Pharmacometric Strategy and Tools in the Design of Precision Dosing for the Electronic Patient Care Environment

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I will present examples that evaluate off label dosing of approved medications.

Objectives

- Discuss the need to evaluate the gap between the phase III study sample and real-world patient population
- Review the pharmacometric considerations to developing precision dosing strategies
- Discuss advances in the electronic patient care environment that can facilitate precision dosing

Current Basis for Drug Dosing

1. Clinical trial evidence for approval

2. Bridging
   a. **Pharmacokinetic/pharmacodynamic modeled link to outcome** [e.g., 1st dose & adjustment to a biomarker associated with outcome]
   b. **Pharmacokinetic bridging.** Determine dosing to match exposure for patients outside the pivotal trial experience (e.g., renal failure, pediatrics) to a reference PK drug profile associated with favorable efficacy/safety

What's the Problem with this Approach?

1. **A large fraction of the real-world patient population excluded**
   a. Patients at the extremes of age, size, and organ function may not be studied, and the data needed to inform dosing for these patients may not be collected
   b. Results in a delay (or a lack of) dosing recommendations for special populations (e.g., pediatric patients, pregnant women)
2. **The drug label usually has univariate dosing recommendations (e.g., based on renal function), whereas dosing may be dependent on multiple factors observed together in the same patient (e.g., renal failure, drug interactions, genetic variation)**
3. **The above issues may not be improved over the drug product cycle, and there may not be an update to reflect the real-world patient population experience once generics are approved**

As many as 58% of Real-World Patients may be Excluded from Clinical Research

Spong CY, Bianchi DW. Improving Public Health Requires Inclusion of Underrepresented Populations in Research. *JAMA*. 2018;319(4):337–338.

Opinion

VIEWPOINT

Improving Public Health Requires Inclusion of Underrepresented Populations in Research

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Advances in genomics have ushered in promising therapies tailored to the individual. Personalized medicine is promoted and has begun to positively influence care. For example, medications such as trastuzumab for the 30% of breast cancers that overexpress *ERBB2* and vemurafenib for patients with late-stage melanoma who carry the V600E variant have been beneficial.[1] Despite these advances, for many sectors of the population—children, older adults, pregnant and lactating women, and individuals with physical and intellectual disabilities—limited evidence-based therapies optimized to their specific medical needs exist. Combined, these groups comprise as much as 58% of the US population (eTable in the Supplement). Research focusing on or at the very least includes members of these groups is critically needed.

Until the initial passage of the Best Pharmaceuticals for Children Act in 2002, pediatric drug doses were based on extrapolation from adults. Importantly, body

cations are often prescribed with minimal evidence to support their use, especially psychotropic drugs with significant adverse effects.

Recently, discussions have arisen about the need for inclusion in research and elimination these gaps. In 2017, the National Institutes of Health (NIH) held a workshop, "Inclusion Across the Lifespan," that highlighted current federal regulations that include protections for "vulnerable populations" (pregnant women, fetuses, neonates, prisoners, and children). Although these regulations were originally designed to protect these individuals, many investigators have called for reconsideration, opting to protect them *through* research, rather than *from* research. Inclusion will likely yield data that will benefit more people.

Many underrepresented populations encounter barriers to participation in research. In a review of 338 phase 3 and 4 NIH-funded actively recruiting studies in

Phase III – Real-World Patient Gap

Eligibility Criteria of Randomized Controlled Trials Published in High-Impact General Medical Journals
A Systematic Sampling Review

- Potential participants were excluded from trial participation due to medical comorbidities in 81.3% of the RCTs
- Patients <16 and >65 years of age were excluded from 60.1% and 38.5% of RCTs, respectively
- Participants receiving commonly prescribed medications were excluded in 54.1% of trials

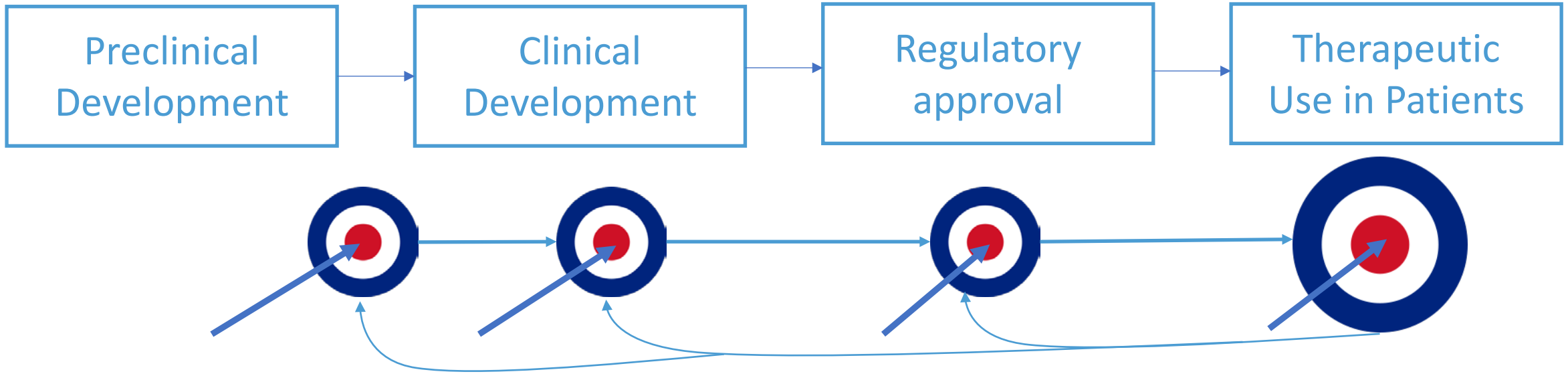
Van Spall HG, et al. *JAMA*. 2007;297(11):1233-40.

Phase III – Real-World Patient Gap

- **Why characterize the gap?**
  - There may be differences in dose-exposure and exposure-response relationships between phase III and real-world patients
- **Which patient characteristics are likely to exist for real world patients for many drugs?**
  - Age extremes (neonate-110 years)
  - Size extremes (adult 30-250 kg)
  - Pregnancy & immediately post-pregnancy
  - Varying renal and liver function
  - Relevant genotypes
  - Drug-drug interactions
- **When to characterize the gap?**
  - Phase I-II
- **How to evaluate the gap?**
  - Best practice recommendations are needed (e.g., data source, methodology)
- **How to communicate the gap?**
  - To FDA: End of phase II meeting and assessment made public
  - To public: product label

Applications of Pharmacometrics in Drug Development, Regulatory Review, and Post-Approval

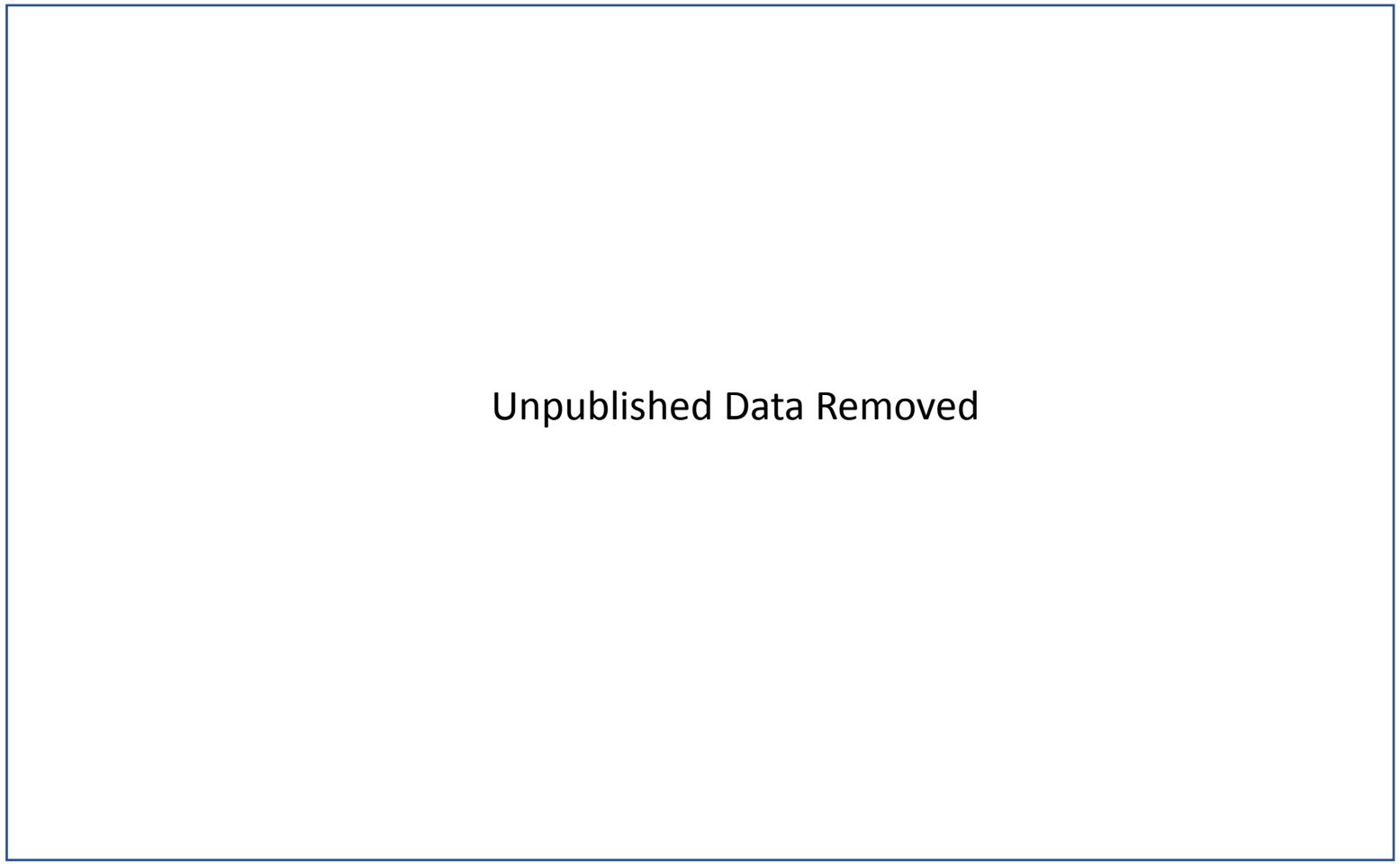
Target Knowledge Integration → Learning



Likely Impact

Patients: Better drugs for more patients
Sponsor: Greater trial & market predictability
Payers: Improved health care quality and reduced costs
FDA: More effective regulatory reviews

Predicted Rivaroxaban AUC for Labeled Dosing in Varying CrCl



*Predictions made using sponsor model: Willmann S, et al. *CPT Pharmacometrics Syst Pharmacol.* 2018;7(5):309-320.
Konicki R, et al. Manuscript in preparation.

CrCl: Creatinine Clearance

Proposed CrCl-Based Dosing Strategy

Unpublished Data Removed

*Predictions made using sponsor model: Willmann S, et al. *CPT Pharmacometrics Syst Pharmacol.* 2018;7(5):309-320.
Konicki R, et al. Manuscript in preparation.

Unpublished Data Removed

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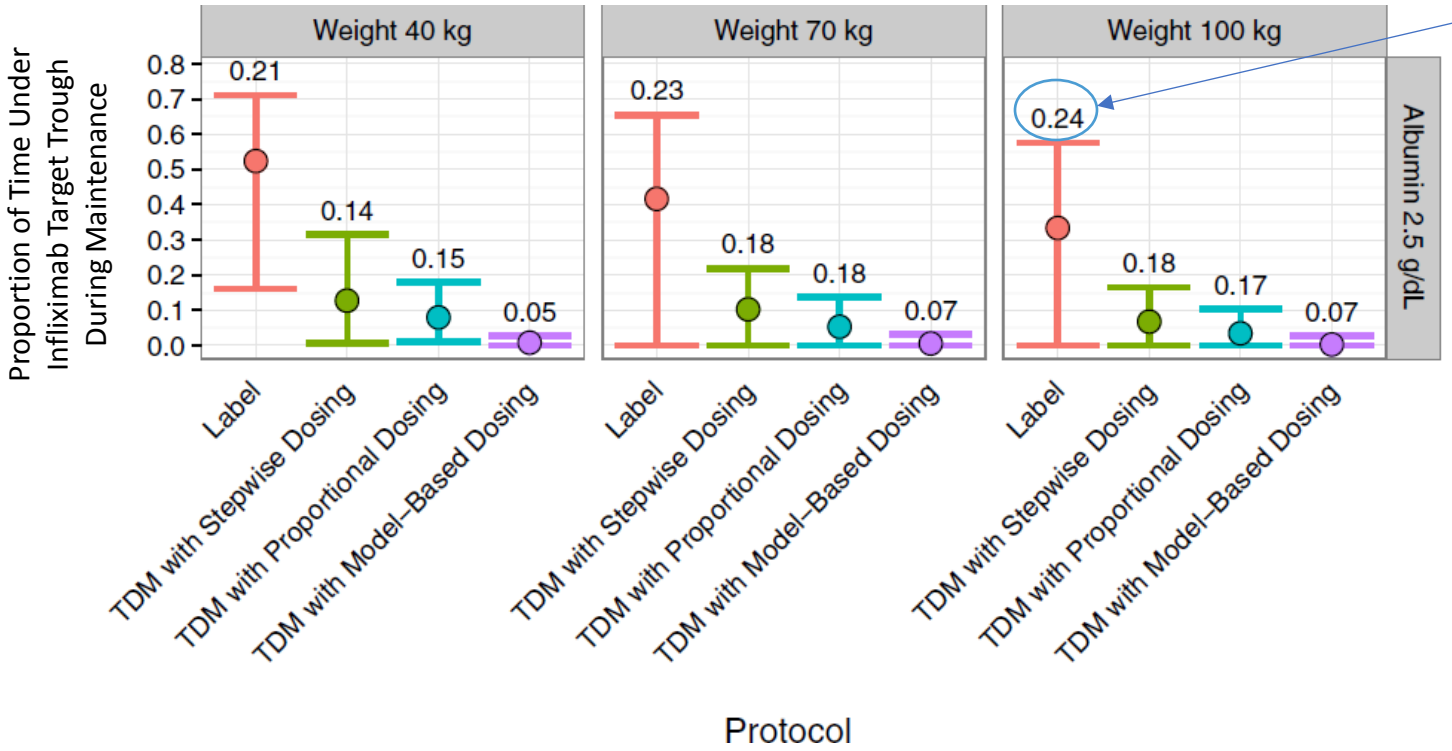
Simulations Suggest Benefit of Model-Based Dosing for Infliximab

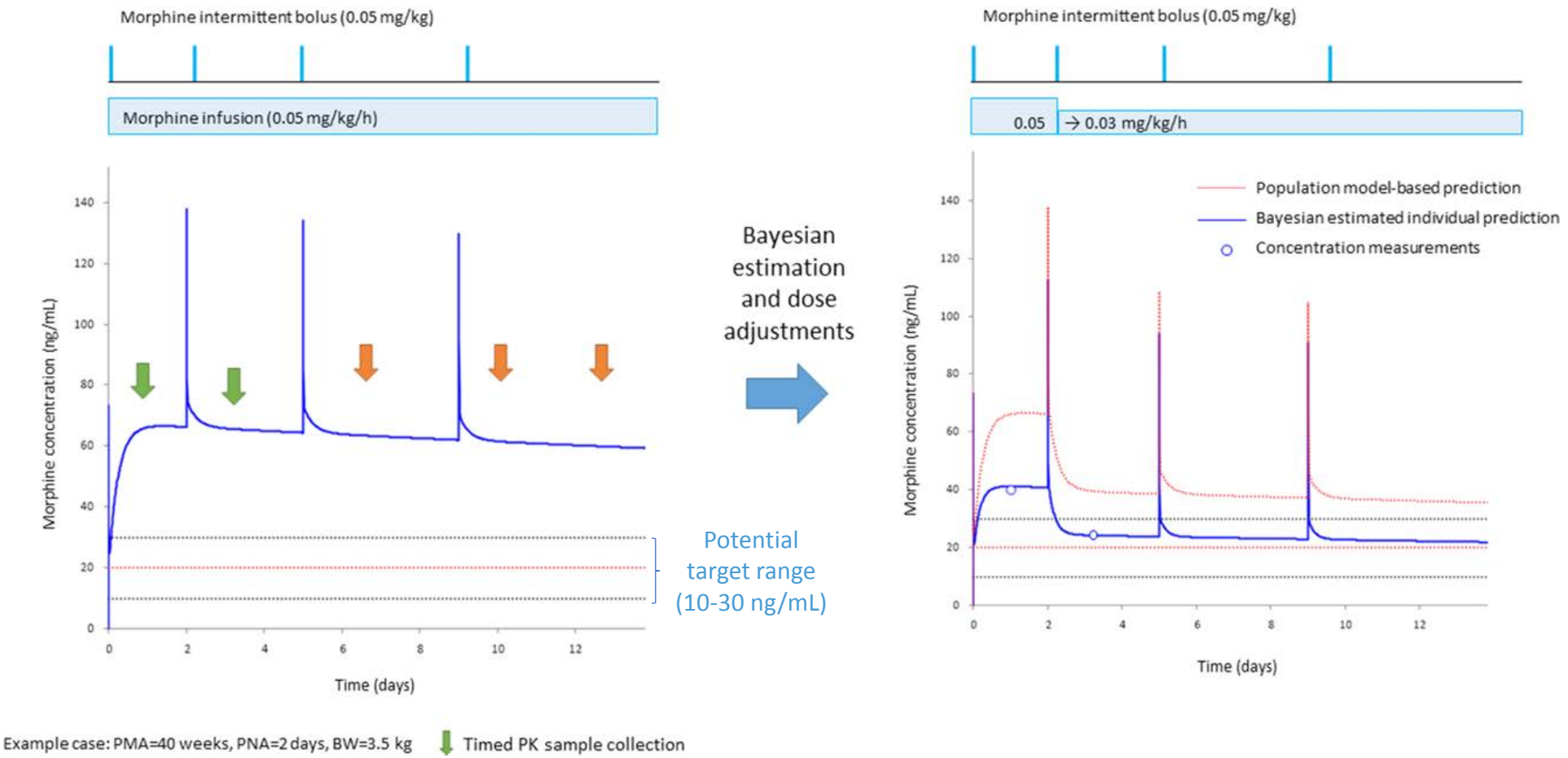


Numbers above error bars: Proportion of individuals developing anti-drug antibodies

Circles and error bars represent median and interquartile range for each covariate subpopulation, respectively. Target trough concentration: 3 mg/L.

Wojciechowski J, et al. *AAPS J.* 2017;19(4):1136-1147.

Morphine Precision Dosing in Neonates



Euteneuer JC, et al. *J Clin Pharmacol.* 2019;59(2):168-176.

Scientific Challenges Related to Model-Informed Precision Dosing

1. **Model selection**
   - Some times many models may be available -> which one do you select?
   - Predictive performance of the model -> does it work well in my patient population?
   - There is a model published, but patients at the extremes are not represented -> can we access the raw data to merge it with new data and update the model?
2. **Model qualification**
   - Covariate-based *a priori* dosing and TDM-based *a posteriori* dosing -> does the model perform as expected?
3. **Model bias**
   - Bias resulting from differences in patient characteristics, parameters estimates, missing or erroneous data, and selection bias -> how to handle it?
4. **Interoccasion variability**
   - Time varying changes in pharmacokinetics/pharmacodynamics-> how to handle it?

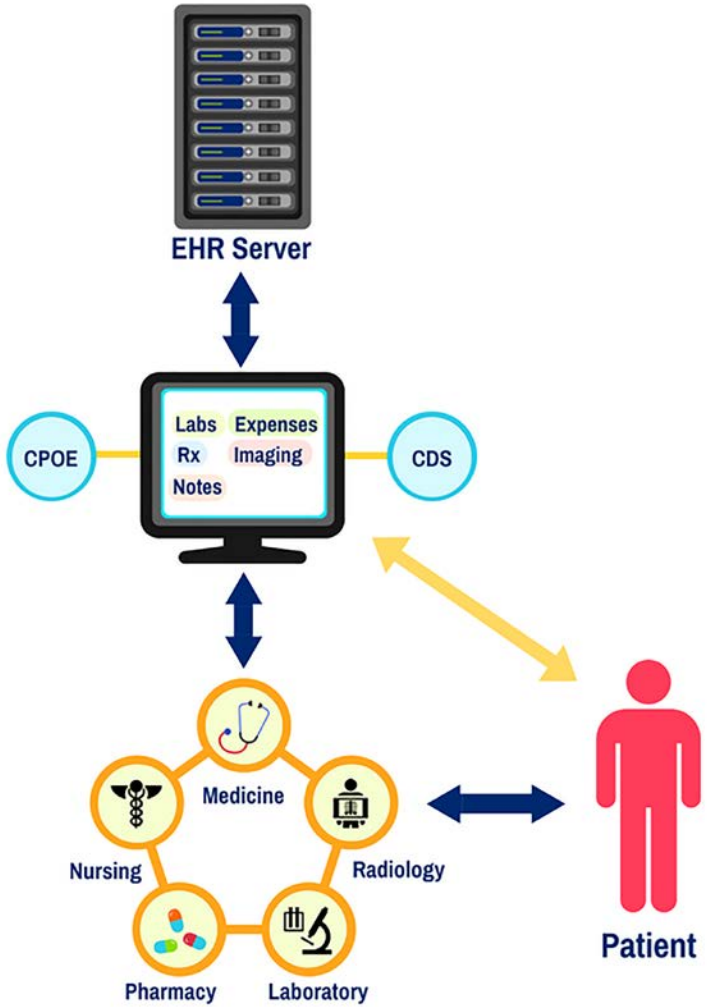
Keizer RJ, et al. *CPT Pharmacometrics Syst Pharmacol.* 2018;7(12):785-787.

Future Directions to Facilitate Precision Dosing

- Quantitate the phase III-real-world patient gap
- PK sampling in phase III trial to relate exposure to outcome
- Availability of clinical data to evaluate dose-exposure and exposure-response relationships across real-world patient populations (e.g., obese, geriatrics, pediatrics)
- Clinical decision support tools to deliver dosing recommendations to prescribers and patients
- Multistakeholder collaborations will be important to validate, implement, and demonstrate the value of precision dosing tools
- Regulatory incentive or requirement

EHR Environment and Precision Dosing

- In 2015, >8 in 10 non-federal acute care hospitals in the U.S. had adopted a basic electronic health record (EHR) system, which will facilitate precision dosing
- Availability of machine learning and artificial intelligence
- Advances in digital health technologies (e.g., mobile applications, wearable devices)

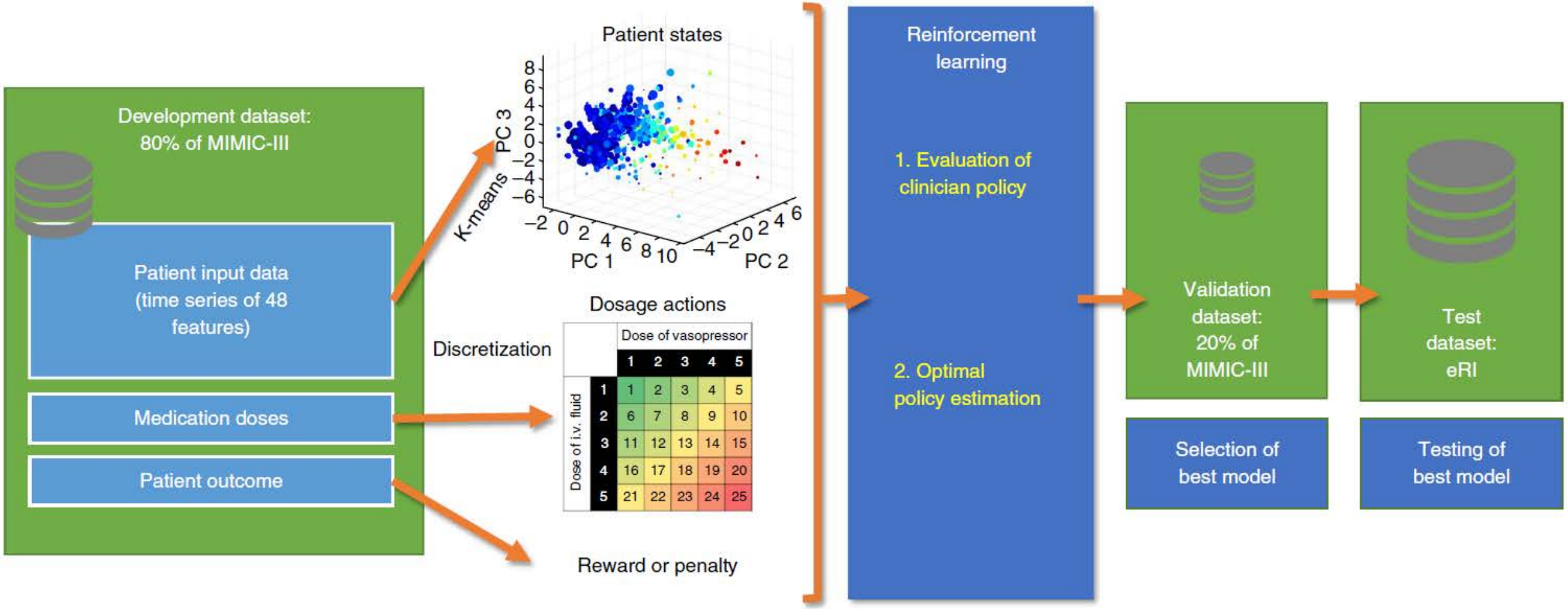


CPOE: computer provider order entry
CDS: clinical decision support

https://dashboard.healthit.gov/

Gonzalez D, et al. *Clin Transl Sci.* 2017;10:443-454.

Application of AI to Optimize Drug Dosing

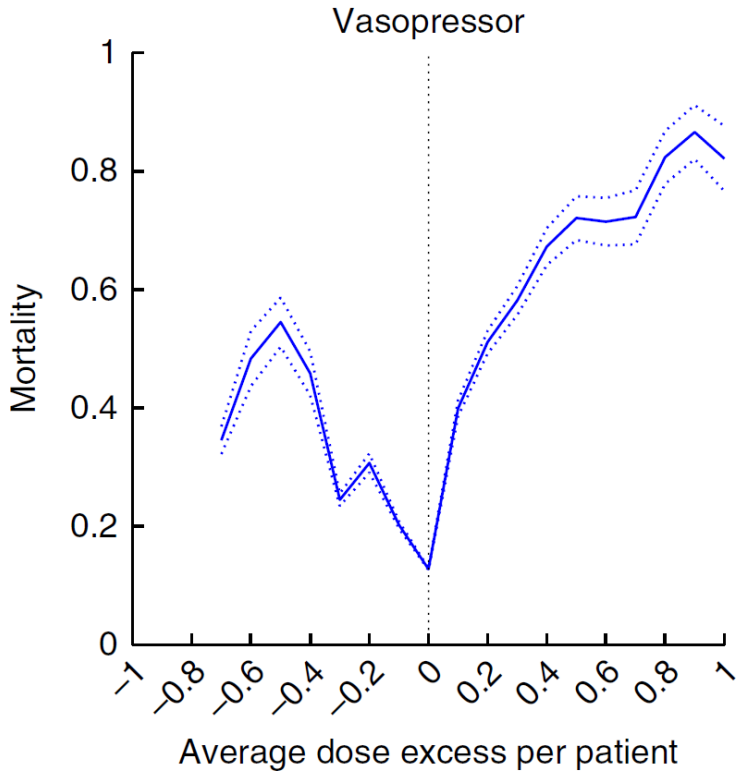


MIMIC-III: Medical Information Mart for Intensive Care version III
eRI: eICU Research Institute Database

Komorowski M, et al. *Nat Med*. 2018;24(11):1716-1720.

Patients that Received Doses Similar to the AI Recommended Dose had a Better Outcome

- Excess dose refers difference between the given and suggested dose averaged over all time points per patient
- Dose-dependent changes in mortality were observed when administering more or less than the AI recommended vasopressor dose



Komorowski M, et al. *Nat Med*. 2018;24(11):1716-1720.

Precision Dosing – Why Now?

- The need to study drugs in more diverse patient populations is now more widely recognized
- Pharmacometrics can be applied to characterize differences in drug exposure and response at the extremes of age, and allow for model-informed precision dosing
- Widespread adoption of electronic health record systems will facilitate precision dosing
- Application of machine learning and artificial intelligence to improve drug treatment strategies

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