Addressing Knowledge Deficits in Pediatric PGx: The GOLDILOKs Initiative at Children's Mercy Hospital

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Grant Support

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

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)

Knowledge Deficits and Challenges for Pediatric PGx

- Clinically useful guidance regarding the Dose → Exposure relationship as a function of genotype (and ontogeny) in pediatric patients reflective those who will be treated with the medication
- The “unknown unknowns”: the limitation of extrapolating/scaling adult data pharmacogenomics data to children
- Addressing variability in drug response
- Considering pediatric patients as individual children

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?

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Atomoxetine Dosing Guidance (Product Monograph)

5.12 Laboratory Tests

Routine laboratory tests are not required.

CYP2D6 metabolism — Poor metabolizers (PMs) of CYP2D6 have a 10-fold higher AUC and a 5-fold higher peak concentration to a given dose of STRATTERA compared with extensive metabolizers (EMs). Approximately 7% of a Caucasian population are PMs. Laboratory tests are available to identify CYP2D6 PMs. The blood levels in PMs are similar to those attained by taking strong inhibitors of CYP2D6. The higher blood levels in PMs lead to a higher rate of some adverse effects of STRATTERA *[see Adverse Reactions (6.1)]*.

5.13 Concomitant Use of Potent CYP2D6 Inhibitors or Use in patients who are known to be CYP2D6 PMs

Atomoxetine is primarily metabolized by the CYP2D6 pathway to 4-hydroxyatomoxetine. Dosage adjustment of STRATTERA may be necessary when coadministered with potent CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, and quinidine) or when administered to CYP2D6 PMs. *[See Dosage and Administration (2.4) and Drug Interactions (7.2)]*.

Atomoxetine Dosing Guidance (Product Monograph)

2 DOSAGE AND ADMINISTRATION

2.1 Acute Treatment

Dosing of children and adolescents up to 70 kg body weight — STRATTERA should be initiated at a total daily dose of approximately 0.5 mg/kg and increased after a minimum of 3 days to a target total daily dose of approximately 1.2 mg/kg administered either as a single daily dose in the morning or as evenly divided doses in the morning and late afternoon/early evening. No additional benefit has been demonstrated for doses higher than 1.2 mg/kg/day *[see Clinical Studies (14)]*.

The total daily dose in children and adolescents should not exceed 1.4 mg/kg or 100 mg, whichever is less.

2.4 Dosing in Specific Populations

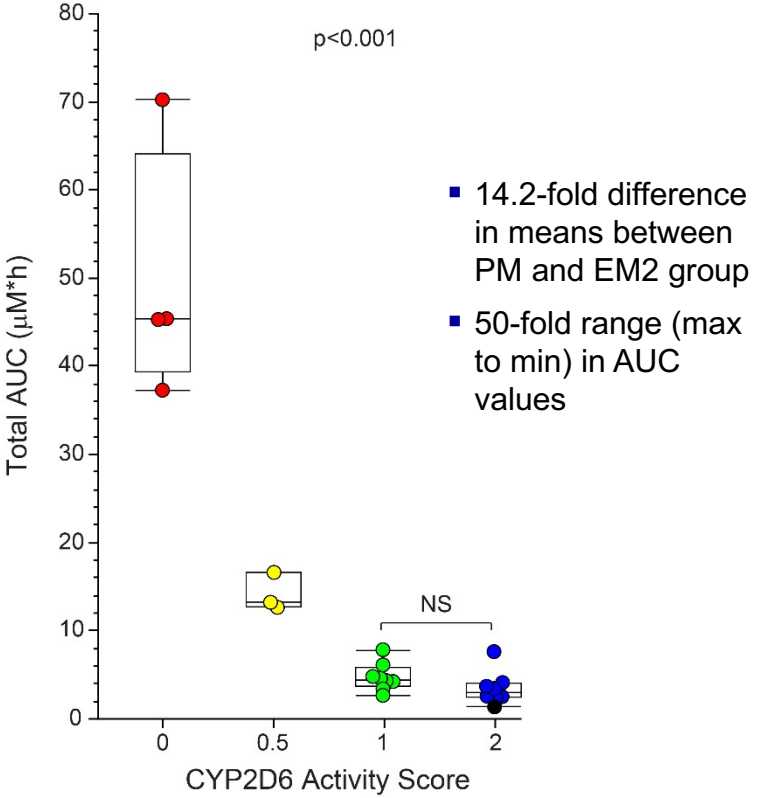
Dosing adjustment for use with a strong CYP2D6 inhibitor or in patients who are known to be CYP2D6 PMs — In children and adolescents up to 70 kg body weight administered strong CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine, or in patients who are known to be CYP2D6 PMs, STRATTERA should be initiated at 0.5 mg/kg/day and only increased to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.

In children and adolescents over 70 kg body weight and adults administered strong CYP2D6 inhibitors, e.g., paroxetine, fluoxetine, and quinidine, STRATTERA should be initiated at 40 mg/day and only increased to the usual target dose of 80 mg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.

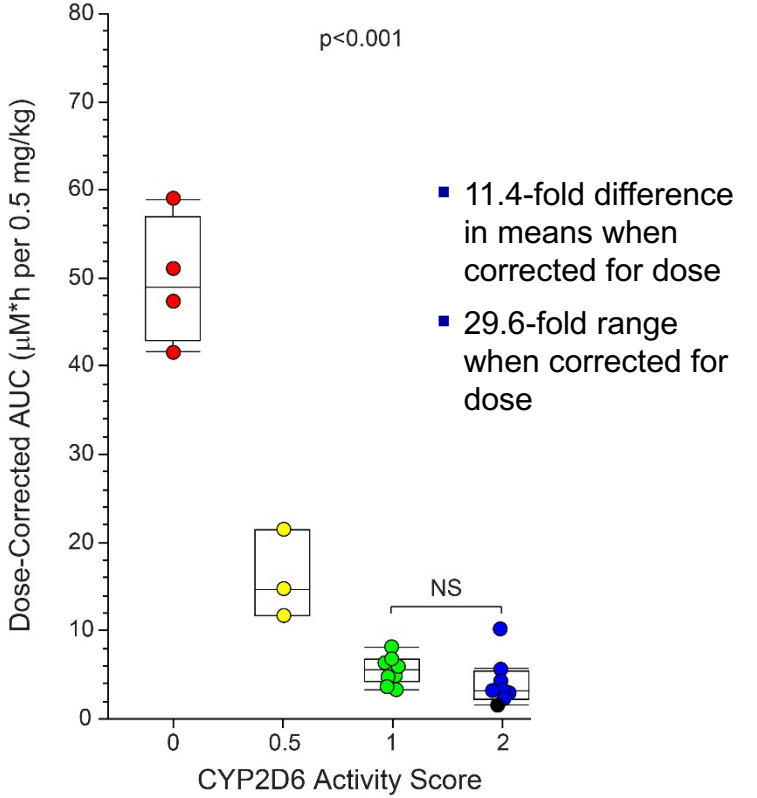
Population-based guidelines for regulatory purposes;
Limited value for patient-based individualization …

Effect of CYP2D6 Genotype on Dose-Exposure Relationship Individual Perspective

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



- 14.2-fold difference in means between PM and EM2 group
- 50-fold range (max to min) in AUC values



- 11.4-fold difference in means when corrected for dose
- 29.6-fold range when corrected for dose

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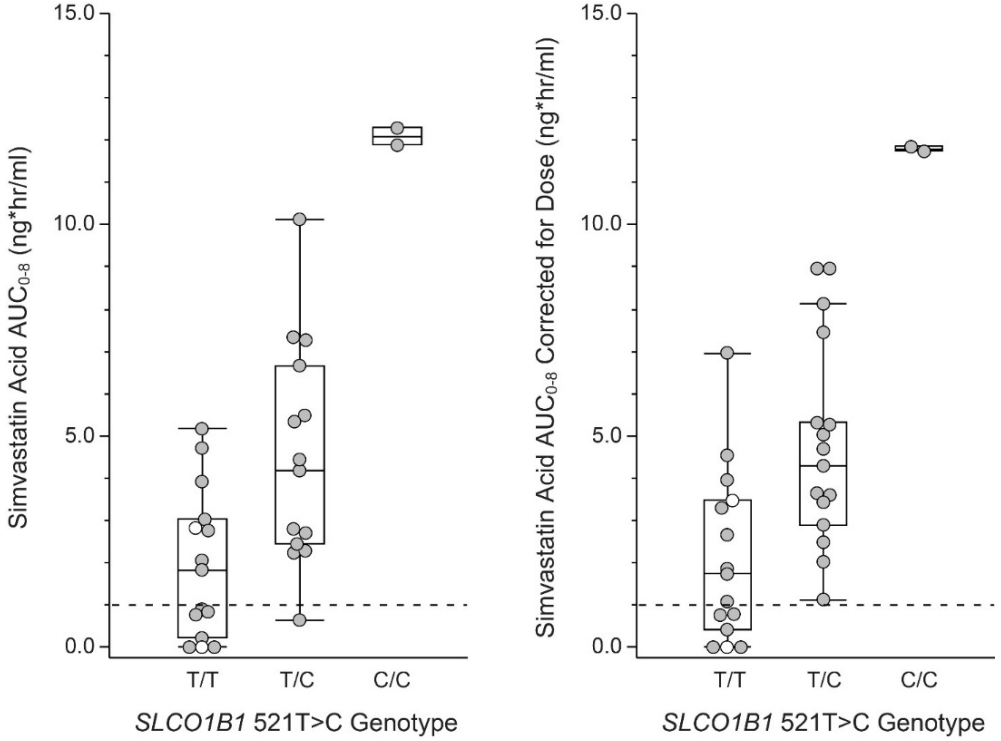
Extrapolation of Adult Data to Pediatrics: Genotype-Stratified PK Study of Simvastatin

- Hydrolysis of lactone to form active acid form
- Assumptions of rapid hydrolysis and CYP3A metabolism
- Genotype-phenotype associations in adults replicated, but magnitude of effect greater in children –CC *vs* TT AUC ratio 6.1-fold *vs* 3.2-fold (adult)
- Sampling strategy based on adult experience; inadequate duration
- 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)

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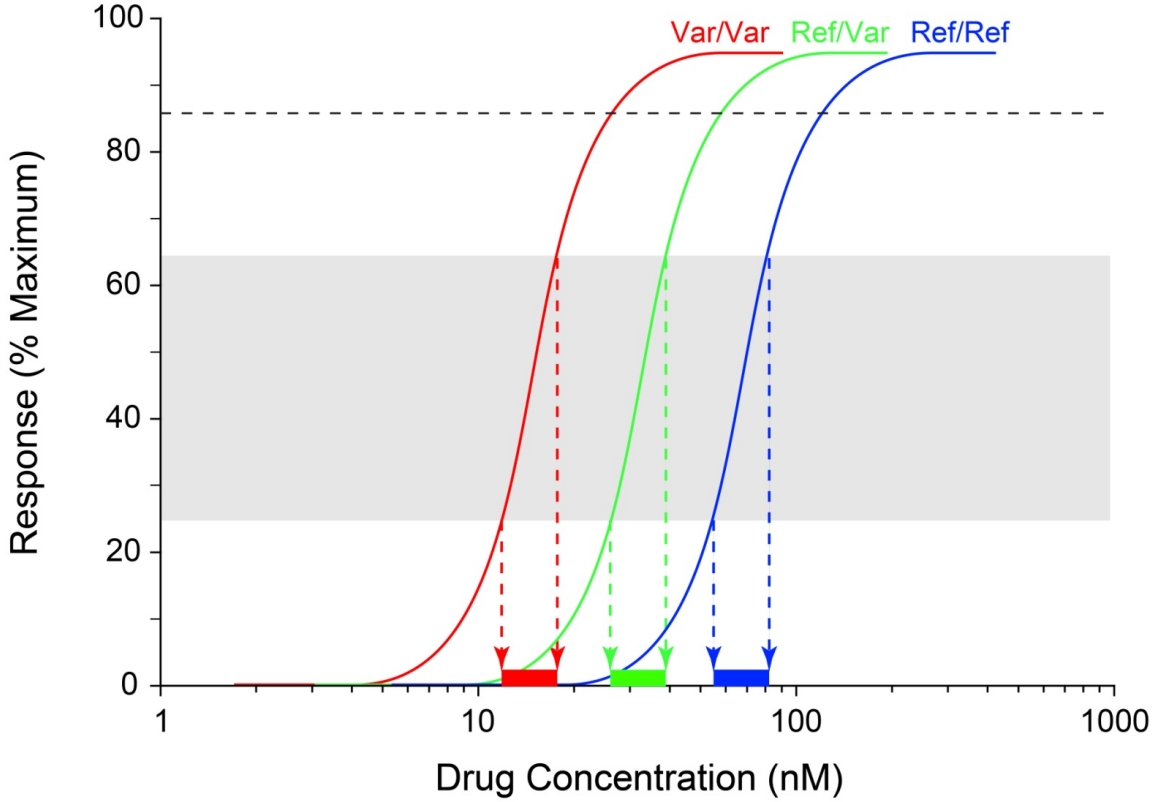
Implications of Focus on Variability in Response at the Target(s) of Drug Action

- 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)

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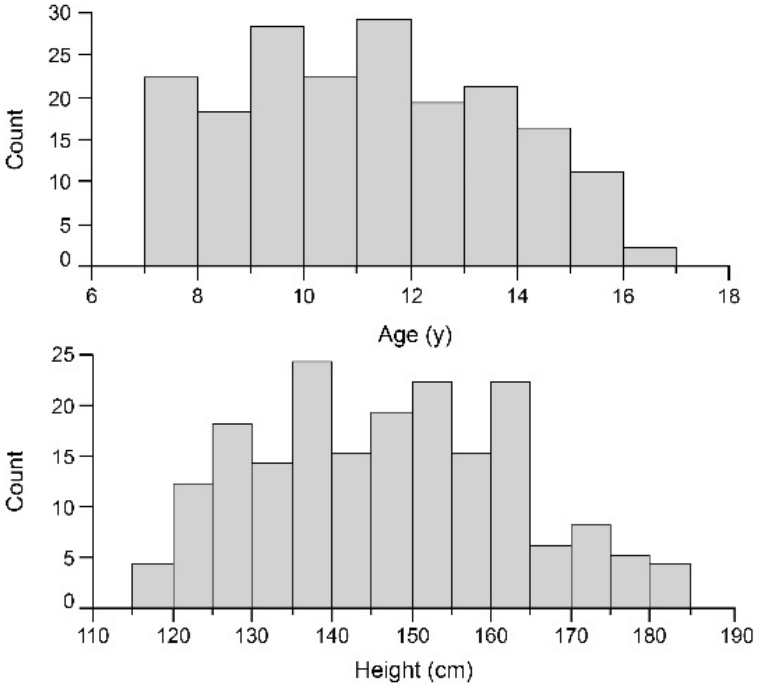
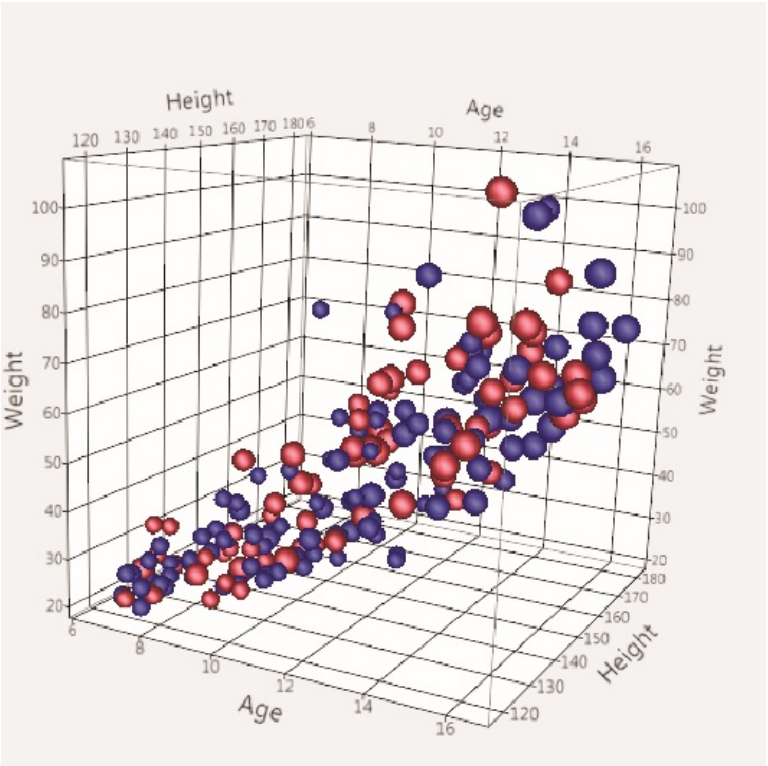
For Precision Therapeutics in Children, Think "Individual", Not "Population"





Take Home Message

Genomic- and

Ontogeny-

Linked

Dose

Individualization and

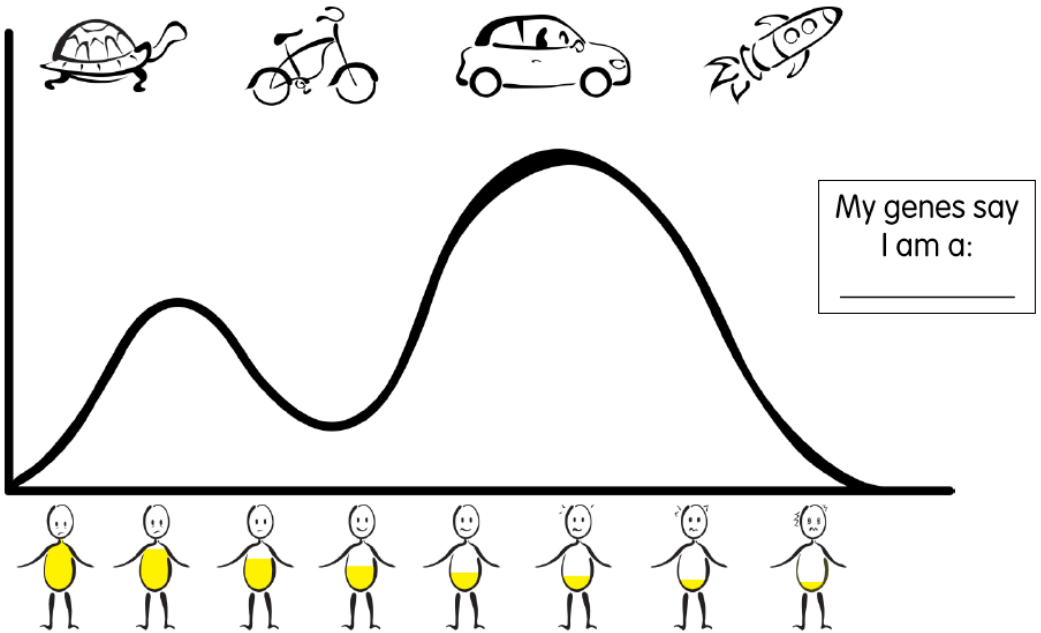
c**L**inical

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

Engaging Patients and Families



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

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:
- Mara Becker, MD, MSCE (Rheumatology
- Ben Black, MD (Development & Behavioral)
- Jen Goldman, MD (Infectious Diseases)
- Bridgette Jones, MD (Allergy & Immunology)
- Tamorah Lewis, MD, PhD (Neonatology)
- Valentina Shakhnovich, MD (Gastroenterology)
- Stephani Stancil, APRN (Adolescent Medicine)
- Jaszianne Tolbert, MD (Oncology)
- Jon Wagner, DO (Cardiology)

Trainees:
- Jean Dinh, PharmD, PhD
- Matt McLaughlin, MD (Rehab Medicine)

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- Lack of prospective validation of marketed pharmacogenetic tests

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%

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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

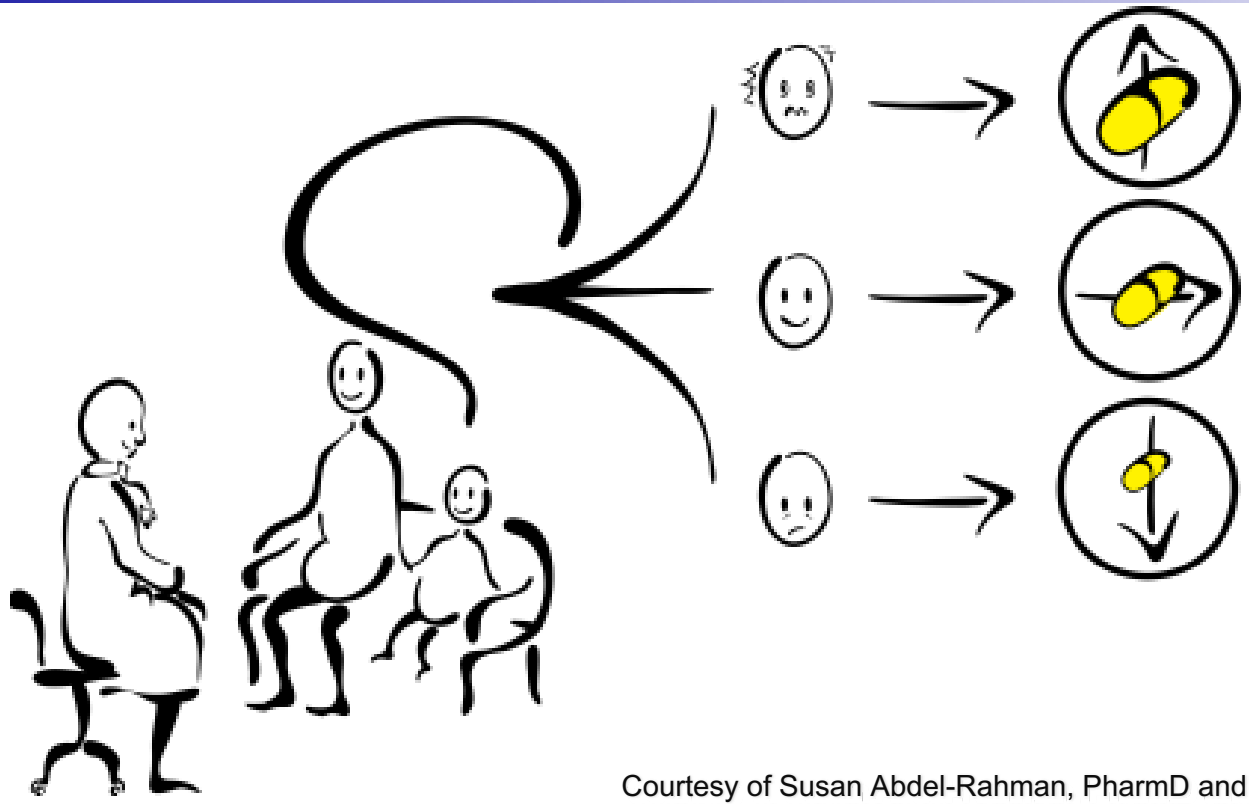
JT McCracken[1], KK Badashova[1], DJ Posey[2], MG Aman[3], L Scahill[4], E Tierney[5], LE Arnold[3], B Vitiello[6], F Whelan[1], SZ Chuang[7], M Davies[7], B Shah[1], CJ McDougle[8] and EL Nurmi[1]

	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%

Engaging Patients and Families



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