

Precision Health in IBD: What's on the horizon?

Canada Future Directions in IBD

Session III: Workshops – Hot Topics from Bench to Policy

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“Precision Health in IBD: What’s on the horizon?”

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Disclosures of potential conflicts of interest:

Grant:

Abbvie

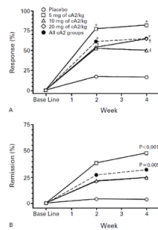
Honoraria:

AbbVie, Boehringer Ingelheim, Ferring, Fresenius Kabi, Galapagos, Gilead, GlaxoSmithKline, InDex Pharmaceuticals, Janssen, Pandion Therapeutics, Pfizer, Takeda Pharma, Roche

Issues for Discussion

- **Why are current biologic Rx only effective in 50% of IBD patients?**
 - Mechanistic Mismatch
 - Genetic determinants- TNFSF1 genotyping for anti-TL1A
 - Molecular and Cellular determinants of response- CD8 T cell Exhaustion
 - Environmental Factors e.g. Microbiome
- **Can we predict response or lack of response?**
- **Can we use this information to select therapy for an individual patient?**

Available therapies

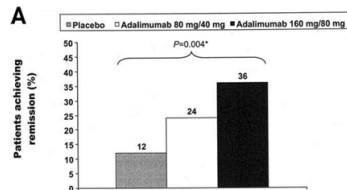


CHIMERIC MONOCLONAL ANTIBODY TO TUMOR NECROSIS FACTOR- α FOR CROHN'S DISEASE

A SHORT-TERM STUDY OF CHIMERIC MONOCLONAL ANTIBODY (A2) TO TUMOR NECROSIS FACTOR- α FOR CROHN'S DISEASE

Stenson R, Tassan M, Dore H, Hsu H, et al. *Gastroenterology*. 2000;118:1000-1008.

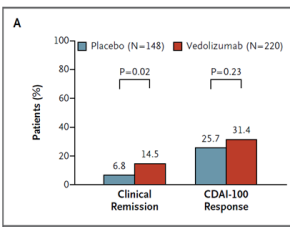
1999



Human Anti-Tumor Necrosis Factor Monoclonal Antibody (Adalimumab) in Crohn's Disease: the CLASSIC I Trial

Stenson R, Tassan M, Dore H, Hsu H, et al. *Gastroenterology*. 2000;118:1000-1008.

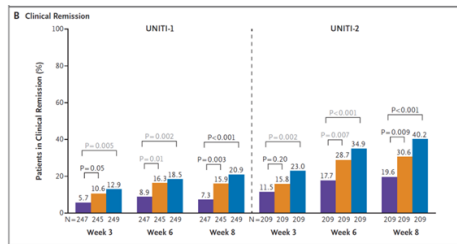
2006



Vedolizumab as Induction and Maintenance Therapy for Crohn's Disease

Williams J, Sandborn M, D'Haens M, et al. *Gastroenterology*. 2013;124:1015-1024.

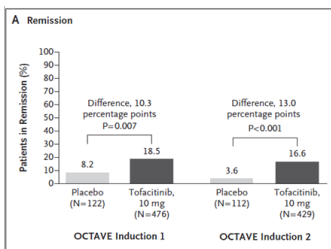
2013



Ustekinumab as Induction and Maintenance Therapy for Crohn's Disease

B.G. Feagan, W.J. Sandborn, C. Gasini, D. Jacobson, Y. Lang, J.R. Friedman, M.A. Blank, J. Johansen, L.L. Gao, Y. Mao, O.J. Abdelou, B.E. Sands, S.B. Hansen, S. Vermeire, S. Targan, S. Ghosh, W.J. de Villiers, J.F. Colombel, T. Tulacz, U. Sandler, B.A. Salzberg, P. Drenthman, S.D. Lee, E.V. Loftus, Jr., L.A. DiStefano, S. Katz, and P. Rutgeerts, for the UNIT-1/UNIT-2 Study Group

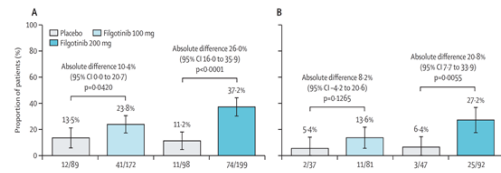
2016



Tofacitinib as Induction and Maintenance Therapy for Ulcerative Colitis

Williams J, Sandborn M, D'Haens M, et al. *Gastroenterology*. 2017;151:1015-1024.

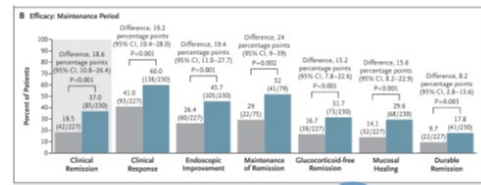
2017



Filgotinib as induction and maintenance therapy for ulcerative colitis (SELECTION): a phase 2b/3 double-blind, randomised, placebo-controlled trial

Wang H, et al. *Lancet*. 2021;397:1015-1024.

2021



Ozanimod as Induction and Maintenance Therapy for Ulcerative Colitis

Williams J, Sandborn M, D'Haens M, et al. *Gastroenterology*. 2021;159:1015-1024.

2021

	UC1				UC2			
	Placebo (N=154)	Upadacitinib 45 mg once daily (N=319)	Adjusted treatment difference, % (95% CI)	p-value	Placebo (N=174)	Upadacitinib 45 mg once daily (N=341)	Adjusted treatment difference, % (95% CI)	p-value
Primary endpoint								
Clinical remission (Adapted Mayo)	7 (5%)	83 (26%)	21.6% (15.8-27.4)	<0.0001	7 (4%)	114 (33%)	29.0% (23.2-34.7)	<0.0001

Upadacitinib as induction and maintenance therapy for moderately to severely active ulcerative colitis: results from three phase 3, multicentre, double-blind, randomised trials

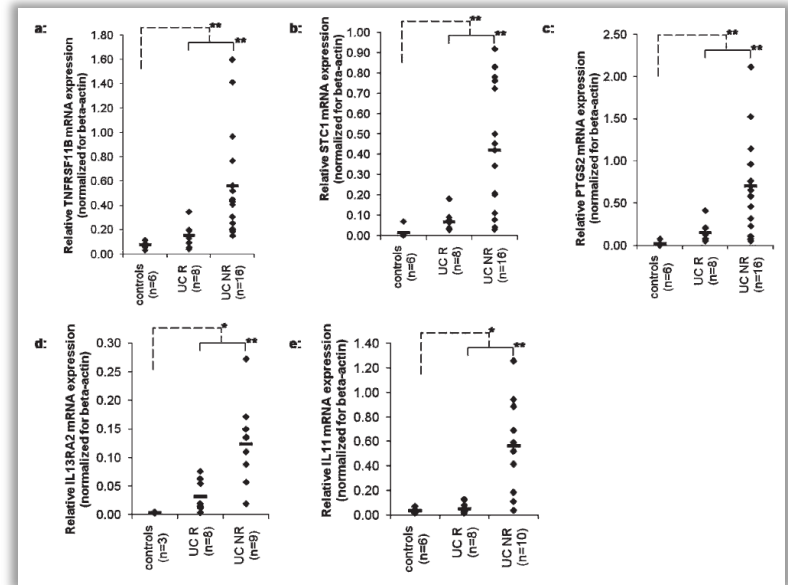
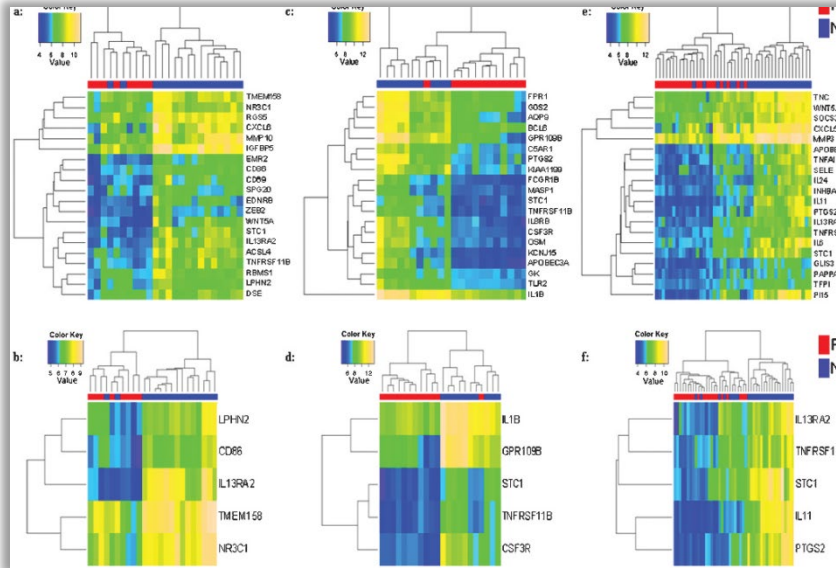
Wang H, et al. *Lancet*. 2021;397:1015-1024.

2021



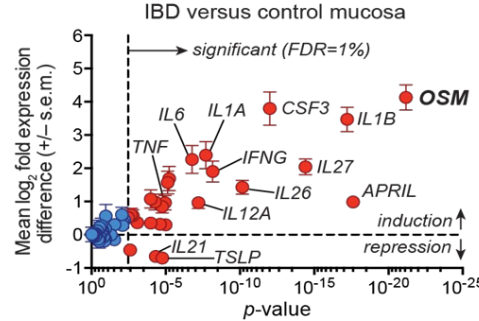
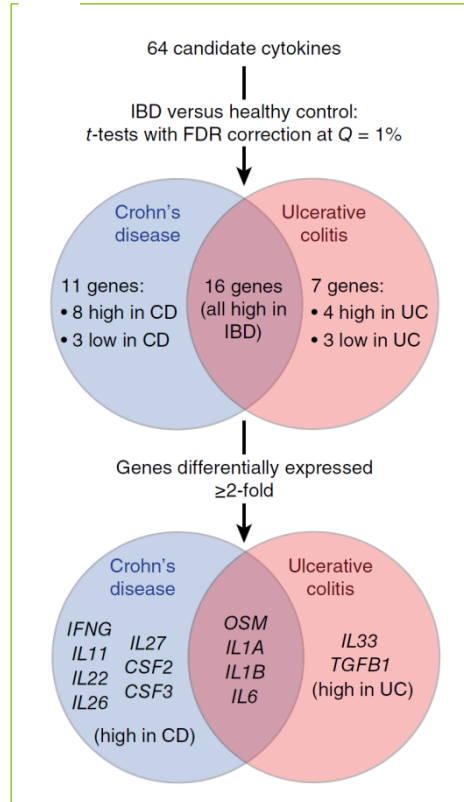
Is there science to inform us on how to choose therapy?

Mucosal gene signature predicts IFX response in UC

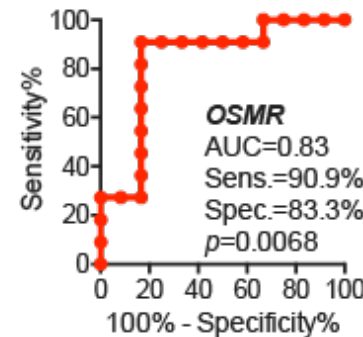
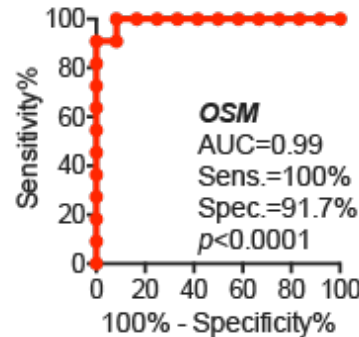
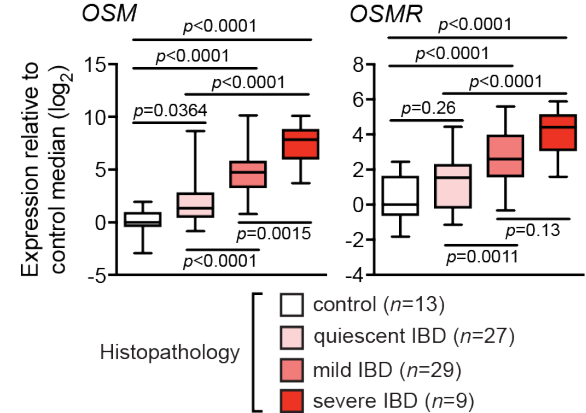


Osteoprotegerin, stanniocalcin-1, prostaglandin-endoperoxide synthase 2, IL-13R alpha 2 and IL-11 predicted response to IFX in UC with 95% sensitivity and 85% specificity

OSM expression in pre-therapy intestinal biopsies predicts non-responsiveness to anti-TNF therapy



RNA sequencing analysis of 64 cytokine genes in pediatric treatment-naïve CD patients ($n=162$) versus non-IBD controls ($n=42$; GEO #GSE57945)

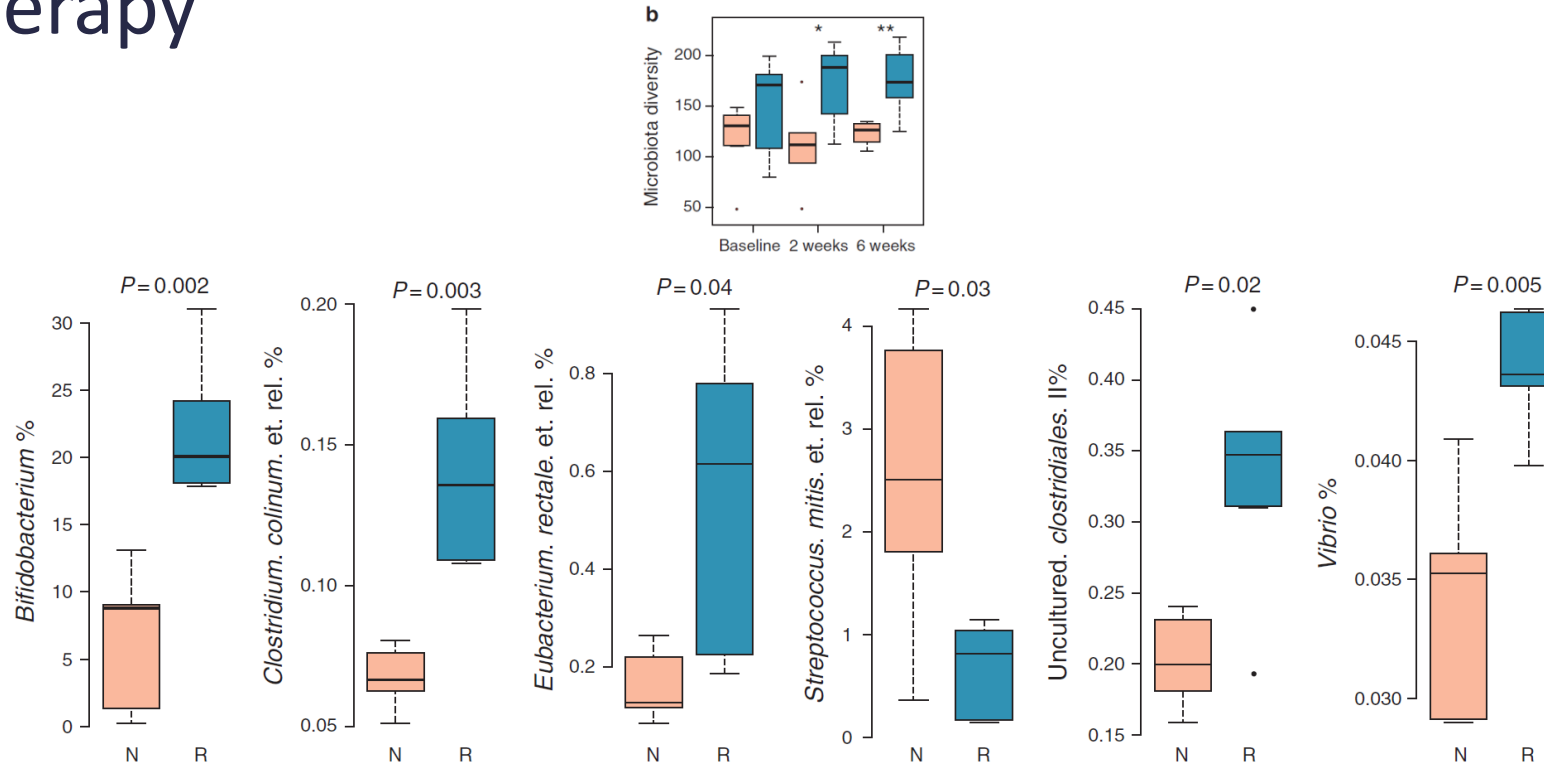




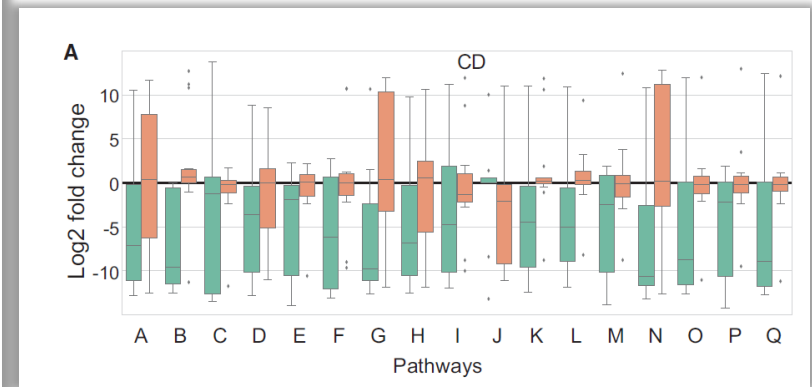
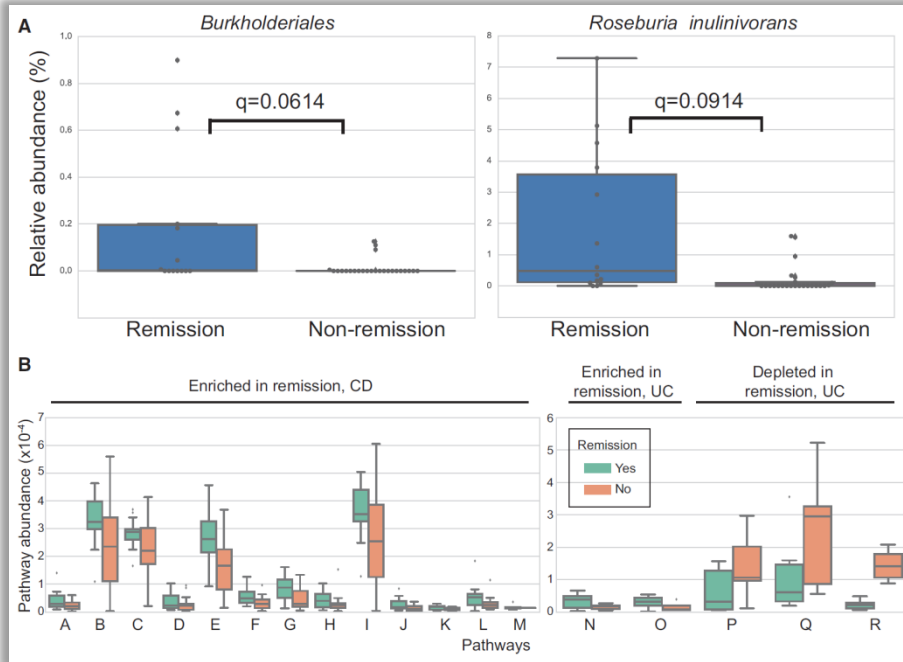
The illustration depicts a large, winding, purple, ribbon-like shape representing the human gut, set against a light green, textured background. Several stylized figures are engaged in agricultural work around and within the gut. One figure in a green shirt and dark pants pushes a red wheelbarrow filled with dark soil, from which a blue plant with round fruits is growing. Another figure in a blue shirt and dark pants is kneeling, planting a pink plant with round fruits into the gut. A third figure in a blue shirt and dark pants is using a shovel to dig in the gut. A fourth figure in a blue shirt and dark pants is kneeling, planting a green plant with round fruits into the gut. There are also several potted plants with various colored flowers (blue, pink, green) and some plants growing directly out of the gut. The overall scene suggests a process of reseeded the gut.

RESEEDING THE GUT

Microbiome as predictor of response to anti-TNF therapy

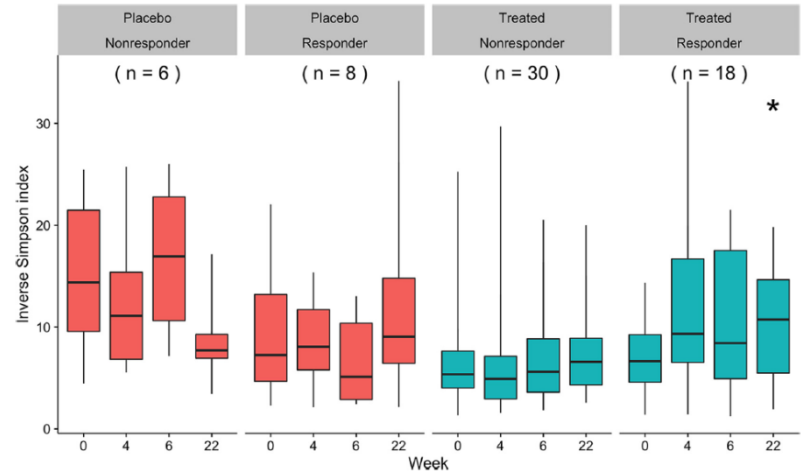
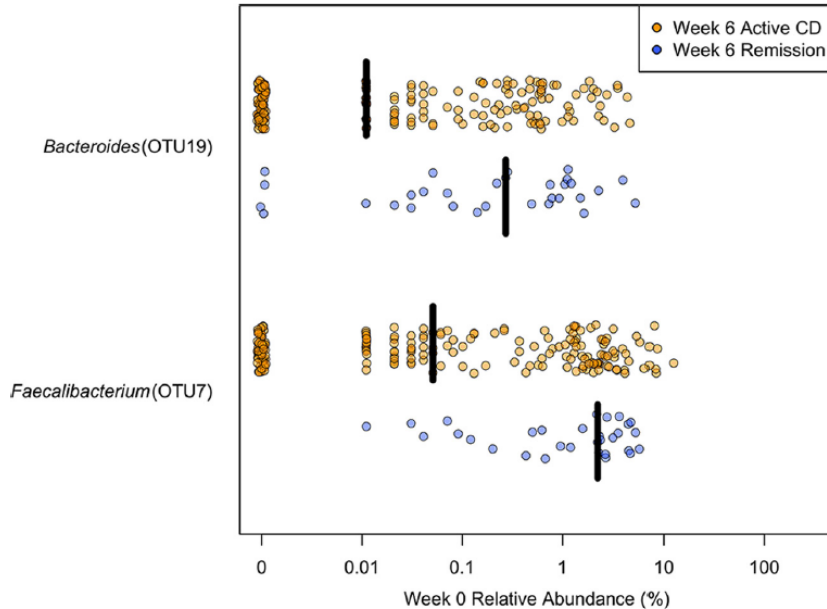


Butyrate producers and enrichment in microbial pathways predict response to VDZ



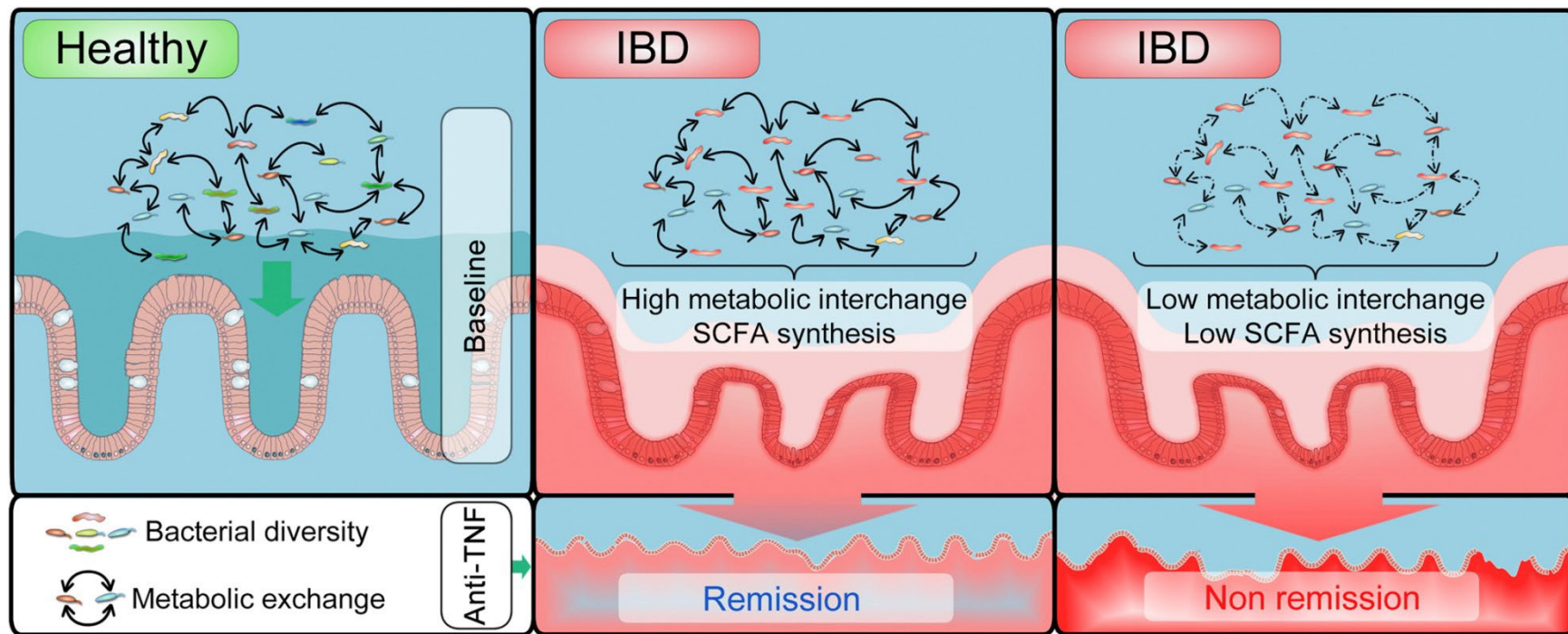
Longitudinal course of early microbiome changes
as a marker of response

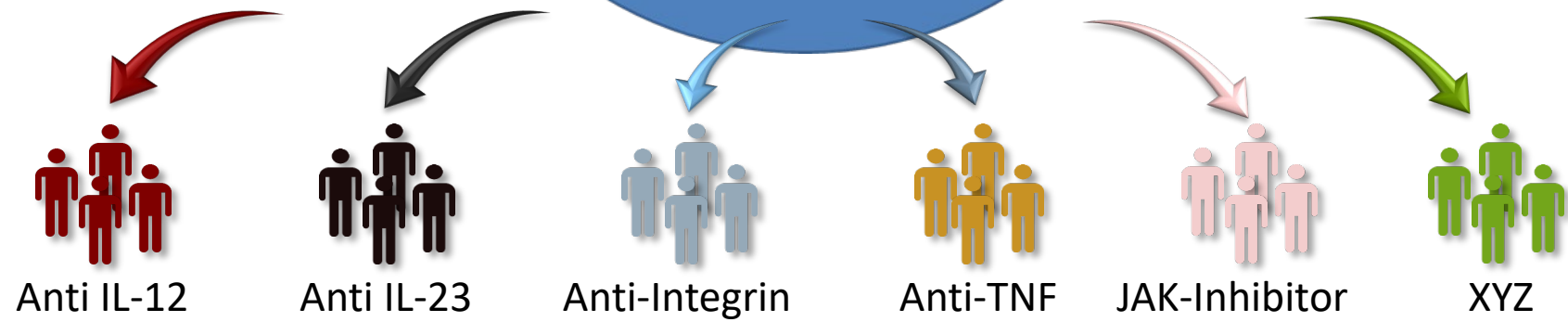
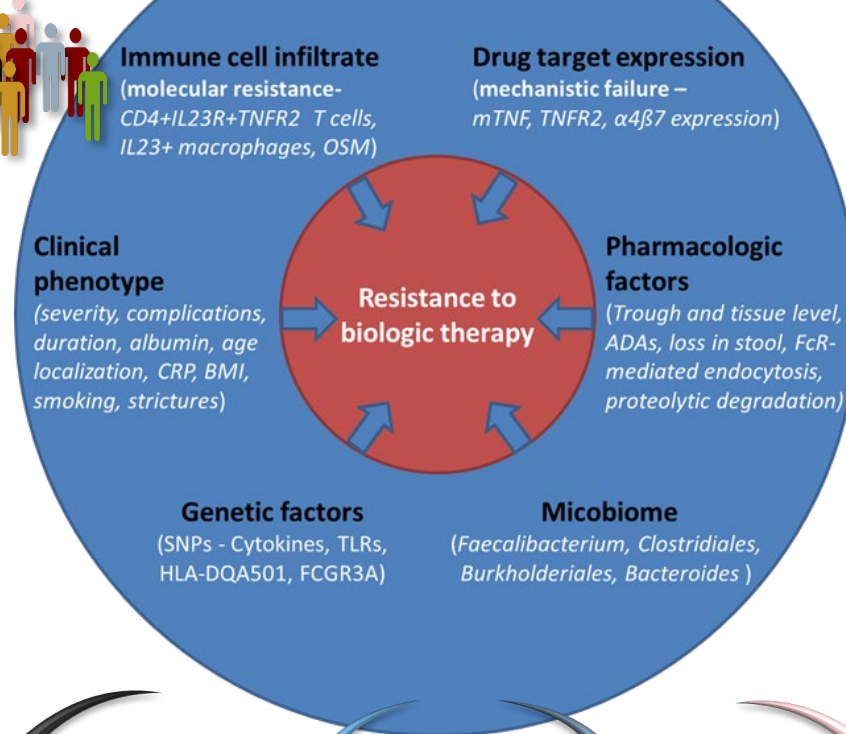
Microbiome as predictor of response in Ustekinumab



Microbial diversity as marker of response

Metabolic Function of the intestinal Microbiota is associated with anti-TNF efficacy





Thank you for your attention!