GENERAL CONSIDERATIONS FOR DEVELOPING DISEASE-DRUG-TRIAL MODELS FOR ASSESSMENT OF EXTRAPOLATION ASSUMPTIONS

Focus on IBD in Adults and Pediatrics

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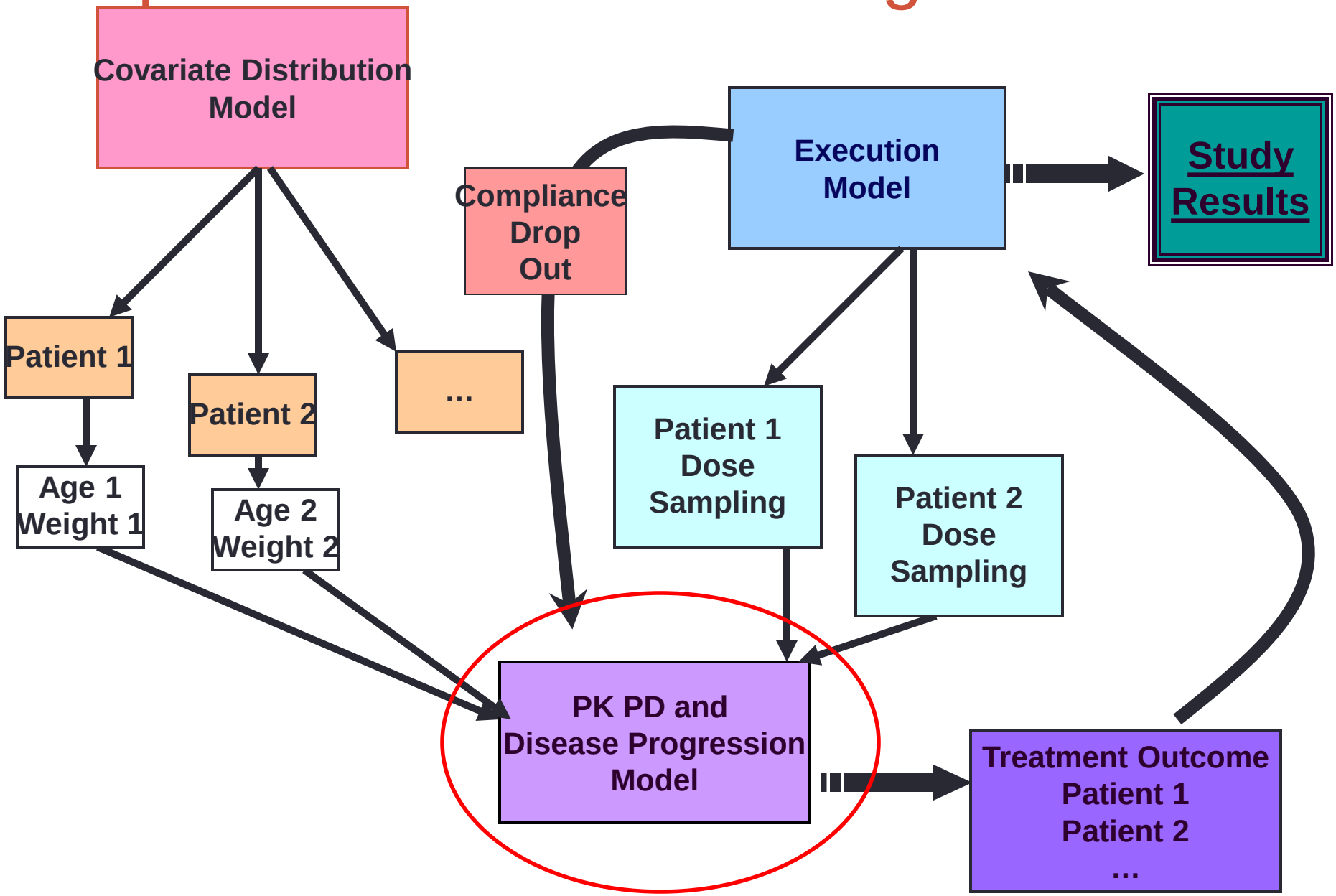
Components of Disease-Drug-Trial Model



PKPD Models

- Pharmacokinetic (dose, concentration, time)
  - Drug disposition in individuals & populations
  - Disease state effects (renal & hepatic dysfunction)
  - Intervention effects (hemodialysis)
  - Concurrent medication effects
  - Pharmacogenetic influences
- Pharmacodynamic (dose or concentration, effect, time)
  - Physiologic & biomarkers
  - Surrogate endpoints
  - Clinical effects and endpoints
- Disease progression models are a subclass of pharmacodynamic models
  - Quantitative model that accounts for the time course of disease status or severity
  - Markers of disease status need to be selected carefully

Developing Disease Progression Models

- What information is needed?
  - Collection of metrics of disease progression in treated and untreated states
    - Note that placebo data are not considered “untreated” owing to placebo effect
    - Untreated progression information may be taken from historical data
    - Information must be collected over a sufficiently long period of time to estimate progression rate
  - Collection of drug exposure data
    - May be a test drug, active control etc.
      - Often use summary metrics such as AUC or dose
      - May require development of a PK model
  - Collection of patient factor data
    - Age, weight, sex, disease duration
  - May be able to develop initially from nonclinical data
    - Helps with untreated progression

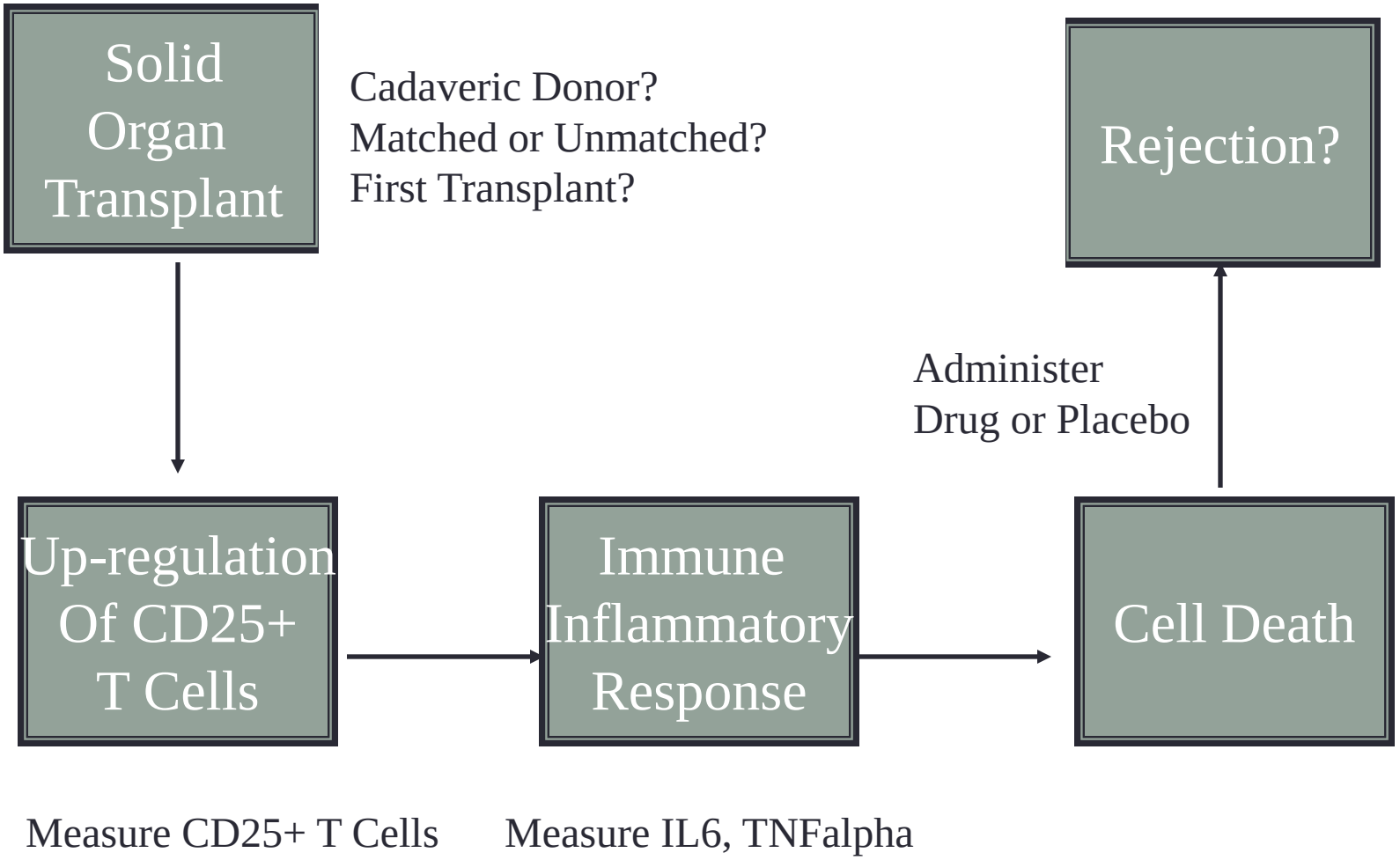
New Objectives for Clinical Trials

- In confirmatory trials, the purpose of that trial is to test the null hypothesis.
  - Hopefully an alternative model that can be accepted in place of the null model
- Testing the null hypothesis is an easy question to answer robustly
  - Traditionally statistics has been focused on questions that are easy to answer but not necessarily on answering the right questions
- “Far better an approximate answer to the right question, which is often vague, than an exact answer to the wrong question, which can always be made precise.” - Tukey

New Objectives for Clinical Trials

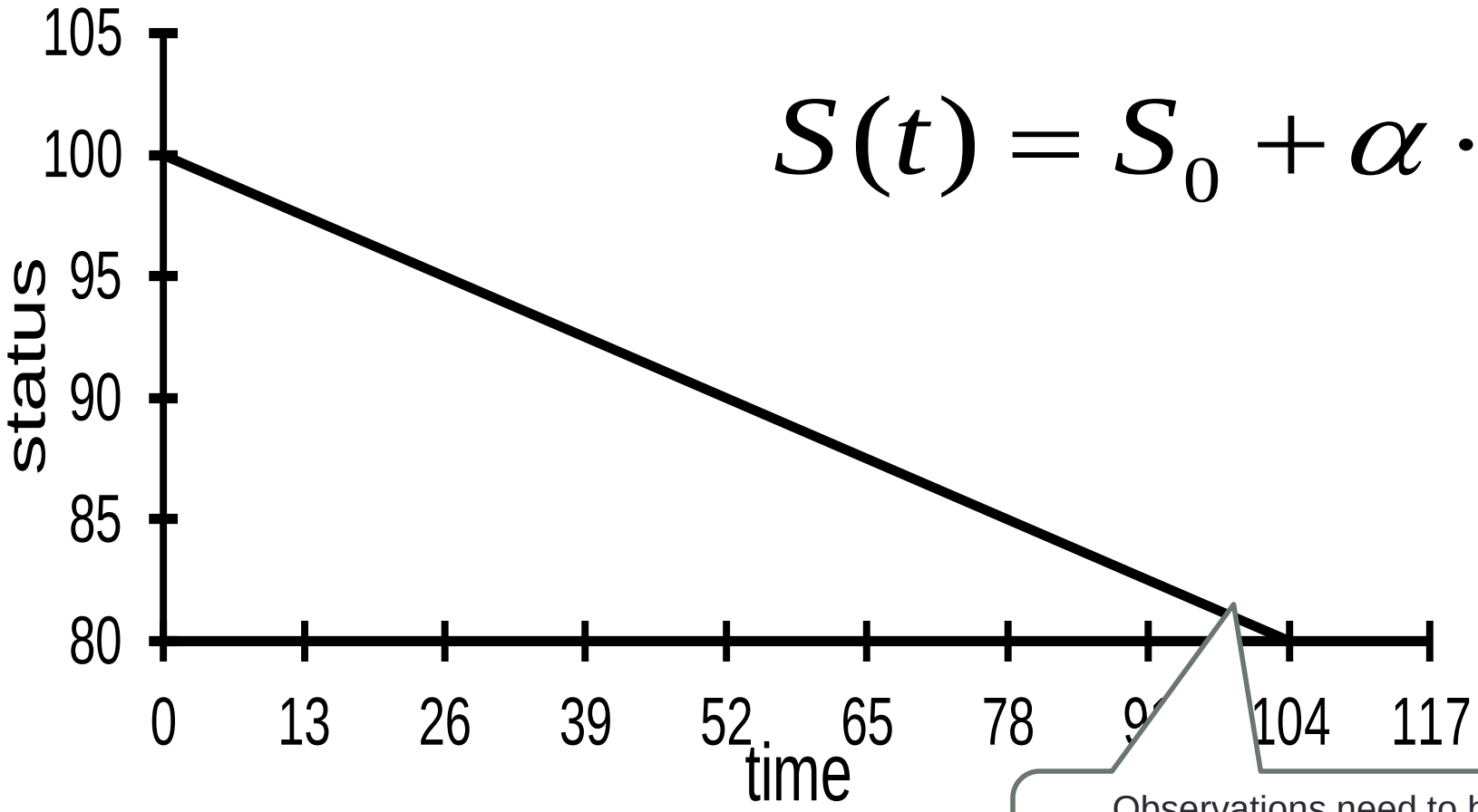
- Developing an exposure response surface is not an easy question to answer but maybe it's the right question to ask
  - Usually requires assumptions which weakens the robustness of the answers
  - Assumptions reduce inferential certainty
    - If the assumptions are wrong, then the model based conclusions are wrong
    - Quality of the attendant assumptions, not their existence, that is the issue
- Patients can have different responses
  - Differing sensitivity contributes to the variability (e.g. noise) in study outcome
  - Need to develop the dose response surface without data from every type of patient given every dose level and duration of therapy
- The time course of disease in the untreated patient is variable
  - Characterizing the time course allows better evaluation of drug effect
- Clinical markers of outcome are inherently variable
  - Repeated measures assessments generally better to evaluate trends in response
- Model based evaluations provides a basis for developing exposure response surface by making scientifically valid assumptions
  - Increase the signal to noise!

Example Construction of a Disease Model



Linear Disease Progression Model

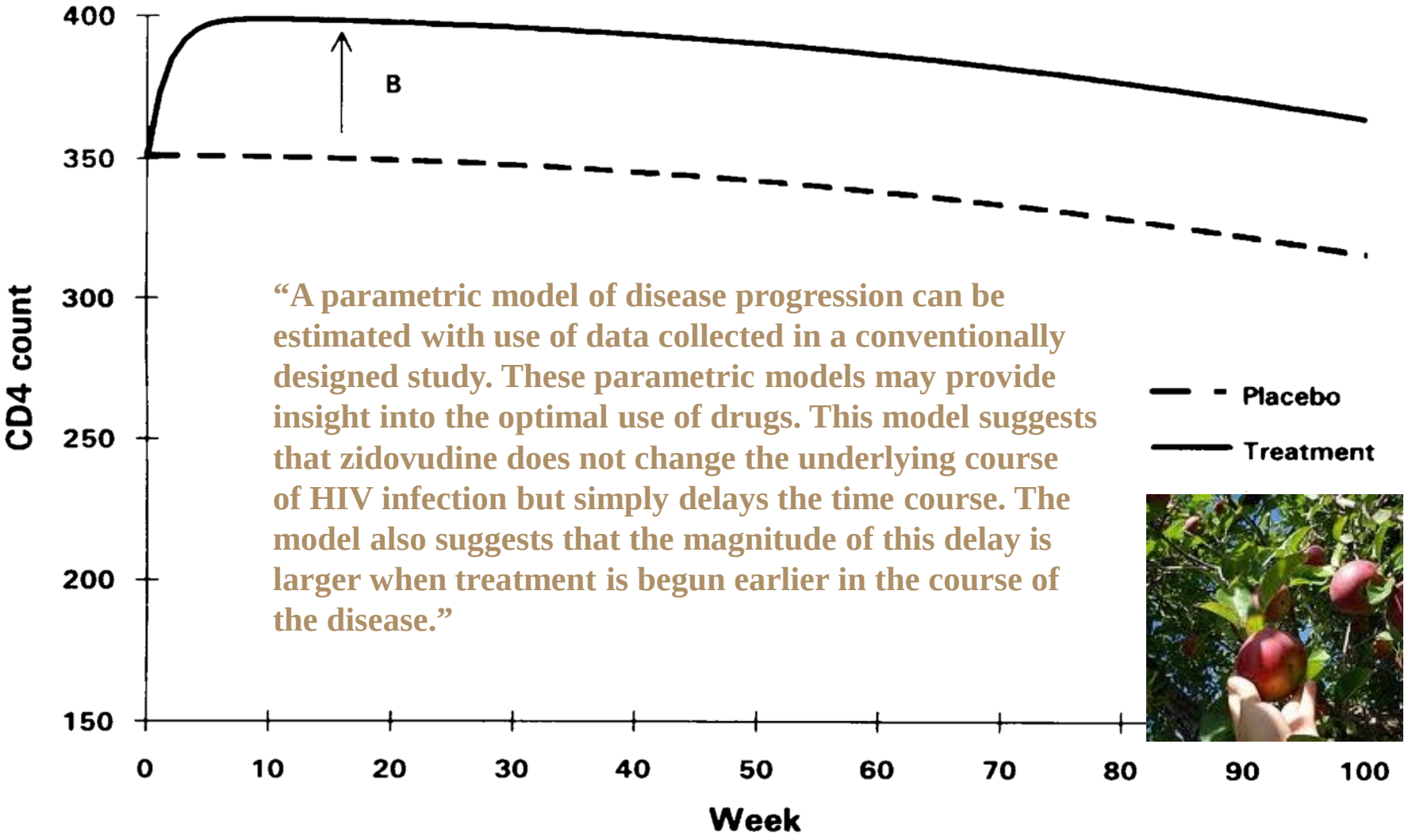
(adapted from Holford 1999)



$$S(t) = S_0 + \alpha \cdot t$$

Observations need to be available over sufficient time to assess progression rate

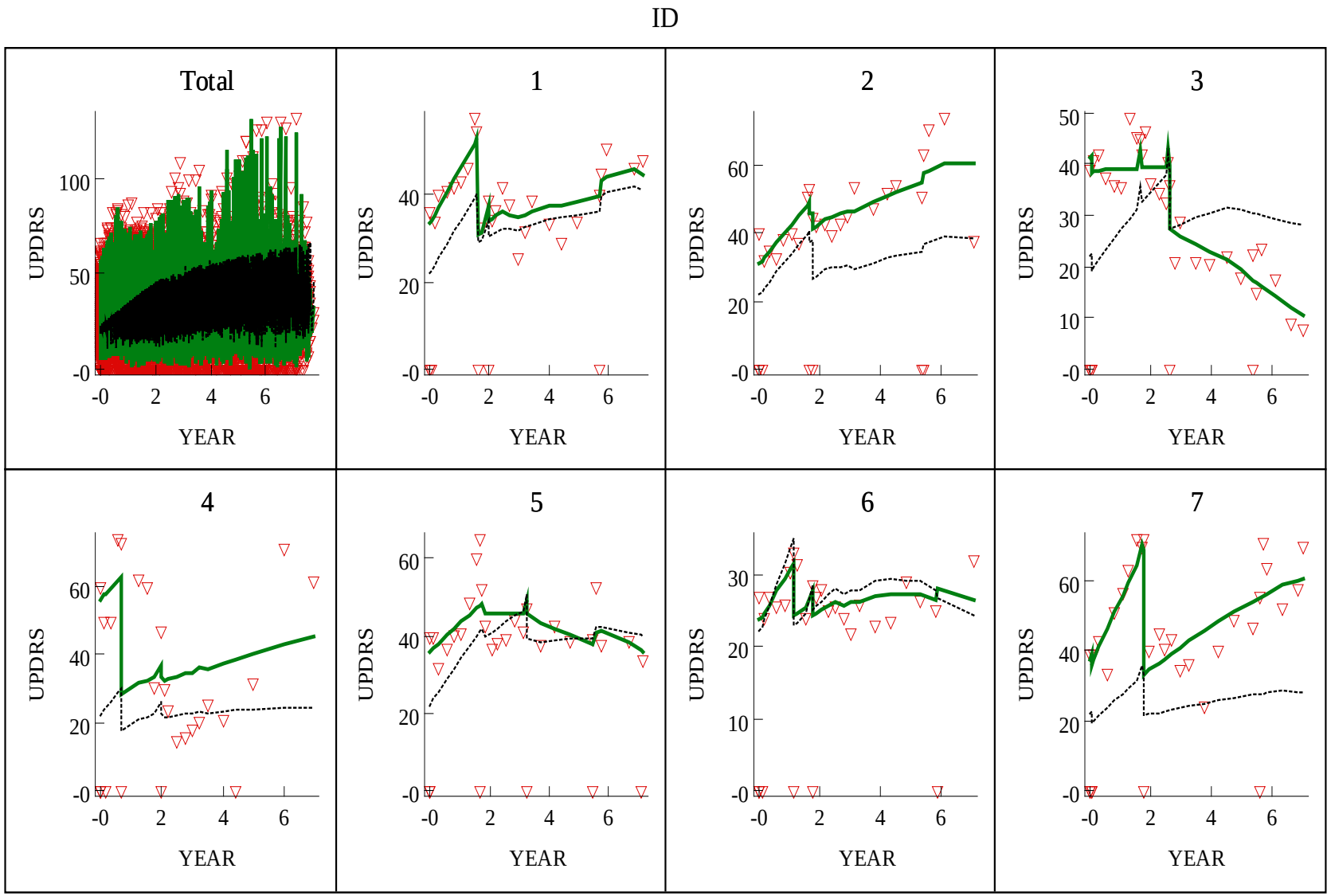
AZT Treatment Effect on HIV



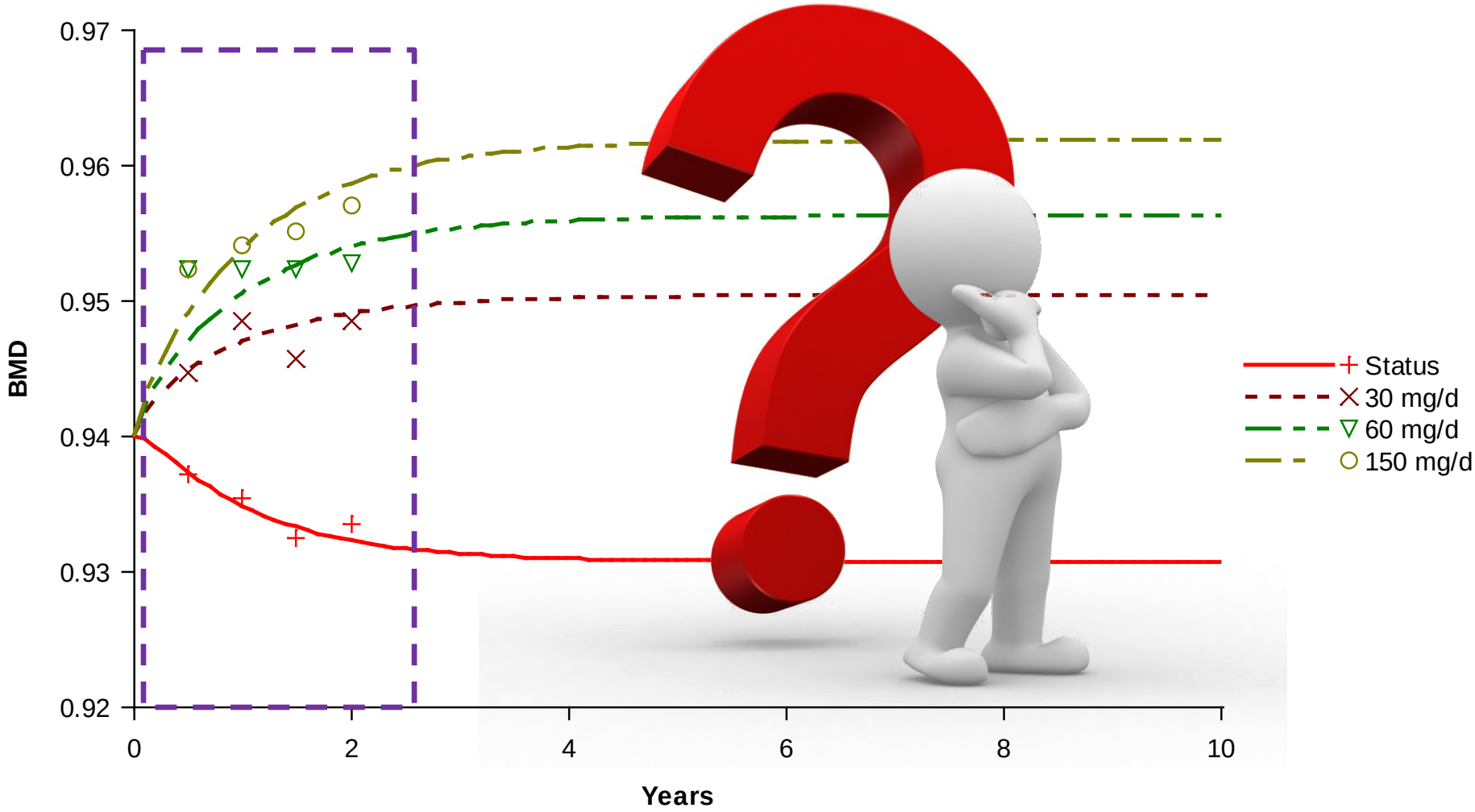
"A parametric model of disease progression can be estimated with use of data collected in a conventionally designed study. These parametric models may provide insight into the optimal use of drugs. This model suggests that zidovudine does not change the underlying course of HIV infection but simply delays the time course. The model also suggests that the magnitude of this delay is larger when treatment is begun earlier in the course of the disease."

Sale M, Sheiner LB, Volberding P, Blaschke TF. "Zidovudine response relationships in early human immunodeficiency virus infection. Clin Pharmacol Ther. 1993 Nov;54(5):556-66.

Parkinson's Study Group DATATOP Cohort



Bone Mineral Density Change with Placebo and 3 doses of Raloxifene



Motivations for Disease Progression Models

- Visualization of the time course of disease in treated and untreated conditions
- Simulation of
  - Future course of disease
  - Various disease interventions to evaluate treatment options
  - Clinical trial designs
- Extrapolation into different patient populations
  - Pediatric patients
- Framework for regulatory submissions

Disease Progression Models

- Disease progression models make an excellent platform for understanding drug action and for extrapolation to pediatrics
- Models of disease progression have been developed for many diseases
  - Rheumatoid arthritis, HIV, diabetes, Alzheimer's Disease, Parkinson's Disease, several cancers, osteoporosis
- Other than probability models, there are no longitudinal models of IBD progression
  - Probability of achieving remission
  - Probability of therapeutic failure
- Why is there no disease progression model for IBD?
  - What marker is a good metric of IBD progression?
- The etiology of IBD is unclear.
  - IBD is multifactorial. It is believed that a complex interaction of environmental, genetic, and immune factors lead to the development of IBD.

Setting the Perspective

"*Supermab* is indicated to reduce signs and symptoms, and to achieve and maintain clinical remission in adults with *moderate to severe Crohn's disease* who have not responded well to conventional treatments."

What is "moderate-severe Crohn's disease"?

Disease Activity vs Disease Severity

Activity

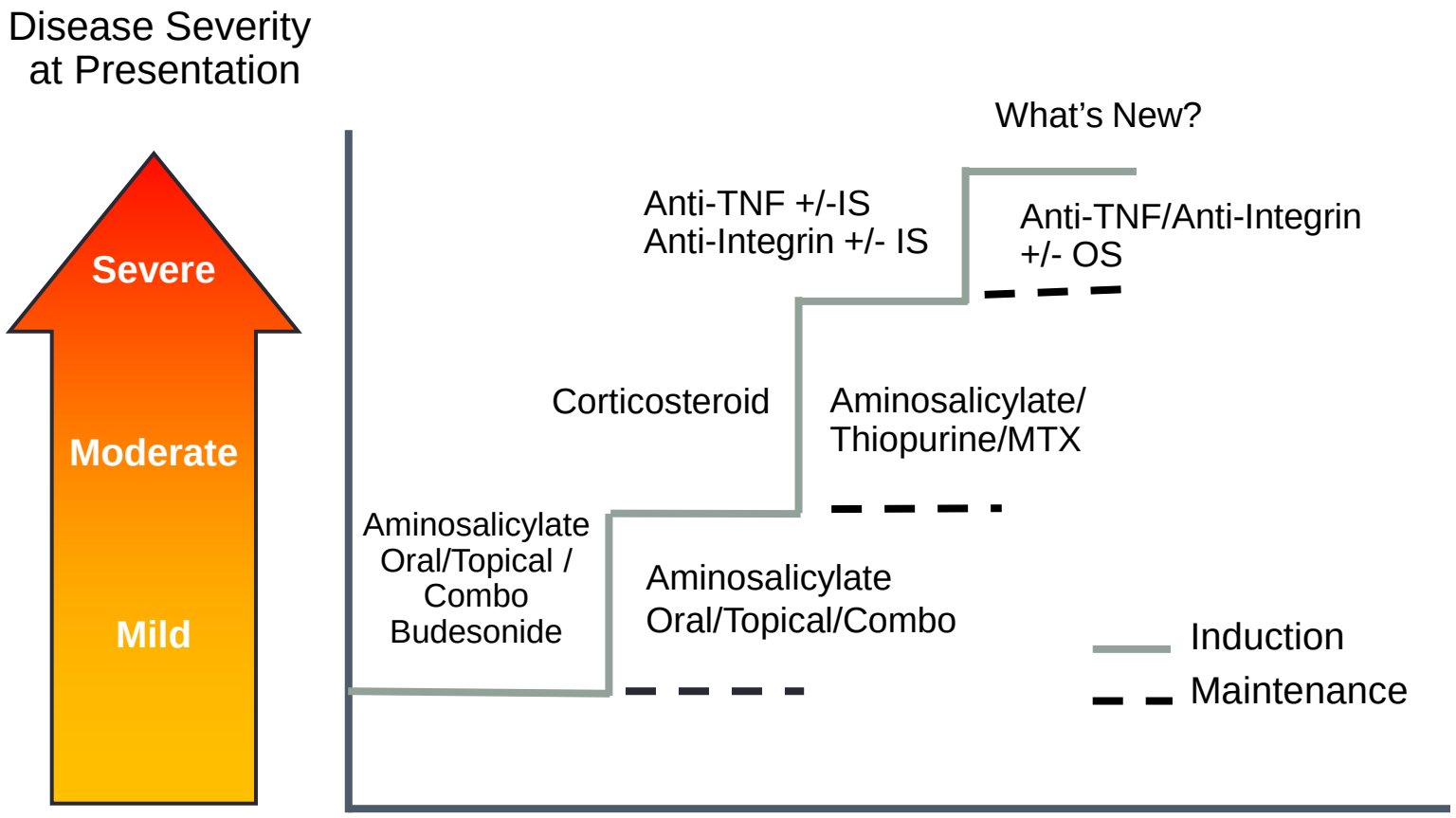
Reflects cross sectional assessment of biological (inflammatory) impact on symptoms, signs, endoscopic, (histologic), and biomarke

This is what we have available to model but doesn't really relate to progressive damage

Severity

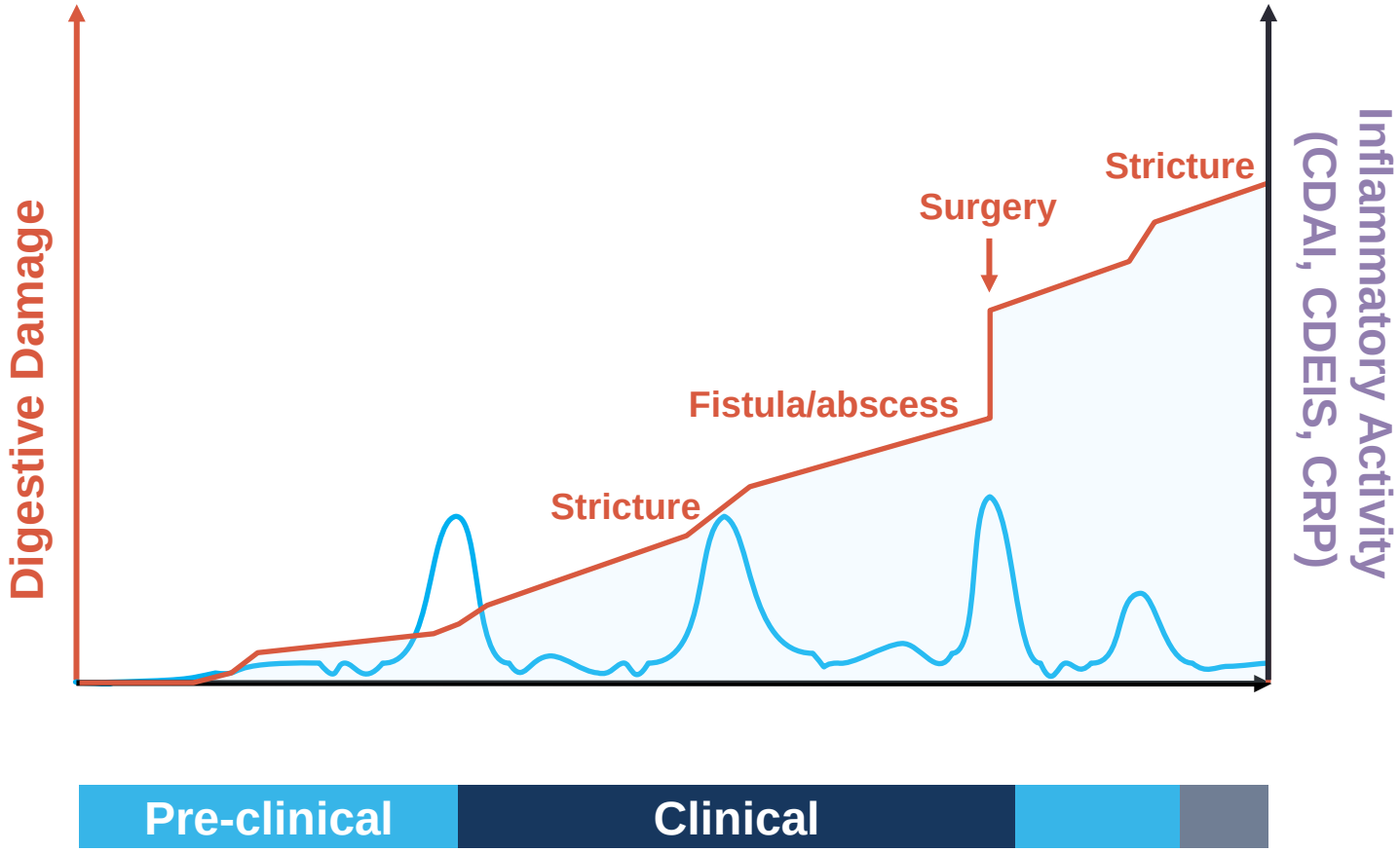
Includes longitudinal (disease course) and historical factors that provide a more complete picture of the prognosis and overall "burden" of disease

Sequential Therapies for IBD



Therapy is stepped up according to severity at presentation or failure at prior step

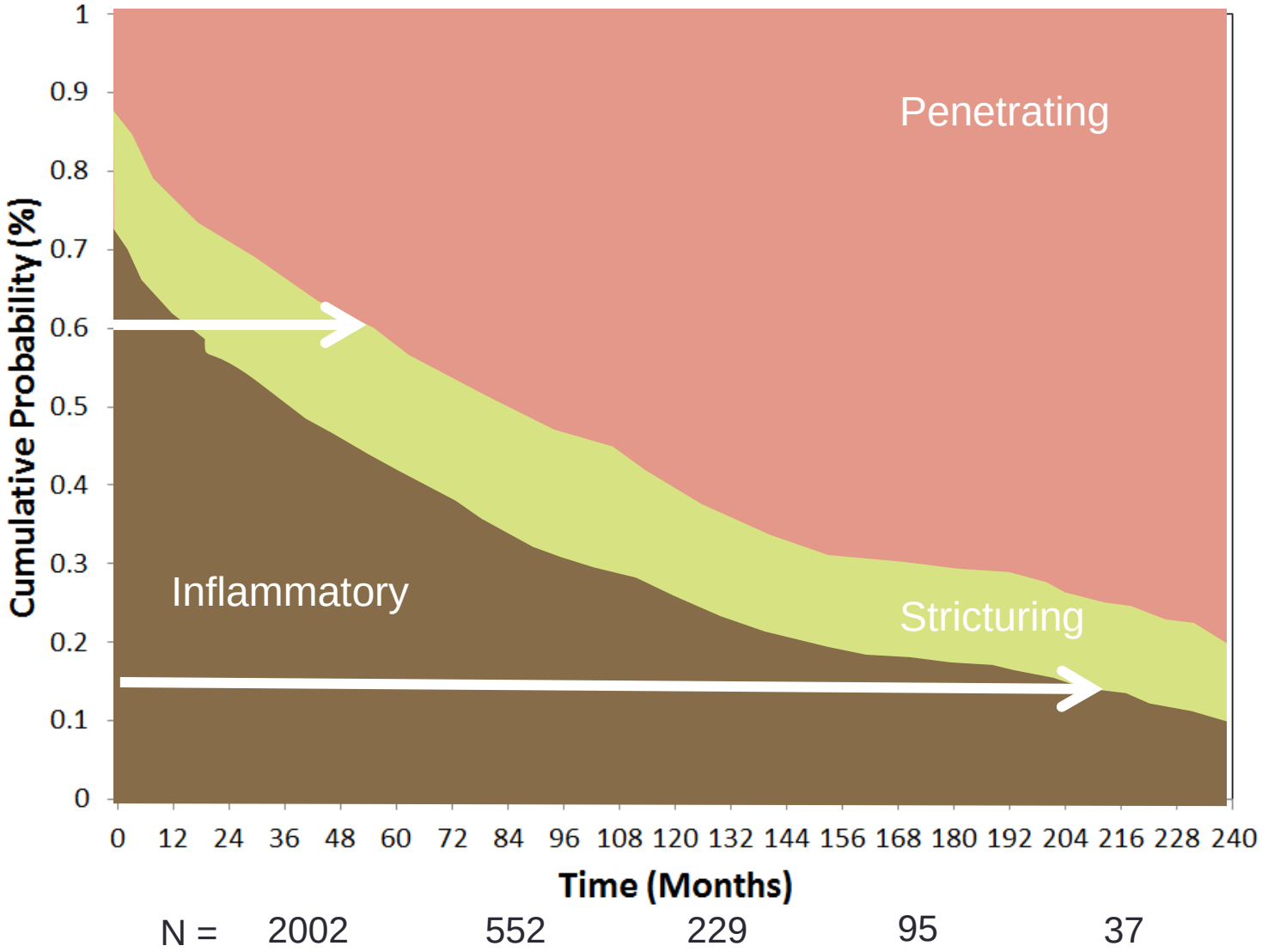
Progression of Digestive Disease Damage and Inflammatory Activity



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

What about Disease Duration?



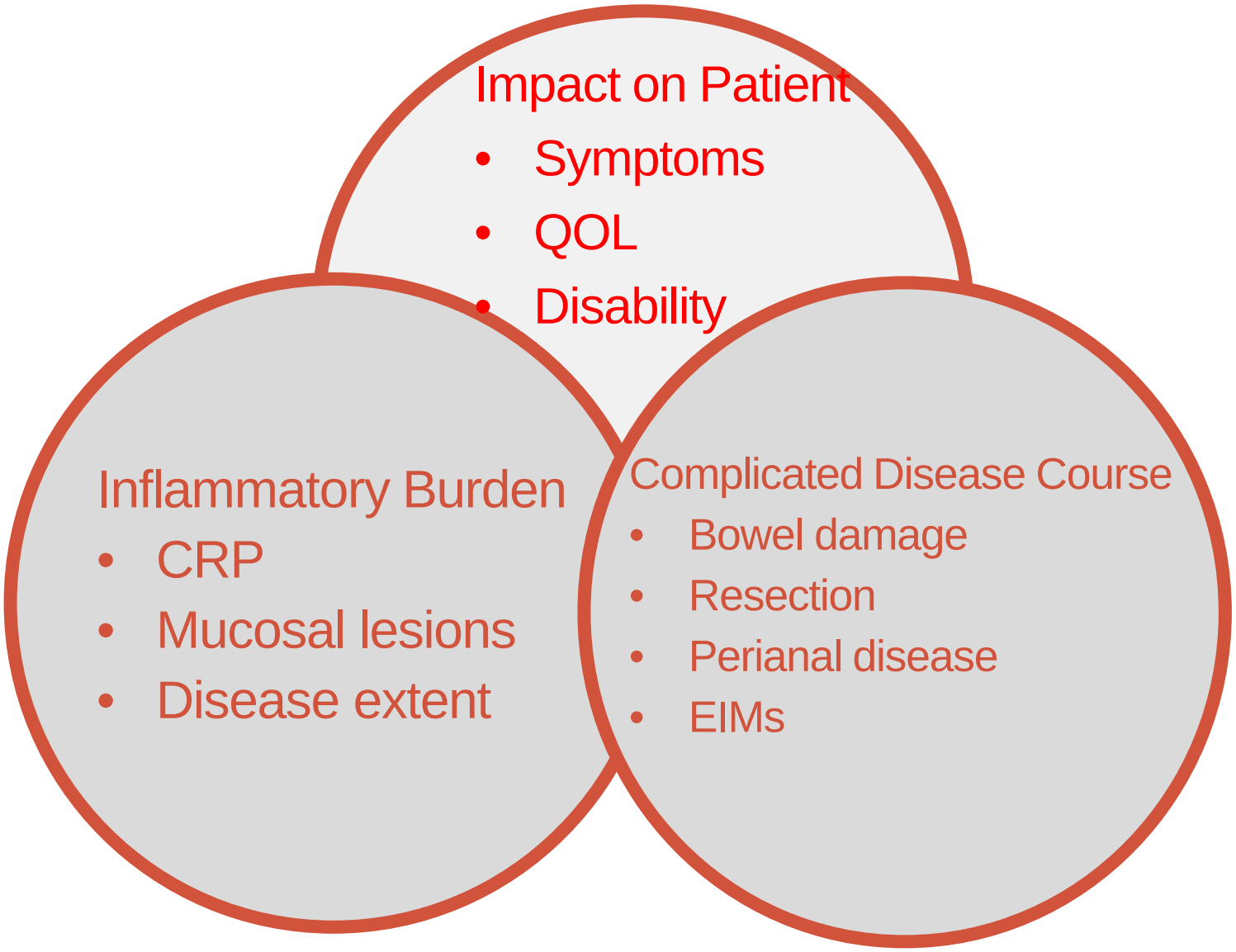
Cosnes J et al. *Inflamm Bowel Dis.* 2002;8:244-250.

Three Domains Relevant to Evaluation of Disease Severity

- Impact of disease on the patient
  - Clinical Symptoms
  - Impact on daily activities
- Inflammatory Burden
  - Serum biomarkers
  - Mucosal lesions (MRI, endoscopy)
- Disease Course
  - Complicated disease
  - Response to medication
  - Disease extent

Siegel, CS, et al (IOIBD) submitted for publication

Redefining Disease Severity in IBD



Pediatric IBD

- The incidence of pediatric inflammatory bowel disease is increasing
  - IBD first presents in childhood and adolescence in approximately 20% of all cases
- Unlike adults, growth failure is an important sign in pediatric onset IBD, most commonly in CD patients.
- Childhood-onset IBD is characterized by extensive intestinal involvement and rapid early progression

Dubinsky M. World J Gastroenterol. 2008 21;14(3):413-20.
Van Limbergent, J, Russell, RK, Drummond, et al. Gastroenterology, 135(4):1114-1122.

Consequences of Therapeutic Failure

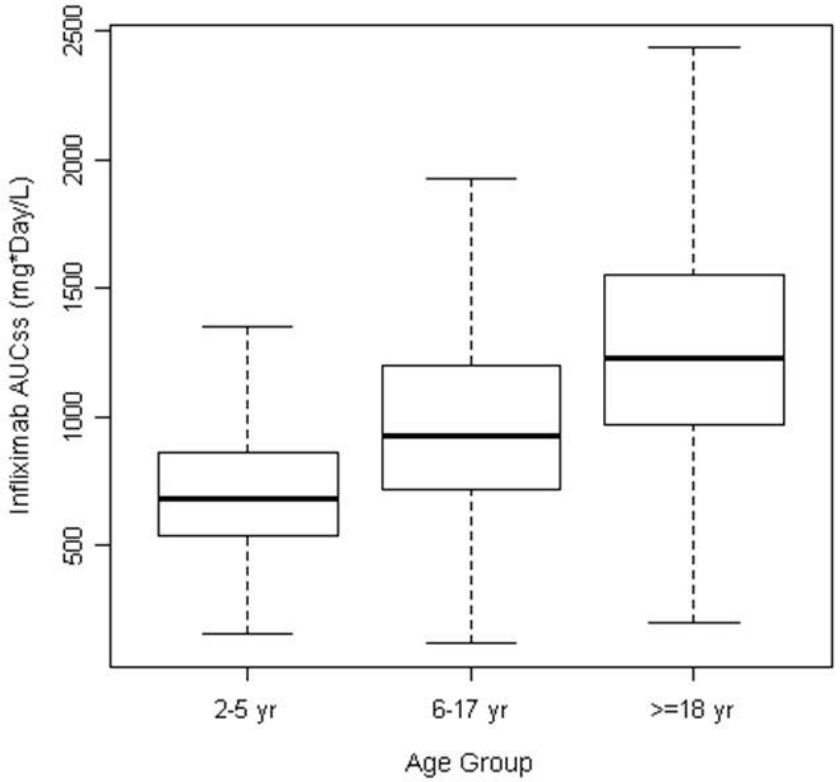
- Progressive damage
- Hospitalization
- Infection
- Transfusion
- Colectomy
- Delayed growth and sexual maturation (pediatric)
- Other systemic issues
- Cancer

Other Problems

- Many of the agents used to treat IBD are MAbs
- Complex pharmacokinetics
  - Many factors impact MAb PK
  - High interpatient variability
- Currently high treatment failure rate in adult
  - More than 33% of patients show no response to induction therapy (primary non-responders)
  - Up to 50% of responders lose response over time (secondary non-responders)
- Frequently lower exposure in pediatrics than adults
  - Higher failure rate in pediatrics

I Ordás, DR Mould, BG Feagan, WJ Sandborn Clin. Pharmacol. Ther. 91(4):635-46 2012

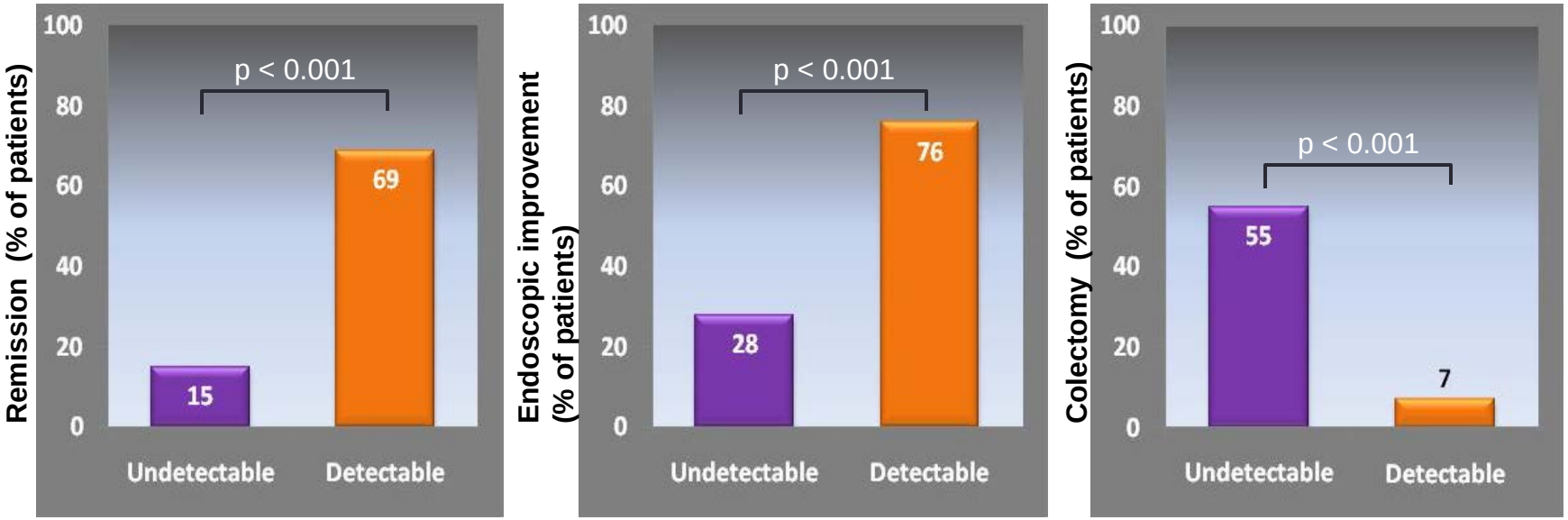
IFX Exposure in Adults and Pediatrics



- Many dosing metrics result in pediatric patients having different exposure than adults

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.

Infliximab trough concentrations associated with clinical outcome in UC patients

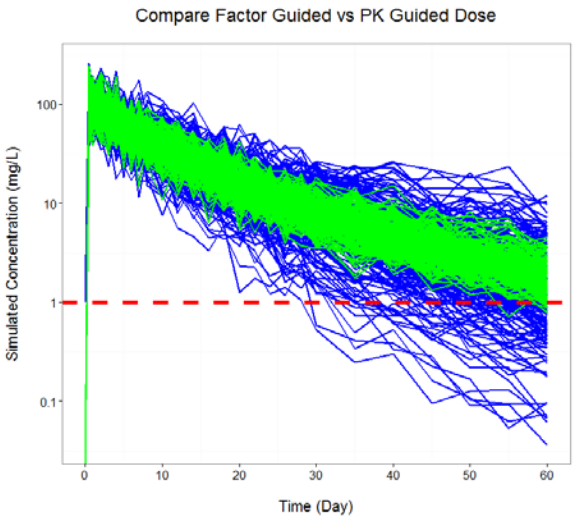


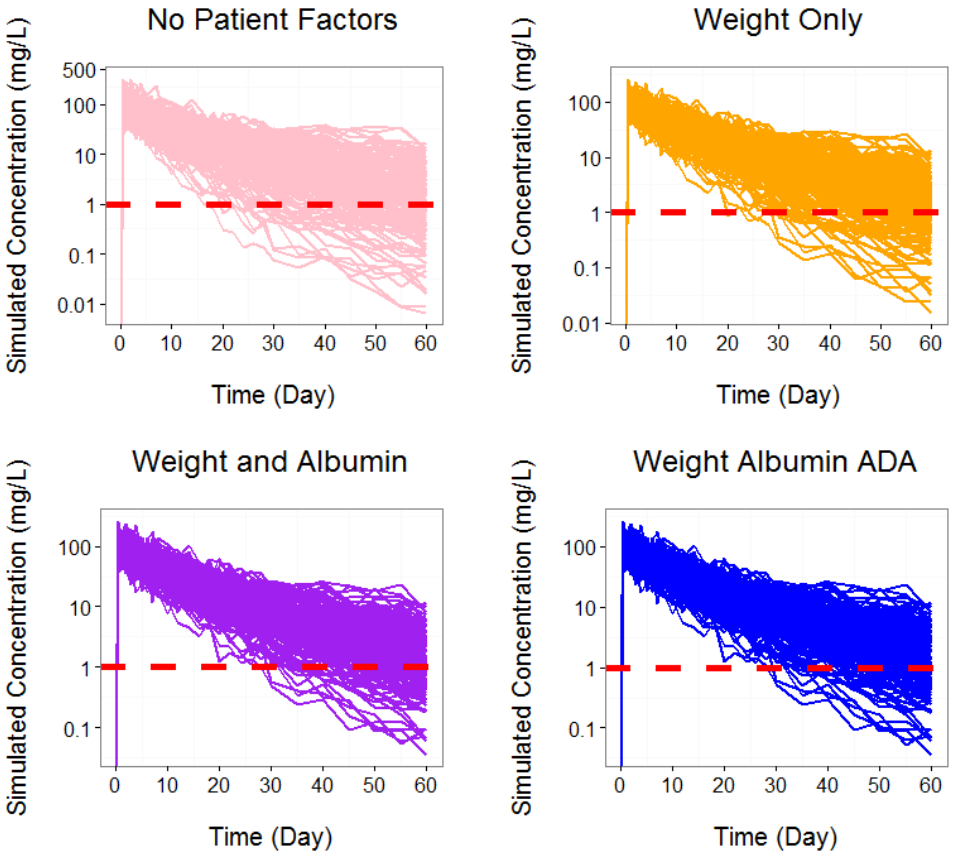
- Maybe instead of modeling disease progression, it is easier and more efficient to assess therapeutic failures

Seow Gut 2010 59: 49-54

Strategies to Maintain Effective Exposure

- Dose adjust based on severity
- Therapeutic drug monitoring is becoming more common
- PK-guided dosing (dashboards) being tested





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

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

Therapeutic Drug Monitoring

- Some of the loss of response is due to ADA but in other patients, low trough levels were associated with poor outcomes
- 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, South America
  - Less common in US
- The use of TDM and individualized dose adjustments have been shown to improve outcomes, and often reduce the cost of therapy

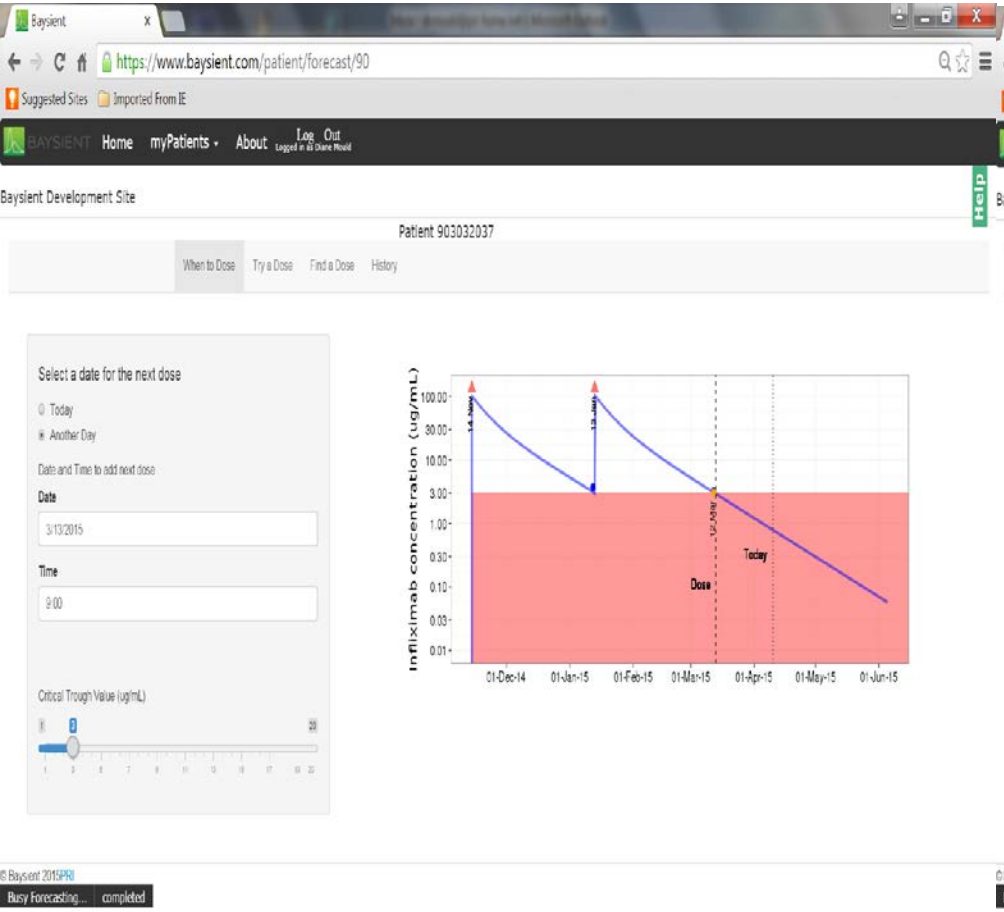
Peyrin-Biroulet, L., et al.. *Clin. Gastroenterol. Hepatol.* **6**, 644–653 (2008).
Seow, C.H. et al. *Gut* **59**, 49–54 (2010).
Vande Casteele N, et al. Gastroenterology. 2015;148(7):1320-9

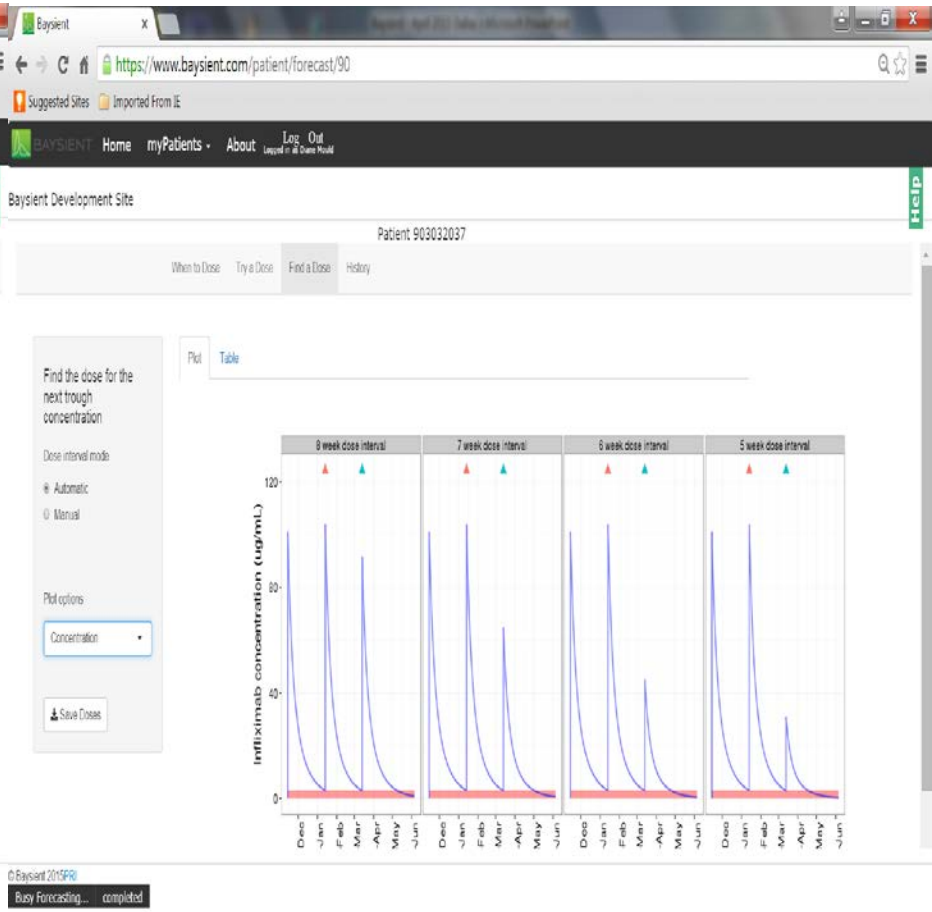
What is a Dashboard?

- 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
  - Tracks response to treatment, prognostic factors
  - Forecast exposure and response - helps determine appropriate doses

Dashboard Process

ENTER PATIENT FACTORS → UPDATE LAB RESULTS → PREDICT TROUGH OUTCOMES → CHOOSE DOSE AND INTERVAL





What have we learned?

- IBD is chronic and progressive
- Development of disease progression model is complex
  - Symptoms do not reflect “inflammatory burden”
  - Disease activity biomarkers do not reflect the true extent of disease progression
- Treating to biologic targets or exposure improve long-term outcomes
  - TDM has shown retrospectively improved outcomes
- Get the most out of initial therapy
  - Reducing incidence of treatment failure may impact disease progression
- PK/PD makes a difference
  - Pediatric patients often have lower drug exposure than adults
  - Disease severity does impact PK and pediatric patients often more severe disease

Where do we need to go?

- Design and run informative studies in adult and pediatric patients, particularly newly diagnosed patients
  - Capture metrics of response more frequently during induction
    - Evaluate at different time points in different groups
  - Attempt to enroll more severe patients if possible
    - Many “severe” patients in clinical trials are just “bad moderate” patients
  - Attempt to capture all medications used to treat disease more completely
    - Capture disease history!
- Identify metrics of actual disease progression or stage
  - Attempt to follow patients over longer periods of time
  - Include factors such as scarring and stricturing in response model
- Better (faster) more selective/sensitive assays for drug and for ADA
- Ongoing studies with dashboard guided dosing in IBD showing good potential

Thank You!

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