Precision medicine with precision tools in Crohn's disease: can we translate science into clinical practice?

United European Gastroenterology Week, October 8–11, 2022.

This symposium is intended for healthcare professionals only. A Takeda-organized symposium during UEG Week 2022.

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Precision medicine: an overview

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Disclosures

- Professor Peyrin-Biroulet has received personal fees from Galapagos, AbbVie, Janssen, Genentech, Alimentiv, Ferring, Tillotts, Celltrion, Takeda, Pfizer, InDex Pharmaceuticals, Sandoz, Celgene, Biogen, Samsung Bioepis, Inotrem, Allergan, MSD, Roche, Arena, Gilead, Amgen, BMS, Vifor Pharma, Norgine, Mylan, Lilly, Fresenius Kabi, OSE Immunotherapeutics, Enthera, Theravance Biopharma, Pandion Therapeutics, Gossamer Bio, Viatris, Thermo Fisher Scientific, ONO Pharma, Mopac, Cytoki Pharma, Morphic Therapeutic, Prometheus, and Applied Molecular Transport

“The good physician treats the disease; the great physician treats the patient who has the disease.”

Sir William Osler, 1903

Slide provided by Professor Laurent Peyrin-Biroulet.

Precision Medicine is Already a Reality in Other Fields of Medicine

Oncology

- Patients with HER2^{+} breast cancer are treated with **anti-HER2 antibody infusions**[1]
- **Pembrolizumab** has been shown to be efficacious for non-small cell lung cancer tumors that express the marker programmed death-ligand 1 in ≥50% of cells[2,3]

Lung disorder

- **Anti-IL-5 monoclonal antibodies** are indicated in patients with asthma who have **high levels of eosinophils** in the blood or respiratory tract[1]

HBV

- Use of **MALDI-TOF mass spectrometry to determine optimal protein profiles** for discrimination between HBV-infected patients with or without HCC[4]
  - Helps **predict drug resistance** to antiviral therapy and **diagnose treatment resistance** based on HBV genotype variations present[4]

HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HER2, human epidermal growth factor receptor 2; IL, interleukin; MALDI-TOF, matrix-assisted laser desorption/ionization-time of flight.

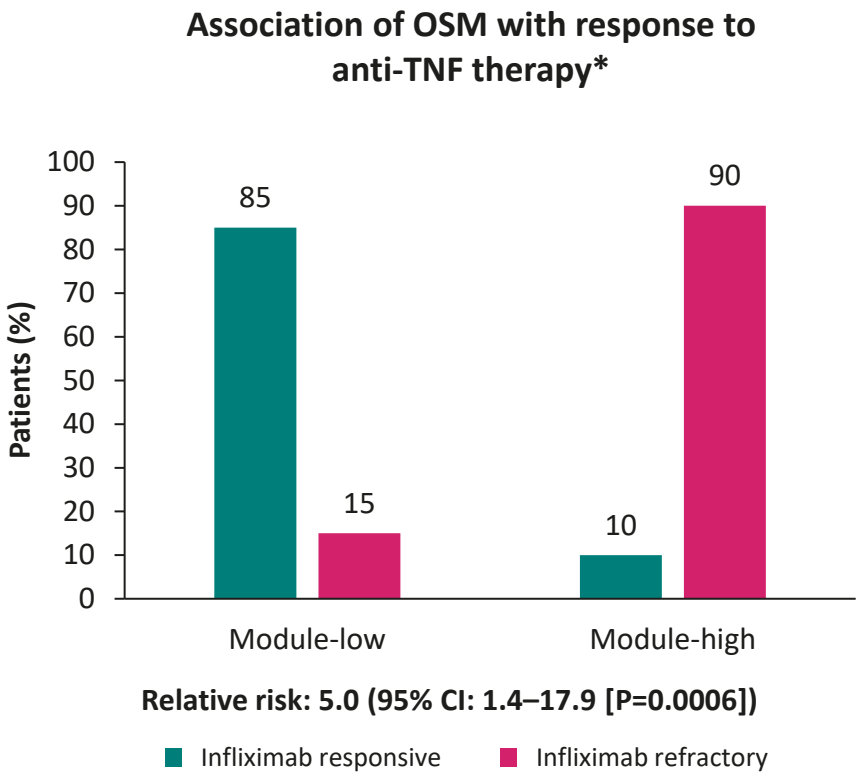
1. Lamb CA, et al. Gastroenterology. 2022;162:1525–42; 2. Ricciuto A, et al. Gastroenterology. 2022;162:1815–21; 3. Reck M, et al. N Engl J Med. 2016;375:1823–;33;
4. Duraisamy GS, et al. Viruses. 2020;12:998.

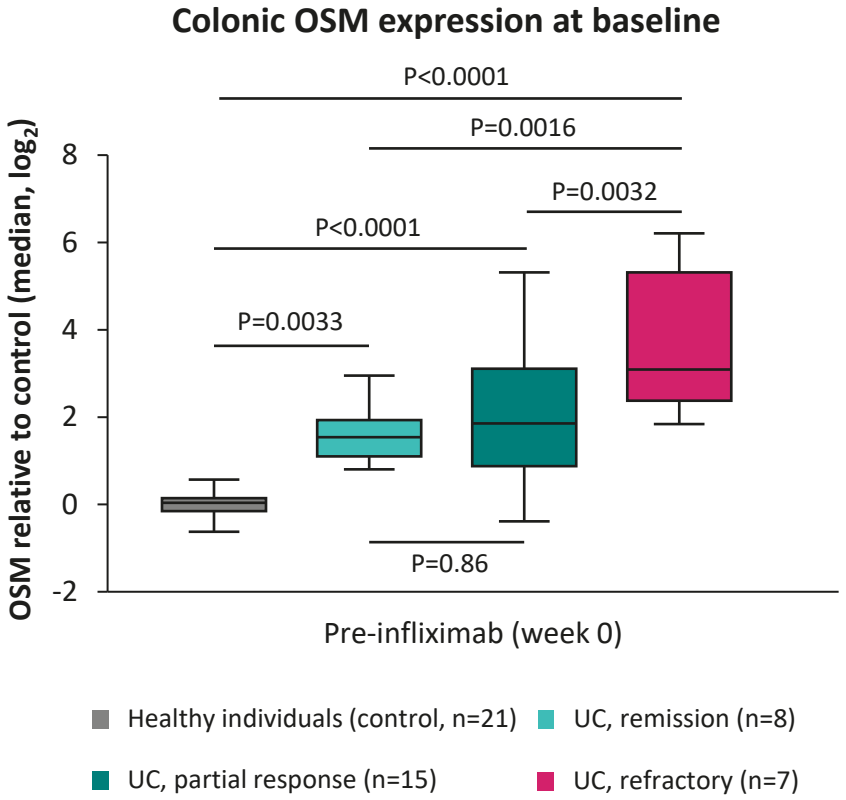
Takeda

Inflammatory Bowel Disease

Image sourced from the public domain.

Oncostatin M Predicts Anti-TNF Response





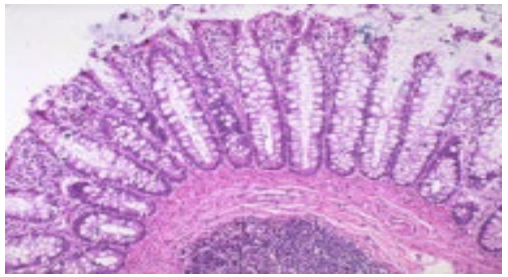
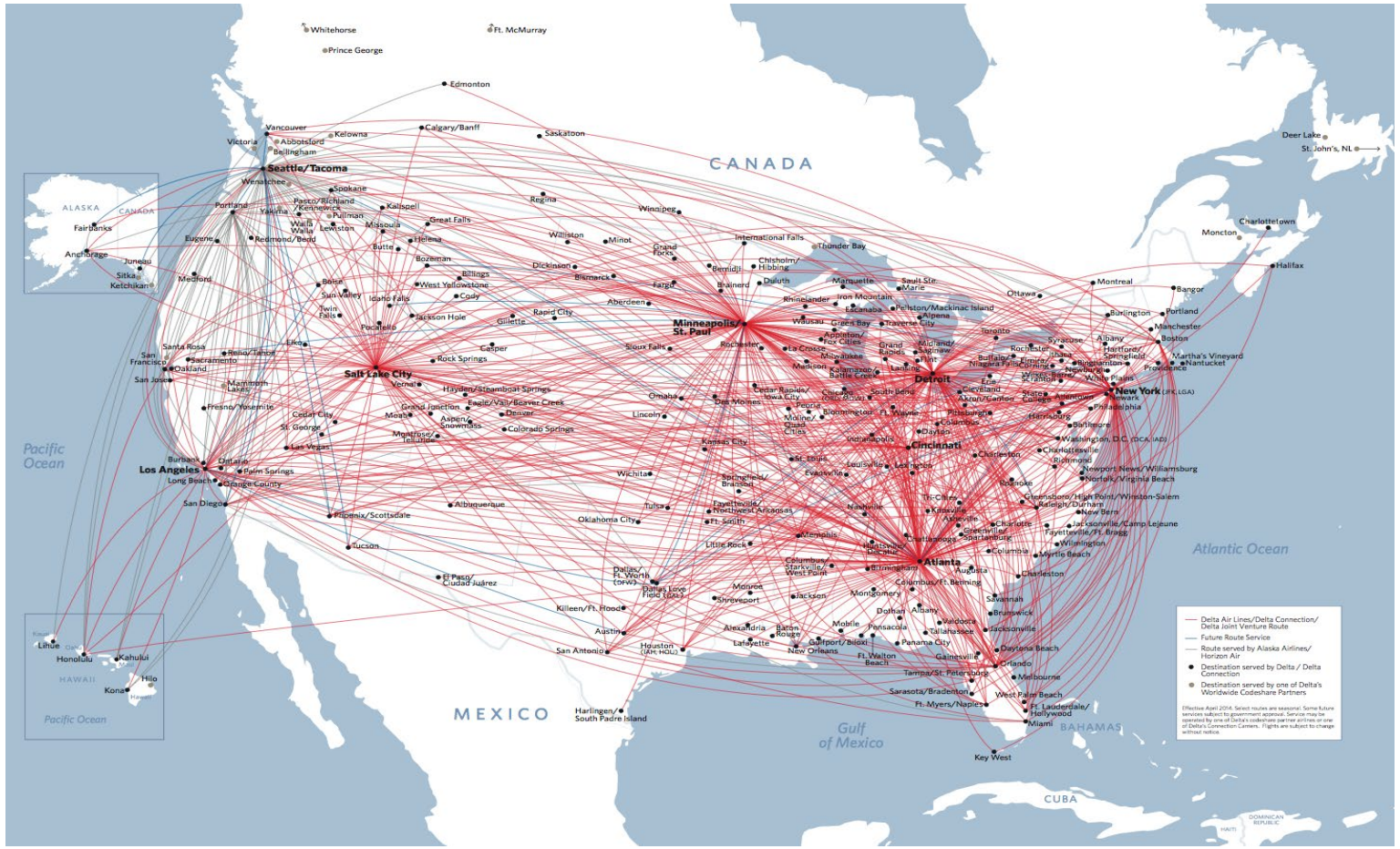


Image included on this slide was provided by Professor Peyrin-Biroulet. This image depicts normal colonic mucosa.
*Fisher's exact test.
CI, confidence interval; OSM, oncostatin M; TNF, tumor necrosis factor; UC, ulcerative colitis.
West NR, et al. Nat Med. 2017;23:579–89.

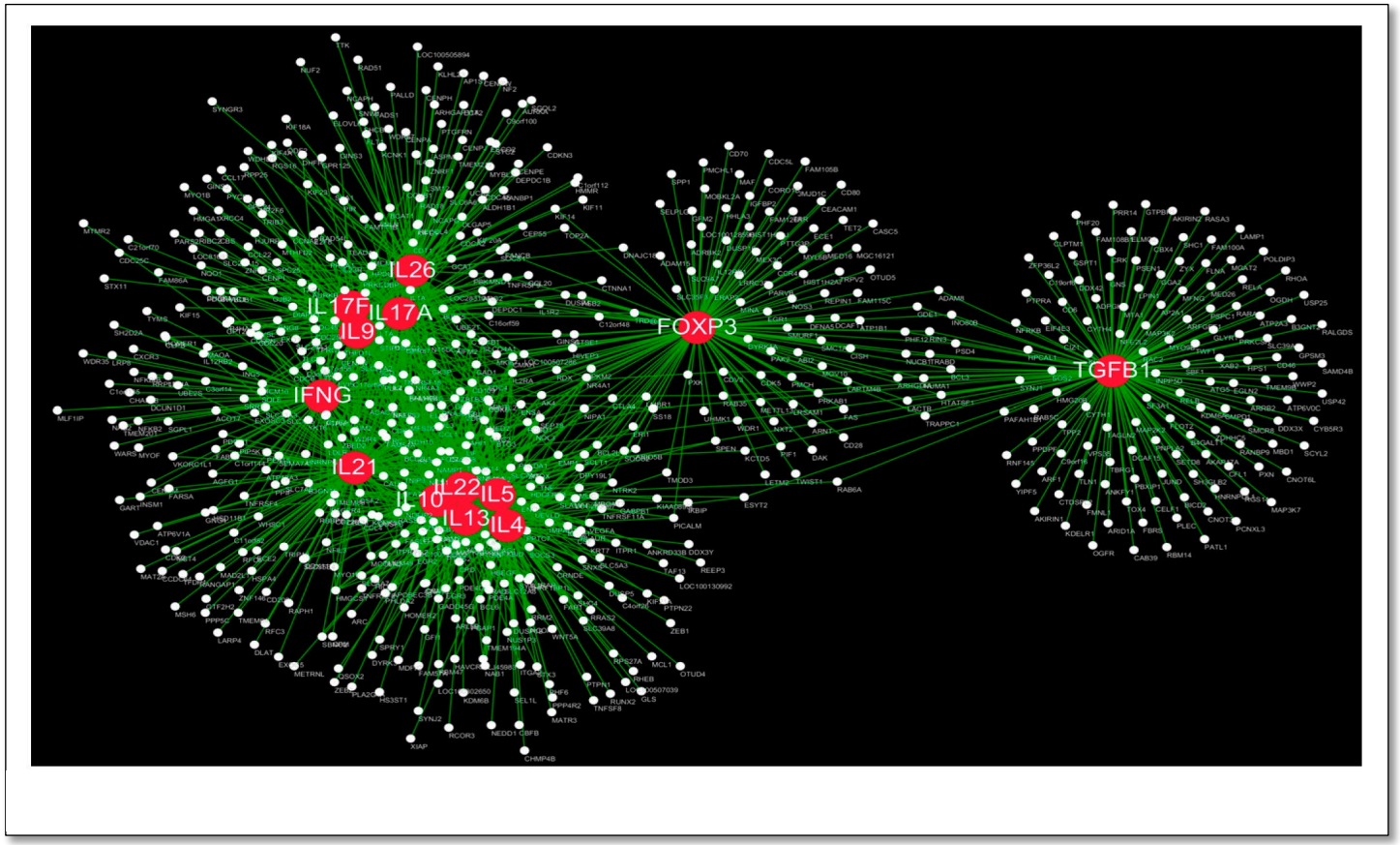
Airline Hubs: Few Controllers, Many Controlled



Delta News Hub. Available at: https://news.delta.com/route-map-us-canada. Accessed September 2022.

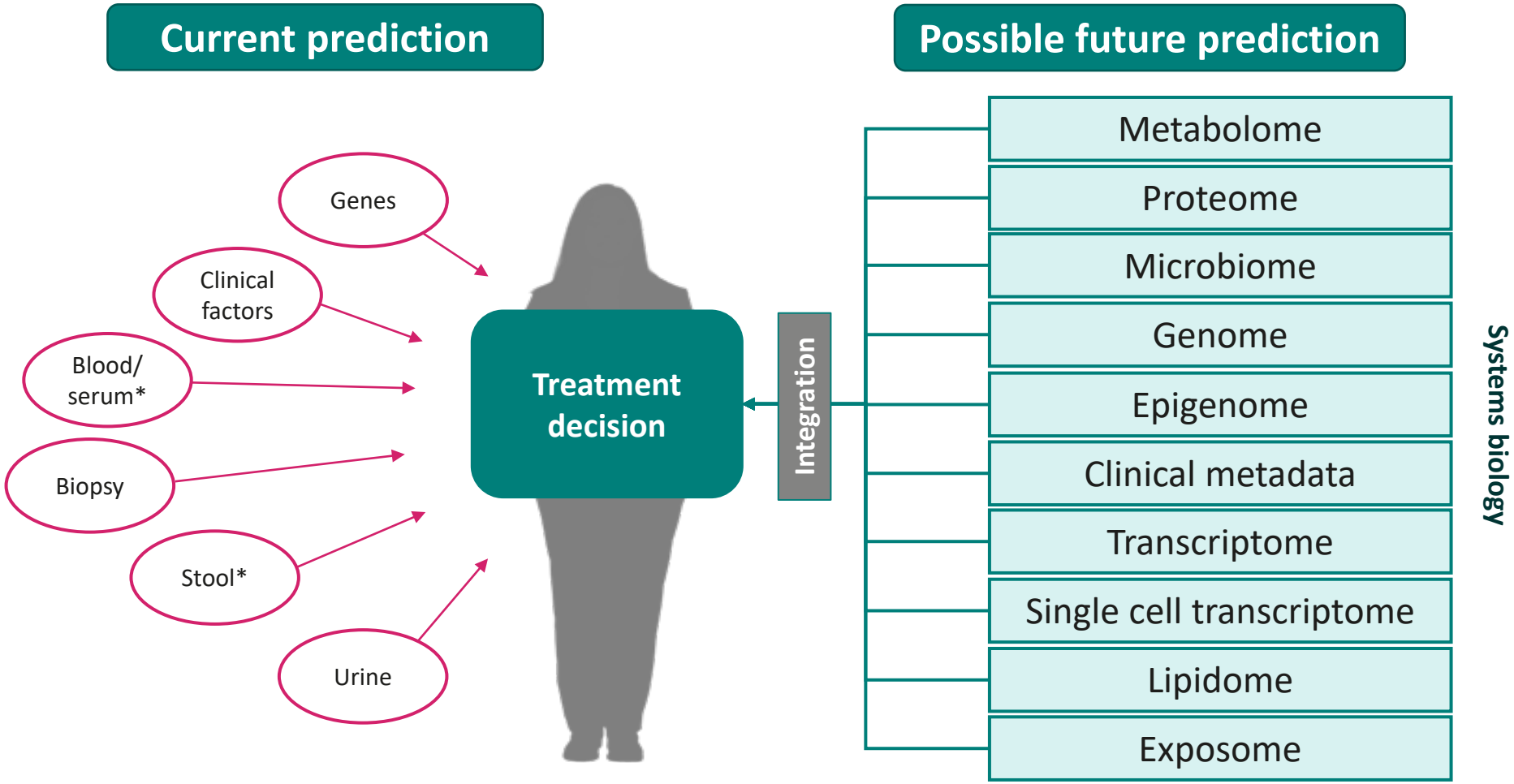
Controllability of Complex Biological Networks: T-Cell Biology Network: Few Controllers (●), Many Controlled (●)

Connections between Th cell subpopulations based on electronic sorting results



Wang P, et al. J Immunol. 2016;197:665–73.
FOXP3, forkhead box P3; IFNG, interferon gamma; IL, interleukin, Th, T helper cell; TGFB1, transforming growth factor beta 1.

Assessments for Precision Medicine in CD and IBD



Integration of multi-omics/system biology

*Including non-invasive biomarkers.
CD, Crohn's disease; IBD, inflammatory bowel disease.
Adapted from: Lamb CA, et al. Gastroenterology. 2022;162:1525–42.

Individual Human Uniqueness: Role of Epigenetic Influences

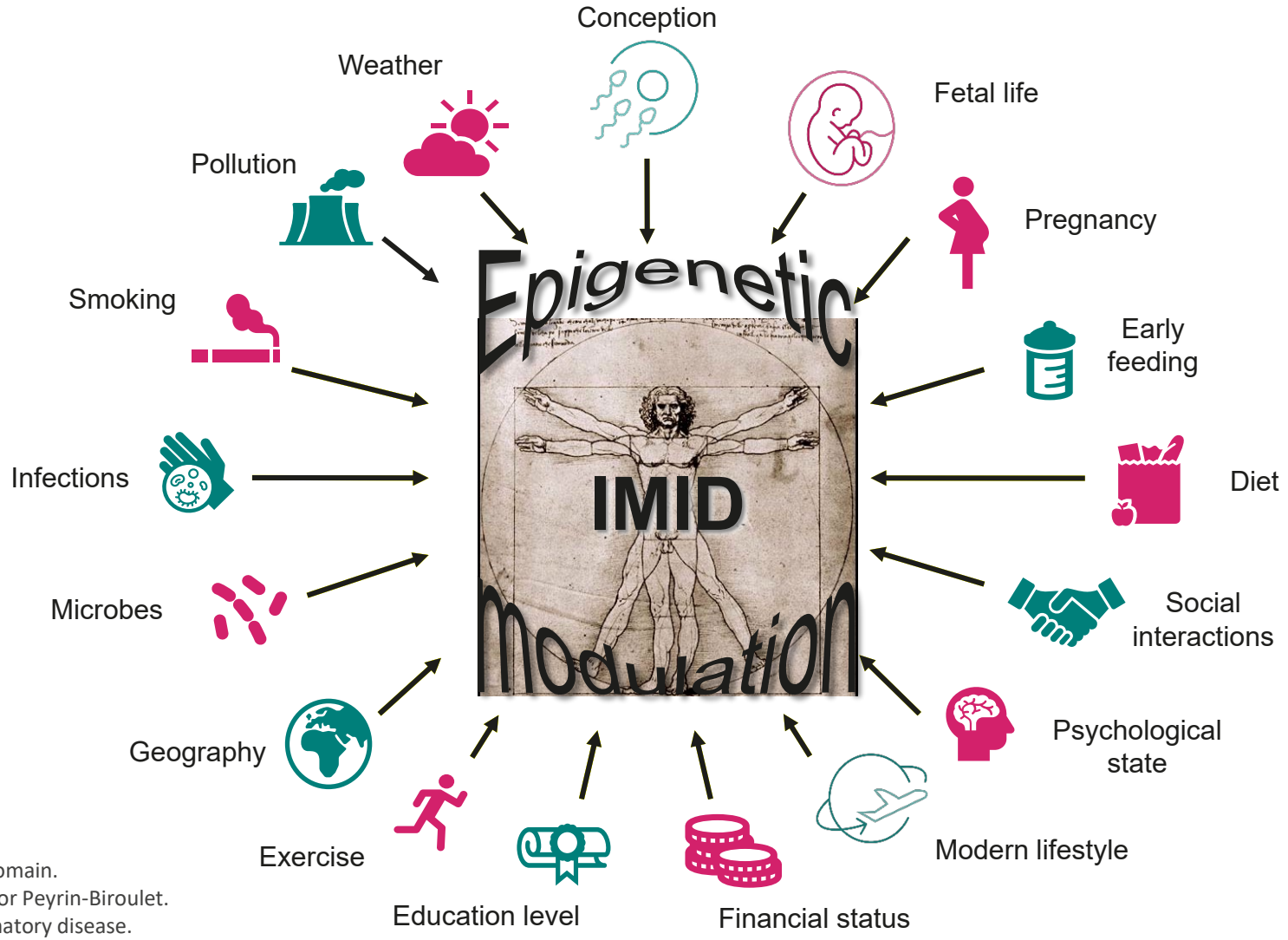


Image sourced from the public domain.
Content was provided by Professor Peyrin-Biroulet.
IMID, immune-mediated inflammatory disease.

Computational Platform for Predicting Temporal Progression of Mucosal Damage and Healing in Patients With Crohn's Disease

Methods[1]

Patient data* from VERSIFY (NCT02425111)[2] N=69

Training dataset (n=46)
A subset of patient data was created to train the model

Test/validation dataset (n=31†)
A test dataset was created to evaluate the final model performance

Input files
Created model that accepted input file in JSON format using patient data from VERSIFY

Responder classification
Assigned the responder profile for matching based on the patient's response to drugs taken previously or during the clinical program

Archetype matching
Assign a digital twin from the virtual library by matching the closest archetype/virtual patient from the patient library based on matched criteria**

Archetype matching
Assign a digital twin from the virtual library by matching the closest archetype/virtual patient from the **updated** patient library based on matched criteria**

Forecast using the model
Simulate the mechanistic model of CD using the digital twin of the patient

Model tuning
Fine tune model parameters related to disease severity and drug response by comparing model outputs from patient data

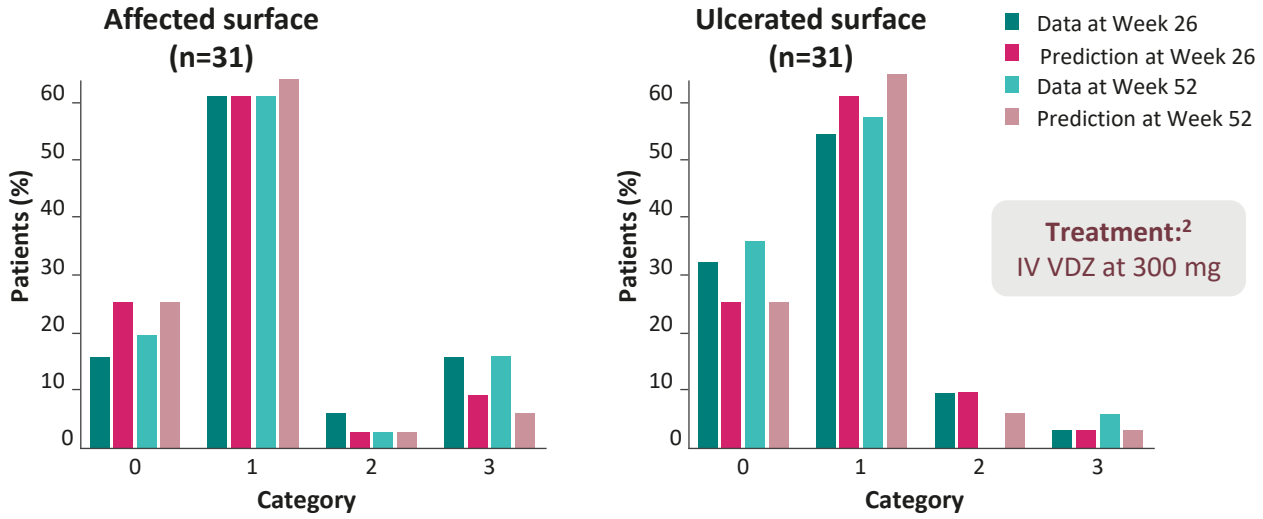
Platform evaluation
The digital twin's simulated time-series data were then compared with the real patient data for objective outcomes (affected area, ulcerated area and ulcer type)

Update virtual patient library
The virtual patient library was regenerated using the updated model from the previous step

Results[1]

Patients with CD from the **VERSIFY study** (n=69‡), treated with **IV VDZ**.
The digital twin of each patient was used to forecast the SES-CD components, i.e. affected surface, ulcerated surface, and size of ulcers, in response to treatment[1,2]

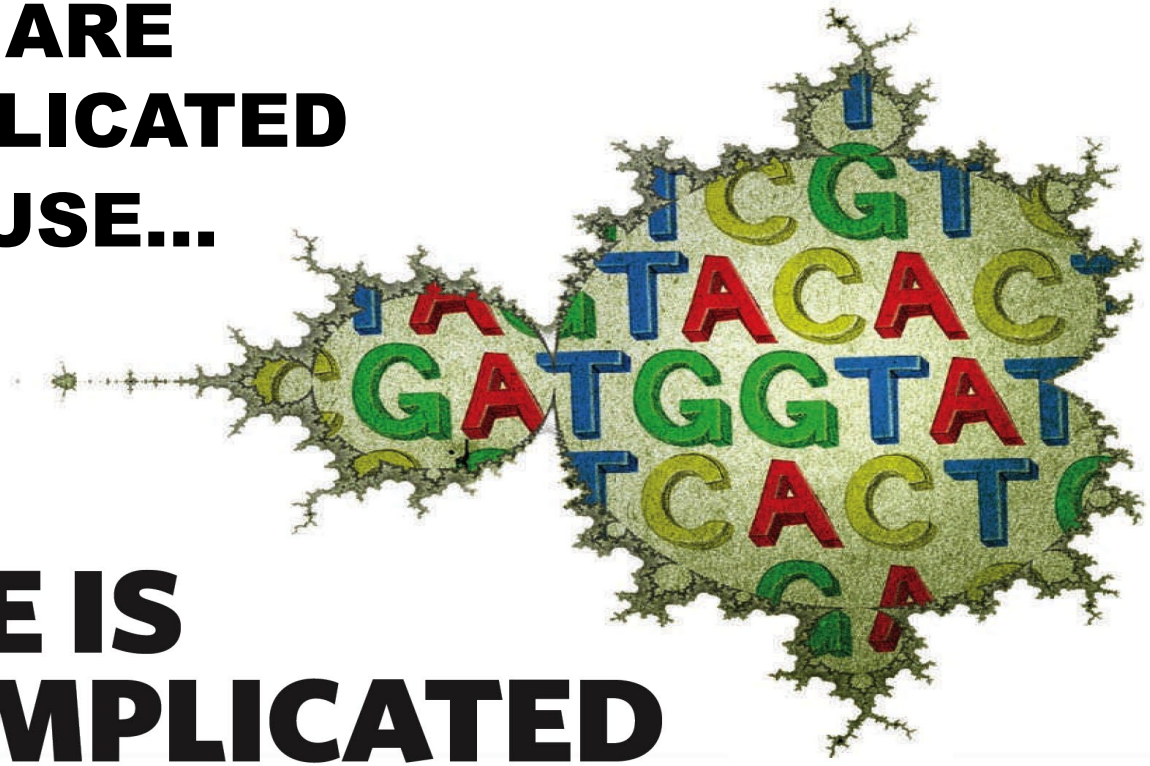
Comparison of predicted and observed disease severity at Weeks 26 and 52 using the SES-CD score categories



*Data including demographics, laboratory and biomarker scores, disease characteristics and treatment history were collected; **Parameters included demographics (age, weight, gender), biomarkers (C-reactive protein), disease parameters (ulcer type, ulcer area, disease area), disease location. †Eight patients from the discarded pool for the classifier model development were added to the validation set for the prediction of treatment response using the mechanistic model. ‡Patients eligible for responder classifier analysis. Affected surface categories: 0: none; 1: <50%; 2: 50–75%; 3: >75%. Ulcerated surface categories: 0: none; 1: <10%; 2: 10–30%; 3: >30%. CD, Crohn's disease; IV, intravenous; JSON, JavaScript Object Notation; SES-CD, simple endoscopic score for CD; VDZ, vedolizumab.

1. Venkatapurapu SP, et al. Adv Ther. 2022;39:3225–47; 2. NCT02425111. ClinicalTrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT02425111. Accessed September 2022.

IMIDs ARE COMPLICATED BECAUSE...



LIFE IS COMPLICATED

The more biologists look, the more complexity there seems to be.

IMID, immune-mediated inflammatory diseases.
Adapted from: Hayden EC. Nature. 2010;464:664–67.

Precision medicine with precision tools in Crohn's disease: can we translate science into clinical practice?

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Precision medicine in CD: evolution and challenges

Professor Shomron Ben-Horin
Sheba Medical Center, Tel-Aviv University, Israel

CD, Crohn's disease.

Disclosures

- Professor Shomron Ben-Horin has received advisory board and/or consulting fees from AbbVie, Takeda, Janssen, Celltrion, Pfizer, GSK, Ferring, Novartis, Roche, Gilead, NeoPharm, Predicta Med, Galmed, Medial Earlysign, BMS, and Eli Lilly, and has received research support from AbbVie, Takeda, Janssen, Celltrion, Pfizer, Galmed, and OutSense

Overview of the Differences Between Individualized Medicine and Precision Medicine

What is individualized/ personalized medicine?[1]

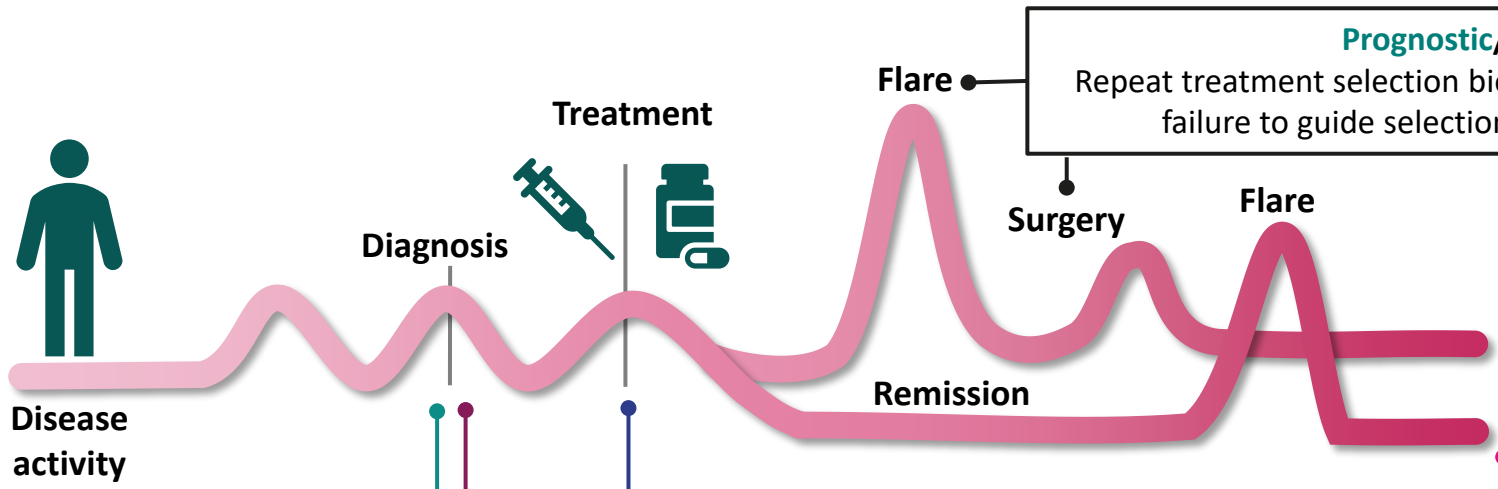
Patient-centered treatment decisions that may help **predict disease course** at diagnosis and hence **tailor medications based on response**, i.e. utilizing patient information to select more targeted therapies

What is precision medicine?[2,3]

Broader approach to developing and identifying effective treatments based on clinical and molecular data, i.e. choosing a **specific treatment** based on an individual patient's **genetics, phenotypic, environmental,** and **lifestyle** parameters contributing to the disease

1. Ashton JJ, et al. Transl Pediatr. 2019;8:56–69; 2. Lamb CA, et al. Gastroenterology. 2022;162:1525–42; 3. Ginsburg GS. Health Aff (Millwood). 2018;37:694–701.

Optimizing the Approach to Patient Characterization/ Stratification



Biomarkers

Prognostic
To stratify patients as low vs high risk for complications/ bowel damage

Current examples
- Serologies (ASCA, ANCA)
- Gene expression profiles from blood (CD8 T cell assay) + translation into whole blood
- Gene expression profiles from biopsies (ECM signature in RISK)
- Composite of clinical, genetic, and serologic markers (PROSPECT)

Therapeutic safety
To guide selection of safe therapy

Current examples
- Blood markers (TPMT, NUDT15, HLA typing)

Treatment predictive
To guide selection of most appropriate first-line therapy

Current examples
- Blood markers (TREM1 mRNA, protein IL-22)
- Tissue markers (OSM, IL13RA2)

Treatment response

ANCA, antineutrophil cytoplasmic antibodies; ASCA, anti-Saccharomyces cerevisiae antibodies; CD8, cluster of differentiation 8; ECM, extracellular matrix; HLA, human leukocyte antigen; IL-22, interleukin-22; IL13RA2, interleukin 13 receptor subunit alpha 2; mRNA, messenger ribonucleic acid; NUDT15, nudix hydrolase 15; OSM, oncostatin M; PROSPECT, Personalized Risk and Outcomes Prediction Tool; TPMT, thiopurine methyltransferase; TREM1, triggering receptor expressed on myeloid cells 1.

Verstockt B, et al. J Crohns Colitis. 2021;15:1431–42.

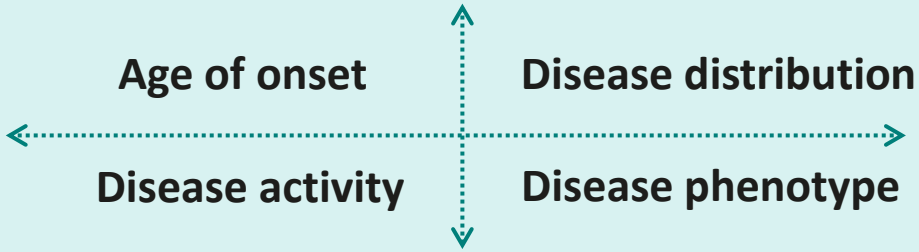
Precision: Patient's Disease Outcomes

Certain Disease Features and Prognostic Factors Correlate With the Disease Course

Patients with CD **may be stratified** by their risk of **clinical relapse, hospitalization**, and **surgery** by examining the **association between their demographics and clinical characteristics**, as well as their subsequent **natural history**[1]

Clinical features[2]

The disease course and management of CD is, in part, predicted by the following clinical features at the time of diagnosis:



Prognostic factors[3]

Several prognostic factors correlate with the disease course of CD:

Biomarkers

Serological markers

Genetic markers

The management of CD may be improved if patients are stratified by risk[1]

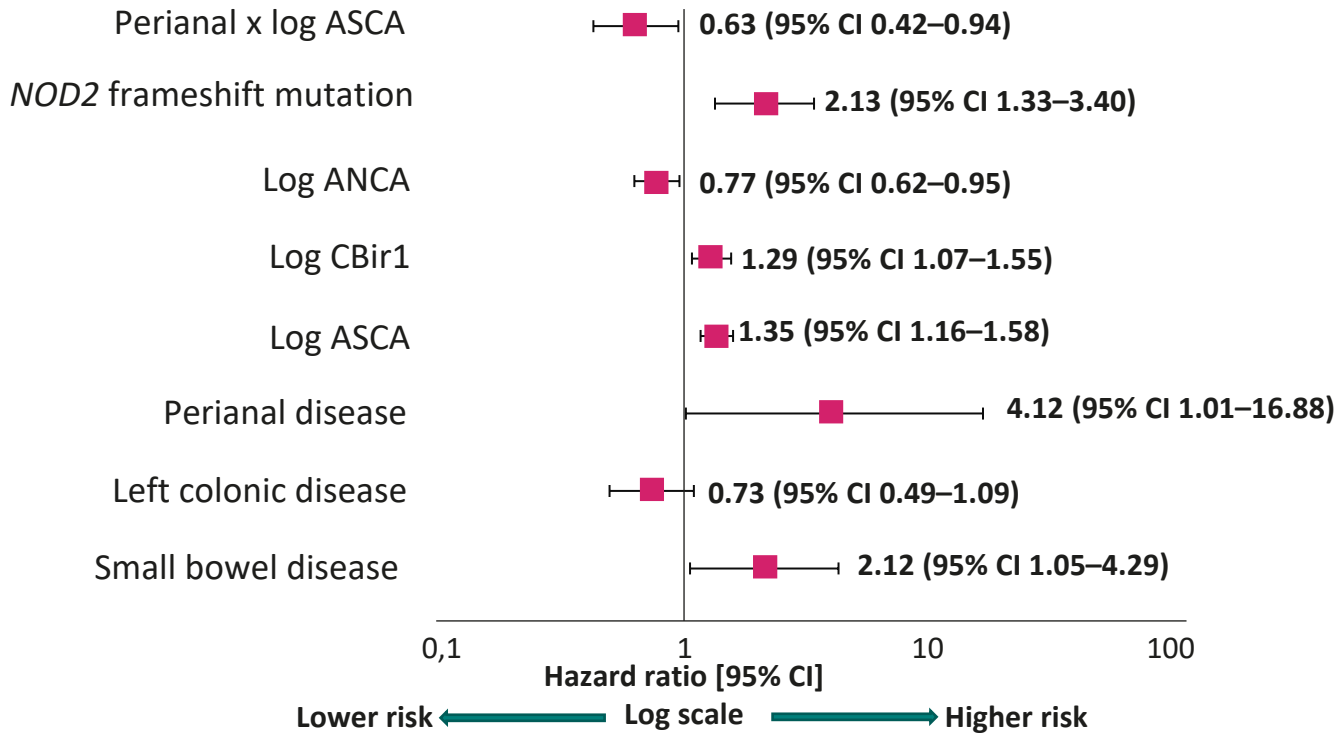
CD, Crohn's disease.

1. Aniwan S, et al. Gastroenterol Clin North Am. 2017;46:463–80; 2. Lichtenstein GR, et al. Am J Gastroenterol. 2018;113:481–517;
3. Lichtenstein GR. Gastroenterol Hepatol (N Y). 2010;6:99–107.

PROSPECT: A Tool to Predict Individualized Risk of CD Complications

Risk stratification at baseline using a clinical dashboard

Multivariate analysis for the risk of CD complication[1]



695 adult patients with CD[1]
Outcome = time to complication of CD[1]

Model concordance[1]

Calibration cohort:
Harrell's C = 0.73

Adult validation:
Harrell's C = 0.73

Pediatric validation:
Harrell's C = 0.75

Absolute value used for all serologic markers. NOD2 considered positive if 1 or 2 polymorphisms with frameshift mutation.
ANCA, antineutrophil cytoplasmic antibody; ASCA, anti-Saccharomyces cerevisiae antibody; CBir1, anti-flagellin; CD, Crohn's disease; CI, confidence interval; Harrell's C, Harrell's Concordance statistic; PROSPECT, Personalized Risk and Outcomes Prediction Tool.

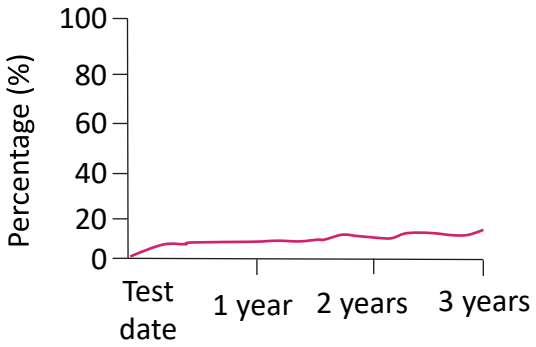
Siegel CA, et al. Aliment Pharmacol Ther. 2016;43:262–71.

CDPATH: Clinical Risk-Stratification Tool for Patients With CD

Risk stratification at baseline using a clinical dashboard

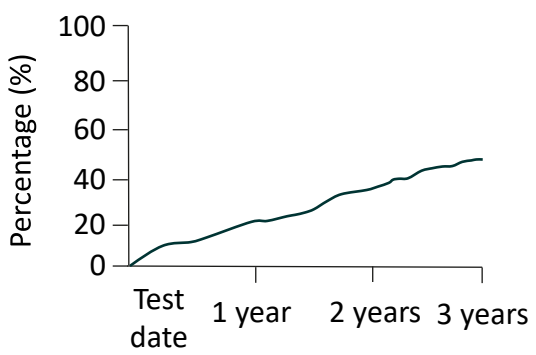
Predicted risk of complication from CD over 3 years[1,2]

Low-risk result



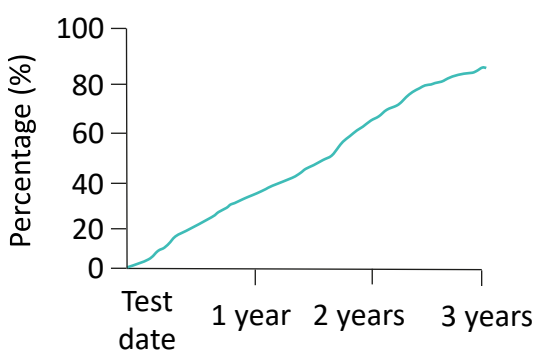
Low risk* (0–19.9%)

Medium-risk result



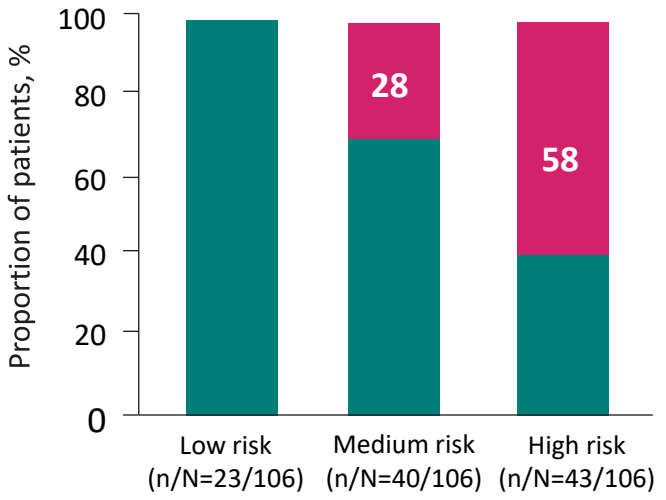
Medium risk* (20–59.9%)

High-risk result



High risk* (60–100%)

Patients developing complications at 3 years based on initial stratification[3]



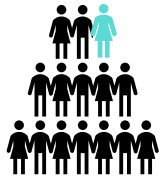
CDPATH is currently available in the US only. *Risk cutoffs were developed in qualitative focus groups and cognitive interviews with patients with CD. In subsequent focus groups, patients who have shown the cutoffs for low (0–19.9%), medium (20–59.9%), and high (60–100%) risk agreed that they represented clinically meaningful decision points. Finally, gastroenterologists were consulted to confirm face validity of these risk groupings, with universal agreement from participants.[3]

CD, Crohn's disease.

1. Siegel CA, et al. Aliment Pharmacol Ther. 2016;43:262–71; 2. CDPATH. An innovative tool for patients with Crohn's disease. Available from: https://www.cdpath.com/. Accessed October 2022; 3. Siegel CA, et al. Crohn's & Colitis 360. 2021;3:otab074.

CDPATH: Performance Characteristics and Accessibility

- CDPATH is an innovative, validated prognostic tool that uses blood tests to help predict the potential risk for developing serious complications* within 3 years in adult patients with CD



Individualized risk profile

Risk assessment specific to your unique, individual case

Innovative predictive tool

CDPATH uses your doctor's evaluation of your CD and information from your blood sample

No cost for eligible patients

Should you and your doctor decide CDPATH is right for you, and you meet eligibility criteria, CDPATH is provided free of charge

CDPATH is being offered free of charge for eligible patients

As part of the program, the costs of CDPATH will be covered as long as patients meet the following eligibility criteria:

18+ Adult CD patients (≥18 years old) diagnosed within the last 10 years

Patients on a commercial healthcare plan or uninsured

Patients who have not experienced serious CD complications, defined as bowel stricture, internal penetrating disease, or non-perianal surgery (bowel resection or stricturoplasty)

Blood draw taken at a physician's office or participating lab

CDPATH is currently available in the US only.

*CDPATH defines serious complications for patients with CD as any fistulas or strictures in your bowels or any surgery in your bowels other than the area in or around the anus.

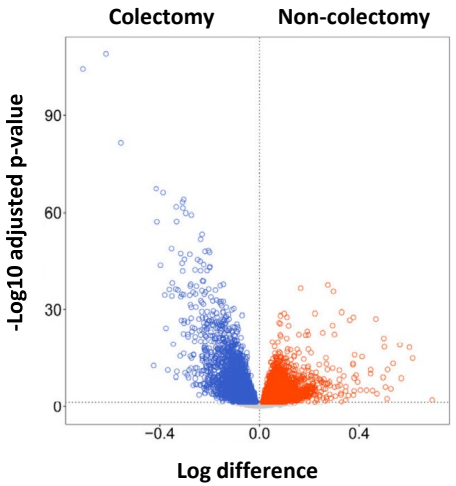
CD, Crohn's disease.

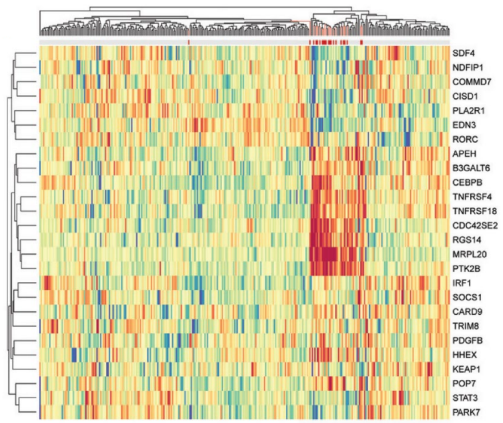
CDPATH. An innovative tool for patients with Crohn's disease. Available from: https://www.cdpath.com/. Accessed October2022.

Molecular-Level Risk-Stratification for Patients With IBD

Polygenic transcriptional risk score identifies UC patients at 5-fold elevated risk of colectomy[1]

Volcano plot of significance against difference in expression on log2 scale*

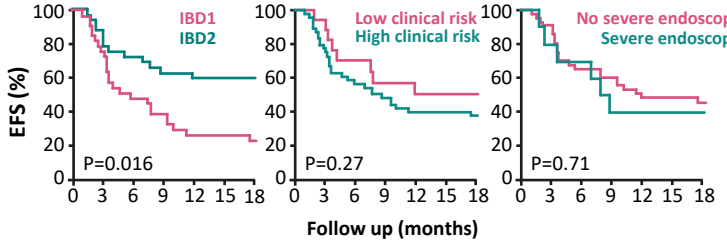




Baseline rectal expression of 26 genes with evidence that the GWAS peak is the same as a blood eQTL (coloc H4 > 0.8)†

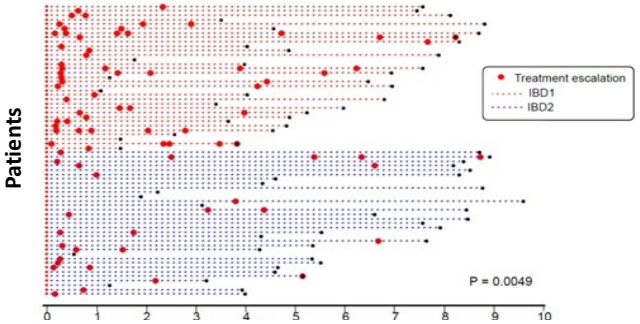
CD8 T-cells, T-cell exhaustion and macrophage-related gene variants predict prognosis in IBD[2]

KM plot of EFS for CD patients in the IBD1 and IBD2 subgroups[2]



No. at risk																			
IBD1	33	26	17	15	10	9	7	17	17	13	10	9	9	8	43	40	29	26	21	20	17
IBD2	33	29	25	21	20	20	19	49	39	29	25	21	20	18	10	9	8	5	5	5	5

Disease course of individual CD patients (dotted lines)[2‡]



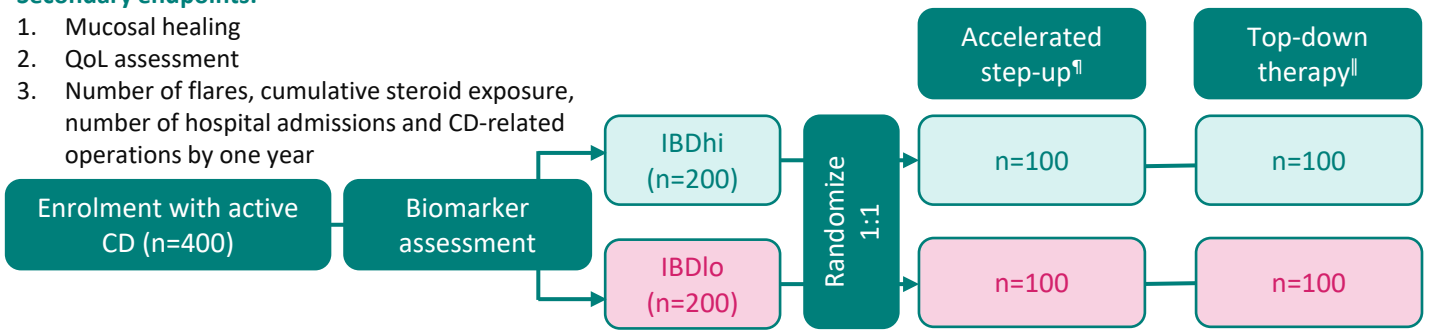
Primary endpoint:

1. Sustained surgery and steroid-free remission (through 48 weeks)

Secondary endpoints:

1. Mucosal healing
2. QoL assessment
3. Number of flares, cumulative steroid exposure, number of hospital admissions and CD-related operations by one year

PROFILE[3§]



*Genes upregulated in colectomy are in blue. †Red represents high expression and blue represents low expression. The bar at the top indicates non-colectomy (gray) and colectomy (red) clinical status, highlighting a cluster of affected individuals for whom most of the genes are differentially expressed. ‡The colour of dotted lines reflects subgroup designation. Statistical significance was determined using a Mann Whitney test. §Inclusion criteria: newly diagnosed CD (within 3 months), active disease, not on immunosuppressant therapy. ¶Prednisolone 8 week reducing course; Flare 1: prednisolone plus azathioprine/methotrexate, Flare 2: add in infliximab. ‖Infliximab and azathioprine/methotrexate.
CD, Crohn's disease; CD8, cluster of differentiation 8; EFS, escalation-free survival; eQTL, expression quantitative trait loci; GWAS, genome-wide association study; IBD, inflammatory bowel disease; IBDhi, patients with high levels of IBD molecular biomarker; IBDlo, patients with low levels of IBD molecular biomarker; KM, Kaplan-Meier; PROFILE, PRedicting Outcomes For Crohn's dIsease using a moLecular biomarker; QoL, quality of life.

1. Mo A, et al. Am J Hum Genet. 2021;108:1765–79; 2. Biasci D, et al. Gut. 2019;68:1386–95; 3. Parkes M, et al. BMJ Open. 2018;8:e026767.

Precision: Timing Treatment Initiation

CD Studies Have Observed Higher Rates of Induction of Remission With Biologics in Early CD

Specifically in CD, earlier disease intervention may be associated with improved efficacy

Aim
Investigate the efficacy of biologics in patients with short-duration disease vs those with long-duration disease

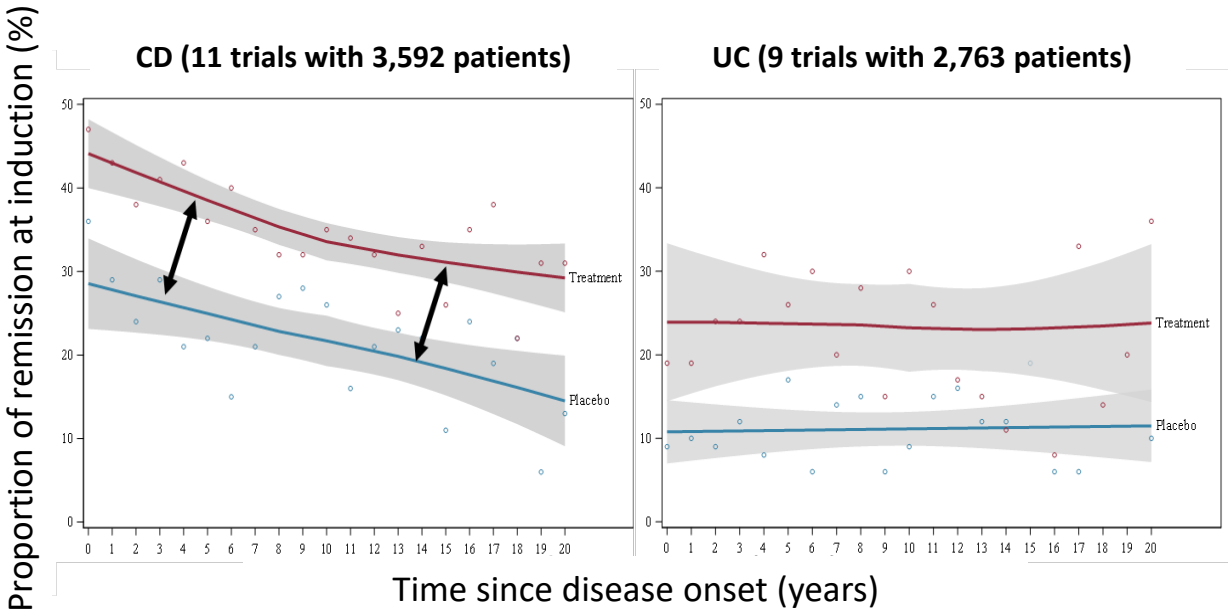
Methods
Systematic review and individual patient data meta-analysis included eligible studies of patients with IBD; 16 CD and 9 UC studies were identified

Primary outcome
Proportion of induction of remission by biologics in short-duration* vs long-duration† patients with IBD

CD trials
N=3,592

Induction of remission
Active arm: 37.8%
Placebo arm: 26.5%

Pooled rate of induction of remission
Short duration: 41.4%
Long duration: 29.8%
OR: 0.75 (95% CI 0.61–0.92)



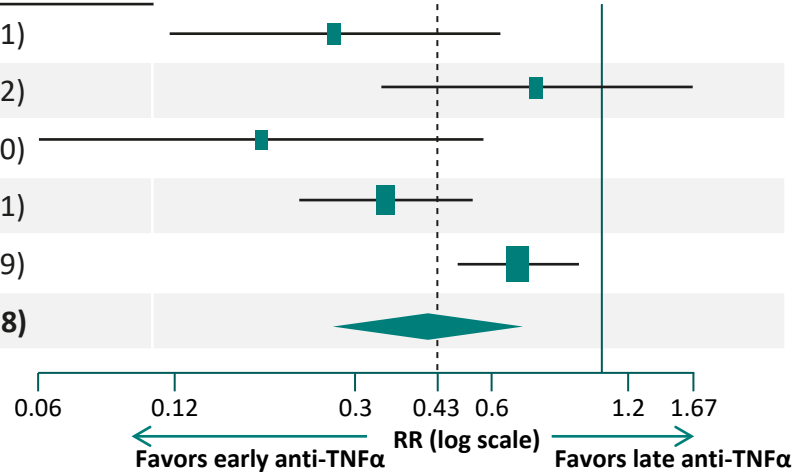
Patients with early CD achieved higher rates of remission with a shorter disease duration compared with a longer disease duration, indicating duration of disease modulates response to therapy

*≤18 months; †>18 months.
CD, Crohn's disease; CI, confidence interval; IBD, inflammatory bowel disease; OR, odds ratio; UC, ulcerative colitis.
Ben-Horin S, et al. Gastroenterology. 2022;162:482–94.

Effective Biologic Therapy Within 3 Years Since Diagnosis Reduced the Need for Surgery and the Rate of Disease Progression by ~50%

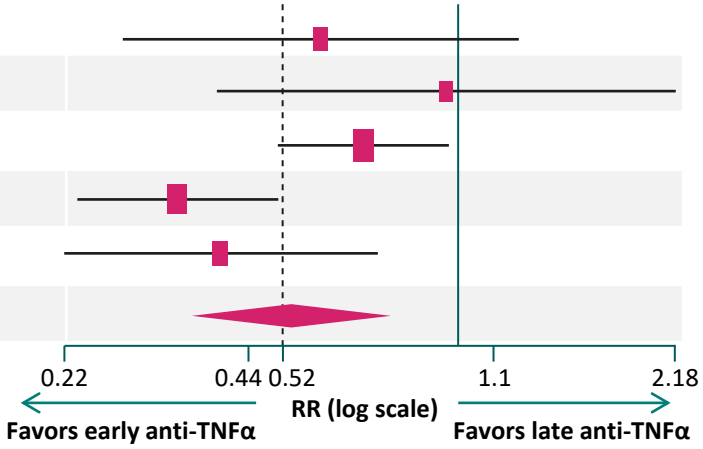
Risk of surgery

Studies	Estimate (95% CI)
De Chambrum et al. 2015	0.268 (0.116–0.621)
Nuji et al. 2015	0.762 (0.347–1.672)
Ma et al. 2016	0.185 (0.060–0.570)
Oh et al. 2017	0.349 (0.225–0.541)
Frei et al. 2019	0.682 (0.501–0.929)
Overall (p=0.013)	**0.431 (0.266–0.698)**



Risk of disease progression

Studies	Estimate (95% CI)
Colombel et al. 2014	0.575 (0.273–1.210)
De Chambrum et al. 2015	0.922 (0.389–2.184)
Ma et al. 2016	0.674 (0.491–0.927)
Oh et al. 2017	0.336 (0.231–0.488)
Frei et al. 2019	0.395 (0.220–0.709)
Overall (p=0.034)	**0.516 (0.355–0.750)**



Systematic review and meta-analysis of 11 studies (N=2,501).
CI, confidence interval; RR, relative risk; TNFα, tumor necrosis factor-α.
Hamdeh S, et al. Inflamm Bowel Dis. 2020;26:1808–18.

Precision: Which Treatment?

A Patient's Severity/Risk Profile Impacts How Patients With CD are Treated to Induce Remission

Mild-to-moderate CD*

Outcome	Recommendation
Induction of remission	• Against use of 5-ASA • **Use budesonide (limited to ileum and/or ascending colon)**

= strong recommendation
= weak recommendation

Moderate-to-severe CD*

Outcome	Recommendation
Induction of remission	• **TNFα inhibitors (IFX, ADA, and CZP)** • **Combination of thiopurine when starting IFX†** • **UST (anti-TNFα–exposed adult outpatients)** • Against use of thiopurines
Induction of clinical response and remission	• **VDZ (anti-TNFα–exposed adult outpatients)** • Systemic corticosteroids • Against combination of ADA and thiopurines over ADA alone
Treatment of active luminal CD	• VDZ or UST (anti-TNFα–exposed adult outpatients)

= strong recommendation
= weak recommendation

*To define disease activity and severity (mild-to-moderate and moderate-to-severe CD) the definitions used by the investigators of the studies selected from the comprehensive literature search were accepted as an evidence basis for the disease categorization and recommendations presented. †Inadequate response to conventional therapy.
5-ASA, 5-aminosalicylic acid; ADA, adalimumab; CD, Crohn's disease; CZP, certolizumab pegol; IFX, infliximab; TNFα, tumor necrosis factor-α; UST, ustekinumab; VDZ, vedolizumab.
Torres J, et al. J Crohns Colitis. 2020;14:4–22.

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The Vedolizumab Clinical Decision Support Tool may be Used to Guide Therapeutic Decisions in Patients With CD

Dynamic tools to monitor endoscopic activity

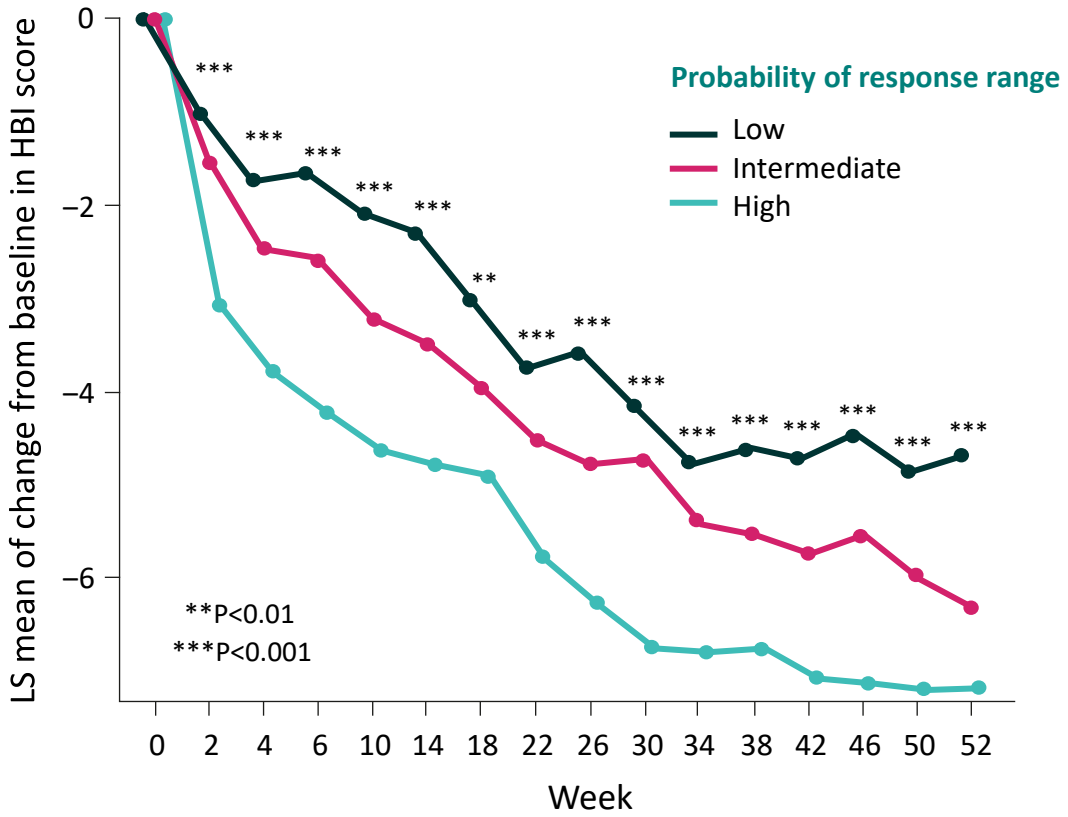
CDST is calculated using the following 5 variables:[1]

1. No prior bowel surgery (+2 points)
2. No prior anti-TNFα therapy (+3 points)
3. No prior fistulizing disease (+2 points)
4. Baseline albumin (+0.4 points/g/L)
5. Baseline CRP (–0.5 points if 3.0–10.0 mg/L; –3.0 points if >10 mg/L)

Probability of response to vedolizumab:[1]

Low	≤13 points
Intermediate	>13 to ≤19 points
High	>19 points

HBI score stratified by probability of response[1]



The vedolizumab CDST predicts clinical remission and steroid-free clinical remission at week 48 for vedolizumab but not ustekinumab in CD patients refractory or intolerant to anti-TNF.[2]
CDST tools are available for other therapies used in active CD, including the ustekinumab CDST and infliximab CDST.[3,4]
CD, Crohn's disease; CDST, clinical decision support tool; CRP, C-reactive protein; HBI, Harvey-Bradshaw Index; LS, least squares; TNFα, tumor necrosis factor-α.
1. Dulai PS, et al. Aliment Pharmacol Ther. 2020;51:553–64; 2. Alric H, et al. Infamm Bowel Dis. 2022;28:218–25; 3. Dulai PS. Am J Gastroenterol. 2019;114:S373;
4. Dulai PS, et al. Clin Gastroenterol Hepatol. 2022;20:e1192–5.

Precision Medicine May Lead to new Classifications of IBD Types

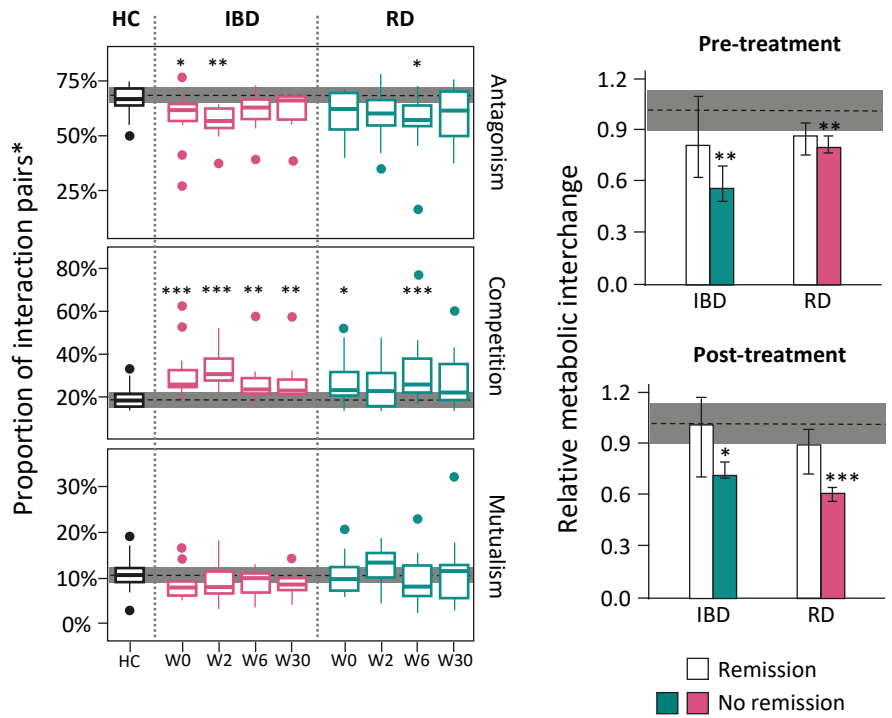
OSM is a potential diagnostic biomarker in patients with IBD[1]

CD	UC
mRNA expression of 64 cytokines was compared in IBD vs healthy control: T-tests with FDR correction at Q = 1%	
11 genes: 8 high in CD 3 low in CD	**7 genes:** 4 high in UC 3 low in UC
Significant hits were further selected using a fold difference threshold of ≥2	
IFNG, IL-11, IL-22, IL-26, IL-27, CSF2, CSF3 (high in CD)	IL-33, TGFB1 (high in UC)

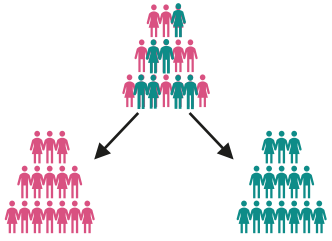
→ **16 genes** (all high in IBD)

→ **OSM, IL-1A, IL-1B, IL-6**

Bacterial metabolic interactions are disrupted in IBD and RD, and metabolic interchange is especially reduced in patients not remitting in response to anti-TNF intervention[2]



Clustering strategies may provide the immunological foundation for understanding IBD heterogeneity[3]



UC1

<10% response (IFX)
13% response (VDZ)

High expression of IL-11, TNF, S100A8, TREM1, IL-8, BCL2A1, CYP26B1

High neutrophils infiltration and degranulation†
High cytokine signaling†

UC2

70% response (IFX)
60% response (VDZ)

High NOX1, NR3C2, PARM1

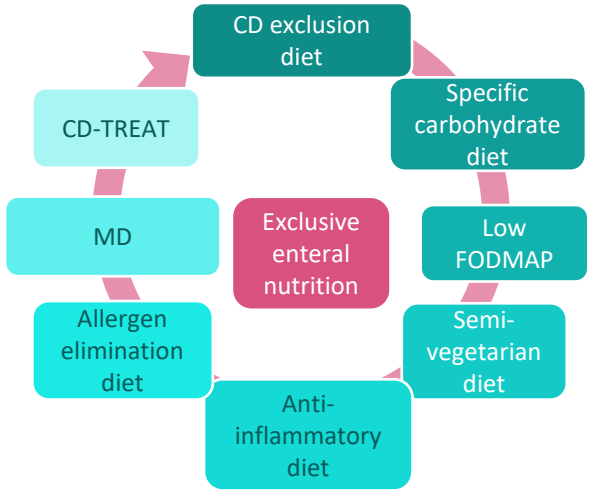
High B-cell activation†

*Asterisks indicate significantly different levels for the respective disease group and time compared with HCs (2-sided Mann Whitney U test, P<0.05).†Based on transcriptomic profiles (to be confirmed).
APRIL, A proliferation-inducing ligand; BCL2A1, B cell lymphoma 2 associated protein A1; CD, Crohn's disease; CSF, colony stimulating factor; CYP26B1, cytochrome P450 26B1; FDR, false discovery rate; HC, healthy control; IBD, inflammatory bowel disease; IFNG, interferon gamma; IFX, infliximab; IL, interleukin; mRNA, messenger ribonucleic acid; NOX1, nicotinamide adenine dinucleotide phosphate oxidase 1; NR3C2, nuclear receptor subfamily 3 group C member 2; OSM, oncostatin M; PARM1, prostate androgen- regulated mucin-like protein 1; RD, rheumatic diseases; S100A8, S100 calcium binding protein A8; TGFB, transforming growth factor beta; TNF, tumor necrosis factor; TREM, triggering receptor expressed on myeloid cells; UC, ulcerative colitis; VDZ, vedolizumab.

1. West NR, et al. Nat Med. 2017;23:579–89; 2. Aden K, et al. Gastroenterology. 2019;157:1279–92.e.11; 3. Selin K, et al. J Crohns Colitis. 2021;15:1959–73.

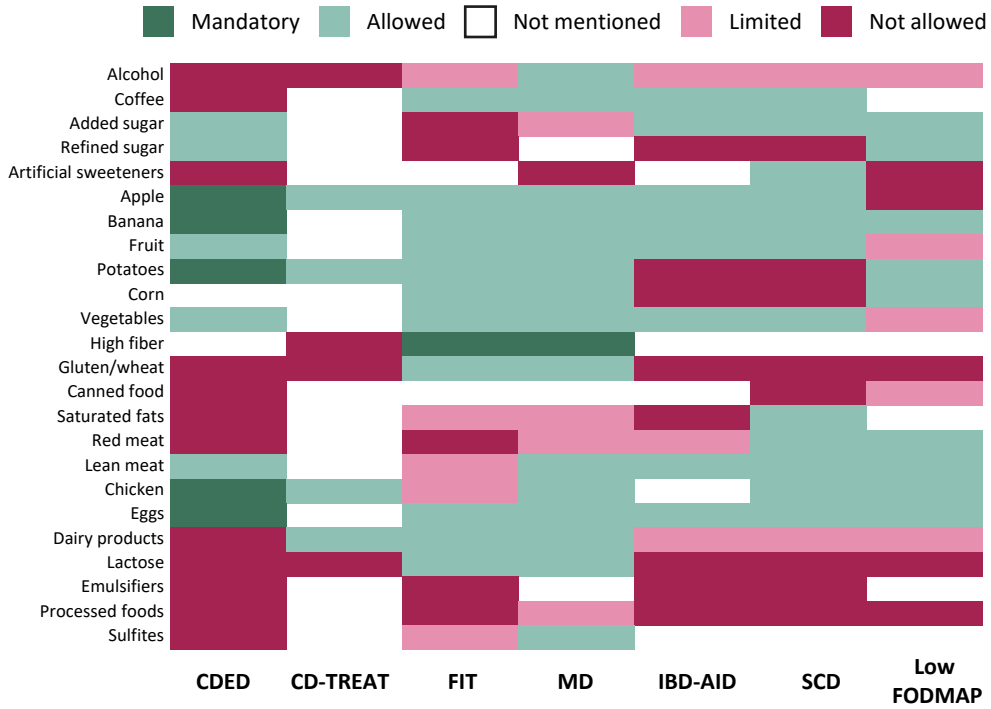
Precision Medicine: Selecting the Correct Diet

Dietary options combining food and partial enteral nutrition may help reduce inflammation in CD[1,2]

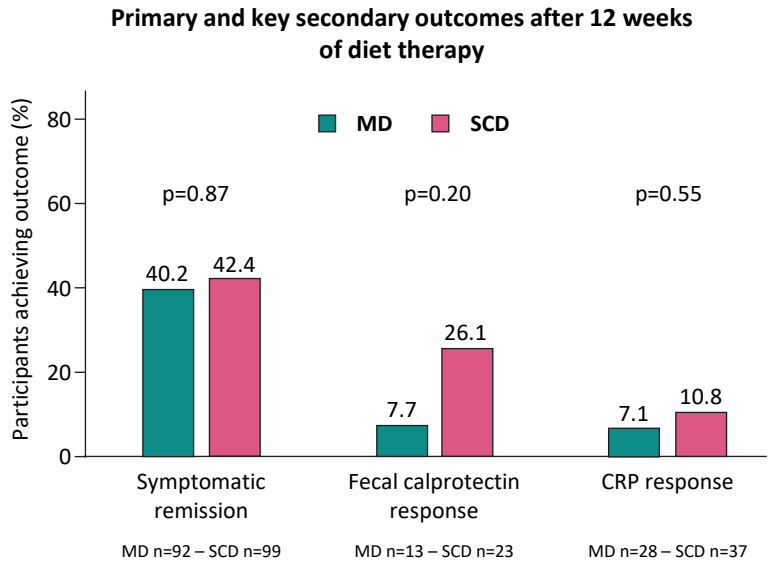


Levine et al. demonstrated that food, combined with partial enteral nutrition, can help reduce inflammation in CD[1]

There is huge variation and occasional disagreement regarding dietary ingredients that should be avoided in CD[2]



Due to the ease of following the MD and associated health benefits, patients with mild-to-moderate CD may prefer the MD vs the SCD[3]



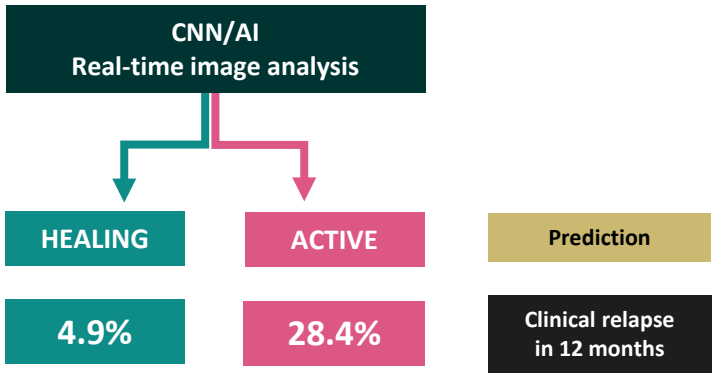
CD, Crohn's disease; CD-TREAT, Crohn's disease treatment-with-eating diet; CDED, Crohn's disease exclusion diet; CRP, C-reactive protein; FIT, food influence on the intestinal microbiota diet; FODMAP, fermentable oligosaccharide, disaccharide, monosaccharide, and polyols diet; IBD-AID, inflammatory bowel disease anti-inflammatory diet; MD, Mediterranean diet; SCD, specific carbohydrate diet.

1. Levine A, et al. Gastroenterology. 2019;157:440–50.e8; 2. Sabino J, et al. Gastroenterology. 2019;157:295–7; 3. Lewis JD, et al. Gastroenterology. 2021;161:837–52.e9.

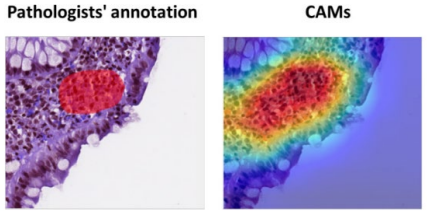
Precision: Monitoring Individual Response

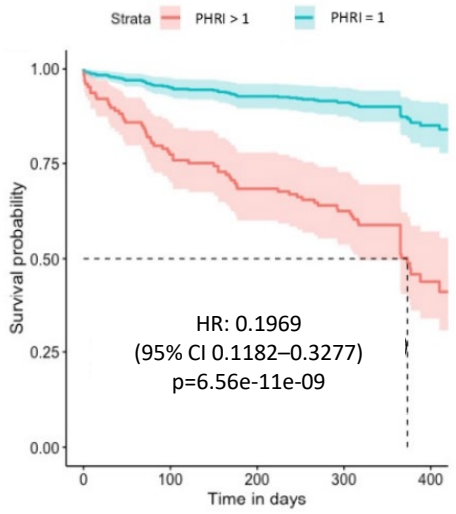
Precision Medicine: Tailoring Management During Remission

Real-time AI-analyzed endocytoscopy*[1]

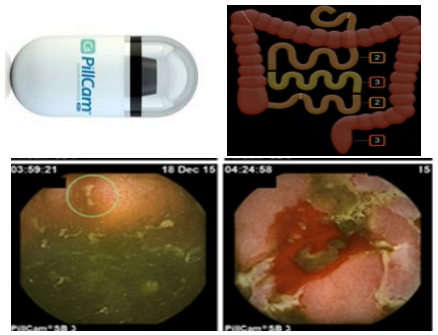


PICaSSO virtual chromoendoscopy index[2]

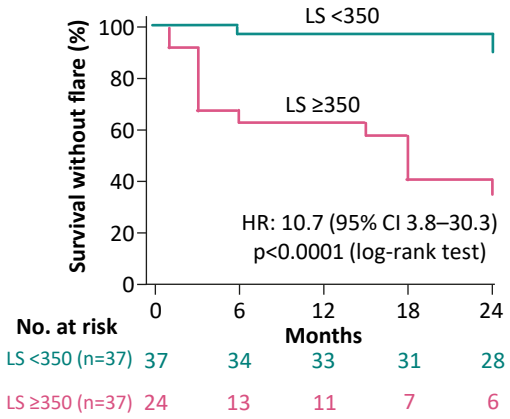




Capsule endoscopy monitoring†[3]



KM analysis of survival without disease flare among pts with a LS ≥350 at baseline vs LS <350



No. at risk					
LS <350 (n=37)	37	34	33	31	28
LS ≥350 (n=37)	24	13	11	7	6

Home passive monitoring: The future*[4]

Wearable device type most willing to wear in routine care

Device type	%
Smart watch	83.4
Wrist band	81.5
Smart jewelry	26.8
E-tattoo	24.4
Sensor patches	18.5
Clip on sensors	16.9
Smart strap	12.9
Headset/earbuds	11.0
Smart clothing/apparel	8.6
Foot/hand worn	5.6
Smart eyewear	4.6

Clip on sensor

*Images obtained via Shutterstock. †PillCam™ is a trademark of Medtronic.

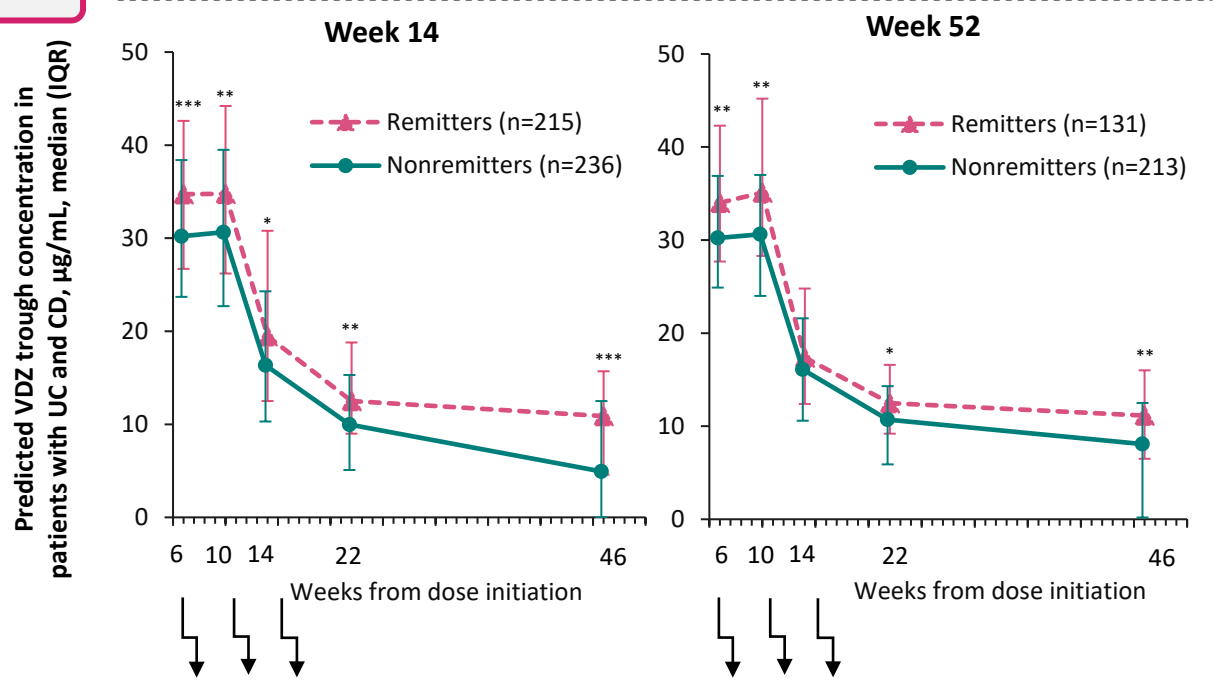
AI, artificial intelligence; CAM, class activation map; CI, confidence interval; CNN, convolutional neural network; HR, hazard ratio; KM, Kaplan–Meier; LS, Lewis score; PICaSSO, Paddington International virtual ChromoendoScopy ScOre; PHRI, PICaSSO Histologic Remission Index; pts, patients.

1. Maeda Y, et al. Gastrointest Endosc. 2022;95:747–56.e2; 2. Gui X, et al. Gut. 2022;71:889–98; 3. Ben-Horin S, et al. Lancet Gastroenterol Hepatol. 2019;4:519–28; 4. Hirten RP, et al. Dig Dis Sci. 2021;66:1836–44.

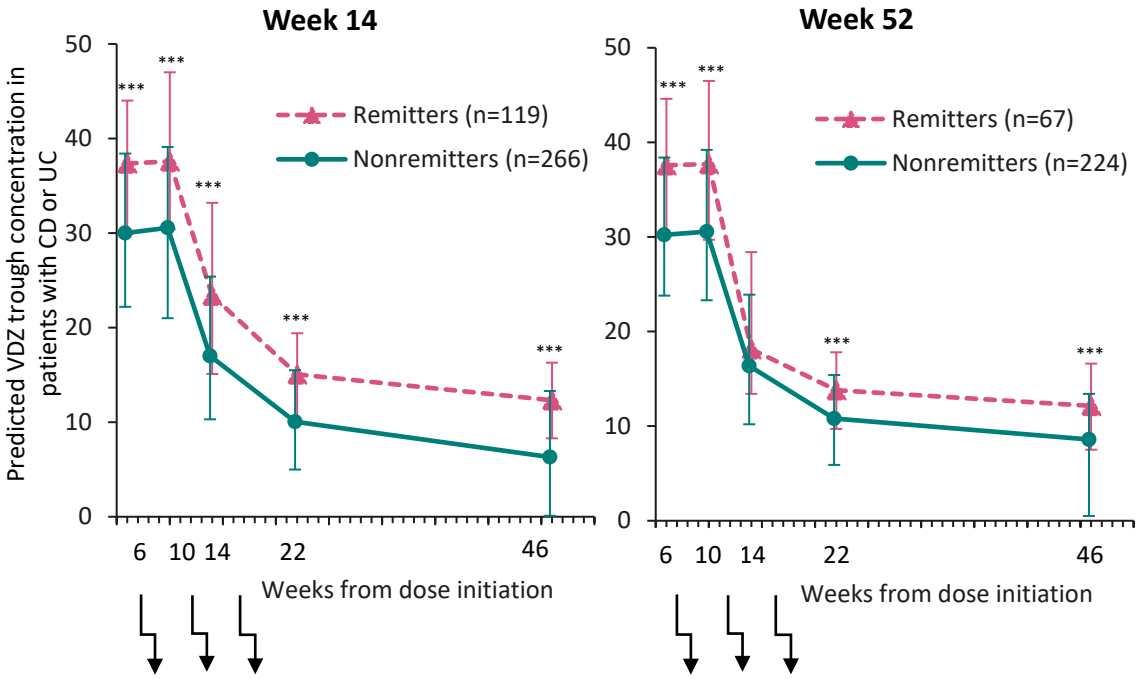
Exposure-Response Relationships Between Serum Vedolizumab Levels and Clinical Outcomes in Patients With IBD

ERELATE

Clinical remission



Deep remission



	Clinical remission						Deep remission					
	Week 14			Week 52			Week 14			Week 52		
Predicted VDZ exposure threshold, µg/ml	31.0	32.1	21.8	32.0	36.5	16.7	30.7	32.1	21.1	32.9	32.7	9.4

Positive exposure-response relationships between predicted VDZ serum concentrations and clinically important outcomes in real-world data of patients with IBD suggest that drug concentrations early in therapy may predict treatment outcomes

assessment was not available.

AUC, area under the curve; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CRP, C-reactive protein; ERR, exposure-response relationship; HBI, Harvey-Bradshaw Index; IBD, inflammatory bowel disease; IQR, interquartile range; MCES, Mayo Clinic Endoscopic Subscore; PGA, physician global assessment; PK, pharmacokinetic; pMCS, partial Mayo Clinic score; ROC, receiver operating characteristic; UC, ulcerative colitis; VDZ, vedolizumab.

Vande Casteele N, et al. Aliment Pharmacol Ther. 2022;56:463–76.

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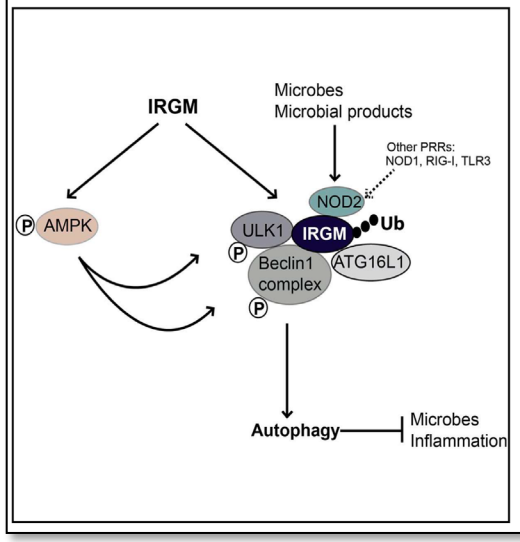
Precision Medicine for Predicting Safety Outcomes

Specific Gene Variants are Associated With Susceptibility to Tuberculosis[1–3]

Molecular Cell

IRGM Governs the Core Autophagy Machinery to Conduct Antimicrobial Defense

Graphical Abstract



Authors

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Correspondence

schauhan1@salud.unm.edu (S.C.), vderetic@salud.unm.edu (V.D.)

In Brief

Chauhan et al. show that human IRGM, a risk factor in Crohn's disease and tuberculosis, organizes the core autophagy machinery. IRGM furthermore links autophagy apparatus with innate immunity sensors. This provides an explanation for how this factor with a hitherto mysterious mechanism of action works in autophagy.

OPEN ACCESS Freely available online

PLoS PATHOGENS

Autophagy Gene Variant *IRGM* −261T Contributes to Protection from Tuberculosis Caused by *Mycobacterium tuberculosis* but Not by *M. africanum* Strains

Christopher D. Intemann[1,2☯], Thorsten Thye[1,2☯], Stefan Niemann[3☯], Edmund N. L. Browne[4], Margaret Amanua Chinbuah[5], Anthony Enimil[6,7], John Gyapong[5], Ivy Osei[5], Ellis Owusu-Dabo[4,7], Susanne Helm[8], Sabine Rüsch-Gerdes[3], Rolf D. Horstmann[1], Christian G. Meyer[1]*

The Scientific World Journal
Volume 2012, Article ID 950801, 5 pages
doi:10.1100/2012/950801

The ScientificWorldJOURNAL

Clinical Study

Association of IRGM Polymorphisms and Susceptibility to Pulmonary Tuberculosis in Zahedan, Southeast Iran

IRGM, immunity-related guanosine triphosphatase family M protein.

1. Chauhan S, et al. Mol Cell. 2015;58:507–21; 2. Intemann CD, et al. PLoS Pathog. 2009;5:e1000577; 3. Bahari G, et al. ScientificWorldJournal. 2012;2012:950801.

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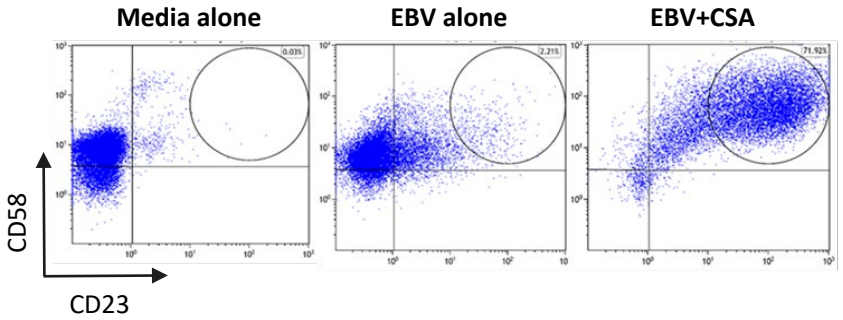
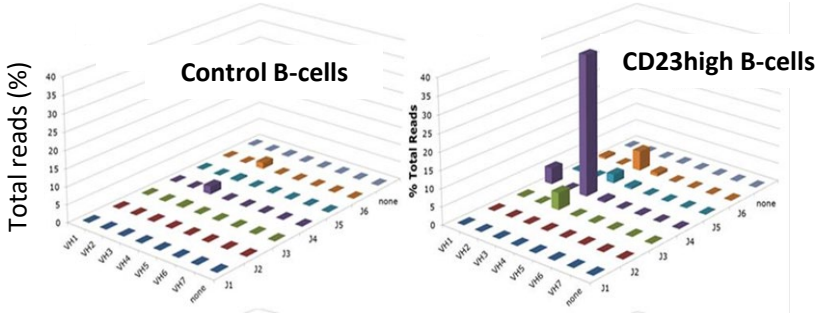
First Steps in Precision Medication–AE–Host Interaction?

EBV-infected B-cells undergo lymphomatous transformation when cultured with CSA or anti-TNF, but not with VDZ

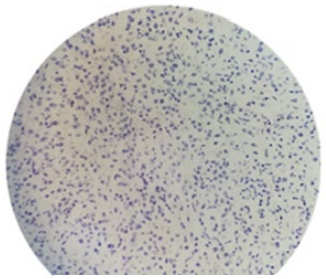
EBV+CSA causes expansion of CD23^{hi}/CD58^{+} B-cells



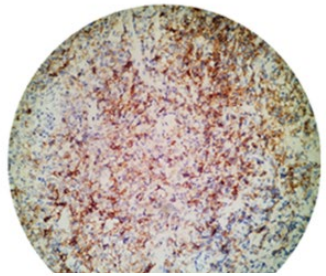
Expanded CD23^{hi} B-cells are oligo-/monoclonal



Immunohistochemistry staining for CD23 in biopsies obtained from PTLD-associated masses in two EBV-positive kidney transplant patients

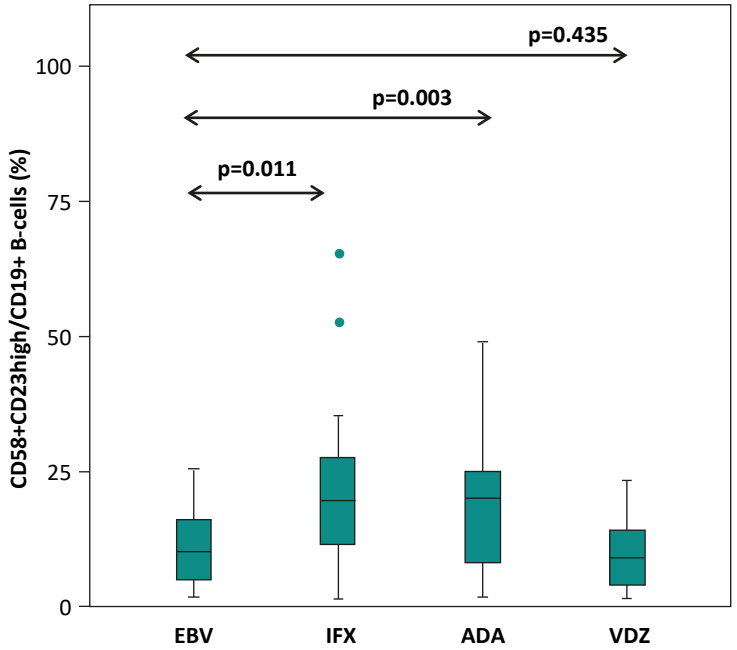


CD23-negative



CD23-positive

ADA/IFX, but not VDZ, cause expansion of transformed B-cells



ADA, adalimumab; AE, adverse event; CD, cluster of differentiation; CSA, cyclosporin A; EBV, Epstein–Barr virus; IFX, infliximab; PTLD, post-transplant lymphoproliferative disorder; TNF, tumor necrosis factor; VDZ, vedolizumab.

Levhar N, et al. Inflamm Bowel Dis. 2020;26:1330–9.

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Summary

- **Precision medicine** is key to increase the efficacy of CD therapy above the therapeutic ceiling
- The remaining **challenges** in precision medicine are:
  - Integrating multi-modality multi-omics prediction markers
  - Predicting the safety profile for the individual
  - Day-to-day responsive home-based therapy adaptation
  - Incorporating personal patient preferences

CD, Crohn's disease.

Precision medicine with precision tools in Crohn's disease: can we translate science into clinical practice?

United European Gastroenterology Week, October 8–11, 2022.

This symposium is intended for healthcare professionals only. A Takeda-organized symposium during UEG Week 2022.

Date of preparation: October 2022 I Job code: VV-MEDMAT-68167

Could precision medicine be an enabler of disease modification in CD?

Professor Stefan Schreiber
University Hospital Schleswig-Holstein, Kiel, Germany

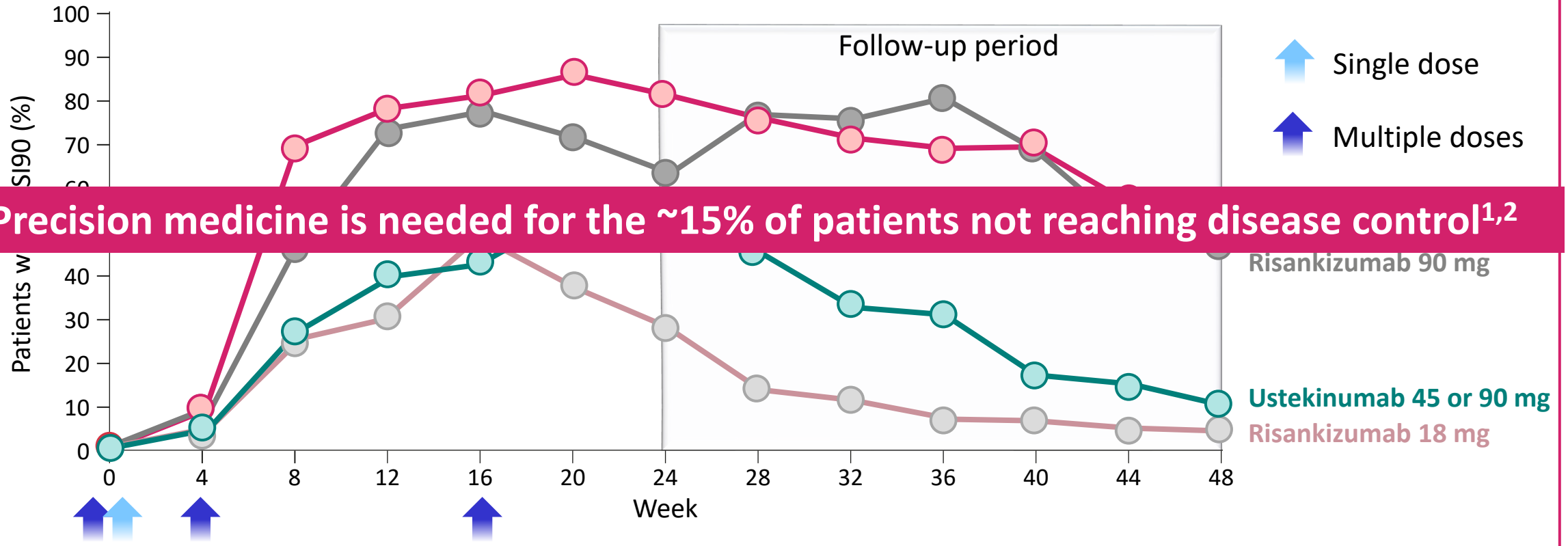
CD, Crohn's disease.

Disclosures

- Personal fees were received from AbbVie, Amgen, Arena, Biogen, Bristol Meyers Squibb, Celgene, Celltrion, Falk, Ferring, Fresenius Kabi, Galapagos, Gilead, IMAB, Janssen, Lilly, MSD, Mylan, Novartis, Pfizer, Protagonist, Provention Bio, Roche, Sandoz/Hexal, Shire, Takeda, and Theravance
- Honorarium was provided for this activity by Takeda

For Whom do we Need Precision Medicine?

Psoriasis patients with a decrease of 90% or more in PASI when treated with risankizumab or ustekinumab



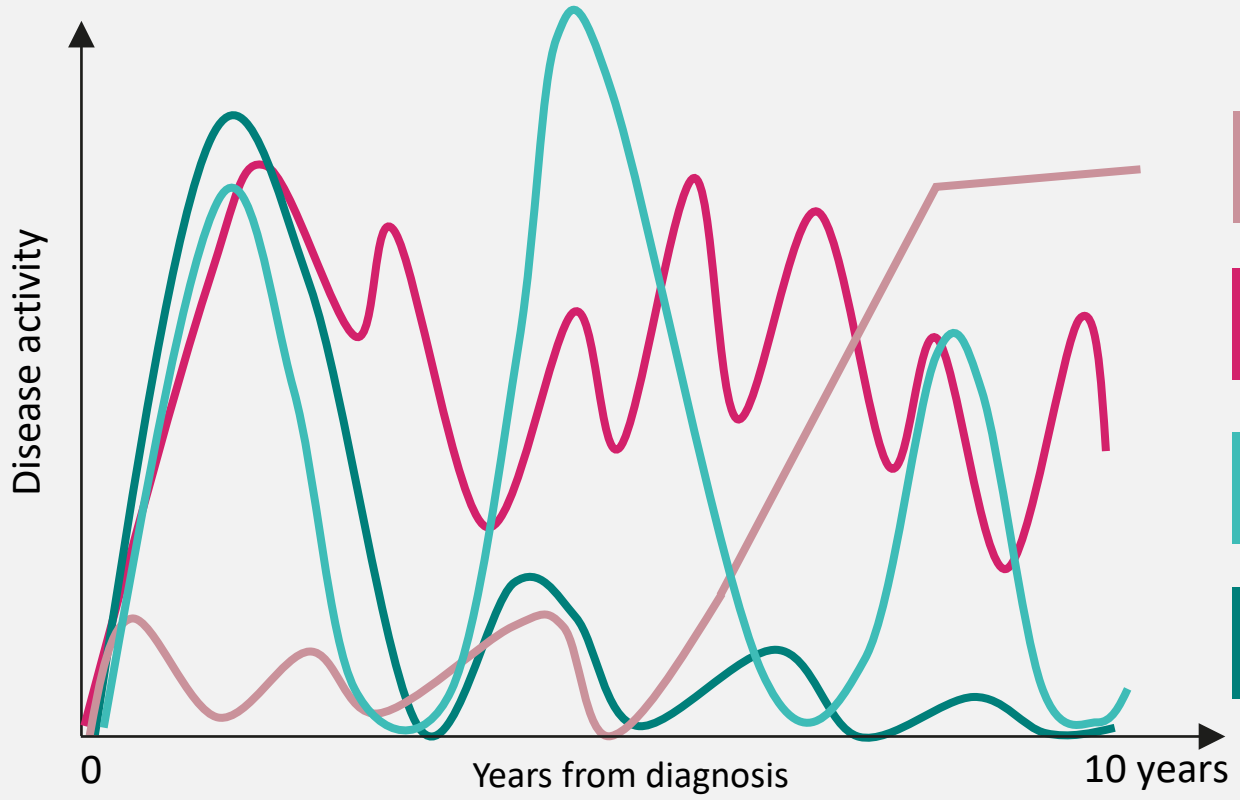
Precision medicine is needed for the ~15% of patients not reaching disease control[1,2]

PASI, Psoriasis Area Severity Index; PASI90, decrease in psoriasis area severity index of ≥90%.

Adapted from: Papp KA, et al. N Engl J Med. 2017;376:1551–60. 1. Sands BE, et al. ECCO 2022; Abstract OP36; 2. Di Giuseppe R, et al. ECCO 2022; Abstract DOP77.

Crohn's Disease is a Progressive Disease

Clinical course of CD over 10 years' follow-up (N=197)*



- **3% (n=6)** Increase in symptom severity
- **19% (n=37)** Chronic continuous symptoms
- **32% (n=63)** Chronic relapsing symptoms
- **43% (n=85)** Decrease in symptom severity

>50% of all CD patients have ongoing disease activity

*Data for 6 patients (3%) were missing.
CD, Crohn's disease.
Adapted from: Solberg IC, et al. Clin Gastroenterol Hepatol. 2007;5:1430–38.

Today: How do we Choose Appropriate Therapies for Patients Developing Complex Courses of IBD?

Patient molecular profile/ drug companion marker

Precision medicine[1]

Comparative effectiveness for gut healing

- Disease location
- Disease behavior
- Type and extent of lesions

Comparative effectiveness for PROs

- Intestinal symptoms
- Extra-intestinal manifestations
- General well being

Treat-to-target[2]

PATIENT PRIORITIES[3]

Comparative efficacy/safety/tolerance

Patient preference/lifestyle/ease of administration

A precision medicine approach, taking into account the **genetic, biological, clinical, and environmental features** of CD, facilitates prediction of the likely course of the disease and the optimum course of management[4]

CD, Crohn's disease; IBD, inflammatory bowel disease; PRO, patient-reported outcome.

1. Seyed Tabib NS, et al. Gut. 2020;69:1520–32; 2. Peyrin-Biroulet L, et al. Am J Gastroenterol. 2015;110:1324–38; 3. Almario CV, et al. Am J Gastroenterol. 2018;113:58–71;
4. Lamb CA, et al. Gastroenterology. 2022;162:1525–42.

Precision Medicine in CD: Limitation of *Ex Ante* Biomarkers

Potential markers for **short-term** response to therapy:[1]

- IL-1β/IL-22 axis
- Excessive neutrophil recruitment
- Accumulation of OSM and TREM1+ inflammatory monocytes
- Activation of IL13RA2+ stromal cells

Treating CD **early in the disease course with biologics** has been shown to be an effective method to **treat inflammation and improve clinical outcomes,** and may be **effective in preventing long-term complications of the disease**[2–7]

The ability to stratify low-risk patients to separate them from those who are at higher risk of rapid progression or CD complications is also needed[2]

Potential markers for **long-term** response to therapy:[1]

- ECM components
- Mesenchymal cell population
- ECM mechanical properties
- Immune phenotype change

CD, Crohn's disease; ECM, extracellular matrix; IL, interleukin; IL13RA2, interleukin-13 receptor alpha 2; OSM, oncostatin M; TREM, triggering receptor expressed on myeloid cells.

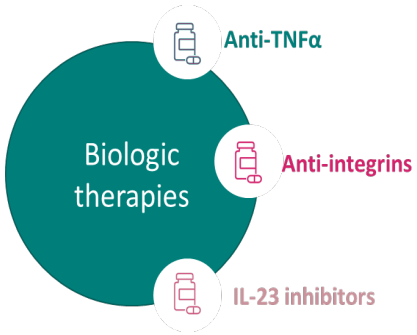
1. Lamb CA, et al. Gastroenterology. 2022;162:1525–42; 2. Siegel CA, et al. Aliment Pharmacol Ther. 2016;43:262–71; 3. Damião AOMC, et al. World J Gastroenterol. 2019;25:1142–57; 4. Cholapranee A, et al. Aliment Pharmacol Ther. 2017;45:1291–302; 5. Hamdeh S, et al. Inflamm Bowel Dis. 2020;26:1808–18; 6. Ungaro RC, et al. Aliment Pharmacol Ther. 2020;51:831–42; 7. Mastronardi M, et al. Front Med (Lausanne). 2019;6:234.

Despite Advancements in CD Therapy, There is Still a Risk of the "Therapeutic Ceiling Effect"

Factors contributing to the "therapeutic ceiling effect" include:[1–3]

- Delayed initial diagnosis
- Ineffective initial treatment
- Absence of risk stratification

Limitations of available treatments:

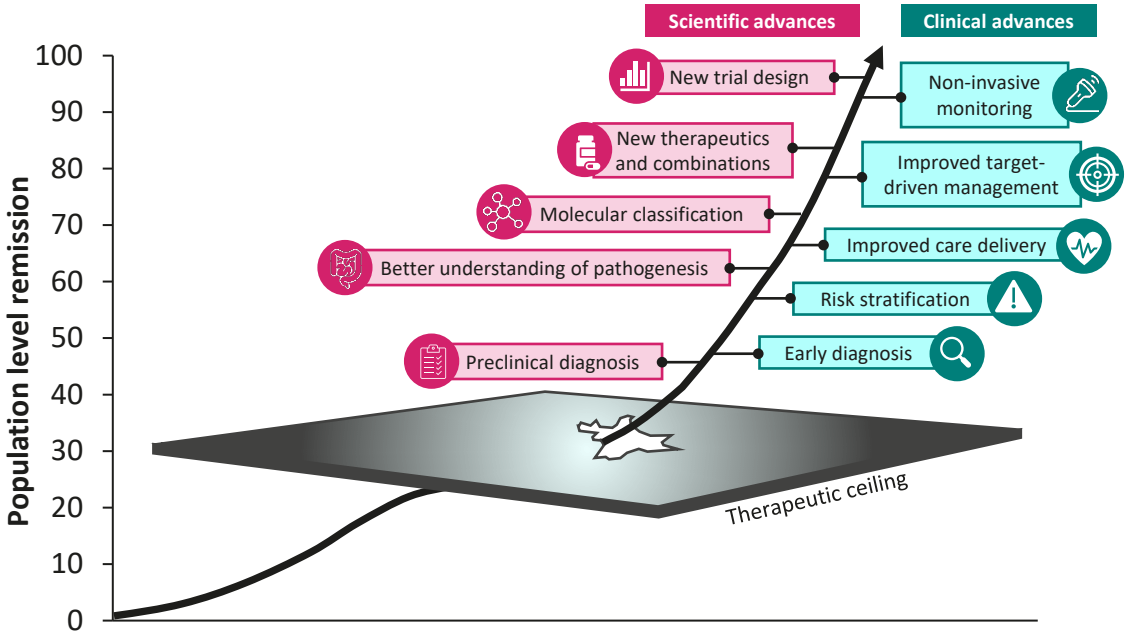


There are still significant rates of:[2–4]
Primary non-response, loss of response, and adverse reactions

Even though CD is generally managed therapeutically, a proportion of patients still require surgery[3]

Potentially only up to 50% of patients with CD are achieving clinical remission[2,5]

Breaking the therapeutic ceiling[1]



Population-level remission rates achieved with contemporary treatments are **at risk of plateauing**, leaving **considerable unmet need**. No single step will break through this ceiling; it will require **several separate but coordinated advances** to break the therapeutic ceiling[1]

CD, Crohn's disease; IL, interleukin; TNFα, tumor necrosis factor-α.

1. Raine T, Danese S. Gastroenterology. 2022;162:1507–11; 2. Peyrin-Biroulet L, et al. Nat Rev Gastroenterol Hepatol. 2013;10:345–51; 3. Guasch M, et al. J Gastroenterol Hepatol. 2020;35:2080–7; 4. Barber GE, et al. Am J Gastroenterol. 2016;111:1816–22; 5. Colombel JF, et al. N Engl J Med. 2010;362:1383–95.

CD Treatment Targets Have Evolved Over Time

Sequential treatment strategy beginning with a less effective treatment strategy with escalation to more highly effective treatments[1,2]

Identifying a predefined target, optimizing therapy, and regular monitoring to prevent adverse long-term outcomes[3]

The ultimate goal of treatment for long-term CD[5]

Step-up treatment approach → **Top-down approach** → **Treat-to-target** → **Early disease control** → **Disease modification**

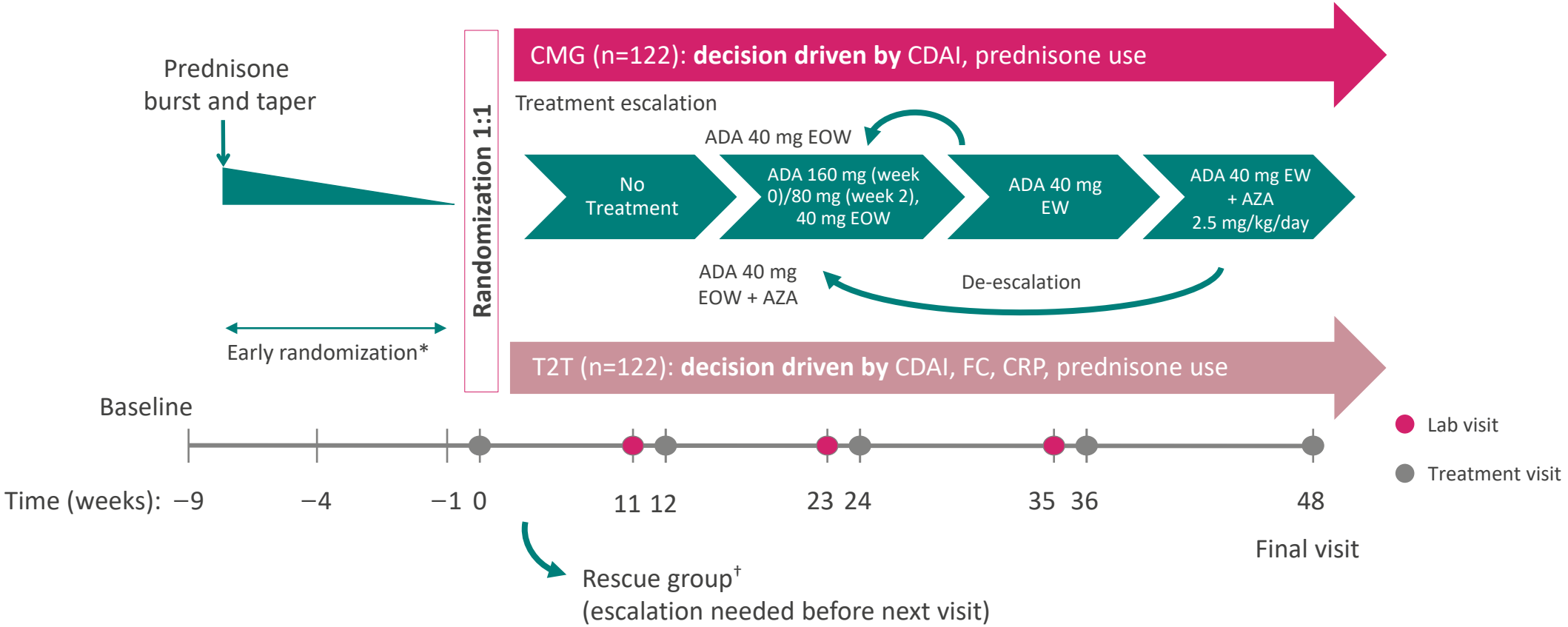
Early introduction of intensive therapies with the aim of interfering with the natural history of the disease[1]

Early treatment initiation with biologics may lead to complete disease control[4]

CD, Crohn's disease.

1. Peyrin-Biroulet L, et al. Gastroenterology. 2008;135:1420–2; 2. D'Haens G, et al. Lancet. 2008;371:660–67 ; 3. Agrawal M, Colombel JF. Gastrointest Endosc Clin N Am. 2019;29:421–36; 4. Danese S, et al. Gut. 2017;66:2179–87; 5. Le Berre C, et al. Gastroenterology. 2022;162:1424–38.

CALM: Study Design

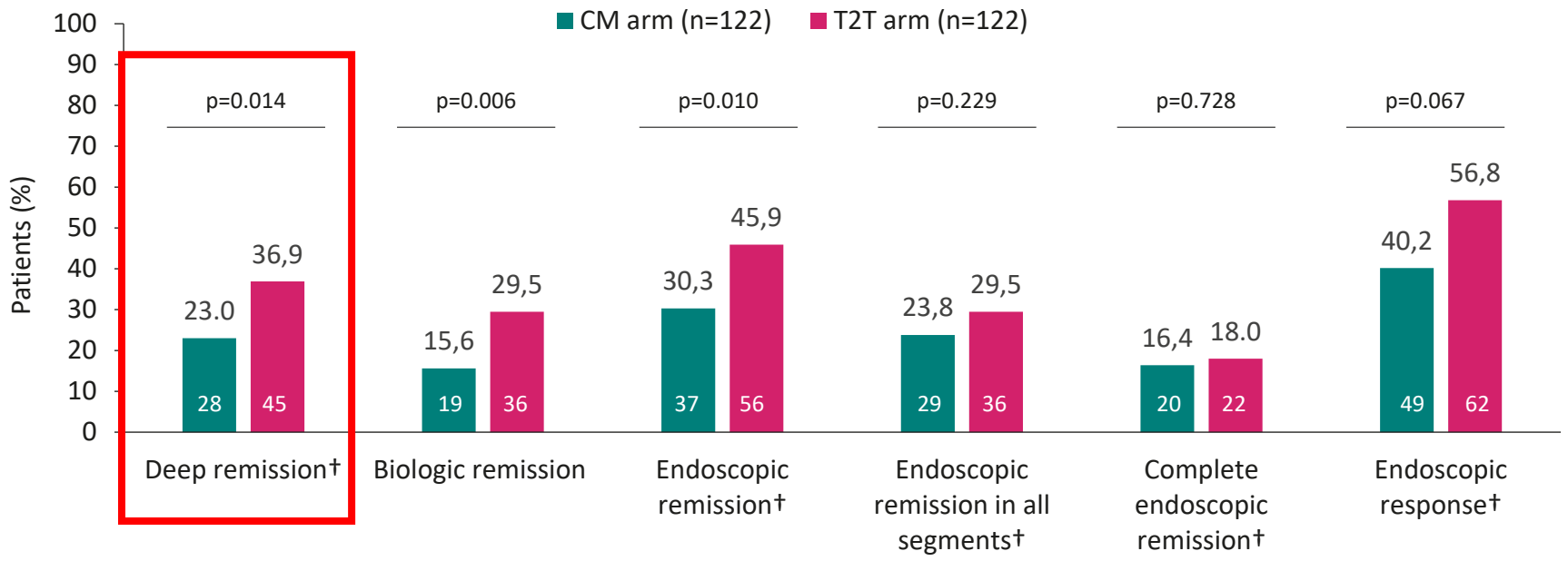


*CDAI >220 AND one of the following: steroid therapy for 4 weeks including 2 week of at least 40 mg prednisone or an equivalent dosage per day (or ≥9 mg budesonide/day), intolerant/contraindication for steroid therapy, best interest of the patient per investigator assessment. †CDAI >300 for 2 consecutive visits 7 days apart or per investigator discretion (elevated CRP/FC, ulceration and prednisone use taken into consideration); moved to T2T group.

ADA, adalimumab; AZA, azathioprine; CDAI, Crohn's Disease Activity Index; CMG, clinical management group; CRP, C-reactive protein; EOW, every other week; EW, every week; FC, fecal calprotectin; T2T, treat-to-target.

Adapted from: Colombel JF, et al. Lancet. 2017;390:2779–89.

CALM Results: Secondary Endpoints at 48 Weeks After Randomization*



Deep remission: CDAI <150, discontinuation from steroids at least 8 weeks, CDEIS <4 and no deep ulcerations and absence of draining fistula
Biologic remission: CRP <5 mg/L, FC <250 µg/g, and CDEIS <4
Endoscopic remission: CDEIS <4

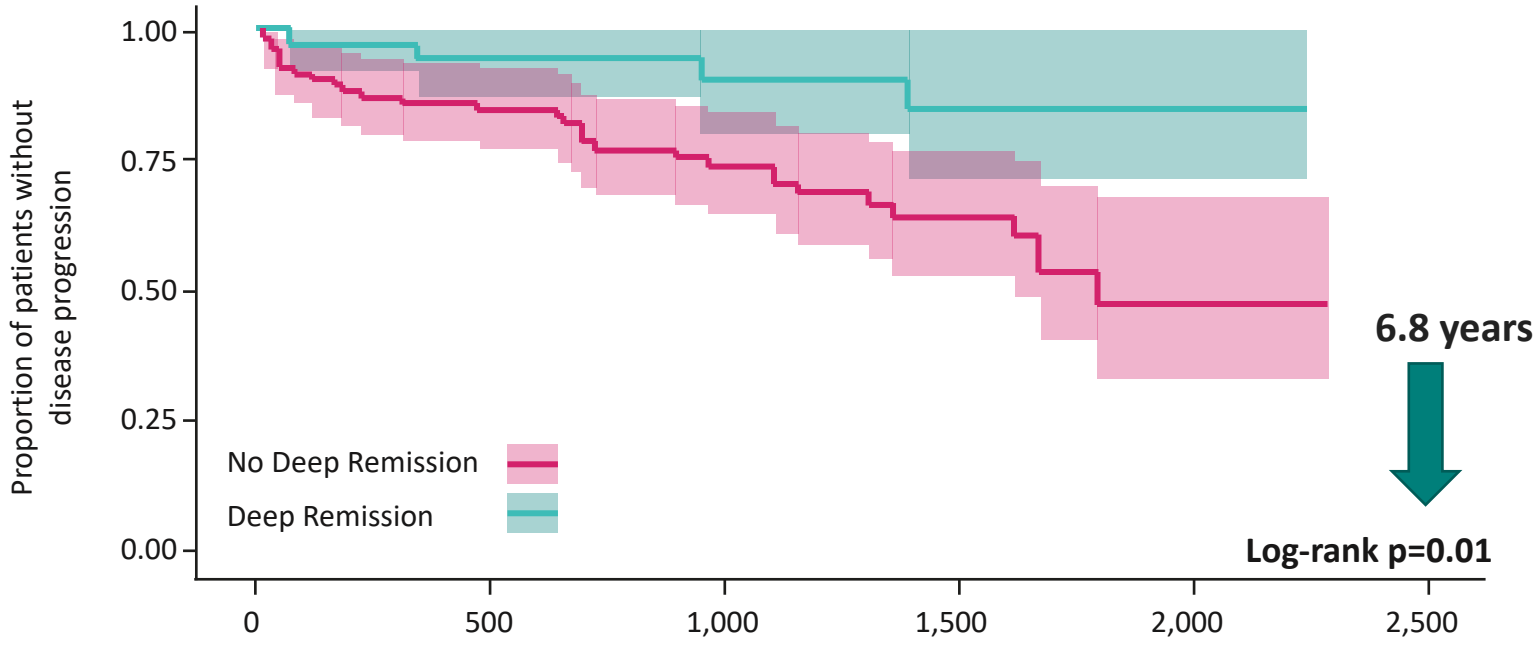
Endoscopic remission in all segments: Overall CDEIS <4 and CDEIS <4 in every segment
Complete endoscopic remission: CDEIS=0
Endoscopic response: CDEIS decrease >5 points

*Cochran–Mantel–Haenszel test stratified by smoking status (yes/no) and weight (<70/≥70 kg) at screening. †Endoscopic scoring is based on site read. NRI analysis.
CDAI, Crohn's Disease Activity Index; CDEIS, Crohn's Disease Endoscopic Index of Severity; CM, clinical management; CRP, C-reactive protein; FC, fecal calprotectin; NRI, nonresponder imputation; T2T, treat-to-target.
Colombel JF, et al. Lancet. 2017;390:2779–89.

Deep Remission is Associated With Lower Risk of Disease Progression in Early Crohn's Disease Patients

Deep remission was associated with an **81% decrease** in risk of adverse outcomes over a median of **3 years (range, 0.05–6.26)†**

Disease progression* based on endoscopic remission in the CALM study

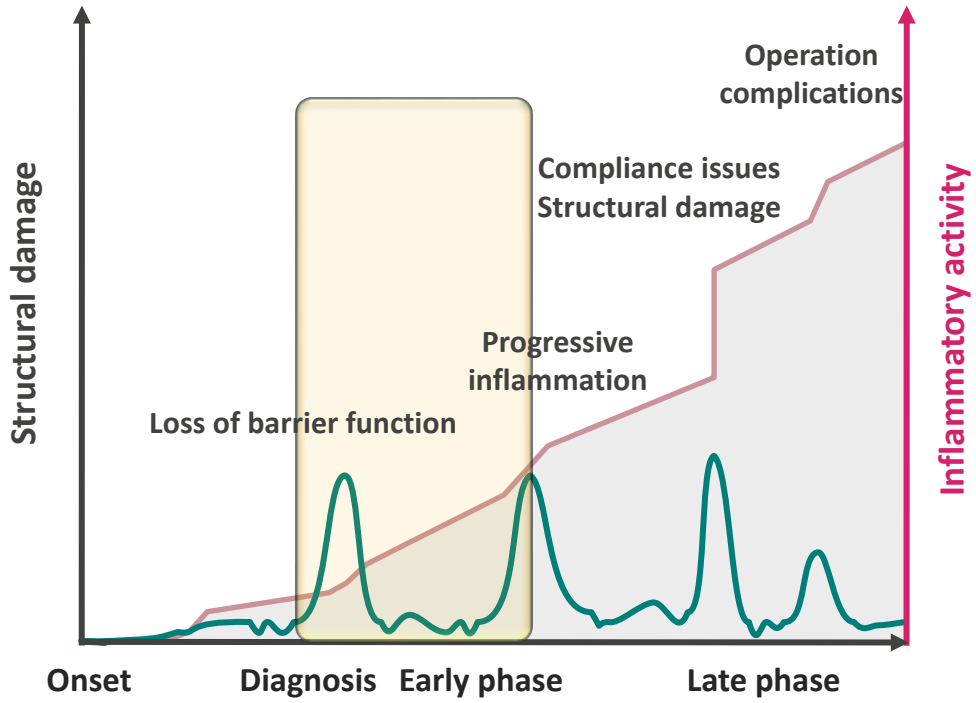


Number at risk:						
No deep remission	86	70	46	21	2	0
Deep remission	36	32	19	12	2	0

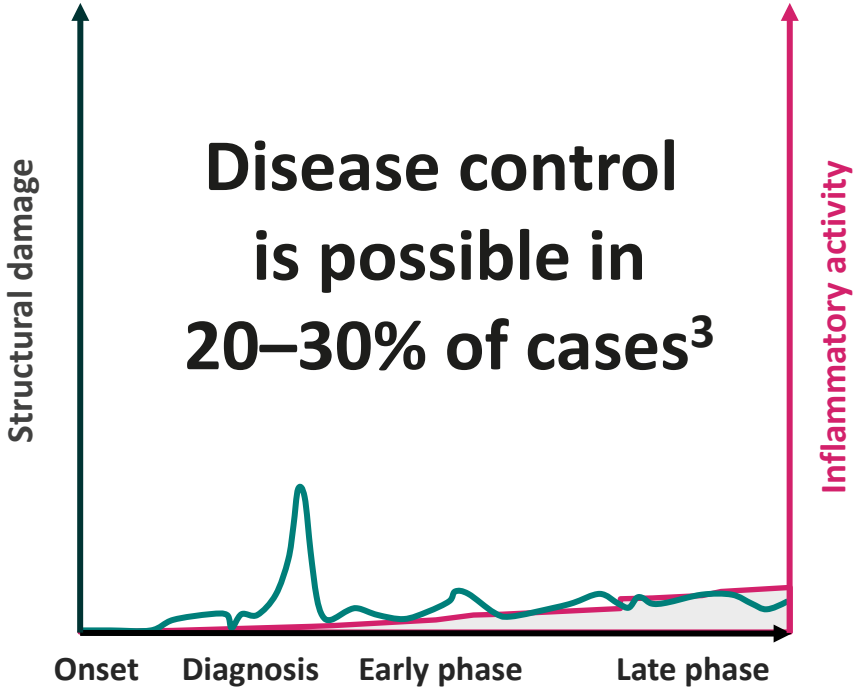
*Disease progression was defined as any major adverse outcome: composite of new internal fistula/abscess, stricture, perianal fistula/abscess, CD hospitalization, or CD surgery since end of the CALM study. †Deep remission was defined as CDEIS <4 with no deep ulcerations or steroid treatment for 8 or more weeks.
CD, Crohn's disease; CDEIS, Crohn's Disease Endoscopic Index of Severity.
Ungaro RC, et al. Gastroenterology. 2020;159:139–47.

Use the “Window of Opportunity”

Chronic inflammatory activity leading to structural damage[1,2]



Early “T2T” reduces/controls inflammation and prevents structural damage[2]



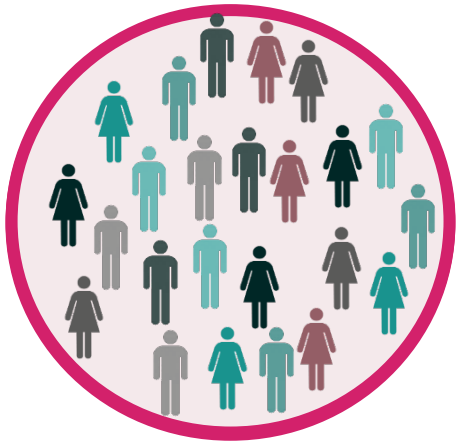
T2T, treat-to-target.

Adapted from: 1. Pariente B, et al. Inflamm Bowel Dis. 2011;17:1415–22; 2. Colombel JF, et al. Gastroenterology. 2017;152:351–61.e5; 3. Sands BE, et al. Presented at: European Crohn’s and Colitis Organisation; February 16–19, 2022; Virtual.

Sub-Segmenting Patients by Therapy Response

***Ex post* prediction – adapted choice algorithm through impact of targeted therapies on disease pathophysiology**

Therapy with targeted MoA



Drug response algorithm

Apply algorithm

Right choice for first treatment

Drug A

Drug B

Drug C

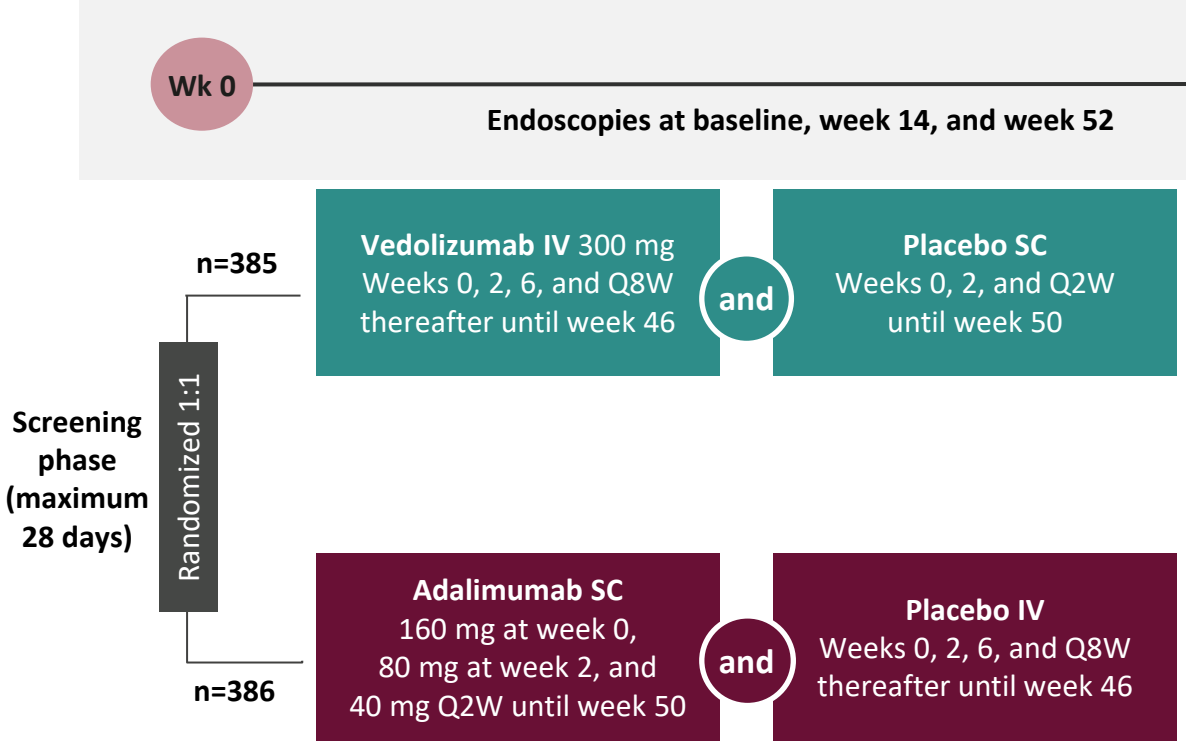
Drug D

Slide is based on the speaker's clinical experience.
MoA, mechanism of action.

Spotlight on Anti-Integrins: VARSITY Trial Study Design

VARSITY

Phase 3b randomized, double-blind, double-dummy, multicenter, active-controlled study in moderate-to-severe UC[1]



Primary endpoint

- Proportion of subjects achieving **clinical remission** (defined as a complete Mayo score of ≤2 points and no individual subscore >1 point) at week 52

Secondary endpoints

- Proportion of subjects achieving **mucosal healing** (defined as a Mayo endoscopic subscore ≤1 point) at week 52
- Proportion of subjects using oral corticosteroids at baseline who **have discontinued corticosteroids** and are in clinical remission at week 52

Endoscopic improvement was defined as Mayo endoscopic subscore ≤1. Histologic improvement was defined as RHI <5. Histologic remission was defined as RHI <3 and Geboes score <2. Disease clearance was defined as clinical remission, endoscopic improvement, and histological remission.[1]

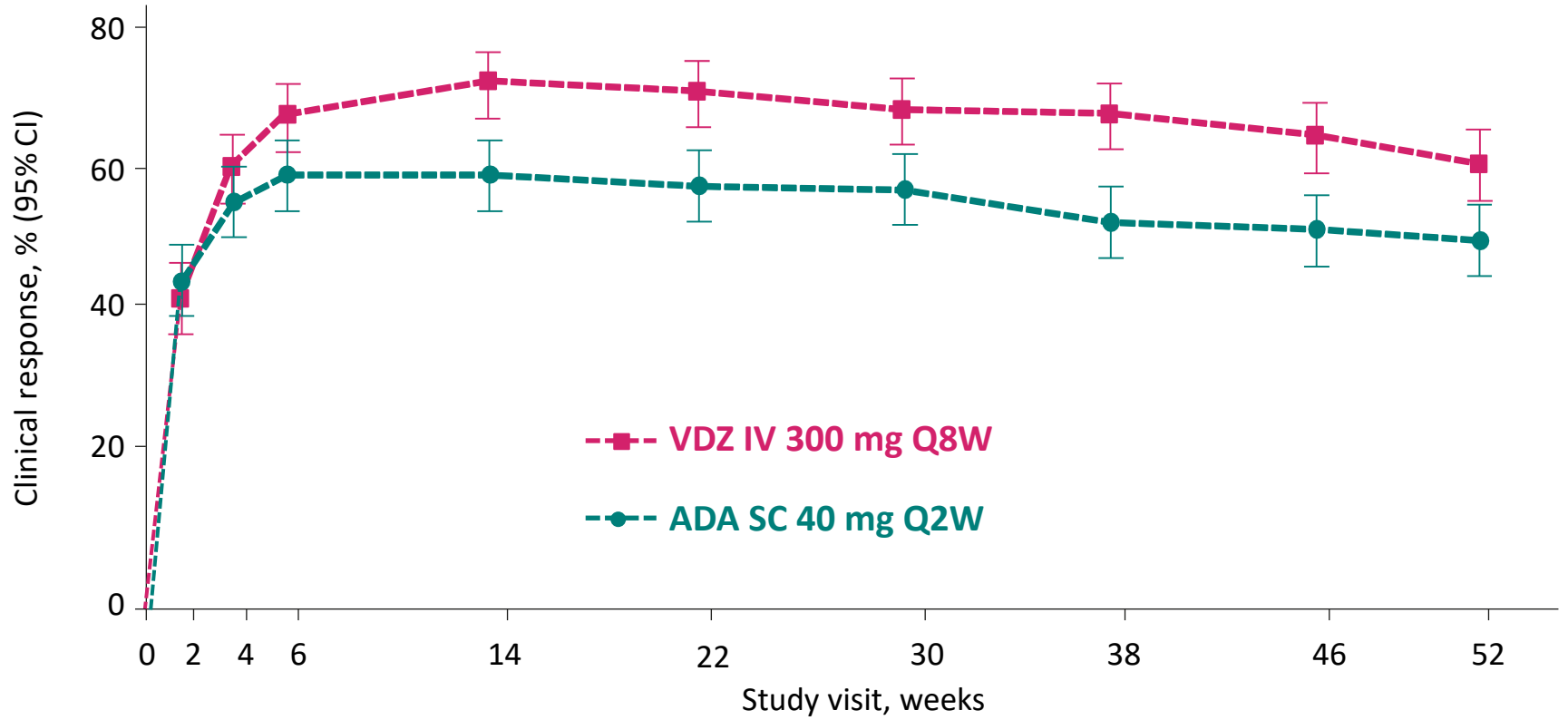
IV, intravenous; SC, subcutaneous; Q2W, once every 2 weeks; Q8W, once every 8 weeks; RHI, Robarts Histopathology Index; UC, ulcerative colitis; Wk, week.

1. Sands BE, et al. N Engl J Med. 2019;381:1215–26; 2. ClinicalTrials.gov. An efficacy and safety study of vedolizumab intravenous (IV) compared to adalimumab subcutaneous (SC) in participants with ulcerative colitis. Available from: https://clinicaltrials.gov/ct2/show/NCT02497469. Accessed October 2022.

VDZ is Superior to ADA in the VARSITY Head-to-Head Trial

VARSITY

Clinical response by change in partial Mayo score from baseline



Clinical response based on partial Mayo score: reduction in partial Mayo score of ≥2 points and ≥25% from baseline, with an accompanying decrease in rectal bleeding subscore of ≥1 point or absolute rectal bleeding subscore of ≤1 point and safety. Patients with missing data on clinical response status were considered non-responders.
ADA, adalimumab; CI, confidence interval; IV, intravenous; Q2W, every 2 weeks; Q8W, every 8 weeks; SC, subcutaneous; VDZ, vedolizumab.
Sands BE, et al. N Engl J Med. 2019;381:1215–26.

Early Modification of Inflammatory Burden Through Treatment With VDZ or ADA is Predictive of Long-Term Treatment Success in Patients With UC

VARSITY

Objective: to examine the utility of FCP, CRP, and albumin biomarkers for predicting clinical remission and disease control outcomes in patients with moderate-to-severe UC* treated with VDZ or ADA (N=769)

Study type: Phase 3b, randomized, multicenter study

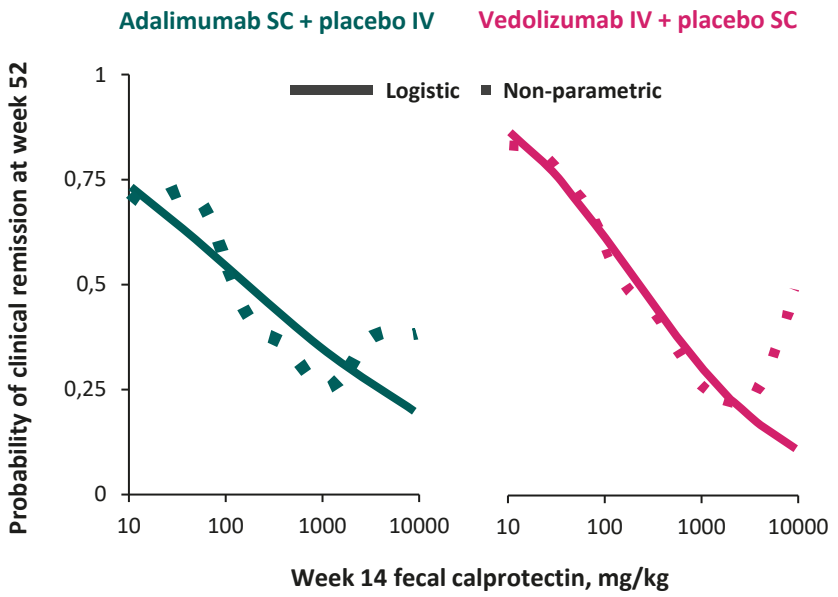
Patients were randomized 1:1 to receive:

- **n=383:*** VDZ IV at 300 mg at weeks 0, 2, and 6, and Q8W until week 46; or placebo SC at weeks 0 and 2 and Q2W until week 50

OR

- **n=386:** ADA SC at 160 mg at week 0, 80 mg at week 2, and 40 mg Q2W until week 50; or placebo IV at weeks 0, 2, and 6, and Q8W until week 46

Low vs high post-induction FCP levels are predictive of clinical remission† at week 52 for both therapies



The probability of clinical remission at week 52 in patients with week 14 FCP levels <100 µg/g was 76% for VDZ-treated and 70% for ADA-treated patients

The probability of achieving disease control at week 52 in patients with week 14 FCP levels <100 µg/g was 74% for VDZ-treated and 63% in ADA-treated patients

Patients with low-risk FCP (<100 µg/g) at week 14 had a greater chance of achieving clinical remission at week 52 than patients with high-risk FCP (VDZ 35%; ADA 33%)

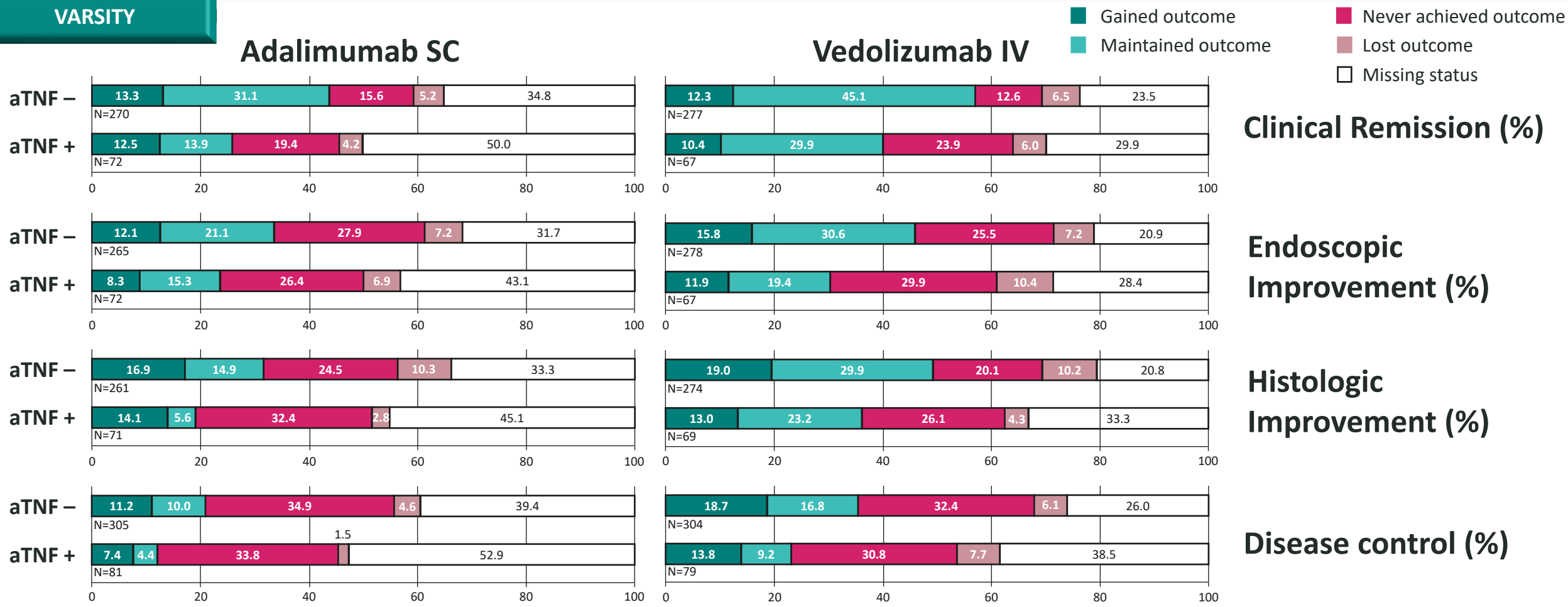
FCP concentrations <100 µg/g is correlated with achieving clinical remission at week 52 in patients with UC.
Week 14 FCP <100 µg/g can be a useful biomarker to predict whether individual patients will achieve long-term benefit from VDZ or ADA treatment at 1 year

*Includes two patients who were randomized but did not receive a dose of VDZ. †Defined as a complete Mayo score of ≤2 points and no individual subscore of >1 point at week 52.
ADA, adalimumab; CRP, C-reactive protein; FCP, fecal calprotectin; IV, intravenous; Q2W, every 2 weeks; Q8W, every 8 weeks; SC, subcutaneous; UC, ulcerative colitis; VDZ, vedolizumab.

Schreiber S, et al. Loftus EV, et al. Tu1452: Early Modification of Inflammatory Burden Through Treatment with Vedolizumab or Adalimumab Is Predictive of Long-Term Treatment Success in Patients with Ulcerative Colitis from the VARSITY Study. Gastroenterology. 2022;162(7):s-966.

Evolving Targets in UC – Disease CONTROL is the Ultimate Goal: VARSITY Study Post-Hoc Analysis

VARSITY



aTNF –, anti-tumor necrosis factor naive; aTNF +, anti-tumor necrosis factor experienced; UC, ulcerative colitis.

Loftus E, et al. S0664: Disease Control and Changes in Individual Treatment Outcomes from Week 14 To Week 52 With Vedolizumab or Adalimumab in Ulcerative Colitis: A VARSITY Trial Post-Hoc Analysis. The American Journal of Gastroenterology. 2020 Oct;115:S332–33.

Yet another problem – drug resistance

Challenges Associated With Anti-TNF-Treated CD Patients

VICTORY

Objective: to estimate the real-world effectiveness and safety of VDZ in adult patients with active moderate-to-severe CD (N=212)

Study type: retrospective cohort study

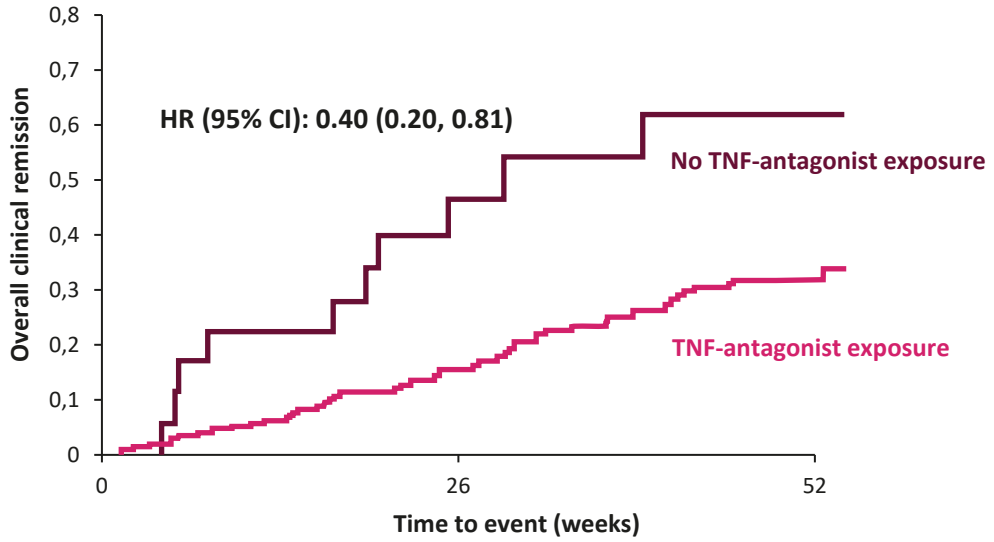
Data were collected from seven medical centers across the USA from May 2014 to December 2015, with a median follow-up period of 39 weeks (IQR: 25–53)

91% of patients included in this study had received **prior TNF-antagonist therapy**

Reasons for discontinuation included:

- Primary non-response: **22.5%**
- Loss of response without optimization: **15.4%**
- Loss of response despite optimization: **35.2%**
- Intolerance: **26.9%**

Cumulative rate of clinical remission for clinical predictors during VDZ maintenance therapy stratified by prior exposure to TNF antagonists vs TNF antagonist-naïve patients



Patients with prior TNF-antagonist exposure were less likely to achieve clinical remission and mucosal healing vs TNF-antagonist naïve patients

The effectiveness of VDZ was significantly influenced by prior TNF antagonist exposure and resulted in a reduction in treatment effectiveness in patients who had received prior TNF antagonist therapy vs TNF-naïve patients

CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; TNF, tumor necrosis factor; VDZ, vedolizumab.

Dulai PS, et al. Am J Gastroenterol. 2016;111:1147–55.

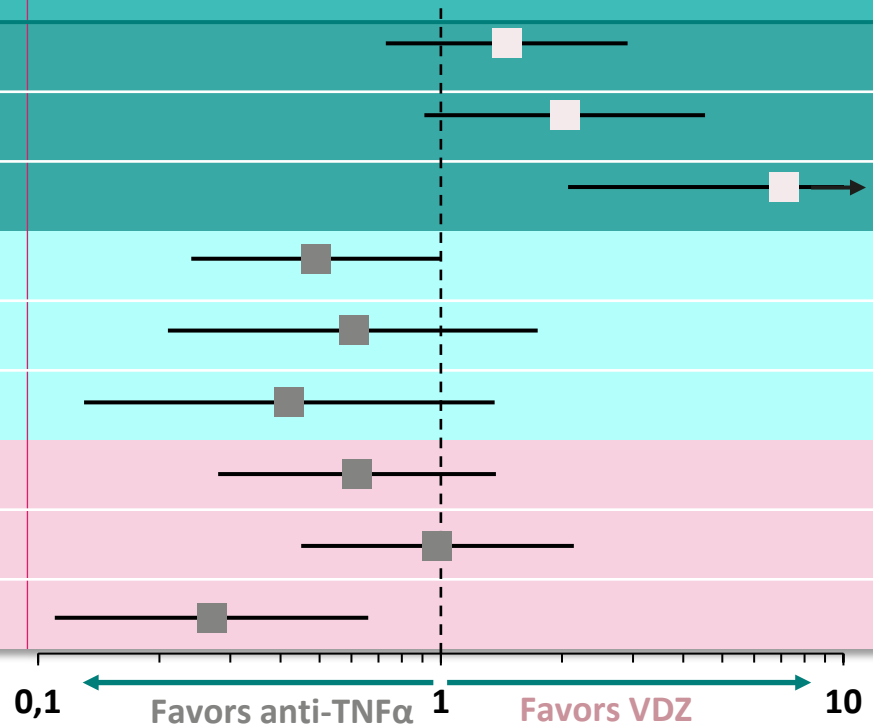
In Early CD (≤2 Years), VDZ Achieved Better Clinical Outcomes, Including Endoscopic Remission, Than Anti-TNF Therapy

Mean disease duration, y (SD): VDZ=12 (13); SC anti-TNF=6 (17); IFX=3 (10)
Anti–TNF-naïve: VDZ=9.3%; SC anti-TNF=43.0%; IFX=52.8%

VICTORY

Comparative effectiveness of VDZ and anti-TNF therapy stratified by disease duration (VDZ: 659; anti-TNF: 607 [SC anti-TNF: 302; IFX: 305])

DISEASE DURATION	OUTCOME	HR (95% CI)
≤2 years	Clinical remission	**1.46** (0.73–2.91)
	Endoscopic remission	**2.03** (0.91–4.53)
	Steroid-free clinical remission	**7.12** (2.07–24.49)
>2 to ≤5 years	Clinical remission	**0.49** (0.24–1.00)
	Endoscopic remission	**0.61** (0.21–1.74)
	Steroid-free clinical remission	**0.42** (0.13–1.36)
5 years	Clinical remission	**0.62** (0.28–1.37)
	Endoscopic remission	**0.98** (0.45–2.14)
	Steroid-free clinical remission	**0.27** (0.11–0.66)



Retrospective, observational cohort (May 2014–December 2017) propensity score-weighted comparison of VDZ vs anti-TNF antagonist therapy (infliximab, adalimumab, certolizumab) in CD. Retrospective review of a North American-based consortium registry. Steroid-free clinical remission limited to patients taking concomitant steroids at baseline. Endoscopic remission limited to patients with follow-up assessment of endoscopic disease activity (n=424 anti-TNF; n=413 VDZ). Endoscopic remission was defined as absence of ulcers/erosions.

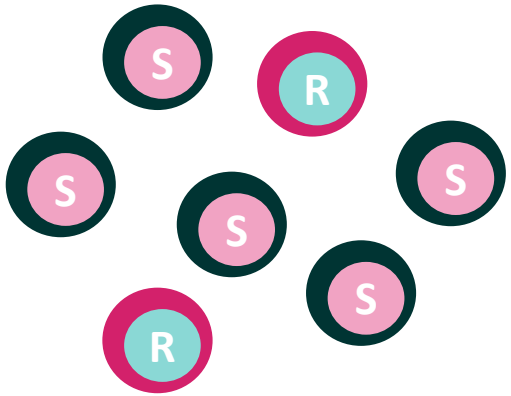
CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; IFX, infliximab; SC, subcutaneous; SD, standard deviation; TNF, tumor necrosis factor; VDZ, vedolizumab; y, years.

Bohm M, et al. Aliment Pharmacol Ther. 2020;52:669–81.

Takeda

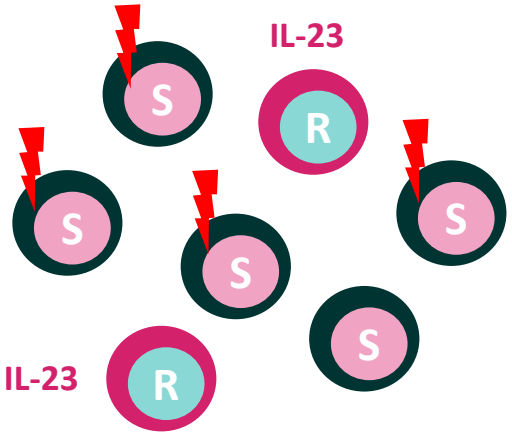
Drug Resistance in IBD – a Molecular Event? Overcome Anti-TNF Resistance Through Combination Therapy?

Immune T-cell infiltrate



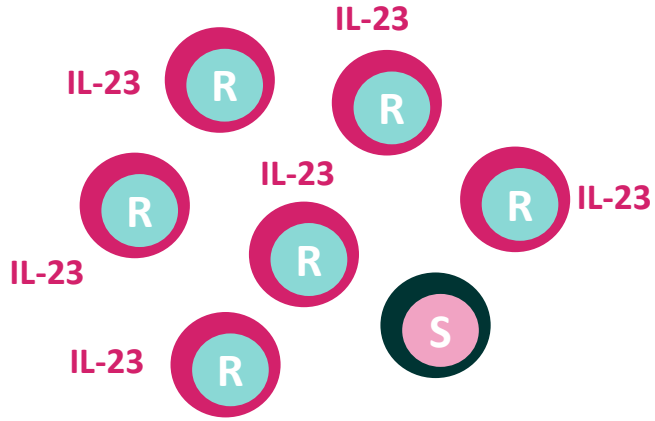
S: Anti–TNFα-sensitive T-cell
R: Anti–TNFα-resistant T-cell

Anti-TNFα therapy



- **Apoptosis induction**
- **Selection pressure**

IL-23 molecular resistance



- **Spread of IL-23R^{+} T-cells**
- **New immune phenotype**
- **Lack of response**

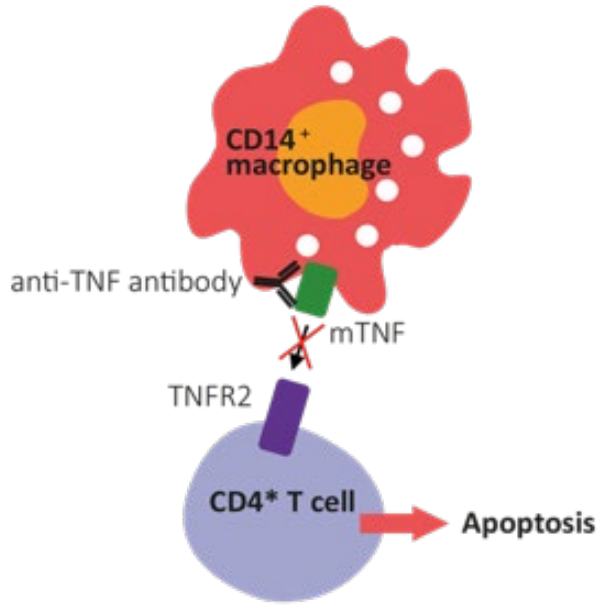
- Sequential, repetitive biological therapy could cause selection and expansion of resistant T-cells, leading to molecular resistance
- IL-23 may be a key driver of molecular resistance to anti-TNFα therapy

IBD, inflammatory bowel disease; IL, interleukin; IL-23R, interleukin-23 receptor; TNFα, tumor necrosis factor-alpha.
Adapted from: Atreya R, Neurath MF. Lancet Gastroenterol Hepatol. 2018;3:790–802.

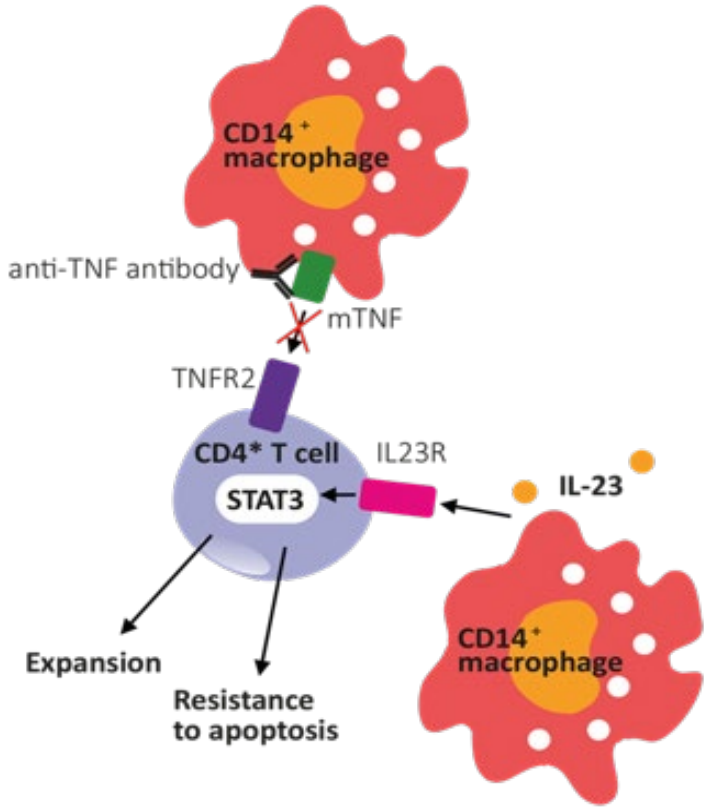
Takeda

IL-23 and Immune Cell Escape in Anti-TNF Therapy

CD responder to anti-TNF therapy



CD non-responder to anti-TNF therapy



CD, Crohn's disease; CD4, cluster of differentiation 4; CD14, cluster of differentiation 14; IL, interleukin; mTNF, membrane-associated tumor necrosis factor; STAT3, signal transducer and activator of transcription 3; TNF, tumor necrosis factor; TNFR2, tumor necrosis factor receptor-2.

Schmitt H, et al. Gut. 2019;68:814–28.

Combination Therapy With GUS Plus GOL May More Effectively Induce Clinical Response and Remission in Patients With UC vs Monotherapy Alone

VEGA

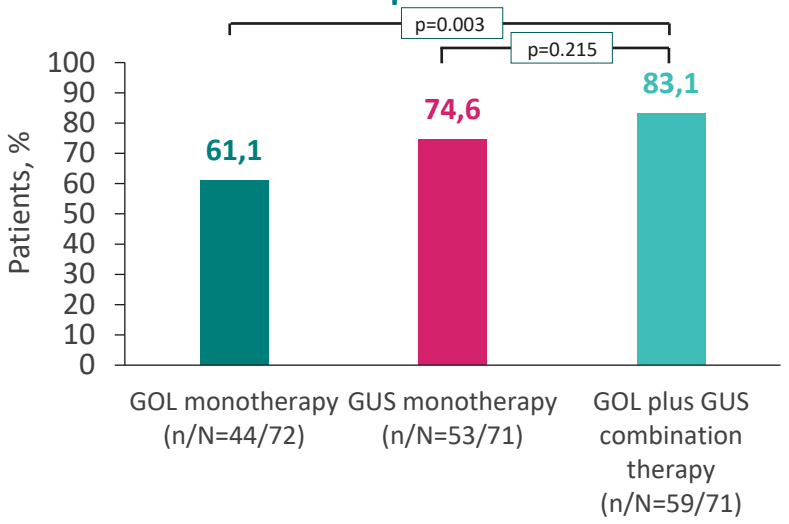
Objective: to evaluate the efficacy and safety of combination induction therapy with GUS and GOL vs GUS or GOL monotherapy in adults with moderately to severely active UC (N=214)*

Study type: Phase 2a, randomized, double-blind, active-controlled, parallel-group, multicenter study

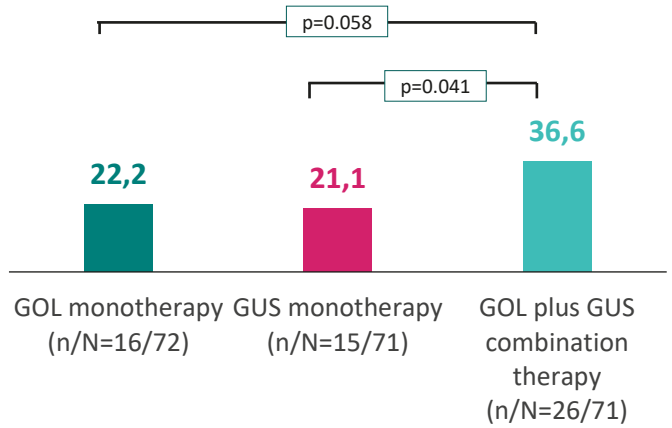
Patients were randomly assigned 1:1:1 to receive:

- **n=71:** GUS 200 mg IV at weeks 0, 4, and 8
- **n=72:** GOL 200 mg SC at week 0; 100 mg SC at weeks 2, 6, and 10
- **n=71:** combination with 200 mg GUS IV plus GOL SC 200 mg at week 0; GOL SC 100 mg at weeks 2, 6, and 10; GUS IV 200 mg at weeks 4 and 8

Clinical response† at week 12



Clinical remission‡ at week 12



Clinical remission by Mayo score, endoscopic improvement, histologic remission, both histologic remission and endoscopic improvement, and biomarker normalization (calprotectin, CRP) rates at week 12 were greater in the combination group vs GUS or GOL

AEs, SAEs, and infection rates were comparable among treatment groups

Combination induction treatment with GUS plus GOL more effectively induced clinical response, clinical remission, and endoscopic improvement at week 12 than either monotherapy alone

*Patients were naïve to TNFα antagonists and refractory or intolerant to conventional therapy. †Defined as a decrease from baseline in the Mayo score ≥30% and ≥3 point, with either a decrease in rectal bleeding subscore ≥1 or rectal bleeding subscore of 0 or 1. ‡Defined as Mayo score ≤2, with no individual subscore >1. AE, adverse event; CRP, C-reactive protein; GOL, golimumab; GUS, guselkumab; IV, intravenous; SAE, serious adverse event; SC, subcutaneous; TNFα, tumor necrosis factor-alpha; UC, ulcerative colitis.

Sands BE, et al. OP36: Efficacy and safety of combination induction therapy with guselkumab and golimumab in participants with moderately-to-severely active Ulcerative Colitis: Results through week 12 of a phase 2a randomized, double-blind, active-controlled, parallel-group, multicenter, proof-of-concept study. Journal of Crohn's and Colitis. 2022 Jan 1;16(Supplement_1):i042–3.

Summary

- "Treat-to-target" works as a mindset guiding patient management but falls too short if applied with only one therapeutic modality
- Selecting patients for "best fit" between MoA and individual pathophysiology
  - Modern targeted therapies lead to super-response and disease control, with response trajectories hidden within the general landmark estimates of response and remission
  - Carving out super-response and disease control requires first-line (early) exposure[1,2]
  - Mismatch between therapy and individual therapy nurtures chronic inflammation due to resistance mechanisms and other forms of attenuation[3]
- Precision medicine requires early change of therapy
  - Determine stopping rules for change of MoA
  - Develop sequencing algorithms through RCTs for educated first, second, and further choices
  - Combination therapy, if side effects are limited, may overcome some of the missing evidence guiding choice of therapies and may overcome resistance mechanisms[4]

Some of the content on this slide is based on the speaker's clinical experience.
MoA, mechanism of action; RCT, randomized controlled trial.

1. Pariente B, et al. Inflamm Bowel Dis. 2011;17:1415–22; 2. Colombel JF, et al. Gastroenterology. 2017;152:351–61; 3. Atreya R, Neurath MF. Lancet Gastroenterol Hepatol. 2018;3:790–802; 4. Sands BE, et al. OP36: Efficacy and safety of combination induction therapy with guselkumab and golimumab in participants with moderately-to-severely active Ulcerative Colitis: Results through week 12 of a phase 2a randomized, double-blind, active-controlled, parallel-group, multicenter, proof-of-concept study. Journal of Crohn's and Colitis. 2022 Jan 1;16(Supplement_1):i042–3.