Clinical Implementation of Precision Therapeutics in Children

J. Steven Leeder, Pharm.D., Ph.D.
Children's Mercy Kansas City
Kansas City, MO

UMKC School of Medicine

Children's Mercy KANSAS CITY

Disclosures

In the past 12 months, I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or providers of commercial services discussed in this presentation.

Grant Support

R01 HD058556: Exogenous and endogenous biomarkers of CYP2D6 variability in pediatrics (JS Leeder and Y Lin)

- Atomoxetine clinical study, PK analysis: Jacob Brown, PharmD; Sue Rahman, PharmD
- CYP2D6 Genotyping: Andrea Gaedigk, PhD
- Analytical method development: Leon van Haandel, PhD

T32 HD069038: Research Fellowship Program in Pediatric Clinical and Developmental Pharmacology (GL Kearns; JS Leeder and SM Rahman)

U54 HD090258: Genomic- and Ontogeny-Linked Dose Individualization and cLinical Optimization for Kids: GOLDILOKs (Leeder, PI)

- *In vitro* Studies: Jean Dinh, PharmD, PhD

Evolution of Thought

- Personalized Medicine
  - Encounters between healthcare providers and their patients are “personal” encounters
- Individualized Medicine
  - Use of information **unique** to the individual patient allows the results of the personal encounter to be “individualized”
- Precision Medicine
  - Greater depth genomic data available to inform diagnosis and treatment
  - Precision Diagnosis
  - Precision Therapeutics

Presentation Goals

- Describe potential sources of variability relevant to drug response in pediatric patients
- Discuss three challenges facing clinical implementation of existing pharmacogenomic information in pediatrics
  1. Application of “population” data to “individual” children
  2. Limitation of extrapolating/scaling adult data to children
  3. Focus on (primary) polymorphic pathway
- Differentiate between the importance of the “right exposure”, rather than the “right dose”, to better understand inter-individual variability in the response to a medication

Presentation Goals Reframed

- Redefine the problem
  - Response → Exposure → Dose
  - Ontogeny and genetic variation of drug targets
  - Controlling systemic drug exposure
- Assess the value and limitations of existing knowledge to inform drug dosing in individual children
  - Think “individual”, not “population
  - Genetic association studies
  - Inter-individual variability; importance of competing pathways
- Getting the tools for implementing precision therapeutics into the hands of those who will use them

Sources of Variability in Drug Response

Redefining the problem:

Response $\rightarrow$ Exposure $\rightarrow$ Dose

Ontogeny and genetic variation of drug targets

Controlling systemic drug exposure

Redefining the Problem

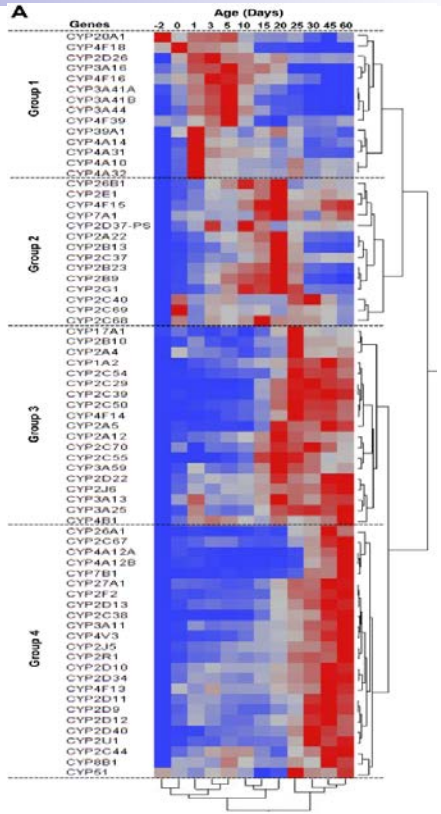
~~Dose~~ → ~~Exposure~~ → ~~Response~~

Response → Exposure → Dose

What is the therapeutic goal of drug administration? → What exposure is required to achieve the desired response? → What dose must be administered to achieve that exposure?

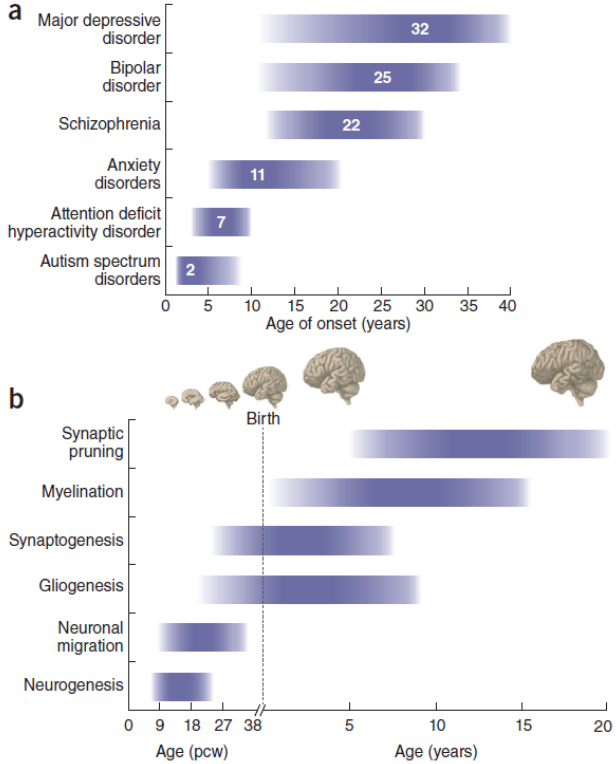
Sources of Variability: Ontogeny of Drug Biotransformation

- Functional drug biotransformation capacity is acquired in gene-specific patterns ("developmental trajectories")
  - Group 1: Primarily fetal expression (CYP3A7; SULT1E1)
  - Group 2: SULT1A1, CYP2C19, CYP3A5*, GSTA1
  - Group 3: CYP1A2, CYP2C9, CYP2D6, CYP3A4, UGTs
  - Observed variability greatest in first 3 months of life
- Developmental patterns of expression (ontogeny) are superimposed upon pharmacogenetic variability
- Genotype-phenotype relationships may change over time; most evident when gene is fully expressed



Review: Hines RN, Pharmacology & Therapeutics 2008; 118:250-267
Mouse data: Peng *et al* Drug Dispos Metab 2012; 40:1198-1209

Sources of Variability: Ontogeny of Brain Maturation



- Several neurodevelopmental, behavioral and psychiatric disorders have an onset during childhood
- Several processes essential for brain development display distinct patterns of development (drug targets?)
- Implications for drug response if target of drug action is not expressed at a given age, or developmental stage
- Introduction of foreign chemicals (drug) may have unintended consequences for “normal” brain development

Marin *Nature Med* 2016; 22:1229-38

Challenge for Precision Therapeutics: Consequences of Interindividual Variability

its blood concentration after dose escalation. Although blood concentration is not related to adverse effects or clinical improvement,[16,17,21] determination of plasma FLX concentrations could provide information about variability in clinical response.[22]

TABLE 4. FLX and NORFLX Concentrations for MDD Patients, Classified (by Means of the CDI) as Responders and Nonresponders

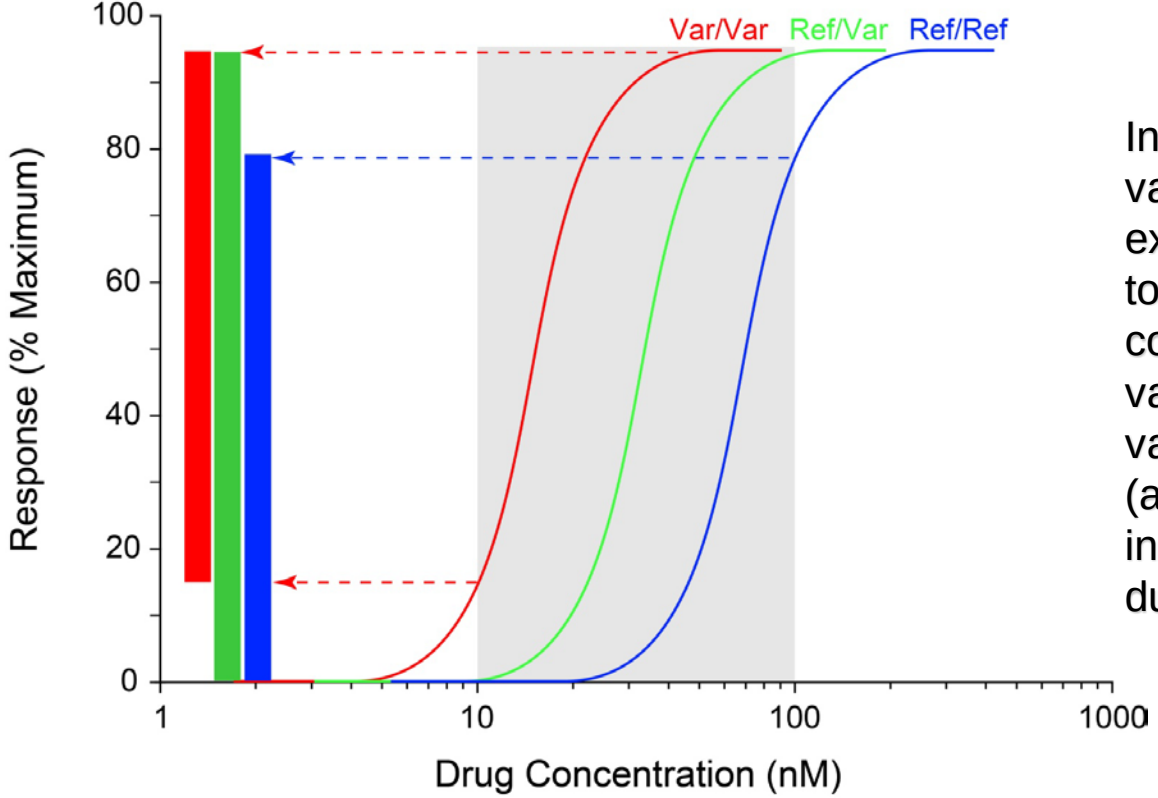
	Week 8				Week 12			
	Responders (15)	Nonresponders (36)			Responders (19)	Nonresponders (32)		
	Mean (SD)	Mean (SD)	*t**	*P*	Mean (SD)	Mean (SD)	*t**	*P*
Dose, mg	17.33 (4.57)	22.56 (7.62)	−2.468	0.02	21.05 (13.70)	22.50 (7.62)	−0.486	0.69
FLX, ng/mL	76.67 (85.33)	101.47 (89.94)	−0.911	0.37	155.41 (188.38)	106.35 (99.36)	1.186	0.24
NORFLX, ng/mL	111.60 (95.36)	116.61 (86.84)	−0.182	0.86	148.53 (117.29)	123.13 (88.85)	0.844	0.40
Sum, ng/mL	188.27 (177.67)	215.31 (157.37)	−0.538	0.59	303.94 (289.241)	229.29 (172.53)	1.123	0.27
Ratio (FLX/NORFLX)	0.67 (0.28)	0.91 (0.55)	−1.690	0.09	0.94 (0.48)	0.90 (0.61)	0.259	0.78

*Student *t* test.

Blázquez *et al.*, J Clin Psychopharmacol 2014;34: 318Y326

Response → Exposure → Dose

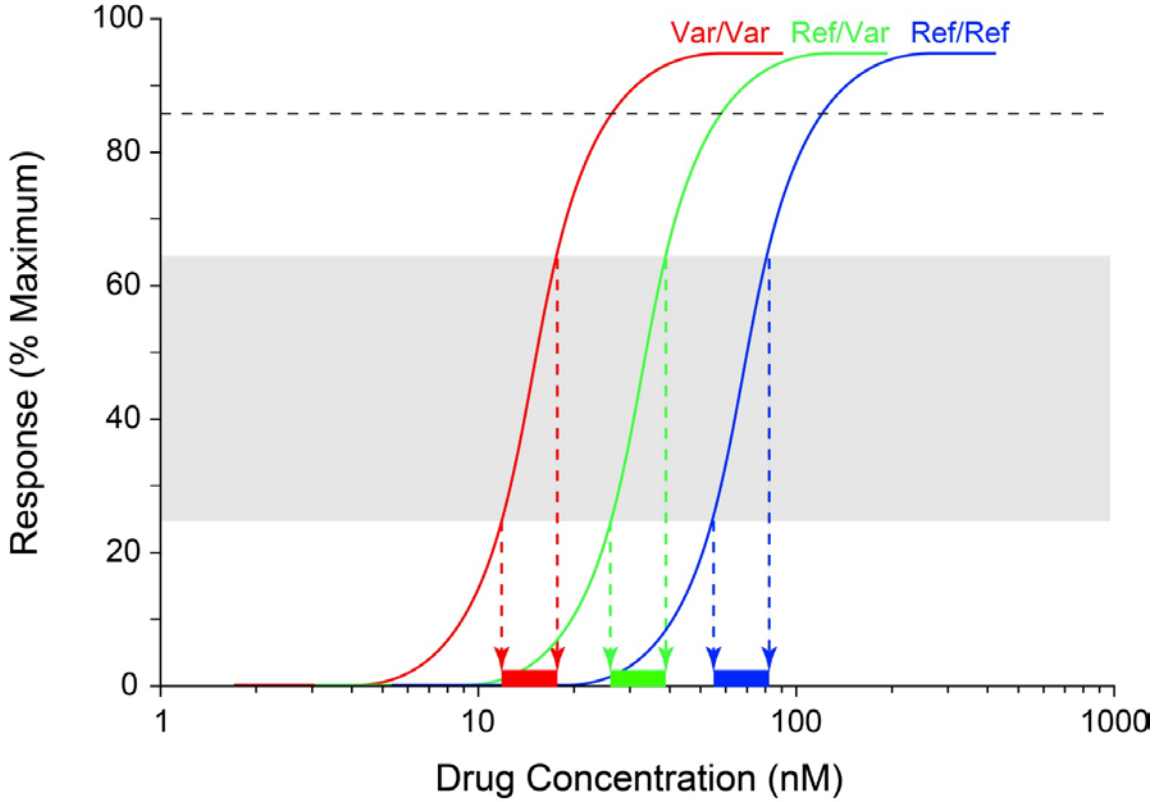
Variability in Expression of Drug Target



In the presence of large variability in drug exposure, it is impossible to characterize the contribution of genetic variation in drug target to variability in response (applies also to variability in drug target expression due to ontogeny

Response → Exposure → Dose

Effect of Variability in Drug Target Expression



Different drug exposures are required to achieve equivalent drug responses, depending on level of drug target expression (or function)

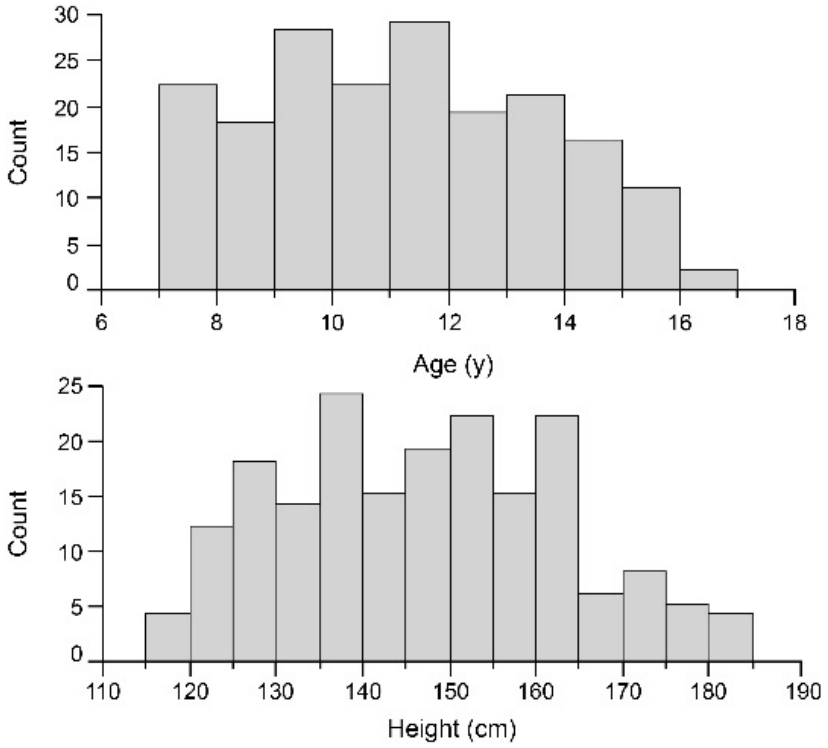
Value and Limitation of Available Data

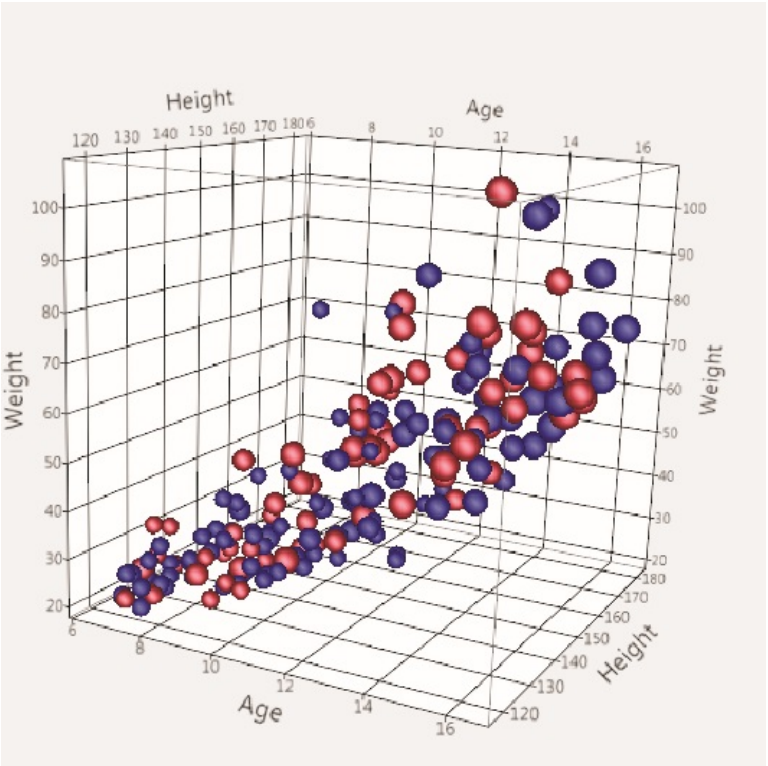
Think “individual”, not “population

Genetic association studies

Inter-individual variability; importance of competing pathways

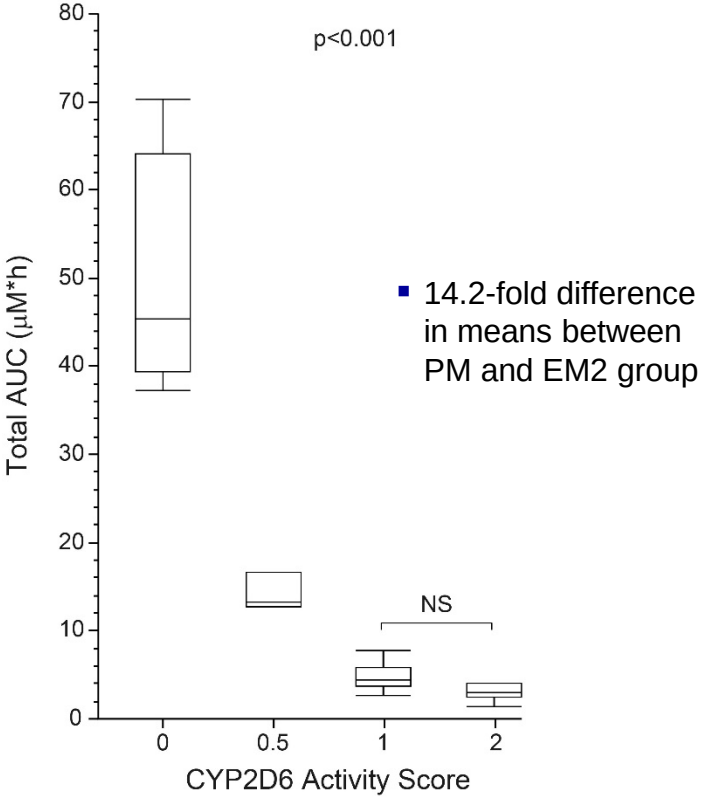
For Precision Therapeutics, Think “Individual”, Not “Population”



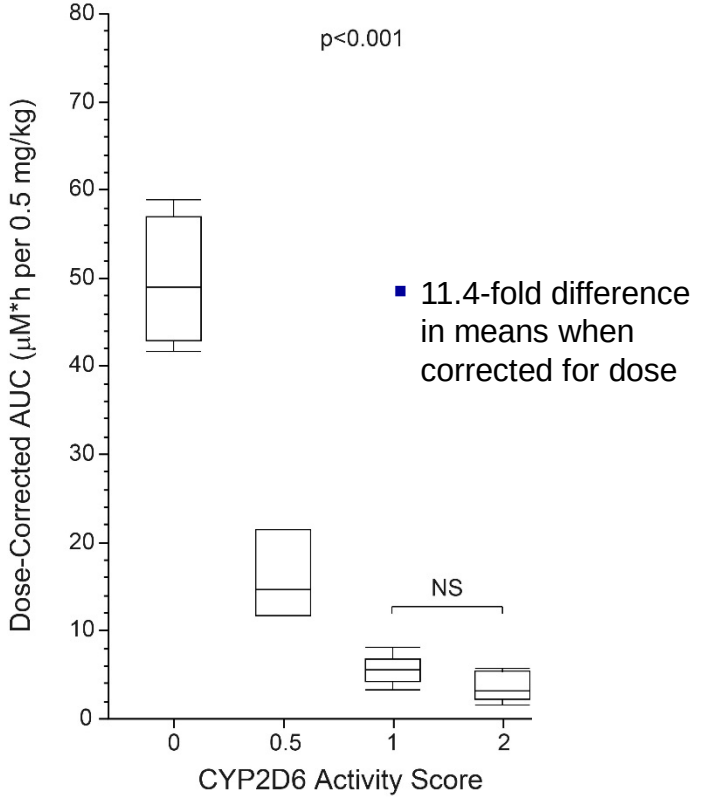


Comparison of “Mean” Atomoxetine AUC: “Population” Perspective

Brown *et al. CPT* 2016; 99:642-50



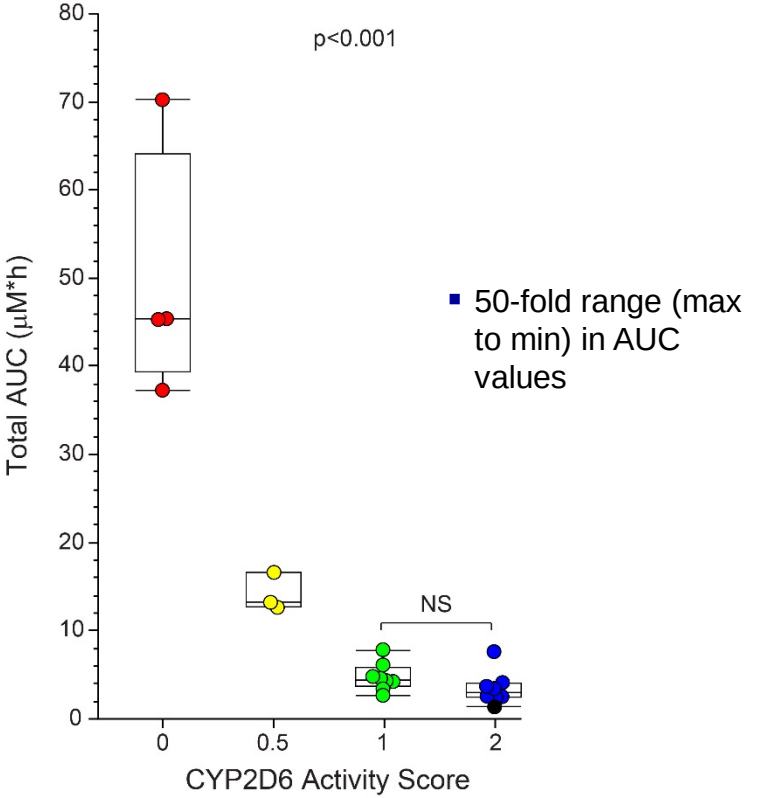
- 14.2-fold difference in means between PM and EM2 group



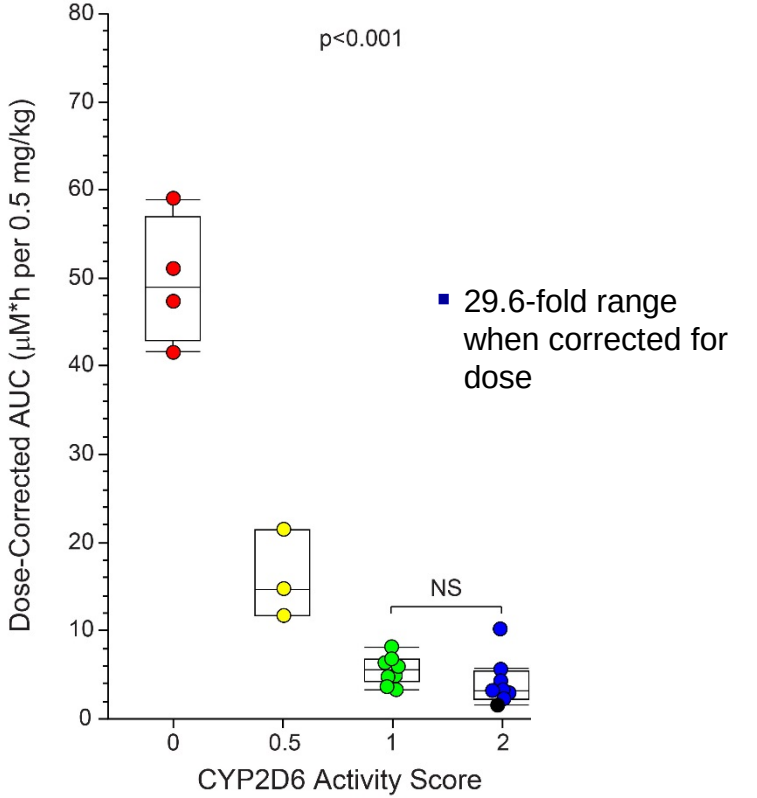
- 11.4-fold difference in means when corrected for dose

Comparison of “Mean” Atomoxetine AUC: “Individual” Perspective

Brown *et al. CPT* 2016; 99:642-50



- 50-fold range (max to min) in AUC values



- 29.6-fold range when corrected for dose

Value and Limitation of Available Data

Think “individual”, not “population

Genetic association studies

Inter-individual variability; importance of competing pathways

Application of Genetic Association Data to Inform Clinical Decisions for Individual Patients

J Neural Transm (2008) 115: 341–345
DOI 10.1007/s00702-007-0835-0
Printed in The Netherlands

Journal of Neural Transmission

ADRA2 rs1800544 (-1291 C>G; f_C=0.62)
Response: ≥50% decrease in SNAP-IV score
p=0.016

Adrenergic α2A receptor gene and response to methylphenidate in attention-deficit/hyperactivity disorder-predominantly inattentive type

T. L. da Silva[1], T. G. Pianca[1], T. Roman[2], M. H. Hutz[3], S. V. Faraone[4], M. Schmitz[1], L. A. Rohde[1]

	G allele (+) (G/G or G/C)	G allele (-) (C/C)
Improvement	29	9
No Improvement	11	10

Sensitivity: 29/38= 76.3%
Specificity: 10/21= 47.6%

Positive Predictive Value= 29/40 =72.5%
Negative Predictive Value= 10/19= 52.6%

Application of Genetic Association Data to Inform Clinical Decisions for Individual Patients

Response: “Much improved” or “very much improved” on CGI
p=0.015

The Pharmacogenomics Journal (2014) 14, 295–302

www.nature.com/tpj

ORIGINAL ARTICLE

Positive effects of methylphenidate on hyperactivity are moderated by monoaminergic gene variants in children with autism spectrum disorders

JT McCracken[1], KK Badashova[1], DJ Posey[2], MG Aman[3], L Scahill[4], E Tierney[5], LE Arnold[3], B Vitiello[6], F Whelan[1], SZ Chuang[7], M Davies[7], B Shah[1], CJ McDougle[8] and EL Nurmi[1]

	G allele (+) (G/G or G/C)	G allele (-) (C/C)
Improvement	12	20
No Improvement	18	8

Sensitivity: 12/38= 31.6%
Specificity 8/26= 30.8%

Positive Predictive Value: 12/30= 40.0%
Negative Predictive Value: 8/28= 28.6%

Limitations of Using “Population” Data to Inform Clinical Decisions for Individuals

- Statistical evaluation of genotype effect involves comparison of means for each genotype group
- Considerable variability in phenotype may exist within a genotype group; most individuals lie outside the mean
- Genetic association studies involving children are generally limited to small “populations”
- Application/extrapolation to individual patients is limited
  - Sampling errors
  - Heterogeneity in actual condition being studied
  - Limited (if any) prospective validation

Value and Limitation of Available Data

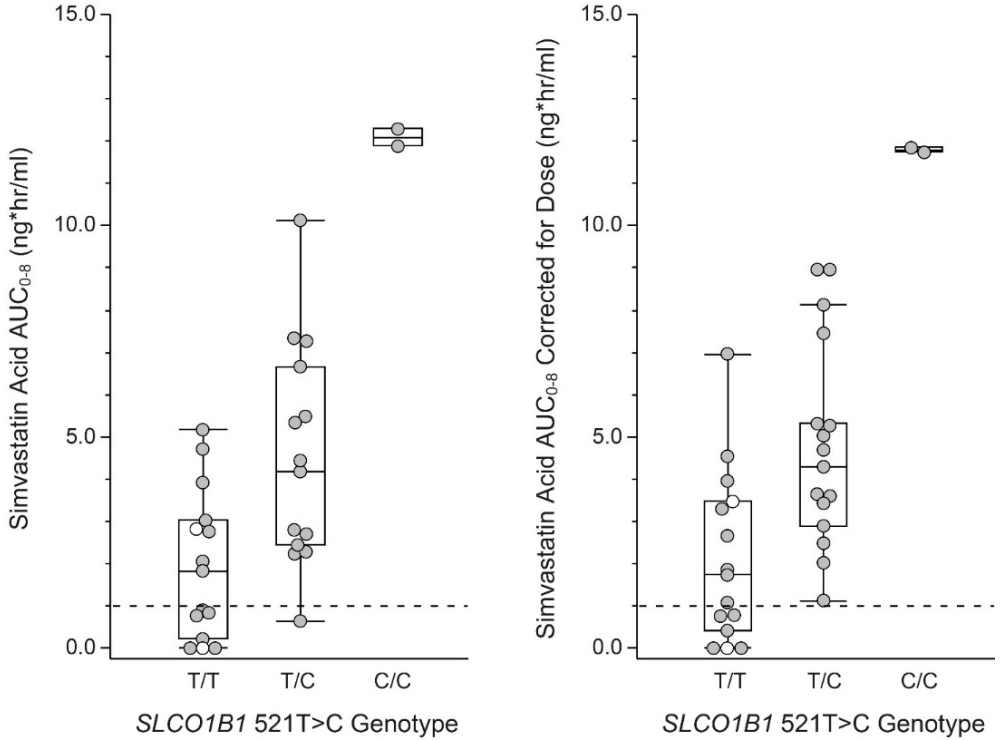
Think “individual”, not “population

Genetic association studies

Inter-individual variability; importance of competing pathways

Extrapolation of Adult Data to Pediatrics: Genotype-Stratified PK Study of Simvastatin

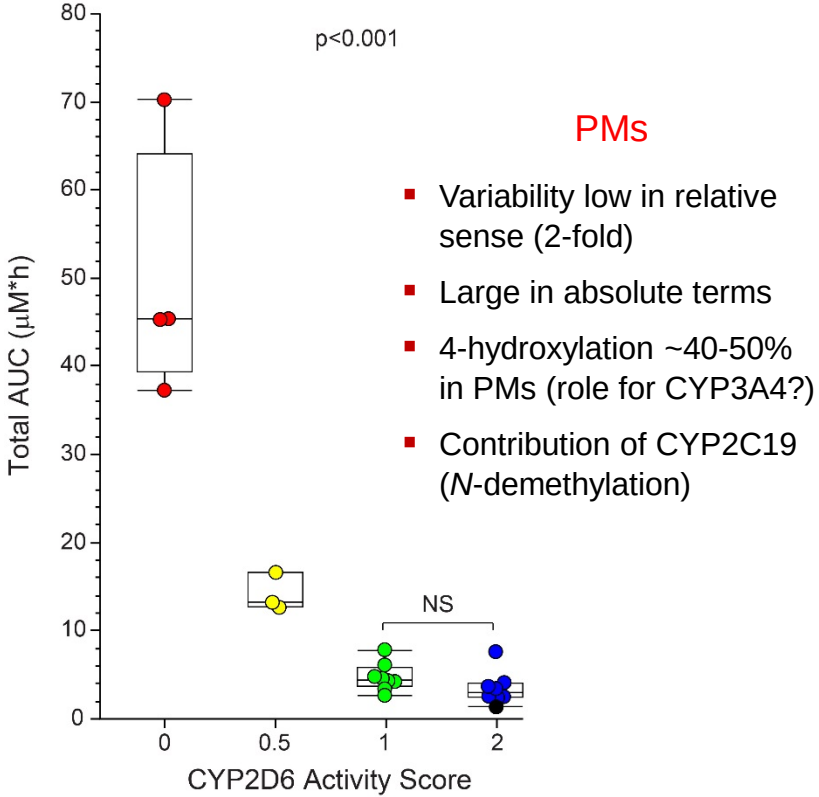
- Hydrolysis of lactone (SVL) to form active acid form (SVA)
- Assumptions of rapid hydrolysis and CYP3A metabolism
- Adult genotype-phenotype associations replicated
- However, sampling strategy based on adult experience; inadequate duration – $AUC_{0\text{-}8}$
- Negligible to undetectable SVA concentrations in 25% of subjects
- Considerable within-genotype variability, especially T/C heterozygotes; SVA formation issue?



Wagner *et al. Circulation* 2016;134:Suppl A15784 (abstract)

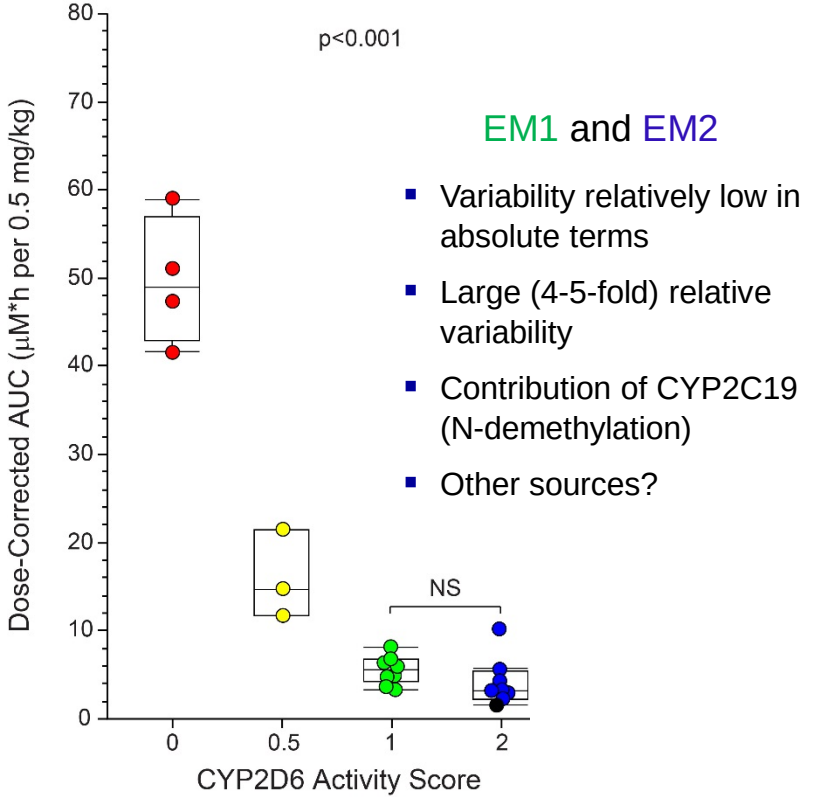
Sources of Within-Genotype Variability: Role for Competing Pathways?

Brown *et al. CPT* 2016; 99:642-50



PMs

- Variability low in relative sense (2-fold)
- Large in absolute terms
- 4-hydroxylation ~40-50% in PMs (role for CYP3A4?)
- Contribution of CYP2C19 (*N*-demethylation)

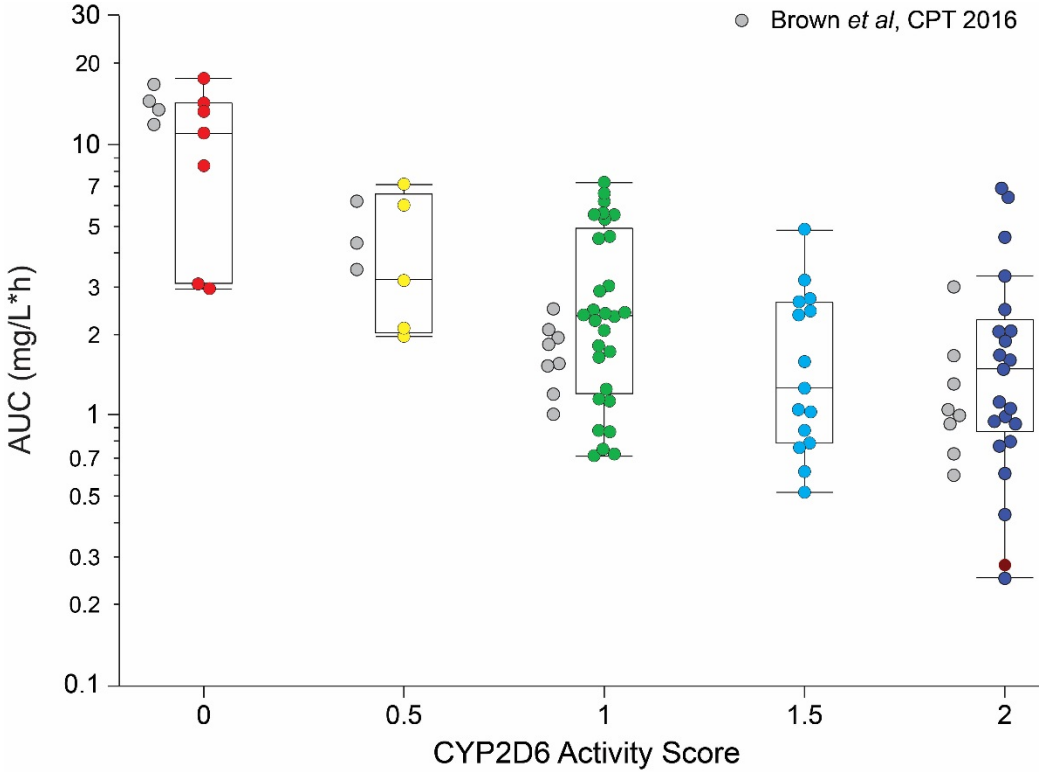


EM1 and EM2

- Variability relatively low in absolute terms
- Large (4-5-fold) relative variability
- Contribution of CYP2C19 (N-demethylation)
- Other sources?

Sources of Within-Genotype Variability: Virtual Child Project

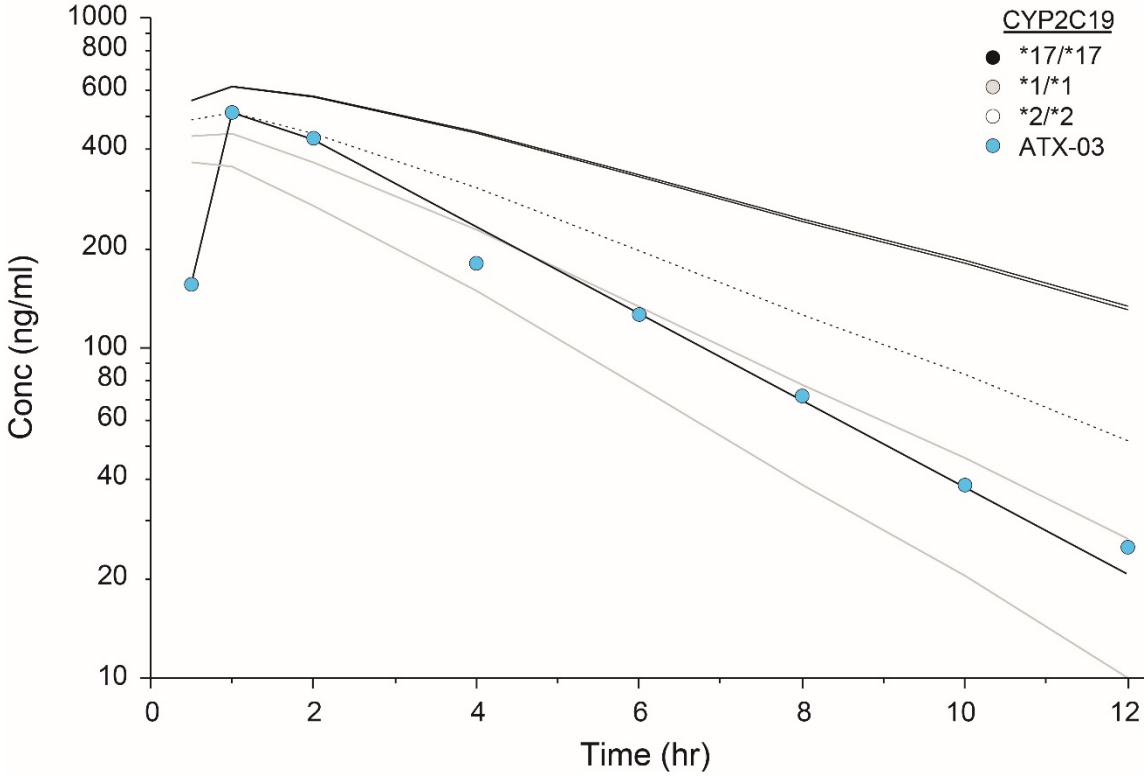
- Pediatric liver samples (n=78) genotyped for CYP2D6, and CYP contents determined by quantitative proteomics
- 4-OH, NDM, 2-OH metabolite formation determined at 10 uM ATX (~Vmax); Km for allelic variants estimated from HLMs and literature
- Virtual children created using Simcyp v15; 0.5 mg/kg dose
- *In vivo* within-genotype variability confirmed *in vitro*
- NDM and 2-OH pathways increase in importance with decrease in CYP2D6 (PM: r^2=0.977, p<0.0001)



Dinh, ASCPT 2017, abstract PT-009

Sources of Within-Diplotype Variability: Virtual Child Project

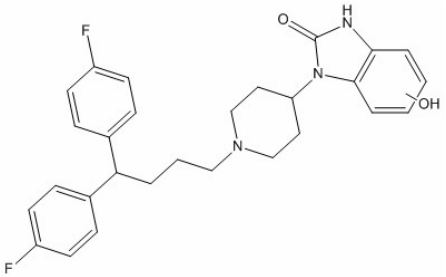
- *CYP2D6*1/*41* participant in validation PK study
- N=5 pediatric liver samples with same *CYP2D6*1/*41* genotype
- ATX PK simulated (Simcyp v15) for each “virtual child”, fixing age (15.3 y) height (166 cm), and weight (58.3 kg)
- 4.4-fold range of ATX AUC values (geo mean, n=100) for same CYP2D6 genotype and 50 mg dose
- AUC correlated with 4-OH formation (r^2=0.905, p=0.013), but not NDM or 2-OH; CYP2D6 protein (r^2=0.639, p=0.103)

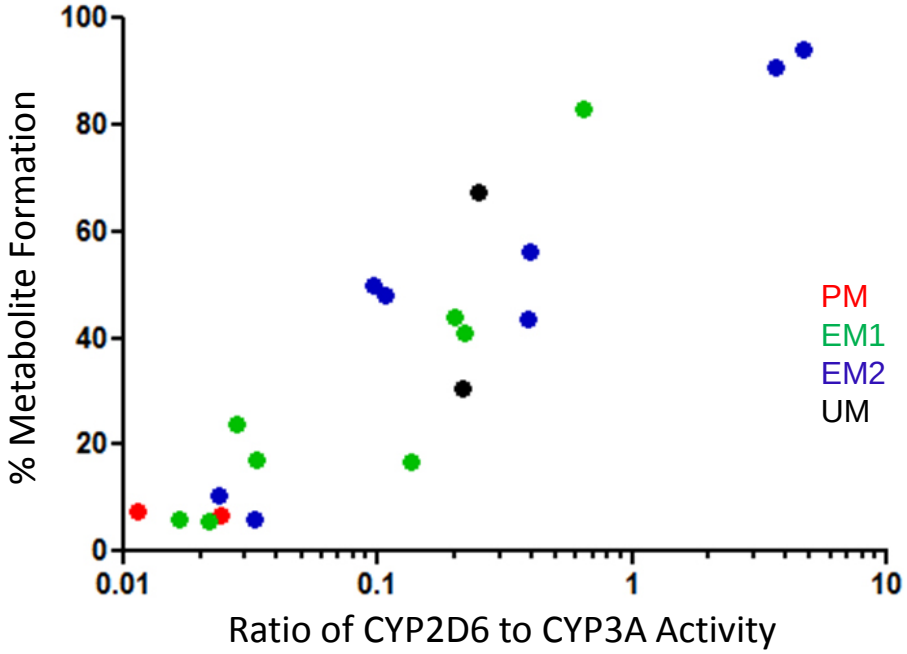


Dinh, ASCPT 2017, abstract PT-009

Contribution of Competing/Secondary Pathways: Pimozide Biotransformation *In Vitro*

- Antipsychotic used to treat Tourette syndrome
- CYP2D6 warning in label (PGx, DDI)
- Pediatric PGx dosing
- CYP2D6 pathway not characterized
- Ring-hydroxylated metabolite formed by CYP2D6
- Increases in abundance as CYP2D6/CYP3A4 ratio increases





Rompca *et al.* 2016 PAS Annual Meeting, [Abstract 2832.287]

Potential Importance of Competing Pathways

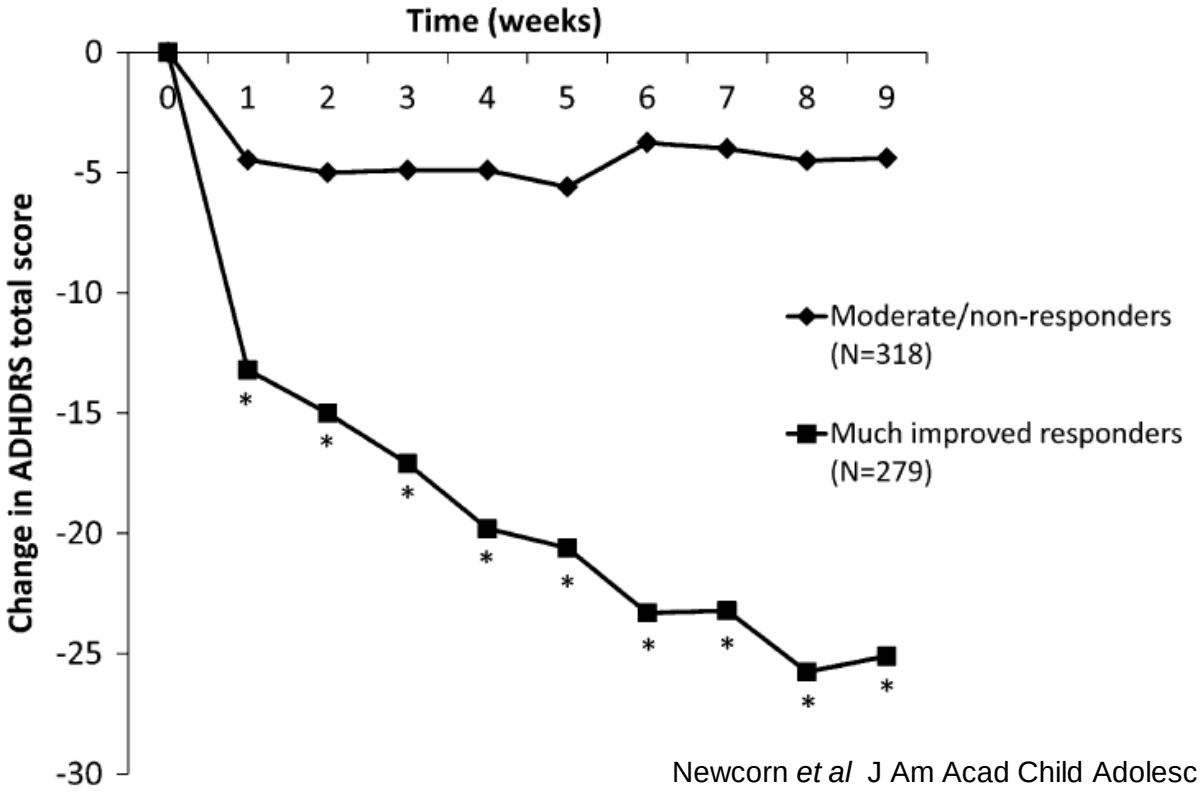
- Tendency to focus on magnitude of effect of genetic variation in primary pathway of elimination
- Value is greatest when polymorphic pathway is responsible for 100% of drug clearance
- For individual patients, alternative pathways increase in importance when primary pathway is absent (PMs), or compromised (IMs)
- More comprehensive approach required
- For CYP2D6 substrates, like pimozide, PGx-based dosing guidelines should consider role of ontogeny and genetic variation in competing pathways (*e.g.,* CYP3A4)

Implementing Precision Therapeutics in Children

“The difficulty lies not so much in developing new ideas as in escaping from old ones.”

- John Maynard Keynes

Precision Therapeutics for Children: Variability in Clinical Response to Atomoxetine



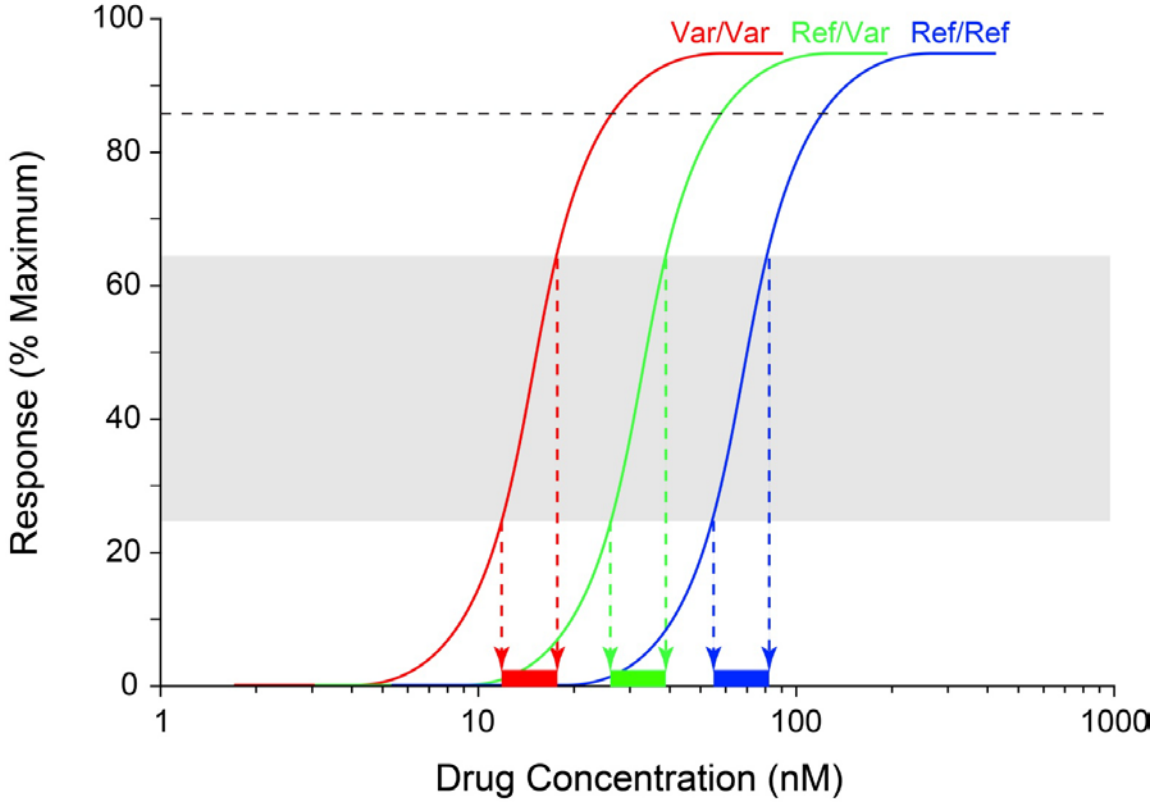
Newcorn *et al* J Am Acad Child Adolesc Psych 2009; 48:511-518

Implications of Focus on Variability in Response at the Target(s) of Drug Action

- With current dosing regimens, different drug phenotypes generally can be ascertained in the treated population (“responders”; “non-responders”; “partial responders”)
- For “non-responders”
  - Inadequate exposure?
  - Low level expression or non-functional drug target?
- What drug exposure is required to elicit the desired response for a given drug target genetic variant?
- For that same individual, what dose is required to provide that exposure?
- Need for tools for individualization of doses to achieve desired exposure

Response → Exposure → Dose

Effect of Variability in Drug Target Expression



Different drug exposures are required to achieve equivalent drug responses, depending on level of drug target expression (or function)

Atomoxetine Prototype

Atomoxetine Dosing Procedure

Body Weight (kg)

50

Height (cm)

125

Gender

- (●) Male
- ( ) Female

Genetic Metabolizer

- ( ) Poor Metabolizer
- ( ) Intermediate Metabolizer
- (●) Extensive Metabolizer 1
- ( ) Extensive Metabolizer 2

Obesity Status

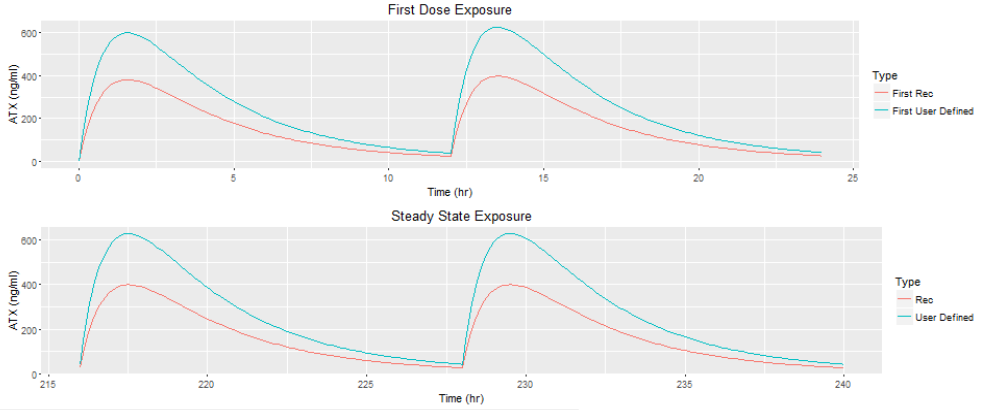
- ( ) Obese
- (●) Not Obese

User Defined (mg)

60

Dosing Regimen

- ( ) QD



	Dose Type	Dose (mg)	AUC (ng*hr/ml)	Cmax (ng/ml)	Tmax (hr)
1	User Defined (SS)	60.00	6481.54	628.57	229.50
2	Model Recommend (SS)	38.18	4124.66	400.00	229.50
3	User Defined (1st)	60.00	6265.28	624.58	13.50
4	Model Recommend (1st)	38.18	3987.04	397.47	13.50

Getting the Tools into the Right Hands

Busulfan Decision Support Tool

Engaging Patients and Families

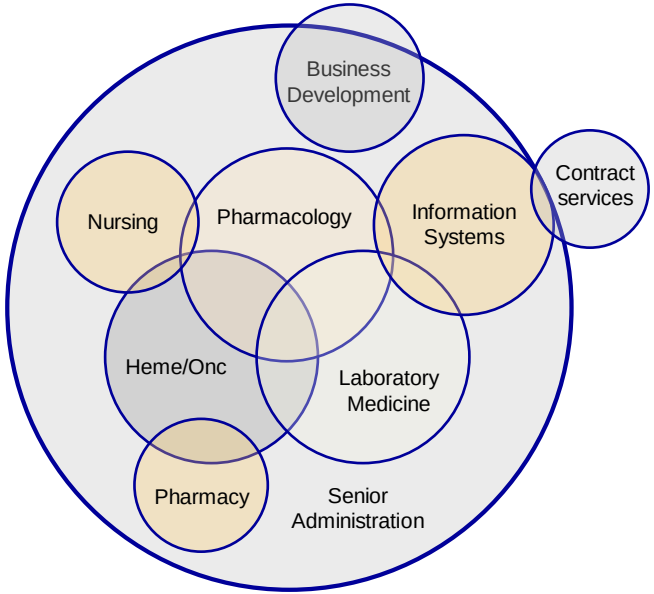
Decision Support Tools for Precision Medicine

Successful DSTs:

- Developed with local users
- Available at time/location of decision making
- Integrate within the charting/order entry system
- Do not require additional data entry
- Justify decision with evidence
- Provide a recommendation

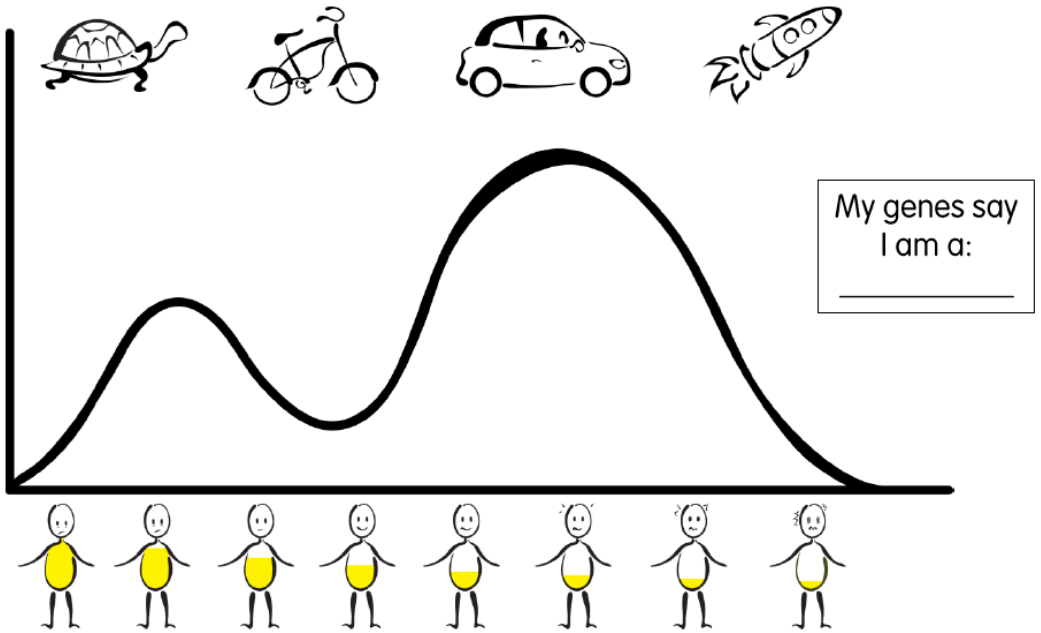
Process

1. Requirements analysis
2. Prototype and design
3. Unit and integration testing
4. Functional testing
   - Structured cognitive walkthroughs
   - Usability testing



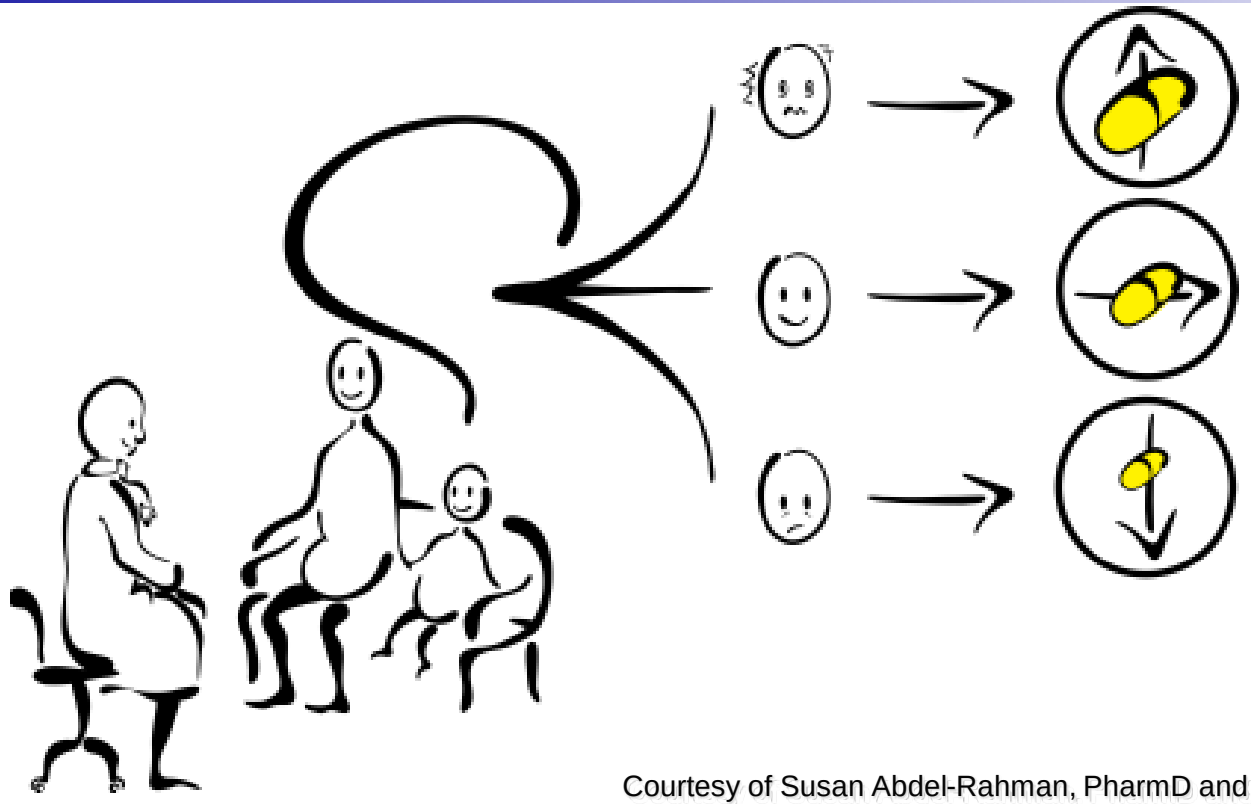
Courtesy of Susan Abdel-Rahman, PharmD

Engaging Patients and Families



Courtesy of Susan Abdel-Rahman, PharmD and Jean Dinh, PharmD, PhD

Engaging Patients and Families



Courtesy of Susan Abdel-Rahman, PharmD and Jean Dinh, PharmD, PhD

Engaging Patients and Families

Courtesy of Susan Abdel-Rahman, PharmD and Jean Dinh, PharmD, PhD

Opportunities for Pediatric Precision Therapeutics

- Create new knowledge in the patient population that will benefit
- Establish dose-exposure relationship
- Focus on “right exposure”, rather than “right dose”, to investigate role of variability in drug targets
- Incorporate metabolomic strategies as measures of drug target variability, disease severity, response to treatment …
- Develop tools with end-users in mind
- Validate, validate, validate
- Role for community participation as “naturalistic” environment to guide real-life implementation

Take Home Message

Genomic- and

Ontogeny-

Linked

Dose

Individualization and

c**L**inical

Optimization for

Kid**s**

- "Not too big, not too small … the dose of medication that is 'just right' for your child"
- Takes into consideration those factors that make each child unique
  - Genome
  - Stage of development (ontogeny)
- "Response → Exposure → Dose" paradigm
- Focus on the individual's drug target genotype, determine the right exposure for that genotype, and the dose required to achieve the desired exposure

Complex Problems, Multidisciplinary Teams

Pharmacogenetics:
- Andrea Gaedigk, PhD
- Roger Gaedigk, PhD

In Vitro/In Vivo Phenotyping:
- Robin Pearce, PhD

Gene Regulation:
- Carrie Vyhlidal, PhD

Analytical chemistry:
- Leon van Haandel, PhD

Quantitative pharmacology:
- Susan Abdel-Rahman, PharmD
- Chelsea Hosey, PhD

Faculty:
- Ben Black, MD
- Jen Goldman, MD
- Bridgette Jones, MD
- Tamorah Lewis, MD, PhD
- Valentina Shakhnovich, MD
- Stephani Stancil, APRN
- Jaszianne Tolbert, MD
- Jon Wagner, DO

Trainees:
- Jean Dinh, PharmD, PhD
- Matt McLaughlin, MD

Collaborators:
- Bhagwat Prasad, PhD (U. Wash.)
- Alex Galetin, PhD (U. Manchester)
- Rima Kaddurah-Daouk, PhD (Duke)
- Brooke Fridley, PhD, (Moffitt)
- Amin Rostami , PharmD, PhD
- Adam Darwich, PhD (U. Manchester)
- Trevor Johnson, Simcyp