Data-Driven Decisions in Crohn's Disease:

Positioning Patients for Success

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Learning Objectives

- Incorporate individual disease characteristics into treatment decisions in Crohn's disease (CD) based on evidence-based recommendations
- Differentiate biologic therapies in CD based on efficacy and long-term safety to achieve a rapid and durable treatment response
- Develop a data-driven treatment algorithm for CD to position treatment choices based on efficacy, safety, and patient characteristics

The Patient Journey

Patient Case: Elle

- 26-year-old teacher who presents with intermittent, severe, right-sided abdominal pain and distention that often results in vomiting x 4 months
- Bowel movements up to 7x daily with urgency; no blood visualized
- Poor appetite, which increases fatigue and makes it difficult to be productive at work
- Non-smoker

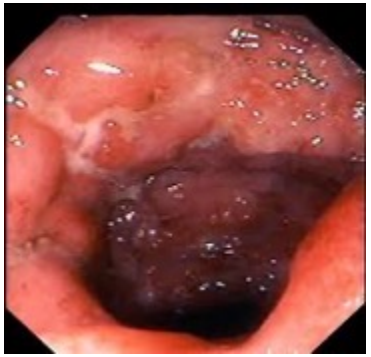
Physical Exam/Labs

- *C. difficile* negative
- Stool cultures negative
- C-reactive protein (CRP): 10.3 mg/L
- Hemoglobin (Hgb): 10 g/dL
- Albumin: 3.1 g/dL

Patient Case: Elle

Endoscopic Features

- Scattered deep ulcers throughout the colon
- Longitudinal, serpiginous, deep ulcerations in the terminal ileum with edema
- Pathology: Severe chronic active ileitis and colitis; no viral inclusions present

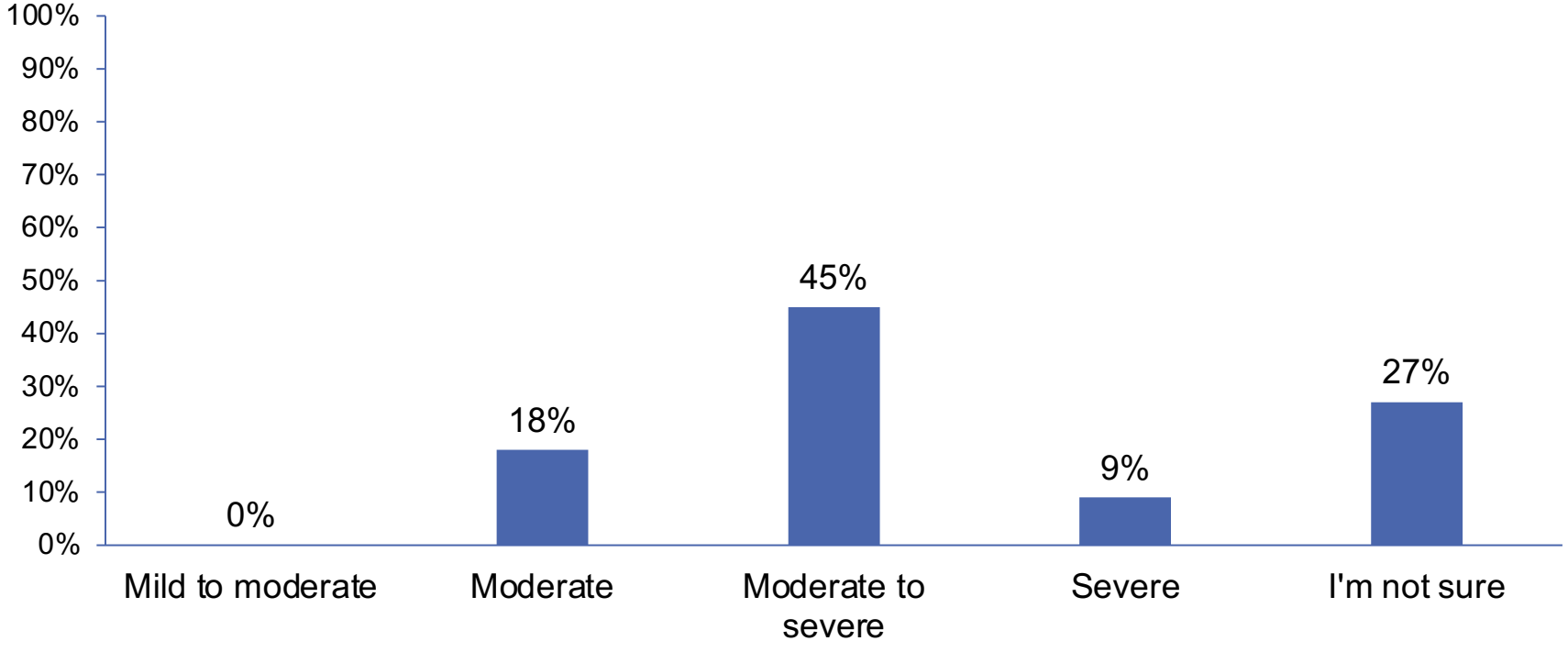


Audience Response

How would you characterize Elle's disease severity?

A. Mild to moderate
B. Moderate
C. Moderate to severe
D. Severe
E. I'm not sure

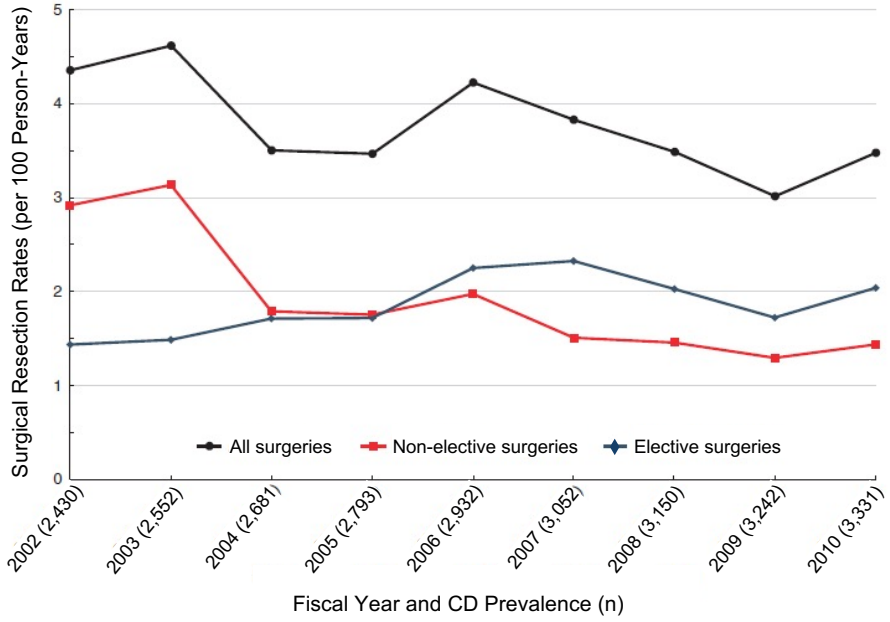
How would you characterize Elle's disease severity?



Results recorded on October 24, 2021

Disease Progression in CD

- Only 20%-30% of patients with CD will have an indolent course
- Up to 80% of patients with CD will require hospitalization
  - 10-year risk of surgery is 40%-55%
  - Perhaps decreasing in biologic era to ~ 30%
  - Increasing rates of elective and fewer emergent surgeries



Lichtenstein GR, et al. *Am J Gastroenterol*. 2018;113(4):481-517. Ma C. et al. *Am J Gastroenterol*. 2017;112(12):1840-1848.

Assessment of Disease Risk in CD

- Assess current and prior disease burden

Low Risk	Moderate/High Risk
• Age at initial diagnosis: > 30 years • Limited anatomic involvement • No perianal and/or severe rectal disease • Superficial ulcers • No prior surgical resection • No stricturing and/or penetrating behavior	• Age at initial diagnosis: < 30 years • Extensive anatomic involvement • Perianal and/or severe rectal disease • Deep ulcers • Prior surgical resection • Stricturing and/or penetrating behavior • Smoking cigarettes

Peyrin-Biroulet L, et al. *Clin Gastroenterol Hepatol*. 2016;14:348-354.

Who Should Receive Early Intensive Therapy? Risk Stratification Is Necessary

Prognostic Factors for Disease Progression in CD

Ileal disease location, upper gastrointestinal involvement, and EIMs → complicated behavior
Younger age and perianal disease at diagnosis → disabling disease course
Smoking → therapy escalation, complicated disease, need for surgery, and postoperative recurrence
Endoscopic severity → penetrating complications
(Serologic reactivity to microbial antigens → complicated behavior)
(Mutations in some genes [e.g., *NOD2*] → complicated behavior)

EIMs = extraintestinal manifestations

American Gastroenterological Association (AGA) Crohn's Disease Clinical Care Pathway. https://gastro.org/guidelines/ibd-and-bowel-disorders/. Accessed October 11, 2021. Torres J, et al. *J Crohn's Colitis*. 2016;10(12):1385-1394.

Endoscopic Severity Scoring

Simple Endoscopic Score for CD (SES-CD)				
Variable	**0**	**1**	**2**	**3**
Size of ulcers (cm)	None	Aphthous ulcers (diameter 0.1-0.5)	Large ulcers (diameter 0.5-2)	Very large ulcers (diameter > 2)
Ulcerated surface	None	< 10%	10%-30%	> 30%
Affected surface	Unaffected segment	< 50%	50%-75%	> 75%
Presence of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

Segments:
Rectum
Left colon
Transverse
Right colon
Ileum

Scoring:
Inactive
Up to 6: mild
7-15 moderate
≥ 16 severe

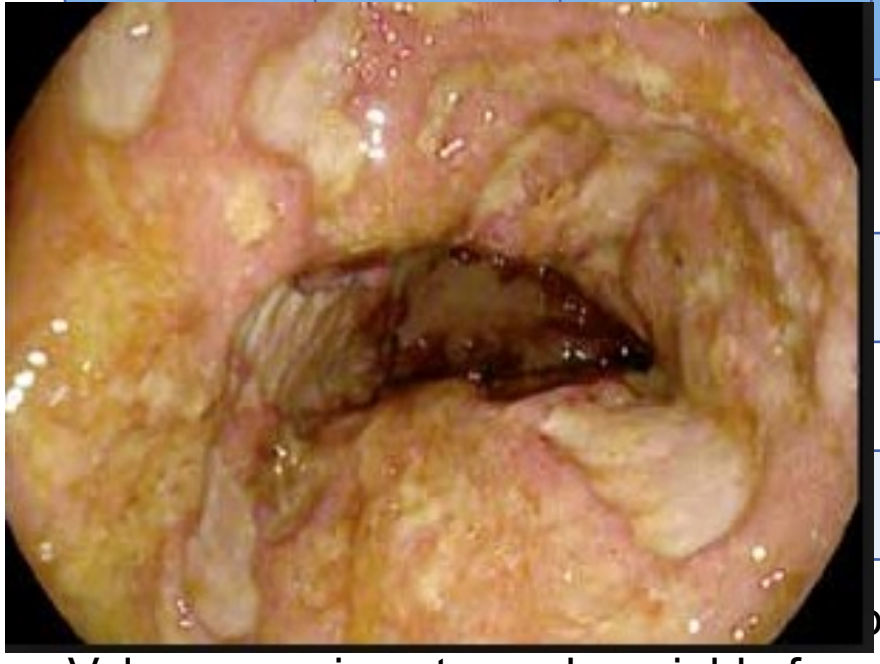
SES-CD = sum of all variable for the 5 bowel segments;
Values are given to each variable for every examined bowel segment

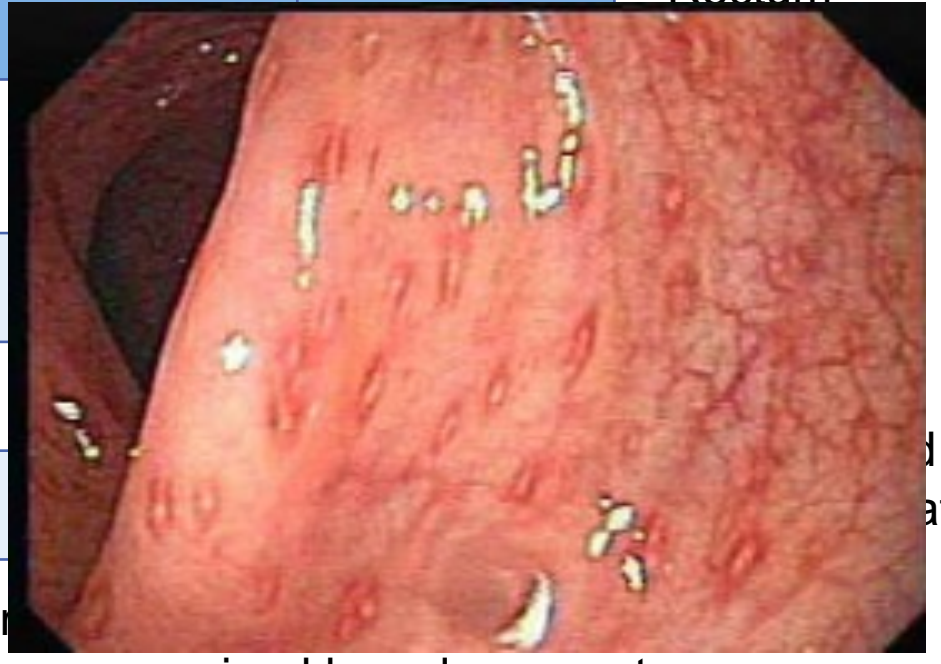
Daperno M, et al. *Gastrointest Endosc*. 2004;60(4):505-512.

Endoscopic Severity Scoring

Simple Endoscopic Score for CD (SES-CD)

Segments:
Rectum





Values are given to each variable for every examined bowel segment

Daperno M, et al. *Gastrointest Endosc*. 2004;60(4):505-512.

Who Should Receive Early Intensive Therapy? Risk Stratification Is Necessary

Prognostic Factors for Disease Progression in CD

Ileal disease location, upper gastrointestinal involvement, and EIMs → complicated behavior
Younger age and perianal disease at diagnosis → disabling disease course
Smoking → therapy escalation, complicated disease, need for surgery, and postoperative recurrence
Endoscopic severity → fibrostenotic disease
(Serologic reactivity to microbial antigens → complicated behavior)
(Mutations in some genes [e.g., *NOD2*] → complicated behavior)

AGA Crohn's Disease Clinical Care Pathway. https://gastro.org/guidelines/ibd-and-bowel-disorders/. Accessed October 11, 2021. Torres J, et al. *J Crohn's Colitis*. 2016;10(12):1385-1394.

Risk of Disease Progression: CD PATH

Input variables

DISEASE LOCATION

- ☐ Upper GI Tract
- ☐ Small Bowel
- ☐ Right Colon
- ☐ Transverse Colon
- ☒ Left Colon
- ☐ Perianal

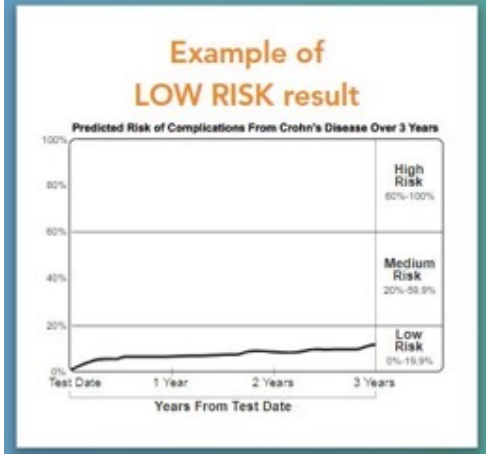
BLOOD TEST MARKERS*

ASCA IgA: 15.1 EU/mL
ASCA IgG: 13.2 EU/mL
anti-CBir1 IgG: 28.3 EU/mL
pANCA: Not Detected

GENETIC TEST*

NOD2 SNP13 (1007fs):
No Variant Detected

The graphs below are examples of patient reports with low-, medium-, and high-risk profiles, respectively[1]:

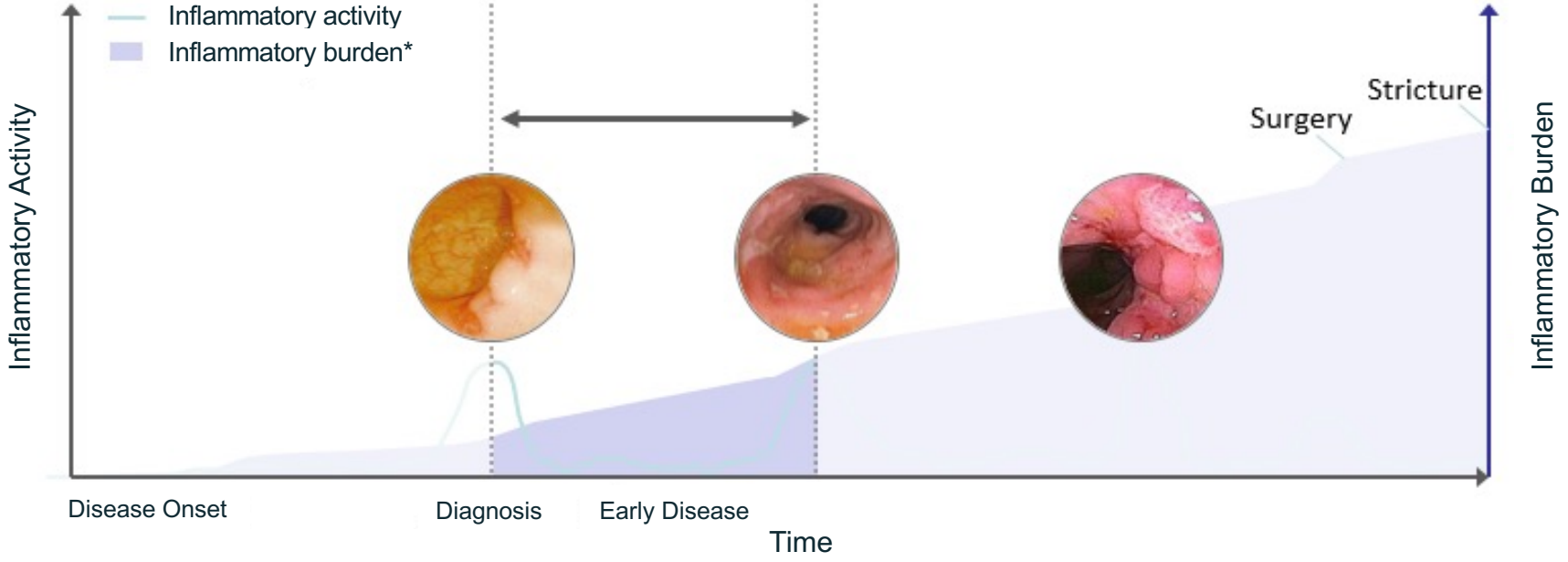


The CDPATH model was designed using multivariate Cox proportional-hazards regression model analysis to identify statistically meaningful clinical, serologic, and genetic factors for predicting the likelihood of risk for CD complications. The ability of the CDPATH model to predict disease-related complications in the validation group was done using a statistical tool called the Harrell's Concordance statistic (C-statistic). The C-statistic for the adult validation group was 0.71, where 0.5 = random chance and 1.0 = perfect prediction. The CDPATH tool was validated in adult patients who had a CD diagnosis within 10 years and had no previous complications.

CDPATH Website. 2021. https://www.cdpath.com/patient/how-it-works. Accessed October 19, 2021.

Window of Opportunity in CD?

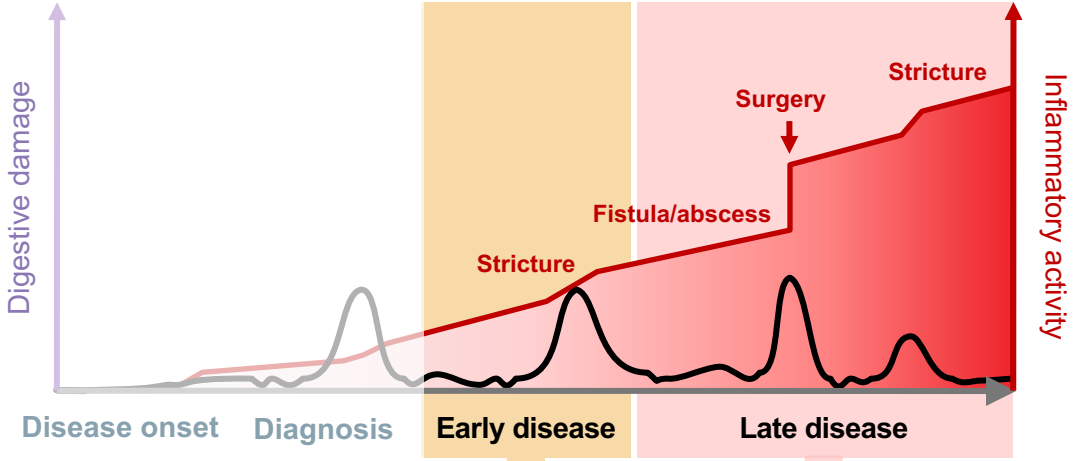
There may be a window of opportunity to minimize risk of permanent bowel damage[1-4]



*Disease activity is a cross-sectional snapshot at one moment in time
Inflammatory burden includes longitudinal and historical factors of disease severity, providing a more complete picture of disease course.[5]

1. Colombel JF, et al. *Gastroenterology.* 2017;152(2):351-361. 2. Pariente B, et al. *Inflamm Bowel Dis.* 2011;17(6):1415-1422. 3. Torres J, et al. *J Crohns Colitis.* 2016;10(12):1385-1394. 4. Torres J, et al. *Lancet.* 2017;389(10080):1741-1755. 5. Siegel CA, et al. *Gut*. 2018;67(2):244-254.

Consider the Patient: Treatment Goals May Differ in Early vs. Late Disease



Treatment goals

No symptoms	Noninflammatory symptoms stabilized
No disease progression, complications, or disability	No progression of damage or disability
Normal quality of life (QoL)	Improved QoL

- Symptomatic remission may not be achievable in late-stage disease[1]
- Mucosal healing as treatment goal may be difficult to achieve in patients[1,2]:
  - Diagnosed late in disease course
  - Who have already experienced a disease complication
- Earliest disease is postoperative prevention

1. Panaccione R, et al. *Inflamm Bowel Dis*. 2013;19:1645-1653. 2. Peyrin-Biroulet L, et al. *Am J Gastroenterology*. 2015;110:1324-1338.

Physical Exam/Labs

- *C. difficile* negative
- Stool cultures negative
- C-reactive protein (CRP): 10.3 mg/L
- Hemoglobin (Hgb): 10 g/dL
- Albumin: 3.1 g/dL

- Stay vigilant about albumin level
- Issues with protein absorption could impact medication choice, especially if thinking about a biologic
- Inflammation downstream will affect iron absorption upstream

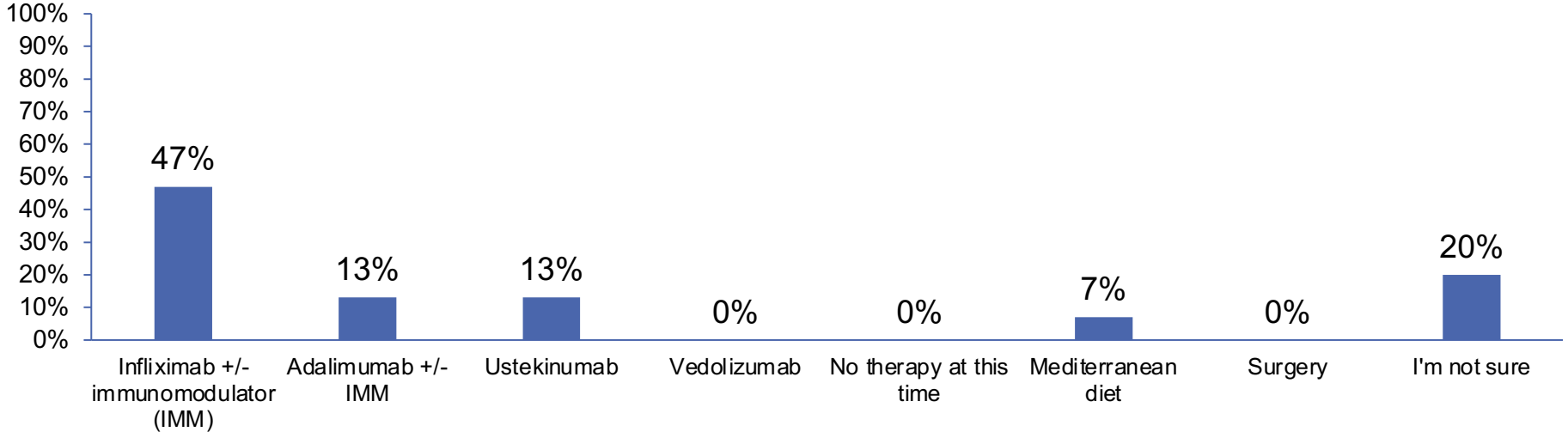
Choosing the Right Treatment for the Right Patient at the Right Time

Audience Response

What would be your treatment recommendation for Elle?

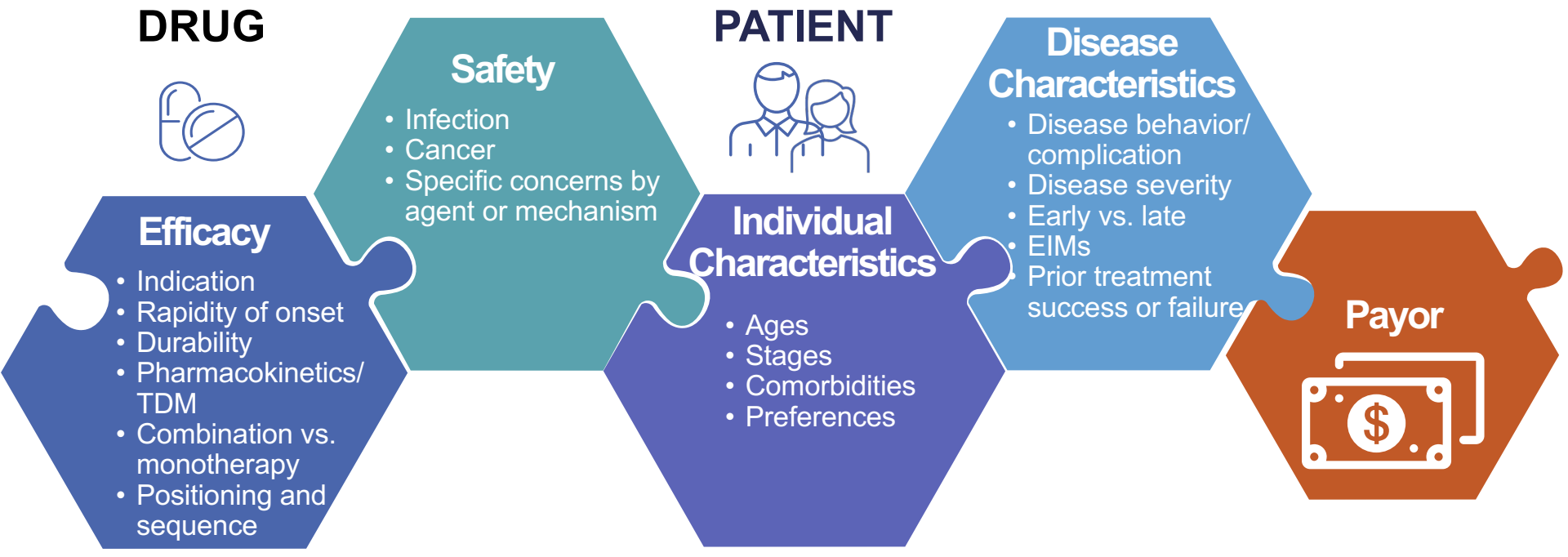
A. Infliximab +/- immunomodulator (IMM)
B. Adalimumab +/- IMM
C. Ustekinumab
D. Vedolizumab
E. No therapy at this time
F. Mediterranean diet
G. Surgery
H. I’m not sure

What would be your treatment recommendation for Elle?



Results recorded on October 24, 2021

How Do We Put Together the Puzzle of Therapy Selection?

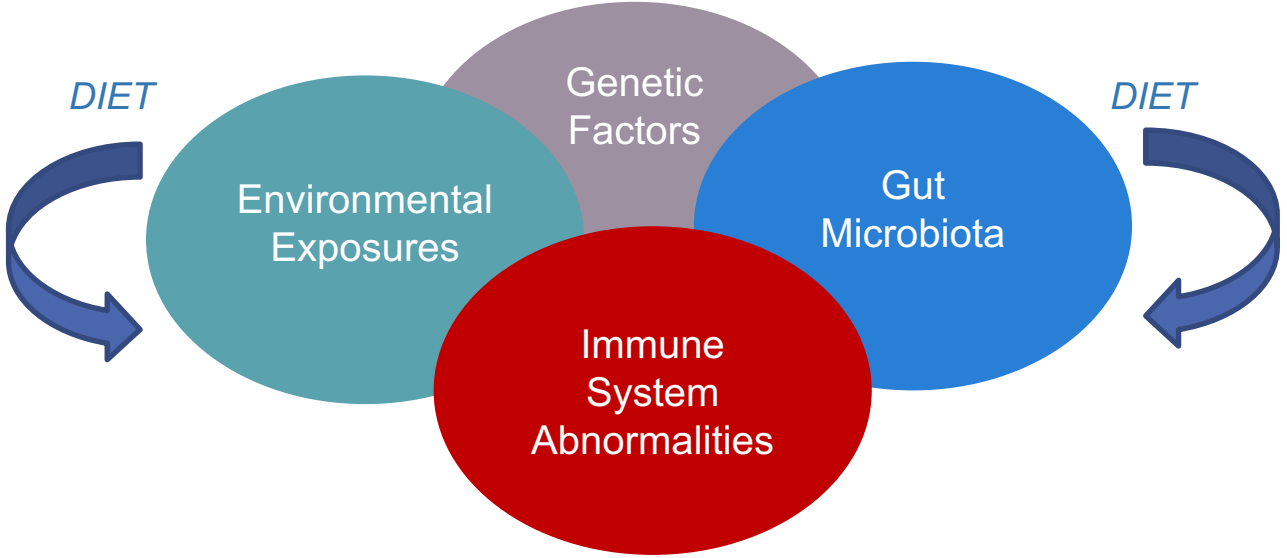


TDM = therapeutic drug monitoring

Diet for CD

- Inflammatory bowel disease (IBD) is thought to arise from a combination of genetic, immune system, and environmental causes as well as alteration of the gut bacteria

Reasonable to think that food/diet may play a role



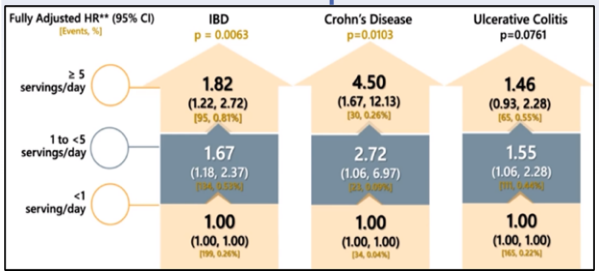
Processed and Ultra-Processed Foods Associated with Increased Risk of IBD

- **Processed food:** Food altered during preparation, including adding preservatives
- **Ultra-processed food:** From substrates extracted from food with additives such as carboxymethyl cellulate, polysorbate 80, carrageenan

1

- Observational cohort study (2003-2016)
- 21 countries, N = 115,037
- Ages 35-70 yrs
- Habitual food intake assessed using country-specific validated food frequency questionnaire

Association between total processed food intake and development of IBD

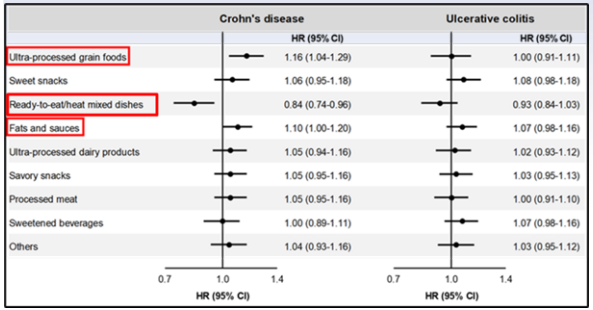


Conclusion: Higher processed food consumption associated with development of IBD

2

- Nationwide prospective cohorts from Nurses Health Study, Nurses Health Study II, and Health Professionals Follow-up Study
- 5,471,215 person-years of follow-up

UPF and Risk of CD and UC



Conclusion: Higher consumption of UPF grains, fats, and sauces and emulsifiers/ thickeners associated with ↑ risk of CD

3

Method

- Case control, observational study
- 195 patients with CD
- Early-life processed food intake and usual food additive intake assessed

Results

- Patients with CD are more likely to have processed meat than their household (p = .03)
- More likely to have consumed processed fruit than their 1st-degree relatives p = .022)
- More likely to have consumed fast food than health controls p < .001)

Conclusion: Patients with CD were more likely to have consumed UPF in early life, indicating a likely trigger for disease initiation

UC = ulcerative colitis; UPF = ultra-processed food

Narula N, et al. Presented at Digestive Disease Week (DDW); 2021. Abstract 393. Lo C, et al. Presented at DDW; 2021. Abstract 389. Trakman G, et al. Presented at DDW; 2021. Abstract 513.

Patients Recently Diagnosed with IBD Have a High Prevalence of Malnutrition and Micronutrient Deficiencies

Aim: Determine the prevalence of malnutrition and micronutrient deficiencies in patients recently diagnosed with IBD and compare the performance of existing malnutrition screening tools in this population

Micronutrient Deficiencies in Patients Recently Diagnosed with IBD

Micronutrient	Micronutrient Deficient n (%)	Median Value (Interquartile Range), [Reference Range]
Folate (n = 40)	1 (3)	12.3 ng/mL (8.6-14.5), [4.0-1,000.0 ng/mL]
Vitamin D (n = 116)	82 (71)	22.8 ng/mL (15.8-31), [30.0-100.0 ng/mL]
Vitamin B12 (n = 115)	25 (22)	431 pg/mL (312-569), [211-911 pg/mL]
Vitamin C (n = 46)	10 (22)	0.7 mg/dL (0.3-1.1), [0.2-2.0 mg/dL]
Zinc (n = 34)	5 (15)	74.5 ug/dL (61-88), [56-134 ug/dL]
Ferritin (n = 119)	50 (42)	25 ng/mL (12-63), [15-150 ng/mL]
Phosphorus (n = 46)	7 (15)	3.3 mg/dL (2.7-3.9), [2.4-4.7 mg/dL]

Performance of Malnutrition Tools for Detecting Malnutrition per ESPEN Criteria

Malnutrition Tools	Sensitivity	Specificity	PPV	NPV
MUST	86.15%	96.55%	93.3%	92.56%
SNAQ	76.5%	94.8%	89.1%	88%
MIRT	95.4%	83.3%	76.5%	96.9%
NRI	35.4%	96.5%	85.2%	72.2%
SASK IBD-NR	56.9%	94.0%	84.1%	79.6%

*BMI ≤ 18.5 or weight loss (>10% over any time period or > 5% over 3 months) and BMI < 20

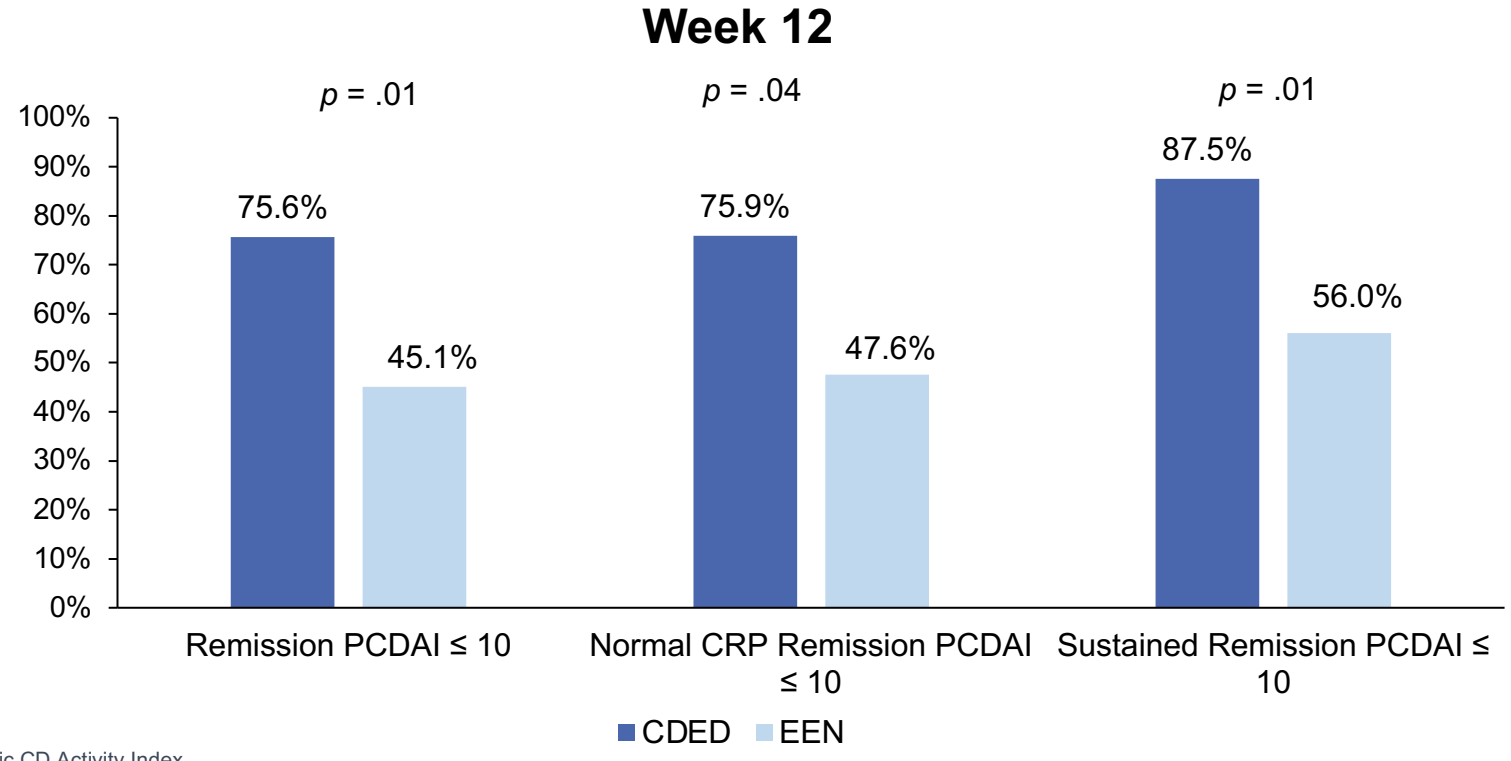
MIRT = Malnutrition Inflammatory Risk Tool; MUST = Malnutrition Universal Screening Tool; NPV = negative predictive value; NRI = Nutritional Risk Index; OR = odds ratio; PPV = positive predictive value; SASK IBD-NR = Saskatchewan IBD Nutrition Risk Tool; SNAQ = Short Nutritional Assessment Questionnaire

Gold AS, et al. Presented at DDW. May 2021. Abstract Sa561.

Dietary Therapies in CD Management Are Evolving Over Time

- To improve nutrition
- To alleviate symptoms
- **To reduce inflammation**
  - **As sole therapy or as adjunctive?**

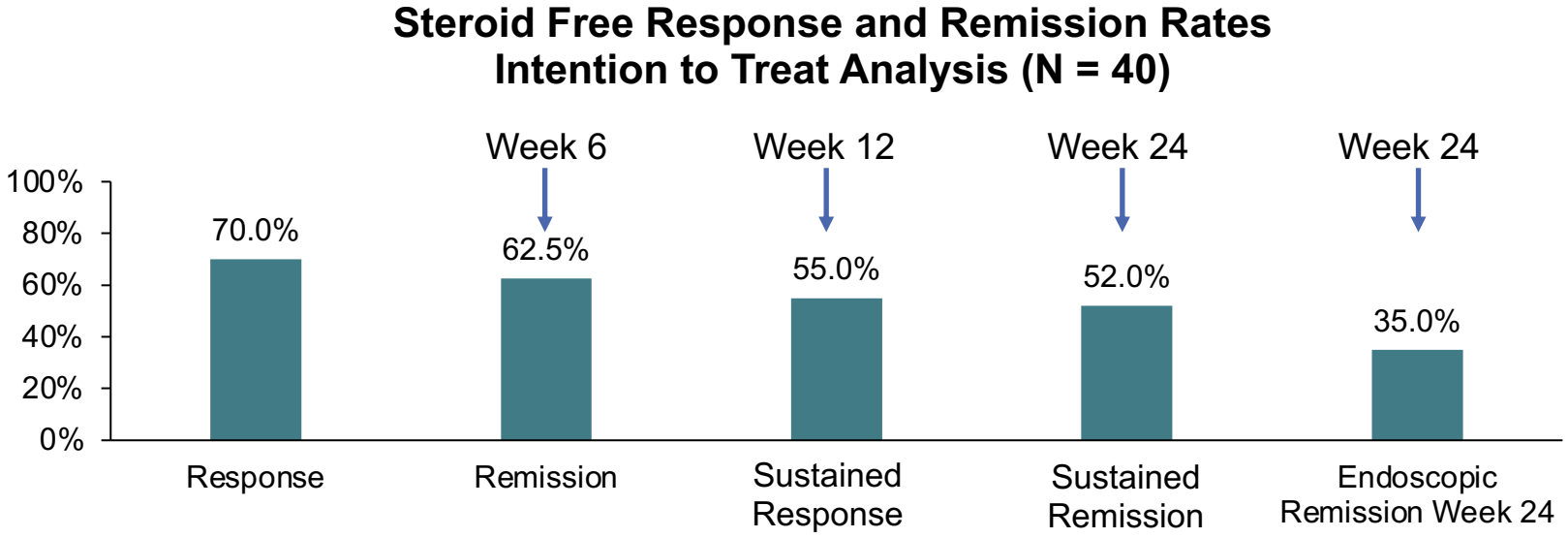
The CD Exclusion Diet (CDED) for Mild-to-Moderate CD Can Induce Biochemical Remission



PCDAI = Pediatric CD Activity Index

Levine A, et al. *Gastroenterology*. 2019;157(2):443-450.

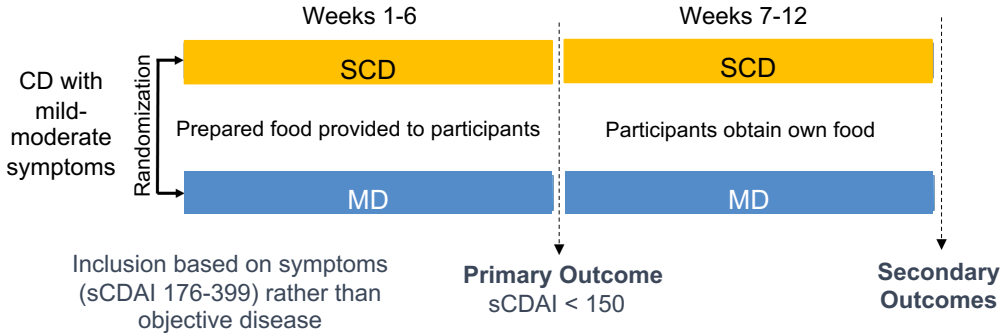
CDED Induces Sustained Clinical and Endoscopic Remission in Adults with Mild-to-Moderate Disease



- Steroid-free clinical remission defined as HBI < 5 points
- Response defined as a drop in HBI ≥ 3 points
- Endoscopic remission defined as SES-CD ≤ 3

Yanai H, et al. Presented at 16th Congress of European Crohn's and Colitis Organisation; 2021 (Virtual). Abstract DOP65.

Mediterranean Diet and Specific Carbohydrate Diet Achieve Similar Clinical Remission Rates in a Randomized Trial in CD

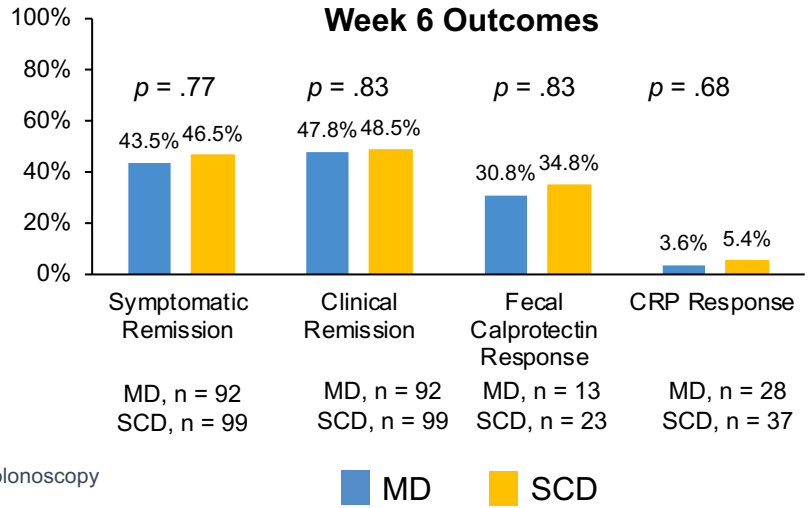


	MD	SCD
High intake	Olive oil Fruits and vegetables Nuts and cereals	Unprocessed meats, poultry, fish, eggs Most vegetables, fruits and nuts
Avoid or Limit	Red/processed meat Sweets	Grains and dairy Sweeteners other than honey

Results:

- N = 191 (92 in MD, 99 in SCD)
- No significant difference in symptomatic or clinical remission
- Neither diet associated with normalization of CRP

Baseline	MD	SCD	*P* Value
Objective inflammation*	**38 (41.8)**	**50 (52.1)**	**.21**
CDAI (Median)	206.8	210.0	.02



*Fecal calprotectin > 250 µg/g or high-sensitivity CRP > 5 mg/L at baseline or definite inflammation on colonoscopy

MD = Mediterranean diet; SCD = specific carbohydrate diet; sCDAI = simple CD activity index

Lewis JD, et al. Presented at DDW; 2021. Abstract 781. Lewis JD, et al. *Gastroenterology* 2021;161(3):837-852.

Diet and Disease Flares of IBD

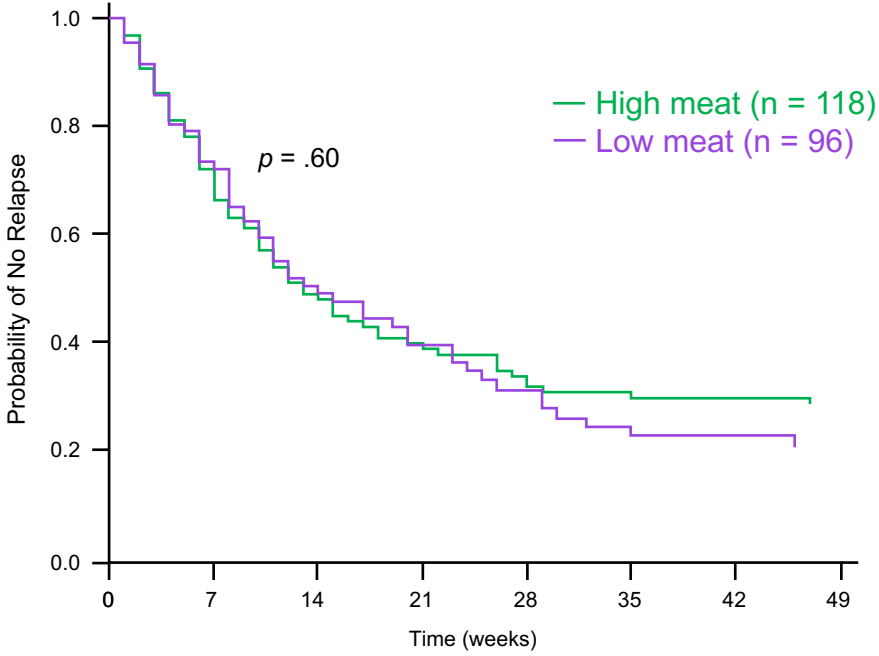
- CCFA Partners survey: Food frequency questionnaires were administered to a large internet cohort of 2,329 patients with IBD
  - 1,121 patients with CD
- Foods that tended to improve symptoms: **yogurt, rice, bananas**
- Foods that tended to worsen symptoms: **non-leafy vegetables, spicy foods, fruit, nuts, leafy vegetables, fried foods, milk, red meat, soda, popcorn, dairy, alcohol, high-fiber foods, corn, fatty foods, seeds, coffee, and beans**
- **Limitations**: Self-reported; no measures of inflammation recorded

Cohen AB, et al. *Dig Dis Sci*. 2013;58(5):1322-1328.

Food and Crohn's Disease Exacerbation Study (FACES)

- Randomized trial of high red/processed meat diet and low red/processed meat diet in patients with CD enrolled in IBD Partners
- Partners participants with sCDAI ≤ 150 who reported consumption of red meat at least 1x per week on baseline diet survey were randomized
- Treatment arms: to consume a minimum of 2 servings/week (high meat) or not more than 1 serving per month (low meat) of red or processed meat for 48 weeks

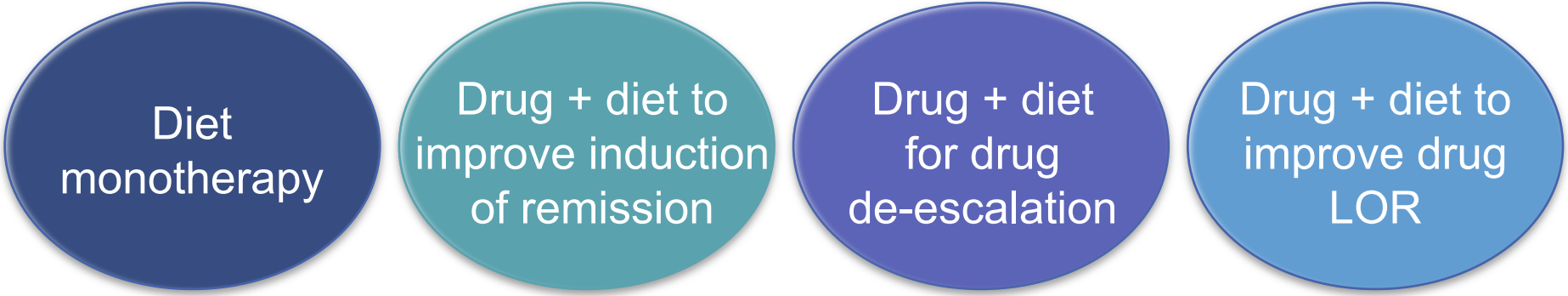
Primary outcome: relapse of CD
(increase in sCDAI by ≥ 70 points and to > 150)



No difference in time to relapse despite low meat group significantly decreasing average weekly red meat consumption

Albenberg L, et al. *Gastroenterology*. 2019;157(1):128-136.

Developing Dietary Treatment Strategies



- Can we identify dietary-responsive patients?
- Identify patient phenotypes that will be responsive to which diet

LOR = level of responsiveness

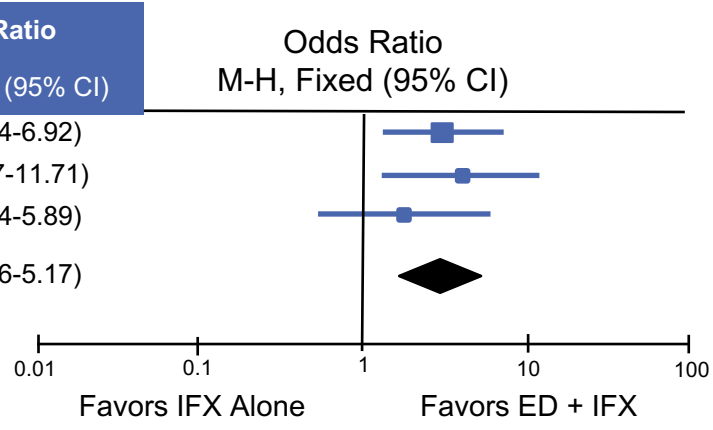
Using Diet as Adjunctive Therapy

- The use of specialized enteral nutrition therapy in combination with infliximab (IFX) appears to be more effective at inducing and maintaining clinical remission among patients with CD than infliximab monotherapy

Study or Subgroup	ED + IFX		IFX Alone			Odds Ratio
	Events	Total	Events	Total	Weight	M-H, Fixed (95% CI)
Hirai et al 2013	31	45	24	57	46.5%	3.04 (1.34-6.92)
Szuka et al 2012	23	29	22	45	25.2%	4.01 (1.37-11.71)
Yamamoto et al 2010	25	32	16	24	28.3%	1.79 (0.54-5.89)
Total (95% CI)		106		126	100.0%	2.93 (1.66-5.17)
Total Events	79		62			

Heterogeneity: $Chi^2 = 1.00$, df = 2 ($p = .61$); $I^2 = 0\%$

Test for overall effect: $Z = 3.71$ ($p = .0002$)



Forest plot of long-term clinical remission among patients on combination therapy with infliximab and enteral nutrition compared with infliximab monotherapy.
df = degrees of freedom; ED = elemental diet; M-H = Mantel-Haenszel
Nguyen D, et al. *Therapeutic Adv Gastroenterol.* 2015;8(4):168-175.

Audience Questions

Recorded on October 26, 2021

- Always ask about a patient's diet, don't wait for them to ask you about it
- Seize the opportunity to educate patients about diet and nutrition—what they eat vs what their body needs
- Address concerns or theories the patient has formed about their diet that they may have read about and are already instituting
- Help the patient understand what is, and what is not supported by data

Options for Medical INDUCTION Therapy: Moderate-to-Severe Disease

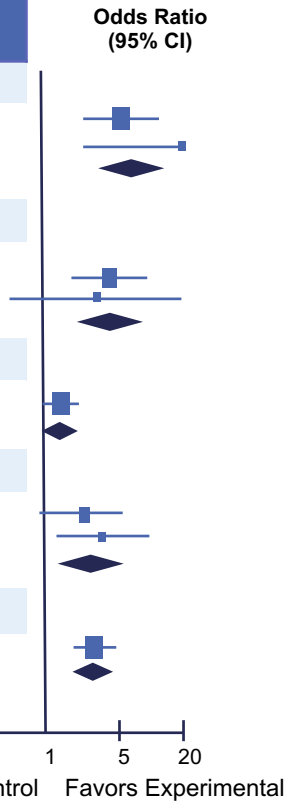
- **Oral steroids** → only for short-term induction agents for inflammatory CD
- **Anti-TNF agents** → steroid-resistant or thiopurine or methotrexate-refractory disease
- **Combination therapy with infliximab** → more effective than monotherapy with thiopurines or infliximab for ***NAÏVE*** patients
- **Anti-integrin** therapy → vedolizumab with or without immunomodulator
- **Ustekinumab** → for patients who failed steroids, thiopurines, methotrexate, anti-TNFs, or anti-TNF naïve

TNF = tumor necrosis factor

Lichtenstein GR, et al. *Am J Gastroenterol*. 2018;113:481-517.

Systematic Review with Network Meta-Analysis: First-Line Induction Therapy for Moderate-to-Severe CD

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Odds Ratio (95% CI)
Infliximab vs. Placebo					
Lemann 2006	43	57	22	58	5.03 (2.25-11.22)
Targan 1997	12	27	1	24	18.40 (2.16-156.68)
Subtotal (95% CI)		84		82	**6.35 (3.04-13.28)**
Adalimumab vs. Placebo					
CLASSIC I 2006	27	76	9	74	3.98 (1.72-9.22)
Watanabe 2011	6	14	2	10	3.00 (0.46-19.59)
Subtotal (95% CI)		90		84	**3.80 (1.76-8.18)**
Certolizumab Pegol vs. Placebo					
Sandborn 2011	68	215	53	209	1.36 (0.89-2.08)
Subtotal (95% CI)		215		209	**1.36 (0.89-2.08)**
Vedolizumab vs. Placebo					
GEMINI II 2013	21	115	7	78	2.27 (0.91-5.62)
GEMINI II 2014	16	51	6	50	3.35 (1.19-9.47)
Subtotal (95% CI)		166		128	**2.68 (1.35-5.31)**
Ustekinumab vs. Placebo					
UNITI-2 2016	80	200	39	200	2.75 (1.76-4.32)
Subtotal (95% CI)		200		200	**2.75 (1.76-4.32)**



Effect size was positive for all treatments except certolizumab pegol (compared to control)

Singh S, et al. *Aliment Pharmacol Ther*. 2018;48:394-409.

What Do We Know About Sequencing or Positioning?

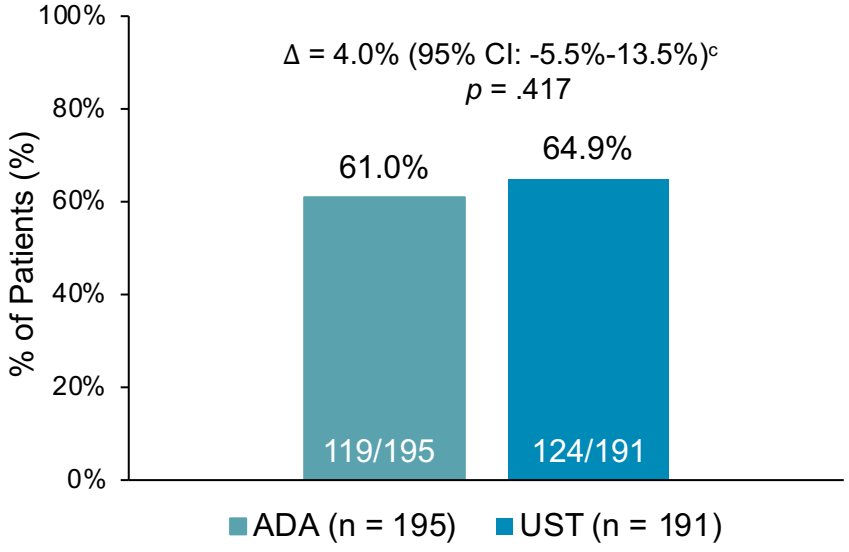
- SEAVUE first randomized controlled trial (RCT) to demonstrate comparative efficacy in CD
- What data do we have for positioning?
  - Reliance on subgroup analyses (SGA) in RCTs, real-world evidence (RWE), and network meta-analysis
- After failure of first TNFi, second-line biologics less effective, including second-line TNFis (SGA)
  - UST still effective after failing ≥ 1 TNFi in CD[1] (SGA)
  - UST also effective after failing VDZ[2] (SGA)
  - TNFi seems effective after failing VDZ[3] (RWE)
  - VDZ is less effective after failing TNFi in CD[4] (RWE) and may have longer onset of effect in CD after TNFi failure[5] (RCT)

TNFi = TNF inhibitor; UST = ustekinumab; VDZ = vedolizumab

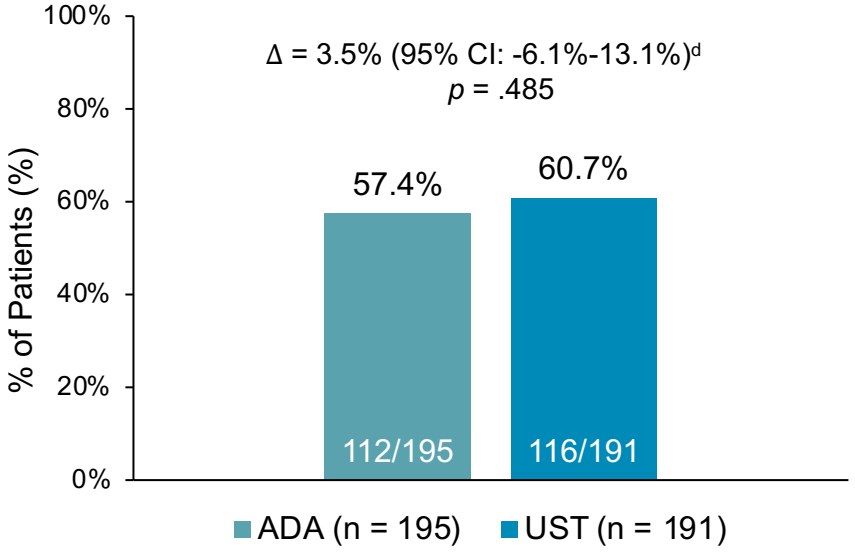
1. Feagan BG, et al. *N Engl J Med*. 2016;375:1946-1960. 2. Kassouri L, et al. *Dig Live Dis.* 2020;52(10):1148-1155. 3. Bressler B, et al. Presented at: American College of Gastroenterology Annual Meeting; Oct. 25-30, 2019; San Antonio, TX. Abstract 40. 4. Dulai P, et al. *Am J Gastroenterol*. 2016;111:1147-1155. 5. Sands BE, et al. *Gastroenterology.* 2014;147:618-627.

SEAVUE Results

Primary Endpoint[a,b]
Clinical Remission (CDAI < 150) at Week 52



Major Secondary Endpoint[a,b,c]
Corticosteroid-Free Clinical Remission at Week 52



ADA = adalimumab

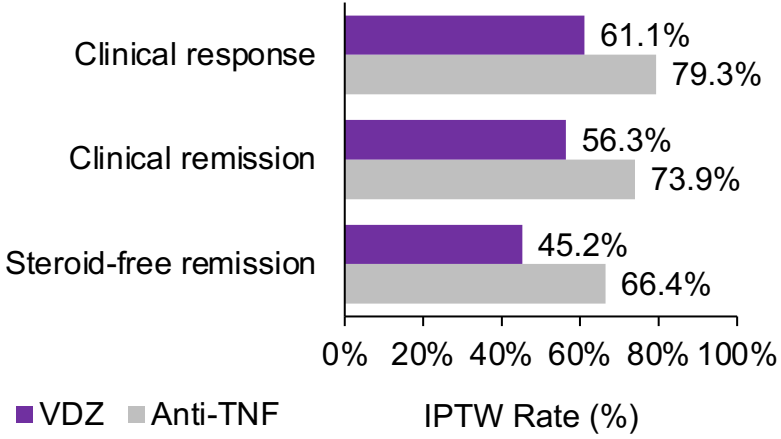
[a]Patients who had a prohibited CD-related surgery had prohibited concomitant medication changes, or discontinued study agent due to lack of efficacy or due to an adverse event indicated to be of worsening CD prior to the designated analysis timepoint are considered not to be in clinical remission; [b]Patients who had insufficient data to calculate the CDAI score at the designated analysis timepoint are considered not to be in clinical remission; [c]Patients who had a missing data value in corticosteroid use at designated analysis timepoint had their last value carried forward; [d]The CIs were based on the Wald statistic with M-H weight; NOTE: not receiving corticosteroids at Week 52 is defined as corticosteroid free for ≥ 30 days prior to Week 52.

Sands BE, et al. *Gastroenterology*. 2021;161(2):E30-E31.

Real-World Effectiveness of Vedolizumab vs. Anti-TNF in Naïve CD

- Biologic-naïve patients with CD in Germany followed for 14 weeks to determine clinical response, clinical remission, and steroid-free remission
- 86 bio-naïve VDZ and 241 bio-naïve anti-TNF CD patients (ADA: 57.7%, IFX: 42.3%) were included
- VDZ was used for older patients, with a less complicated though longer disease course, with a history of comorbidities
- Propensity score analysis to account for differences
- Anti-TNF was superior to VDZ for response and remission

Characteristics	VDZ Naïve	Anti-TNF Naïve
N	86	241
Age, yrs	53.3 (34.5-61.9)	37.1 (27.8-52)
Disease duration	6.6 yrs (1.2-12.1)	4.5 yrs (.84-14.8)
Comorbidities, %	44.2%	35.3%



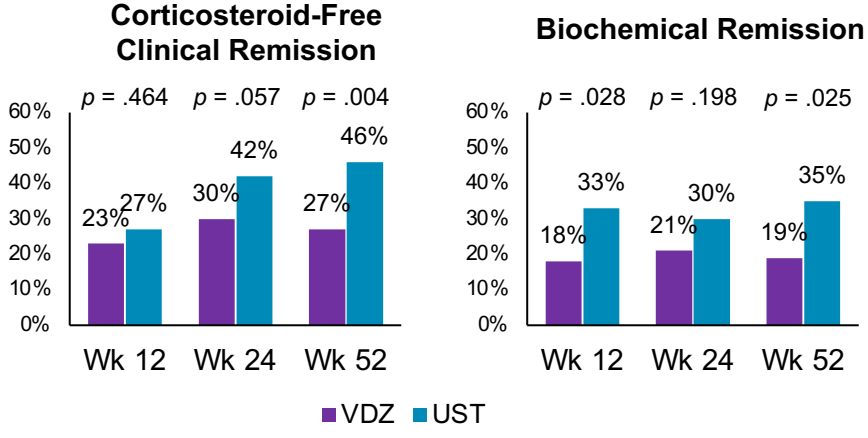
IPTW = probability of treatment weighting

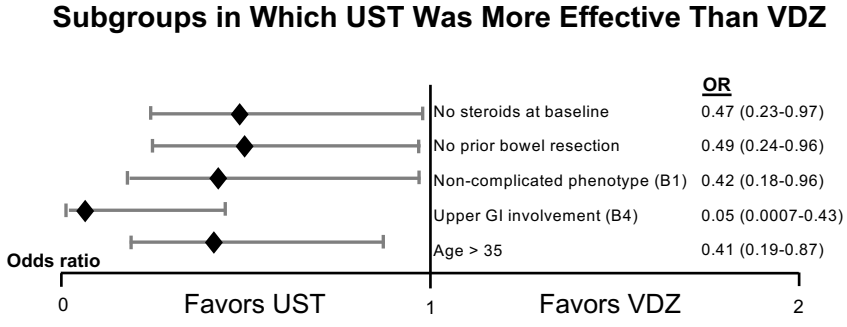
Bokemeyer B, et al. Presented at United European Gastroenterology (UEG) Week; 2021.

Ustekinumab Is Superior to Vedolizumab in Patients with CD with Prior Anti-TNF Failure

- Prospective observational study of patients with CD on UST or VDZ[1]
- Clinical/biochemical assessment: Weeks 0, 12, 24, 52
- Propensity score matching: N = 69 VDZ, N = 69 UST

- Retrospective study from two centers in France[2]
- UST was more effective to achieve early and long-term efficacy than VDZ in patients with CD who previously failed anti-TNFs





1. Biemans B, et al. Presented at DDW; 2020. Abstract 1028. 2. Buisson A, et al. Presented at DDW; 2021. Abstract 26.

Patient Case: Elle

- Elle is placed on adalimumab monotherapy 160/80 mg and 40 mg every other week and returns at 3 months feeling well
- Exam: benign, non-tender

Repeat labs:

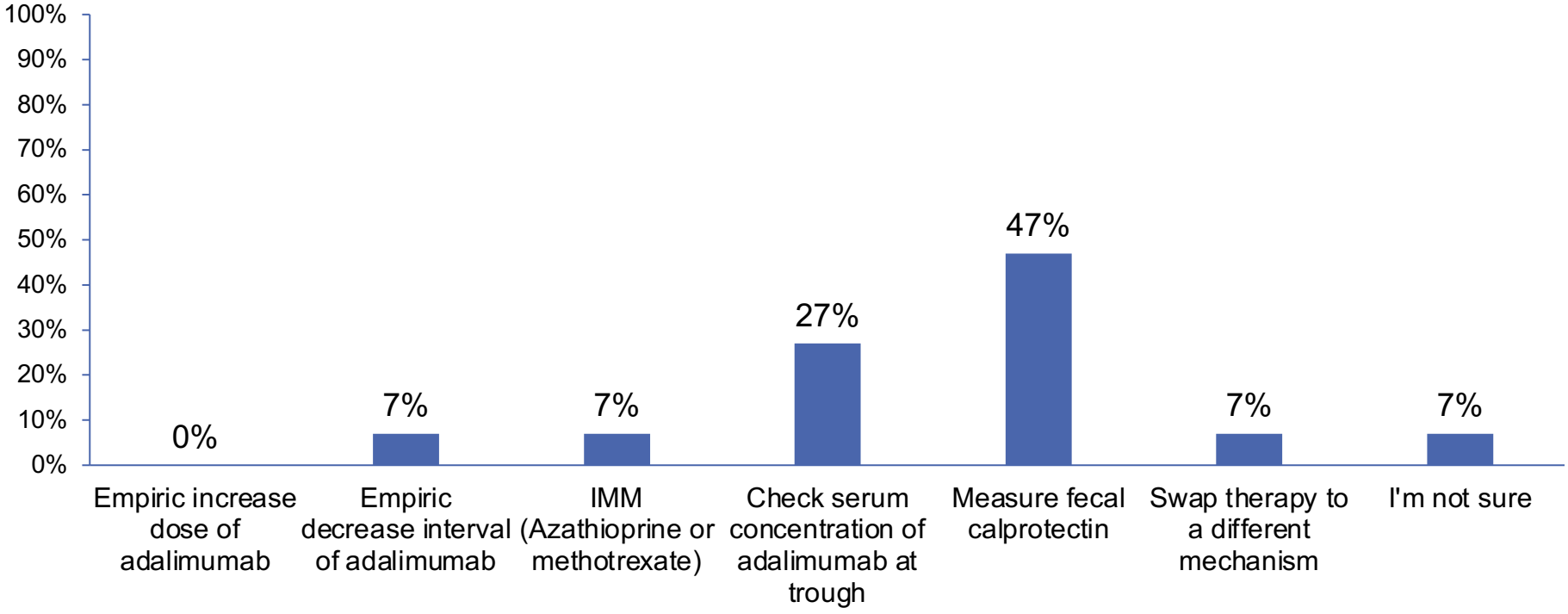
- Hgb: 11 g/dL
- CRP: 8 mg/L
- Albumin: 3.6 g/dL

Audience Response

What would you recommend for Elle?

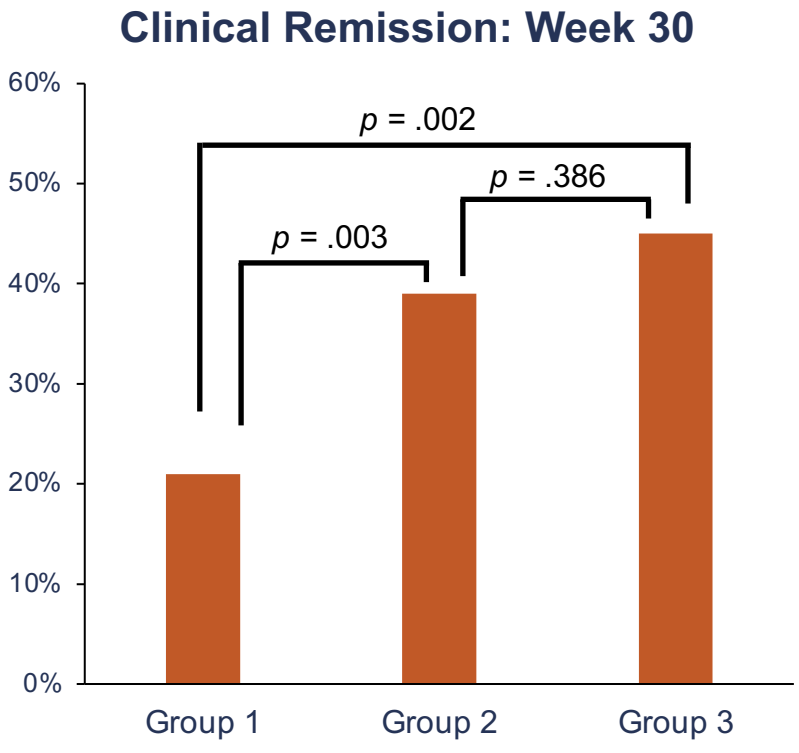
A. Empiric increase dose of adalimumab
B. Empiric decrease interval of adalimumab
C. Add immunomodulator (azathioprine or methotrexate)
D. Check serum concentration of adalimumab at trough
E. Measure fecal calprotectin
F. Swap therapy to a different mechanism
G. I’m not sure

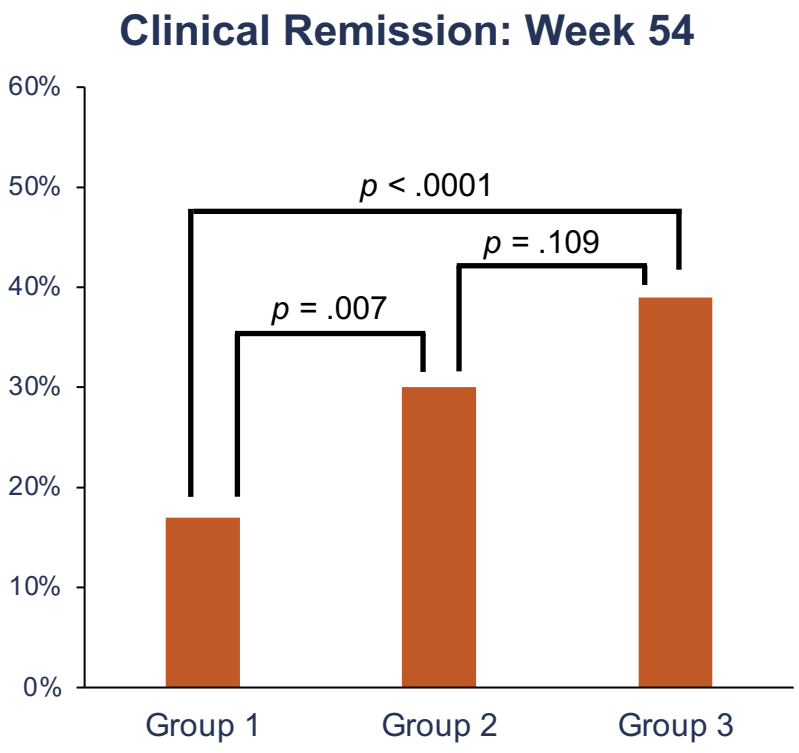
What would recommend for Elle?



Results recorded on October 24, 2021

Maintenance Infliximab for CD: ACCENT 1

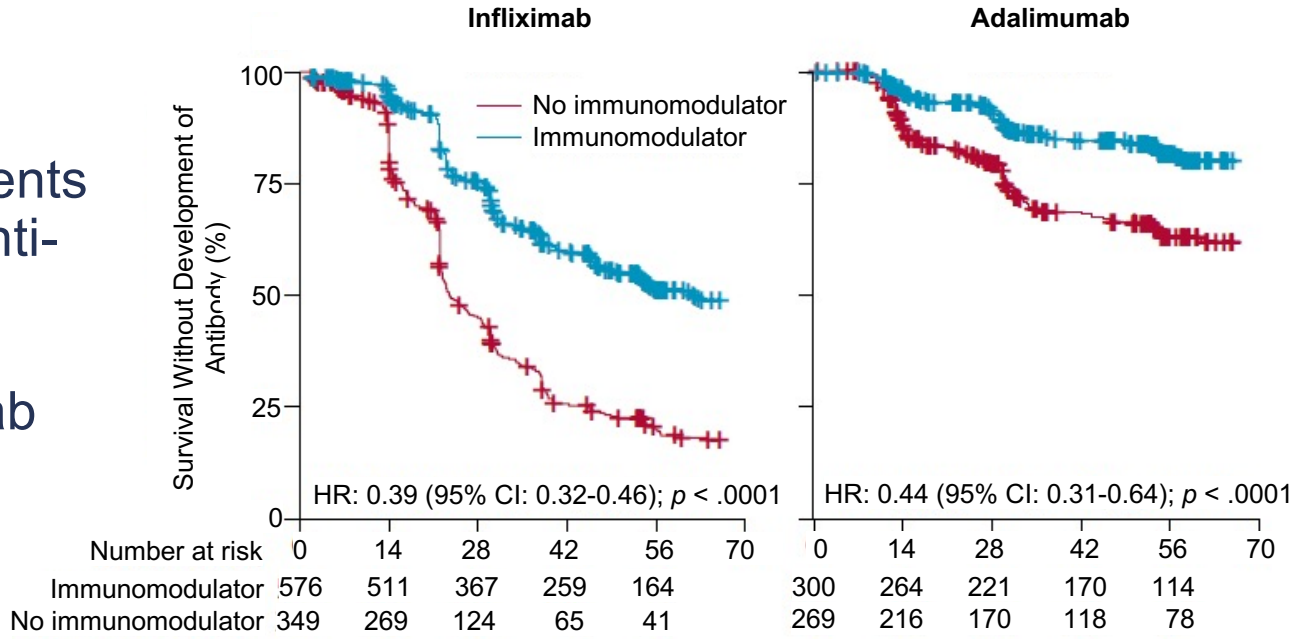




Hanauer SB, et al. *The Lancet*. 2002;359(9317):1541-1549.

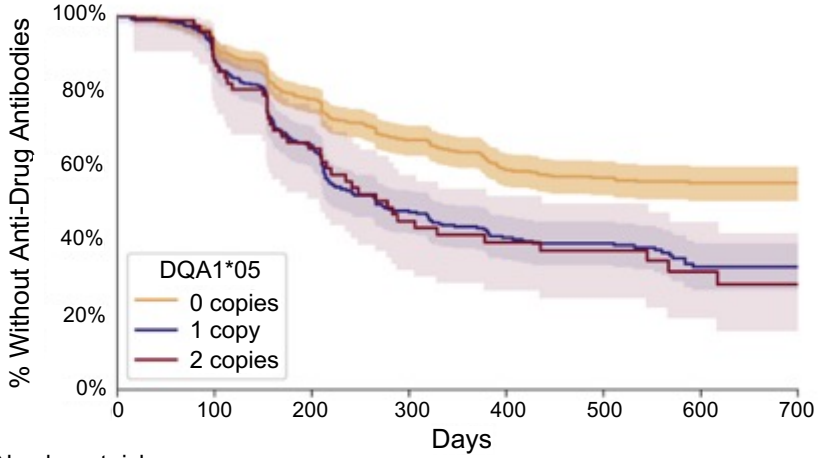
PANTS: Personalized Anti-TNF Therapy in CD

- High rates of immunogenicity: Proportion of patients who developed anti-drug antibodies: 62.8% infliximab, 28.5% adalimumab



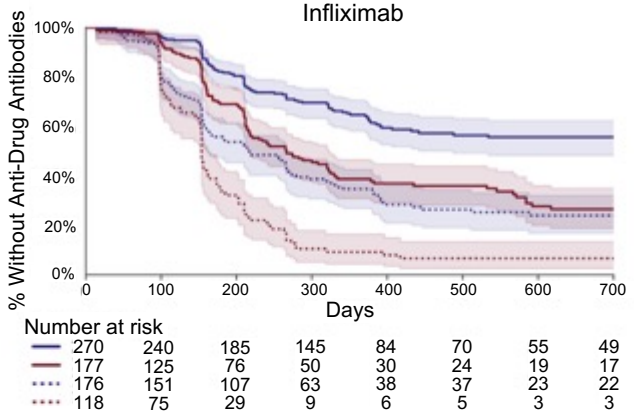
Kennedy NA, et al. *Lancet Gastroenterol Hepatol.* 2019;4(5):341-353.

PANTS: HLA-DQA1*05 and Immunogenicity



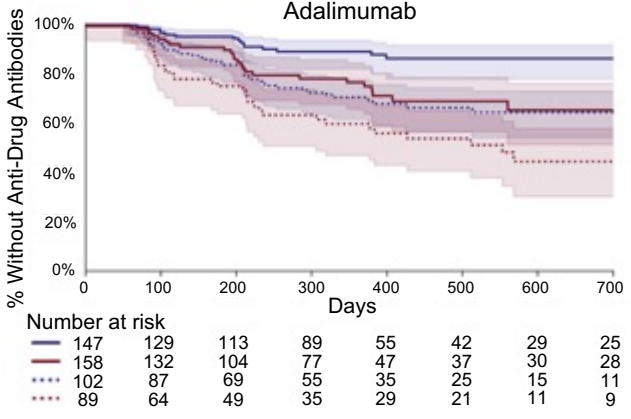
Number at risk

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



Number at risk

	270	240	185	145	84	70	55	49
	177	125	76	50	30	24	19	17
	176	151	107	63	38	37	23	22
	118	75	29	9	6	5	3	3



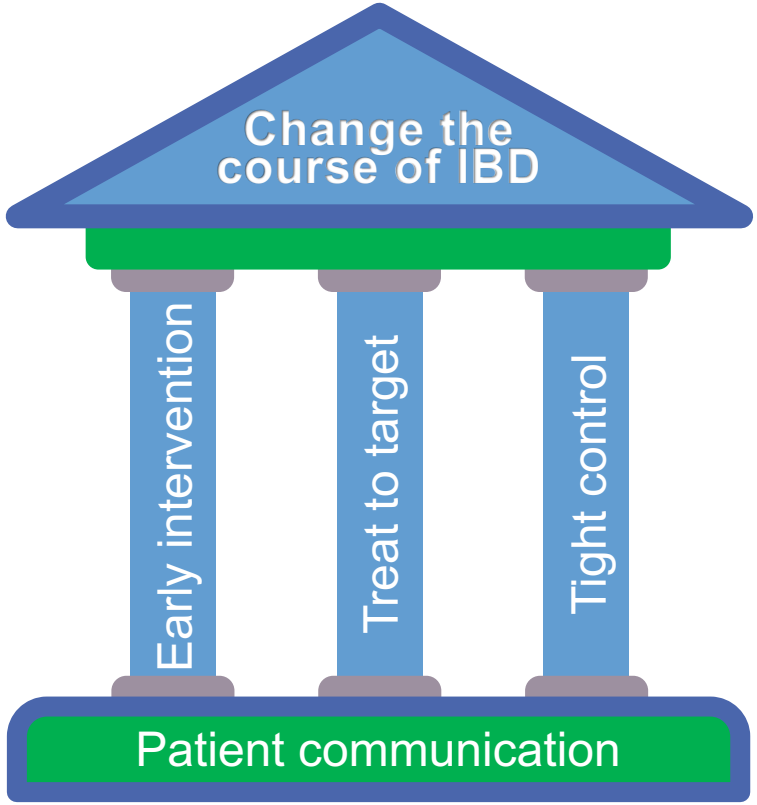
Number at risk

	147	129	113	89	55	42	29	25
	158	132	104	77	47	37	30	28
	102	87	69	55	35	25	15	11
	89	64	49	35	29	21	11	9

Blue = non-carriers
Red = carriers
Dotted = monotherapy
Solid = combination therapy

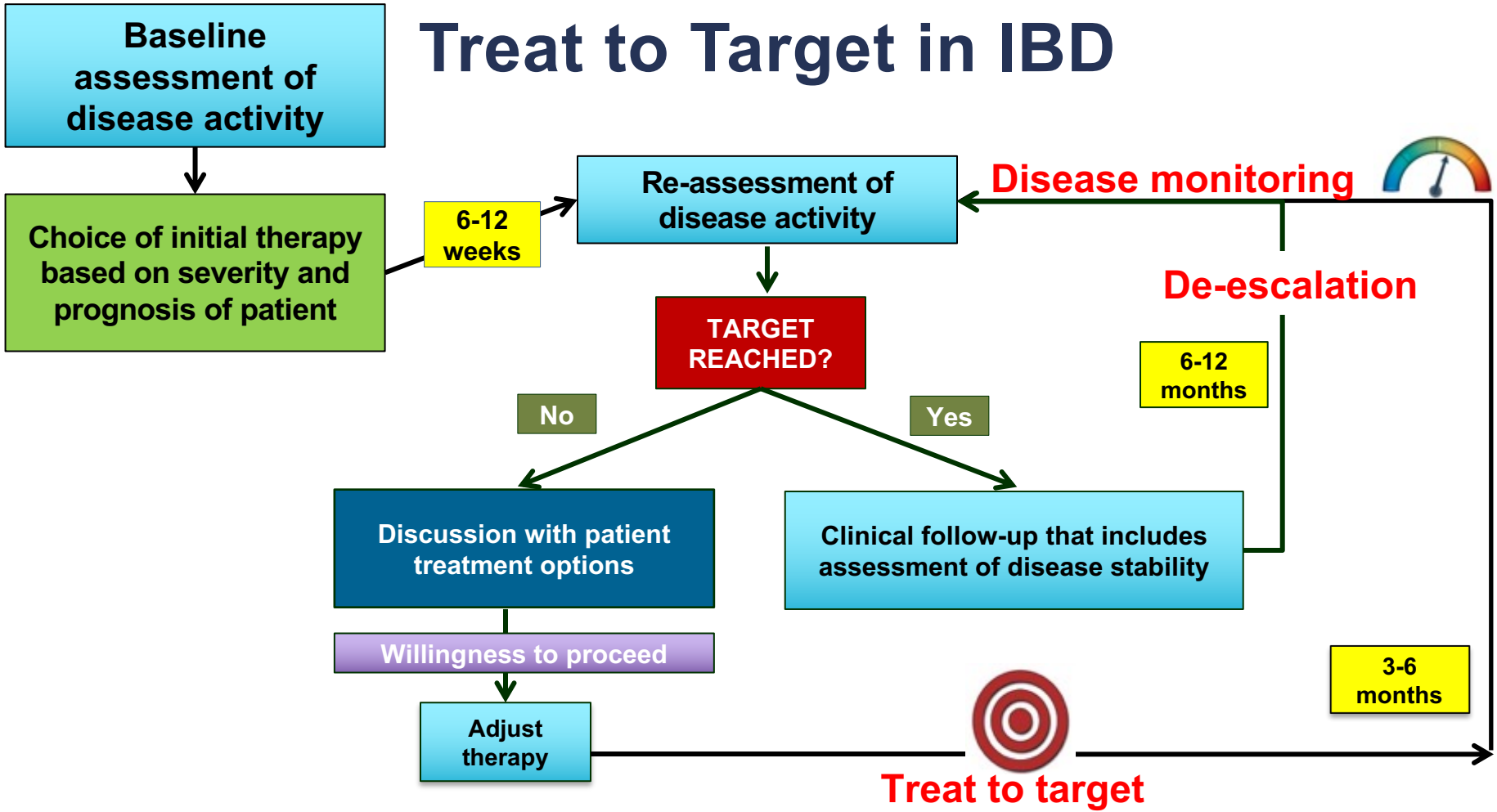
Sazanovs A, et al. *Gastroenterology*. 2020;158(1):189-199.

The Three Pillars of IBD Care



Colombel JF, et al. *Gastroenterology*. 2017;152(2):351-361. Danese S, et al. *Curr Drug Targets*. 2014;15(11):1056-1063.

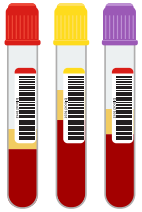
Treat to Target in IBD



Christensen B, Rubin DT. In: Baumgart DC, ed. *Crohn's Disease and Ulcerative Colitis*. 2nd ed. Cham, Switzerland: Springer Nature; 2017:267-278.

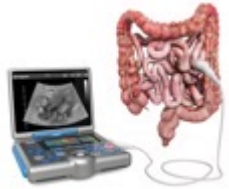
Monitoring Is Key

- Serum markers
  - CRP
  - Hemoglobin
  - Endoscopic Healing Index (EHI)



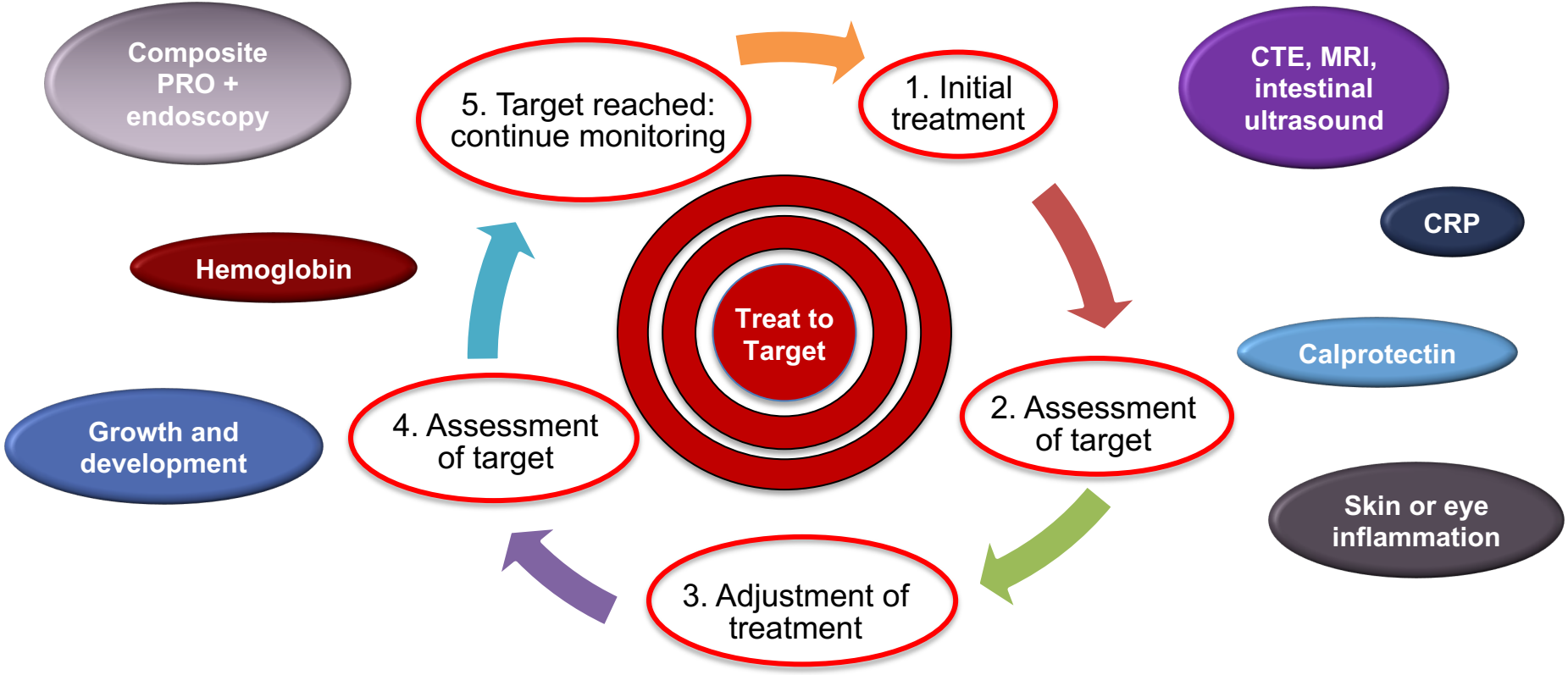
- Stool markers
  - Calprotectin
  - Lactoferrin

- Endoscopy
- Radiology
  - CTE
  - MRE
  - Intestinal ultrasound



CTE = computed tomography enterography; MRE = magnetic resonance enterography

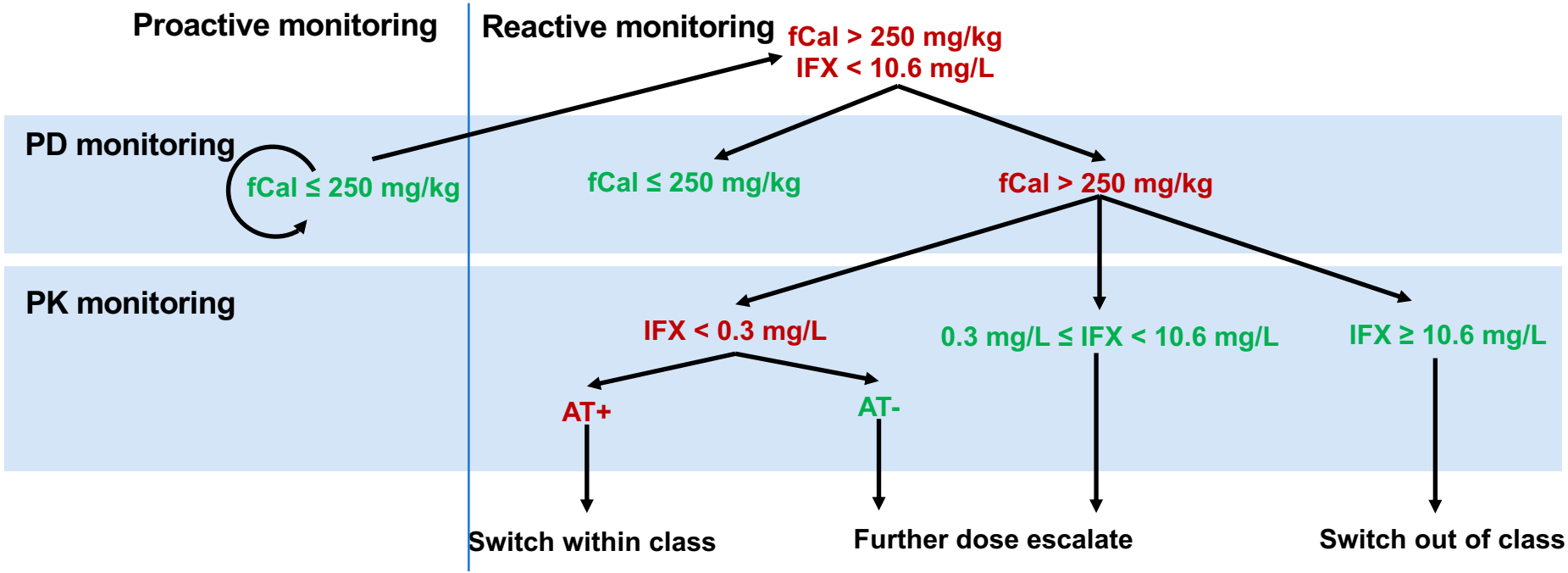
Targets Can Be Individualized



MRI = magnetic resonance imaging

Peyrin-Biroulet L, et al. *Am J Gastroenterol*. 2015;110:1324-1338. Turner D, et al. *Gastroenterology*. 2021;160(6):1570-1583.

Subclinical Disease Activity Defines Reactive TDM

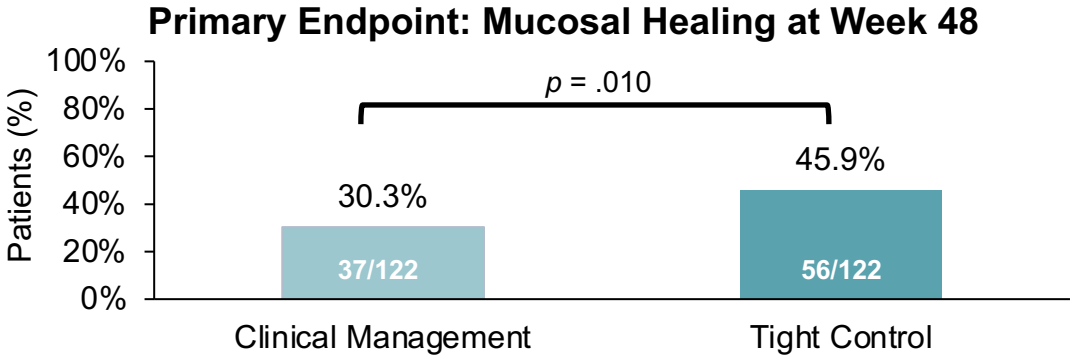


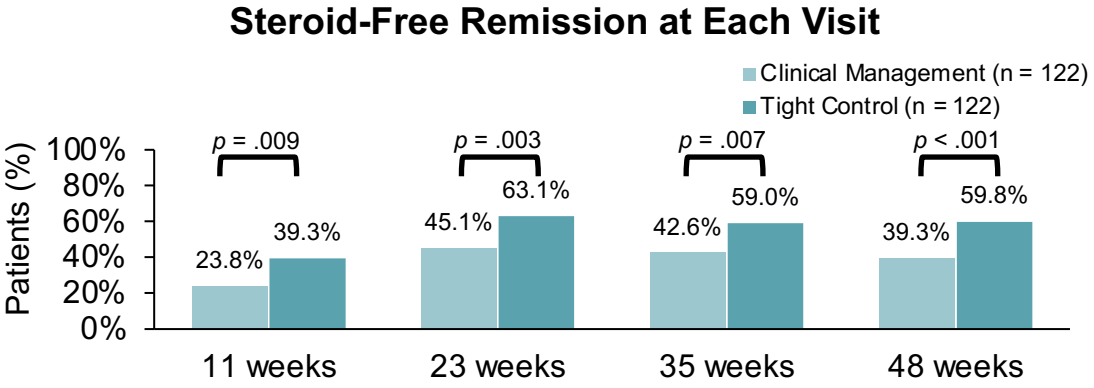
ATI = antibodies to infliximab; fCal = fecal calprotectin; PD = pharmacodynamic; PK = pharmacokinetic

Dreesen E, et al. *Clin Gastroenterol Hepatol*. 2020;18(3):637-646.e11.

CALM Trial: More Mucosal Healing and Steroid-Free Remission at Week 48 with Tight Control Monitoring

- Tight control group
  - Fewer hospitalizations
  - Longer periods of remission
  - Higher costs due to monitoring
  - Increase quality adjusted life-years



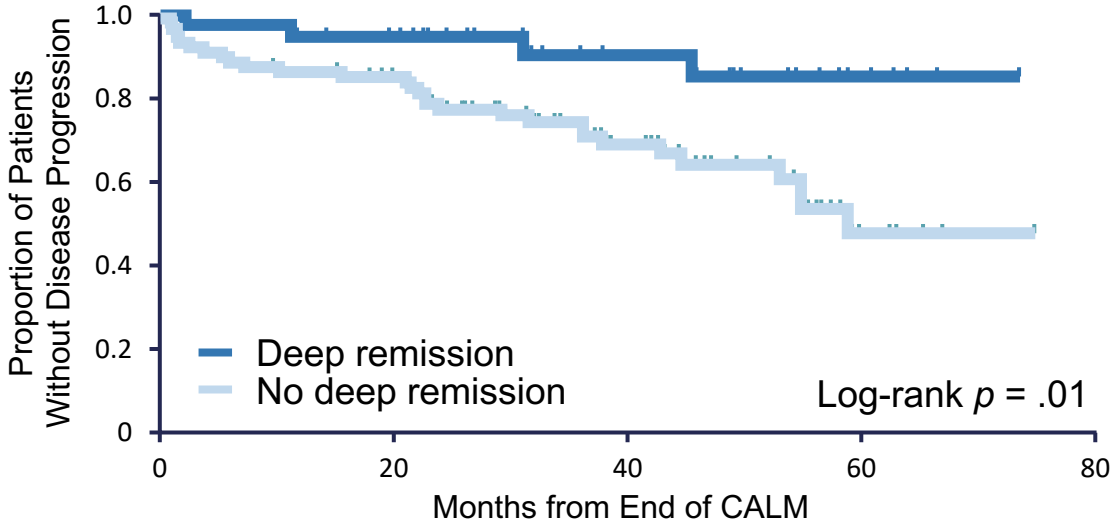


Colombel JF, et al. *Lancet.* 2017;390:2779-2789.

CALM Follow-up: Impact of Induction of Deep Remission on Disease Progression in CD

CD patients achieving endoscopic or deep remission after 1Y of tight control are less likely to have disease progression* over a median of 3 years

Kaplan-Meier Estimates of CD Disease Progression Based on Deep Remission at 1 Year



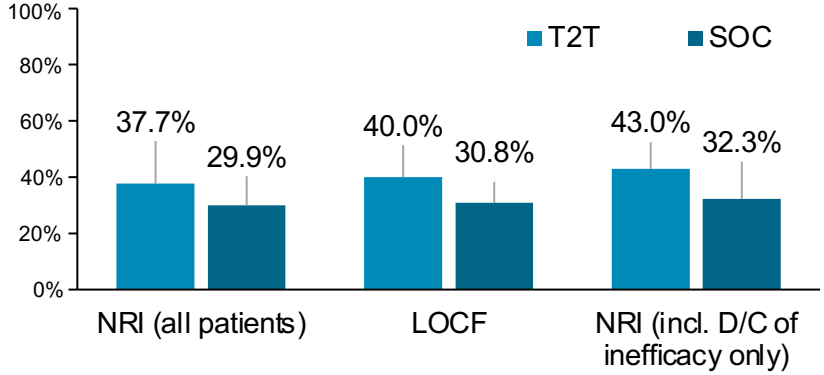
*Disease progression defined as composite of new internal fistula/abscess, stricture, perianal fistula/ abscess, CD hospitalization, or CD surgery since end of CALM

Ungaro RC, et al. *Gastroenterology*. 2020;159(1):139-147.

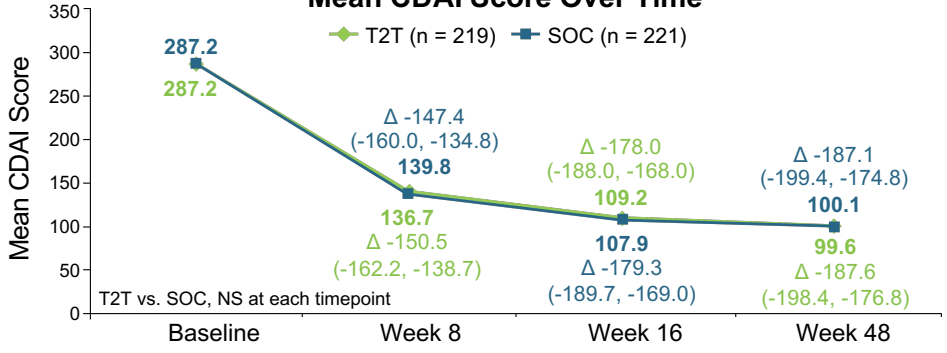
STARDUST: Treat-to-Target vs. Standard of Care with Ustekinumab in CD

- Primary endpoint:
  - Week 48 endoscopic response (defined as ≥ 50% ↓ in SES-CD from baseline)
- 441/500 patients re-randomized at week 8
  - T2T n = 220
  - SOC n = 221
- Week 48 completion: 79.1% T2T vs. 87.3% SOC
  - Similar improvements in SES-CD, mucosal healing, steroid-free endoscopic response, CDAI, and biomarkers between groups
  - No new safety signals

Endoscopic Response (SES-CD Improvement ≥ 50% [95% CI]) at Week 48 (RAS)



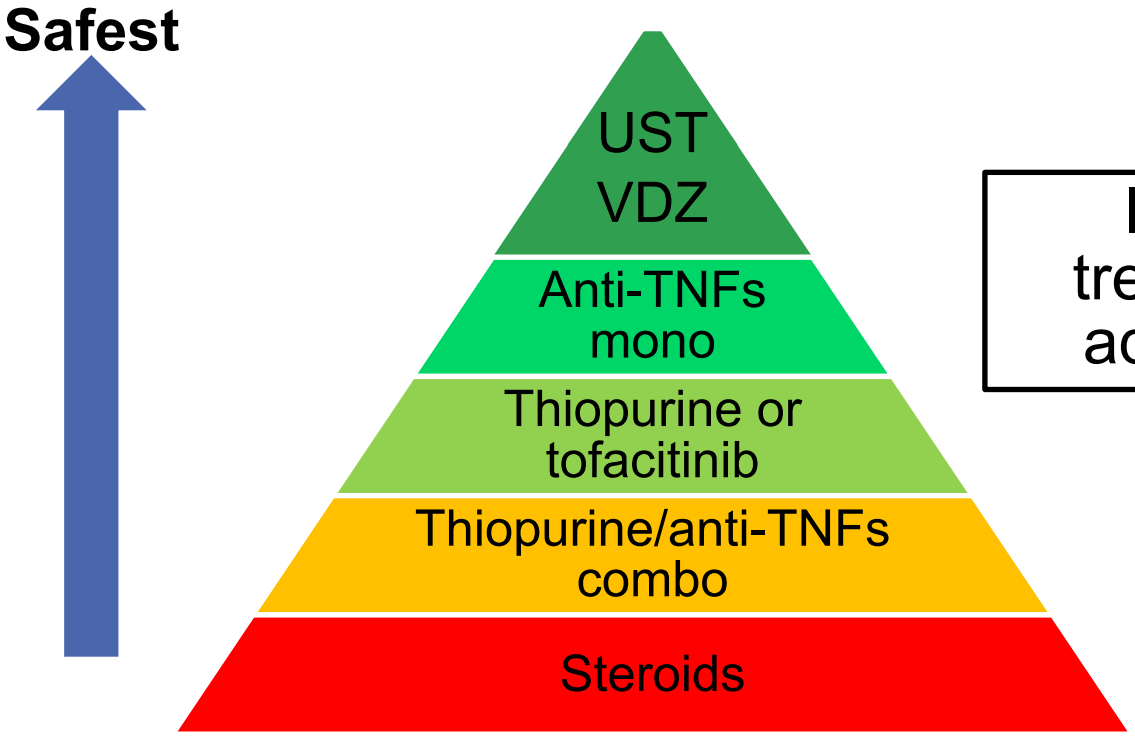
Mean CDAI Score Over Time



LOCF = last observation carried forward; NRI = nonresponder imputation; NS = nonsignificant; SOC = standard of care; T2T = treat-to-target

Danese S, et al. Presented at DDW; 2021. Abstract 105.

Safety Pyramid of Current IBD Medications



Inadequate treatment is an adverse event

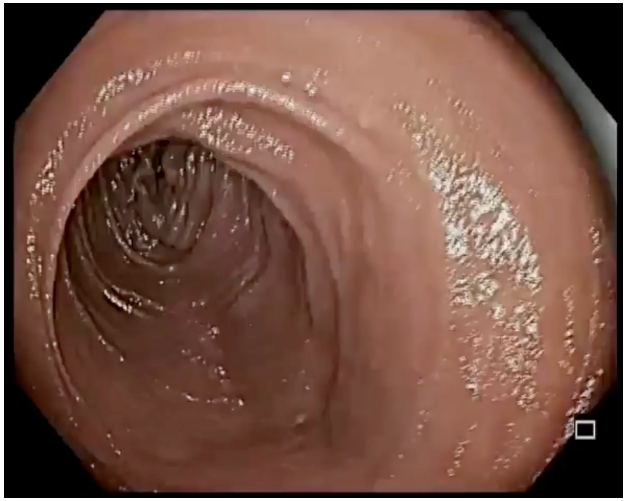
Click B, Regueiro M. *Inflamm Bowel Dis*. 2019;25(5):831-842.

Patient Case: Elle

- Adalimumab level is 14, no anti-drug antibodies
- Dose adjustment to weekly
- After 2 months (8 doses), CRP = 12, symptomatic

Patient Case: Elle

- Change to ustekinumab loading and injection therapy
- Scheduled for colonoscopy at 4 months



Patient Case: Elle

- Adalimumab level is 14, no anti-drug antibodies
- Dose adjustment to weekly
- After 2 months (8 doses), CRP = 12, symptomatic

- Inflammatory marker provide a predictive value, even when someone is feeling well
- It may be a sign that they may lose response, and still active inflammation driving this

SMART Goals

Specific, Measurable, Attainable, Relevant, Timely

- Personalized, targeted therapy best sets patients up for success throughout their journey
- Integrate risk stratification and disease prognosis into your treatment decision-making
- Factor efficacy, safety, tolerability, and convenience into your treatment decisions
- Optimize treatment by implementing an established monitoring plan

QUESTIONS & ANSWERS

Recorded on October 24, 2021

CME OUTFITTERS

Visit the Gastroenterology Hub

Free resources and education to educate health care providers and patients with Crohn's disease

https://www.cmeoutfitters.com/gastrohub/

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To receive CME/CE credit for this activity, participants must complete the post-test and evaluation online.

Participants will be able to download and print their certificate immediately upon completion.