THERAPEUTIC DRUG MONITORING: OVERCOMING THE HURDLES

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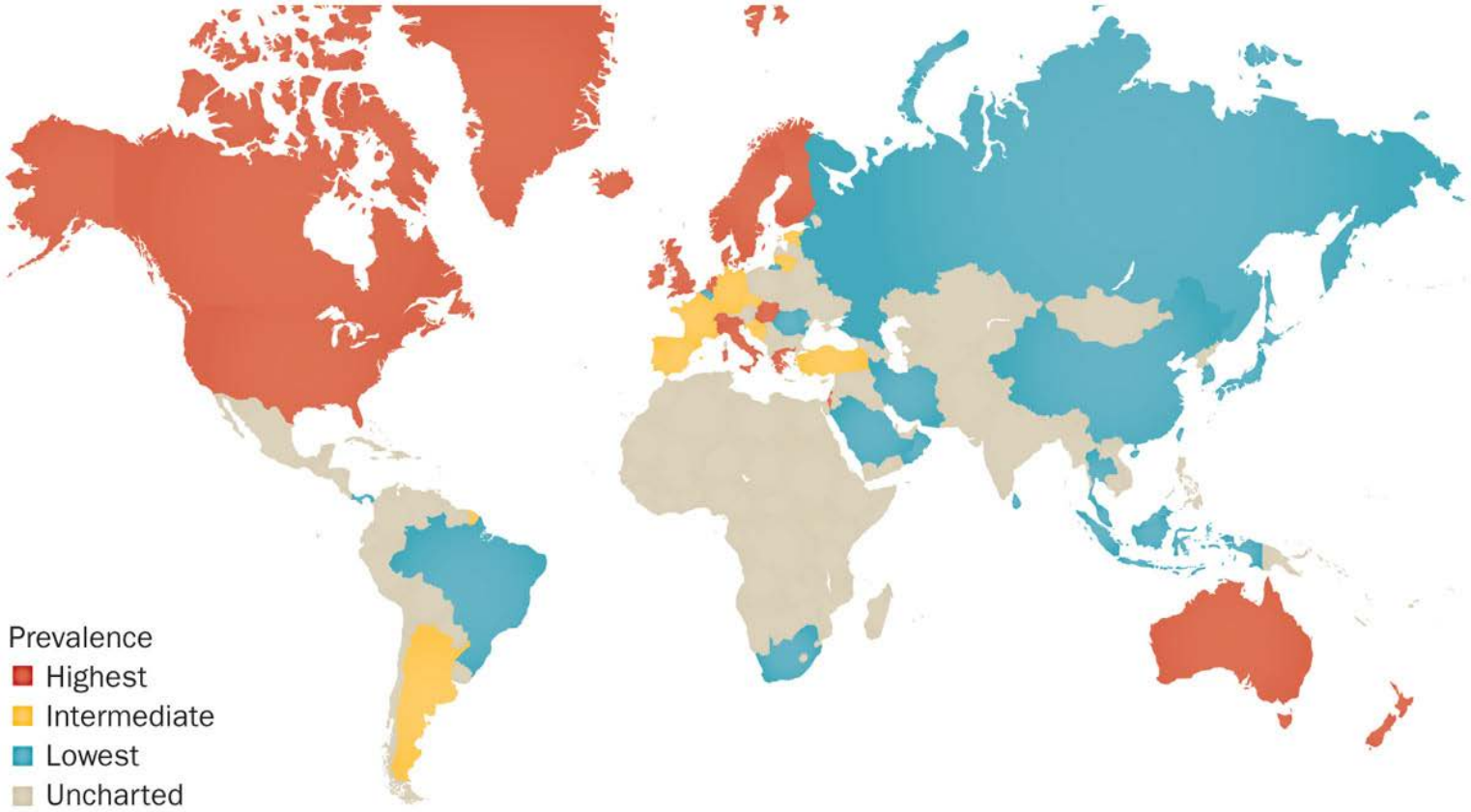
DISCLOSURES

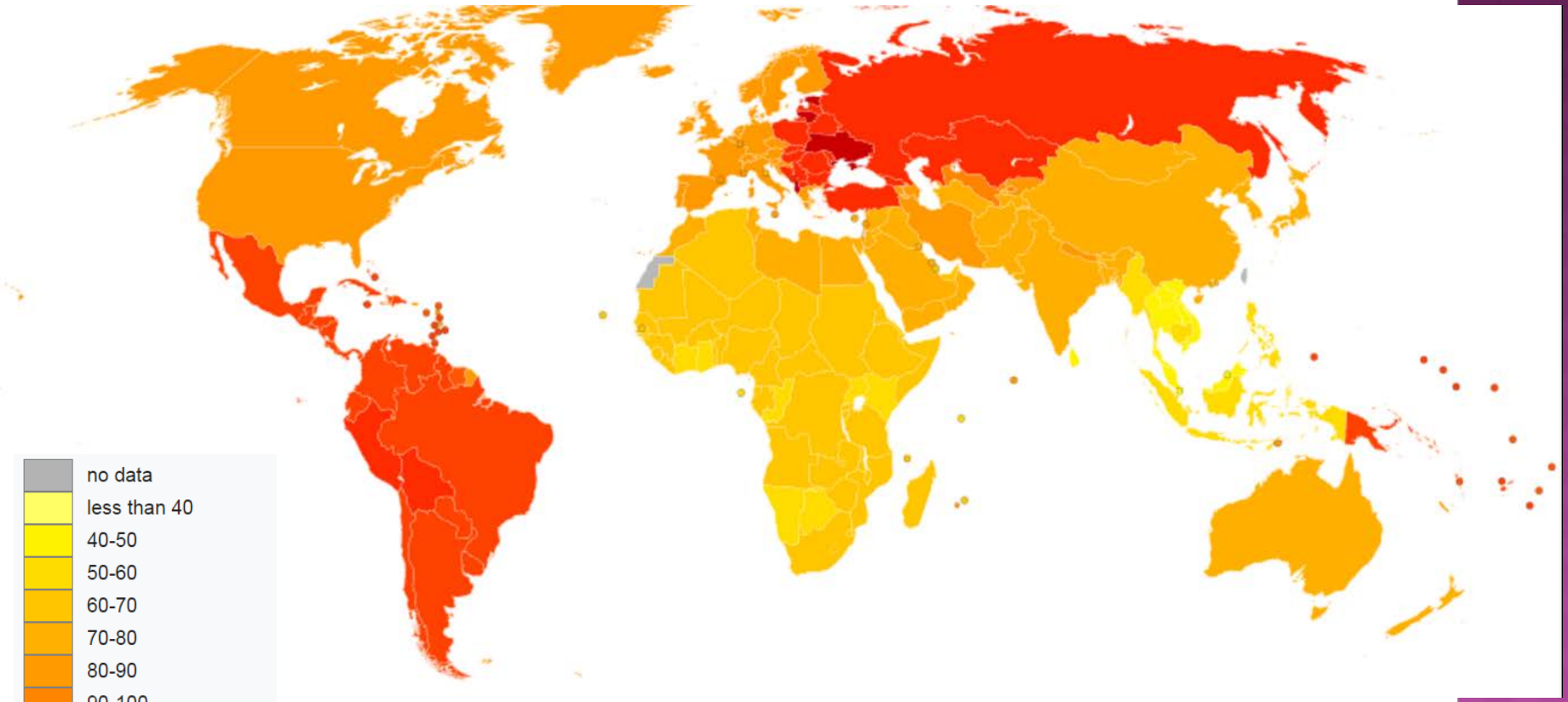
- Diane Mould is president of Projections Research Inc., a consulting company working with the pharmaceutical industry

GLOBAL PREVALENCE OF IBD



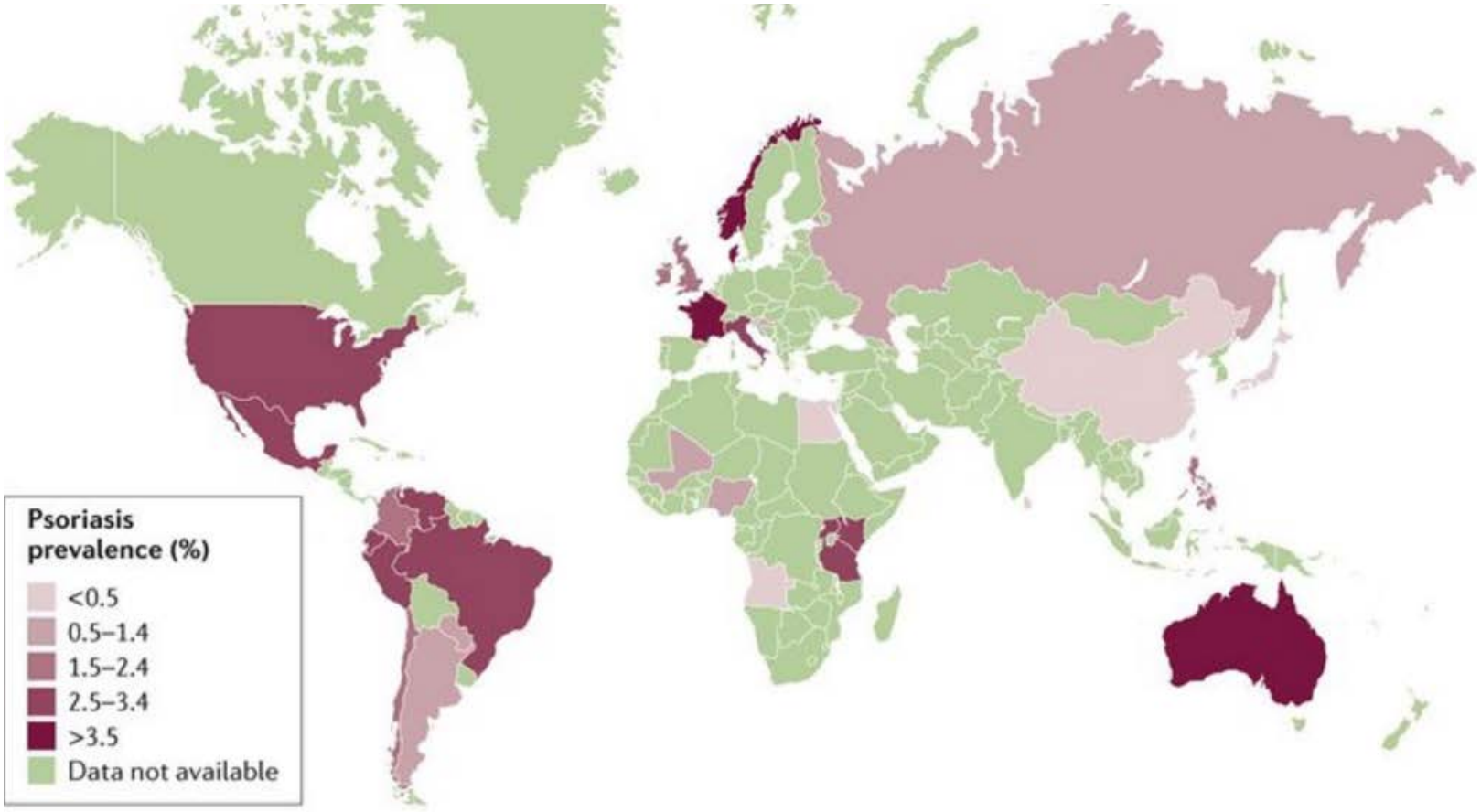
Kaplan, G. G. *Nat. Rev. Gastroenterol. Hepatol.*.2015.150

GLOBAL PREVALENCE OF RA



Age-standardized disability-adjusted life year (DALY) rates from Rheumatoid arthritis by country (per 100,000 inhabitants)

GLOBAL PREVALENCE OF PSORIASIS



Greb JE Psoriasis Nature Reviews 24 November 2016

COMORBIDITY WITH RA

Co-morbidity	n (%)
Hypertension (HTN)	**122 (35.9)**
Diabetes mellitus (DM)	105 (30.9)
Osteoporosis	88 (25.8)
Dyslipidemia	66 (19.4)
Peptic ulcer disease (PUD)	35 (10.3)
Hypothyroidism	29 (8.5)
Chronic liver disease (CLD)	26 (7.6)
Ischemic heart disease (IHD)	25 (7.4)
Bronchial asthma	23 (6.8)
Tuberculosis (TB)	**15 (4.4)**
Cardiovascular accidents (CVA)	**13 (3.3)**
Interstitial lung fibrosis (ILF)	9 (2.7)
Malignancy	**9 (2.7)**
Chronic renal failure (CRF)	8 (2.4)
Deep venous thrombosis	7 (2.1)
Hyperthyroidism	4 (1.2)
Inflammatory bowel disease (IBD)	1 (0.3)
Other	36 (0.0)

J Al-Bishri Clin Med Insights Arthritis Musculoskelet Disord. 2013; 6: 11–18.

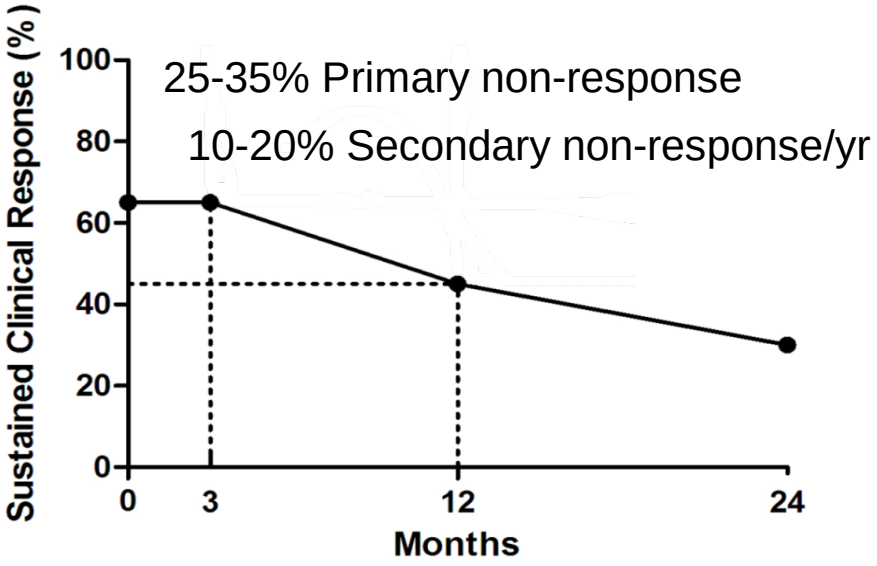
COMORBIDITY WITH IBD

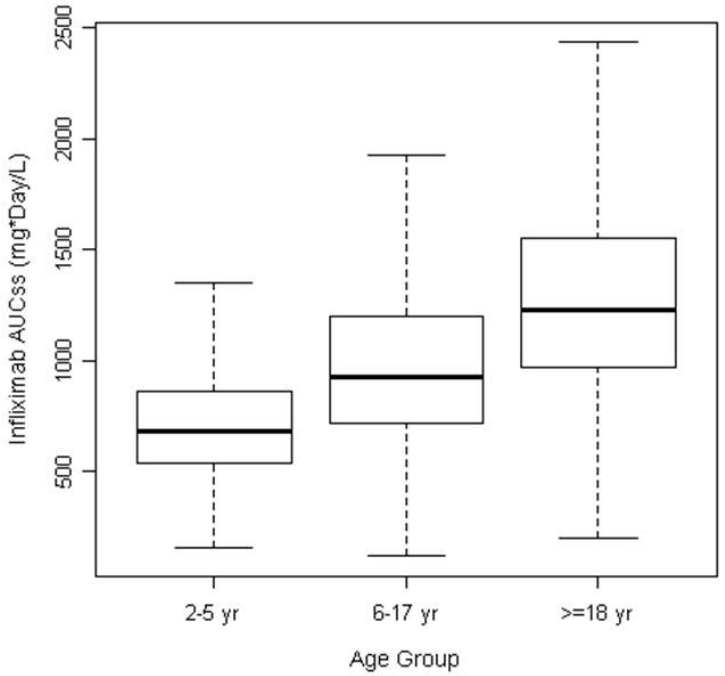
Extraintestinal manifestations	Adverse effects of treatments	Comorbid conditions	Direct consequences of the disease
Peripheral and axial arthritis	Steroids: cataracts, glaucoma, mood changes, osteoporosis…	Cardiovascular	Abdominal and retroperitoneal scarring: hydronephrosis, intestinal obstruction, female infecundity…
Erythema nodosum, pyoderma gangrenosum, oral aphtae	Immunosuppressors : infections, neoplasia, liver toxicity, myelosuppression…	Hepatic, biliary, pancreatic, digestive	Consequences of intestinal resection: malabsorption, short bowel syndrome, oxalate nephrolithiasis
Uveitis, episcleritis, blepharitis	Biologics: infections, neoplasia, demyelinizing disease, infusion	Metabolic: obesity	Persistent inflammation: osteoporosis, amyloidosis
Primary sclerosing cholangitis	Reactions, drug-induced lupus	Neuropsychiatric	

Antonio López San Román and Fernando Muñoz Comorbidity in inflammatory bowel disease.World J Gastroenterol. 2011 Jun 14; 17(22): 2723–2733.

OVERVIEW

- Many of the agents used to treat inflammatory diseases are MAbs
- Complex pharmacokinetics
  - Many factors impact MAb PK
  - High interpatient variability
  - PD affects PK
- Currently high treatment failure rate in adult
  - Many patients show no response to induction therapy (primary non-responders)
  - Responders can lose response over time (secondary non-responders)
- Frequently lower exposure in pediatrics than adults
  - Higher failure rate in pediatrics
- Some of the loss of response is due to ADA but in other patients, low trough levels were associated with poor outcomes

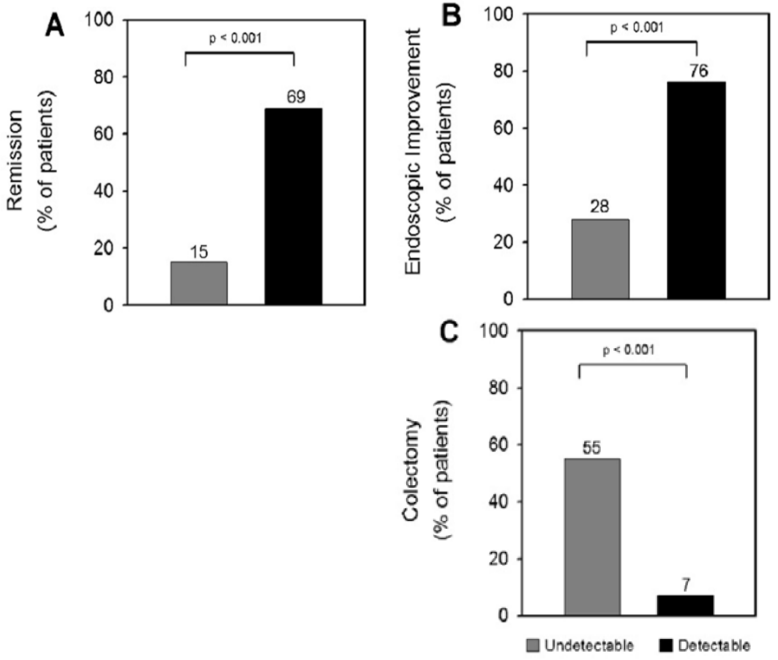


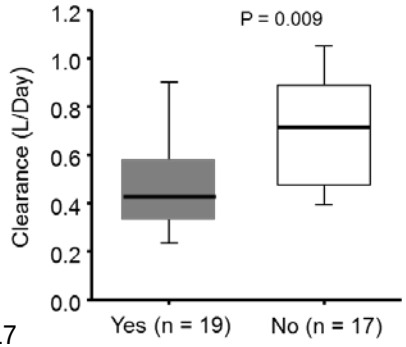


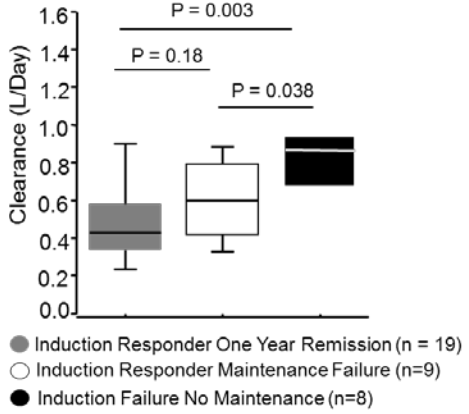
I Ordás, DR Mould, BG Feagan, WJ Sandborn Clin. Pharmacol. Ther. 91(4):635-46 2012
Z Xu, DR Mould, C Hu, et al "A Population-Based Pharmacokinetic Pooled Analysis of Infliximab in Pediatrics" ACCP National Meeting 2012 San Diego CA.

JUSTIFICATION OF PK ASSOCIATION WITH THERAPEUTIC FAILURES

- Association of low troughs with therapeutic failure
  - Published studies of MAb PK don't point to high variability but covariate impacts are large
    - Data from severe patients often not included in these assessments
- Association of high clearance with therapeutic failures

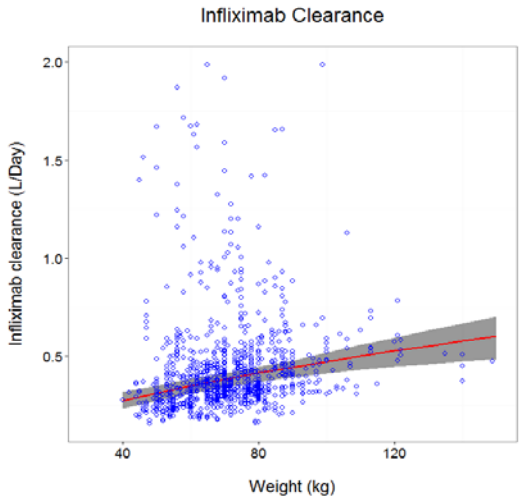


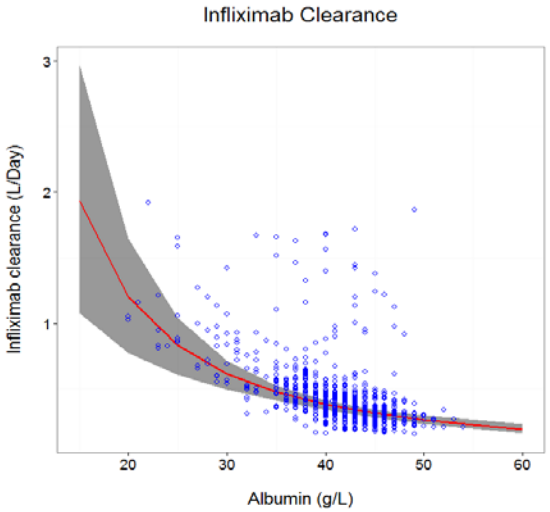


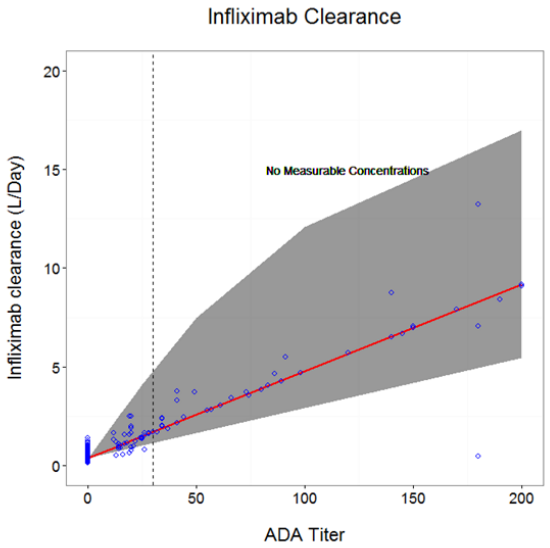


Seow CH. et al . Gut. 2010;59(1):49-54
M. Silverberg et al Alimen Pharmacol Ther submitted 2017

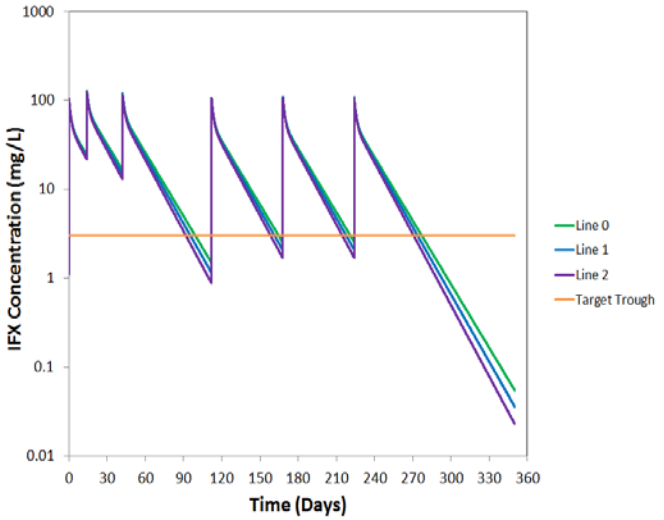
MULTIPLE FACTORS IMPACT MAB PK





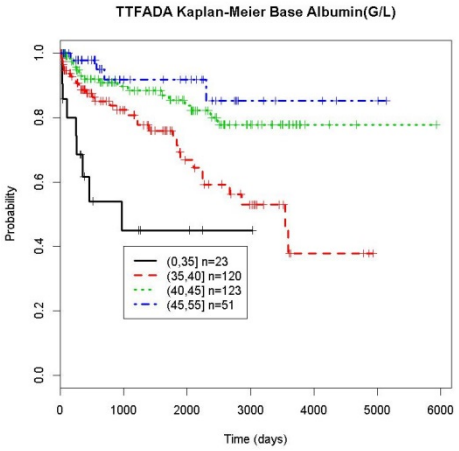


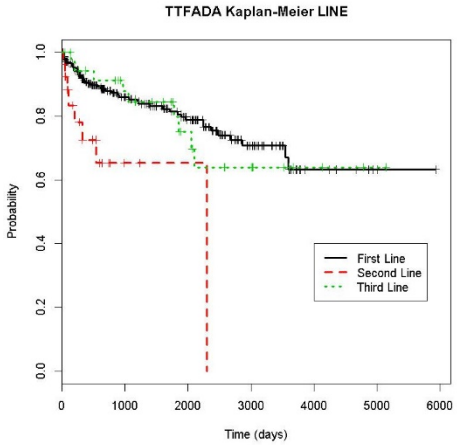
- Impact of low ALB and high ADA titer very large
  - Low ALB or high ADA implies fast clearance
- Impact of weight minor
  - High weight, high clearance
- Other factors
  - Diabetes/hyperglycemia can increase clearance > 20%
  - Concomitant immunosuppressants can decrease clearance by 20%
  - Disease severity
  - Route of administration can impact ADA
  - FcRn saturation

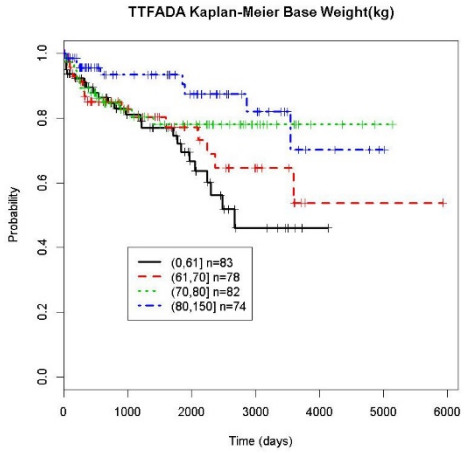


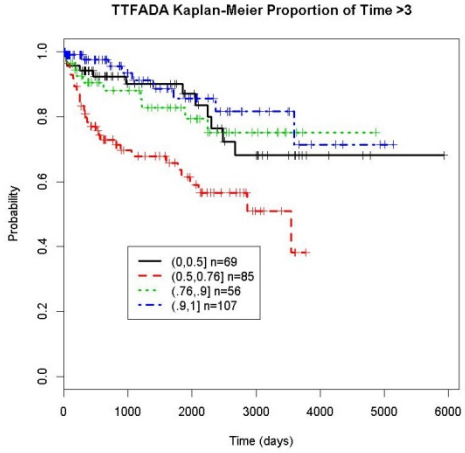
Brandse JF, et al. Presented at 10th Congress of ECCO; February 18-21, 2015; Barcelona, Spain. Abstract P473.

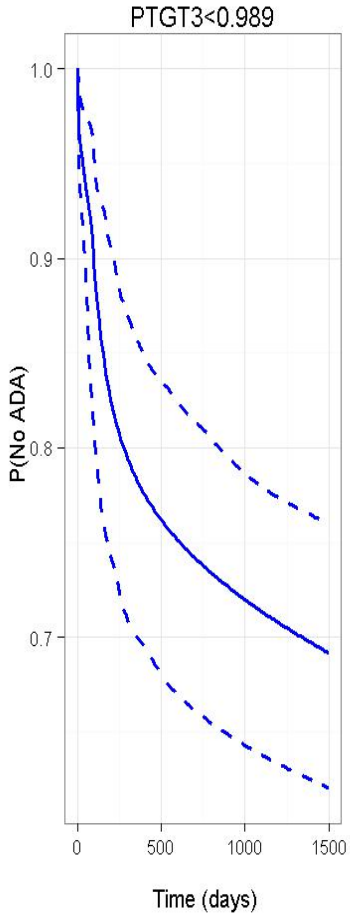
MAINTAINING MEASURABLE CONCENTRATIONS IS IMPORTANT

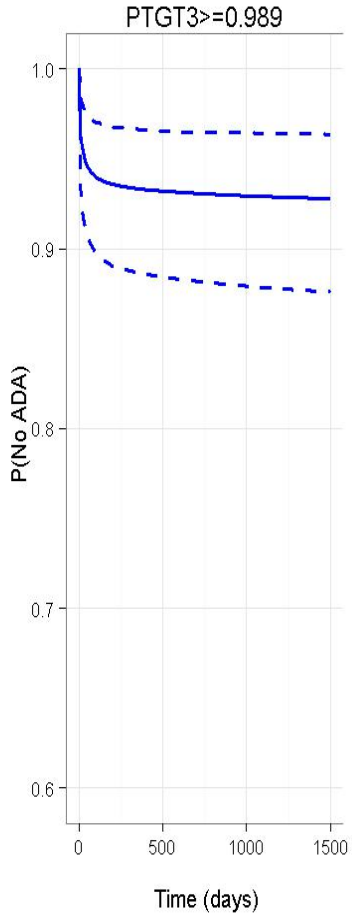












ECCO = European Crohn's and Colitis Organisation.
Brandse JF, et al. Presented at 11th Congress of ECCO; March 18, 2016; Amsterdam, The Netherlands. Abstract DOP068.

THERAPEUTIC DRUG MONITORING FOR MABS

- Unlike TDM for small molecules, MAbs generally don't have narrow therapeutic window
  - TDM application here is not to avoid adverse events, but potentially to improve efficacy
- No prospective correlation between exposure (troughs) and response for many marketed MAbs
  - What trough is appropriate?
- Expect between subject variability for PD to be higher than PK

Papamichael K et al Clin Gastroenterol Hepatol. 2016 Apr;14(4):543-9

THERAPEUTIC DRUG MONITORING

- TNF antagonists have shown benefits in randomized controlled trials for inducing and maintaining clinical remission in inflammatory diseases
- Owing to the high variability in drug exposure the use of therapeutic drug monitoring (TDM) has become common in clinical practice
  - Common in EU, Asia, middle east, Canada
  - Less common in US
- The use of TDM and individualized dose adjustments retrospectively shown to improve outcomes, and often reduce therapy costs

Peyrin-Biroulet, L., et al.. *Clin. Gastroenterol. Hepatol.* **6**, 644–653 (2008).
Seow, C.H. et al. *Gut* **59**, 49–54 (2010).
Vande Casteele N, et al. Gastroenterology. 2015;148(7):1320-9

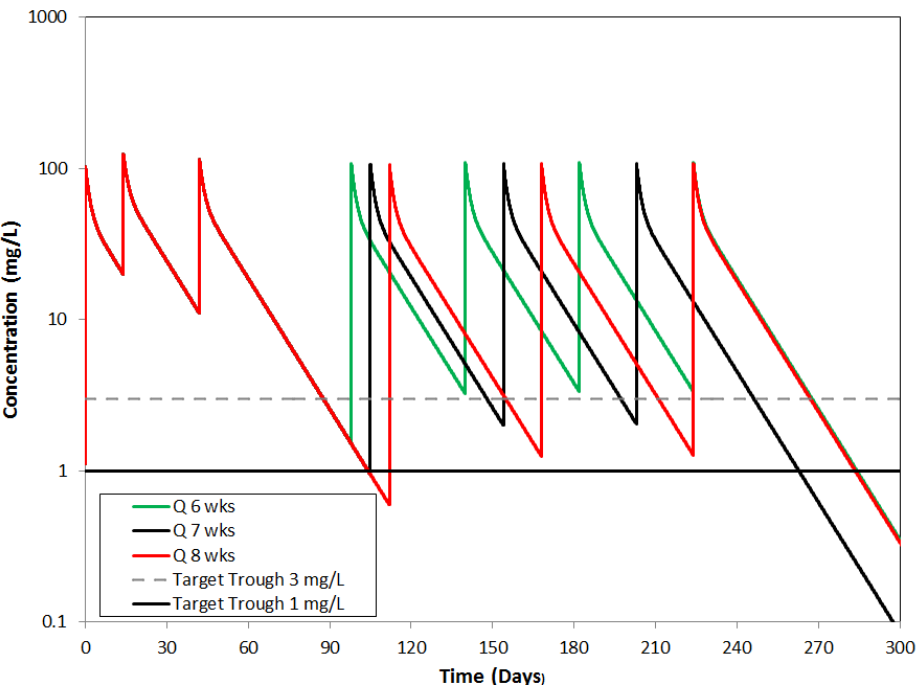
ISSUES WITH IMPLEMENTING TDM

- Many US insurance companies do not reimburse for this expense
  - TDM is not in the prescribing instructions for marketed MAbs
  - No prospective trials showing clear benefit
    - While there are publications suggesting clinical benefit and cost reduction, most are retrospective
    - Need to test all MAbs? All indications?
- Assay costs in US can be quite high ($250 to $2500 per assay)
- Turnaround time long (5-7 days for contract labs) so information comes in after dose was administered.
  - Point of care assays needed
- Difficulty in interpreting results (complex PK, increasing dose doesn't always result in higher troughs)

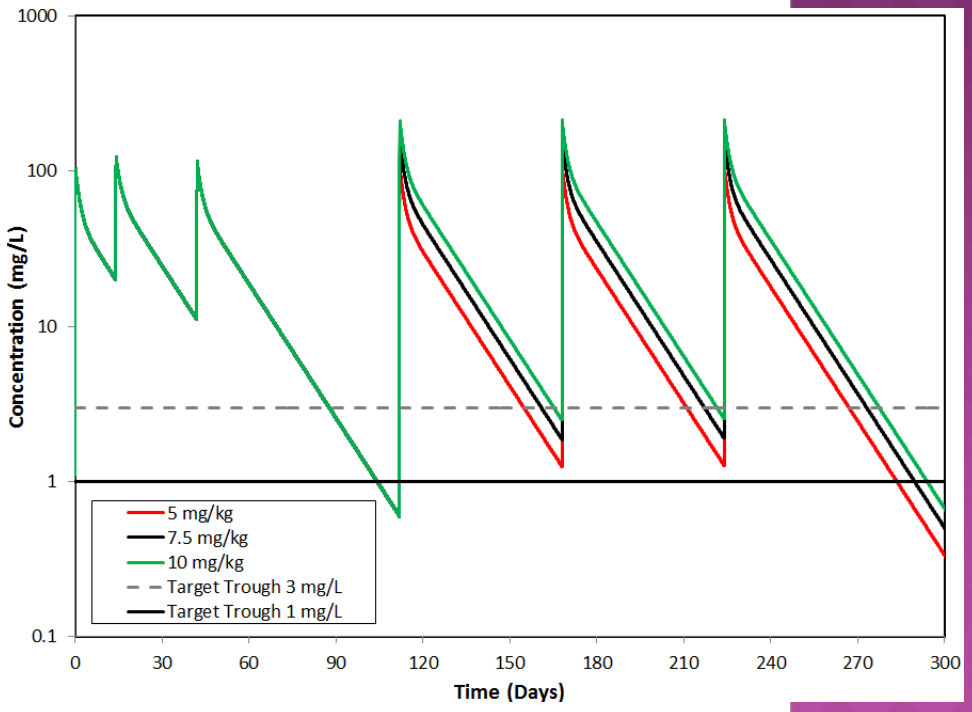
TREATMENT ADJUSTMENTS BASED ON TDM

- Patients treated with therapeutic anti-TNF MAbs often dose adjusted to maintain concentrations above a therapeutic trough
  - Panel A – shorten interval
  - Panel B – Increase dose
- Owing to the impact of multiple factors on PK, dose adjustment not intuitive

A



B

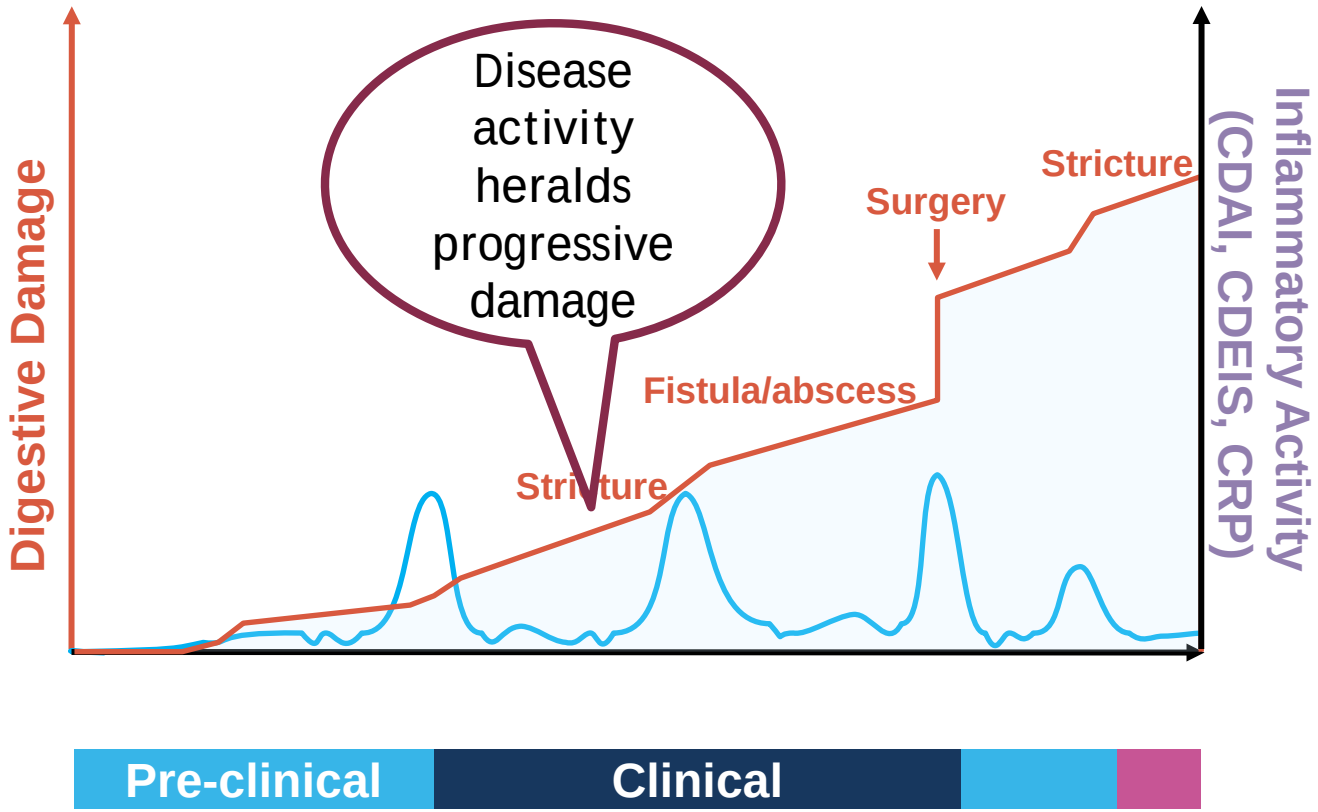


I Dotan et al *Inflamm Bowel Dis*. 2014 Dec;20(12):2247-59

INCORPORATING TDM AND DASHBOARDS INTO DISEASE MANAGEMENT

- Are therapeutic failures due to insufficient drug exposure?
  - Can loss of response be reversed with appropriate dosing?
  - Can ADA be managed with dashboards?
- Can TDM combined with dashboard guided dosing reduce failure rate
  - Integration into workflow
  - How often to monitor
  - How to find the “right trough” for each patient
  - Many unanswered questions
- MAbs have complex PK but it’s a simple PK problem.
  - However underlying computations are complex

PROGRESSION OF DIGESTIVE DISEASE DAMAGE AND INFLAMMATORY ACTIVITY



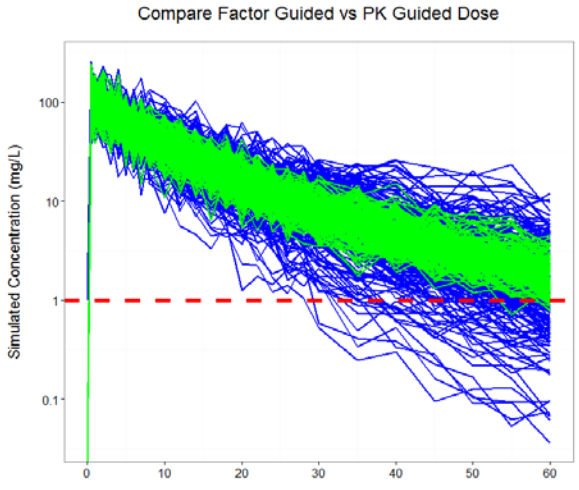
Can we prevent disease flare by more effective PK control? What are effective dose approaches?

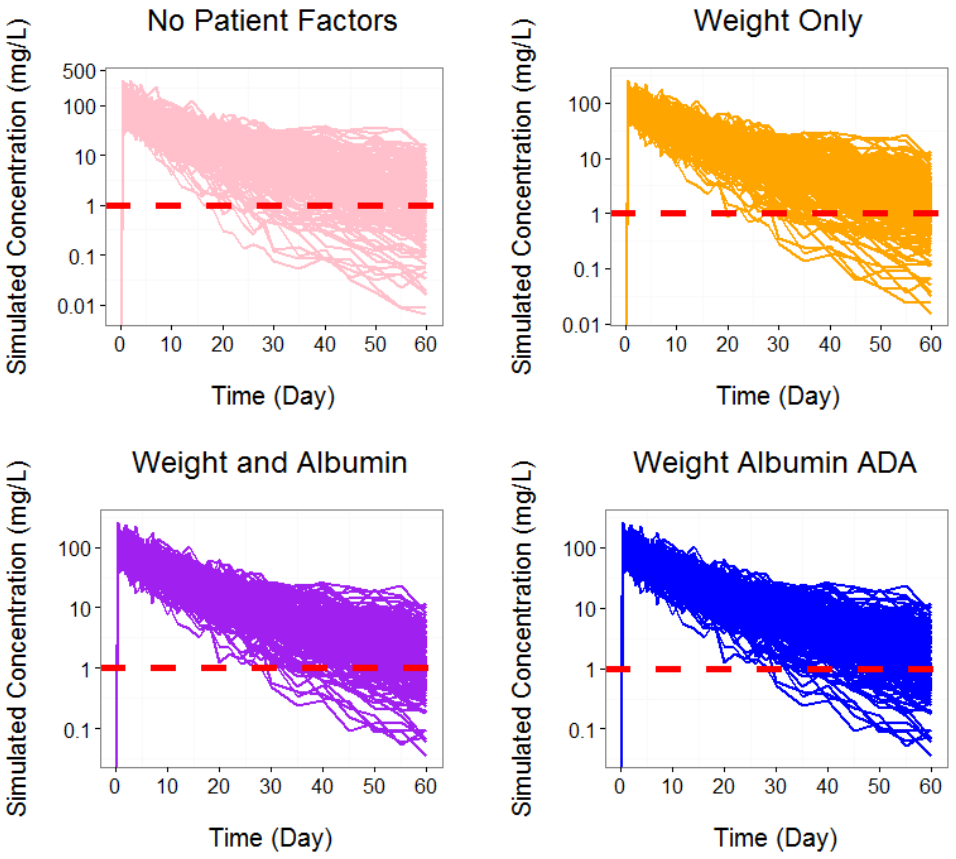
CDAI = Crohn's disease activity index; CDEIS = Crohn's disease endoscopic index of severity; CRP = C-reactive protein

Pariente B, et al. *Inflamm Bowel Dis.* 2011;17(6):1415-1422.

STRATEGIES TO MAINTAIN EFFECTIVE EXPOSURE

- Consider shortening the dose interval for patients with low albumin
- Consider increasing dose for patients with low weight
- Therapeutic drug monitoring is useful, consider PK-guided dosing





- Blue is dosing based on weight albumin ADA
- Green is PK guided

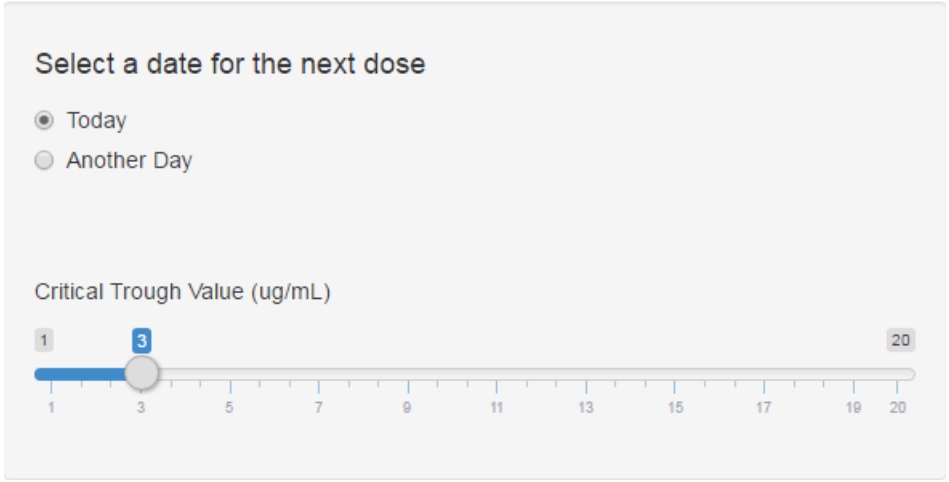
Dotan I, et al. *Inflamm Bowel Dis*. 2014;20(12):2247-2259.

WHAT IS A DASHBOARD?

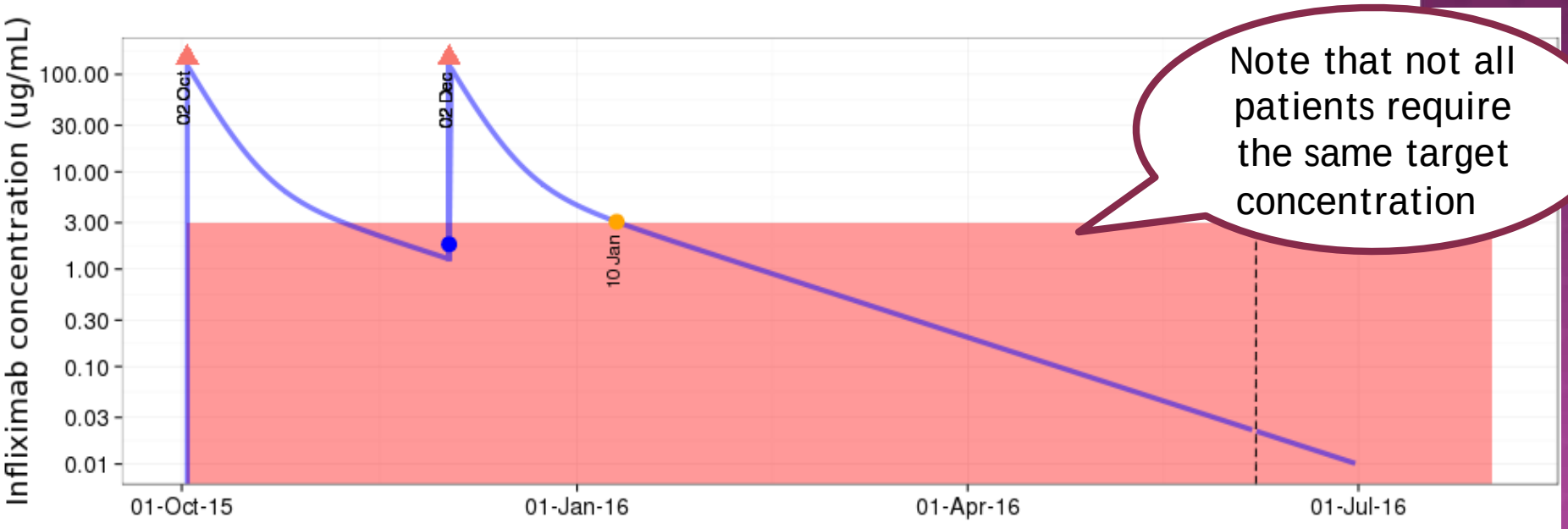
- Helps manage information
  - In a car, provides information on speed, gas, oil pressure
  - Here, includes GPS + computer that can forecast lap speed, performance issues
- Similar to dashboards in clinical practice
  - Links to EMR to utilize “bedside data”
  - Makes use of population PK model as a prior (“big data”)
  - Tracks response to treatment, prognostic factors
  - Forecast exposure and response - helps determine appropriate doses

DASHBOARD PROCESS

ENTER PATIENT → **UPDATE INFORMATION** → **PREDICT TROUGH OUTCOMES** → **CHOOSE DOSE AND INTERVAL**

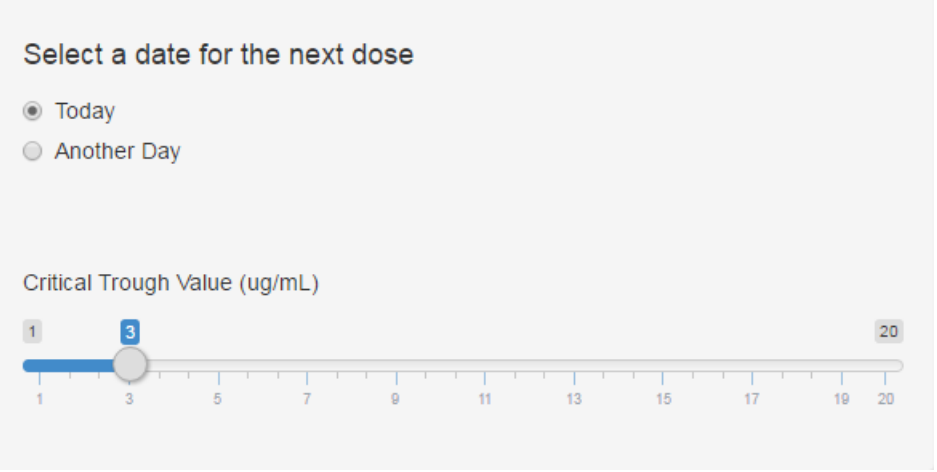


48 kg, 250 mg
5.2 mg/kg every 8 weeks
CRP = 150
Albumin = 3.2

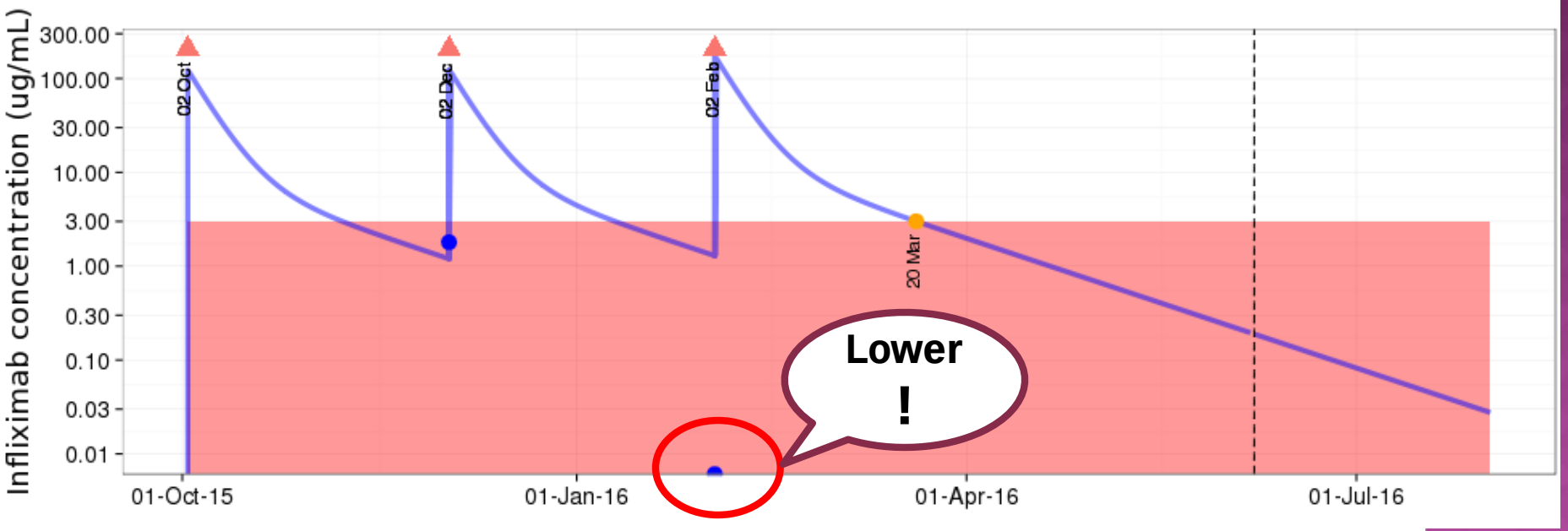


- Shorten interval or increase dose?
  - Increase dose → 350 mg

'Because I do not dare to give it every 4 weeks…'



48 kg, 350 mg
7.3 mg/kg every 8 weeks
CRP = 150
Albumin = 3.2



- Shorten interval or increase dose?
  - Shorten interval → 4 weeks

Select a date for the next dose

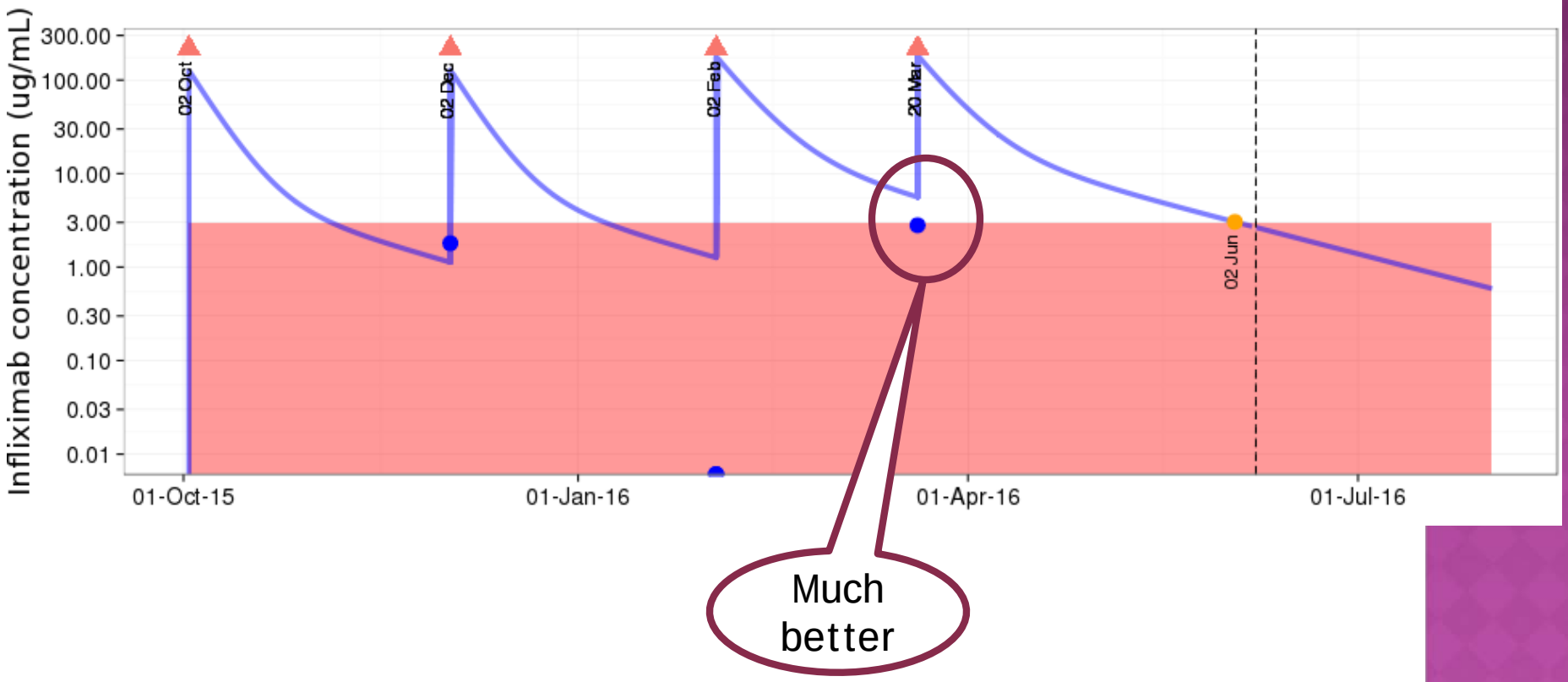
- (•) Today
- ( ) Another Day

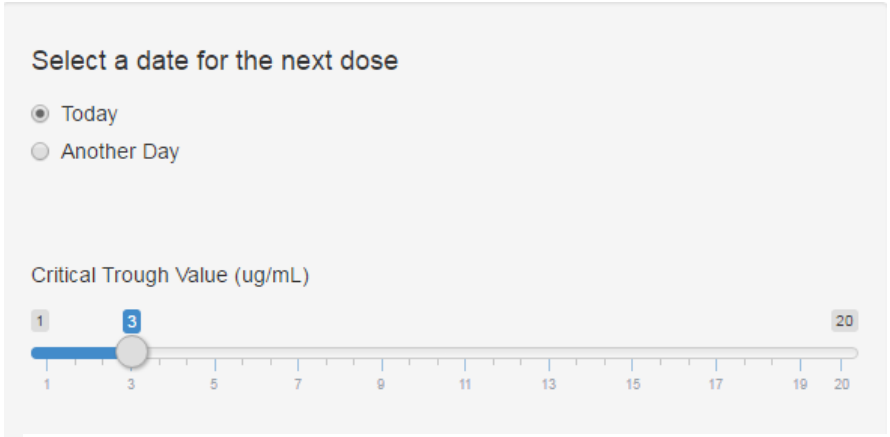
Critical Trough Value (ug/mL)

1 3 20

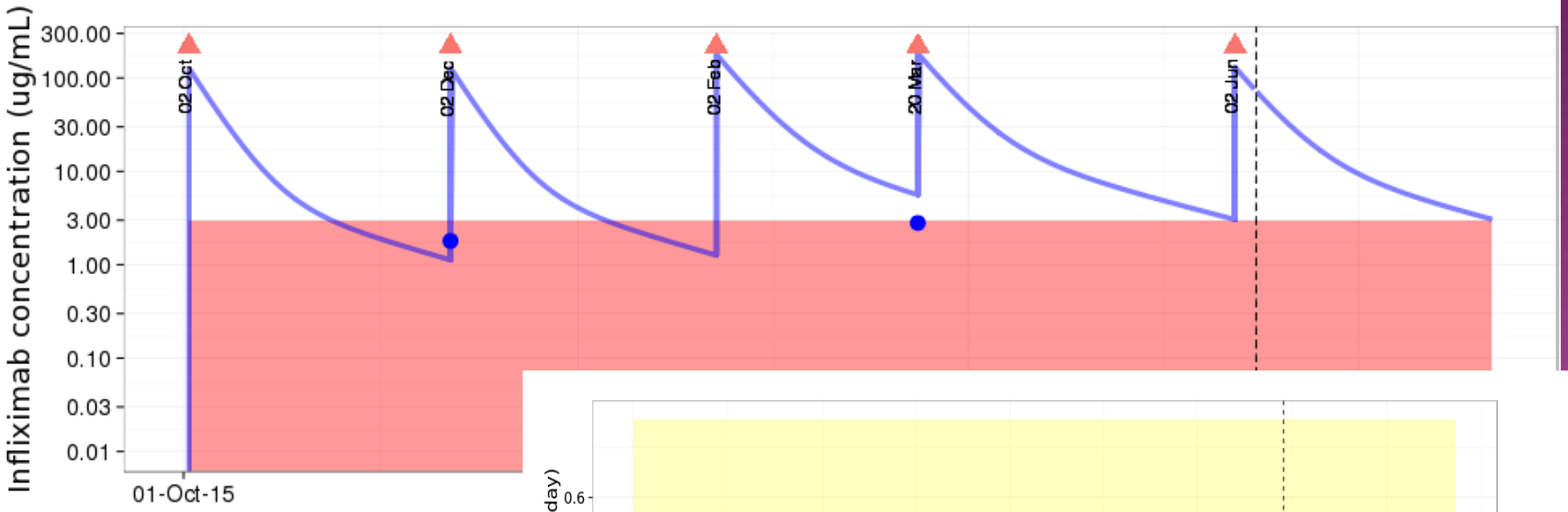
1 3 5 7 9 11 13 15 17 19 20

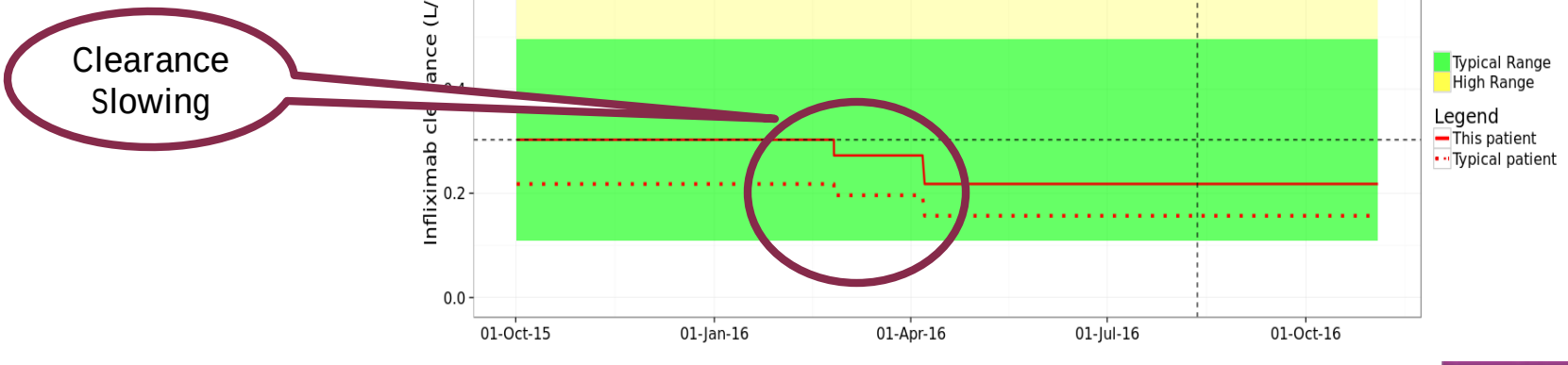
48 kg, 350 mg
7.3 mg/kg every 4 weeks
CRP = 40
Albumin = 3.5





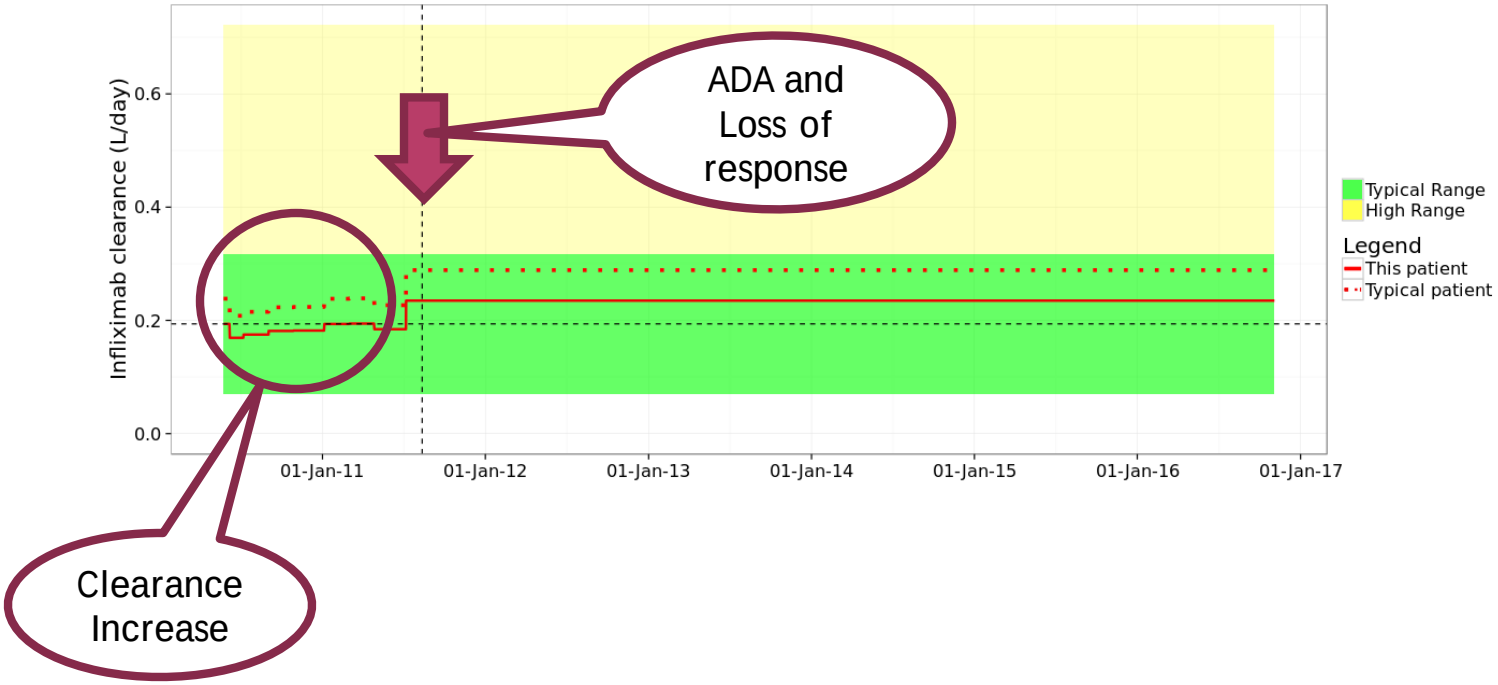
48 kg, 320 mg
5.2 mg/kg every 6 weeks
CRP = 5.0
Albumin = 3.8





USING CLEARANCE AS A BIOMARKER OF RESPONSE

- What we are learning: MAb clearance is often a good indicator of impending flare and loss of response!



- An additional benefit of dashboards is that all relevant data on treatment and response brought together, resulting in better data for modeling or updating models

CONCLUSIONS

- Correlations between low MAb exposure and loss of response or therapeutic failure
  - Primarily retrospective
- MAb PK quite different than small molecules
  - Many possible routes for clearance
  - MAb PK (and thus exposure) is influenced by multiple factors
    - Weight, albumin, concomitant administration of immune suppressants, ADA, disease type, and severity
    - High weight, low albumin, presence of ADA lack of concomitant immune suppressants and more severe disease usually indicates clearance is fast (and half-life is short)
- Incidence of ADA associated with many factors
  - Low dose, SC route of administration, manufacturing considerations, intermittent exposure
  - Similar predictive factors regarding PK
- Therapeutic drug monitoring potential
  - Difficult to interpret
  - Primarily retrospective evaluations
- Dashboards being investigated to answer questions!

THANK YOU!

My thanks to Dr Stephen Hanauer and Dr Marla Dubinsky for their input
Questions? Send to DRMould@PRI-Home.net