Beyond the label: Dose Optimization Approaches in Specific Populations

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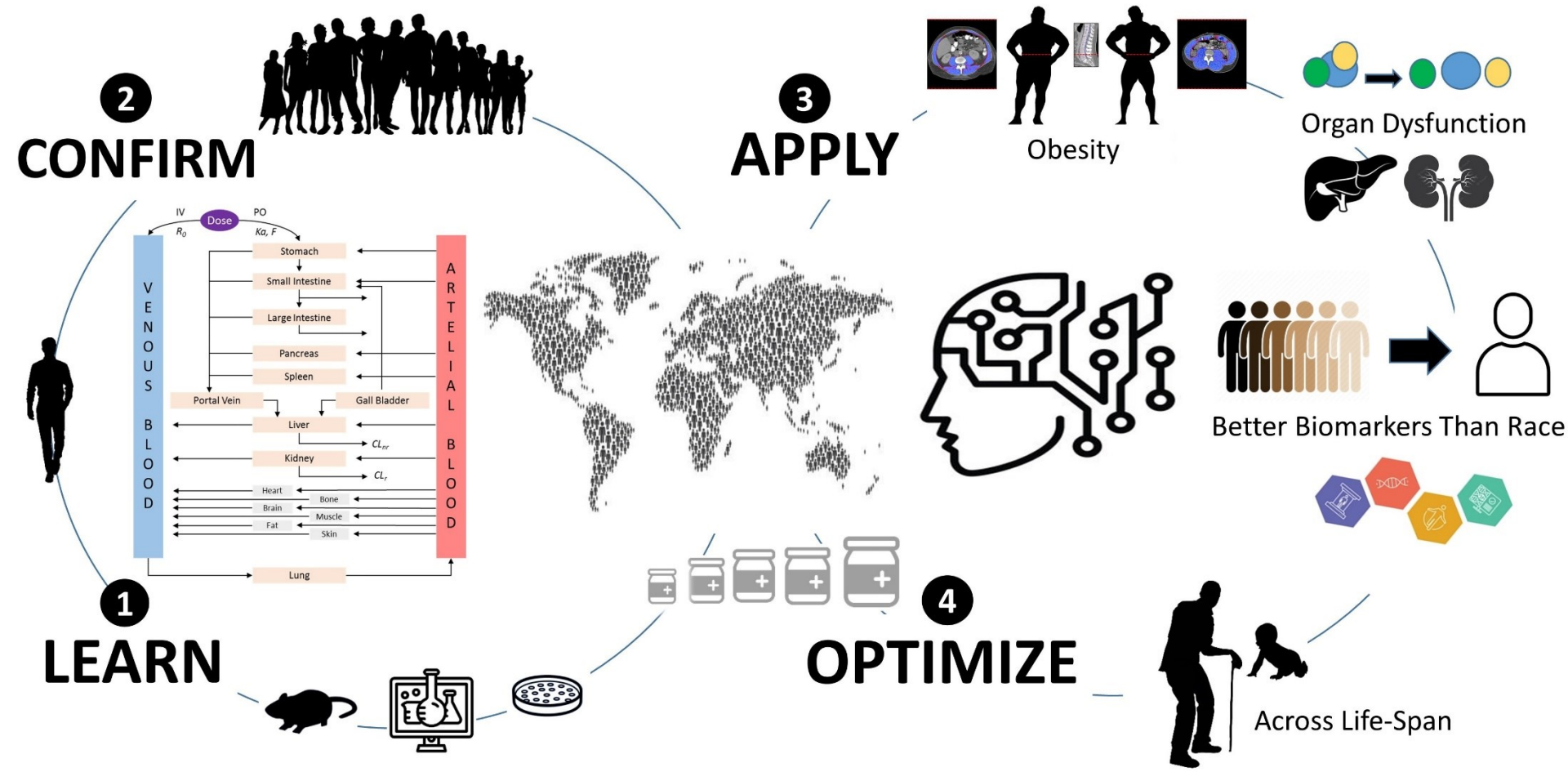
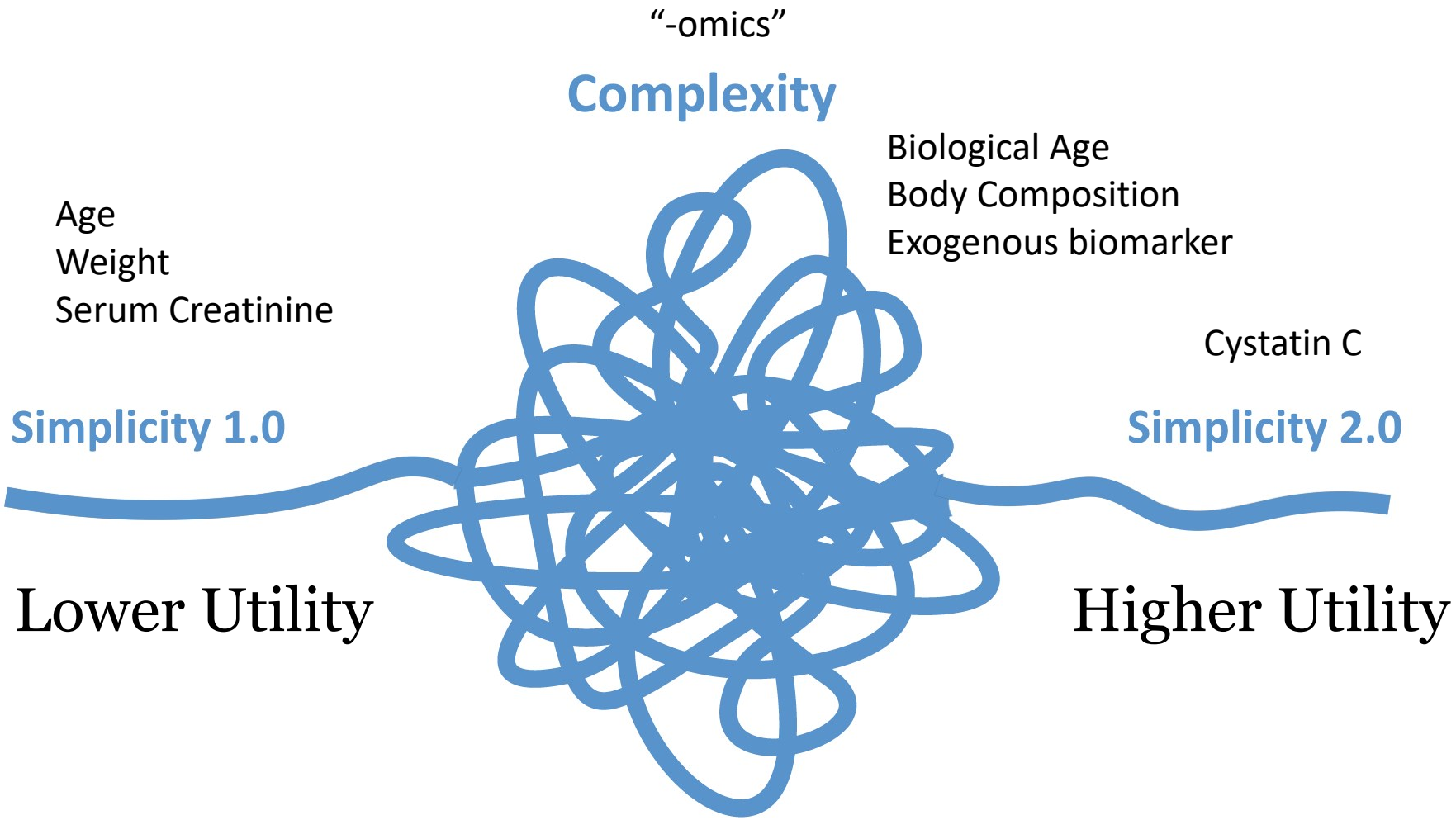
@DosingMatters


2
CONFIRM
3
APPLY
Obesity
Organ Dysfunction
IV
PO
Dose
R_0
Ka, F
Stomach
Small Intestine
Large Intestine
Pancreas
Spleen
Portal Vein
Gall Bladder
Liver
CL_{nr}
Kidney
CL_r
Heart
Bone
Brain
Muscle
Fat
Skin
Lung
VENOUS BLOOD
ARTELIAL BLOOD
Better Biomarkers Than Race
1
LEARN
4
OPTIMIZE
Across Life-Span

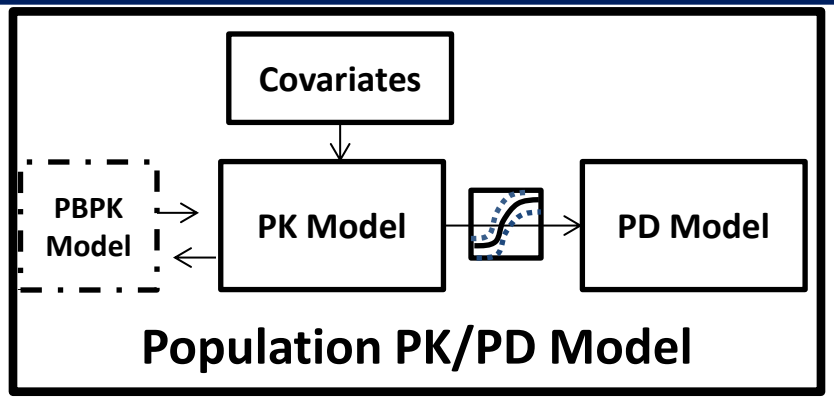
The Outline



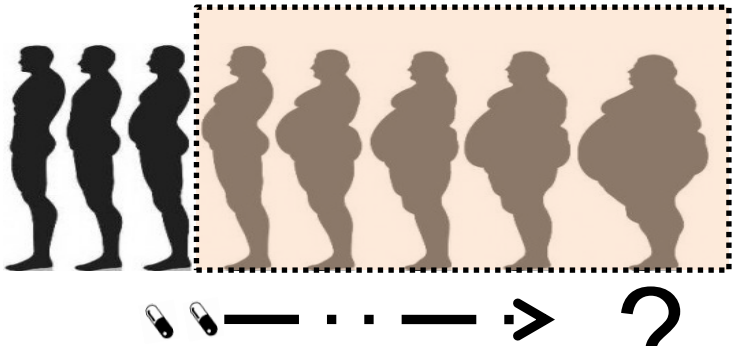
Aiming for simplicity on the other side of complexity

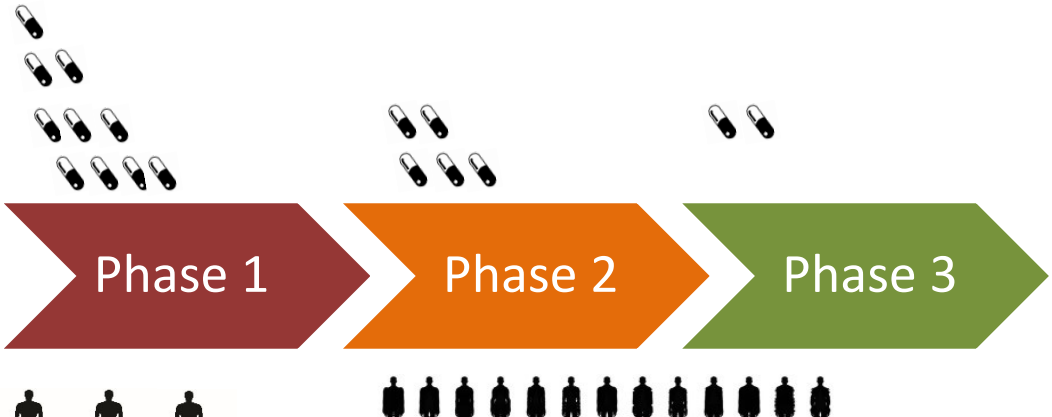
— Oliver Wendell Holmes

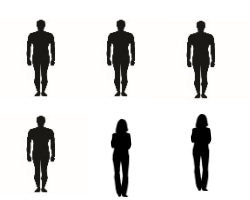
The Problem

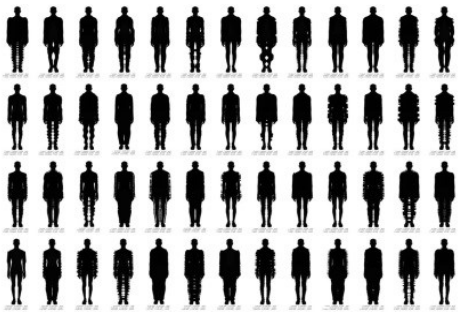


There is a gap between the populations we study and the populations we treat







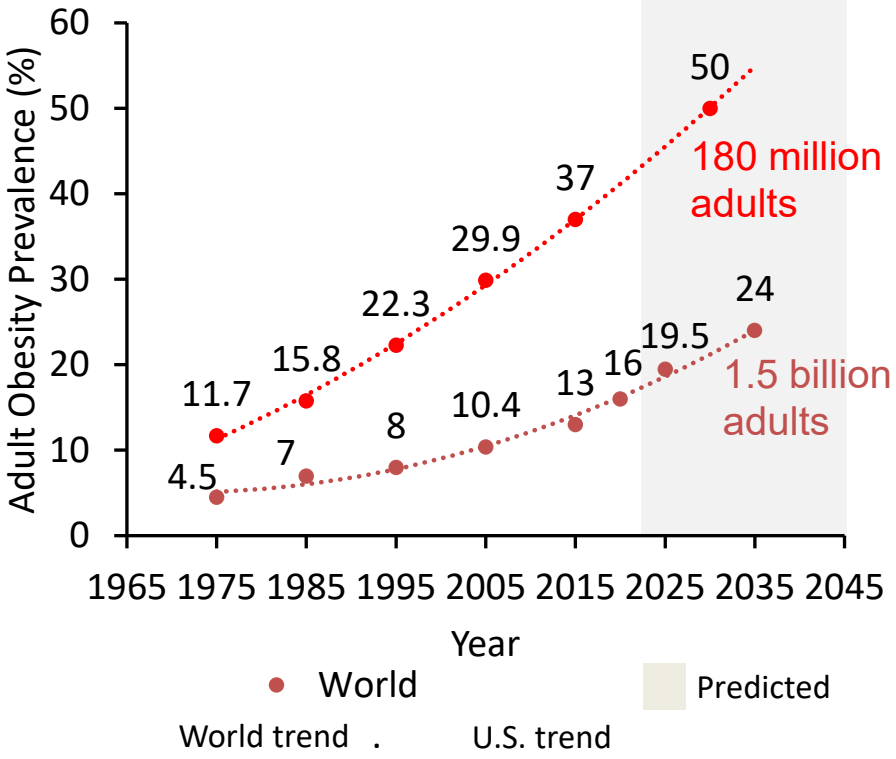


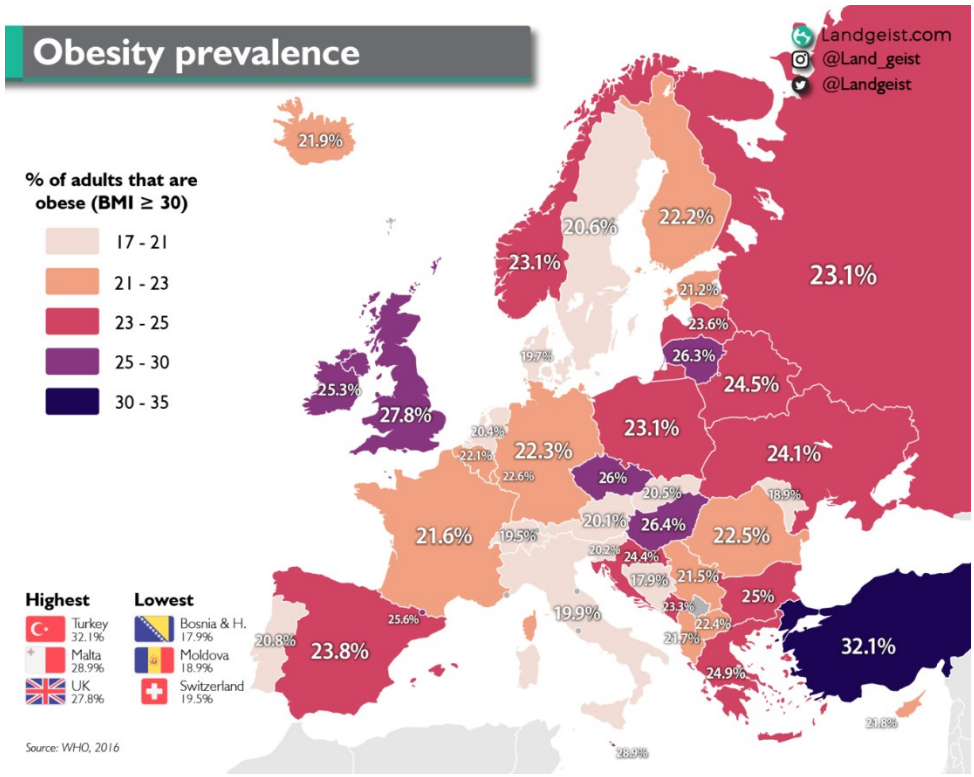
Healthy Subjects

Well Defined Patients

Underrepresented Populations

Obesity Trends

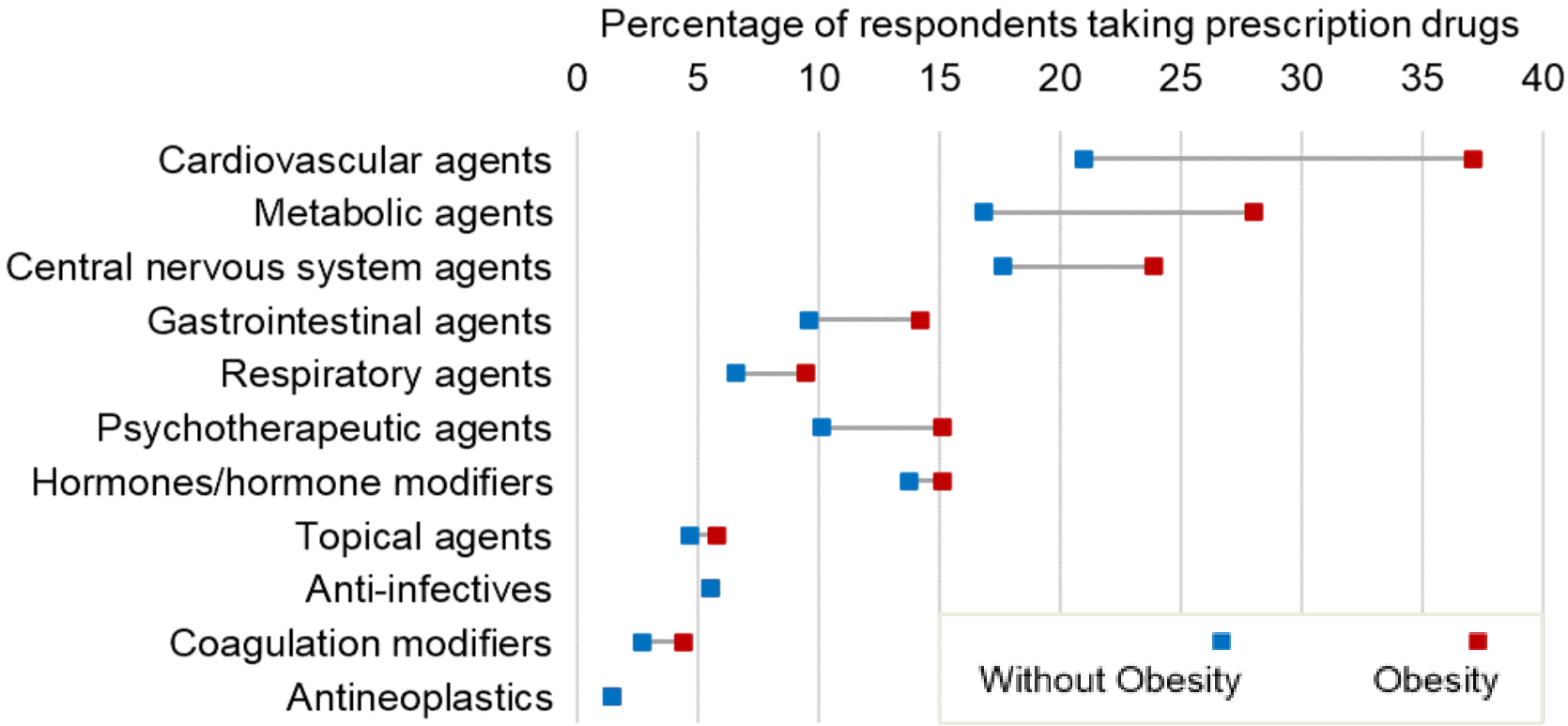




Data source: NCD Risk Factor Collaboration 2016, WHO Global Health Observatory 2022, World Obesity Atlas 2023

Obesity is associated with diabetes, hypertension, cardiovascular disease, cancer, and can impact the therapeutic outcomes associated with infection

Medication Use



Barrett et al. *PLoS One* (2022)

Lack of obesity representation in clinical studies/trials

- Most drug product labels lack dose adjustment guidance for patients with obesity

Regulatory Approach

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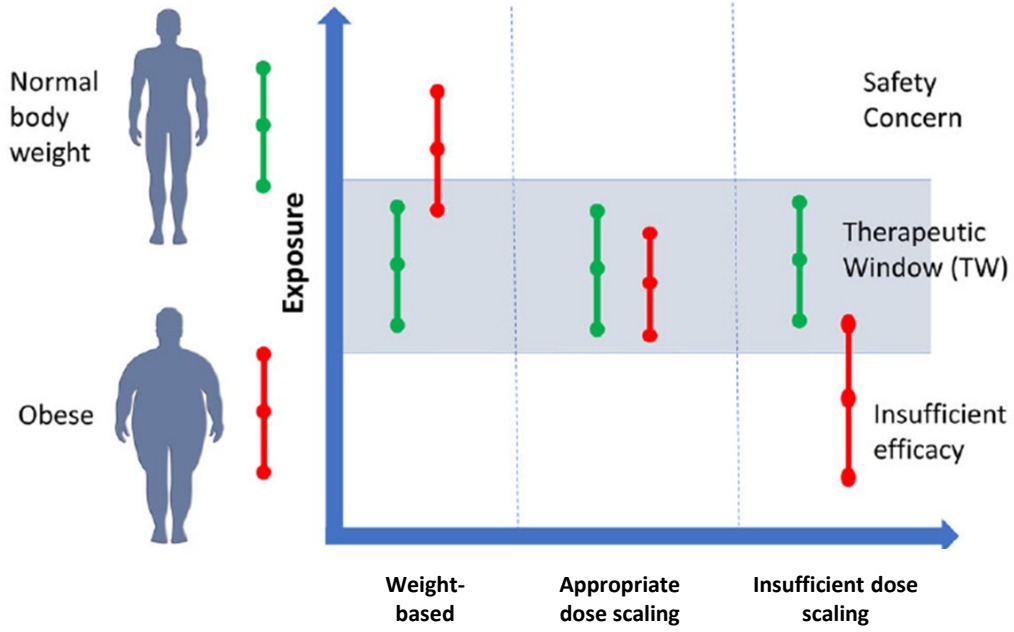
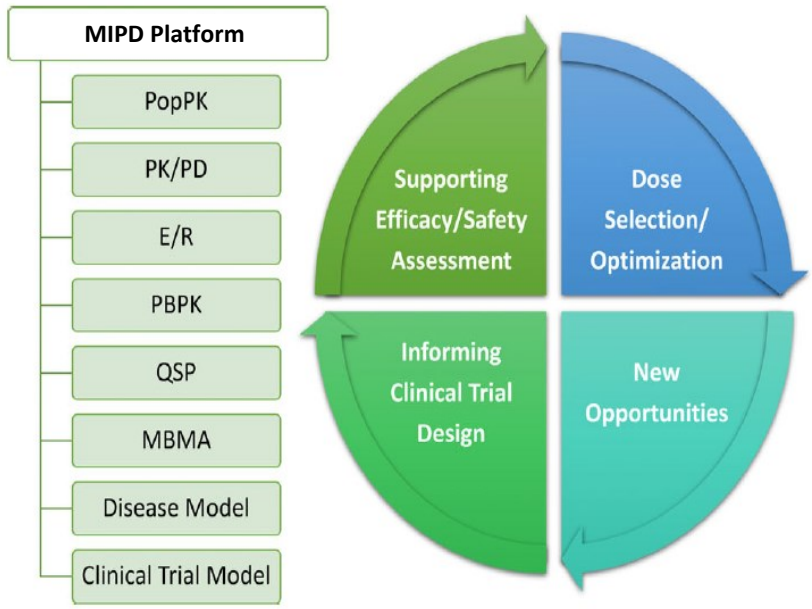
Exposure-Matching Strategy for Patients with Obesity



Model-Informed Precision Dosing



Pan et al. *J Clin Pharmacol* (2023)

American College of Clinical Pharmacology **Call for Action** (2023)

- Learn and characterize the effect of obesity on the PK, PD, efficacy, and safety of drugs, leveraging applicable MIPD tools.
- Include participants with obesity in clinical trials/studies.
- Include dosing information in relation to body size descriptors in drug labels when appropriate to guide their safe use in patients with obesity.

The Paradigm

Fixed Dosing

Weight-Based Dosing

Body Surface Area-Based Dosing

The Risks & Costs

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Fixed Dosing

↑Treatment Failure
Obese Patients

Weight-Based Dosing

↑ Toxicities
Obese Patients

Drug Waste $

Use an **Alternate Weight Descriptor**

Ideal Body Weight
Adjusted Weight
Dosing Weight
Lean Body Weight

Body Surface Area-Based Dosing

↑ Treatment Failure
Obese Patients

Drug Waste $

Use the equation correctly

Don’t always cap the dose

Alternate Body Size Descriptors

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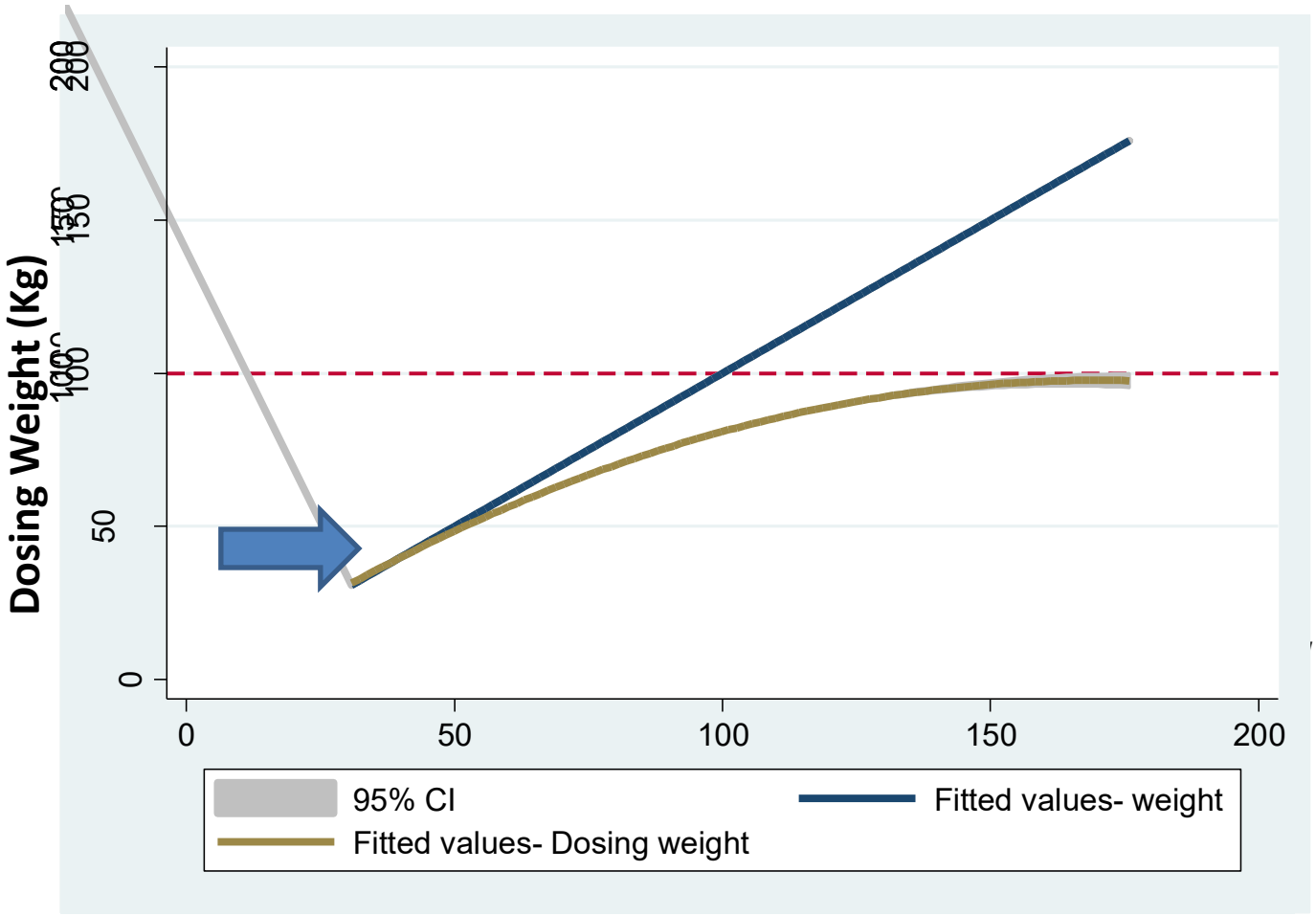
Body Size Descriptor	Sex	Equation
Weight	Male or Female	None, measured in kg
Height	Male of Female	None, measured in cm or inches
Body Mass Index	Male or Female	$\text{Weight in kg} / \left(\frac{\text{Height in cm}}{100}\right)^2$
Body Surface Area (BSA)[1]	Male or Female	$\frac{\sqrt{(Weight\ in\ kg \times Height\ in\ cm)}}{3600}$
Ideal Body Weight (IBW)[2]	Male	$50 + 2.3 \times (Height\ inches - 60\ inches)$
	Female	$45.5 + 2.3 \times (Height\ inches - 60\ inches)$
Adjusted Body Weight (AdjBW)[3]	Male or Female	$\text{IBW} + 0.4 \times (\text{Weight} - \text{IBW})$
Lean Body Weight (LBW)[4]	Male	$(9270 \times Weight\ in\ kg)/(6680 + 216 \times BMI)$
	Female	$(9270 \times Weight\ in\ kg)/(8780 + 244 \times BMI)$

1. Mosteller et al. *N Engl J Med* (1987)
2. Devine et al. *Drug Intell Clin Pharm* (1974)
3. Bauer et al. *Eur J Clin Pharmacol* (1983)
4. Janmahasatian et al. *Clin Pharmacokinet* (2005)

Common Approach in the Clinic

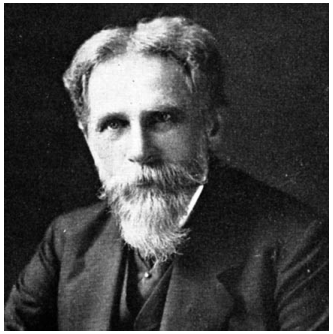
Use of a piece-wise function to define dosing weight through a combination
Of total body weight (TBW), ideal body weight (IBW) , and adjusted body weight (AdjBW)
TBW if <IBW
IBW if TBW<1.25 x IBW
AdjBW if TBW≥ 1.25 x IBW

$$DW = 3 \times TBW^{0.72}$$



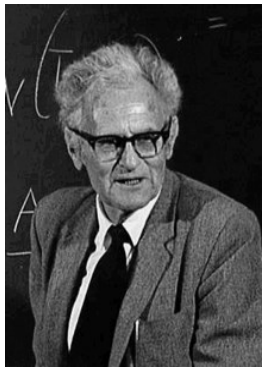
Similar to Allometric Scaling

Max Rubner (1883)

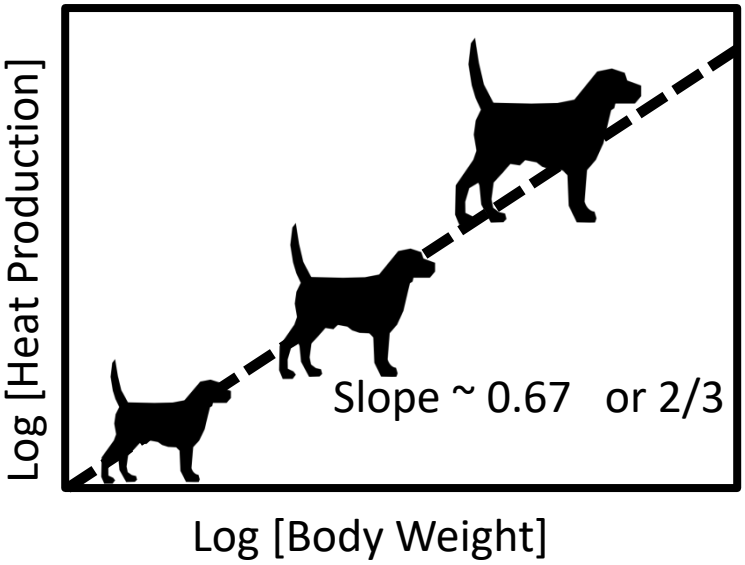


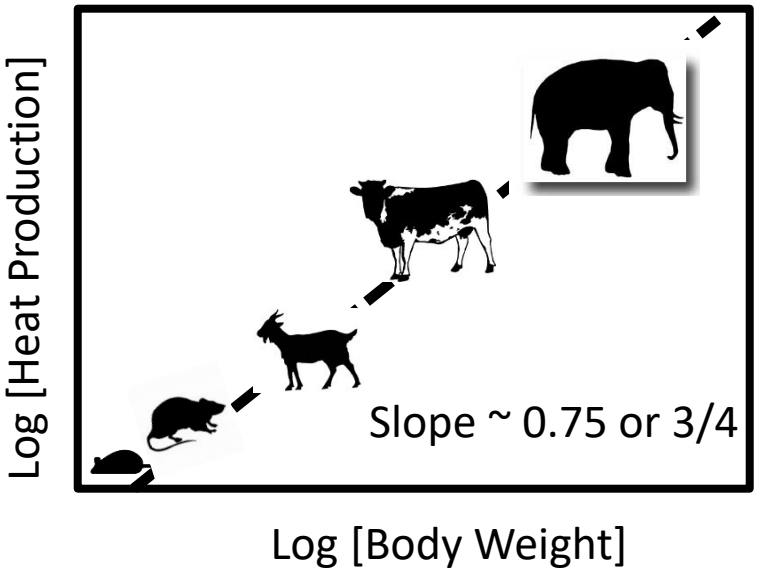
Meeh (1870)

Area = K x Weight$^{2/3}$



Max Kleiber (1932)





Rubner M (1883). Über den einfluss der körpergrösse auf stoff- und kraftwechsel. *Zeit. Biol.* **19**, 536-562.
Kleiber M (1932). Body size and metabolism. ***Hilgardia*** **6, 315-353.**

25 years of Work

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Drug	Current Dosing Method	Improvement Suggested
Vancomycin	Weight-Based	Capped Dose, Kidney Function Based
Daptomycin	Weight-Based	Fixed Dose
Telavancin	Weight-Based	Fixed Dose
Voriconazole	Weight-Based	Fixed Dose (Genotype)
Anidulafungin	**Fixed-Dose**	**LBW – Based Dosing, Increased Fixed Dose**
Levofloxacin	Fixed-Dose	Higher Dose (Obese – Kidney Function)
Meropenem	Fixed-Dose	Higher Dose (Obese – Kidney Function)
Linezolid	Fixed-Dose	Kidney Function Directed TDM
Oseltamivir	Fixed-Dose	No Change
Ceftaroline	Fixed- Dose	No Change
Tigecyline	Fixed-Dose	No Change
Tedizolid	Fixed-Dose	No Change

Dosing can be improved but height and weight are suboptimal

EXAMPLE OF A TRADITIONAL APPROACH

Anidulafungin Example

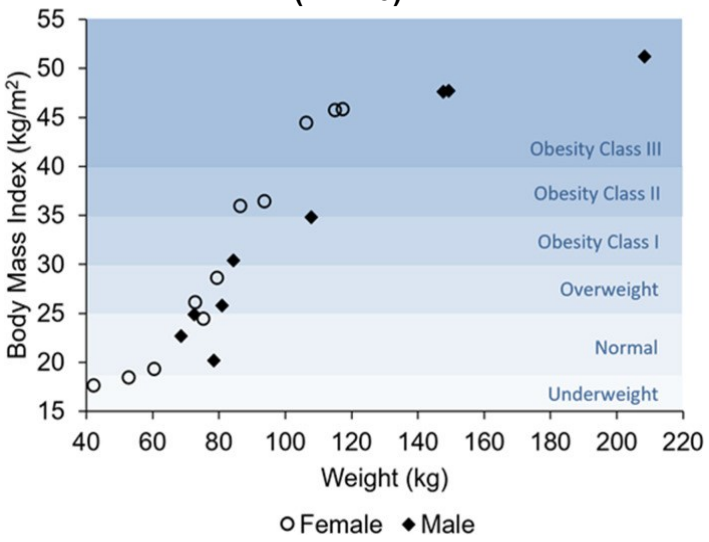
Anidulafungin - first-line therapy for candidemia & invasive candidiasis

200 mg loading dose on Day 1 + 100 mg once daily maintenance dose

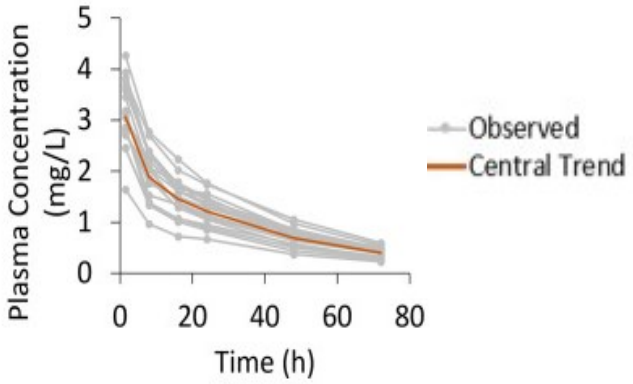
- A key feature of defining doses in a population - ensuring a wide distribution of individuals within identified covariate groupings.
- For anidulafungin, studies have primarily included normal-weight or class III (morbid) obesity participants.

We conducted a single-dose study across the BMI spectrum.

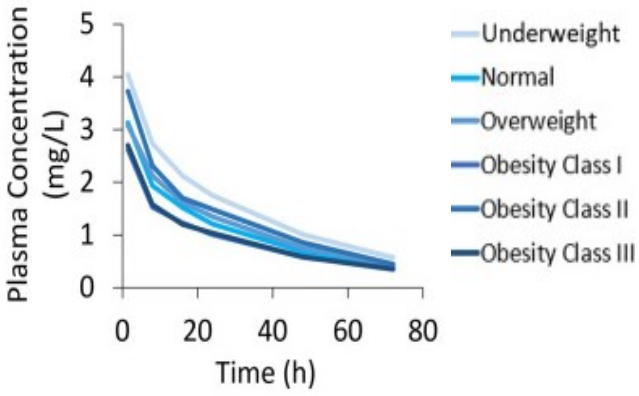
Weight and BMI distribution of enrolled participants (N = 20)



Observed anidulafungin concentration-time profile



Geometric mean plasma concentrations of BMI categories

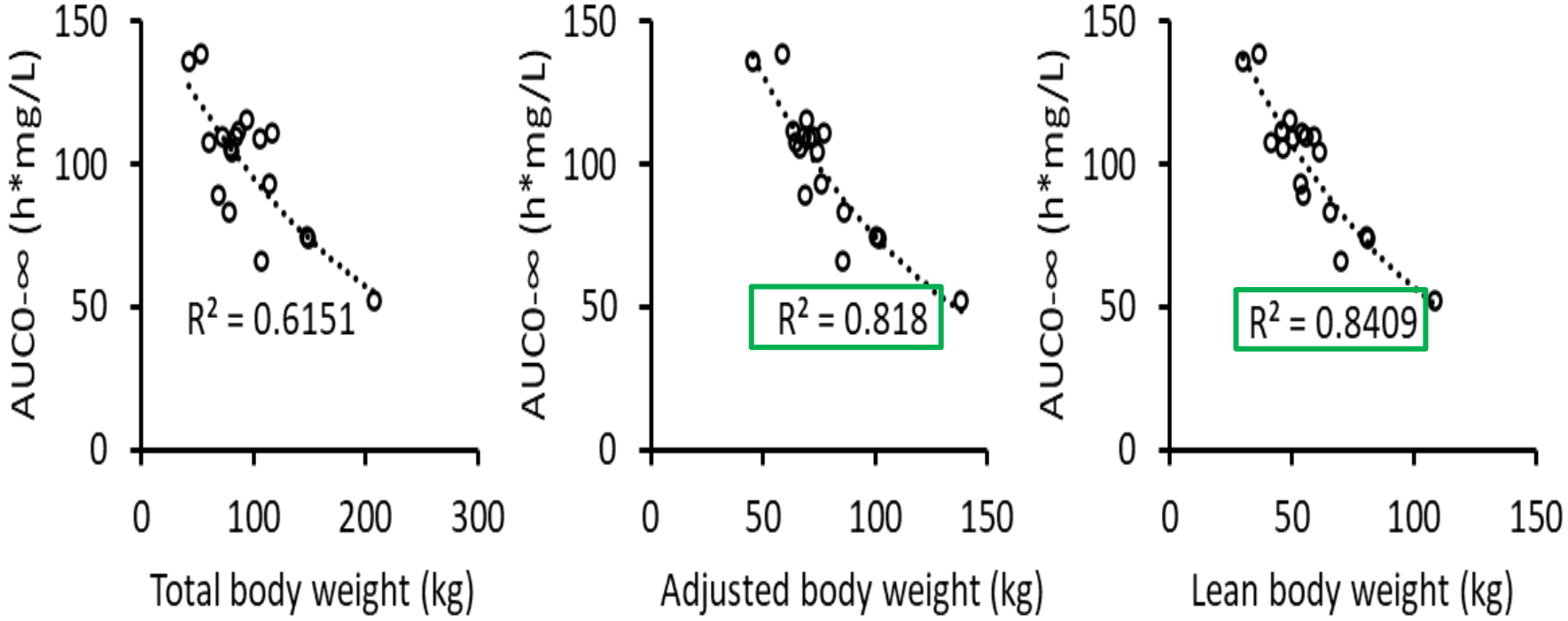


Subjects with obesity had decreased anidulafungin exposure.

Publication: *Antimicrob Agents Chemother*. doi:10.1128/aac.00820-23

Body Size Correlations

Optimizing anidulafungin dosing



AdjBW and LBW had a stronger correlation with anidulafungin exposure (AUC) than total body weight.

1. Mosteller et al. *N Engl J Med* (1987)
2. Mosteller et al. *N Engl J Med* (1987)
3. Devine et al. *Drug Intell Clin Pharm* (1974)
4. Bauer et al. *Eur J Clin Pharmacol* (1983)
5. Janmahasatian et al. *Clin Pharmacokinet* (2005)

Covariate Fitting

Optimizing anidulafungin dosing

Examining patient-specific factors' impact on drug PK in a population.

Population PK modeling: base model determination

Compartment Model	Error Model (Distribution)	AIC	RSE
One-compartment	Constant (normal)	92.25	OK
Two-compartment	Constant (normal)	-82.41	OK
	Constant (lognormal)	-95.01	OK
	Proportional (normal)	-97.69	OK
	Proportional (lognormal)	-92.91	Large
	Combined1 (normal)	-93.67	Large
	Combined1 (lognormal)	-95.46	OK
	Combined2 (normal)	-93.15	Large
	Combined2 (lognormal)	-93.33	Large

AIC, Akaike information criteria values; RSE, relative standard error

Constant: $Y = Y_p + a \times \varepsilon$
Proportional: $Y = Y_p + b \times Y_p \times \varepsilon$
Combined1: $Y = Y_p + (a + b \times Y_p \times \varepsilon)$
Combined2: $Y = Y_p + (a^2 + (b \times Y_p)^2)^{0.5} \times \varepsilon$

Population PK modeling: covariate testing

Model	AIC	ΔAIC (compared to Base)
Base model	-97.69	0
Weight on CL	-112.39	-14.70
BSA on CL	-118.55	-20.86
AdjBW on CL	-126.89	-29.20
LBW on CL	-127.02	-29.33
AdjBW on CL, V_1, V_2, Q	-174.30	-76.61
LBW on CL, V_1, V_2, Q	-175.35	-77.66

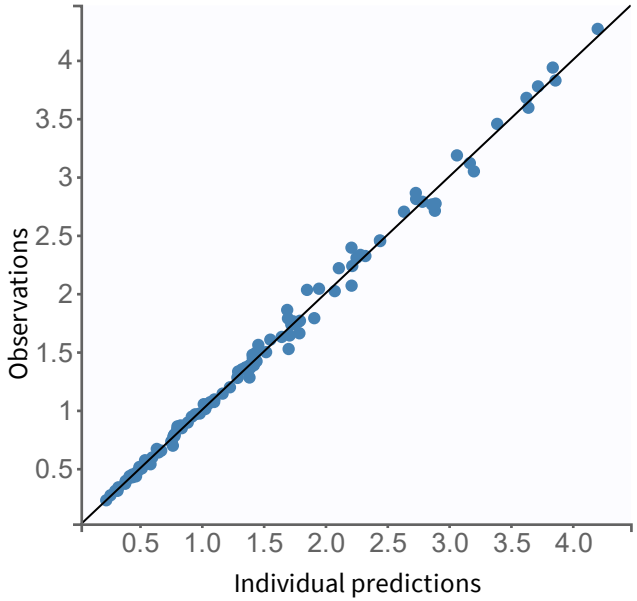
AUC = Dose/**CL**

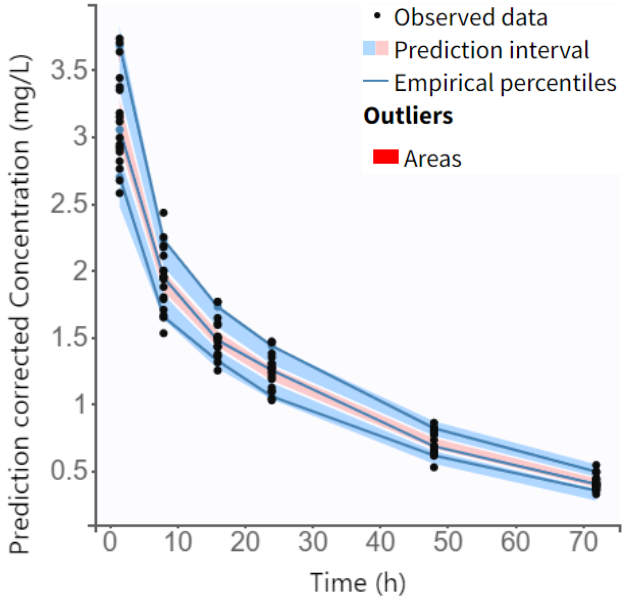
Lean body weight was a significant covariate on all PK parameters and the LBW model fitted the data better than the total body weight model.

PK Centric Model Fit

Optimizing anidulafungin dosing

Goodness-of-fit of the final population PK model (LBW on all PK parameters)





The model adequately captured our observed anidulafungin concentrations.

Dose used in the study
New dose

Math model

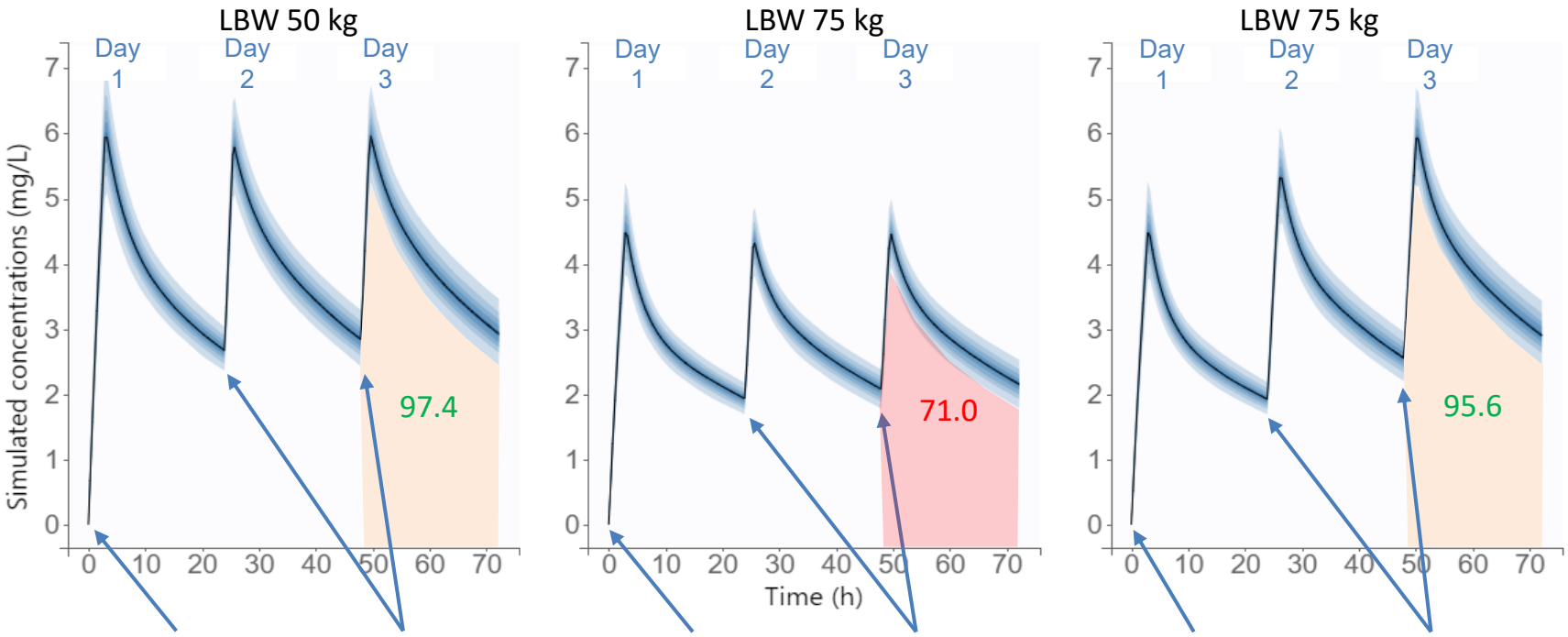
Observed drug exposure
Expected drug exposure

(PK simulation)

Exposure Matching

Optimizing anidulafungin dosing

Target exposure: $AUC_{0\text{-}tau} \geq 82$ h·mg/L.



A Proposed Intervention

Optimizing anidulafungin dosing

Probability of target attainment (PTA (%)) using maintenance doses of 100 mg, 150 mg, and 200 mg.

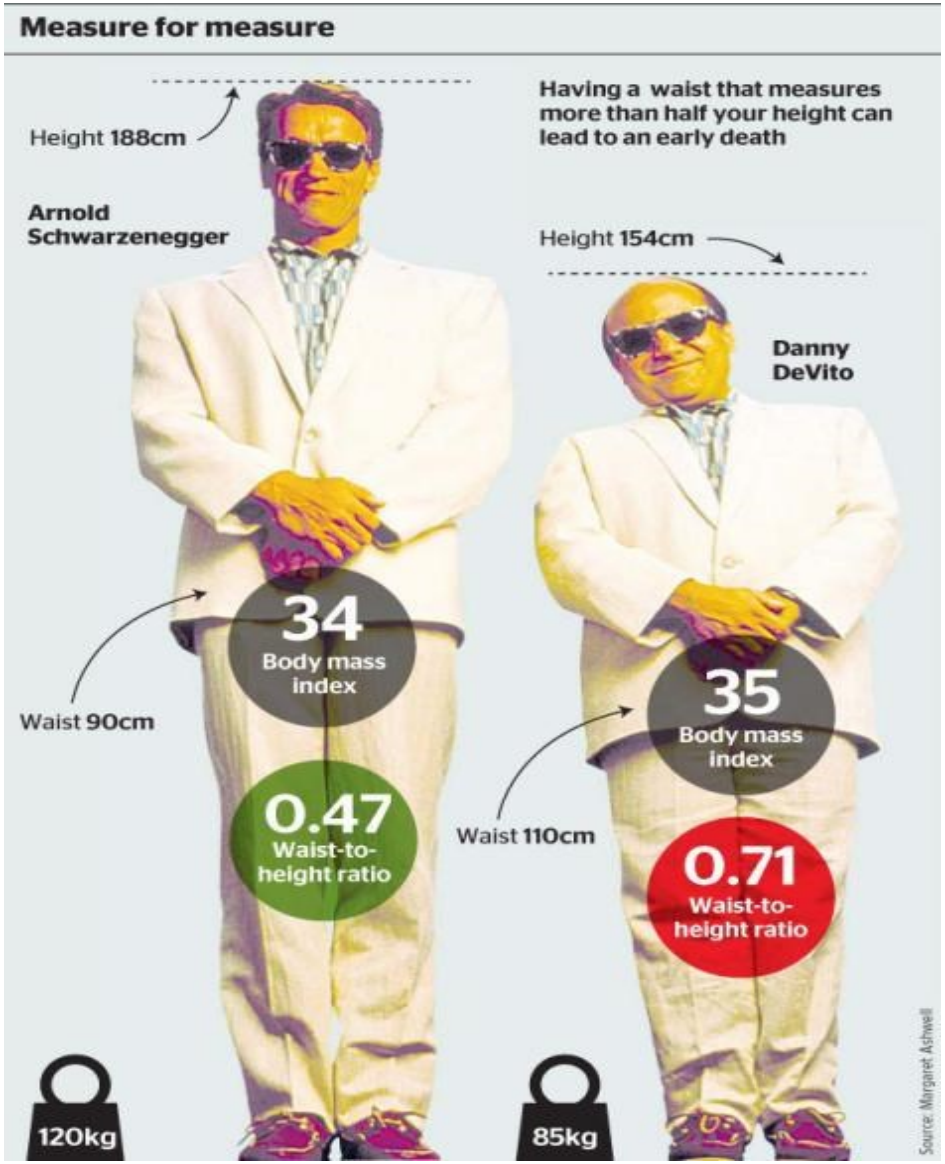
LBW (kg)	Current Maintenance Regimen		Proposed Maintenance Regimen	
	Daily Dose (mg)	PTA (%)	Daily Dose (mg)	PTA (%)
30	100	100	100	100
40	100	100	100	100
50	100	99	100	99
55	100	93	150	100
60	100	80	150	100
70	100	34	150	100
80	100	9	150	100
90	100	1	150	96
100	100	0	200	100
110	100	0	200	100

ASSUMPTION : The target exposure is $AUC_{0\text{-}tau} \geq 82$ h·mg/L.

Summary & Key findings

- Echinocandins such as anidulafungin are fixed dosed without adjustment for body weight.
- Our findings show that exposures decrease with increasing body size.
- We identified a pragmatic approach to dose modification in adults with obesity **that should be tested prospectively.**

Imprecise Classification



Body Mass Index (BMI)

- Simple to compute
- Not a perfect index especially at the extremes of height
- Cannot distinguish fat from lean mass
- Global standard , ≥30 kg/m^2

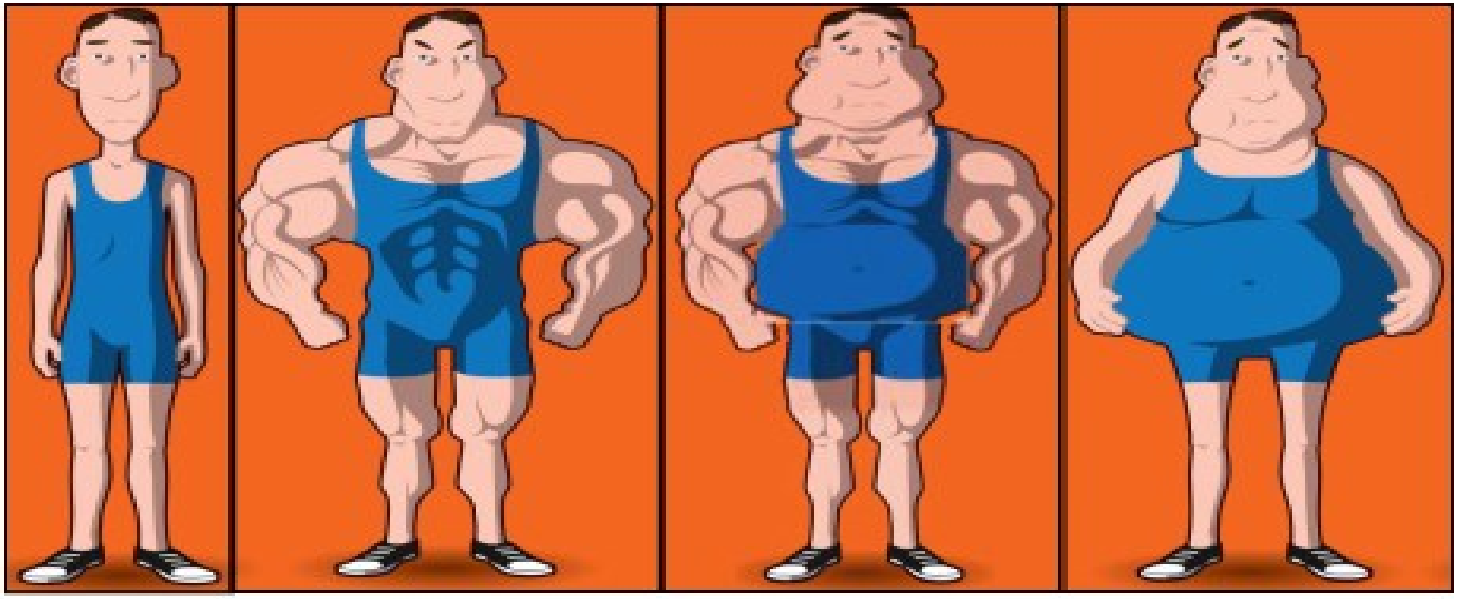
Ideal Body Weight (IBW)

- Based on height and gender
- Simple rule
- Used in pharmacokinetic studies, >20-30% above IBW

World Health Organ Tech Rep Ser. 1995; 854():1-452.

Diverse Phenotypes

Body Composition and Obesity Phenotypes



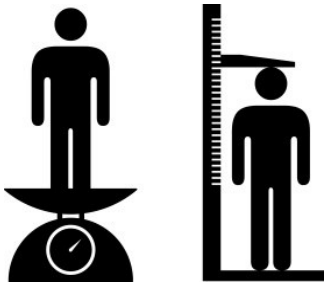
	Normal weight	Athlete	Nonsarcopenic Obese	Sarcopenic Obese
BMI (kg/m^2)	18.5-25	≥30	≥ 30	≥ 30
Fat Mass	Normal	Decreased	Increased	Increased
Lean Mass	Normal	Increased	Increased	Decreased
Cardio - Respiratory Fitness	Normal	Increased	*Mild Impairment?*	*Severe Impairment?*

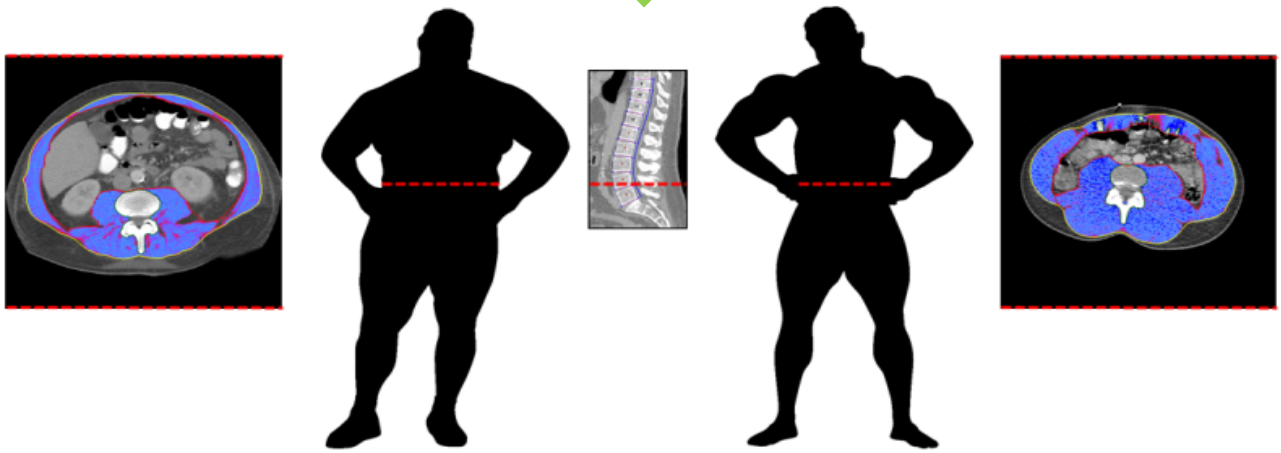
Trobec K, et al. PLoS One. 2013 Nov 8;8(11):e79603.

Can we do better than height and weight?

The Pitch

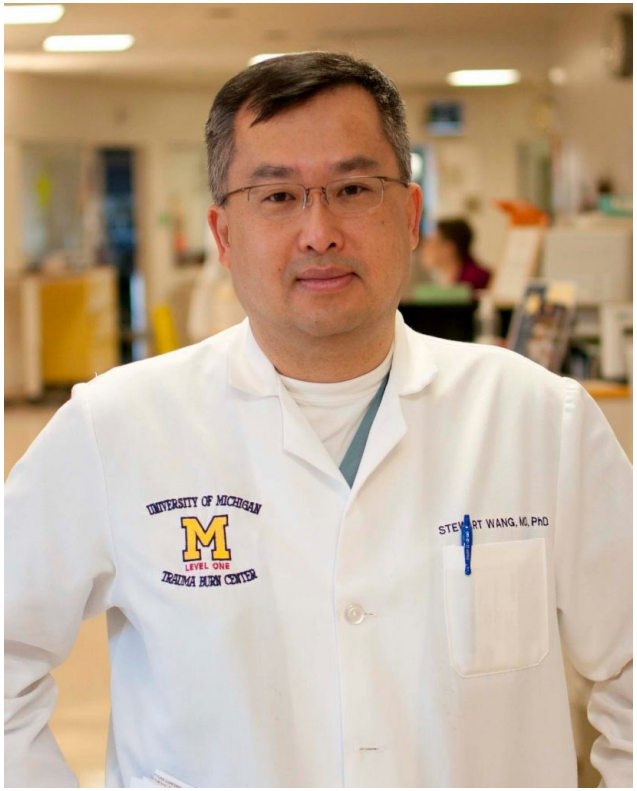
Alternate Dosing Scalars Are Needed

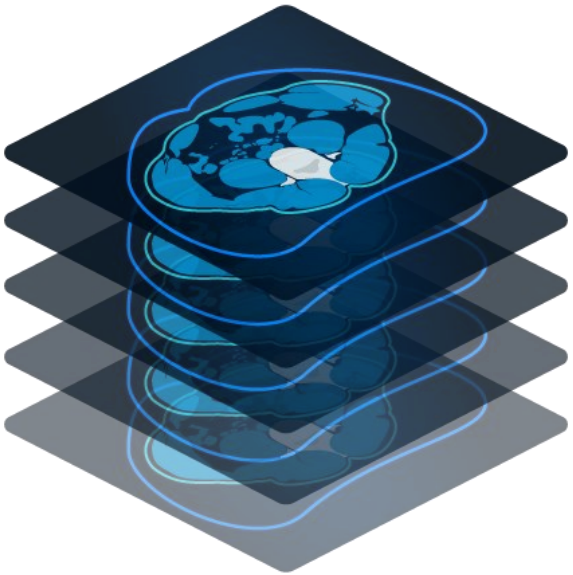


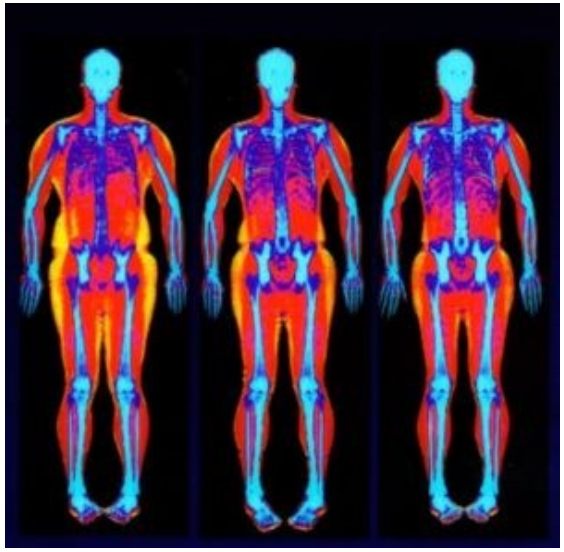


Height:	1.73 m	1.73 m
Weight:	82 kg	82 kg
BMI:	27.4	27.4

Repurpose CT Scans



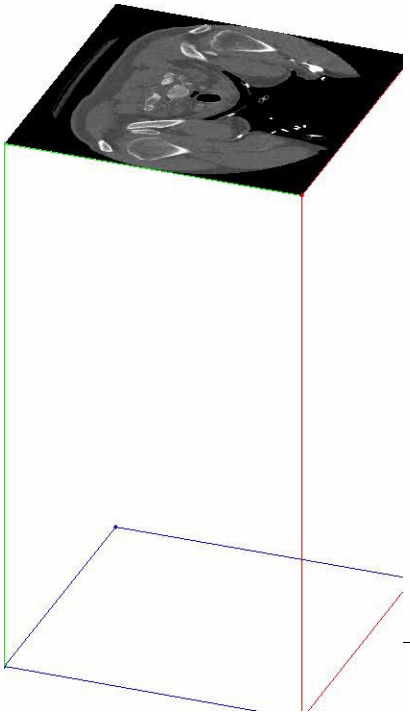


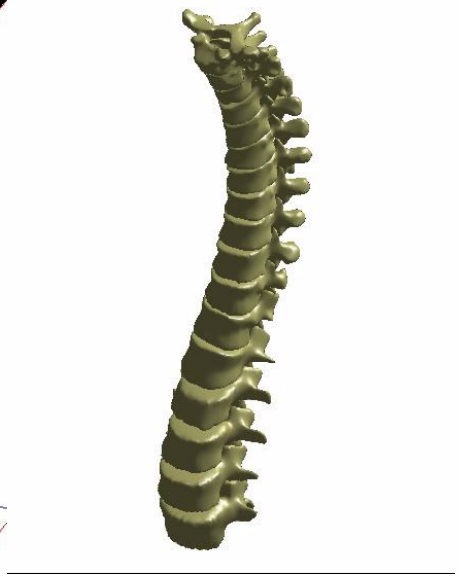


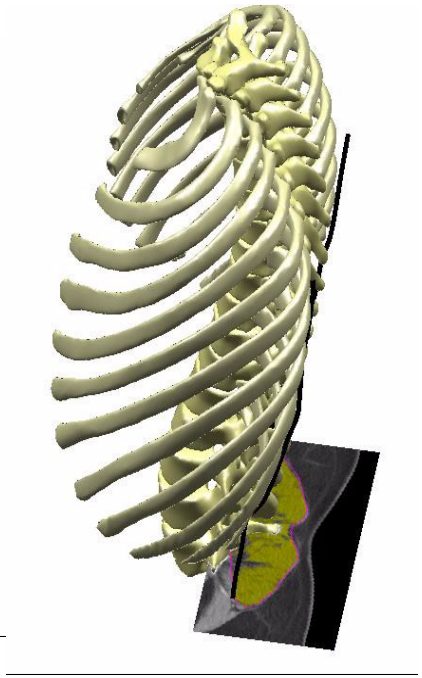
Dr. Stewart Wang

International Center for Automobile Medicine Morphomics Analysis Group

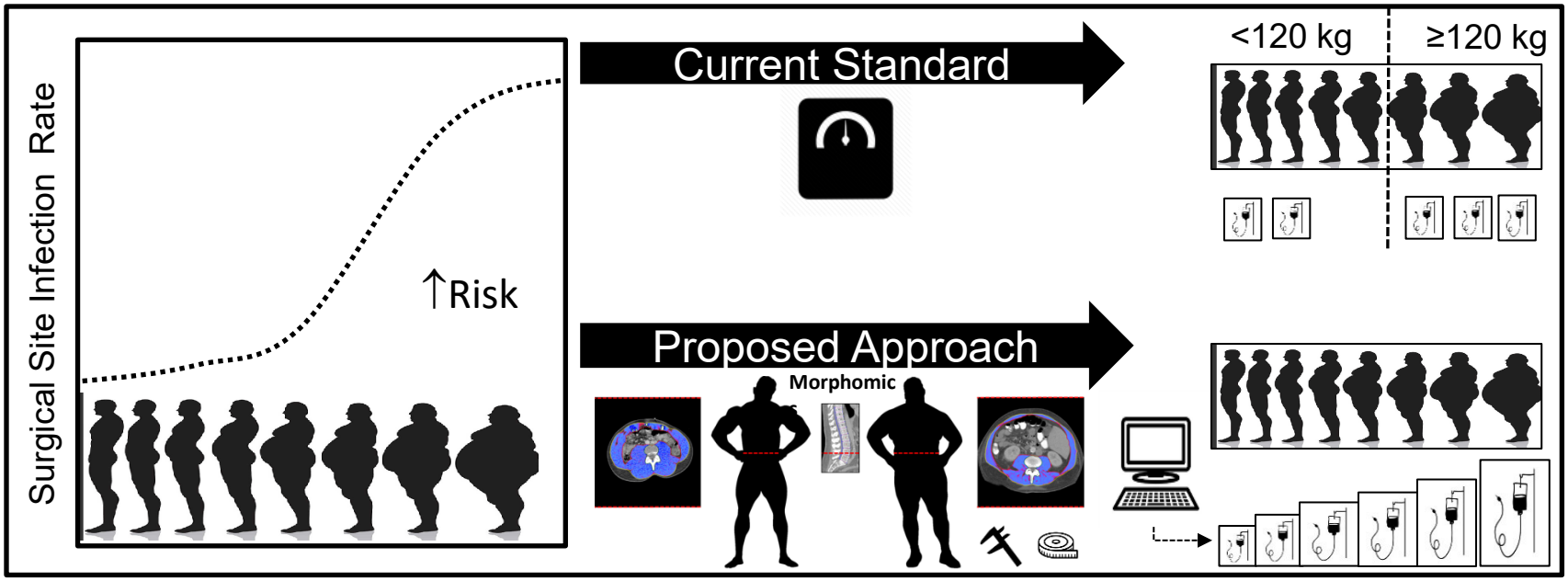
Analytic Morphomics







Cefazolin Surgical Prophylaxis



Proposed approach to lower surgical site infection risk in patients with obesity

Compare morphomic metrics to standard body-size measures (weight and BMI) as predictors of plasma and surgical site tissue concentrations.

Develop a pragmatic dosing algorithm based on morphomics and patient variable

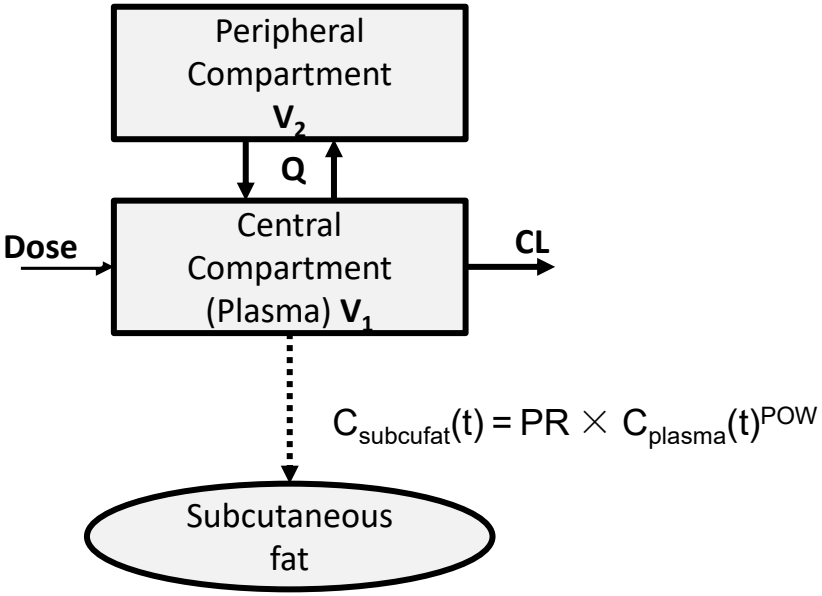
Pilot and evaluate the effectiveness of this morphomic-based precision antibiotic prophylaxis

Optimizing cefazolin dosing

Colorectal surgery patients with CT scans (n = 58)

Blood, subcutaneous fat, and colon tissue samples

Two-compartment model



PR, plasma-to-subcutaneous fat partition ratio
POW, power function that allows the PR to change with plasma concentrations.

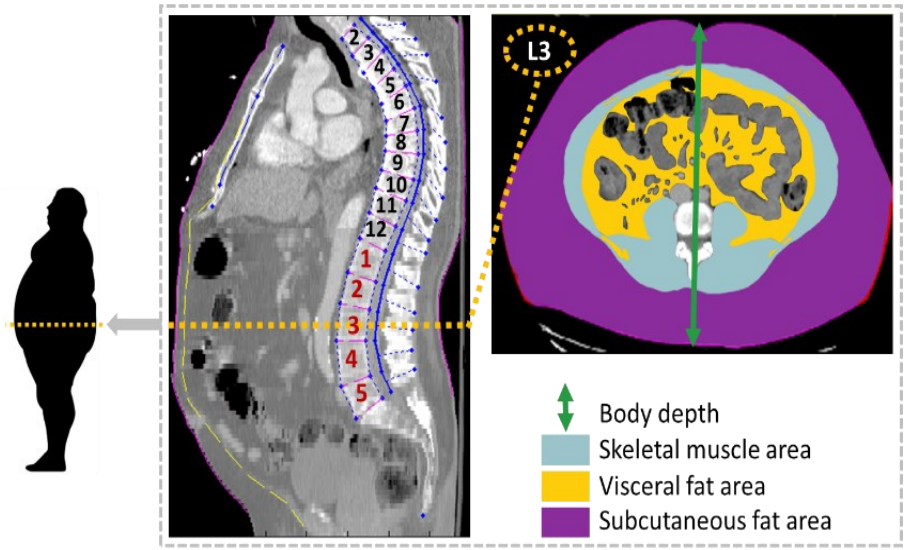
Covariate testing

Traditional body size descriptors, 36 unique morphomics variables, and estimated kidney function (eCLcr)

- TBW, BMI, BSA, LBW, IBW, AdjBW etc. – not significant

PopPK modeling identified key covariates:

- eCLcr on CL
- L3 body depth on plasma-to-subcutaneous fat partition ratio (PR)



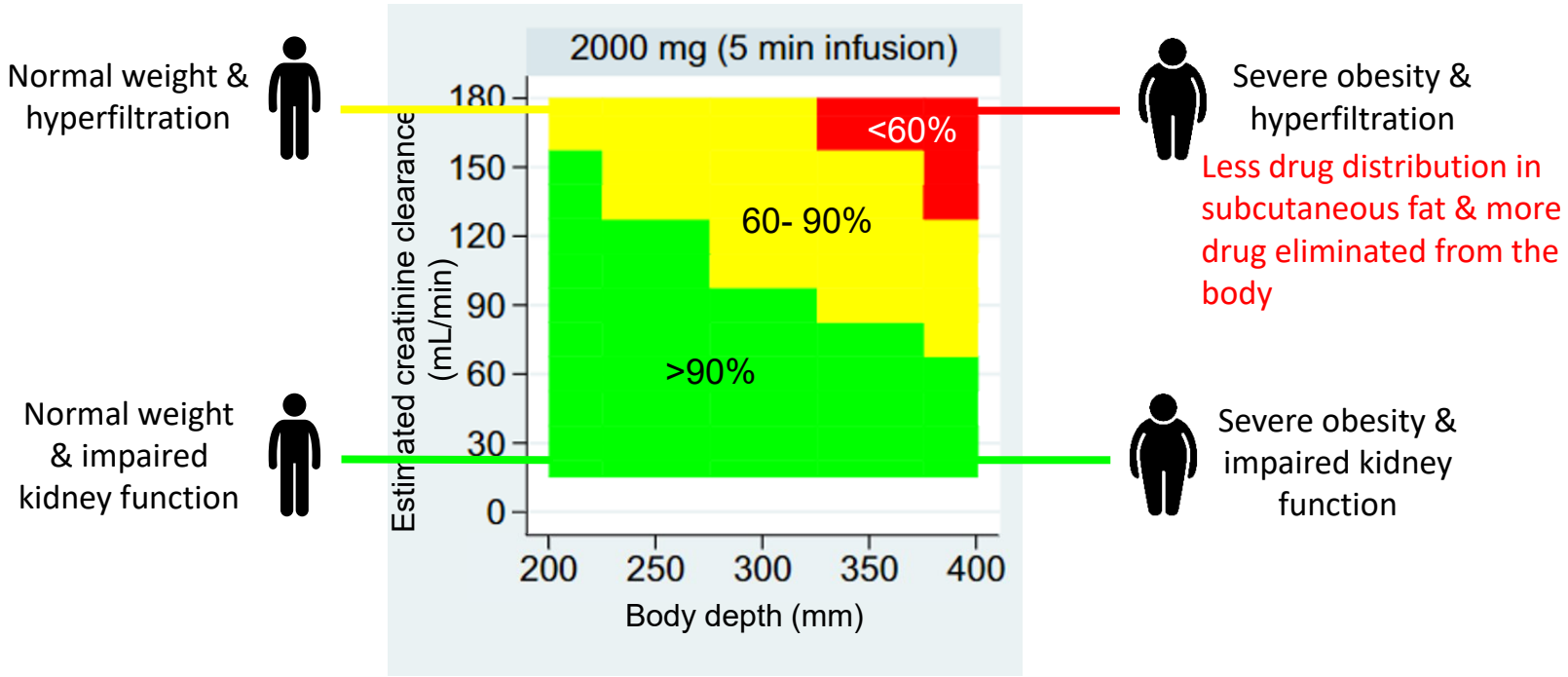
Optimizing cefazolin dosing

Target: achieving a subcutaneous fat conc ≥ 2 µg/mL for 4 hours of surgery time.

Virtual patients
with different body depth and kidney function

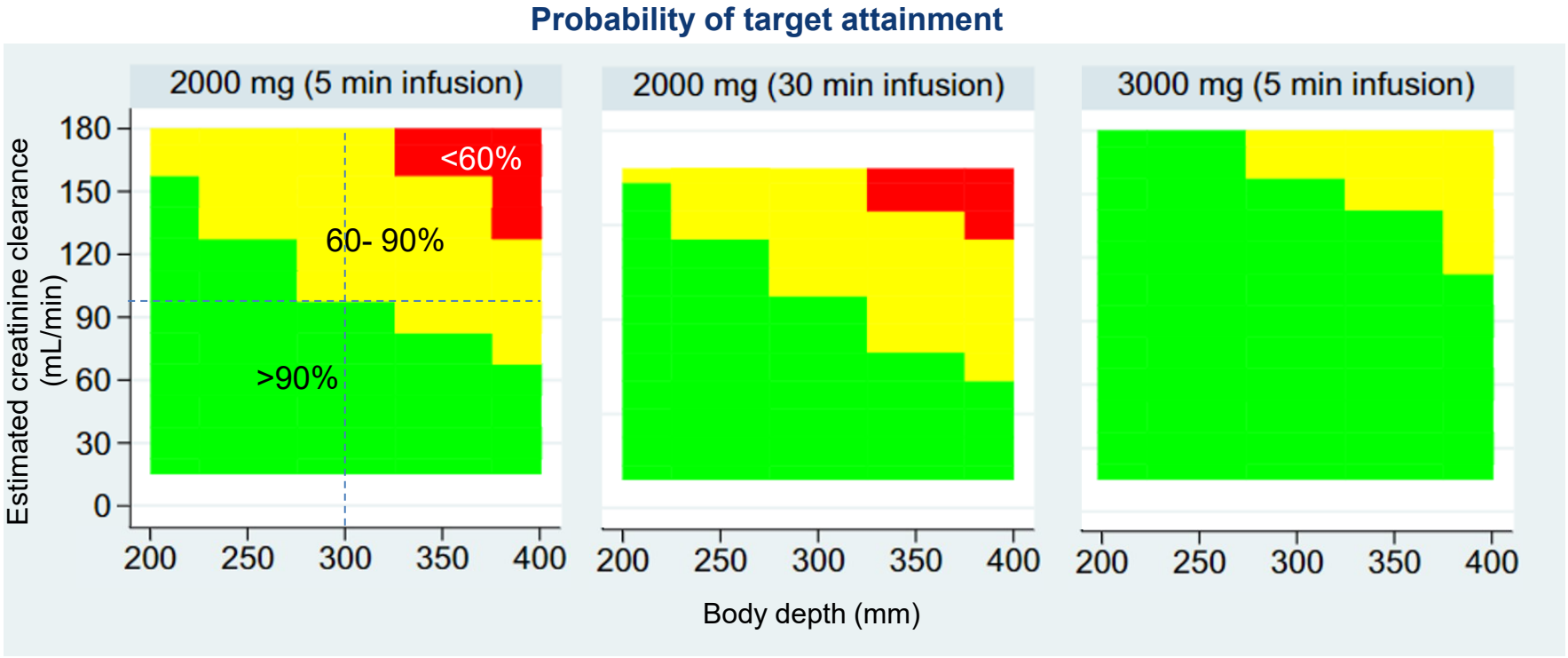
PK simulation
- Who needs a dosing adjustment?
- How to adjust the dosing? (infusion time, dose)

Probability of target attainment



Testing this Potential New Intervention

Target: achieving a subcutaneous fat conc ≥ 2 μg/mL for 4 hours of surgery time.



If eCLcr ≥100 mL/min and/or body depth_L3 ≥ 300 mm → **3 g**
(less sensitive to infusion rate)

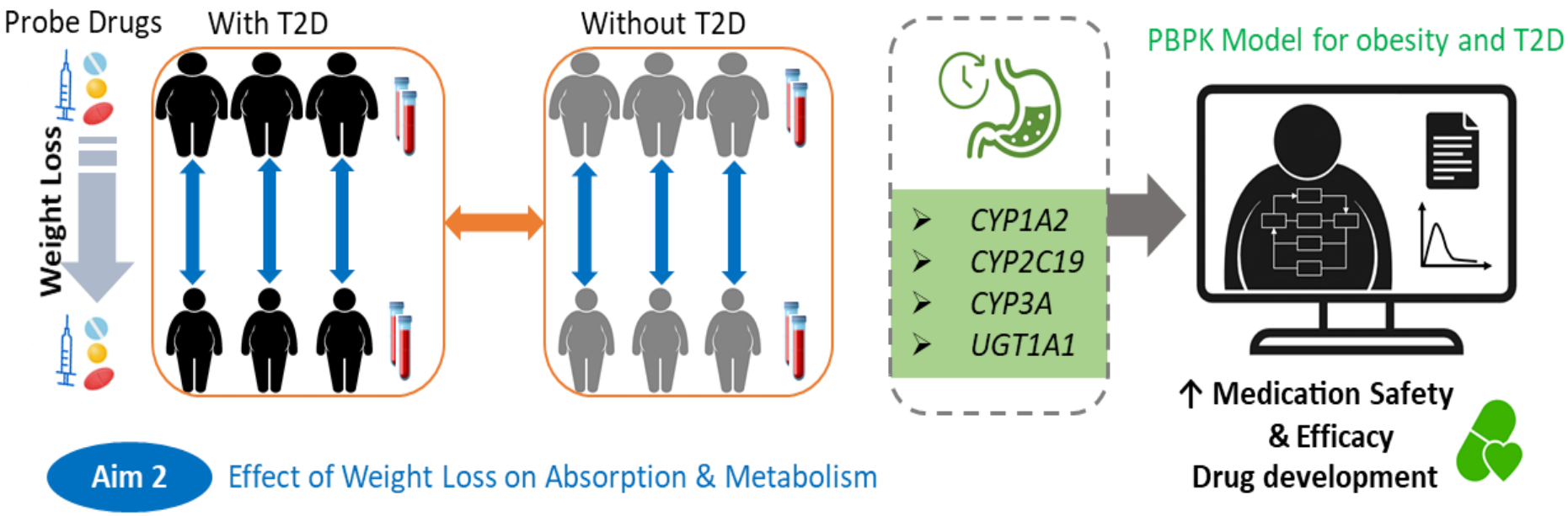
Shuhan Liu, PhD
Abbvie

COLLEGE OF PHARMACY UNIVERSITY OF MICHIGAN

Engineering a Type 2 Diabetes Precision Drug Dosing Model

Aim 1 Absorption & Metabolism Differences

Aim 3



Aim 2 Effect of Weight Loss on Absorption & Metabolism

Study scheme. Two PK studies will be conducted before and after weight loss in obese patients with and without T2D using probe drugs,

Using a 4-drug cocktail to probe drug metabolism changes in patients with obesity

Summary & future directions

Traditional models work

PK models with traditional body size descriptors can provide pragmatic solutions.

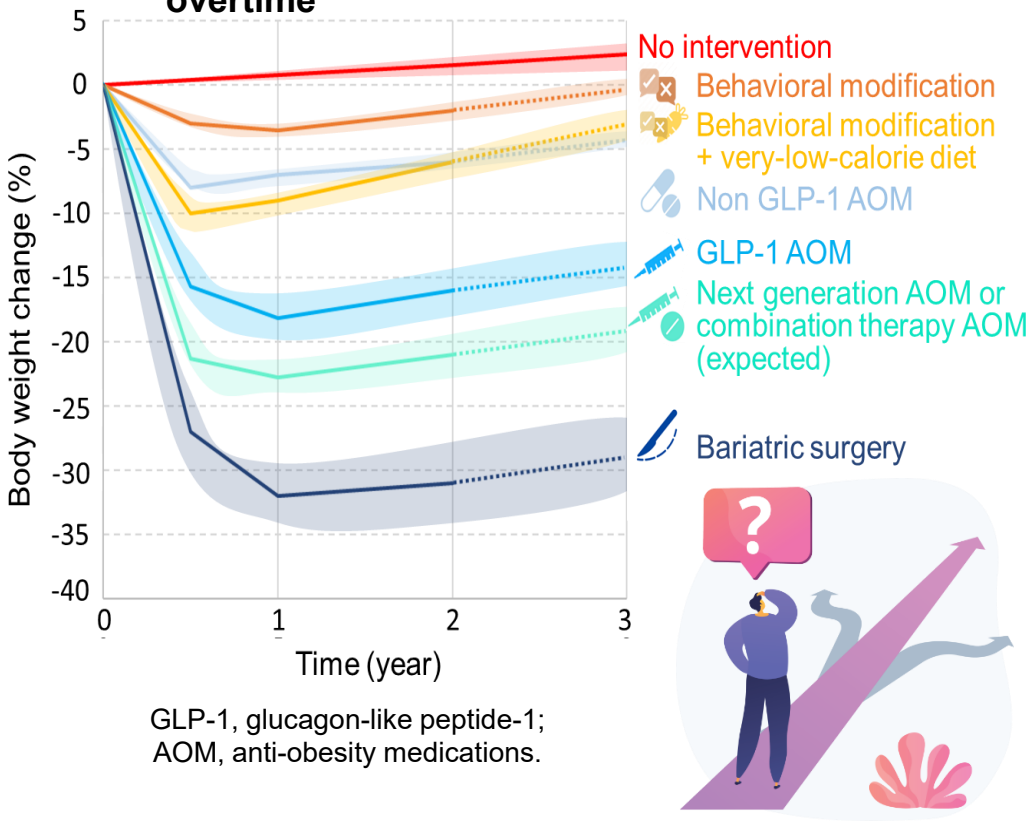
We can do better

Repurposing CT scans opens new dimensions in our exploration - granular body composition measurements.

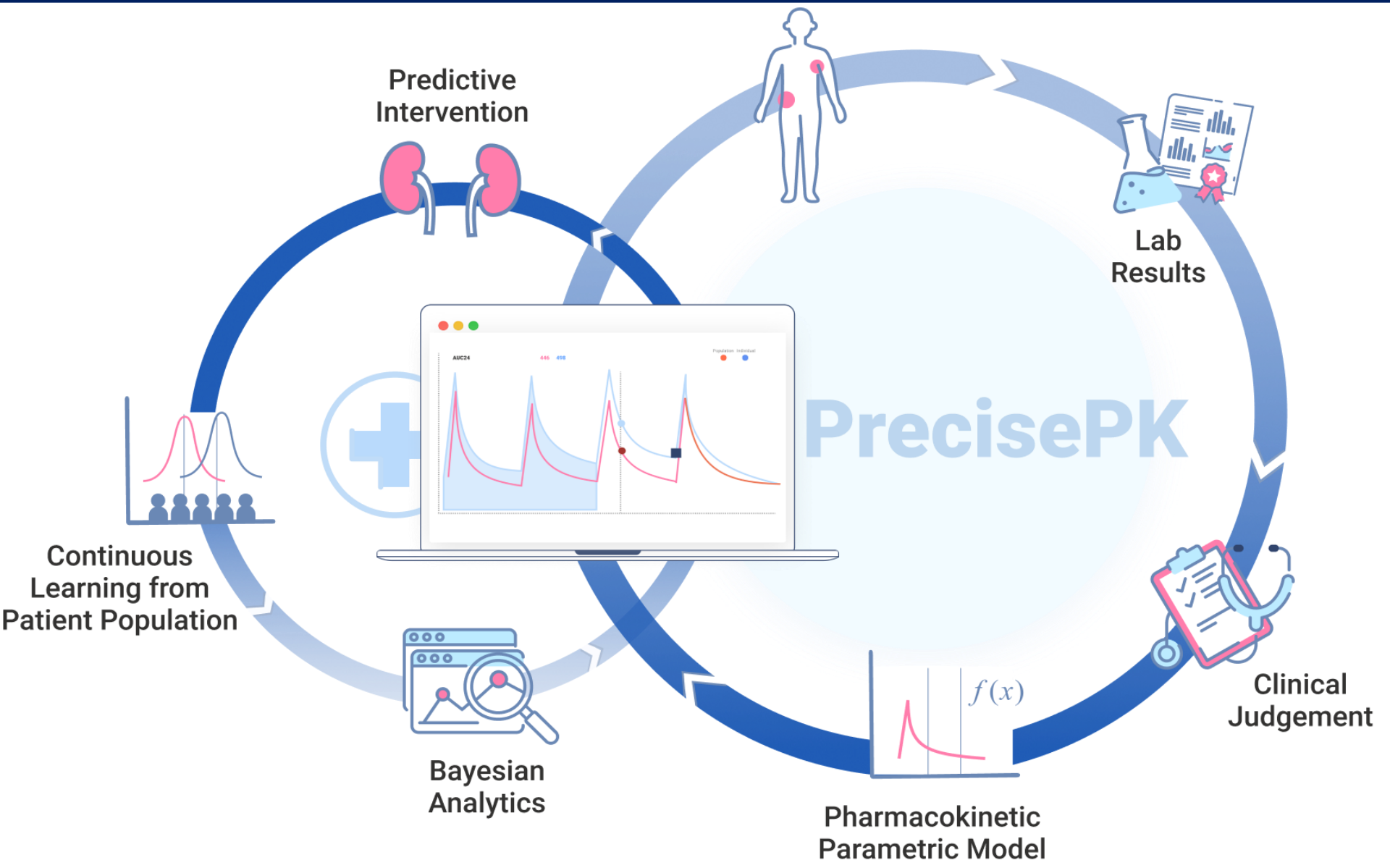
We can be more mechanistic

One-sample cocktail strategy for efficient characterization of drug absorption and metabolism.

Effectiveness of obesity treatments overtime



GLP-1, glucagon-like peptide-1; AOM, anti-obesity medications.


Patient Characteristics
Predictive Intervention
Lab Results
PrecisePK
Continuous Learning from Patient Population
Clinical Judgement
Bayesian Analytics
Pharmacokinetic Parametric Model
f(x)

Testing New Strategies to Support Precision Dosing

Single Sample AUC

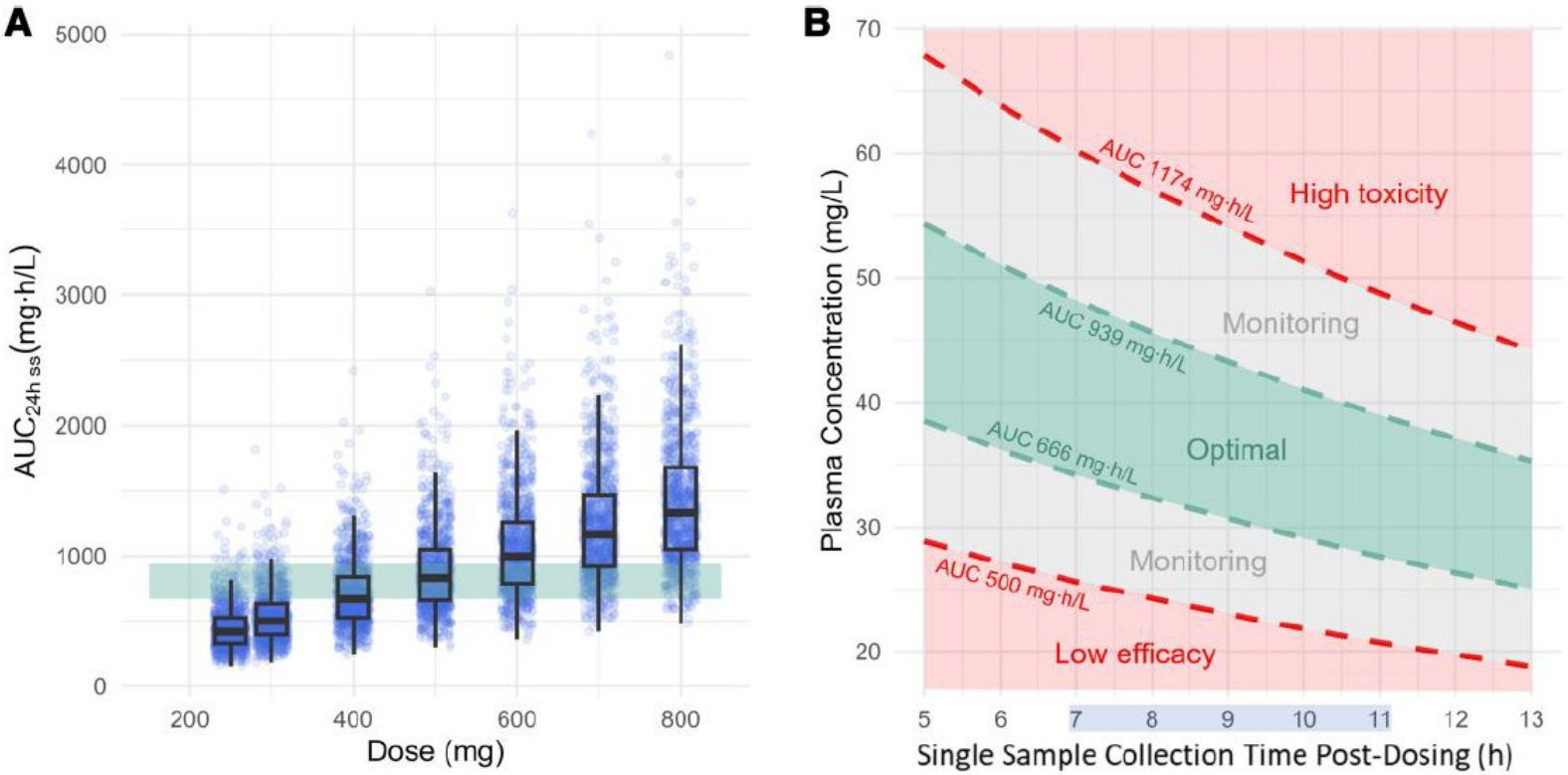


Figure 1. *A*, Simulated steady-state area under the curve of daptomycin ($AUC_{24h\ ss}$) across a wide dose range with a 24-hour dosing interval. The green region highlights the optimal AUC range of 666 to 939 mg · h/L. *B*, Nomogram for daptomycin dose modification based on single sample plasma concentrations post-dosing. The 7 to 11 hours post-dosing is the recommended time range for collecting a single sample. The green region highlights the optimal concentration range associated with an AUC of 666 to 939 mg · h/L. The upper red region highlights the high toxicity concentration range associated with an AUC ≥1174 mg · h/L (125% of 939 mg · h/L) where a dose reduction is needed. The lower red region highlights the low-efficacy concentration range associated with an AUC ≤500 mg·h/L (75% of 666 mg · h/L) where a dose increase is needed. The gray regions represent concentration ranges where monitoring is suggested.

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Volumetric Absorptive Sampling

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ORIGINAL ARTICLE

Clinical validation of two volumetric absorptive microsampling devices to support home-based therapeutic drug monitoring of immunosuppression

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Funding information
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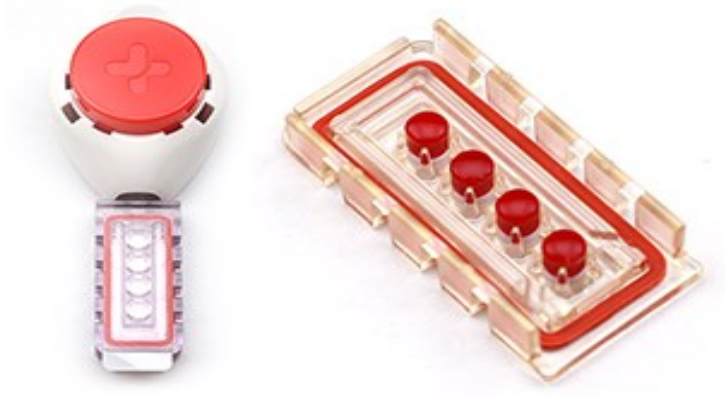
Aims: Dried blood volumetric absorptive microsamples (VAMS) may facilitate home-based sampling to enhance therapeutic drug monitoring after transplantation. This study aimed to clinically validate a liquid chromatography–tandem mass spectrometry assay using 2 VAMS devices with different sampling locations (Tasso-M20 for the upper arm and Mitra for the finger). Patient preferences were also evaluated.

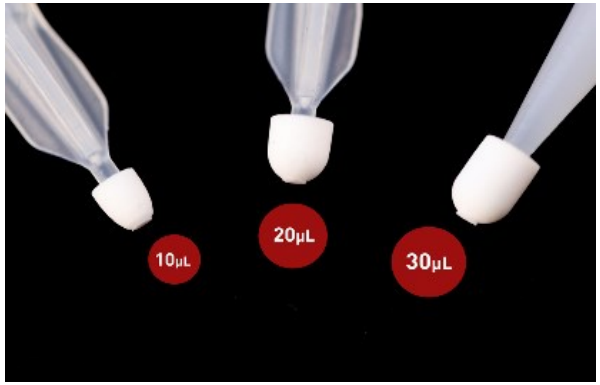
Methods: Clinical validation was performed for tacrolimus and mycophenolic acid by comparison of paired VAMS and venipuncture samples using Passing–Bablok regression and Bland–Altman analysis. Conversion of mycophenolic acid VAMS to serum concentrations was evaluated using haematocrit-dependent formulas and fixed correction factors defined a priori. Patients' perspectives, including useability, acceptability and feasibility, were also investigated using established questionnaires.

Results: Paired samples ($n = 50$) were collected from 25 kidney transplant recipients. Differences for tacrolimus whole-blood concentration were within ±20% for 86 and 88% of samples from the upper arm and fingerstick, respectively. Using correction factors of 1.3 for the upper-arm and 1.47 for finger-prick samples, 84 and 76% of the paired samples, respectively, were within ±20% for mycophenolic acid serum concentration. Patient experience surveys demonstrated limited pain and acceptable useability of the upper-arm device.

Conclusions: Tacrolimus and mycophenolic acid can be measured using 2 common VAMS devices with similar analytical performance. Patients are supportive of home-based monitoring with a preference for the Tasso-M20 device.

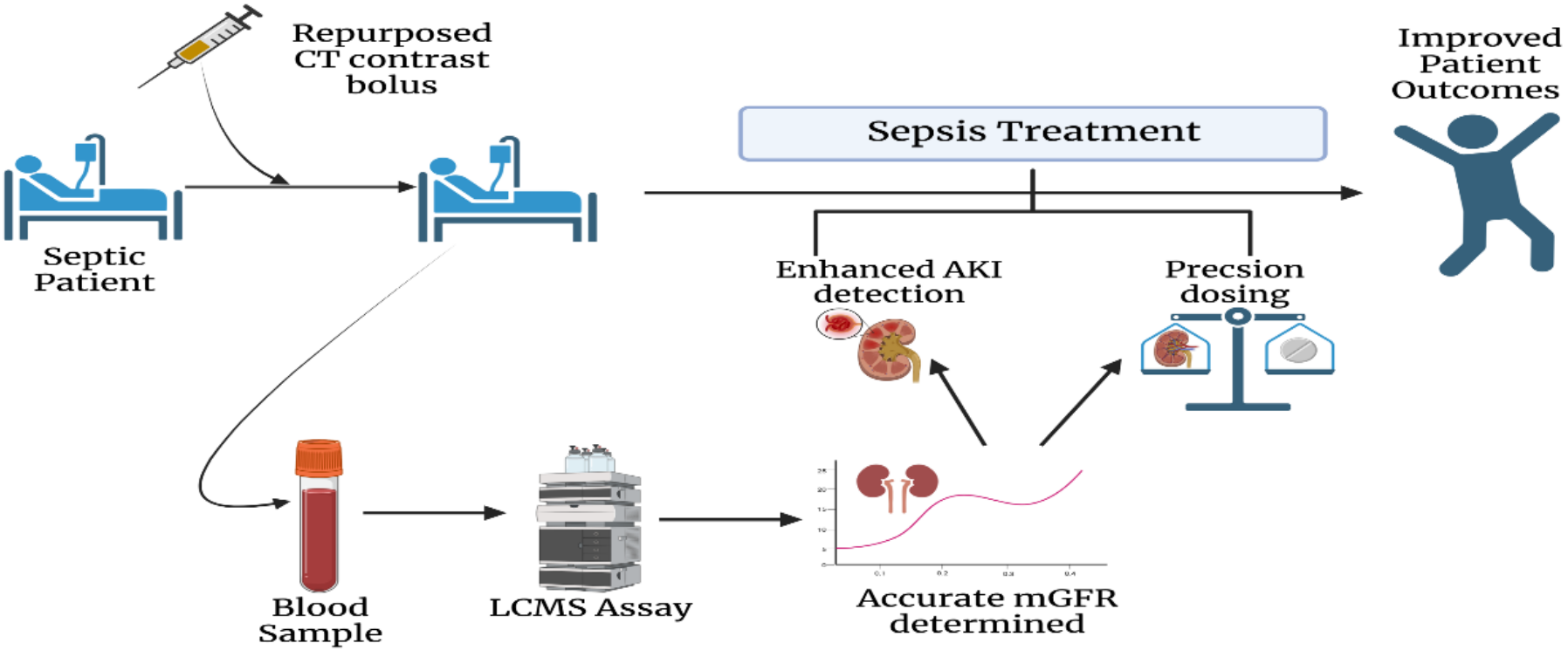
KEYWORDS
clinical validation, immunosuppression, volumetric absorptive microsampling





Assessment of MODS and Personalized Exposures of Antibiotics
PediatRic sEpiS induCed MODS: Relationship of Immune-Phenotypes and AntiBiotic Exposures Study (PRESCRIBE)

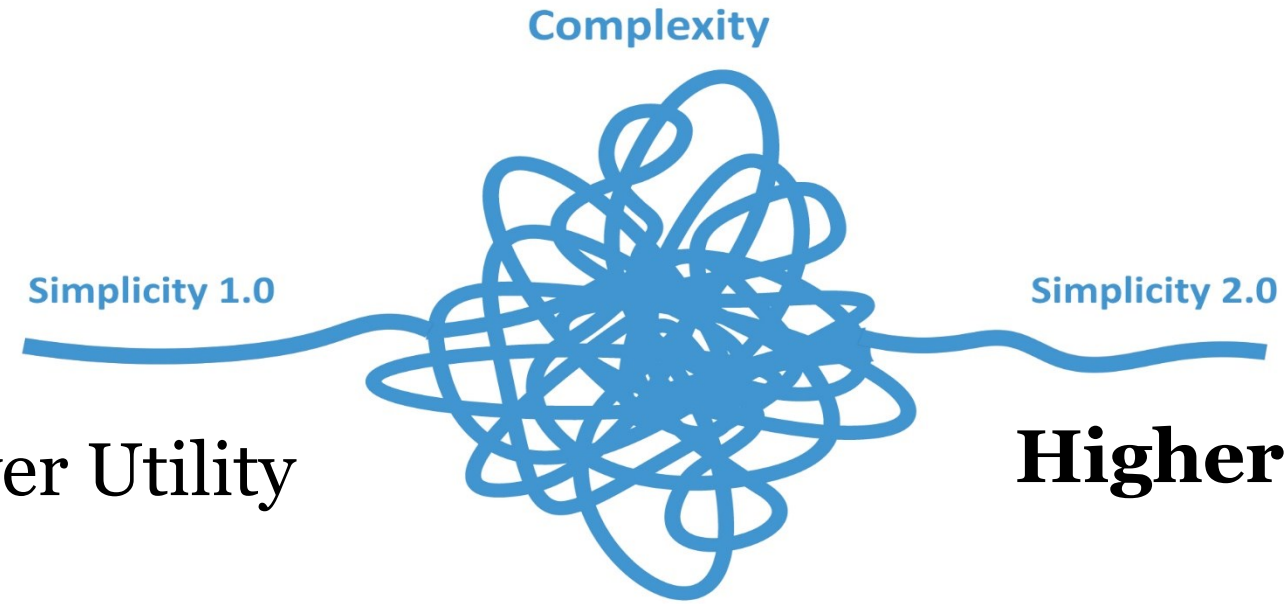
Levi Hooper, PharmD (May 2023)
CPTS PhD Student (3rd year)



Creating Pragmatic Tools for Reliable Kidney Function Measurements in Patients with Kidney Impairment

Supported by a MICHR T32

Work in Progress



Lower Utility

Higher Utility

THANK YOU
FOR YOUR ATTENTION

The Team! x 3

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