Improved Prediction of Infliximab Clearance Using Erythrocyte Sedimentation Rate and Anti-infliximab Antibody in Pediatric Patients with Inflammatory Bowel Disease

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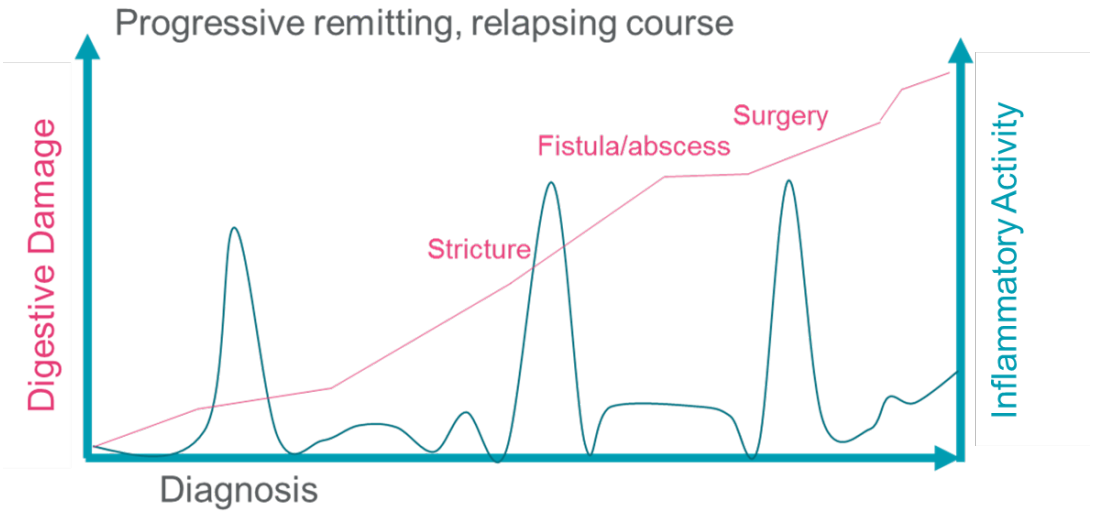
Inflammatory Bowel Disease in Pediatrics

- Inflammatory bowel disease (IBD) is consisted of Crohn's disease and ulcerative colitis.
- Affecting ~1.4 million people in North America, pediatric onset accounts for ~ 20% of overall IBD population.
- Pro-inflammatory cytokine TNF-α localized in bowel induce tissue damage in IBD patients.



Goal of treatment: prevent bowel damage

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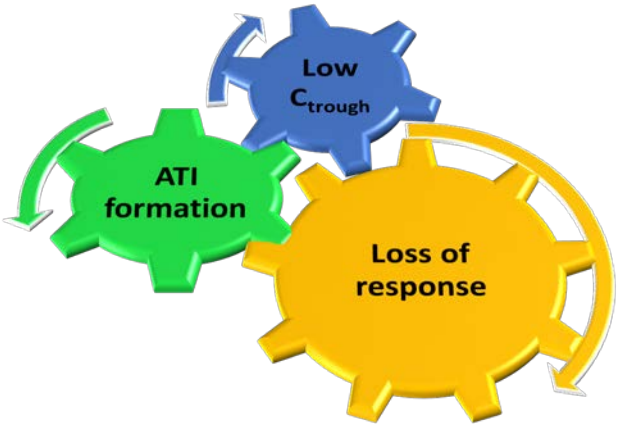
Pariente et al. *Inflamm Bowel Dis*. 2011

Infliximab Treatment in Pediatric IBD

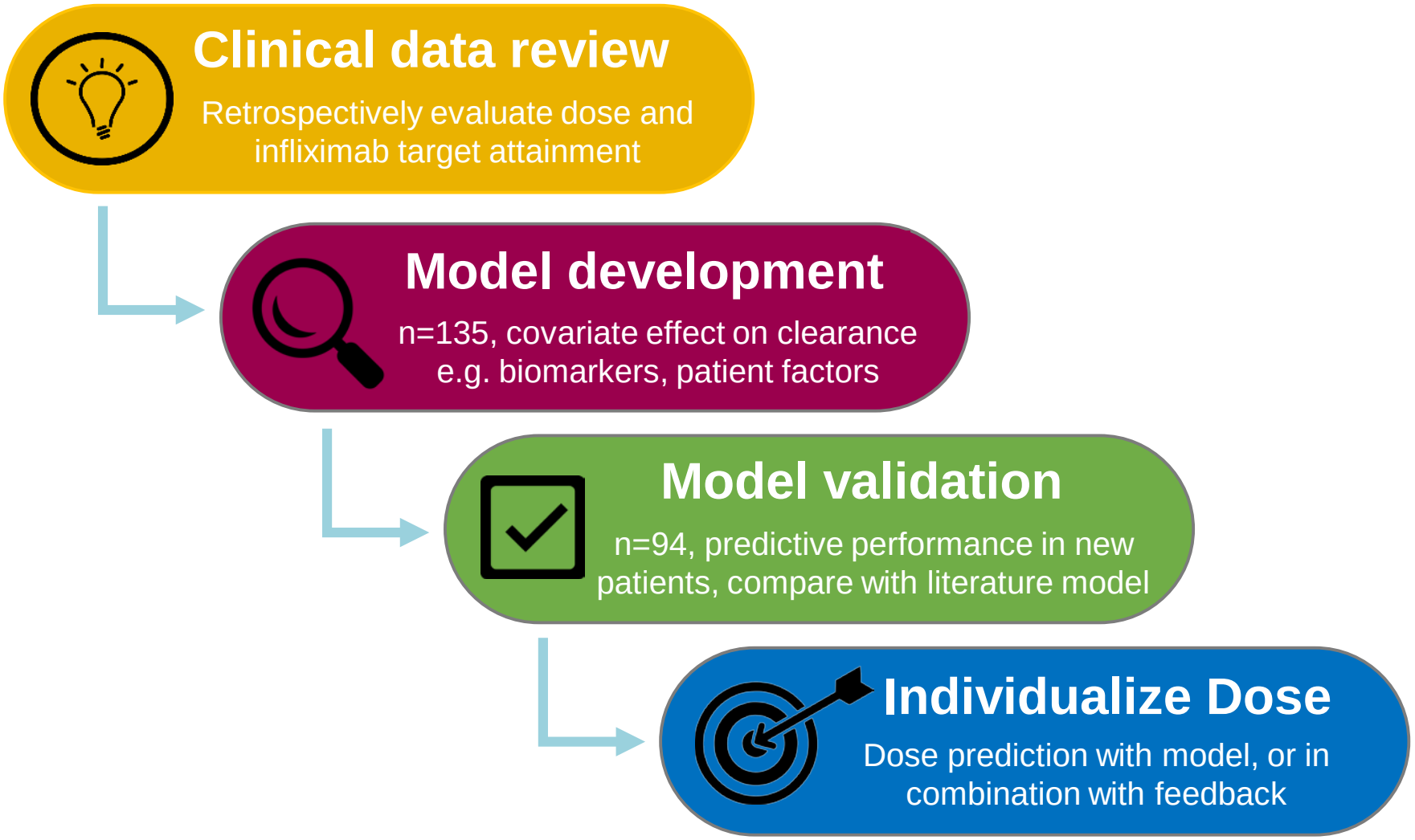
- ✓Infliximab (Remicade®) is anti-TNFα antibody, a mainstay choice in treating moderate to severe IBD.
- ✓Widely used in pediatric patients (35-55%)
- ✓Patients on infliximab for up to 7 years with great efficacy and safety.

Loss of response (~40% of patients) is associated with failure to maintain target trough concentrations.

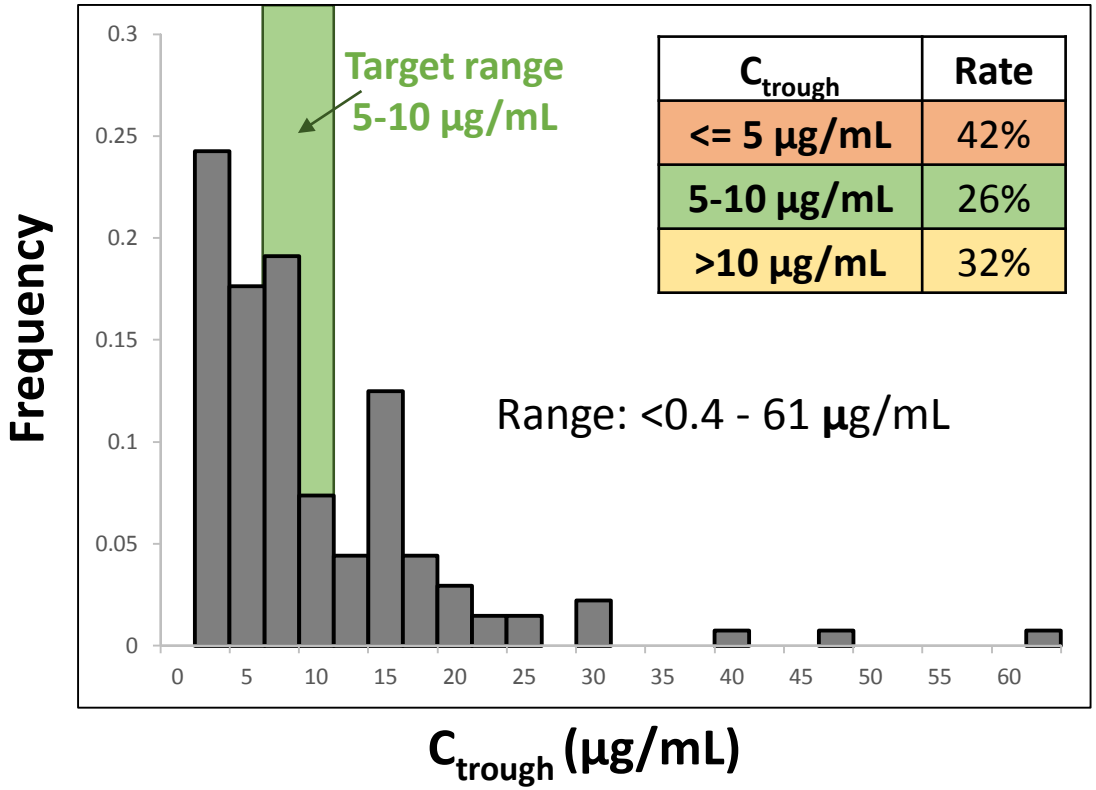


Identify influential <u>patient- and disease-related</u> factors that can lead to better prediction of the variability and allows optimization of the dosing strategy.

METHODS


Clinical data review
Retrospectively evaluate dose and infliximab target attainment
Model development
n=135, covariate effect on clearance e.g. biomarkers, patient factors
Model validation
n=94, predictive performance in new patients, compare with literature model
Individualize Dose
Dose prediction with model, or in combination with feedback

Large Variability in Infliximab Trough Concentrations



C_{trough}	Rate
<= 5 µg/mL	42%
5-10 µg/mL	26%
>10 µg/mL	32%

Infliximab Treatment

The median dose in current practice is:

Amount: **8.5** mg/kg (3.6-14.9)

Interval: **7.3** weeks (1.4-15.3)

n=136 (maintenance)

- **74% were outside of target C_{trough} range**
- **42% did not reach the target C_{trough}**

Target range: Vaughn et al. *Inflamm Bowel Dis*. 2014

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Patient Characteristics at 1st IFX C_{trough} Record

- 135 patients for model development
- 80% of patients were diagnosed with Crohn's
- 40% of patients were females
- Anti-infliximab antibody (ATI) was detected in 66% patients
- A broad spectrum of laboratory values were available for covariate analysis: albumin (ALB), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), hematocrit, platelets, etc

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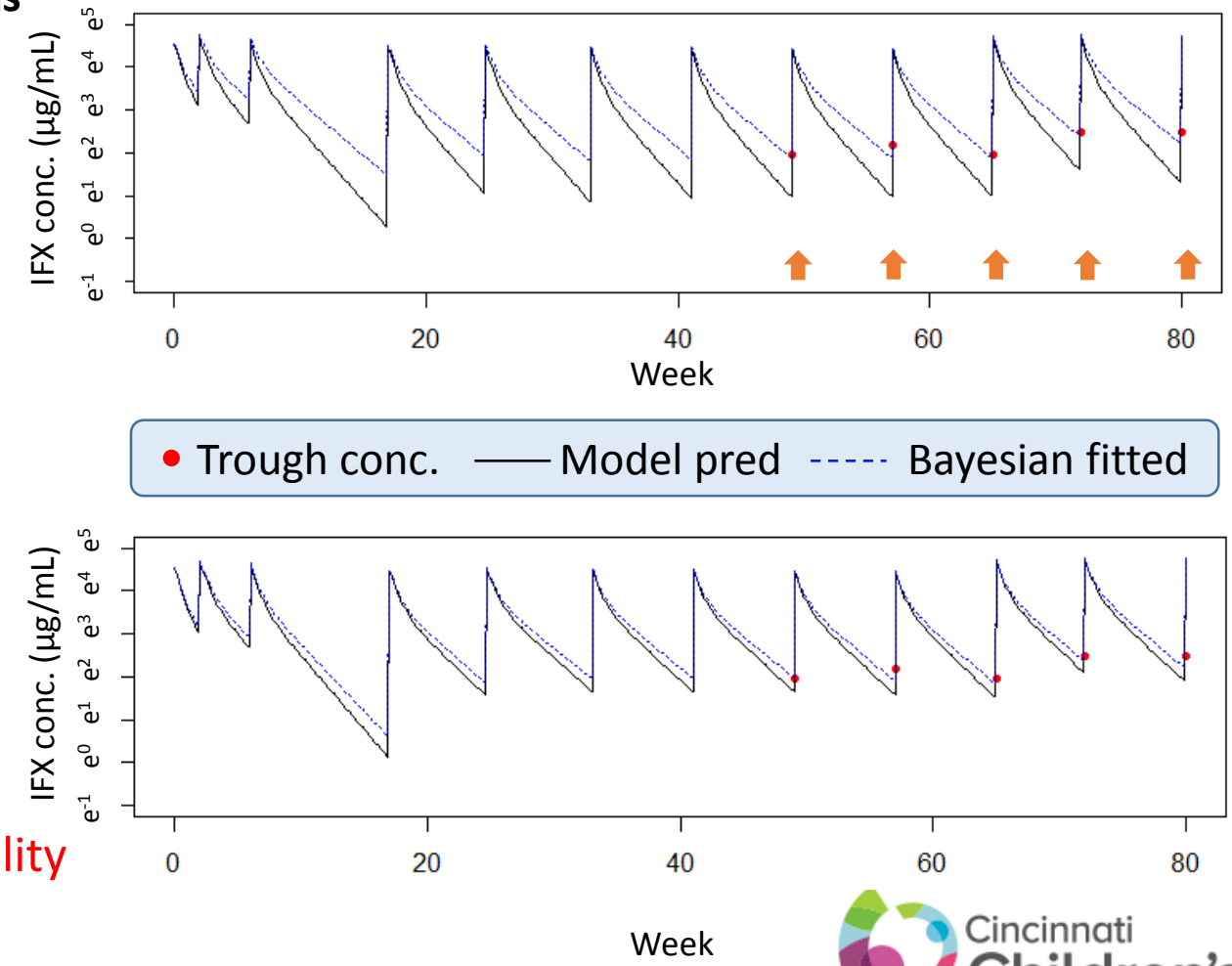
Refine Population PK Model with Pediatric Data from Clinical Practice

Stepwise covariate analysis

- Weight
- + ALB
- + ATI level
- + ESR



Between subject variability reduces by 26%

Model: Adapted from existing model (Fasanmade 2011) of pediatric cohort, to explicitly examine disease markers or factors that influence PK behavior of infliximab

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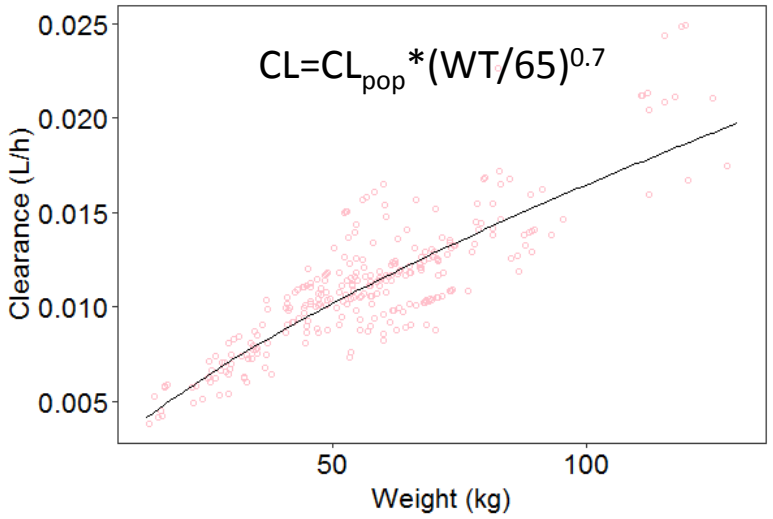
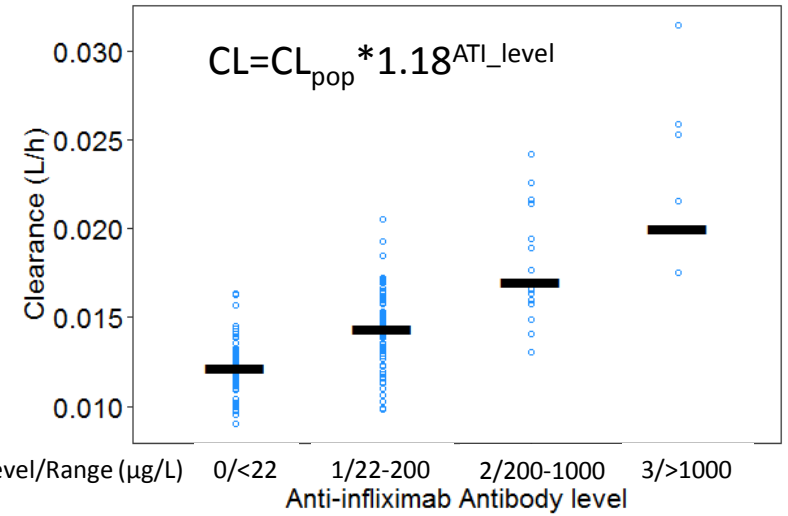
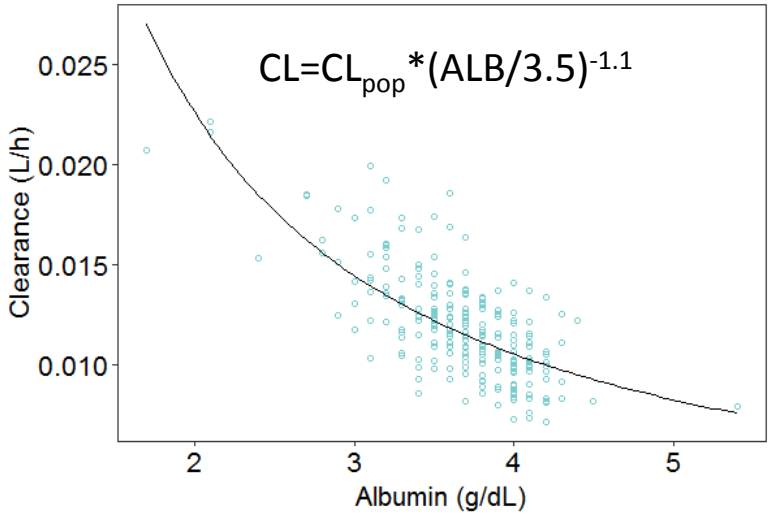
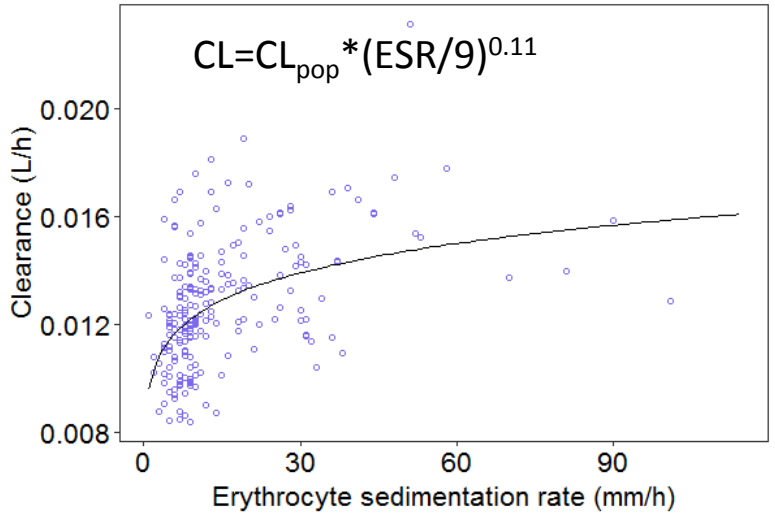
Covariate Effect on Clearance

$$CL_{ind} = CL_{pop} \times (WT/65)^{0.7} \times (ALB/3.5)^{-1.1} \times 1.18^{ATI\ level} \times (ESR/9)^{0.11}$$







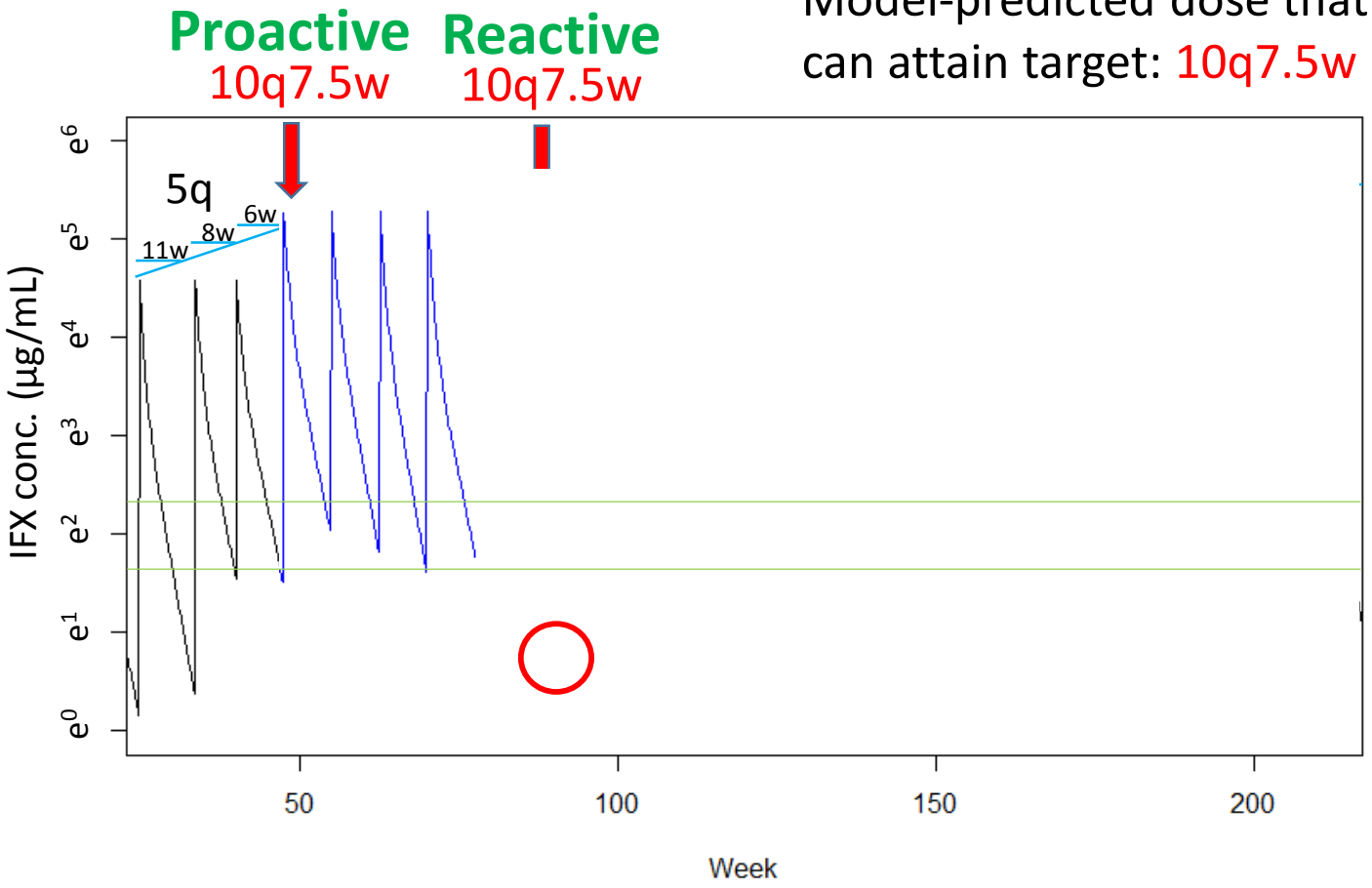


*Additional informative covariates were identified that further explain the variability

Individualized Dosing Strategy - Proactive vs Reactive

Case: 16 yo
WT: 69.5 kg
ALB: 3.5 g/dL
ATI: 36 (level 1)
ESR: 29 mm/h
(at 1st IFX measurement)

Model-predicted dose that can attain target: 10q7.5w



- Trough conc.
— Model pred

❖ Not effective dose intensification for 4 years

Current practice: Dose adjustment driven by symptoms and trough concentration

SUMMARY

- High body weight, erythrocyte sedimentation rate, anti-infliximab antibody level, and low albumin values were associated with increased infliximab clearance.

- The extended covariate model has potential to proactively individualize dosing regimen.

NEXT STEP

- Build individualizing application and incorporate into EHR
- Evaluate the proactive dosing strategy in comparison to current strategy

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Patient Characteristics at 1st IFX C_{trough} Record

Number of Patients	N=135	% Crohn's Disease	80.1%
		% female	39.7%
Variables		**Median (SD or IQR)**	
Age (years)		14.5 (3.8)	
Body Weight (kg)		55.9 (22.3)	
Infliximab Level*(mg/L)		4.8 (1.9-11.3)	
ATI Level*(ng/mL)		22 (22.0-48.5)	
% Positive ATI (>22 ng/mL)		66.2	
Infusion Number		7.2(5.2)	
Hematocrit (gm/dL)*		38.9 (36.3-41.6)	
Platelets (k/mcL)		304.4 (109.1)	
WBC (k/mcL)		7.4 (2.8)	
ESR (mm/hr)		15.5 (14.9)	
CRP (mg/dL)		1.6 (1.6)	
Albumin (gm/dL)		3.6 (0.5)	
AST (u/L)		25.4 (21.6)	
ALT (u/L)		26.6 (17.0)	
Total Bilirubin (mg/dL)		0.37 (0.2)	

Presented as median and SD (or IQR for non-central distributed parameters)