Clinical Implementation of PK/PD Model-Informed Decision Support Tools for Precision Dosing

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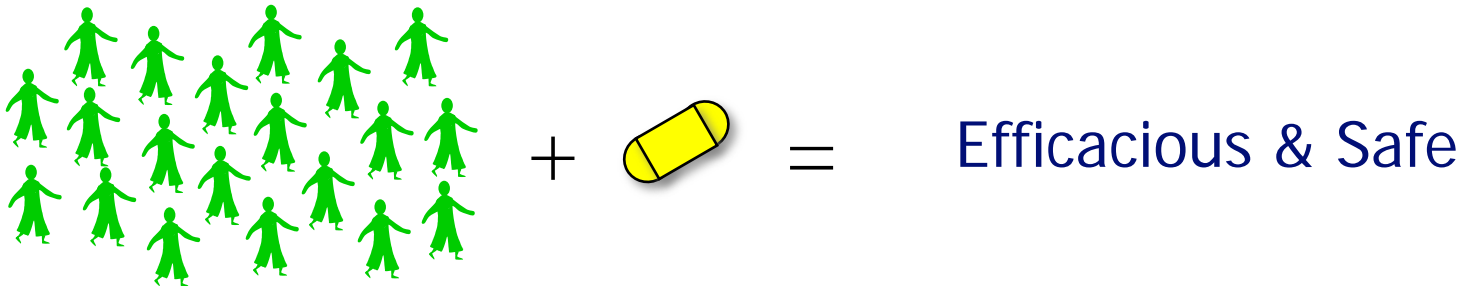Scientific Director, Pharmacy Research in Patient Services

Co-director, Genetic Pharmacology Service

Cincinnati Children's

changing the outcome together

Objectives

- Highlight the ongoing paradox of precision medicine and the drug development process resulting (typically) in doses for the average patient.

- Describe clinical decision support using model-informed precision dosing to improve treatment outcomes by identifying the optimal dose for each individual patient.

- Present examples of the development and implementation of model-informed decision support for precision dosing at Cincinnati Children's.

Continuing Paradox of Drug Development

1. Clinical trials provide evidence of efficacy and safety at <u>usual doses</u> in *populations*

\+ 💊 = **Efficacious & Safe**

2. Physicians treat *individual patients* who can <u>vary widely</u> in their response to drug therapy

\+ 💊 = → **Adverse Drug Reaction**

→ **Efficacious & Safe**
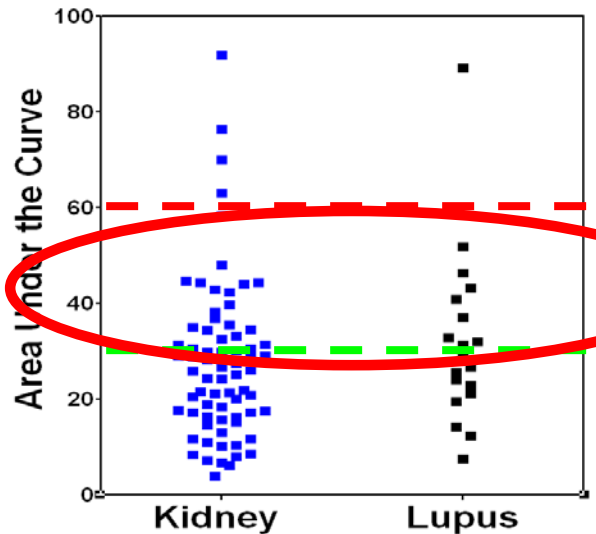
→ **No Response**

Mycophenolate exposure at standard dose

Continuing Paradox of Drug Development

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Efficacious & Safe

2. Physicians treat *individual patients* who can <u>vary widely</u> in their response to drug therapy

Mycophenolate exposure at standard dose
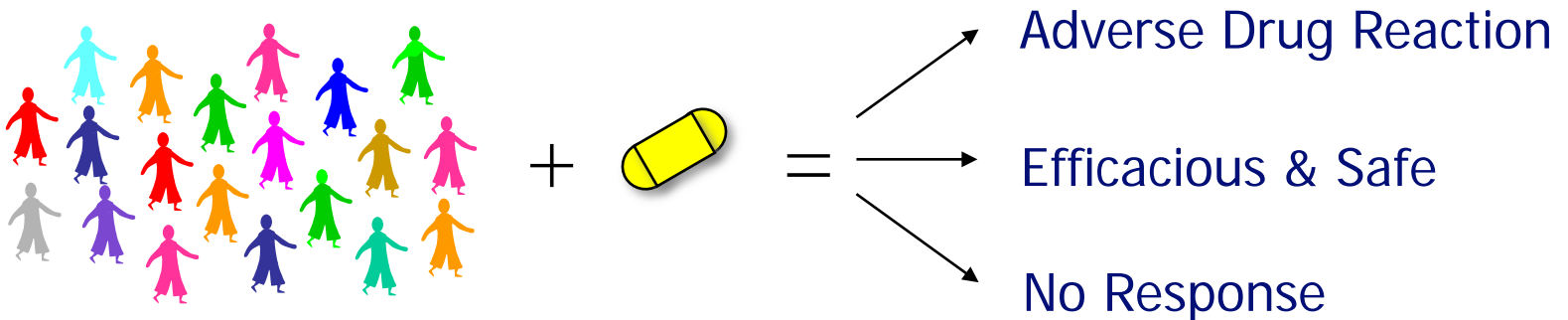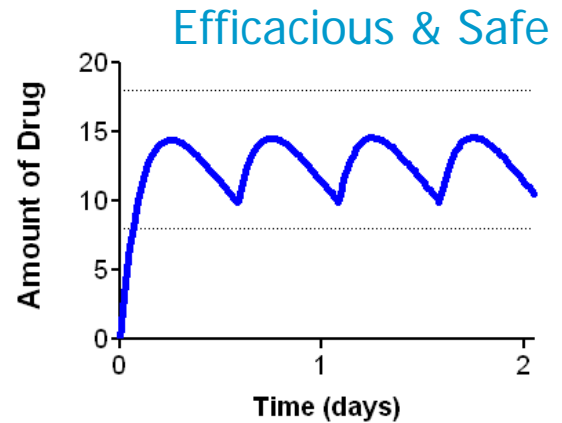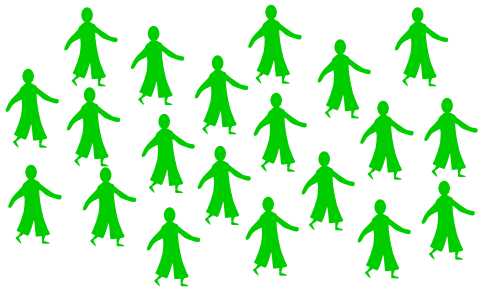
Precision Medicine based on *Pharmacokinetics & Pharmacodynamics*

- Wouldn't it be amazing if we could follow the amount of drug and biomarkers in the body as our **'molecular status', *in vivo,* and in real time**?

- So … **why can't we do it now?**

Because we lack *real-time assays* for concentrations (PK) and biomarkers (PD)

**And we don't have *simple tools*
for clinical interpretation
using EHR integrated decision support**

EHR – Electronic Health Record

Assessment of paper spray ionization for quantitation of pharmaceuticals in blood spots

Nicholas E. Manicke [a,c], Qian Yang [b,c], He Wang [b,c], Sheran Oradu [a,c],
Zheng Ouyang [b,c,*], R. Graham Cooks [a,c,**]

[a] Department of Chemistry, Purdue University, West Lafayette, IN 47907, USA
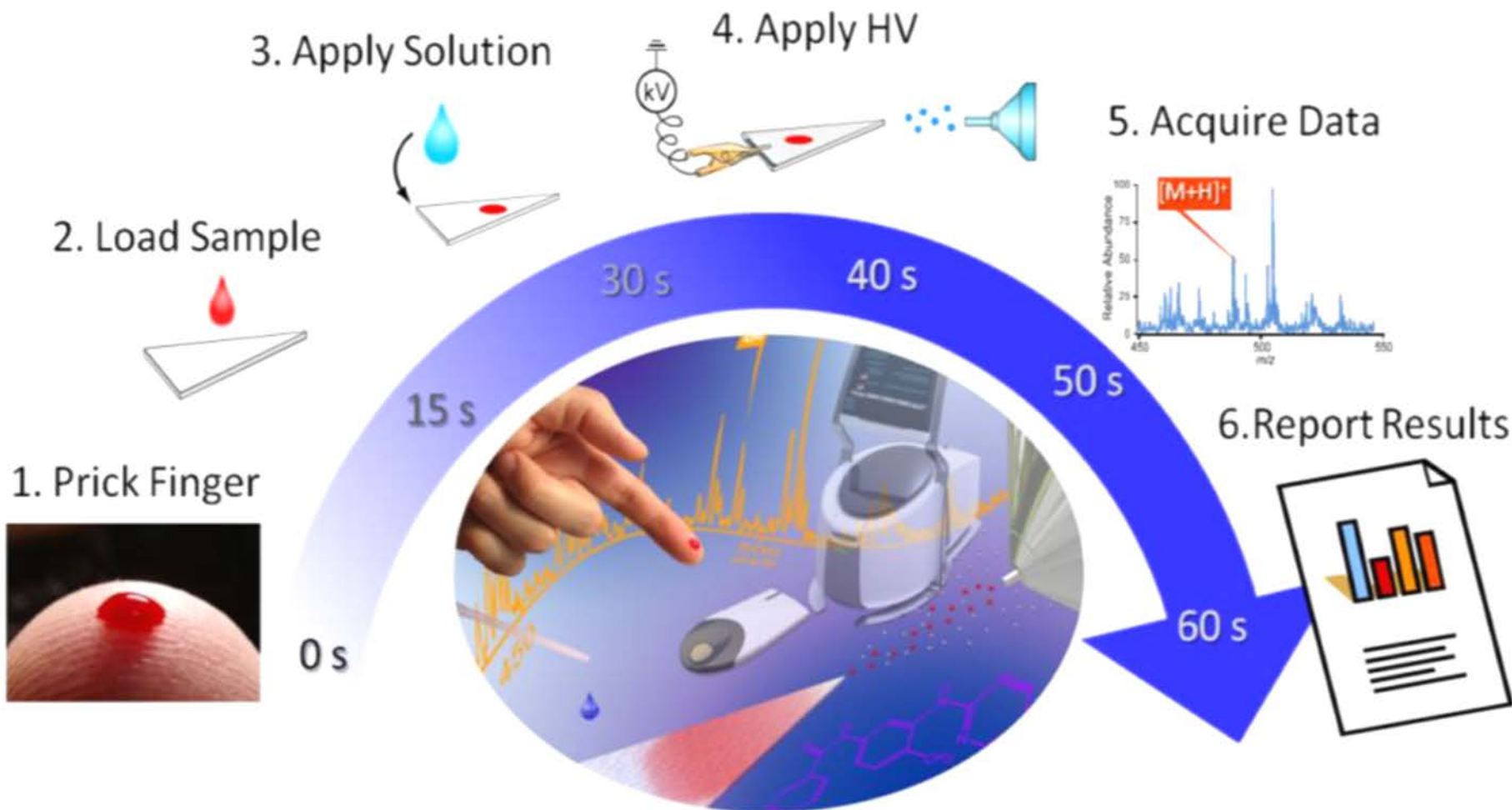[b] Weldon School of Biomedical Engineering, Purdue University, West Lafayette, IN 47907, USA
[c] Center for Analytical Instrumentation Development, Purdue University, West Lafayette, IN 47907, USA

Ongoing development at CCHMC:

- Anticancer drugs - **melphalan**, cyclophosphamide, busulfan

- Pain medication - **morphine** and metabolites

- Neonatal abstinence syndrome (NAS) drugs - methadone, buprenorphine
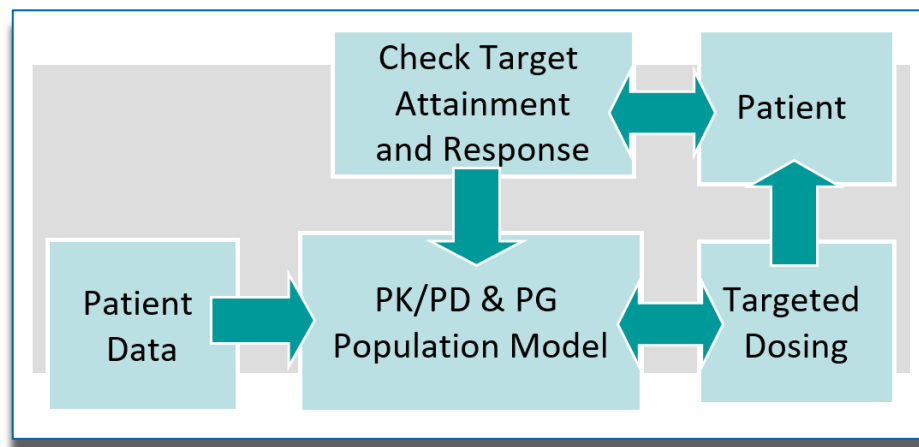

Point of Care Therapeutic Drug Monitoring & QuantIon Ion Source

3. Apply Solution

4. Apply HV

5. Acquire Data

2. Load Sample

$[M+H]^+$

30 s

40 s

50 s

15 s

6. Report Results

1. Prick Finger

0 s

60 s

Power of Modeling & Simulation

PK/PD driven decision support

Cloud based

Precision Dosing -> Improved Outcomes

PKPD

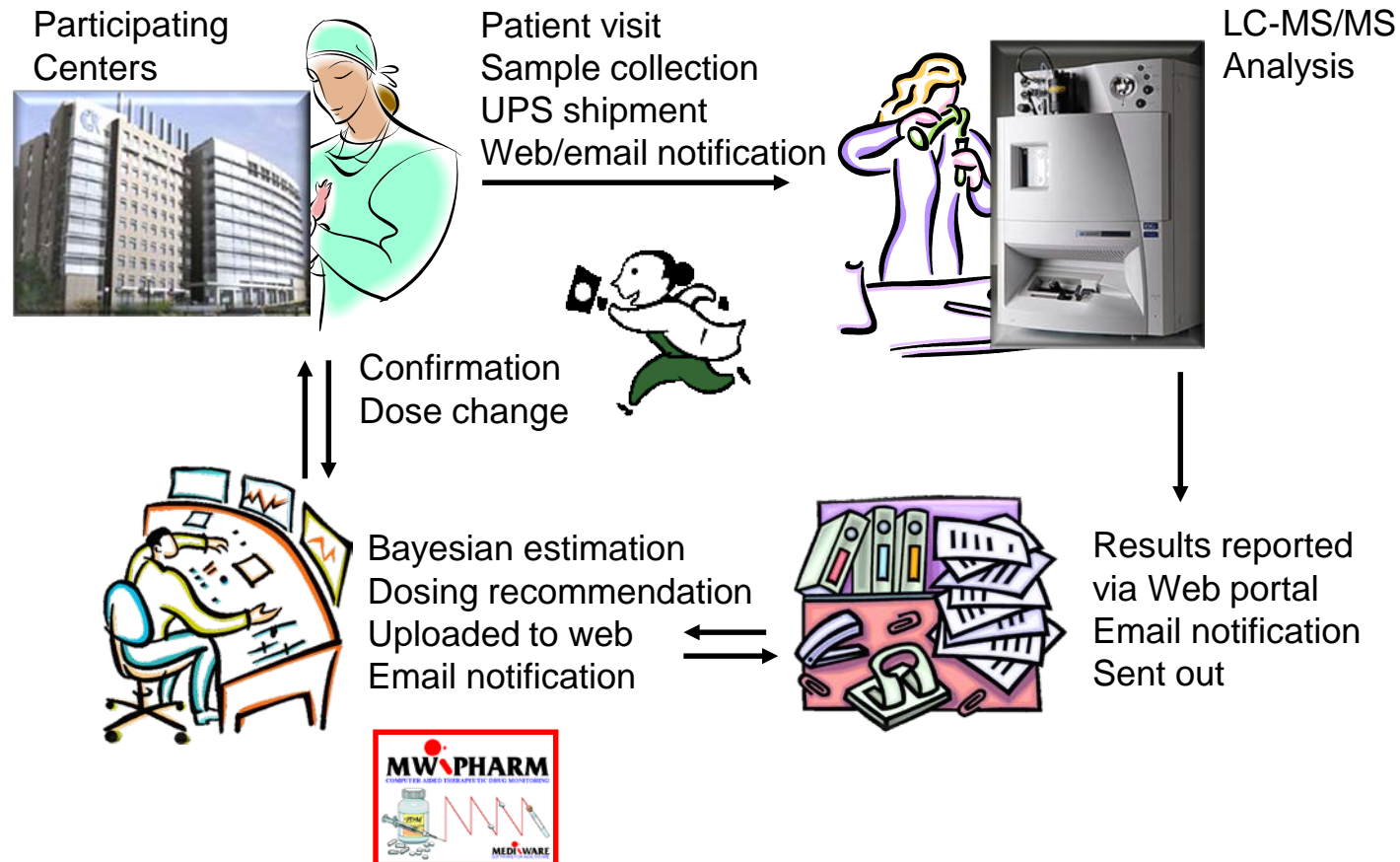|	Check Target Attainment and Response	Patient
Patient Data	PK/PD & PG Population Model	Targeted Dosing

Jelliffe et al. 1998. Model-based, goal-oriented, individualized drug therapy. Linkage of population modelling, Bayesian feedback and individualized target goals. Clin Pharmacokinetics, 34(1):57-77.

PK/PD model-informed Precision Dosing Process for concentration-controlled trials

Participating Centers

Patient visit
Sample collection
UPS shipment
Web/email notification

LC-MS/MS Analysis

Confirmation
Dose change

Bayesian estimation
Dosing recommendation
Uploaded to web
Email notification

Results reported
via Web portal
Email notification
Sent out

MW\PHARM

Model-informed clinical decision support initiative at Cincinnati Children's

> *Integration of pharmacogenetics with model-based PK/PD algorithms in a decision support platform as part of the Electronic Health Record for individualized precision dosing in real time*

The not too distant future of availability of drug sensors

2018 - FDA approves first continuous glucose monitoring system with a fully implantable glucose sensor and compatible mobile app for adults with diabetes.
<https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm611454.htm>.
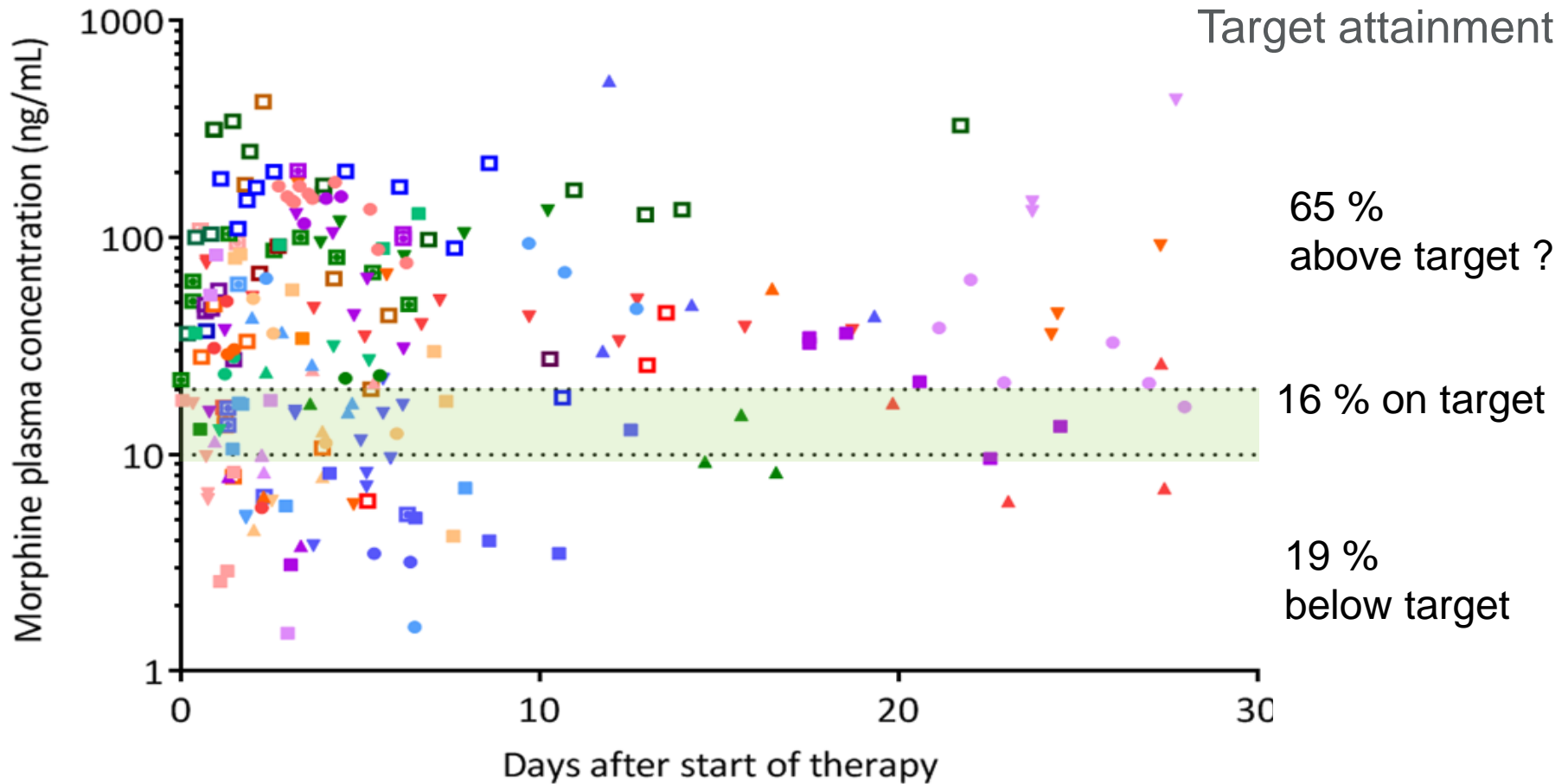
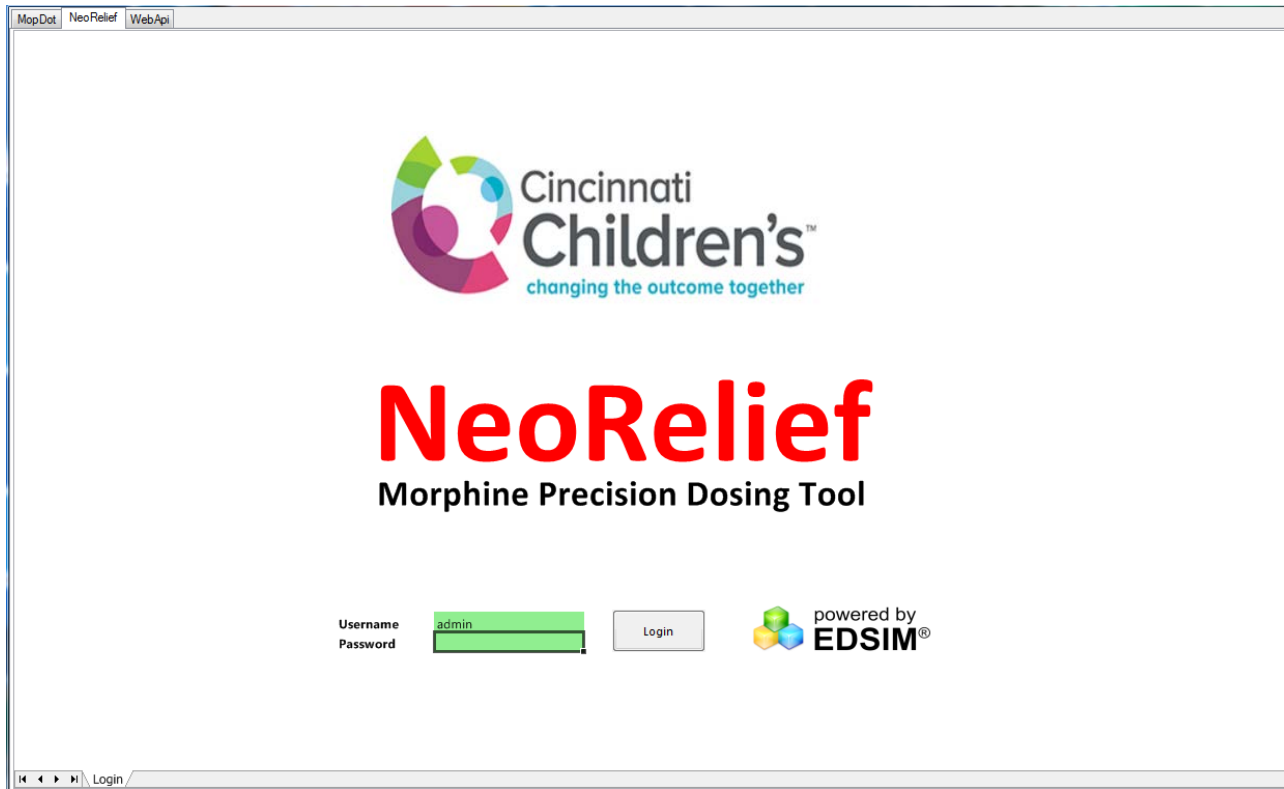# Model-informed precision dosing can have many applications

- **Melphalan** – *individualized micro dosing strategy to control variability in high dose melphalan exposure in reduced intensity conditioning in allogeneic hematopoietic cell transplantation for non-malignant disorders*

- **Hydroxyurea** – *improving the timeline to achieve maximum tolerated dose and improved response in patents with sickle cell anemia*

- **Morphine,** Midazolam, Acetaminophen - ***NeoRelief™ decision support platform** for individualized pain treatment in neonates*

- **Methadone and buprenorphine** – *MIPD for tailored neonatal abstinence syndrome treatment*

- **Biologics** – ***RoadMap™ physician driven decision support** for precision dosing of monoclonal antibodies in the treatment of Inflammatory Bowel Disease*

Pain management in the Neonatal Intensive Care Unit
- *large variability in exposure with standard doses* -

Target attainment

65 %
above target ?

16 % on target

19 %
below target

Euteneuer et al. 2019. Morphine PK variability in the NICU - 229 observations in 56 neonates

Electronic Health Record-embedded Decision Support for Morphine Precision Dosing

Neonatology   Pharmacy

Clinical Pharmacology

T32

Med Informatics

Information Services

Innovation Ventures

Medimatics

Euteneuer et al. Suggestions for Model-Informed Precision Dosing to Optimize Neonatal Drug Therapy. J Clin Pharmacol. 2018.
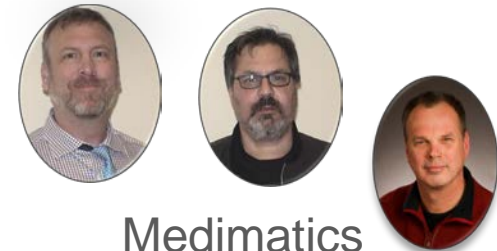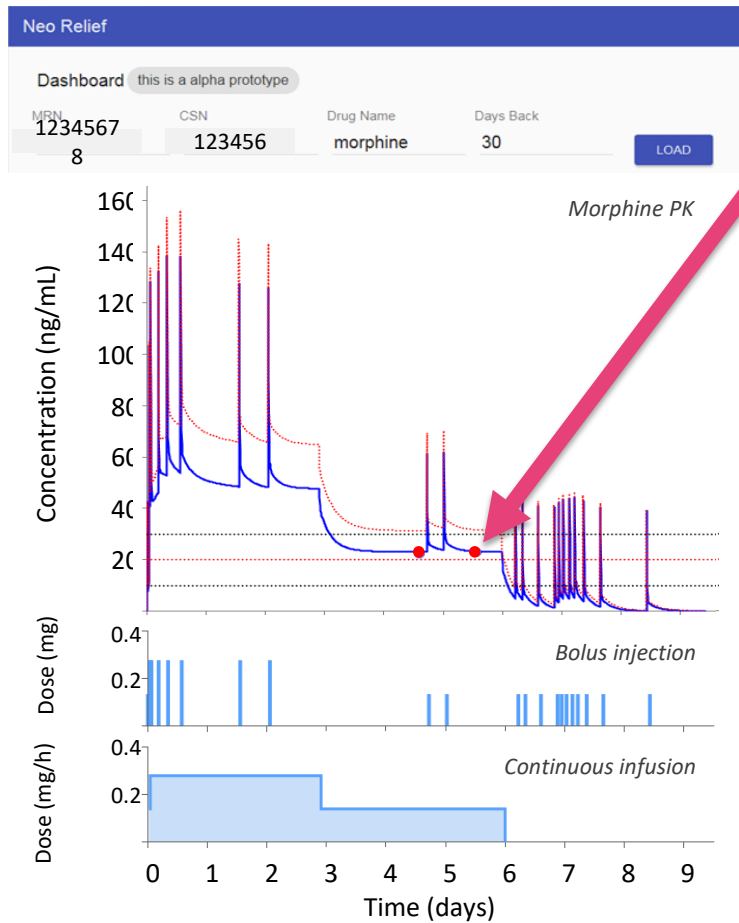
NeoRelief Prototyping

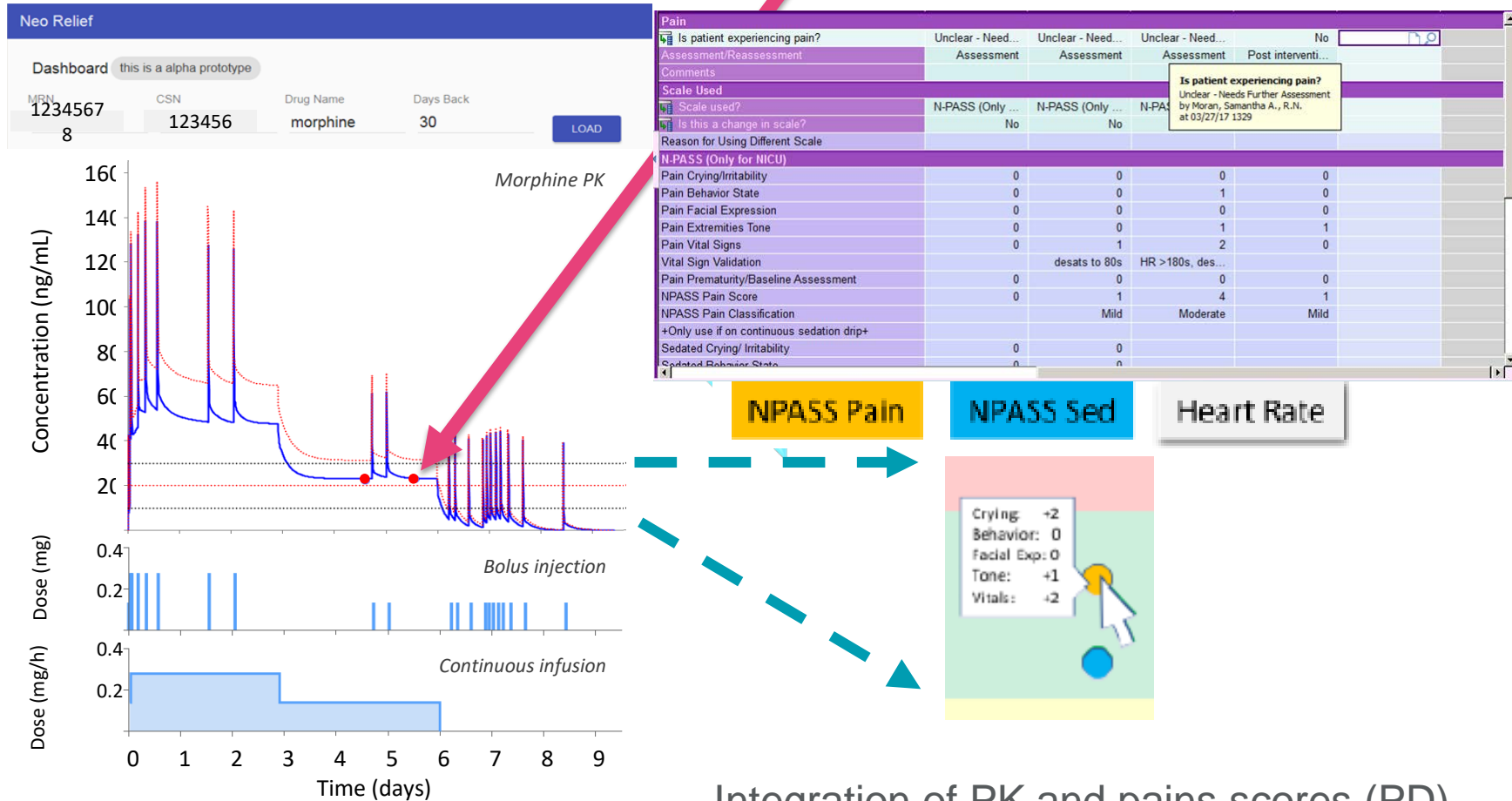Real time measurement & feedback

Concentration read-out

Dosing input

NeoRelief Prototyping

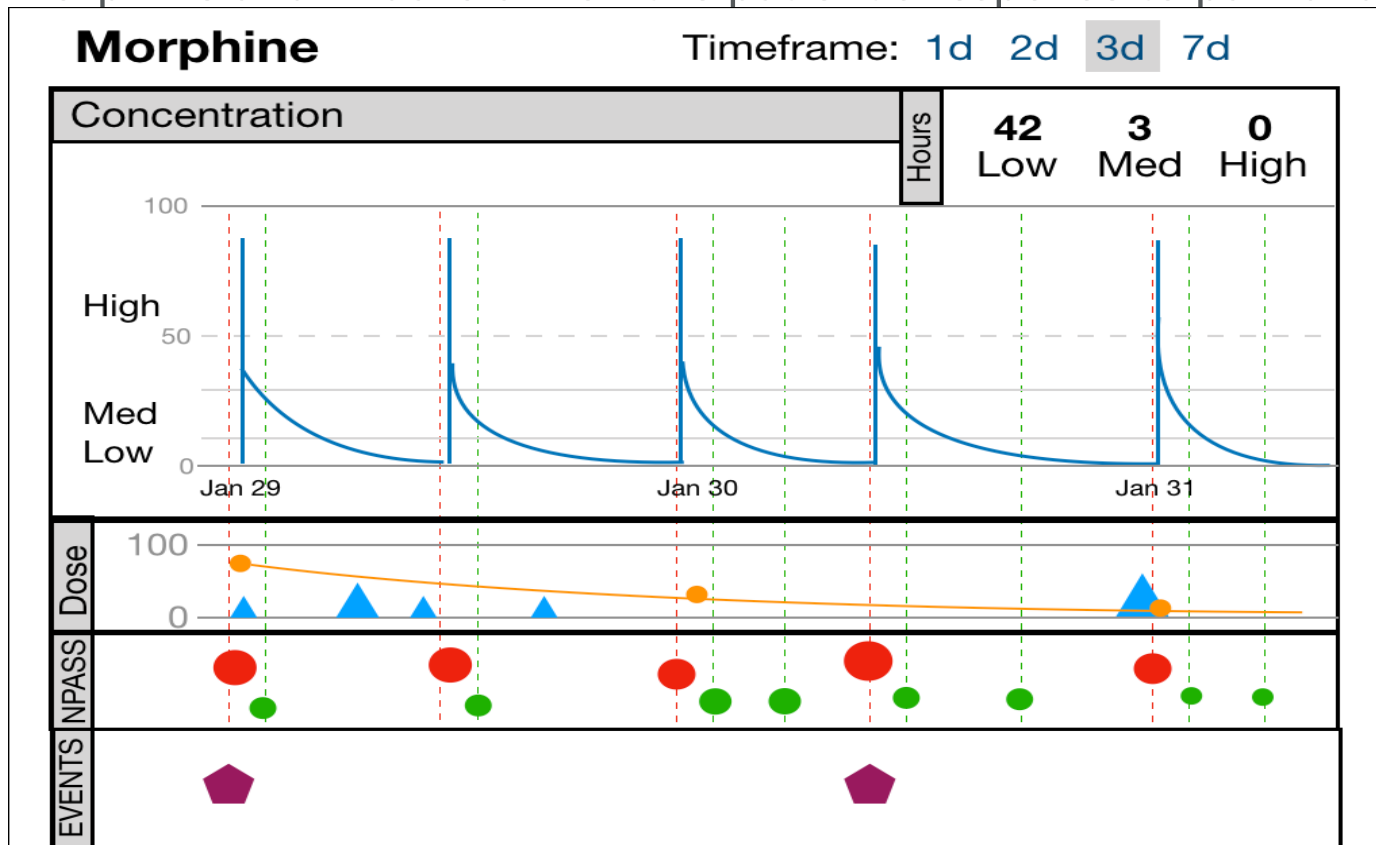Real time measurement & feedback

Integration of PK and pains scores (PD) in an intuitive dashboard

Human Factors engineering:
NeoRelief™ Precision Dosing Application

- Help clinicians recognize the importance of optimal dosing and impact of morphine and midazolam on the patient's response to pain and sedation.

NeoRelief prototype after human factors engineering process

Why model-informed precision dosing should become a common clinical reality!

- *'Our son was diagnosed with Crohn's last year and was started on Remicade. **His trough level has frequently been sub-therapeutic**.*

- *Our sense is there are multiple possible reasons for this but I imagined you would say **most of them are avoidable with the right pharmacologic approach**.*

- *Have you had any experience with Remicade (infliximab) for therapeutic monitoring? **Seems like an area ripe for work given the cost of the drug and the risks of sub-therapeutic levels**.*

- *We'd be curious about any thoughts you might have - **that might help us and potentially the approach to Crohn's**. I'd be interested to meet if you think there are some opportunities to explore.'*

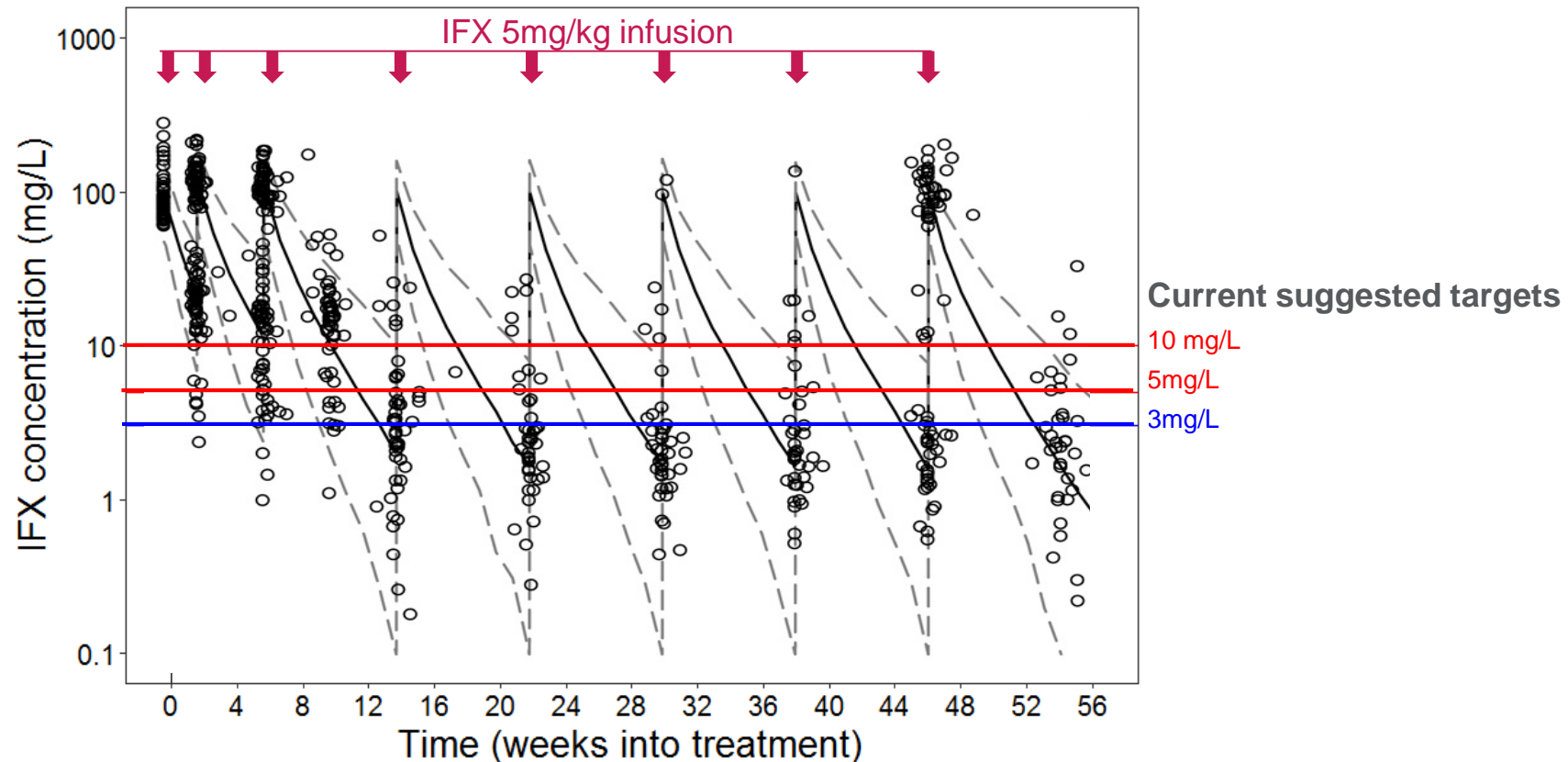Gastroenterology   ImproveCareNow   CHRF   Clinical Pharmacology   Medimatics
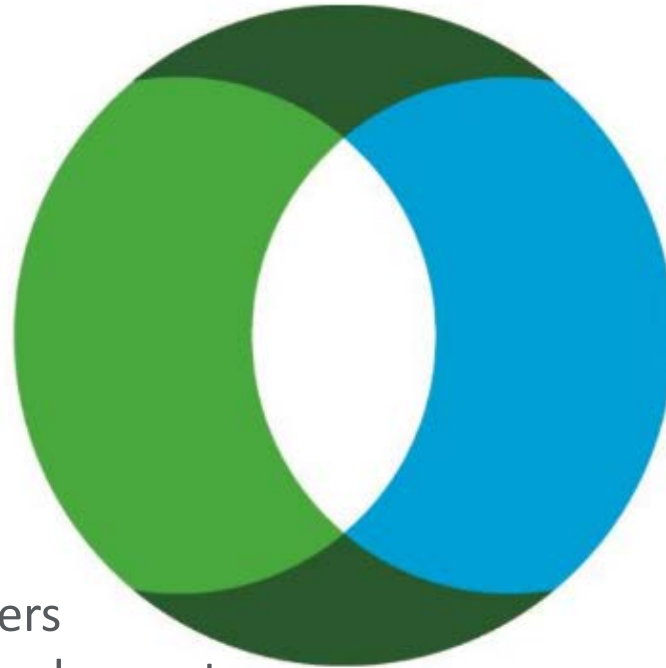
Pivotal study for FDA approval of infliximab in children with Crohn's disease

- Impressive response rates observed after induction at week 10: in 88.4% of patients with 58.9% achieving clinical remission.
- However - approximately half (55.8%) of patients receiving infliximab maintenance therapy had favorable response or clinical remission at the end of the study at week 54.
- Many patients in the pivotal trial had what now would be considered 'below target' exposures during and toward the end of the study.

Fasanmade et al. Pharmacokinetic Properties of Infliximab in Children and Adults with Crohn's Disease: A Retrospective Analysis of Data from 2 Phase III Clinical Trials. Clin Ther; 33:7: 947-64.

Learning Health Systems as Facilitators of Precision Medicine - *IBD ImproveCareNow Network*


> 100 GI Care Centers

> 30,000 patients and parents

> 950 physicians

> 60% of all patients with Inflammatory Bowel Disease

Learning Health Systems as Facilitators of Precision Medicine - *IBD ImproveCareNow Network*

➤ **A network case study to illustrate how the concept of precision medicine can be achieved through a Learning Health System in a real-world clinical environment.**

Ramsey LB, Mizuno T, Vinks AA, Margolis PA. Learning Health Systems as Facilitators of Precision Medicine.
Clin Pharmacol Ther. 2017;101(3):359-67.
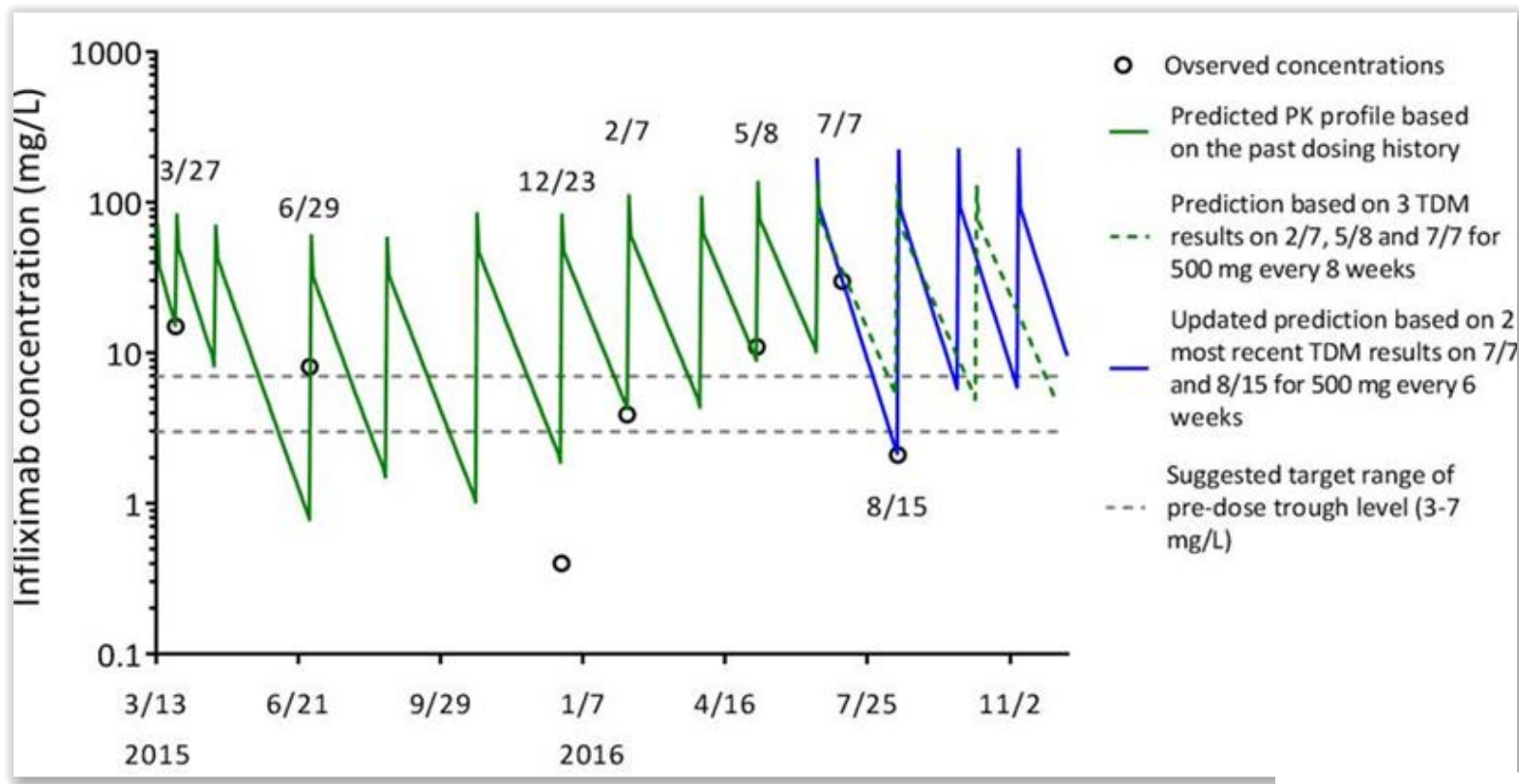
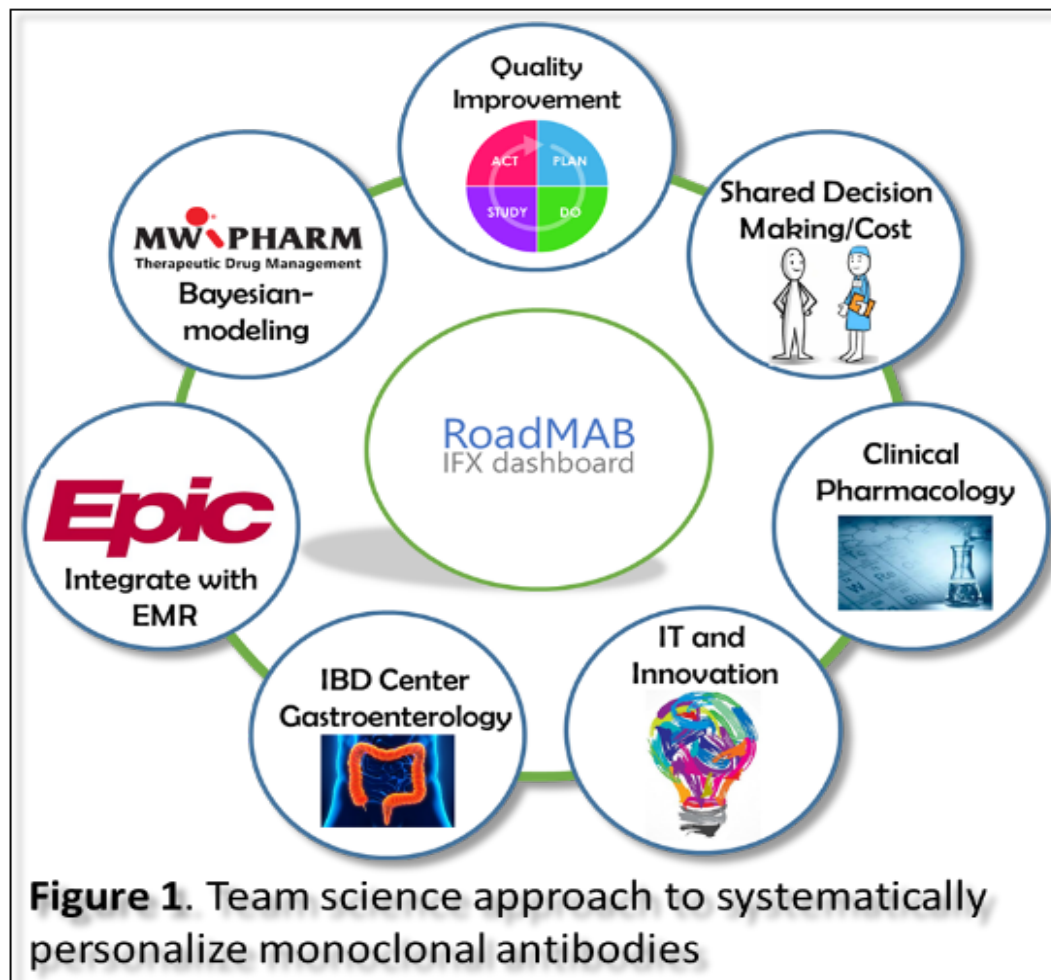# Infliximab Model-informed Predictive Performance
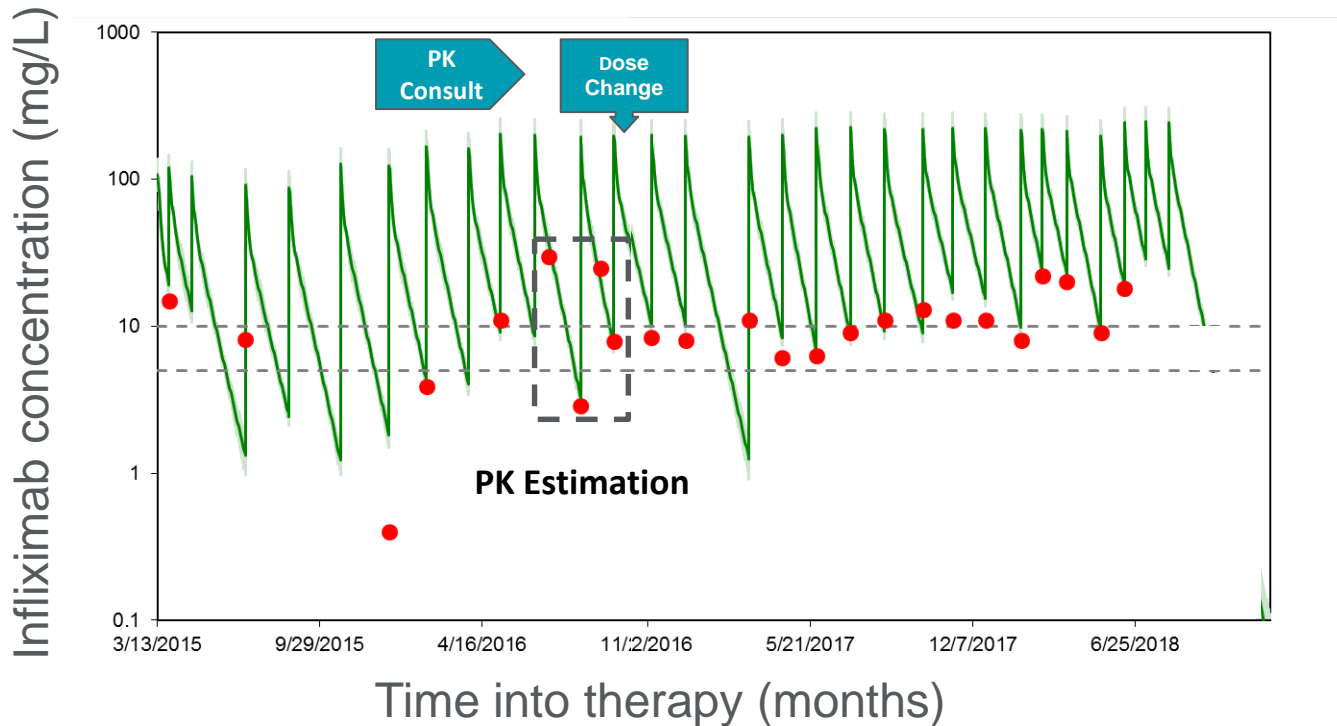
PK consult: Individual PK parameters were estimated using the data shown in the dashed box and using the CCHMC infliximab population PK model.

The model predicted the PK profile very well as confirmed by the measured concentrations
Predictive covariates: Weight, Albumin, Erythrocyte Sedimentation Rate, Anti-drug antibody level.

Ramsey et al. *Clin Pharmacol Ther*. 2017 Mar;101(3):359-367

Exposure control for biologics – a learning health system

Figure 1. Team science approach to systematically personalize monoclonal antibodies

Courtesy: Phillip Minar, MD. Division of Gastroenterology, Hepatology, and Nutrition, Cincinnati Children's Hospital Medical Center

Exposure control for biologics – a learning health system

Infliximab RoadMAB (prototype)

Patient			
Weight (kg)	65	ALB (g/dL)	2.3
Combination immunemodulator			MTX
ESR (mm/h)	55	nCD64	4.5

Infusion 5 Target concentration

Ref Range — Min **5** — Max **10**

Infusion 5 Target Fecal Calprotectin

Ref Range — Min **<16** — Max **250**

sim — Each graph represents a different dose & interval

Dose	5
Schedule	Q 4 weeks
Trough	5.6
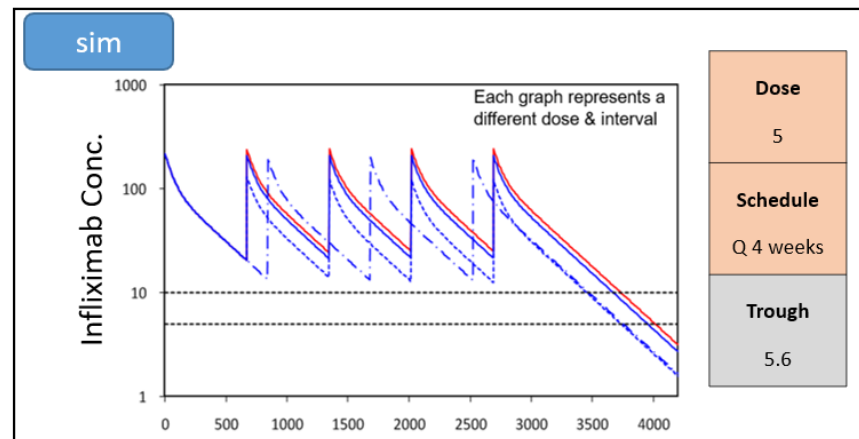
Recommended Dosing

Dose (mg/kg)	9	Flat Dose (mg)	600
Schedule	Q 4 weeks	Interval (week)	Q 4 weeks
Estimated Trough 7.9		**Estimated Trough 8.2**	

Conclusions

- *This Time is Different*: model-informed therapeutic drug management is here and clinically feasible
- *Learning Health Systems* represent an attractive platform for collecting and analyzing big EHR data sets using machine learning and AI to integrated new knowledge in *a timely fashion* into care to improve health
- A large evidence base is developing on the utility of model-informed precision dosing for narrow therapeutic index drugs
- Next iterations will have to expand emphasis on pharmacodynamics, disease progression and pro-active anticipatory intervention!

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Information Services!
Patients and Parents!