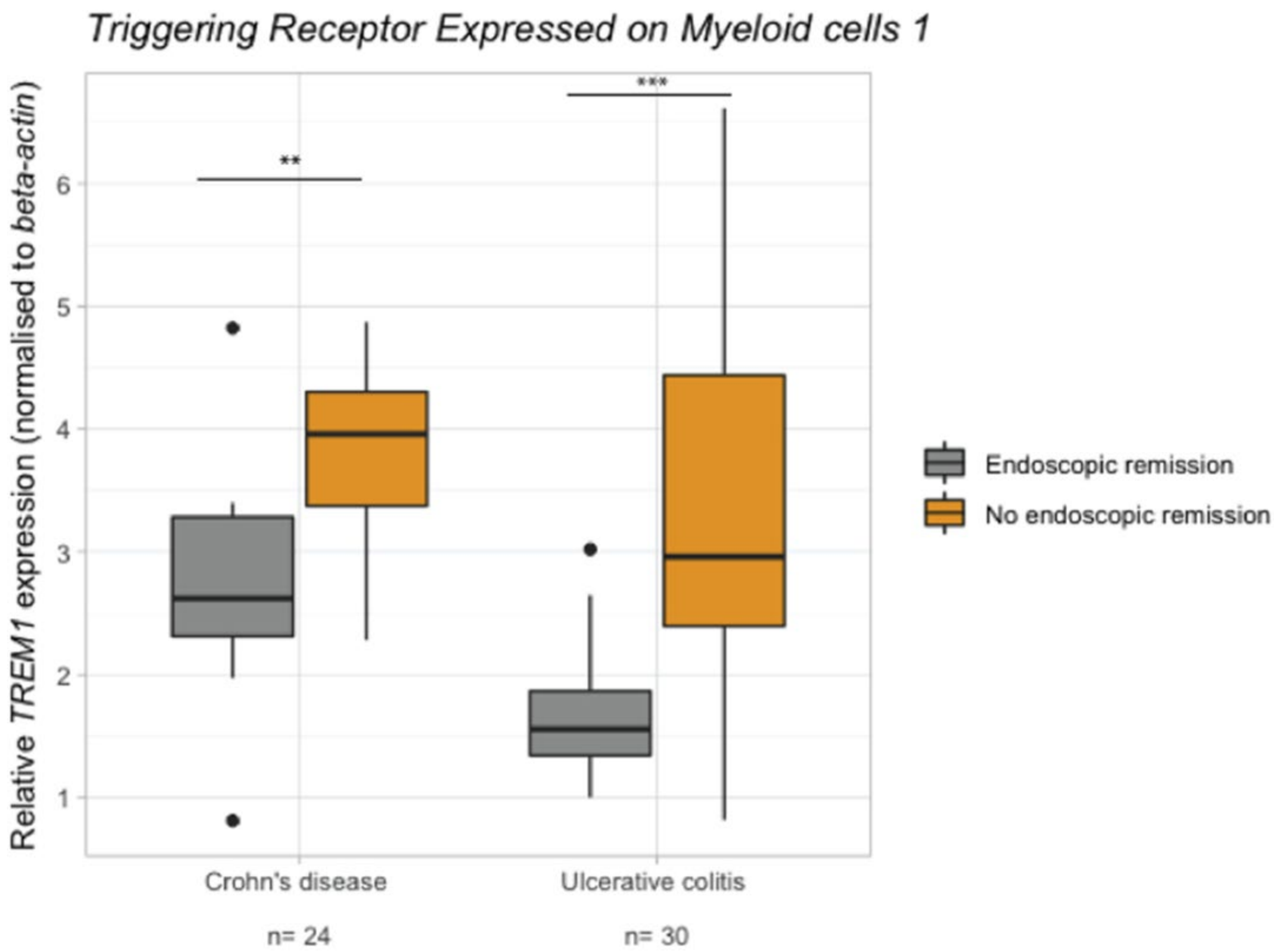
Gaujoux, Gut 2019

TREM-1 expression in blood predicts anti-TNF non-response at baseline in Crohn's patients



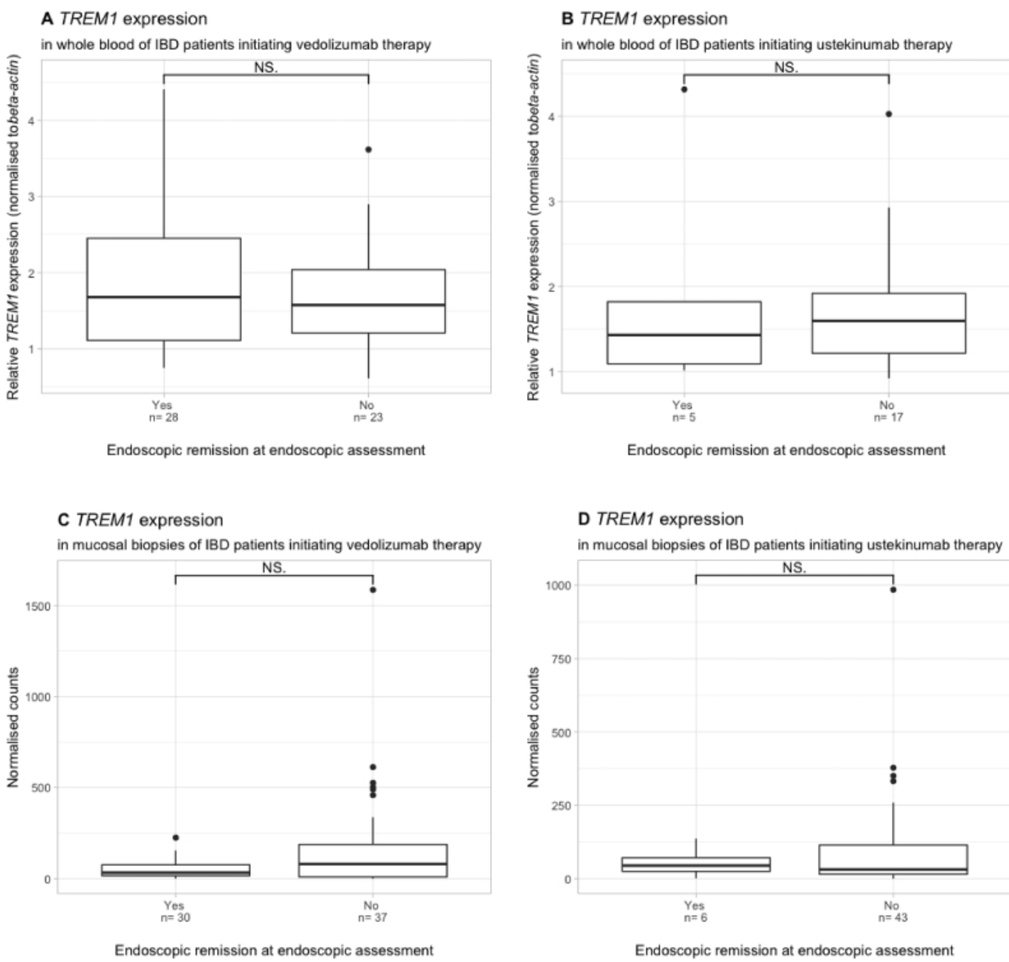
Gaujoux, Gut 2019

Low TREM1 expression in whole blood predicts anti-TNF response in IBD



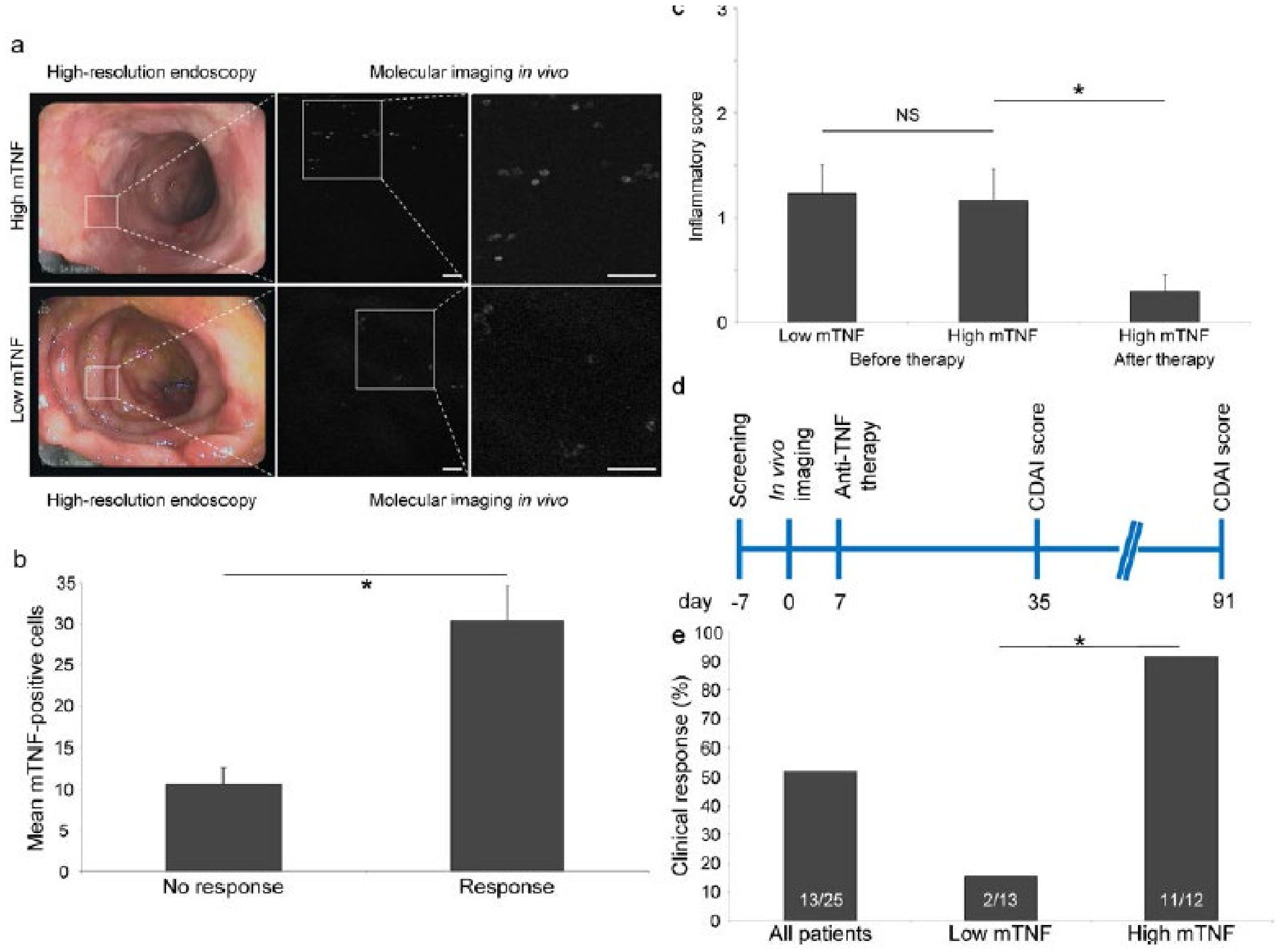
Verstockt, Ebiomedicine 2019

No association between baseline whole blood and mucosal TREM1 expression and endoscopic remission in vedolizumab or ustekinumab treated patients



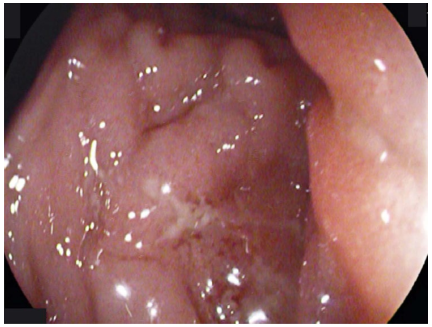
Verstockt, Ebiomedicine 2019

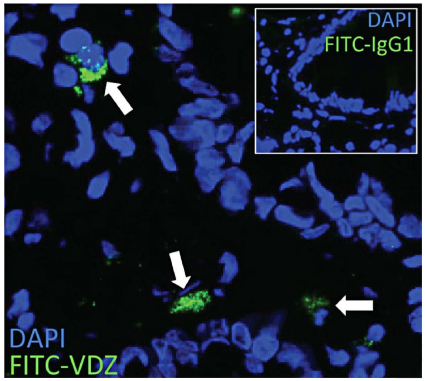
In vivo imaging using fluorescent antibodies to tumor necrosis factor predicts therapeutic response in Crohn's disease

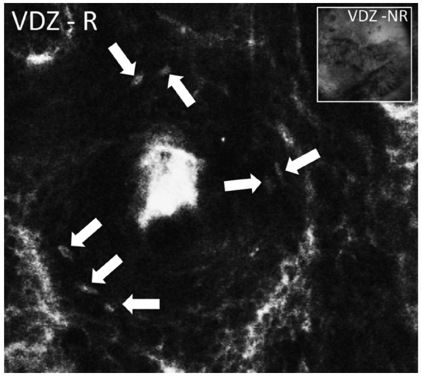


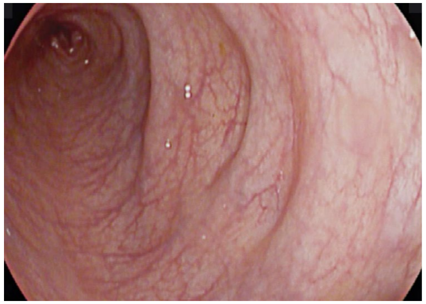
Atreya, Nat Med 2014

Molecular imaging of mucosal α4β7 integrin expression with the fluorescent antiadhesion antibody vedolizumab in Crohn's disease



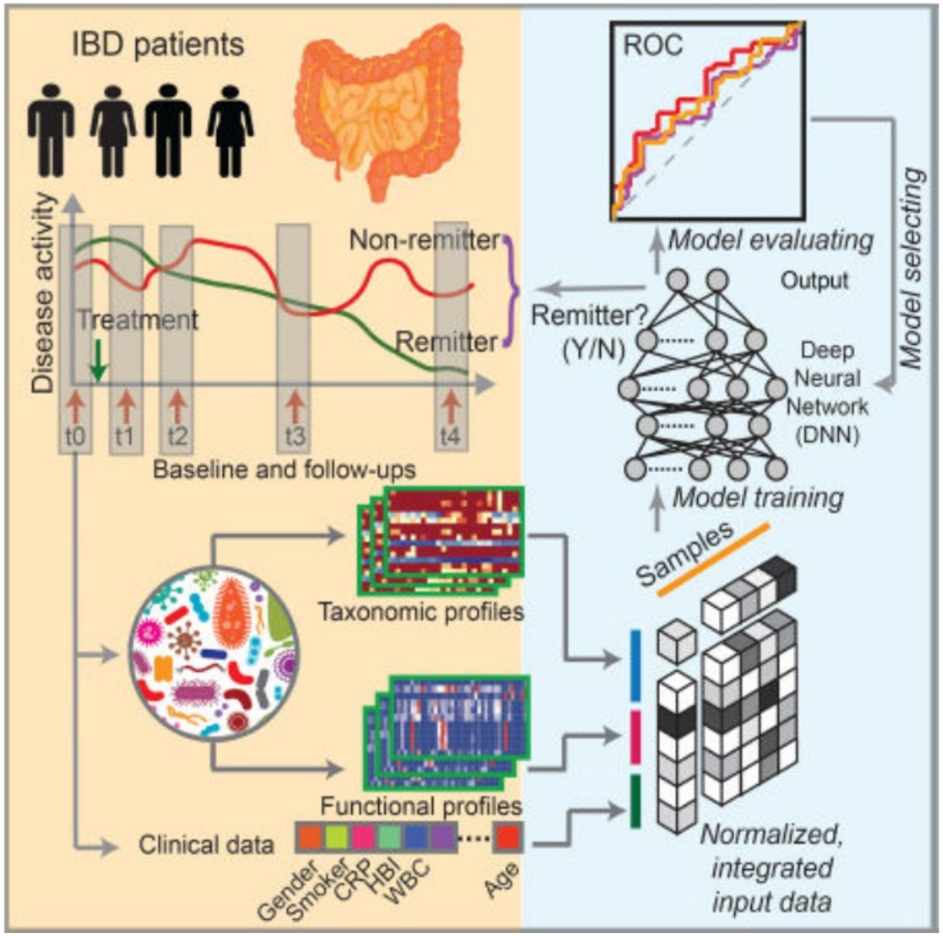






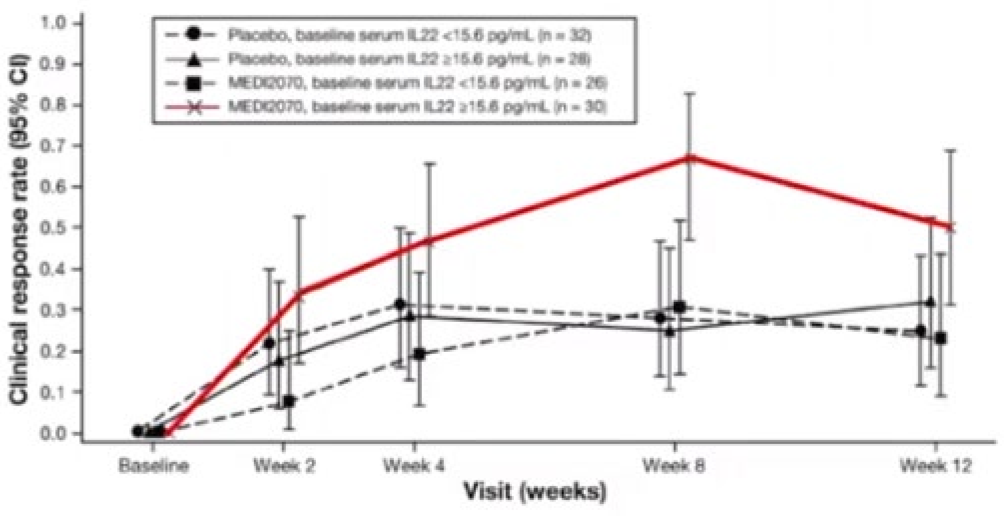
Rath, GIE 2017

Gut microbiome function predicts response to anti-integrin biologic therapy in Inflammatory Bowel Diseases



Ananthrakrishnan, Cell Host Microbe 2017

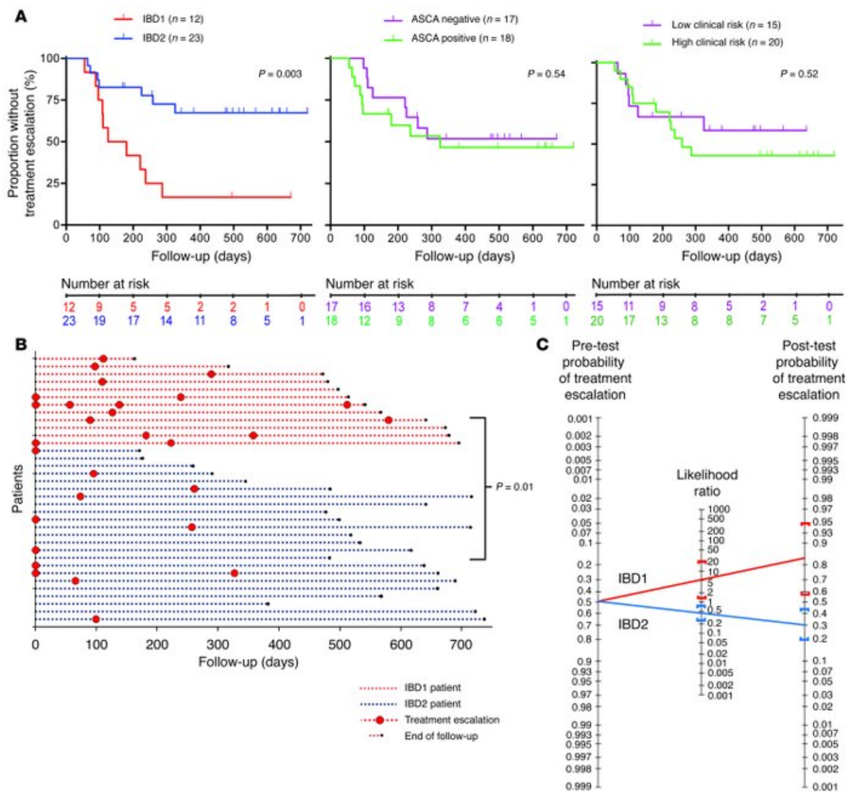
Higher baseline serum concentrations of IL22 were associated with greater likelihood of response to MEDI2070 (Antibody Against Interleukin 23)



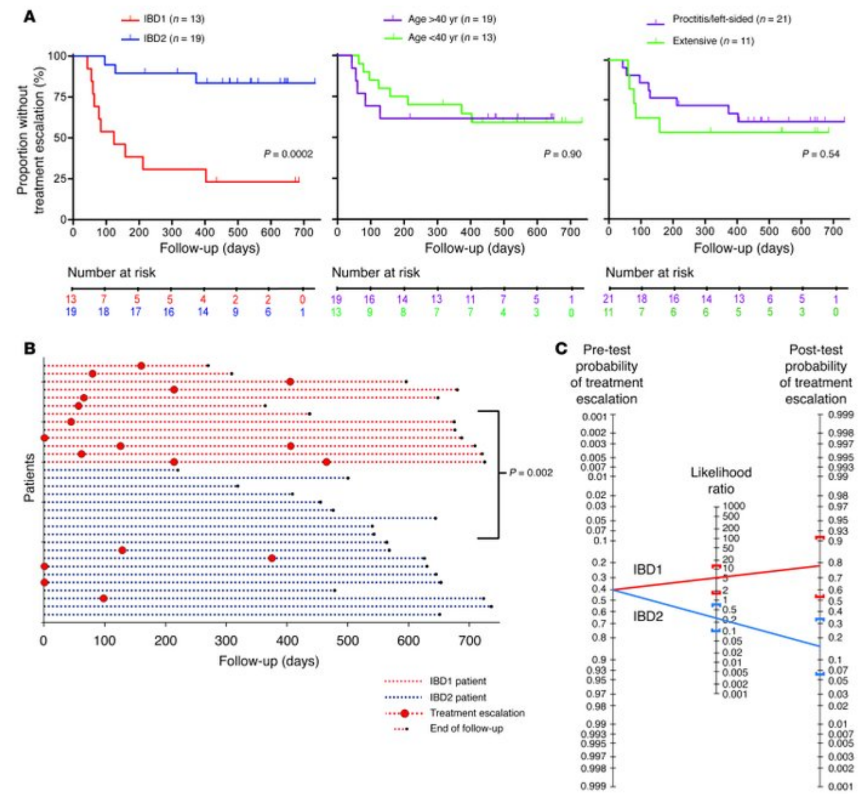
Sands, Gastroenterology 2017

Gene expression profiling of CD8^{+} T cells predicts prognosis in IBD patients

Crohn's Disease



Ulcerative Colitis



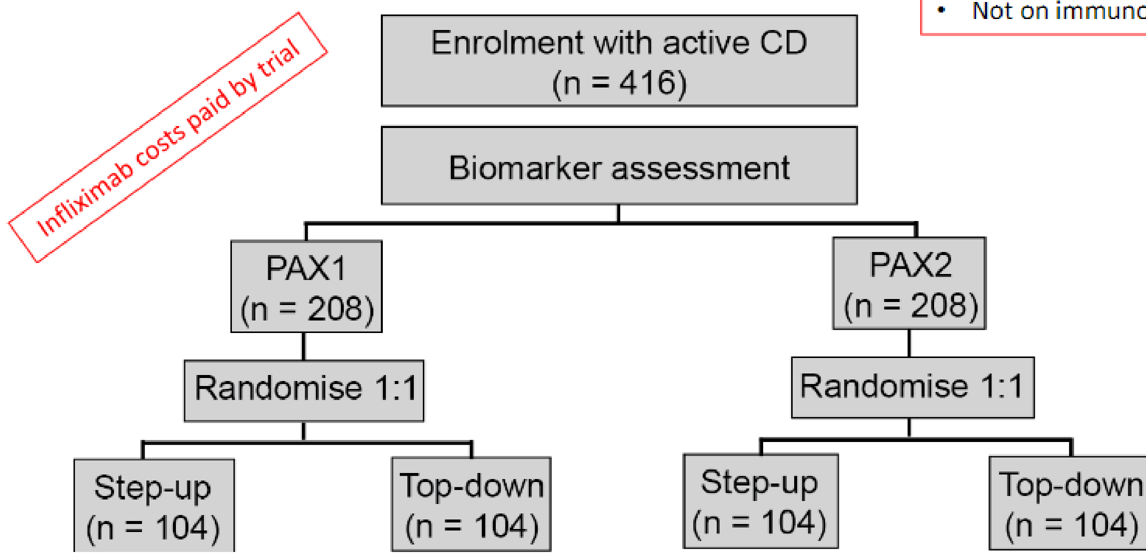
Lee, JCI 2011

Biomarker Based Therapy

PRedicting **O**utcomes **F**or Crohn's disease us**I**ng a mo**L**ecular biomark**E**r

PROFILE

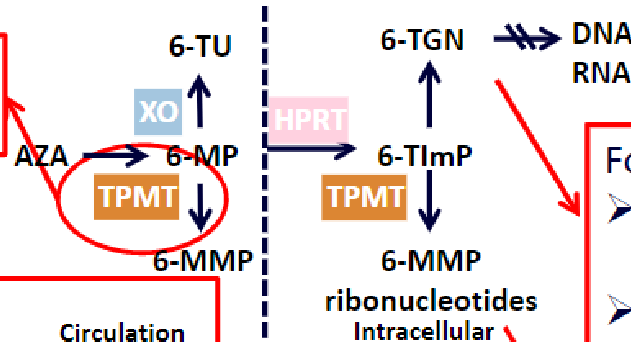
- Newly diagnosed CD (within 3 months)
- Active disease
- Not on immunosuppressive therapy



Azathioprine Pharmacogenomics

Prior to initiation:
TPMT activity (>genotype*)

Thiopurine Metabolic Pathway



Following initiation:

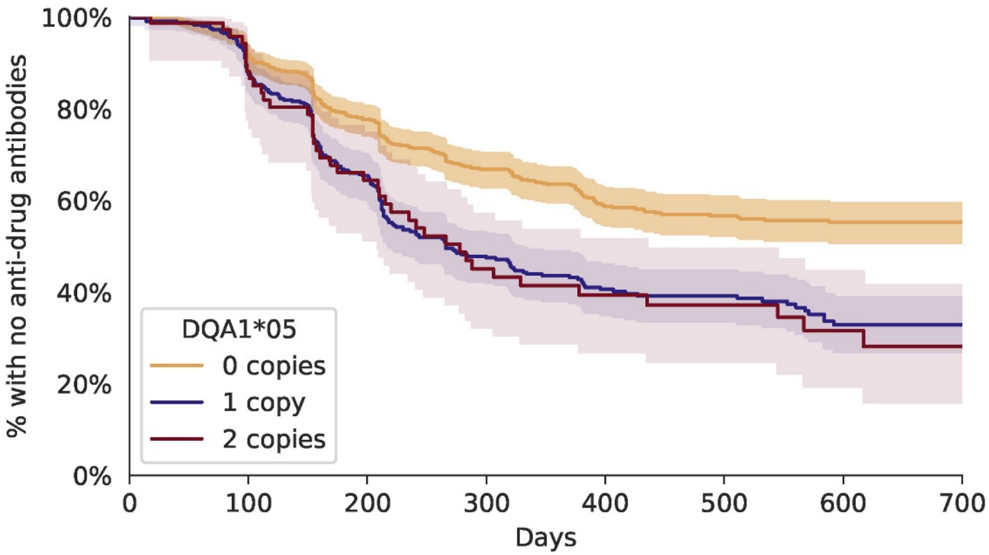
- >230 pmol/8 10^8 RBCs increased efficacy
- > 400 pmol/8 10^8 RBCs increased myelosuppression

NUDT15 gene variant:
Thiopurine-related myelosuppression in IBD and ALL. Homozygous patients: Tolerated ~ 8% of thiopurine dose

- >5700 pmol/8 10^8 RBCs 3-fold risk of hepatotoxicity

Yarur AJ et al, World J Gastroenterol 2014
Kopylov U et al, Ann Gastroenterol 2014
Seinen ML, et al, J Crohns Colitis 2013
Friedman A, et al, Gastroenterology 2015
Yarur AJ, et al, Clin Gastroenterol Hepatol 2015
Yang, SK, et al, Nat Genet 2014
Yang, JJ, et al, J Clin Oncol 2015
Chao K, et al, P096 ECCO 2017

HLA-DQA1*05 carriage Associated with development of Anti-Drug Antibodies to Infliximab and adalimumab in Patients with Crohn's Disease

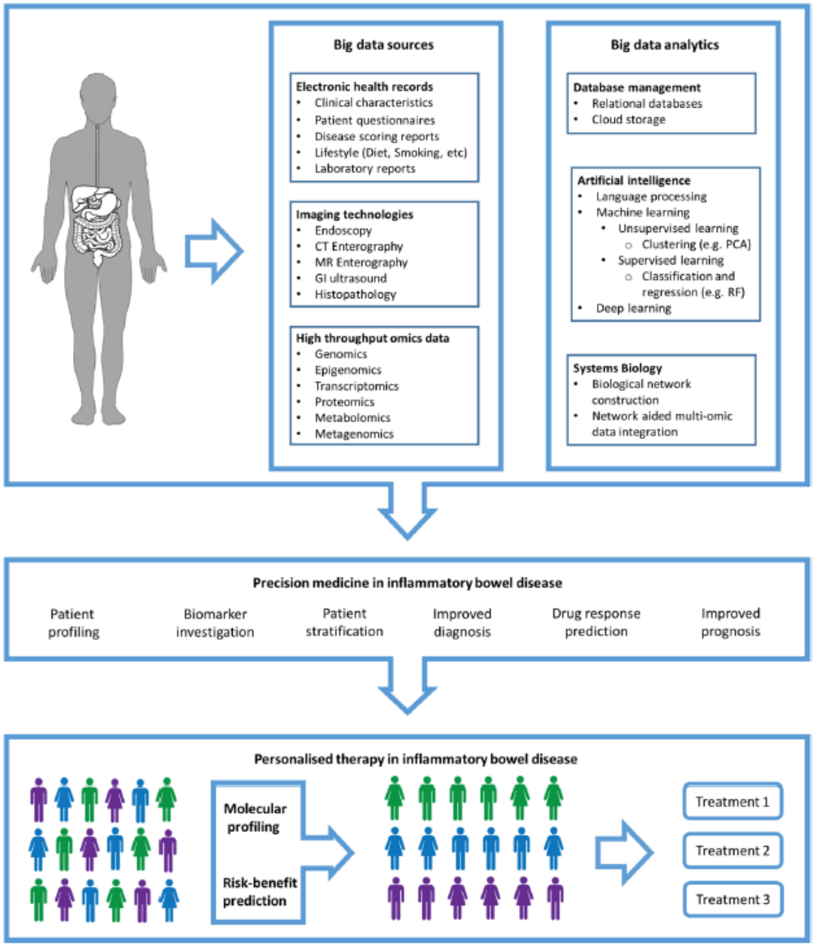


Number at risk

	0	100	200	300	400	500	600	700
0 copies	752	626	478	361	216	173	133	119
1 copy	410	320	216	137	90	72	43	39
2 copies	75	57	38	25	18	16	9	6

Sazonovs, Gastroenterology 2010

Precision Medicine in IBD?
Big Data, Machine Learning, Systems Biology



Tabib, Gut 2020

Personalized Medicine-OMICS Pitfalls

- Observational, Retrospective, Weak Associations, Lack External Validation
- Subjective Response (Clinical, Biochemical, Mucosal Healing, Histology)
- IBD Subgroups: UC vs CD, ileal vs colonic CD, bionaive vs bioexposed, etc…
- Tissue Biopsy, Blood, Stool, Urine?
- Genetics: Susceptibility ≠ Prognosis
- Transcriptomics: Bulk, Single Cell, Parameters > Samples
- Financial Support, Academia-Industry, New Drugs vs Theragnostics
- Interpretation, Training, Cost, Diffusion
- Big Data vs Basic Research: Causality
- Breakthrough…

Hepatitis C:
The *IL28B* polymorphism was discovered too late to significantly impact clinical practice in the new era of DAA therapy

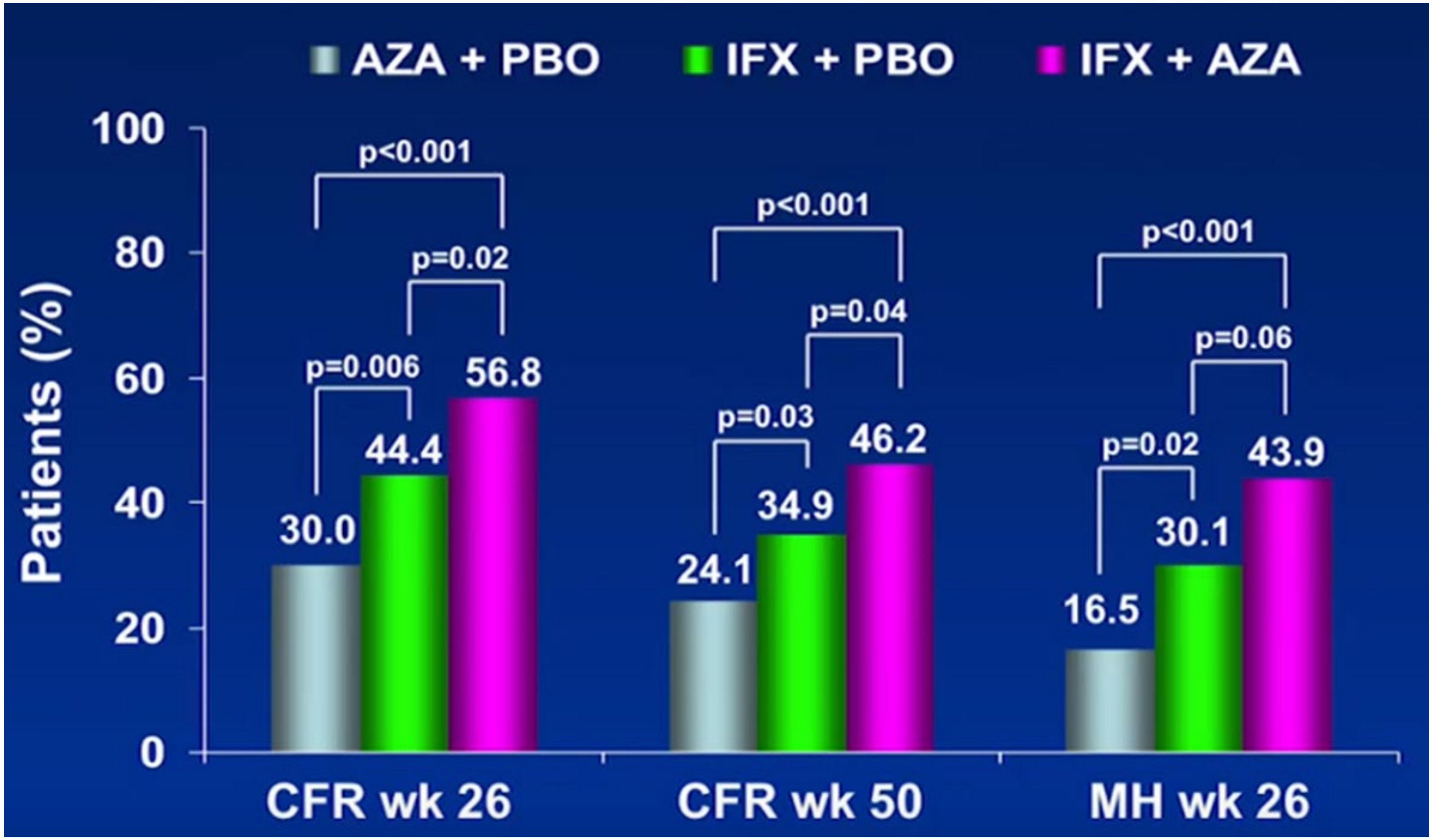
Table 3 Factors associated with NVR by logistic regression model

Factors	Odds ratio	95% CI	*P* value
rs8099917 (G allele)	37.68	16.71–83.85	<0.0001
Age	1.02	0.98–1.07	0.292
Gender (Female)	3.32	1.49–7.39	0.003
Re-treatment[a]	1.12	0.55–2.33	0.750
Platelet count	0.93	0.87–1.01	0.080
Aminotransferase level	1.00	0.99–1.00	0.735
Fibrosis stage[20]	1.10	0.73–1.66	0.658
HCV-RNA level	1.01	0.99–1.02	0.139

[a]Re-treatment, non-response to previous treatment with interferon-α (plus RBV).

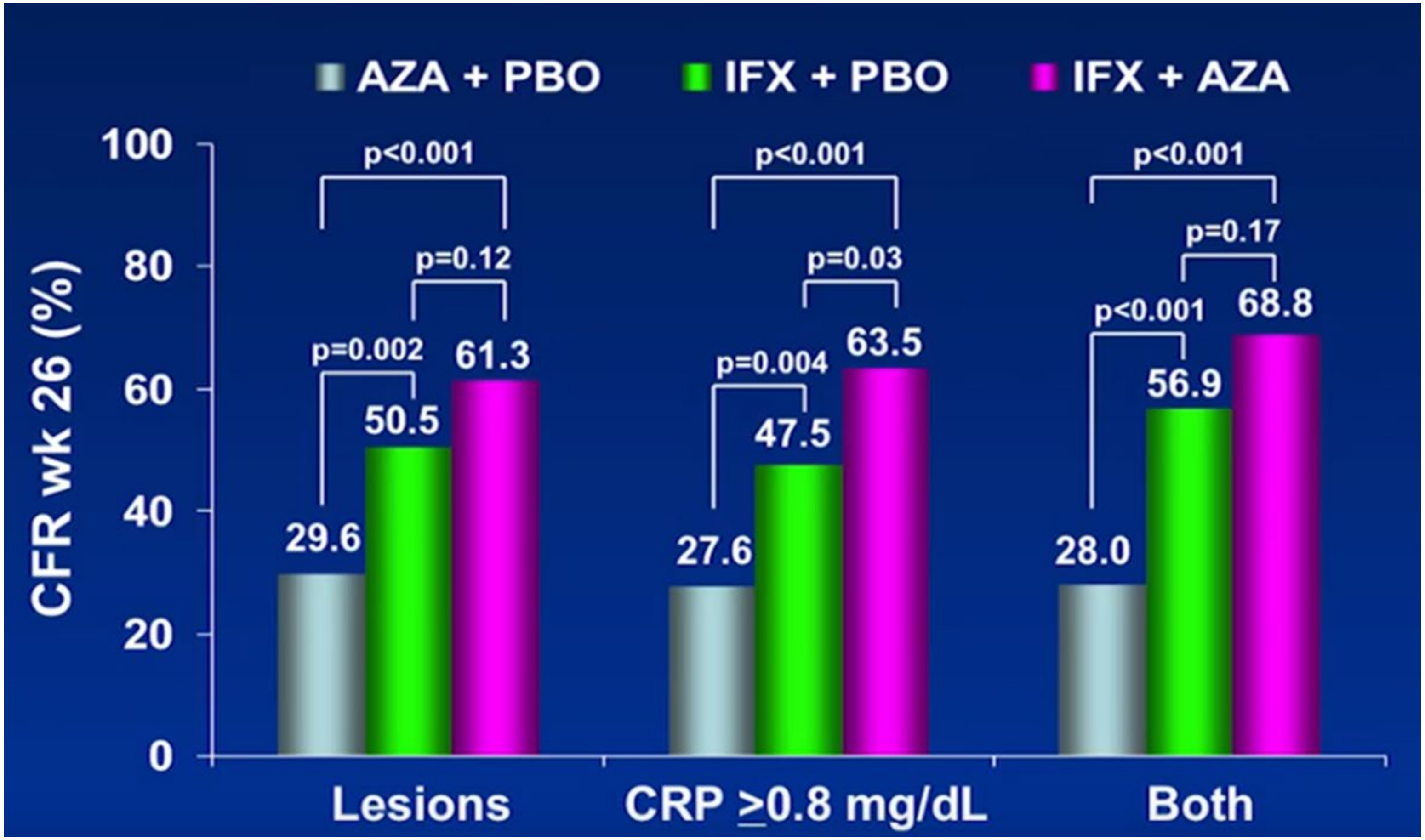
Tanaka, Nature Genetics 2009

Μελέτη SONIC:
Bionaive, Νόσος Crohn, Συνδυασμένη Ανοσοκαταστολή



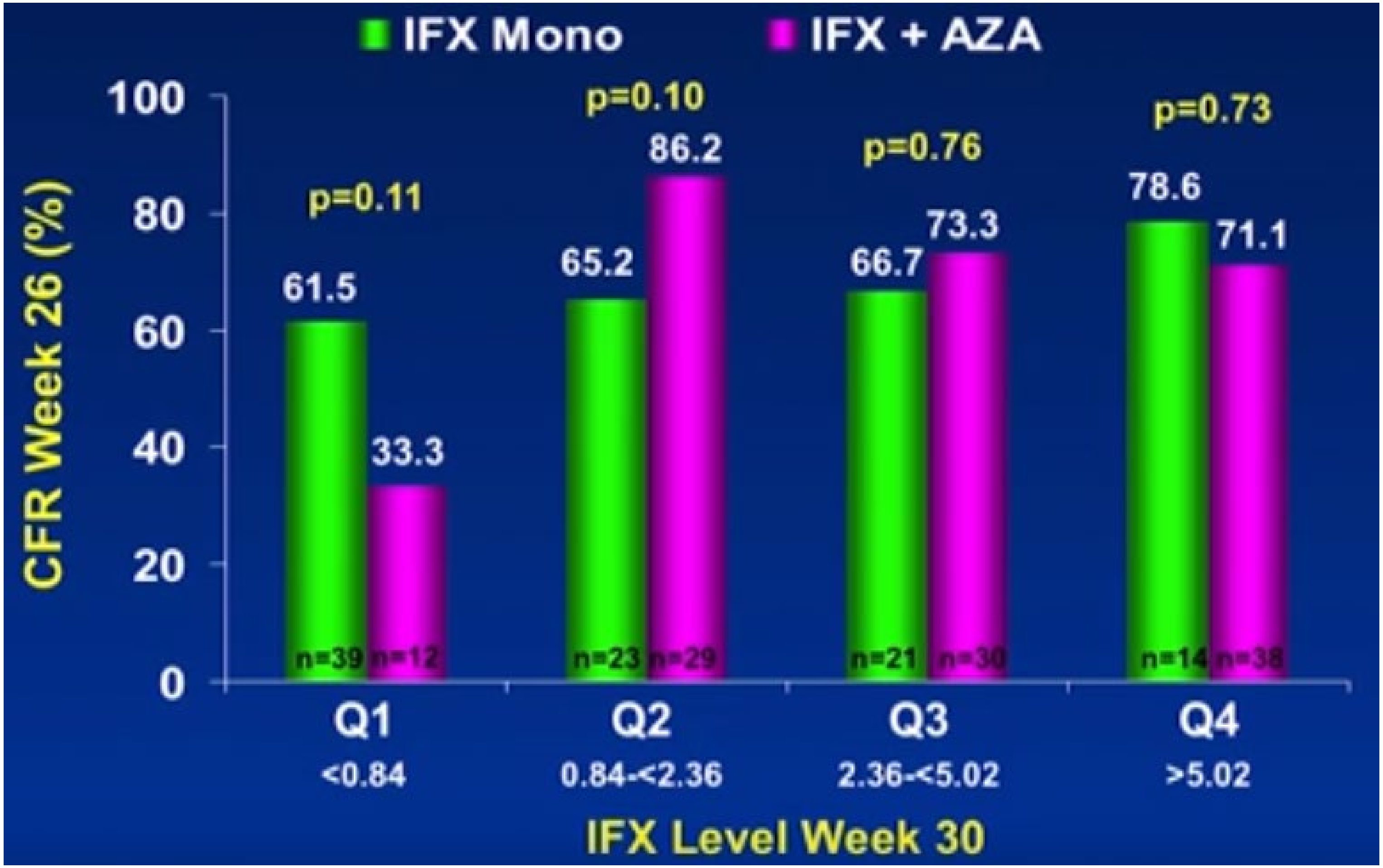
Colombel, NEJM 2010

SONIC refined:
CRP, Ενδοσκοπική Ενεργότητα



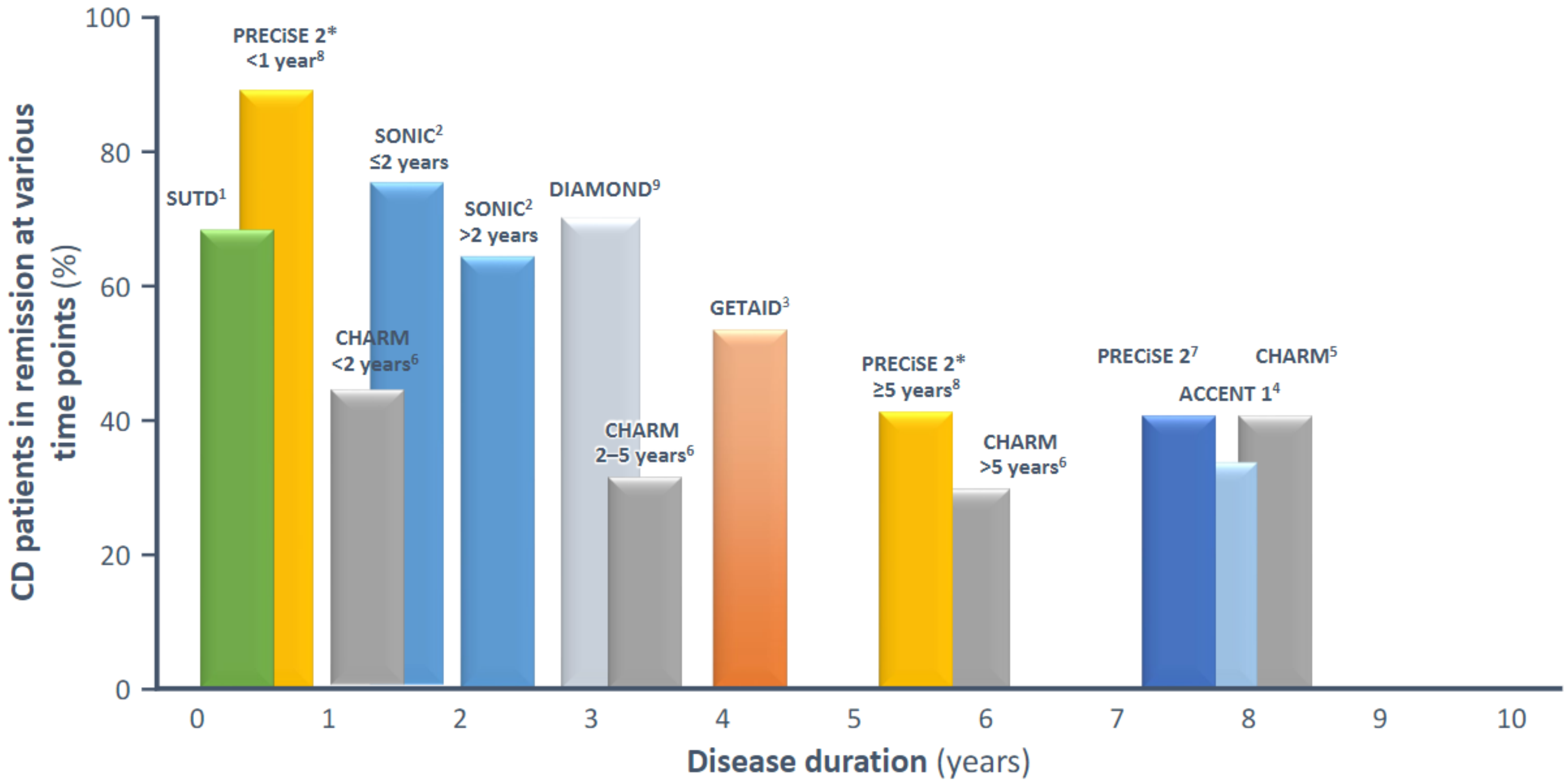
Colombel, NEJM 2010

SONIC more refined:
TDM, Therapeutic Drug Levels



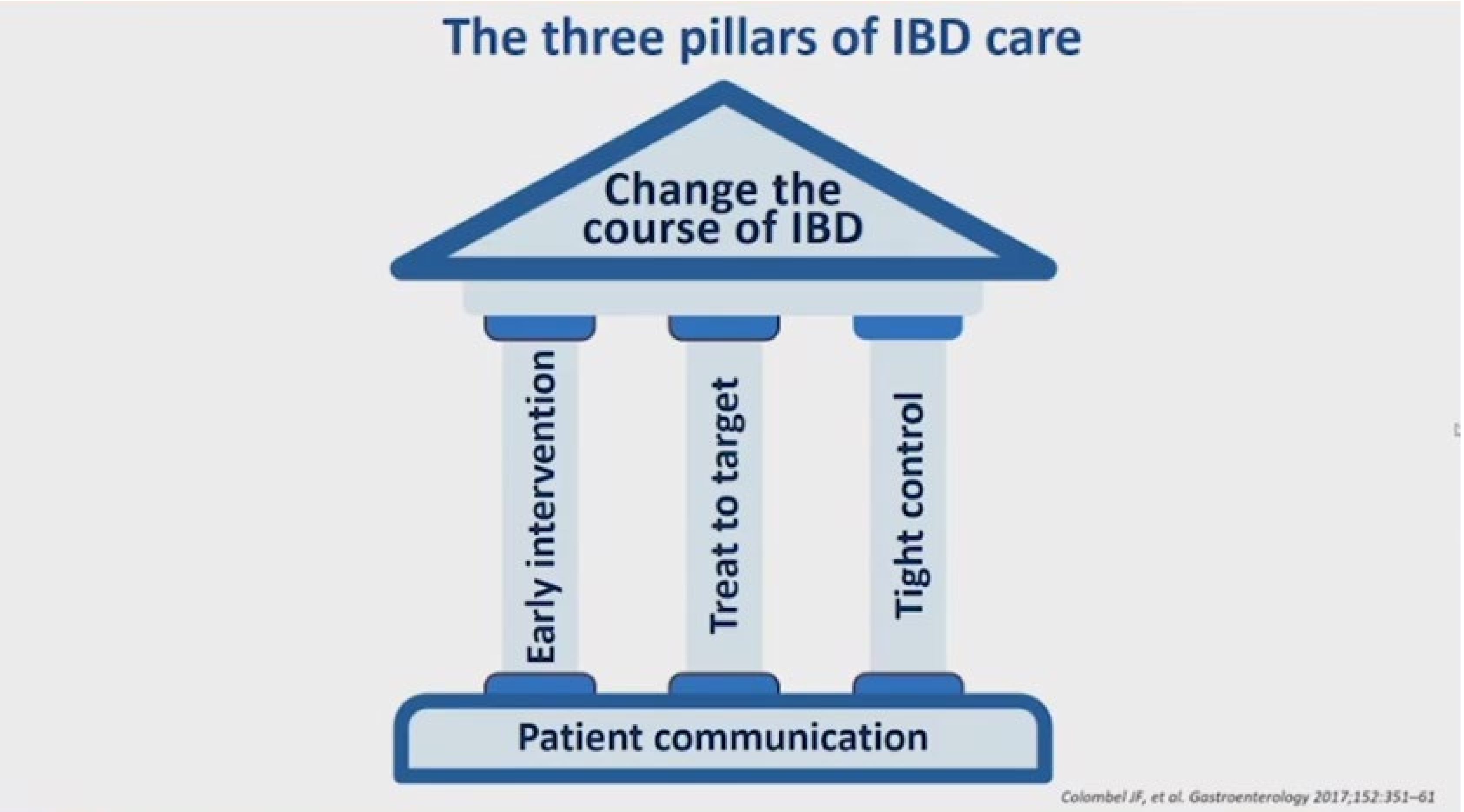
Colombel, NEJM 2010

Early Intervention Crohn's Disease

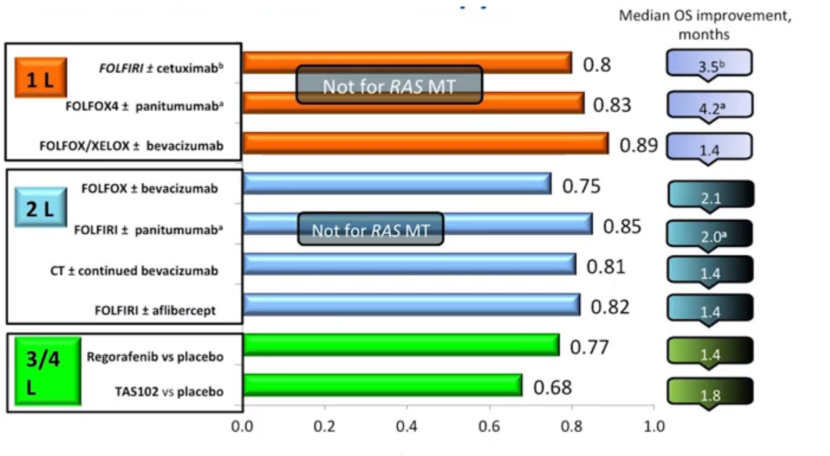


1. D'Haens G, et al. *Lancet* 2008;371:660–67; 2. Peyrin-Biroulet L, et al. *Gut* 2014;63:88–95; 3. Lémann M, et al. *Gastroenterology* 2006;130:1054–61; 4. Hanauer S, et al. *Lancet* 2002;359:1541–49; 5. Colombel JF, et al. *Gastroenterology* 2007;132:52–65; 6. Schreiber S, et al. *J Crohns Colitis* 2013;7:213–21; 7. Schreiber S, et al. *New Eng J Med* 2007;357:239–50; 8. Schreiber S, et al. *Am J Gastroenterol* 2010;105:1574–82; 9. Matsumoto T, et al. *J Crohns Colitis* 2016 Aug 26 [Epub ahead of print]

Σοφή 1η Επιλογή ή Σοφή Παρακολούθηση/Φροντίδα;



Ογκολογία:
Μεταστατικός Καρκίνος Παχέος Εντέρου



[a]KRAS WT subset; *P* value = not significant.
[b]KRAS WT subset; *P* value = significant.

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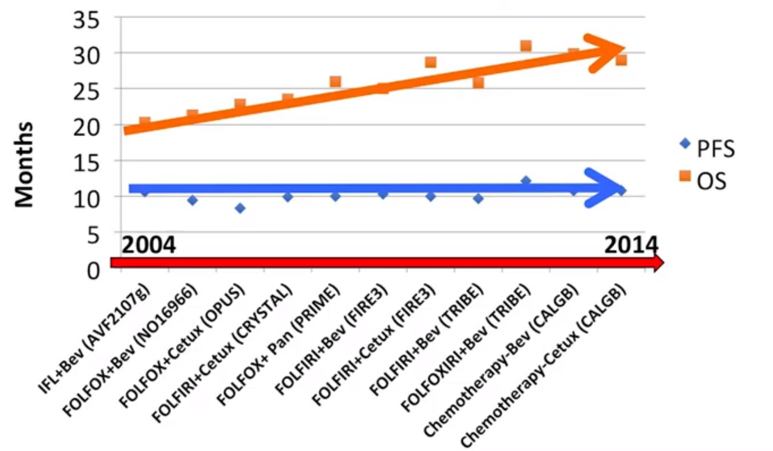

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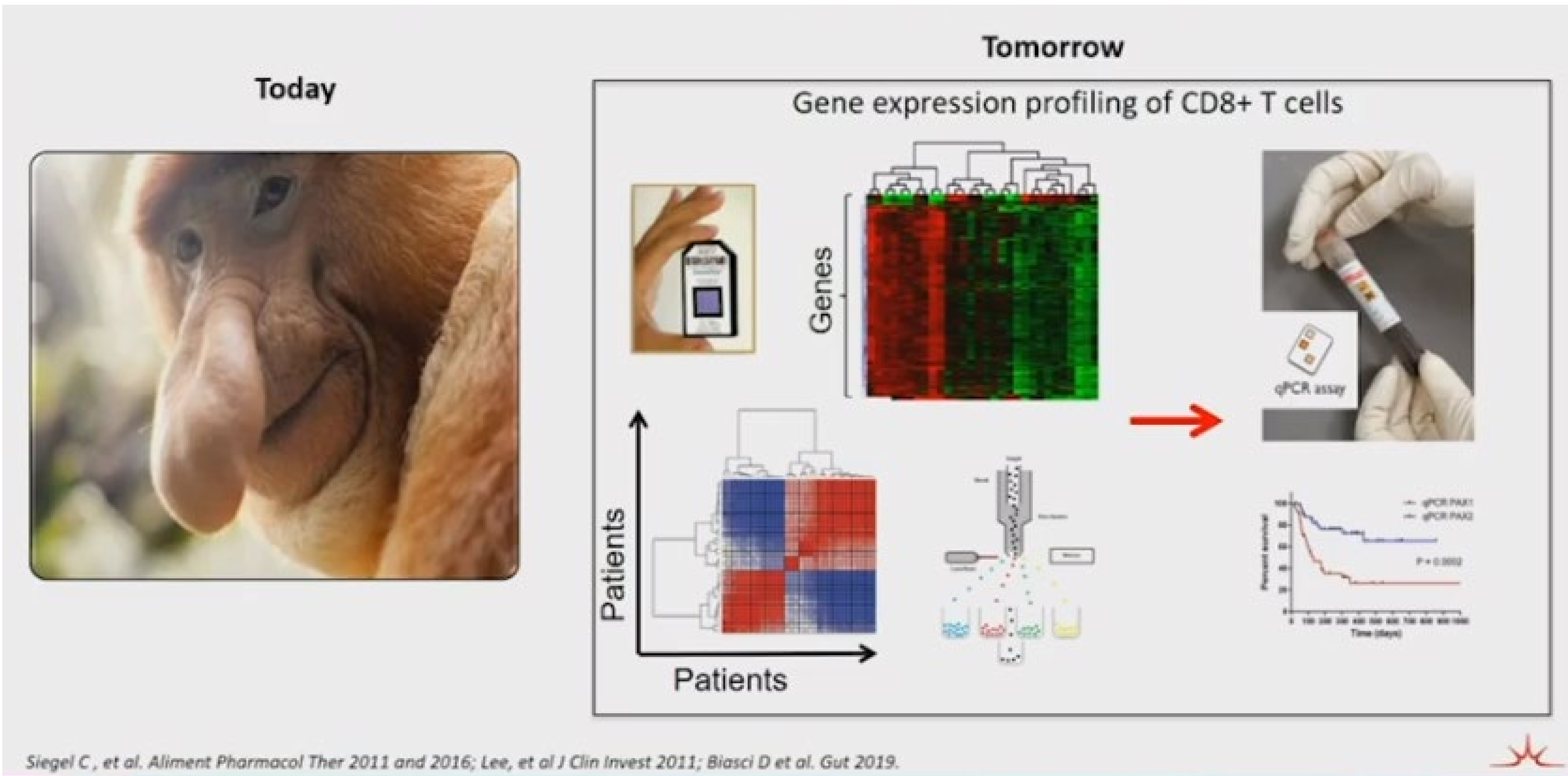
Choose, Optimize, Sequence and Refine Therapy…

Από Grothey, ESMO GI 2019

Προβλέποντας την Θεραπευτική Ανταπόκριση: Σήμερα………………………………………………………..Αύριο



Από Colombel, AIBD Regionals 2019