Clinical Implementation of Precision Therapeutics in Children

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Disclosures

- In the past 12 months, I have no financial relationships with the manufacturer(s) of any commercial product(s) and/or providers of commercial services discussed in this presentation
- Atomoxetine PK Study supported by R01HD058556: Exogenous and endogenous biomarkers of CYP2D6 variability in pediatrics (JS Leeder and Y Lin)
  - PK analysis: Jacob Brown, PharmD; Sue Rahman, PharmD
  - CYP2D6 Genotyping: Andrea Gaedigk, PhD
  - Analytical method development: Leon van Haandel, PhD

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

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R01 HD081299: PKPK prediction of ontogeny mediated alteration in drug elimination (B Prasad)

U54 HD090258: **G**enomic- and **O**ntogeny-**L**inked **D**ose **I**ndividualization and c**L**inical **O**ptimization for **K**ids: GOLDILOKs; Specialized Center for Research in Pediatric and Developmental Pharmacology (Leeder, PI)

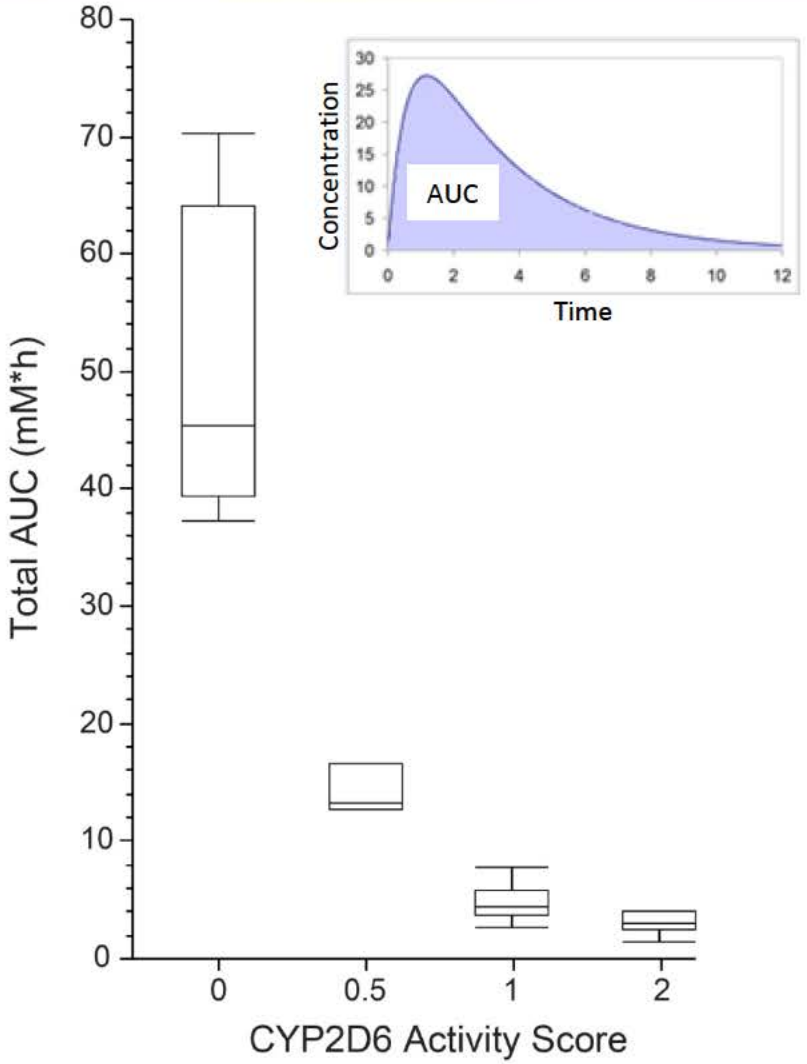
Goals of Presentation

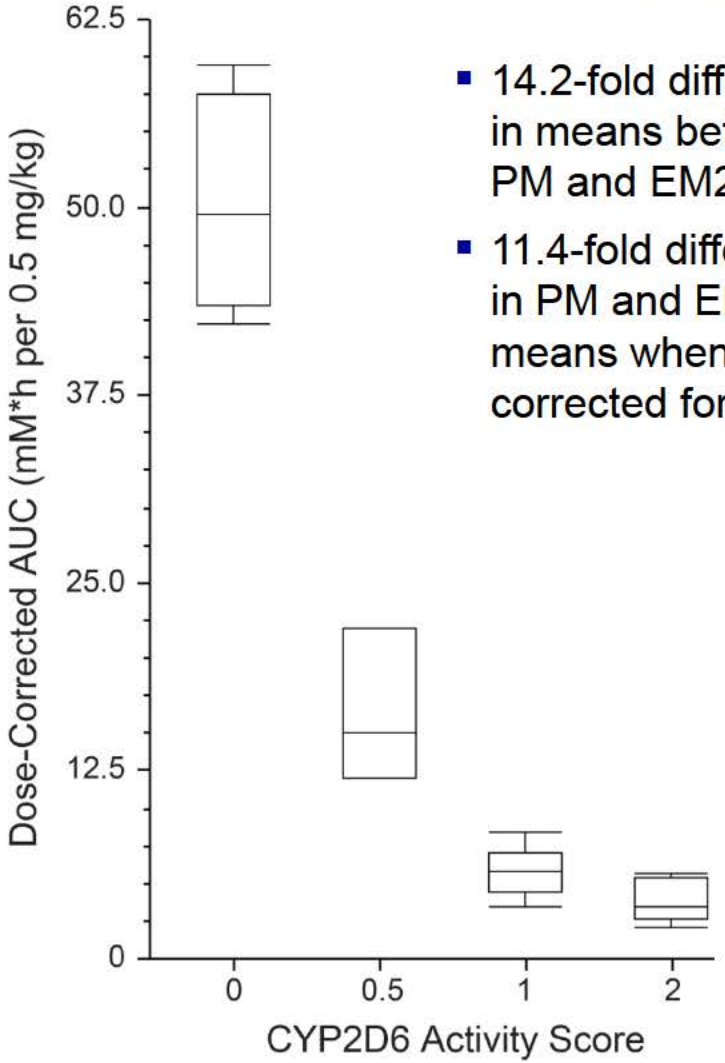
- Describe three challenges facing clinical implementation of pharmacogenomics information in pediatrics
  1. Application of “population” data to “individual” children
  2. Focus on (primary) polymorphic pathway
  3. Limitation of extrapolating/scaling adult data to children
- Differentiate between the importance of the “right exposure”, rather than the “right dose”, to better understand inter-individual variability in the response to a medication
- Discuss alternative study designs to efficiently generate required data to inform regulatory and clinical decisions

1. Application of “population” data to inform decisions at the level of “individual” patients

Relevance of "Population" Data to "Individuals": Comparison of "Mean" Atomoxetine AUC

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





- 14.2-fold difference in means between PM and EM2 group
- 11.4-fold difference in PM and EM2 means when corrected for dose

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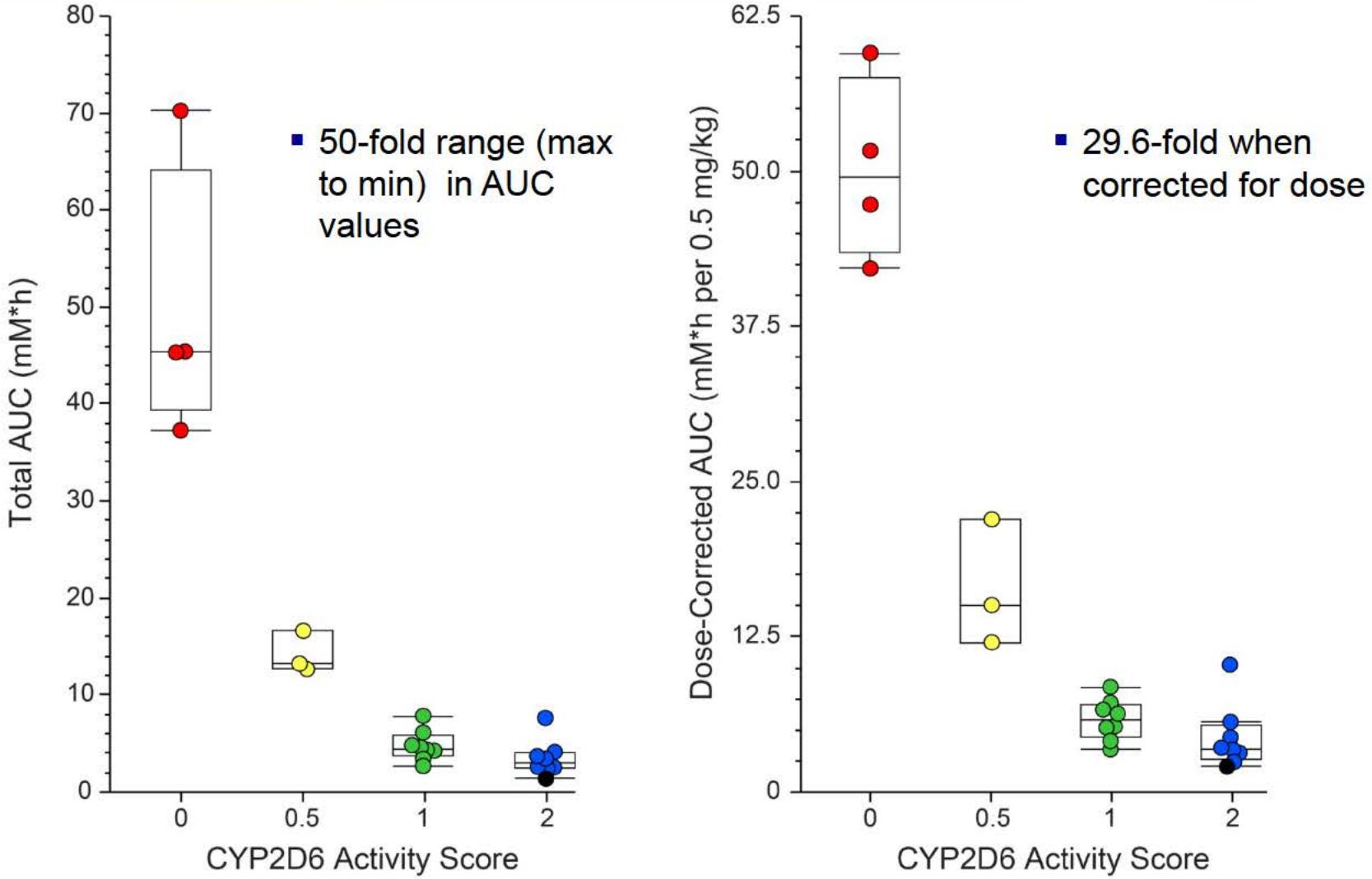


Application of Population Data to Inform Clinical Decisions for Individual Patients

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

ADRA2
rs1800544 (-1291 C>G)

Journal of Neural Transmission

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 Population Data to Inform Clinical Decisions for Individual Patients

OPEN

ADRA2
rs1800544 (-1291 C>G)

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%

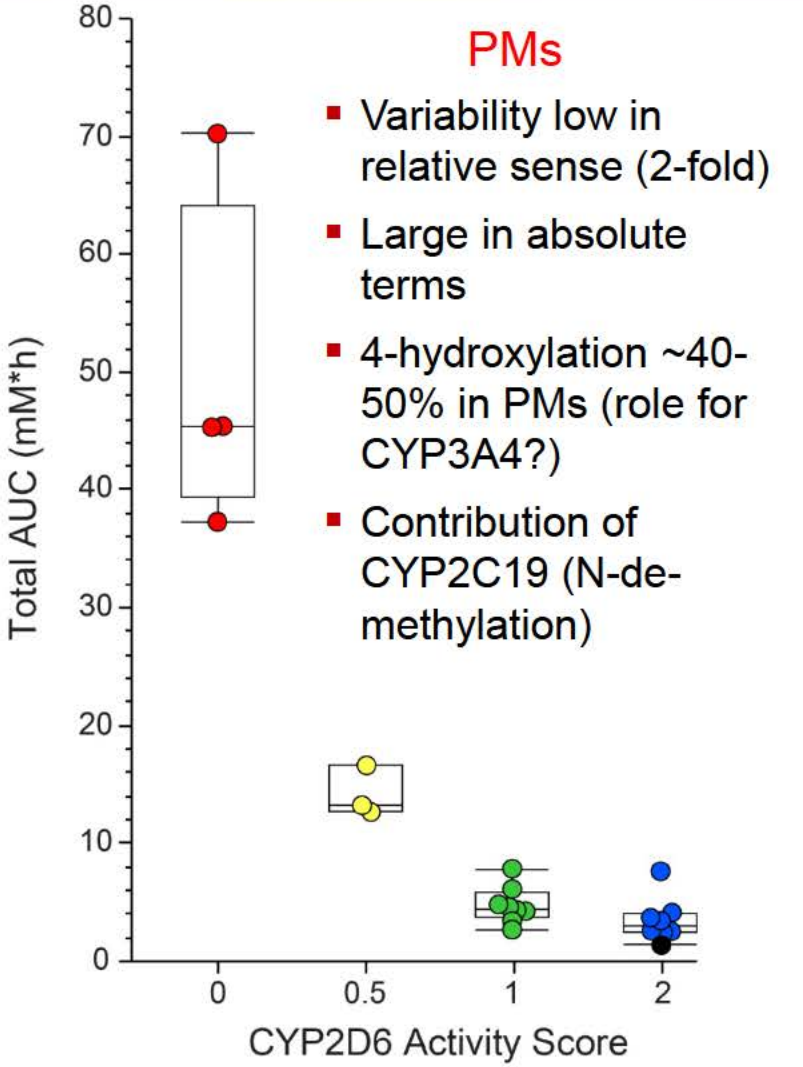
Implications of Using "Population" Data to Inform Clinical Decisions for Individuals

- 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
- Genotype data underlying commercial PGx testing are derived from genetic association studies, often involving small "populations"
- Application/extrapolation to individual patients is limited
  - Sampling errors
  - Actual condition being studied
  - Limited (if any) prospective validation

2. Competing pathways as sources of inter-individual variability in the dose-exposure relationship

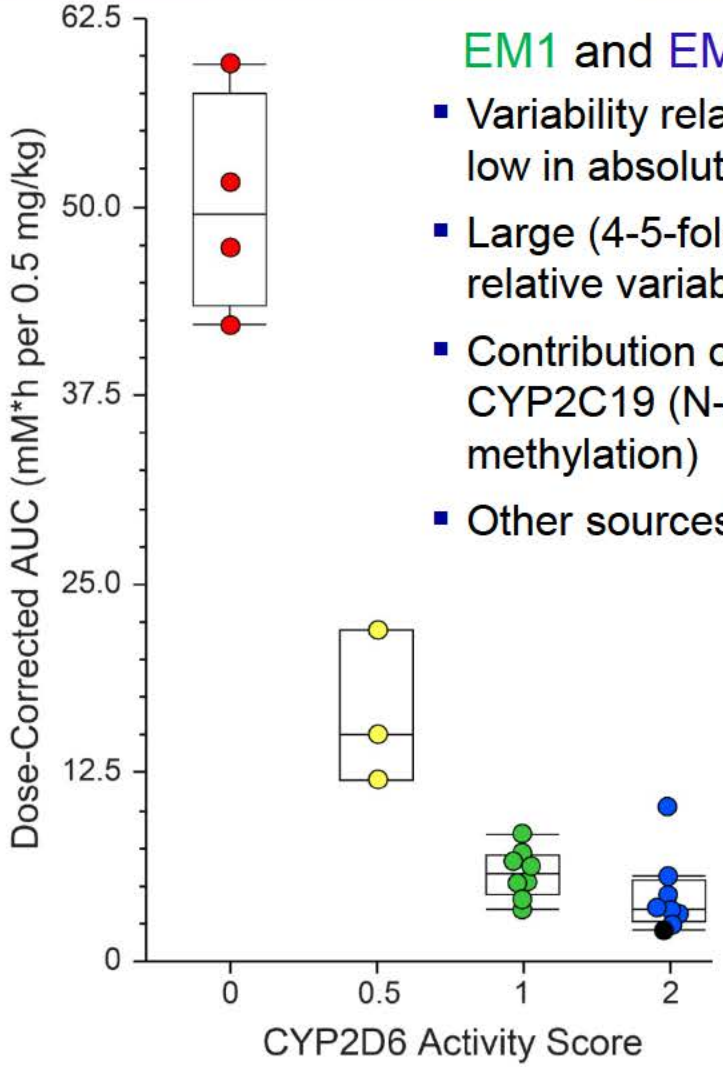
Contribution of Competing/Secondary Pathways: Intra-Genotype Variability in Atomoxetine AUC

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



PMs

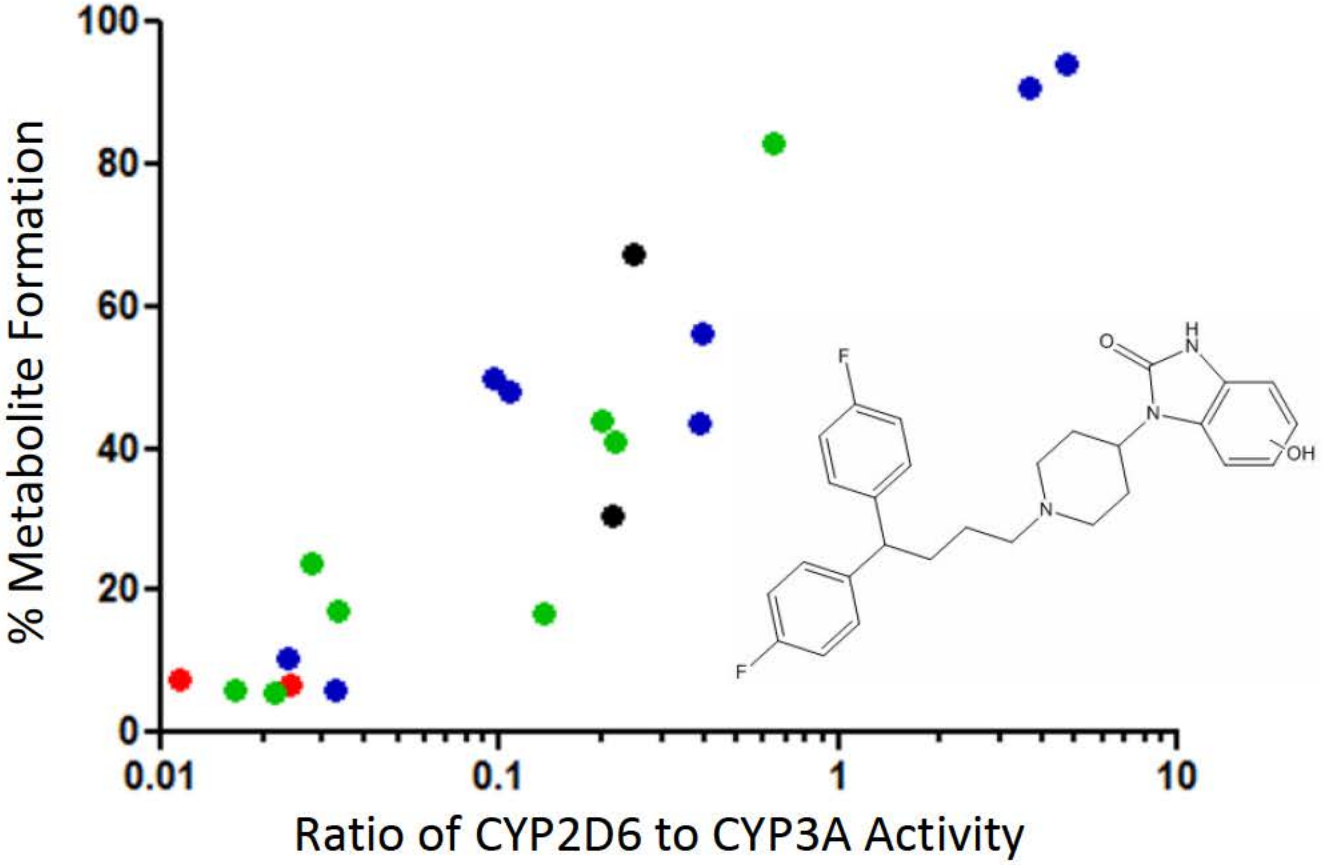
- Variability low in relative sense (2-fold)
- Large in absolute terms
- 4-hydroxylation ~40-50% in PMs (role for CYP3A4?)
- Contribution of CYP2C19 (N-de-methylation)



EM1 and EM2

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

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



- Antipsychotic used to treat Tourette syndrome
- CYP2D6 warning in label (PGx, DDI)
- Pathway not characterized
- Ring-hydroxylated metabolite formed by CYP2D6

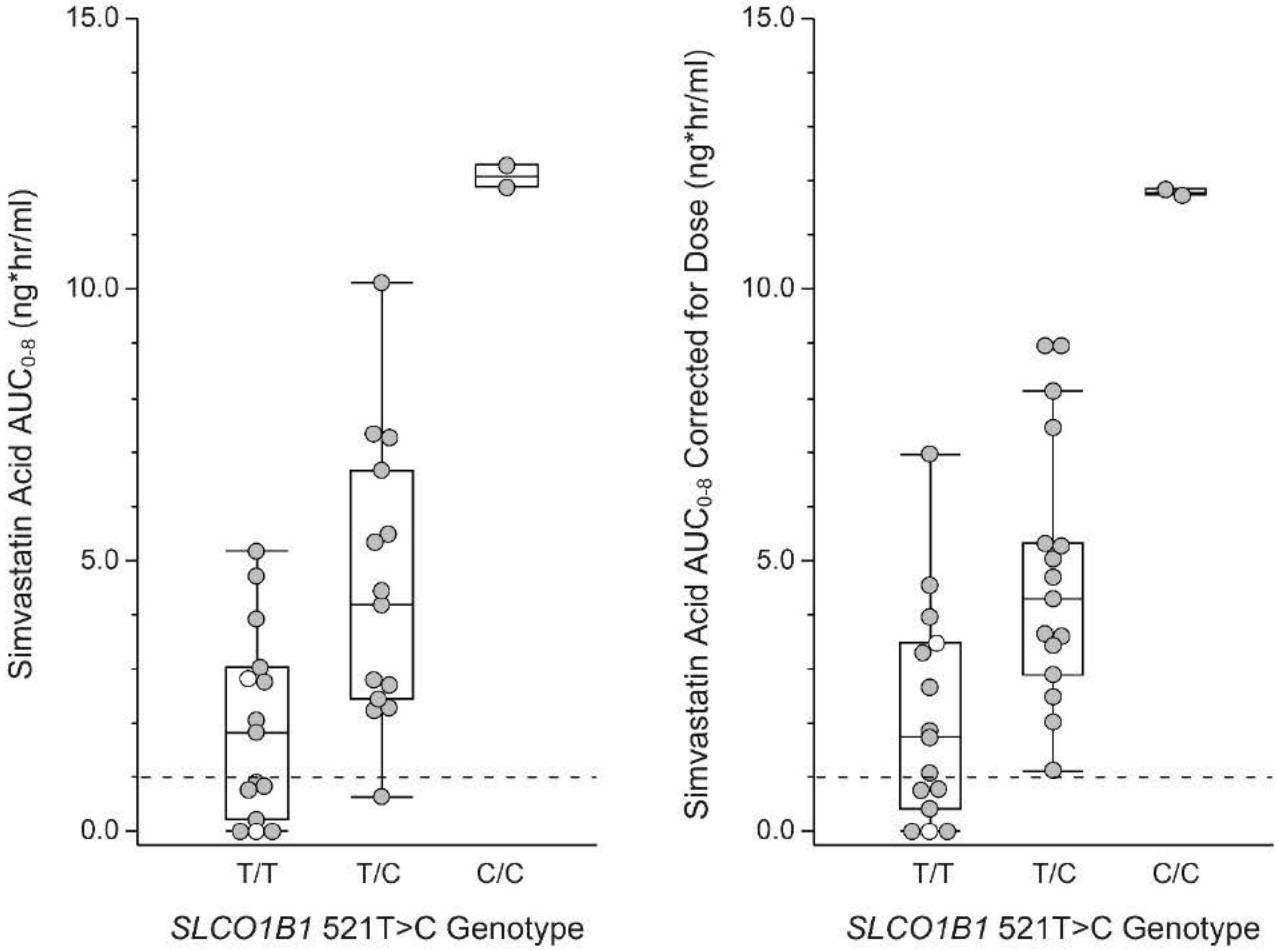
Rompca *et al.* 2016 PAS Annual Meeting, [Abstract 2832.287]

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)
- For CYP2D6 substrates, like pimozide, PGx-based dosing guidelines should consider role of ontogeny and genetic variation in competing pathways (*e.g.*, CYP3A4)

3. Extrapolation of adult data to children

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
- Sampling strategy based on adult experience inadequate duration
- Undetectable SVA concentrations in 25% of subjects

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

4. Concept of “Right Exposure”

Variability in Drug Response

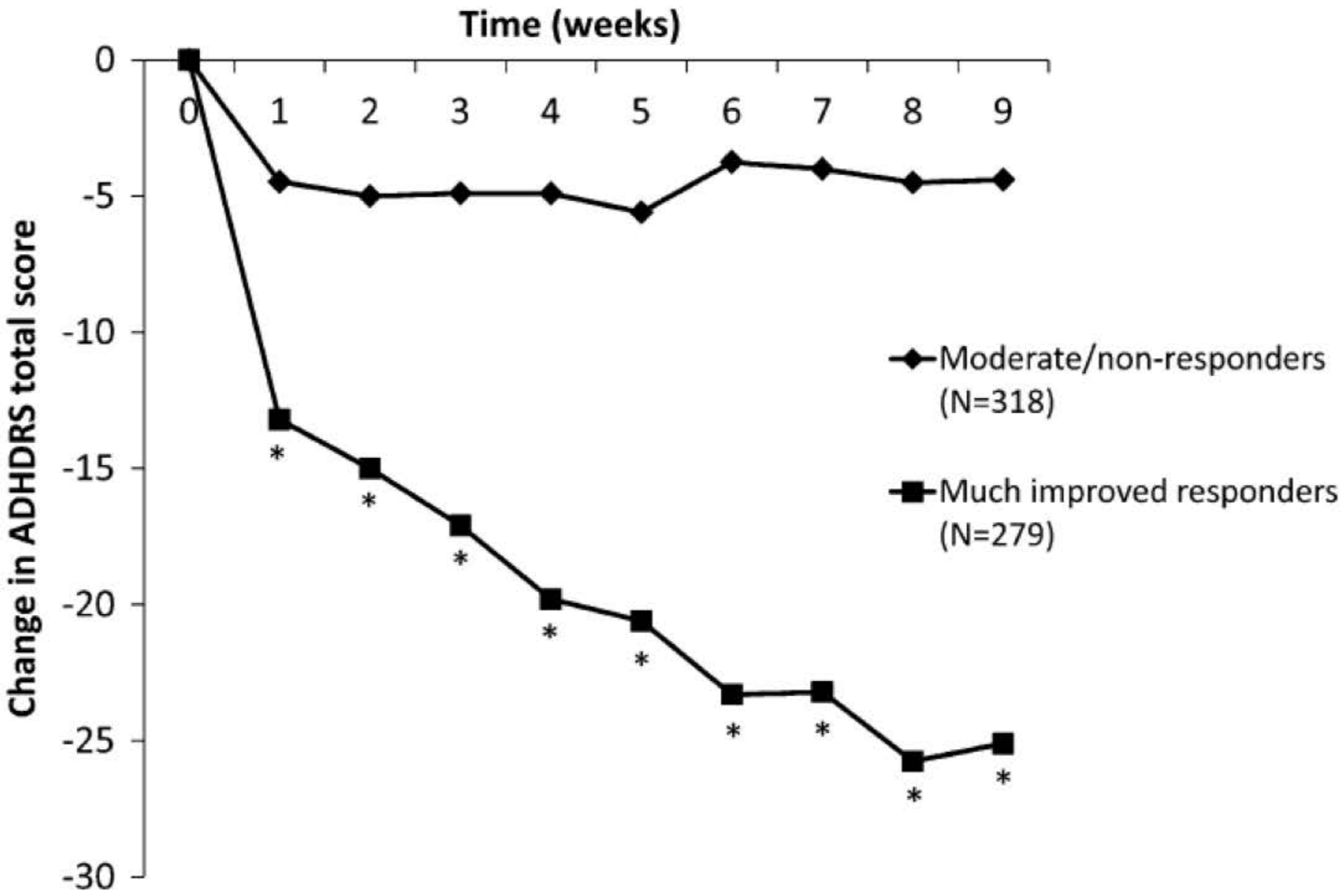
~~Dose~~ → ~~Exposure~~ → ~~Response~~

Response → Exposure → Dose

"The difficulty lies not so much in developing new ideas as in escaping from old ones"

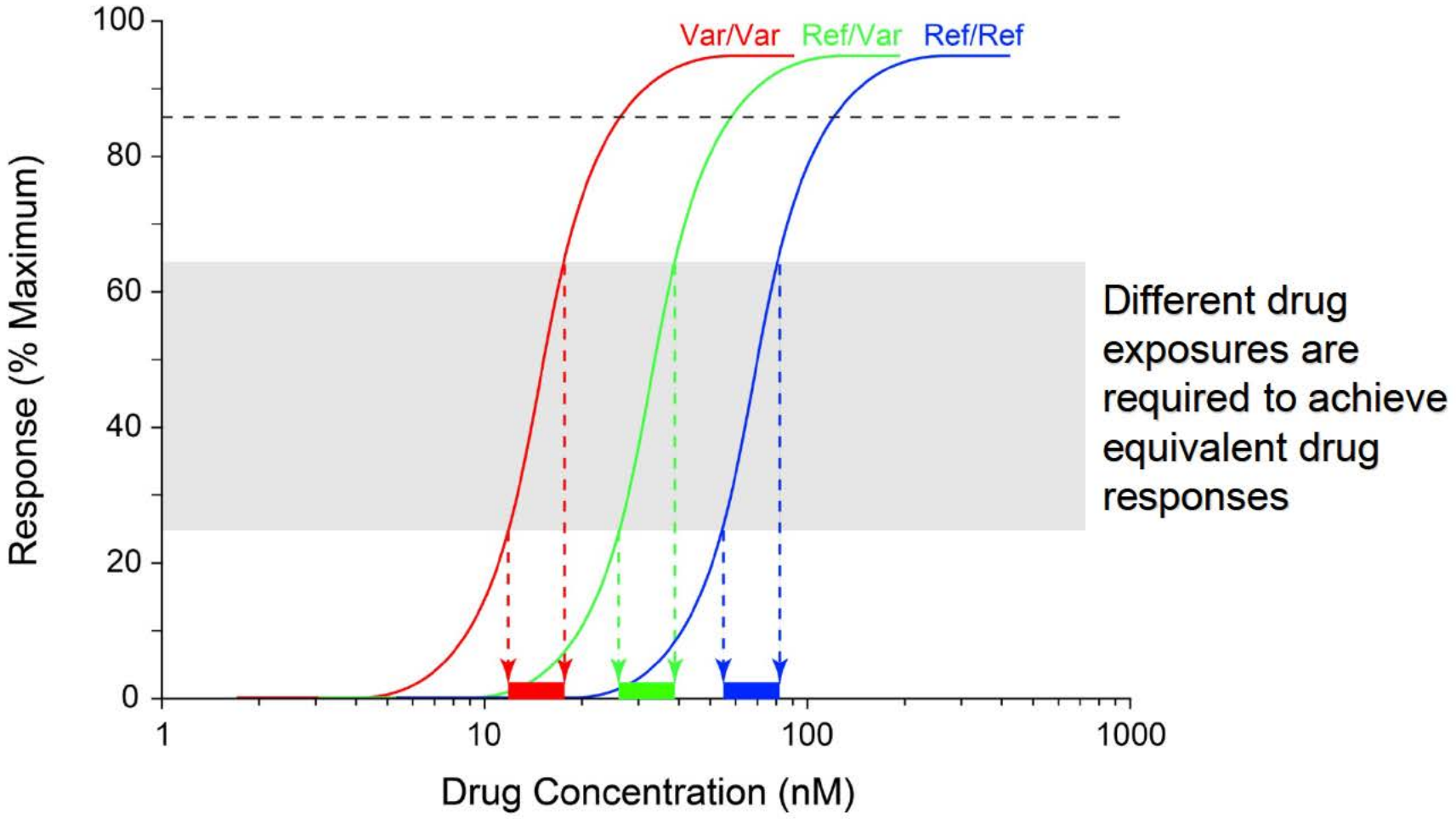
- John Maynard Keynes

Variability in Clinical Response to Atomoxetine



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

Genetic Variability in Drug Target Contributes to Variability in Response



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?

5. Alternative study designs

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

Genotype-Stratified Pharmacokinetic Study Designs

- Cohort of patients for which genotype is known, or can be determined from existing biorepository of genomic DNA
- Combination patient registry and biorepository
  - Parental permission and participant assent to be contacted for future studies
- Selected of participants based on genotype; *e.g. CYP2D6*
  - 2 (or more) functional alleles ("EM2; UM")
  - 1 functional allele ("EM1")
  - 0.5 functional alleles ("IM")
  - 0 functional alleles ("PM")
- "Extremes" of dose-exposure relationship for a given population more likely to be captured with a relatively small sample size

Genotype-Stratified Pharmacodynamic (PD) Study Designs

- Based on hypothesis that different drug target genotypes require different drug exposures to elicit the same clinical response
  - Regulatory region variants affect how much target may be present
  - Variants in protein-coding regions affect how target function
- Stratification of participants by drug target genotype
- Requires appropriate (validated) models to individualize doses to achieve a target exposure based on either Cmax or AUC
  - Control the dose-exposure relationship to minimize possibility that absence of response is not due to inadequate exposure
- Escalation of exposure at intervals determined by pharmacokinetic properties and clinical response to assess the exposure-response relationship

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

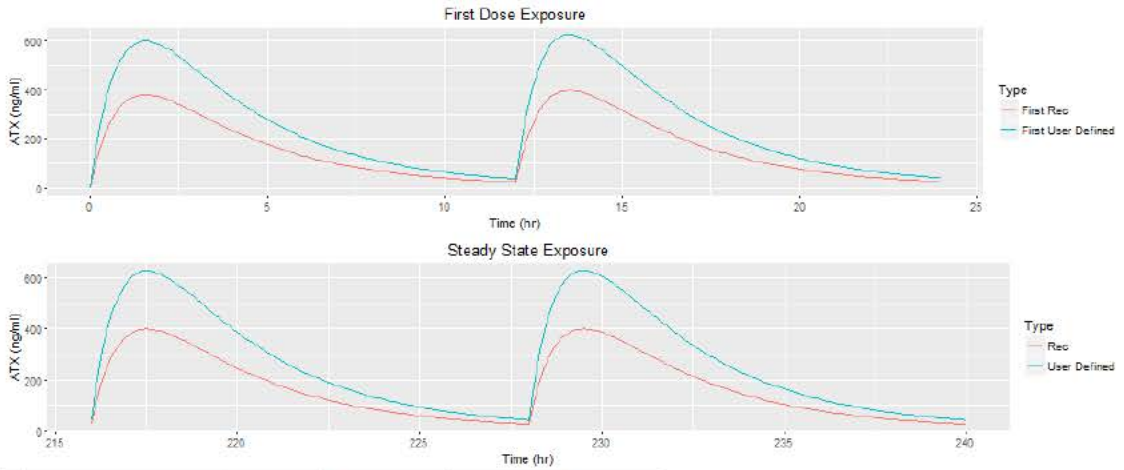
- ( ) Obese
- (●) Not Obese

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

Precision Therapeutics for Children: "GOLDILOKs"

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

Conclusions

- To address the challenges facing clinical implementation of pharmacogenomics information in pediatrics …
  1. Prospective validation of population-based genotype data for clinical application to "individual" children
  2. Detailed characterization of all pathways of drug clearance
  3. Generate data in pediatric population in which drug will be used
- If the goal is drug response, investigate the role of ontogeny and genetic variation of drug targets
  - Proximal phenotype for CYPs and drug metabolizing enzymes is metabolite formation and systemic drug exposure, not drug response
- Genotype-stratified PK study designs allow for effect of genotype on dose-exposure relationship to be assessed in a relatively small cohort
- Genotype-stratified PD study designs require means of controlling the dose-exposure relationship to assess exposure-response relationship

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

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- Tao Lin, MS
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- Bridgette Jones, MD
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- Valentina Shakhnovich, MD
- Stephani Stancil, APRN
- Jaszianne Tolbert, MD
- Jon Wagner, DO

APPEARS THIS WAY ON ORIGINAL