New Era, New Science, New Antibodies

Niels Vande Casteele, PharmD, PhD
Assistant Professor
Department of Medicine
University of California San Diego

Waqqas Afif, MD
Associate Professor
Department of Medicine
McGill University

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Conflicts of interest

Niels Vande Casteele

- Investigator Initiated Research
  - R-Biopharm, Takeda, UCB
- Consulting & Speaker Fees
  - Alimentiv, Celltrion, Prometheus, R-Biopharm, Takeda, UCB

Waqqas Afif

- Consultant and investigator
  - Arena, Abbvie, Janssen, Takeda
- Consultant
  - Amgen, Ferring, Innomar, Merck, Mylan, Novartis, Pfizer
- Investigator
  - Prometheus/Theradiag/Dynacare

Case

- 25M, student, 50 kg BW, recently diagnosed with extensive UC 6 BM/day (5 more than baseline) with rectal bleeding and colonoscopy demonstrating ulcerations (Mayo Score: 9).
- Elevated CRP: 80 mg/L and albumin: 28 g/L. Started on oral prednisone (40 mg) with minimal help in clinical symptoms after 2 weeks, but still tolerating fluids and does not want to be admitted. Patient starting on IFX.

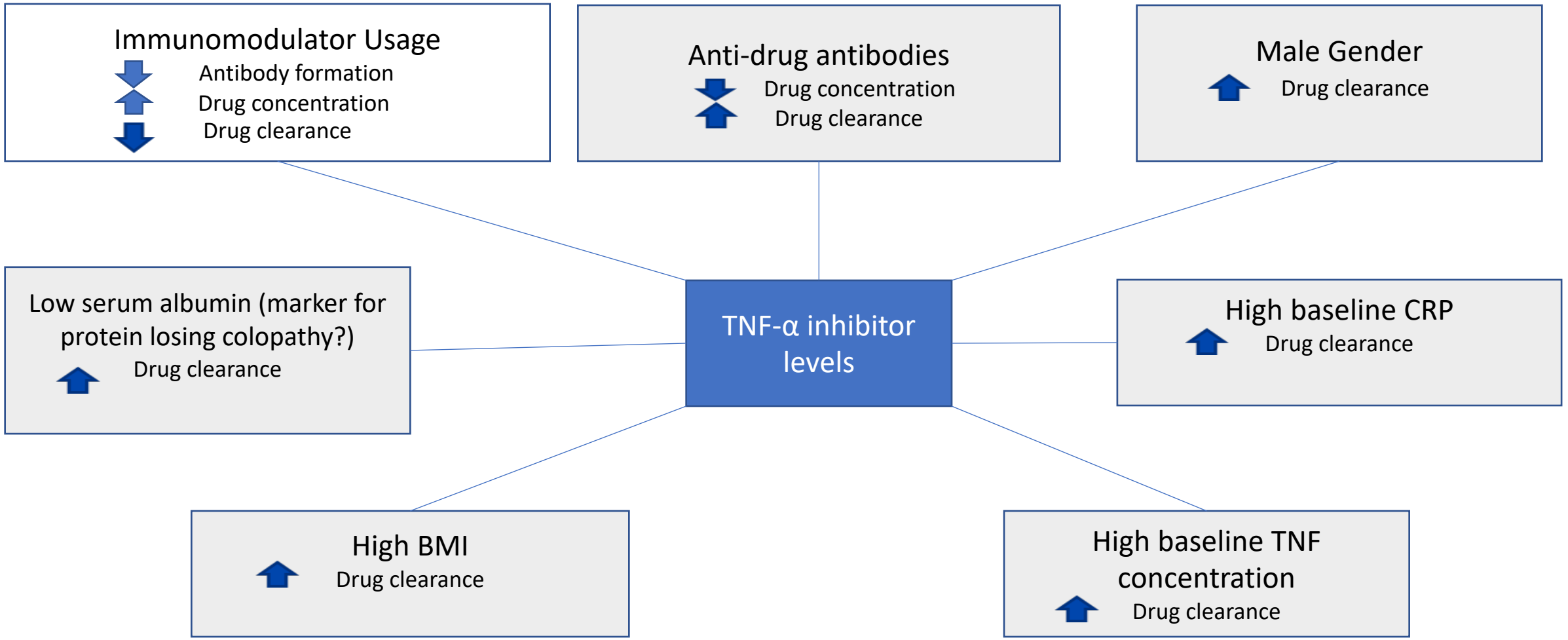
- ***<u>Discussion Points</u>: Would population pharmacokinetic models help to guide dosing? How can predictive models guide treatment monitoring? Would early proactive TDM during induction be useful and change clinical management?***

AGA guidelines on TDM : Reactive vs proactive

Statement	Strength of recommendation	Quality of evidence
In adults with active IBD treated with anti-TNF agents, the AGA suggests reactive therapeutic drug monitoring to guide treatment changes. Conditional recommendation, very low quality of evidence.	Conditional recommendation	Very low quality
In adult patients with quiescent IBD treated with anti-TNF agents, the AGA makes no recommendation regarding the use of routine proactive therapeutic drug monitoring.	No recommendation	Knowledge gap

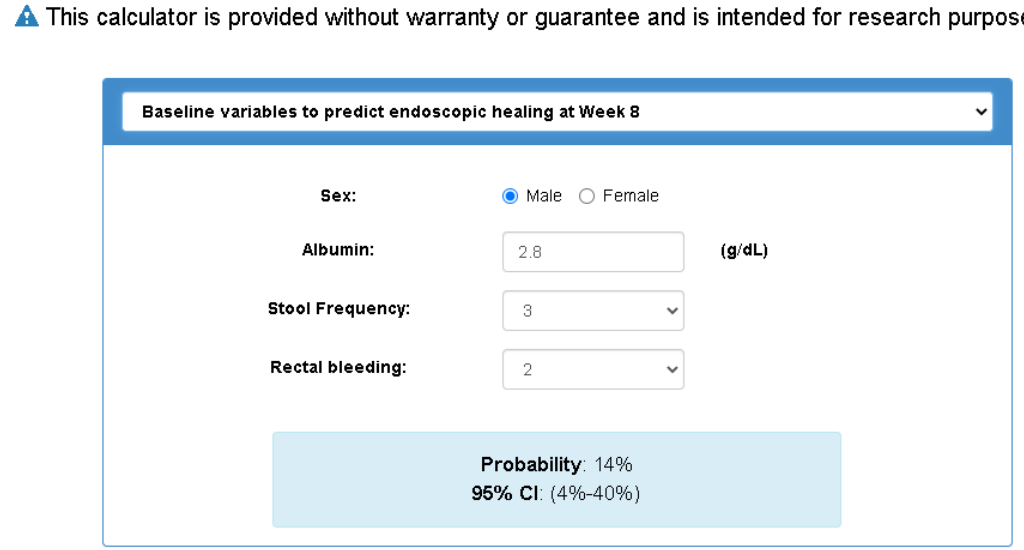
Vande Casteele, N. et al (2017) *Gastroenterology*, 1-23

Variables affecting TNF-α inhibitor concentrations

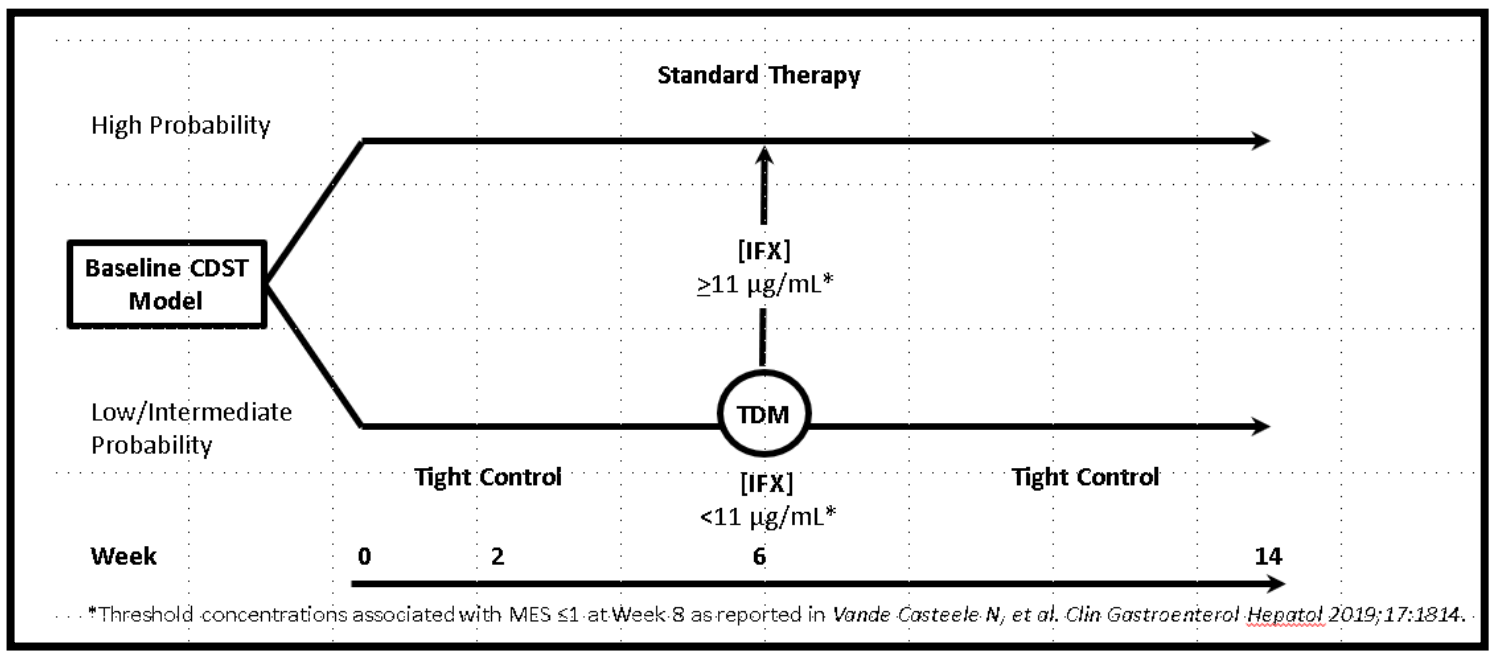


Ordás I, et al. Clin Gastroenterol Hepatol. 2012 Oct;10(10):1079.

Identifying patients at risk for accelerated drug clearance



www.premedibd.com



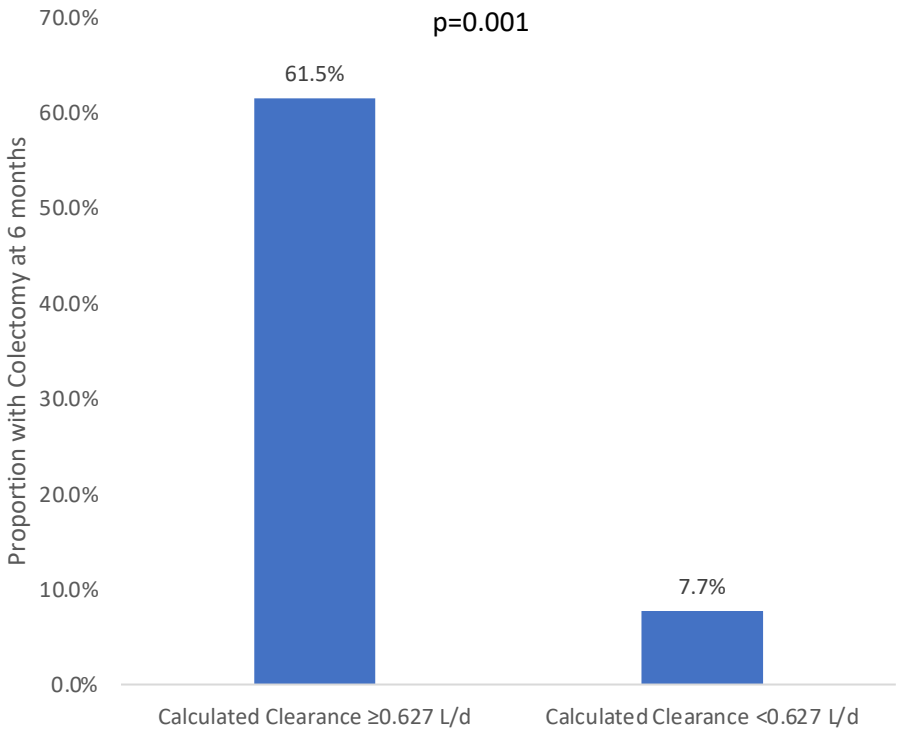
Vande Casteele N, *et al. Clin Gastroenterol Hepatol* 2020

Baseline clearance as a risk factor for colectomy in acute severe ulcerative colitis

- Hospitalized patients with acute severe ulcerative colitis (N=39)
- Calculated infliximab clearance at baseline

$$CL=0.407*(ALB/4.1)^{-1.54}*(1.471)^{ATI}*(0.764)^{sex}$$

- Threshold of 0.627 L/day (80% sensitivity, 83% specificity, AUC 0.80) associated with colectomy at 6m



Battat R, *et al. Clin Gastroenterol Hepatol* 2020 [Epub ahead of print]

Endoscopic Remission (IFX-UC)

Post hoc analysis ACT 1 & 2

- Endoscopic healing at Week 30 (MES ≤1)
  - Week 14 ≥5.1 µg/mL
  - Week 30 ≥2.3 µg/mL
- Endoscopic healing at Week 30 (MES =0)
  - Week 14 ≥6.7 µg/mL
  - Week 30 ≥3.8 µg/mL

Vande Casteele N, *et al. Clin Gastroenterol Hepatol* 2019;17:1814

Week 2 and 6 IFX Are Associated with Mucosal Healing at Week 12

TAILORIX

Endoscopic Remission at Week 12

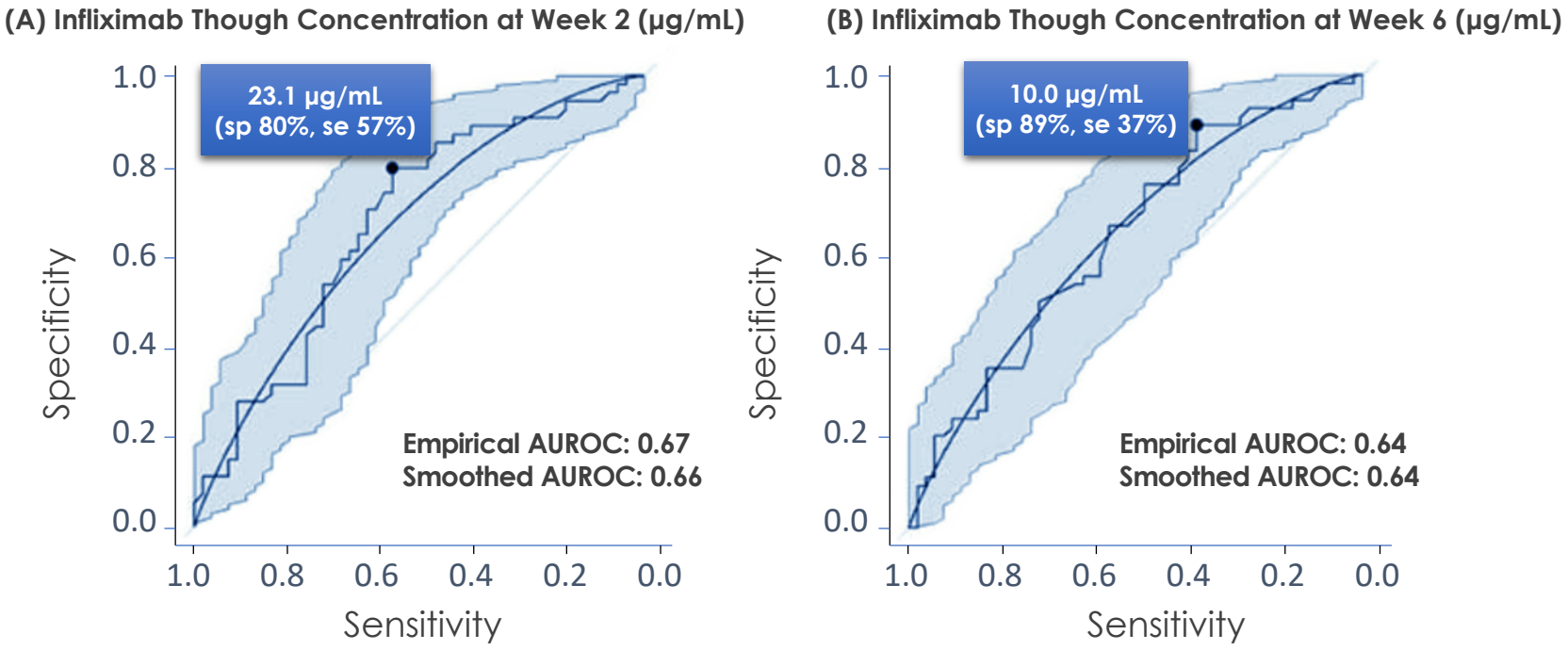


Figure 1. Receiver operating characteristic (ROC) curves of infliximab trough concentrations at (A) week 2 and (B) week 6, as a predictor of endoscopic remission at week 12.
se: sensitivity; sp: specificity; AUROC: area under the ROC curve.

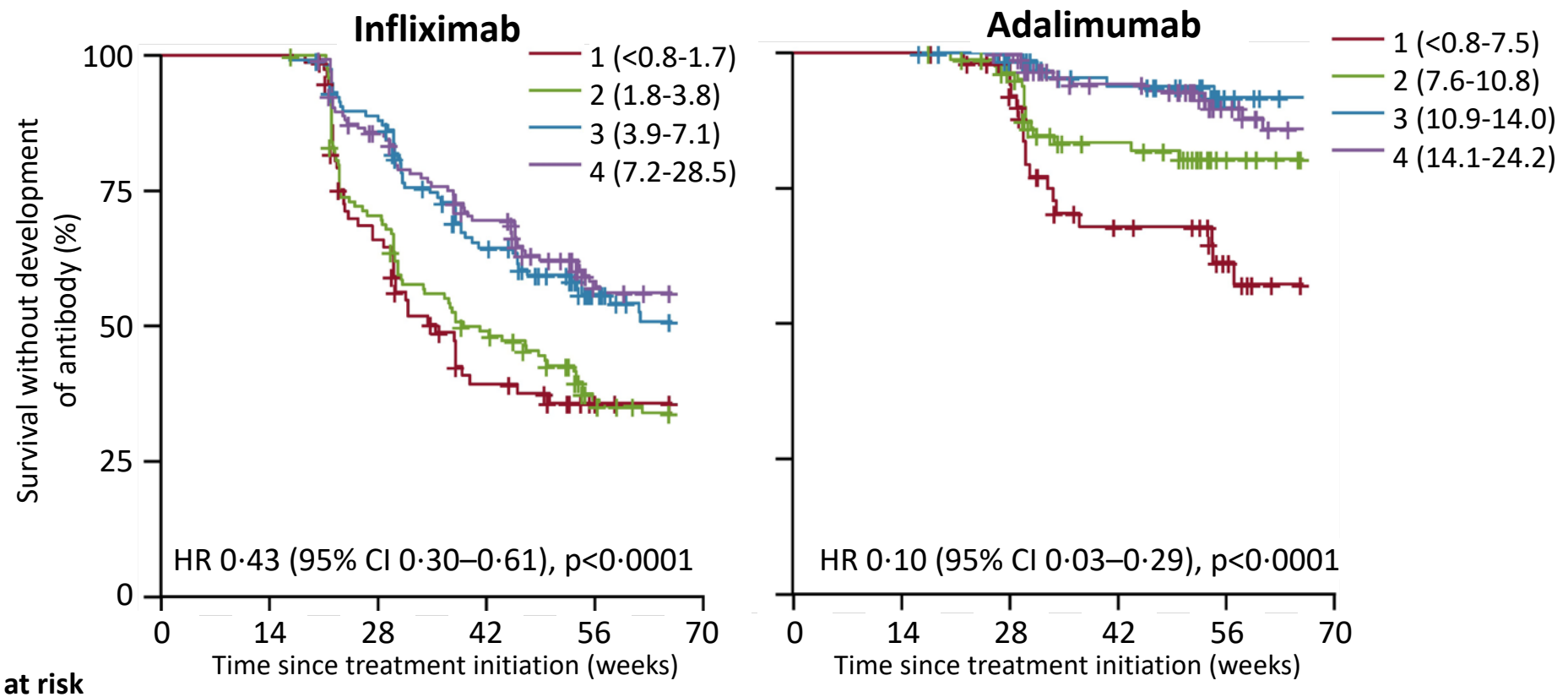
D'Haens et al., ECCO 2018, DOP047

Reduced time to immunogenicity was associated with lower Week 14 drug concentration quartiles

In MVA, drug concentration at week 14 was the major independent risk factor associated with time to immunogenicity for both drugs after that timepoint

Smoking (infliximab)/obesity (adalimumab) was also related to increased immunogenicity

HLA-DQA1*05 allele, carried by approximately 40% of Europeans, significantly increased the rate of immunogenicity (hazard ratio [HR], 1.90; 95% confidence interval [CI], 1.60–2.25; $P = 5.88 \times 10^{-13}$).



Number at risk

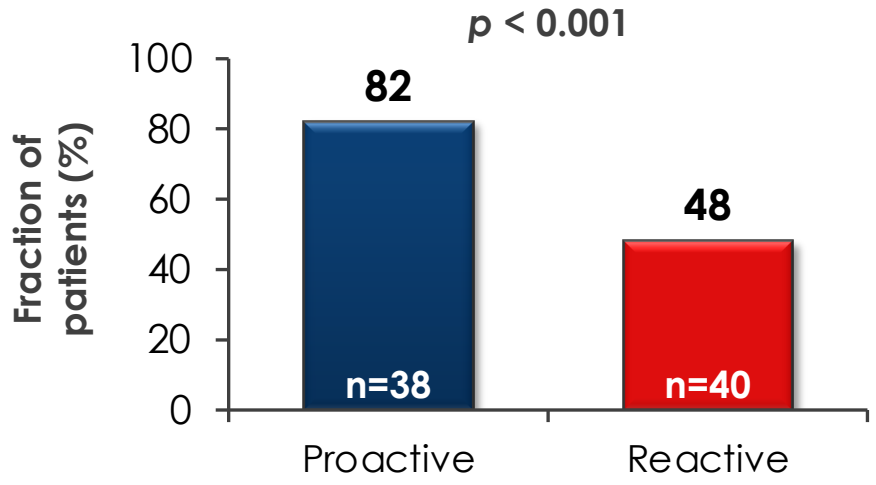
4 (highest)	136	136	112	88	56	94	94	93	75	51
3	118	118	103	67	39	77	77	71	57	38
2	120	120	83	56	32	85	86	78	57	39
1 (lowest)	79	79	49	24	15	55	55	49	26	17

Kennedy NA et al. *Lancet Gastroenterol Hepatol* 2019; 4: 341–53

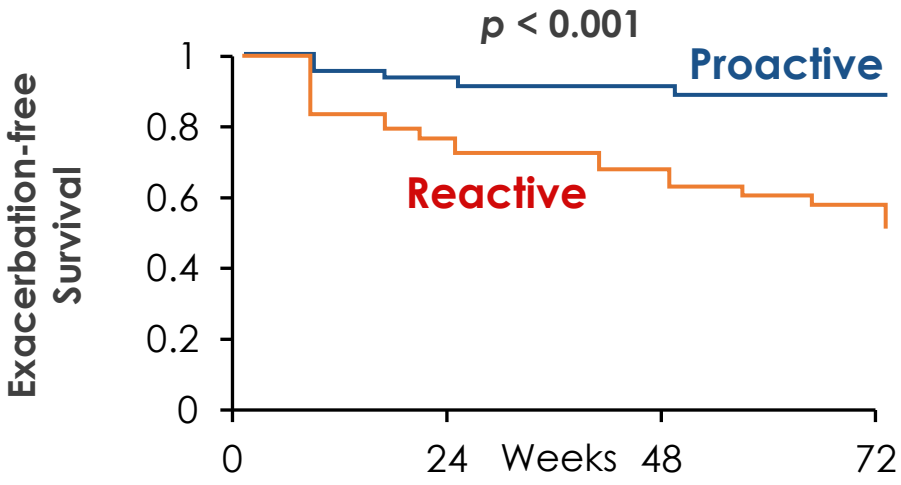
Proactive Adalimumab Trough Measurements Increase CS-Free Clinical Remission in Pediatric CD

PAILOT

Sustained CS-Free Remission (PCDAI<10) Week 8-72



Time to Disease Exacerbation



- OL RCT N=80 Bx-naïve ped CD pts – ADL responders randomized to proactive or reactive TDM (wk 4, 8 & q8wk to wk 72): Target TL = 5µg/mL; Co-IS (45%)
- Proactive ADL TDM led to more dose adjustments (87% vs. 60% p<0.001) and resulted in improved clinical outcomes

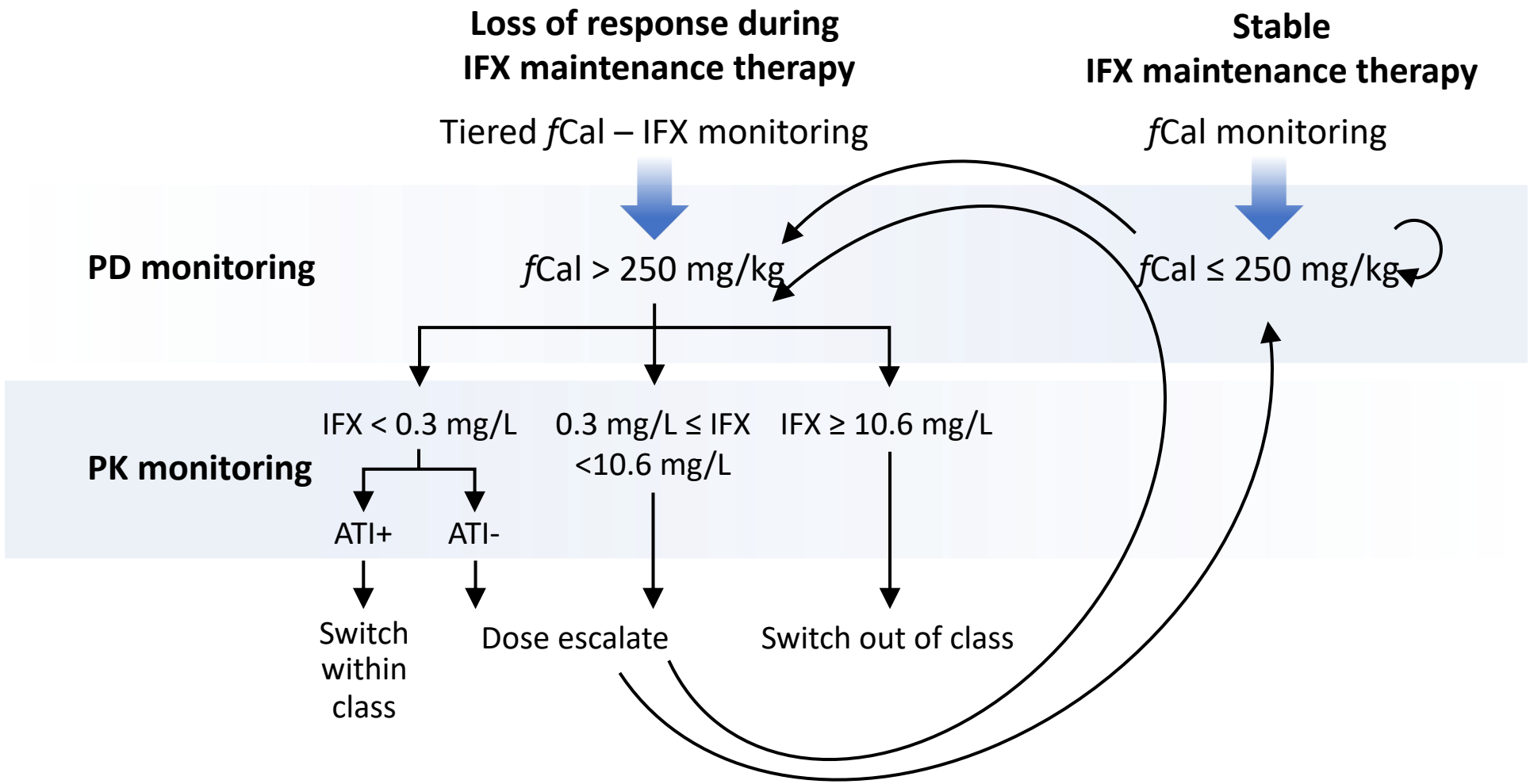
Assa et al. ECCO 2019, OP18

Case (continued)

- Patient achieves clinical and endoscopic remission on IFX post dose escalation to 5 mg/kg Q6 weeks.
- After 6 months, loss of response with partial Mayo score of (4). CRP: 20 mg/L and FCP: 450 µg/g. Sigmoidoscopy shows left sided Mayo 2 colitis.

- ***<u>Discussion Points</u>: Reactive TDM (dose escalation vs changing biologics) with anti-TNF's: Would a reactive TDM be useful and would it change clinical management?***

Proposed algorithm for LOR



ATI: antibodies to IFX, fCal: fecal calprotectin, IFX: infliximab, PD: pharmacodynamic, PK: pharmacokinetic

ECCO 2018: Post Hoc:: D'Haens et al., Gastroenterology, Jan 2018

Case (continued)

- Given high titer antibodies patient is switched to a biologic with lower immunogenicity. Patient starts ustekinumab. At 4 months, partial response on Q8 weeks.

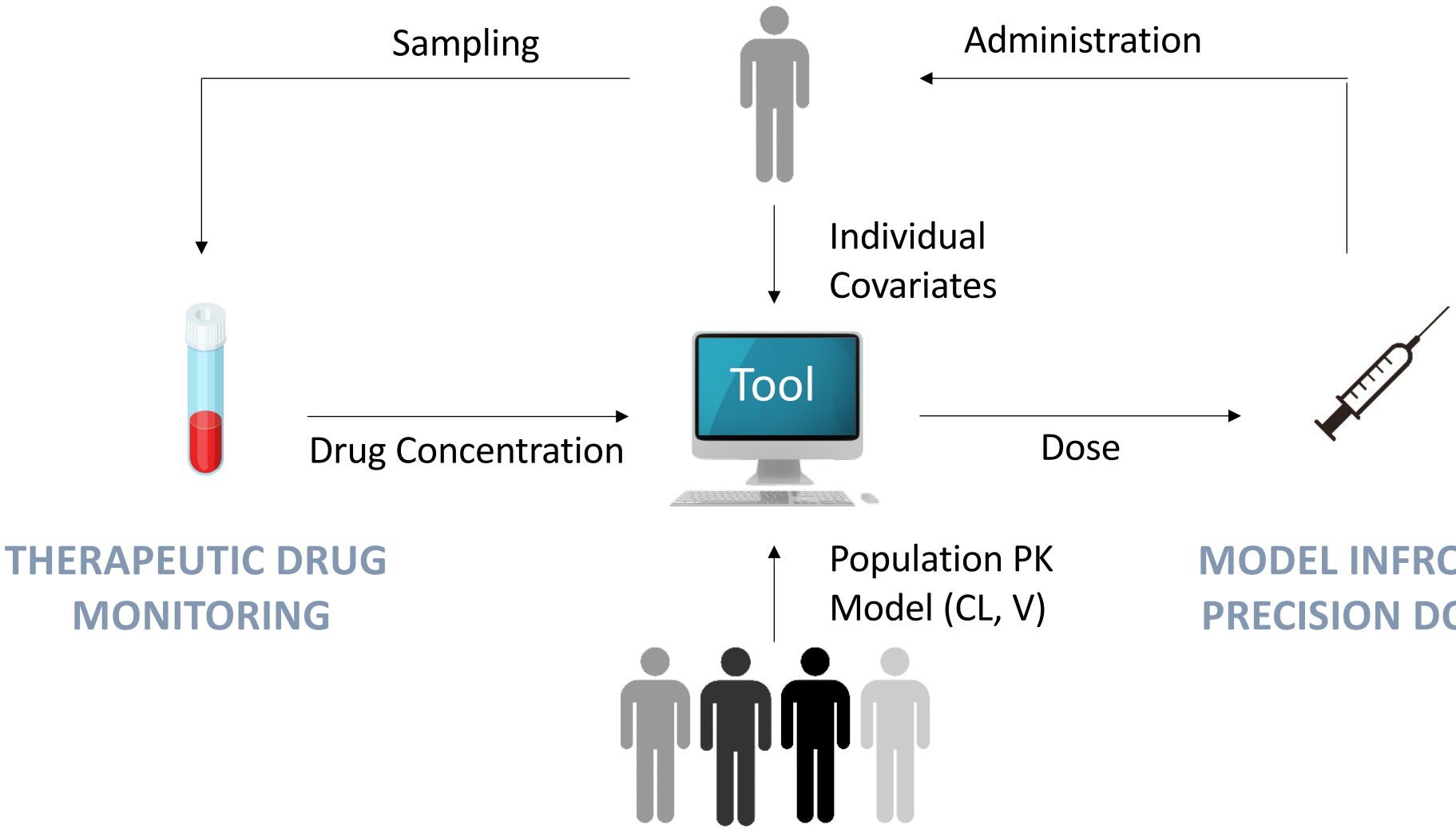
- ***<u>Discussion Points:</u> Reactive TDM with non-anti-TNF biologics: Would a reactive TDM be clinically useful and would it change clinical management? Would this approach be different if the patient was on vedolizumab? Would the advent of machine learning approaches have changed anything?***

Trough concentrations of UST and VDZ associated with improved outcomes

Drug	Time Period	Approximate trough concentrations associated with improved outcome	Outcome Measure
Ustekinumab	Induction (Week 8)	3.2-3.9 ug/ml	Clinical
	Maintenance	1.0-2.0 ug/ml	Clinical/Endoscopic
Vedolizumab	Induction (Week 6)	33.7-38.3 ug/ml	Clinical/Endoscopic
	Maintenance (Q8 dosing)	5.1-11.0 ug/ml	Clinical/Endoscopic

Restellini, Khanna and Afif et al, IBD 2018

Model Informed Precision Dosing (MIPD)

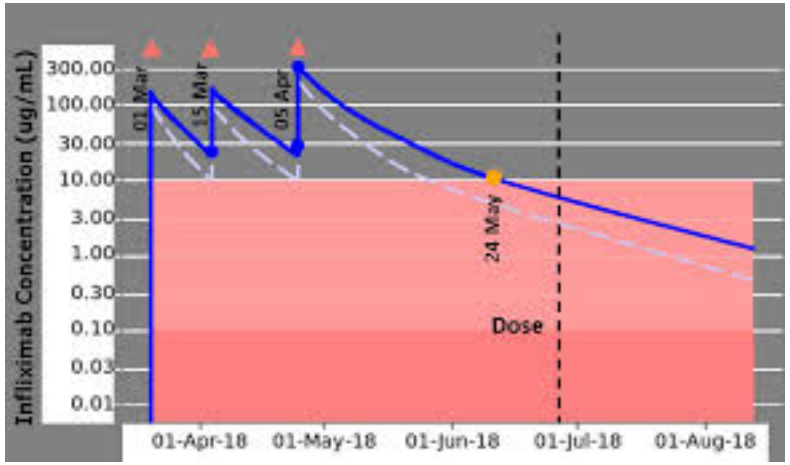


iDOSE

- Developed by Baysient

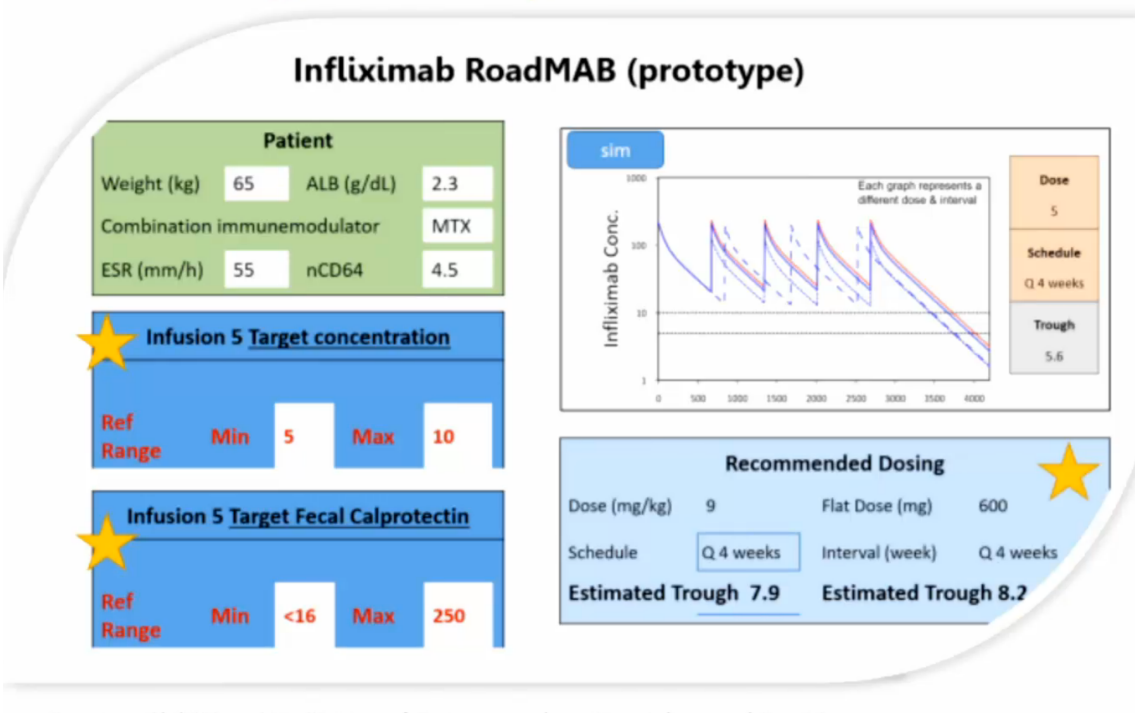
- Calculates dose for individual patient based on
  - Target trough concentration
  - Dosing history
  - Covariates
  - Observed level (Bayesian stats)

Dashboard system



Strik A, et al. DDW, San Diego, CA, 2019

RoadMAB



- Developed by UNC
- Calculates dose for individual patient based on
  - Target trough concentration
  - Dosing history
  - Covariates
  - Observed level (Bayesian stats)
- Will be integrated in REDCap

Vinks S, et al. FDA Precision Dosing Workshop, Silver Spring, MD, Aug 12 2019