The evolution of clinical decision support tools that enable precision dosing at the point of care

FDA Precision Dosing Workshop

Sirj Goswami

August 12th, 2019

Agenda / Learning Objectives

(1) Describe the **current state of precision dosing tools** and highlight macro-level factors that enable broad adoption of CDS platforms

(2) Highlight approaches to overcome **electronic health record integration** barriers and develop an **optimal user experience**

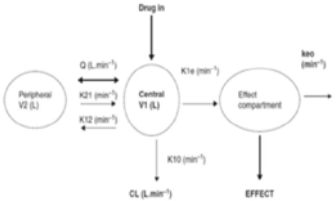
(3) Highlight the importance of an **analytics framework and dashboard** to improve platform scalability and demonstrate value

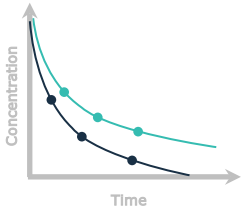
An ideal CDS platform should be **user friendly, scalable**, integrated into the **clinical workflow** and **improve healthcare outcomes**

HISTORICAL CONTEXT

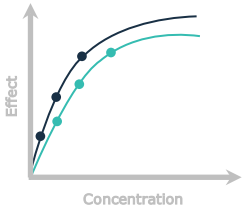
First **model-informed precision dosing (MIPD) tool** developed in 1969

PK/PD Models to support clinical decisions





Pharmacokinetics



Pharmacodynamics

ELSEVIER

Computers and Biomedical Research

Volume 2, Issue 6, December 1969, Pages 507-518

Computer-aided long-term anticoagulation therapy

Lewis B. Sheiner*

Show more

https://doi.org/10.1016/0010-4809(69)90030-5

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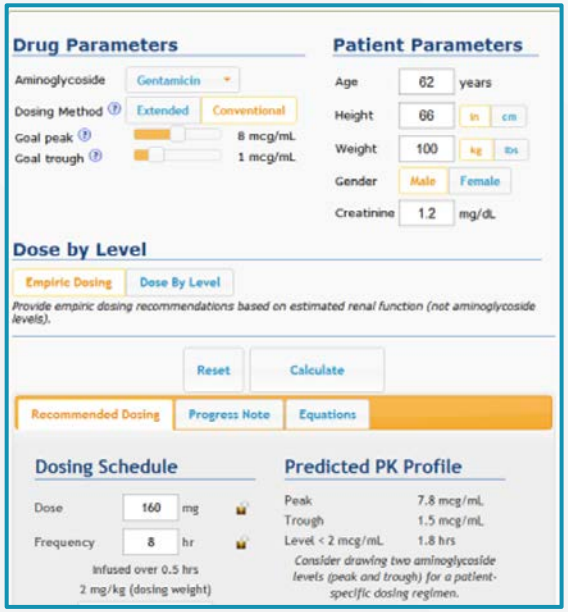
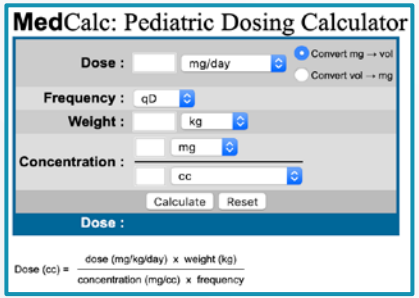
Abstract

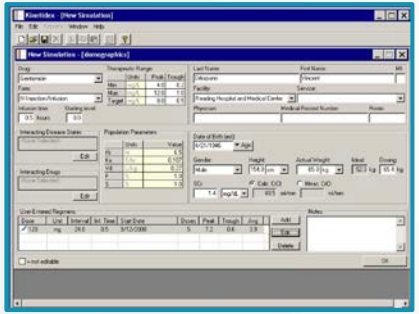
A computer program is described which calculates a suggested daily anticoagulant dose schedule for a patient. The program requires previous prothrombin times and drug dosages as well as physician determined therapeutic goals and limits. A simple compartmental response model is used to predict prothrombin time responses from previous drug doses. Suitable future dose suggestions are calculated from these prothrombin time predictions. A retrospective study provided a test of the program's performance relative to that of resident physicians and three staff cardiologists at a large teaching hospital. The doses computed by the program were found to compare favorably with those of the pilot sample of physicians.

Current environment: **Fragmented** dosing calculators and spreadsheets that **do not** leverage the power of MIPD

- *Imprecise (not-model based)*
- *Difficult to use*
- *Fragmented*
- *Requires manual entry*
- *Lack of standardization*





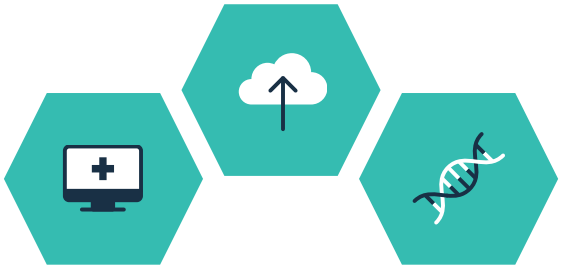


The **time is right** to adopt CDS Platforms and MIPD in healthcare

Technical Barriers Eliminated

Cloud-based infrastructure for healthcare, computational power

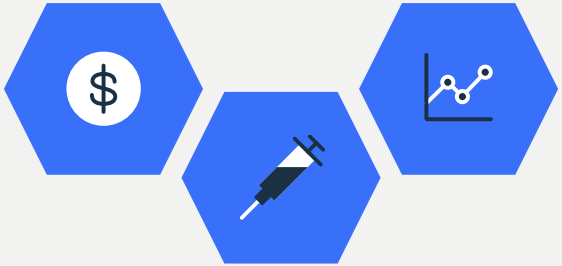
Transition to Electronic Medical Records



Rise of diagnostics

Macro-level Industry Trends

Value-based healthcare (pay for value)



Data-driven patient care

Precision medicine

CDS Platforms outside of MIPD have undergone a transformation over the past several years

Key Evolving Characteristics

- User interface/experience
- Software integration
- Clinical workflow implementation
- Analytics

User interface (UI) / user experience (UX)

UI/UX

UI/UX in healthcare lags behind other industries

- Electronic health record (EHR) systems are outdated
- Complex clinical workflows
- Multiple stakeholders involved in decision making
- Waterfall software design process
- Clinical user is NOT the buyer
- Developers are NOT users and NOT in tuned with clinical need
- Complexity of data inputs and data outputs
- Abundance of idiosyncratic terminologies (e.g. AUC)

UI/UX

What constitutes an optimal **user experience?**

The product is **useful**

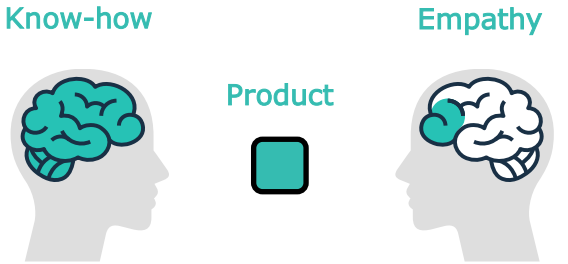
- It addresses real paint points and problems for the user population.

The product is **user friendly**

- Users can intuitively, or with relatively little training, repeatedly use the product’s functionality.

The product is **simple**

- Users demand a simple platform that does not compromise quality.



Expert

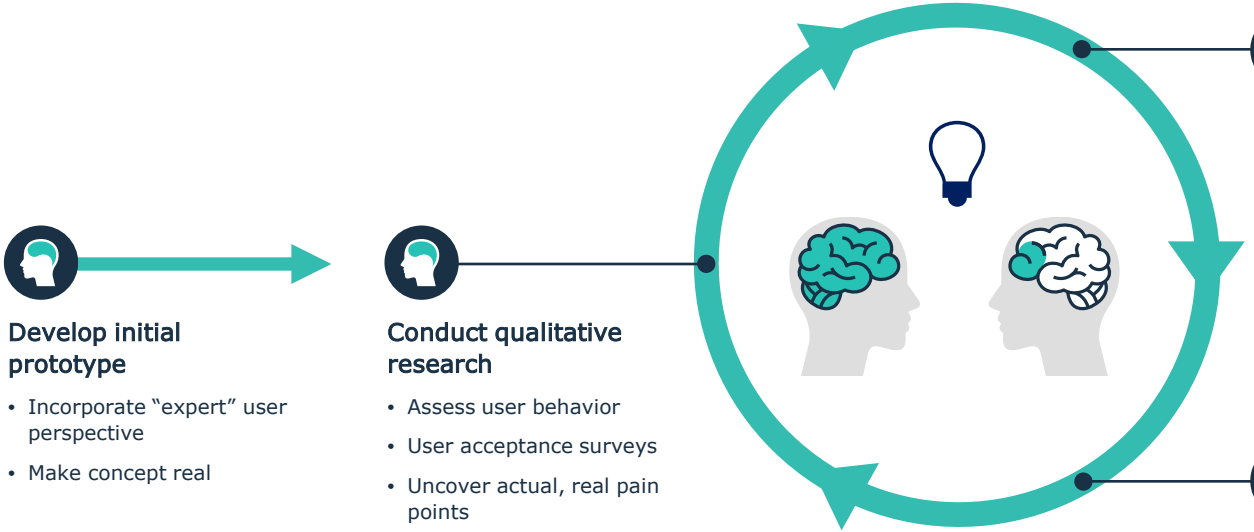
- Domain expert
- **Clinical pharmacologist**
- **Specialized pharmacists**

Typical user

- Not a domain expert
- **Physician**
- **Pharmacist**

UI/UX

Usability research studies help us achieve an optimal product design



Develop initial prototype

- Incorporate "expert" user perspective
- Make concept real

Conduct qualitative research

- Assess user behavior
- User acceptance surveys
- Uncover actual, real pain points

Translate insights into product design

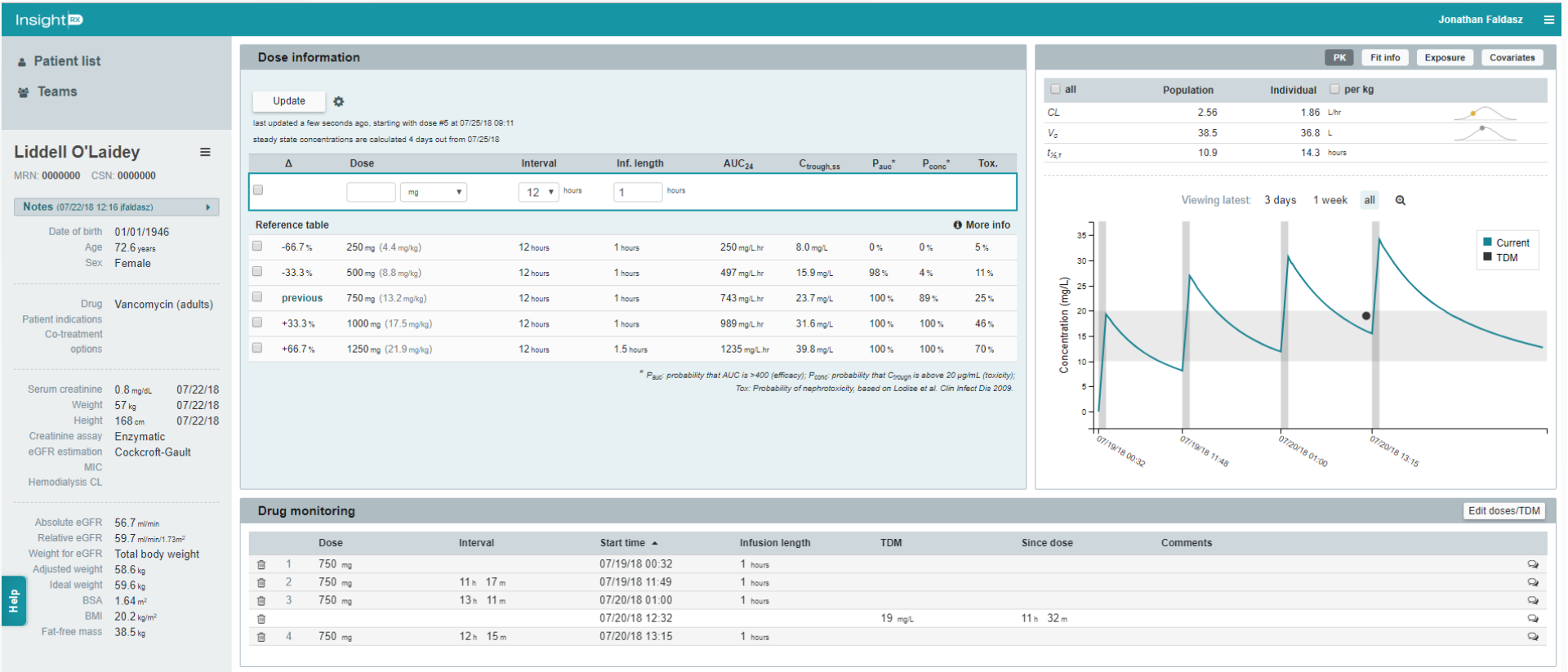
- Develop mockups and frameworks
- Merge observations with heuristics

Validate and continuously improve product design

- Update actual CDS UI/UX
- Iterate on usability with user-feedback

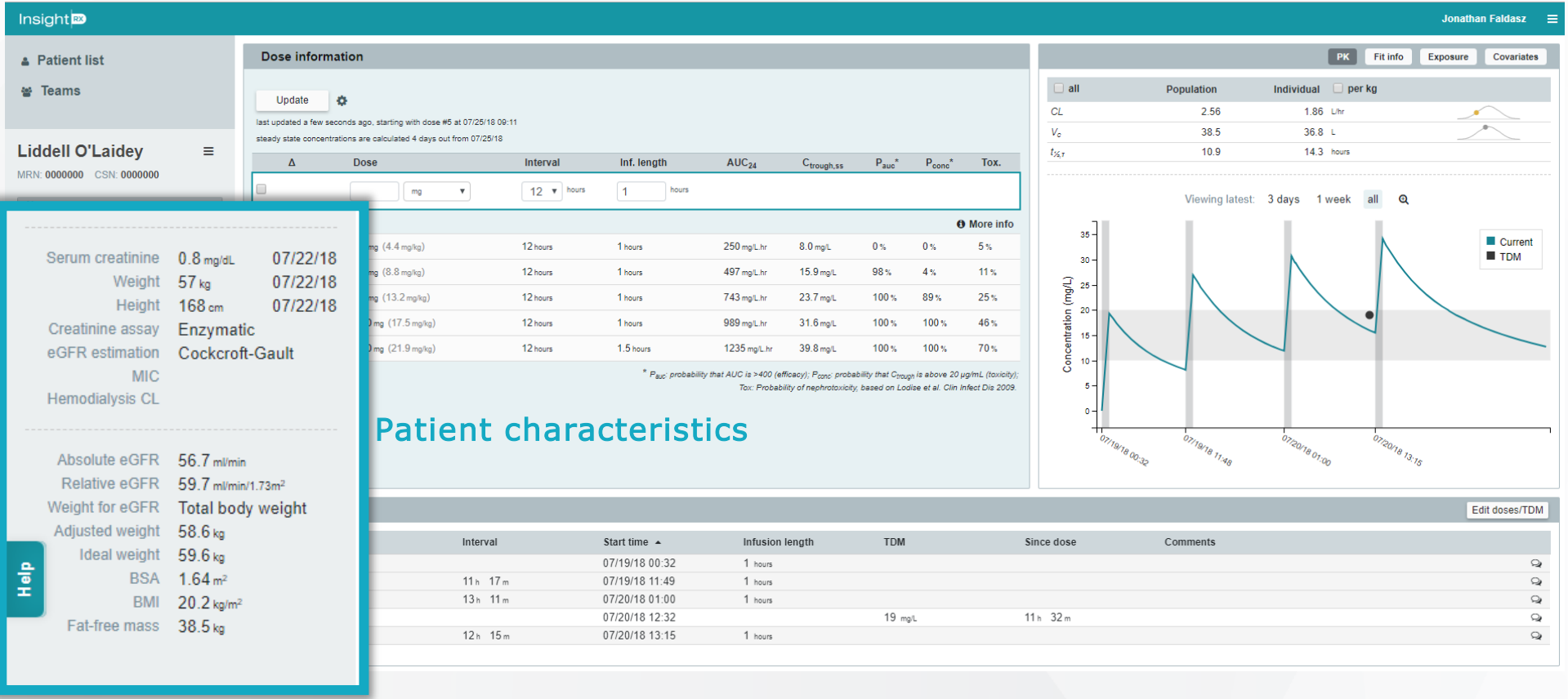
UI/UX

Updated User Interface Resulting From Usability Studies



UI/UX

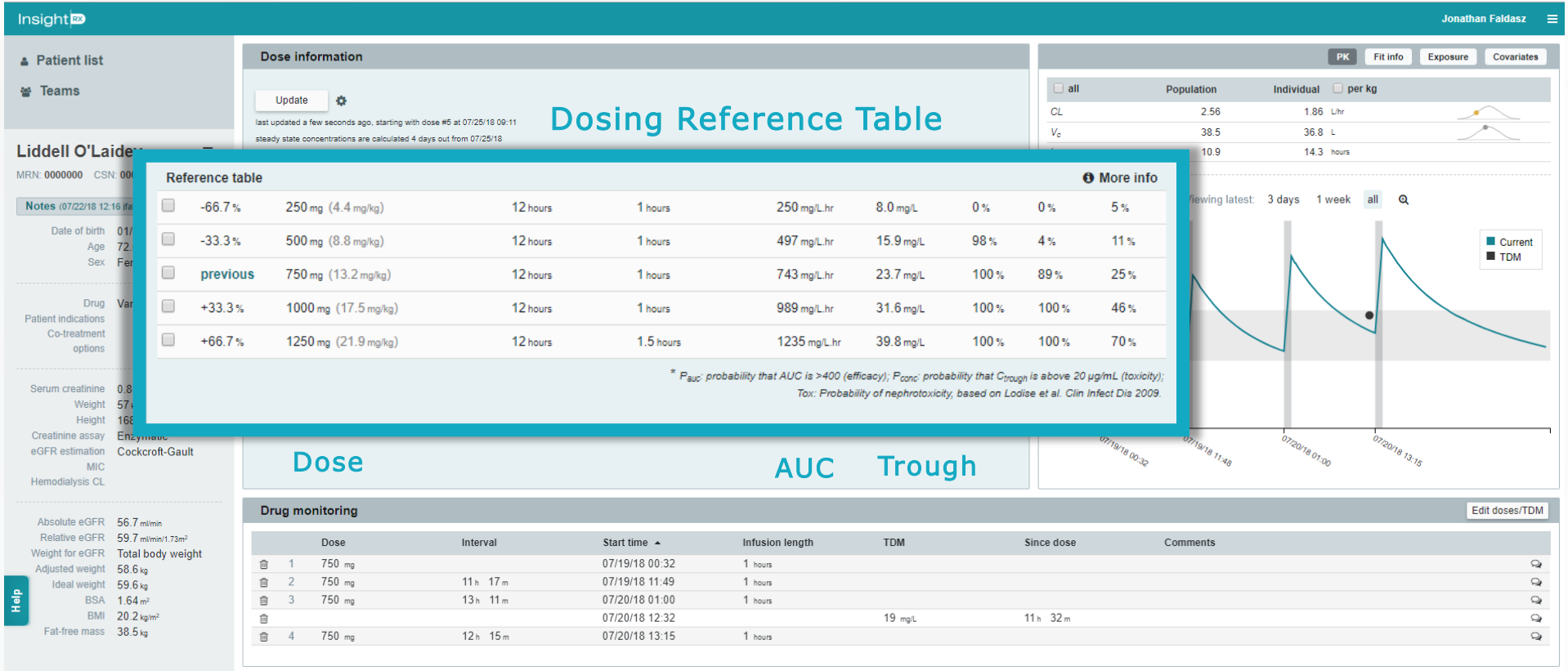
Consolidated Dashboard Improves Workflow Efficiency



Patient characteristics

UI/UX

Consolidated Dashboard Improves Workflow Efficiency



UI/UX

Consolidated Dashboard Improves Workflow Efficiency

Insight RX — Jonathan Faldasz

- Patient list
- Teams

Liddell O'Laidey

MRN: 0000000 CSN: 0000000

Notes (07/22/18 12:16 ifaldasz)

Date of birth	01/01/1946	
Age	72.6 years	
Sex	Female	
Drug	Vancomycin (adults)	
Patient indications		
Co-treatment options		
Serum creatinine	0.8 mg/dL	07/22/18
Weight	57 kg	07/22/18
Height	168 cm	07/22/18
Creatinine assay	Enzymatic	
eGFR estimation	Cockcroft-Gault	

Dose information

Update

last updated a few seconds ago, starting with dose #5 at 07/25/18 09:11

steady state concentrations are calculated 4 days out from 07/25/18

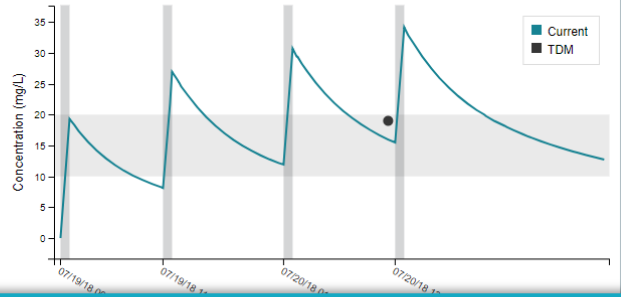
Δ	Dose	Interval	Inf. length	AUC_{24}	$C_{trough,ss}$	P_{auc}*	P_{conc}*	Tox.
	mg	12 hours	1 hours					
Reference table								More info
-66.7 %	250 mg (4.4 mg/kg)	12 hours	1 hours	250 mg/L.hr	8.0 mg/L	0 %	0 %	5 %
-33.3 %	500 mg (8.8 mg/kg)	12 hours	1 hours	497 mg/L.hr	15.9 mg/L	98 %	4 %	11 %
previous	750 mg (13.2 mg/kg)	12 hours	1 hours	743 mg/L.hr	23.7 mg/L	100 %	89 %	25 %
+33.3 %	1000 mg (17.5 mg/kg)	12 hours	1 hours	989 mg/L.hr	31.6 mg/L	100 %	100 %	46 %
+66.7 %	1250 mg (21.9 mg/kg)	12 hours	1.5 hours	1235 mg/L.hr	39.8 mg/L	100 %	100 %	70 %

* P_{auc}: probability that AUC is >400 (efficacy); P_{conc}: probability that C_{trough} is above 20 µg/mL (toxicity); Tox: Probability of nephrotoxicity, based on Lodise et al. Clin Infect Dis 2009.

PK | Fit info | Exposure | Covariates

	all	Population	Individual	per kg
CL		2.56	1.86	L/hr
V_c		38.5	36.8	L
$t_{½,T}$		10.9	14.3	hours

Viewing latest: 3 days 1 week all



Biomarker/TDM Table

Drug monitoring

Edit doses/TDM

	Dose	Interval	Start time	Infusion length	TDM	Since dose	Comments
1	750 mg		07/19/18 00:32	1 hours			
2	750 mg	11 h 17 m	07/19/18 11:49	1 hours			
3	750 mg	13 h 11 m	07/20/18 01:00	1 hours			
			07/20/18 12:32		19 mg/L	11 h 32 m	
4	750 mg	12 h 15 m	07/20/18 13:15	1 hours			

Help

Integration into the clinical workflow

EHR INTEGRATION

Why is it so challenging?

- EHR systems are very closed off (Not interoperable)
- Many different standards and architectures for exchange
- Many different implementations of data interchange
- EHR integration requires scarce IT resources
- Clinical workflow within EHR is unclear

EHR INTEGRATION

Different methodologies to overcome integration challenges

Method	Description	Pros	Cons
Custom Integration	Custom integration involves the consideration and agreement between integration partners of the methods of integration (technology stack, security methods, onsite/VPN vs internet, batch processing vs real-time, embedded vs standalone, etc.)	• Control over integration approach • Can potentially allow integrations when there are no other options	• IT staff needs to be highly skilled at custom integration work and have capacity • IT time/effort • Not scalable/reusable • Minimal support
HL7	HL7 integration involves setting up import/export data endpoints for the transmission of standardized HL7 messages but with the generation of a mapping/transform layer to handle customizations.	• International messaging standard for clinical data • Widely adopted (as of 2018)	• Extensive customization resulting in extra integration work • IT time/effort • Message semantics not necessarily consistent
EMR Vendor APIs (e.g. Epic, AllScripts, Cerner, Athena Health)	EMR vendors provide their own access methods to their data. External parties must get approval from both the vendor and institutions that use their systems as well as implement vendor-specific data access solutions through the APIs that the vendors provide.	• EMR vendor responsible for data access and support • Web-based APIs available	• Each vendor has their own set of APIs • Technologies may be complex and difficult to use • Data access methods may be mixed (e.g. APIs + HL7)
EHR Vendor App Stores **(e.g. Epic AppOrchard, Athenahealth MDP marketplace)**	EHR vendors also provide solutions modeled after the Apple App Store or Google Play distribution service where 3rd parties can develop their applications (under the vendor's protocol for app store development) and make them available for distribution through the store.	• Use of standardized, modern REST APIs in most cases (FHIR) • Scalable / easier application distribution • Simplified integration setup	• Cost of integration with EHR vendor
Third Party Applications **(Open Standards Based Integration using FHIR)**	If a clinical application/data provider has a FHIR server that is made accessible to 3rd parties seeking data, these 3rd parties can develop FHIR API clients which have the ability to access this data using a modern, standards-based, REST API.	• Standards-based APIs and protocol • Modern REST-based APIs and authentication schemes • Granular access to clinical data • Ability to easily integrate applications into EMRs via HTML5	• 3rd parties may not have full implementations of FHIR resources • FHIR specification evolves at a faster pace than adoption (version issues)

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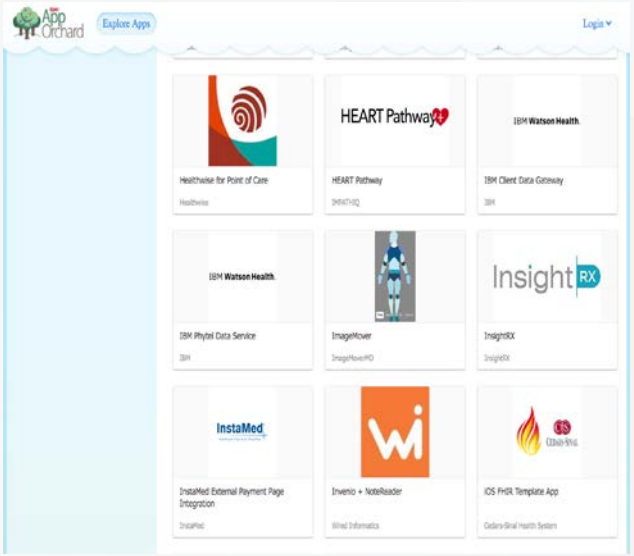
Most scalable

EHR INTEGRATION

Integration through a **EHR app store**

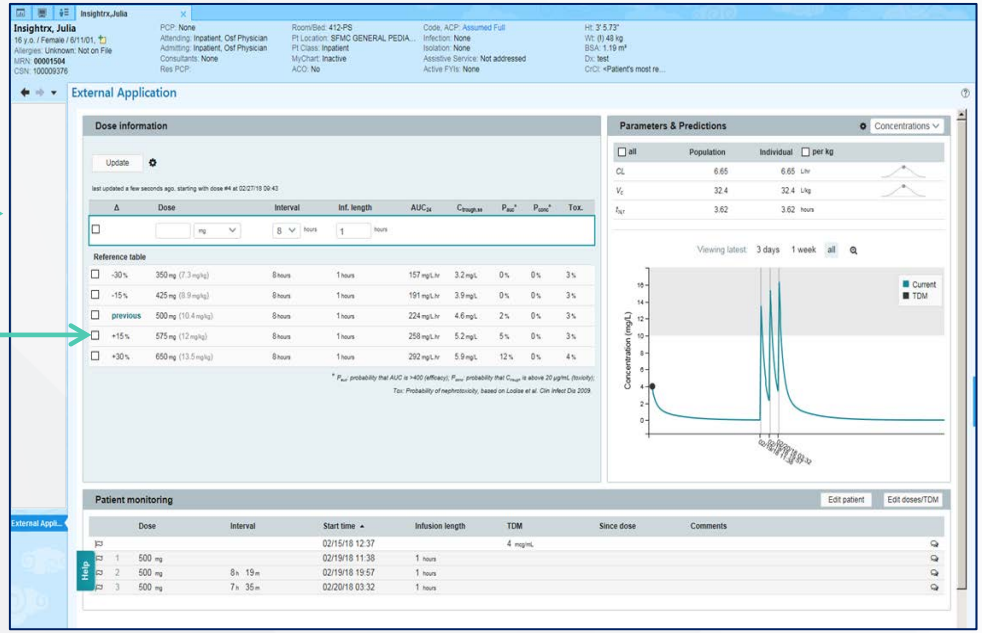
App Store



EHR System

CDS Tool

Clinical Workflow

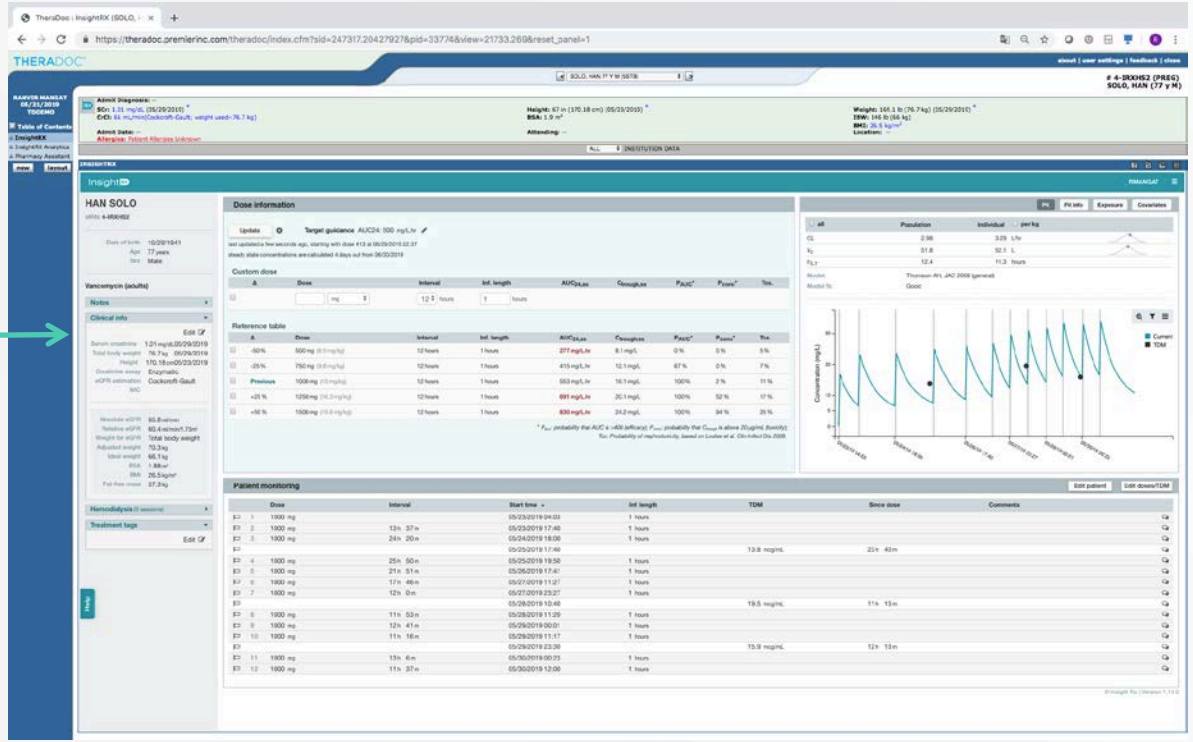


EHR INTEGRATION

Third Party Applications: Integration through open standards using FHIR

Clinical surveillance system (Theradoc)

CDS Tool



Clinical Analytics

CLINICAL ANALYTICS

Why is data collection post-implementation necessary?

Key Questions Post-Implementation

Institution-specific

- What is the clinical benefit to using the tool?
- Will we save money by improving patient outcomes?
- Are users satisfied with the product? Is it being used?
- What is the operational benefit to my organization?
- Will the module work in other indications? Other patient populations?

Beyond the institution

- How do we improve implementation process at other institutions?
- How can we collect the right the data to demonstrate clinical value and identify the right predictors of drug response?

Key Hospital Stakeholders

Chief Medical Officer

Director of Pharmacy

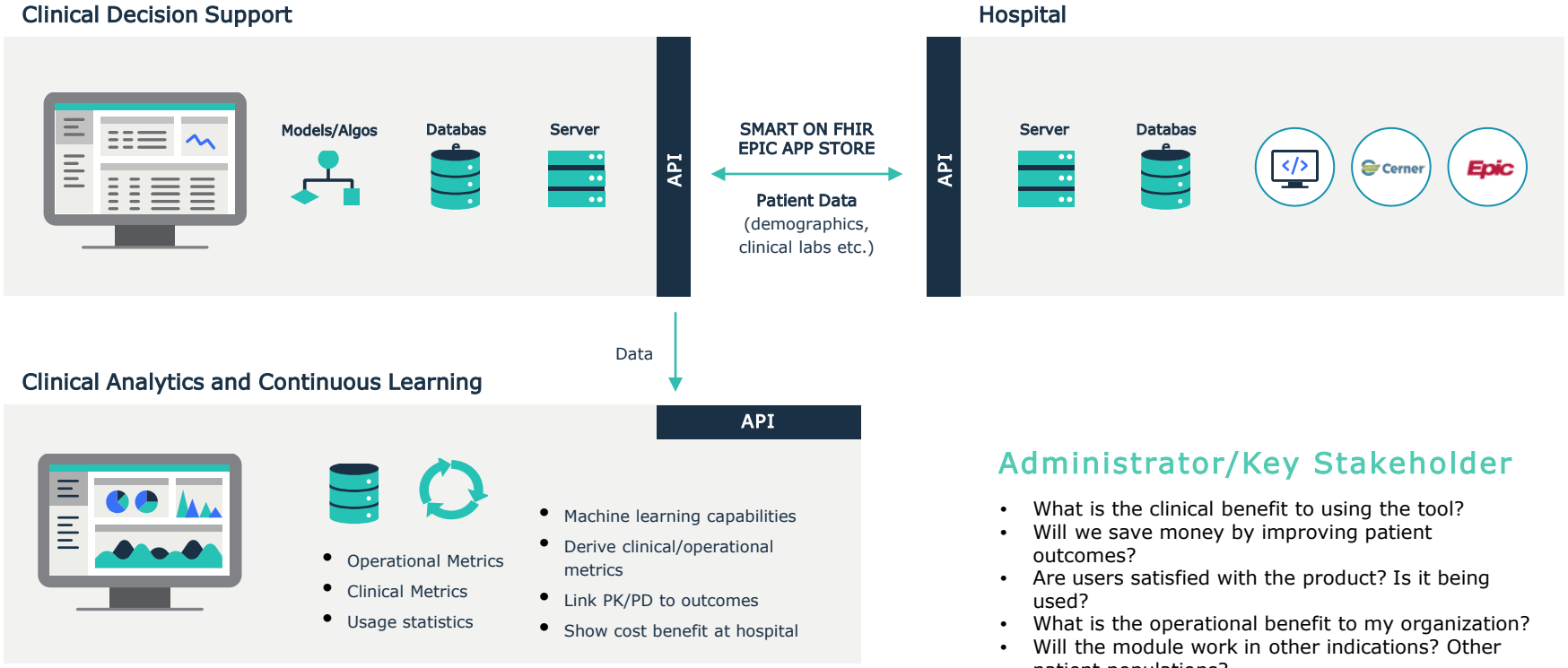
Chief Quality Officer

Clinical Pharmacist

Physician

CLINICAL ANALYTICS

A well **architected** framework will enable the proper collection of data to address post-implementation questions



Administrator/Key Stakeholder

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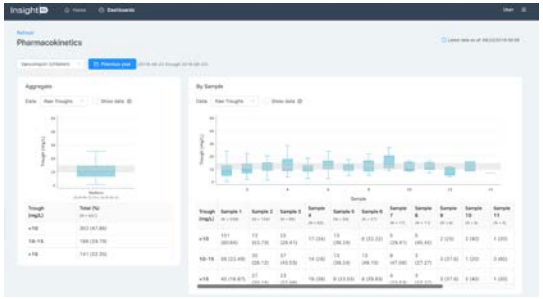
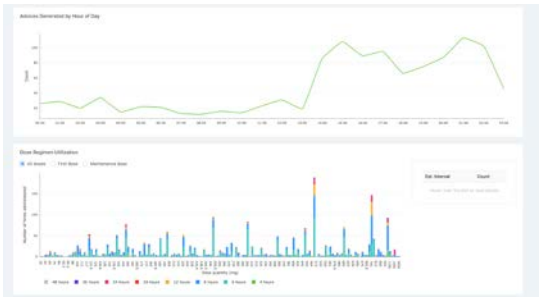
CLINICAL ANALYTICS

Framework enables a real-time assessment of clinical and operational data

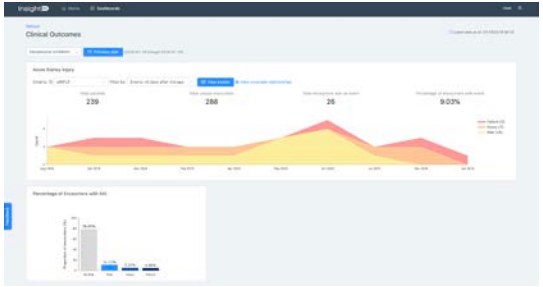
Pharmacokinetic assessment



Treatment utilization



Clinical outcomes



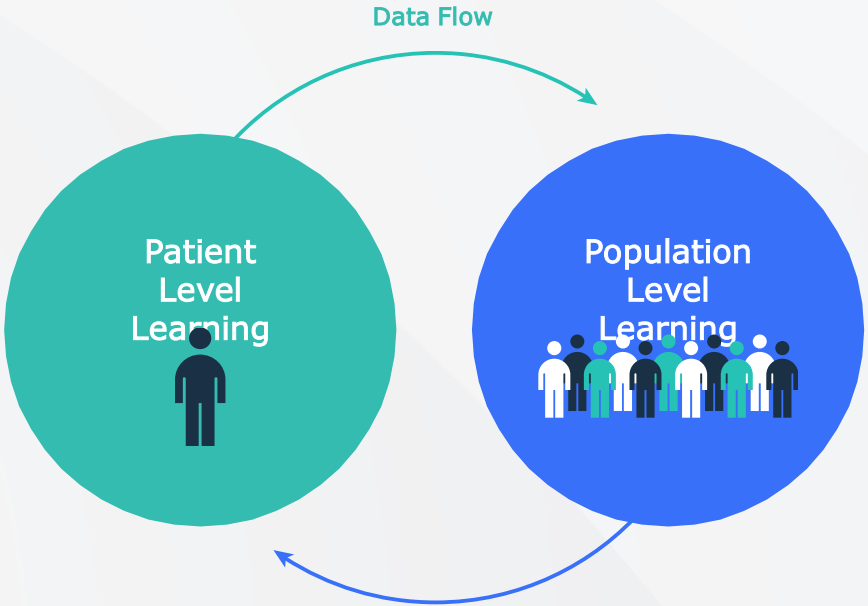
Data exploration

Future of Precision Dosing

Precision dosing by leveraging **patient** and **population** level learning

Companion Application

- Model-informed precision dosing
- Bayesian forecasting



Clinical Analytics

- Machine learning
- Optimize treatment guidelines and models

Thank you

Further Reading:

1. Keizer, R. J., ter Heine, R., Frymoyer, A., Lesko, L. J., Mangat, R., & Goswami, S. (2018). Model-Informed Precision Dosing at the Bedside: Scientific Challenges and Opportunities. *CPT: Pharmacometrics & Systems Pharmacology*, *7*(12), 785–787.
2. Goswami, S., Krishnamurthi, A, Jamal, D. (2018), Does Healthcare Need Its Own OS?. *Towards Data Science*
3. Goswami, S., Overcoming Adoption Barriers of Cloud-Based Precision Dosing. ASCPT Webinar (2018)

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