History of Pediatric Pharmacogenetics:
Adults are Just Big Children

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Progress in Pediatric Pharmacogenetics:
Our Heritage and Vision for the Future

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Disclosures

This is my wife, Donna’s first ASCPT meeting; it is likely to be her last because I have embarrassed her, but I am nonetheless deeply appreciative of her support over the years

The content of this presentation reflects my personal perspective, and, as a consequence, is likely to be selective and biased

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.

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Complex Problems, Multidisciplinary Teams

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- Robin Pearce, PhD

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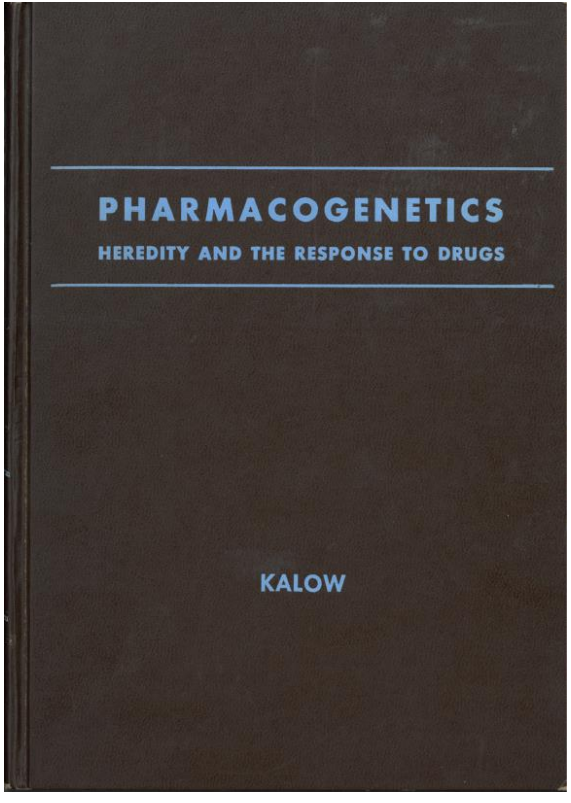
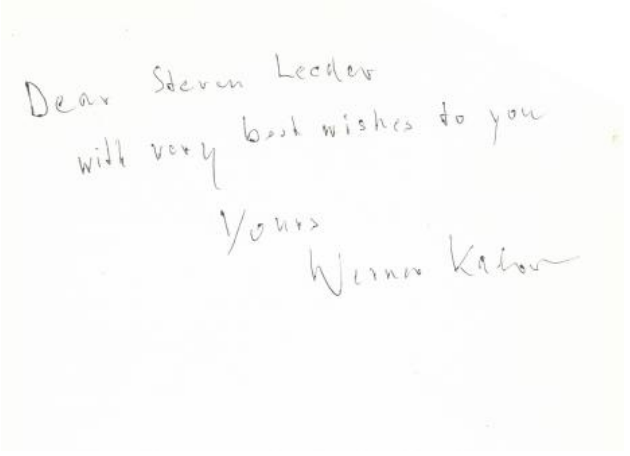
- Amin Rostami , PharmD, PhD
- Adam Darwich, PhD (U. Manchester)
- Trevor Johnson, Simcyp

Presentation Goals

- Explore the close ties between pediatric pharmacogenetics and pediatric clinical pharmacology as it matured as a discipline
- Review the role of genetic variation as a factor contributing to variability in drug disposition and response in pediatric patients in the context of progress made over the past 40 years
- Present some approaches to be considered to translate pediatric pharmacogenetics into precision therapeutics for children

In the Beginning (1962) …

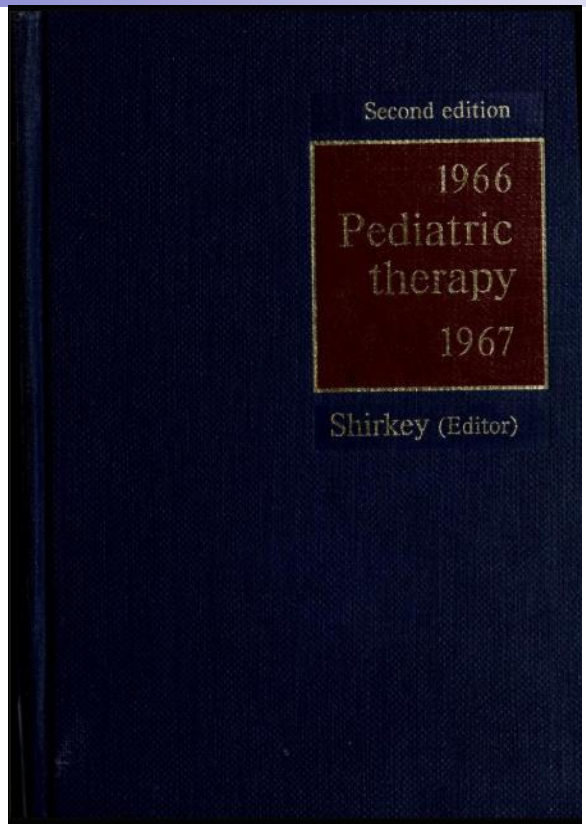




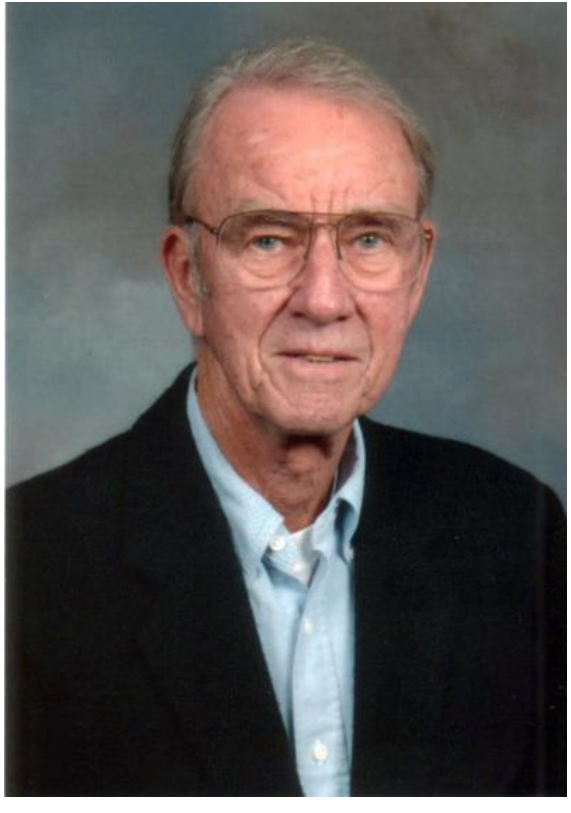
Pediatric Pharmacogenetics: The Early Days

- Who is this, and what is his relationship to pediatric pharmacogenetics?

Harry C. Shirkey, MD (1966)



Early Days of Pediatric Pharmacogenetics: Primarily Genetic Perspective



Chapter 15

Pharmacogenetics

William L. Nyhan

Pharmacogenetics[1, 2] is a newly recognized discipline which is concerned with alterations in response to drugs that result from genetic differences among individuals. The genetic analysis of human variation has been refined and substantially accelerated by the addition of biochemical genetics to consideration of form and appearance. It has more recently been appreciated that some populations can be distinguished only by their response to drugs. Individuals with the trait in question may be perfectly normal in all other respects. It is only following the use of an exogenous chemical agent that it becomes apparent that they are different from others. Drug responses then provide an important additional tool for the geneticist. This is the particular significance of vealed by the effects of drugs. Some of the more common examples will be considered as models for many as yet unrecognized.

THE DRUG-SENSITIVE ERYTHROCYTE (GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY)

(see also p. 703)

Drug-induced hemolytic anemia represents a heritable metabolic defect, in which instance the primary expression of the abnormal gene is in the abnormal function of an enzyme. However, the involved erythrocytes appear quite normal except when challenged from outside, in this case by the administration of certain drugs (Table 37, p. 704). The recognition of this abnormality is, therefore, of

Pediatric Pharmacogenetics: The Early Days

- Who is this, and what is his relationship to pediatric pharmacogenetics?

Sumner J. Yaffe, MD (1968)

SUMNER J. YAFFE, M.D.

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PHARMACOGENETICS

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Sumner Yaffe: Early Recognition of Importance of Ontogeny and Genetic Variation

PART III. GENETIC VARIATIONS THAT MODIFY DRUG RESPONSE

VARIATIONS IN DETOXICATION ENZYMES DURING MAMMALIAN DEVELOPMENT*

Sumner J. Yaffe, Joseph Krasner and Charlotte S. Catz
Department of Pediatrics, School of Medicine
State University of N. Y. at Buffalo

It has been repeatedly demonstrated that the developing fetus and newborn infant are more sensitive than the adult to the effects of many pharmacologic agents.[1,2] Differences in absorption, distribution, and excretion may be present in the newborn organism, but the principal factor in this response differential appears to be variation in the rates of detoxication. Drug metabolic processes have been studied in vitro in several animal species and, in most instances, activities are lower in the newborn organism compared with the adult.[3,4] Variations in drug metabolism appear to be genetically determined and the enzymic activity observed at any given age is dependent upon the species and strain of organism as well as the substrate employed in the reaction. Our primary objective in our initial studies was to determine how soon after birth one could detect and differentiate the contribution to drug metabolism made by genetic endowment.

Sumner Yaffe: Early Recognition of Importance of Genetic Variation and Ontogeny (mostly ontogeny)

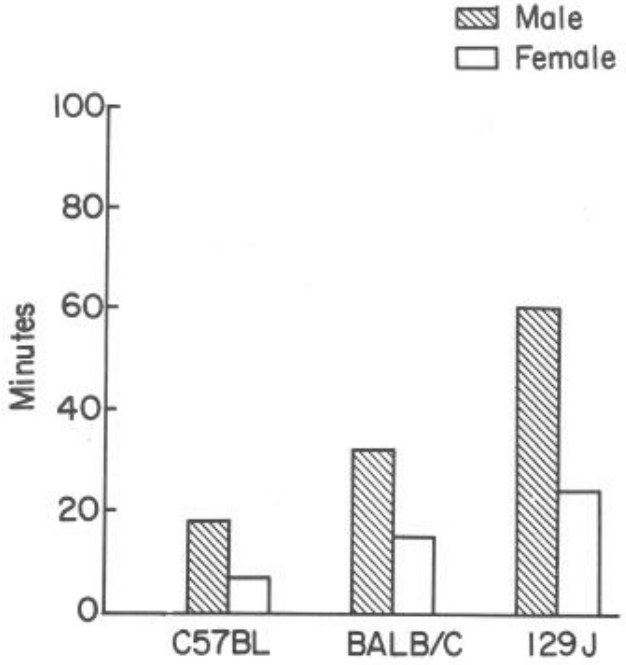


FIGURE 1. Strain variation in sleeping time. The height of each bar represents the mean value for sleeping time in minutes following i.p. injection of 100 mg/kg of hexobarbital. Twelve adult animals of each sex and strain were used in the assay procedure.

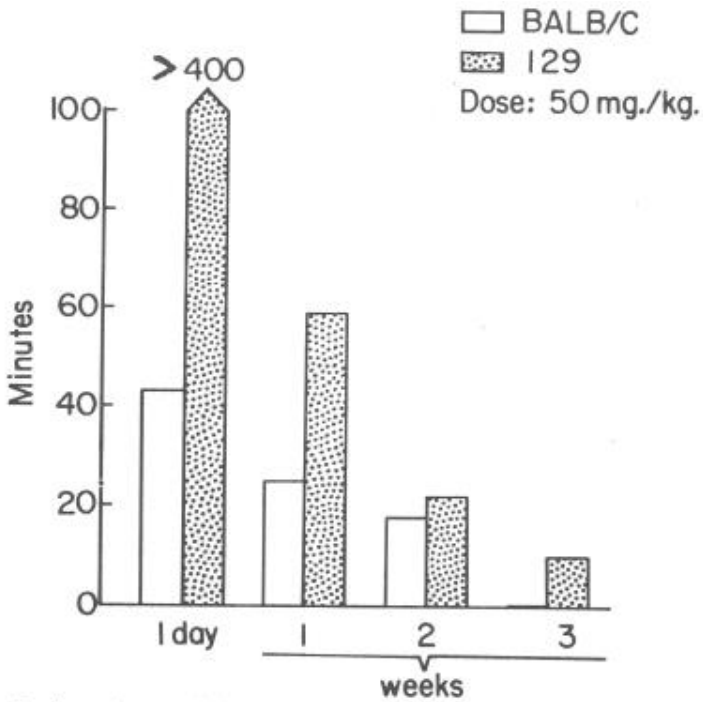
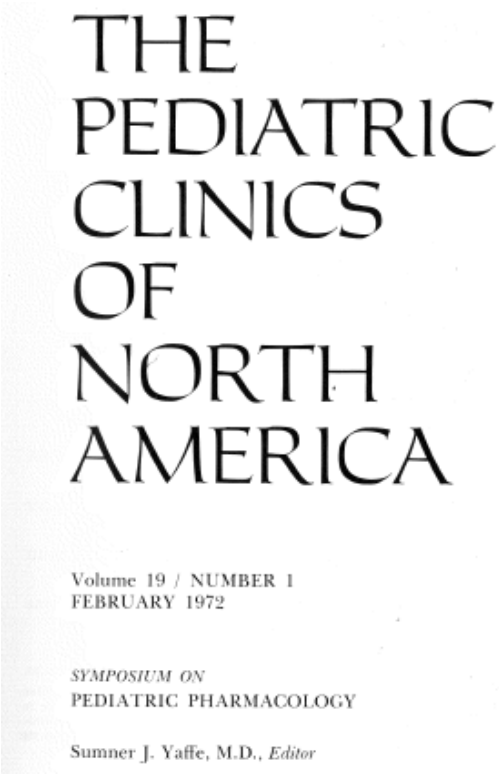


FIGURE 2. Strain and age variation in sleeping time. The height of each bar represents the mean value for sleeping time (in minutes) following i.p. administration of 50 mg/kg of hexobarbital. Twelve (or more) male mice of each age and strain were used for the determination.

Sumner J. Yaffe, MD



THE PEDIATRIC CLINICS OF NORTH AMERICA

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SYMPOSIUM ON
PEDIATRIC PHARMACOLOGY

Sumner J. Yaffe, M.D., *Editor*

Pharmacogenetics

*Sanford N. Cohen, M.D.,**
*and Wendell W. Weber, M.D., Ph.D.***

Pharmacogenetics may also affect children …

It is well known that among adult patients receiving isoniazid, the slow acetylators are at risk to develop a peripheral neuropathy.[21, 66] Such a reaction is so common in the general population that many physicians prescribe pyridoxine routinely for all patients taking isoniazid. It is also well known that the neurologic side-effects of this drug among childhood patients are so rare that they can be ignored as a hazard to a child who is taking isoniazid. The rarity of this troublesome pharmacogenetically determined side-effect among children has not been explained.

Pediatric Pharmacogenetics: The Early Days

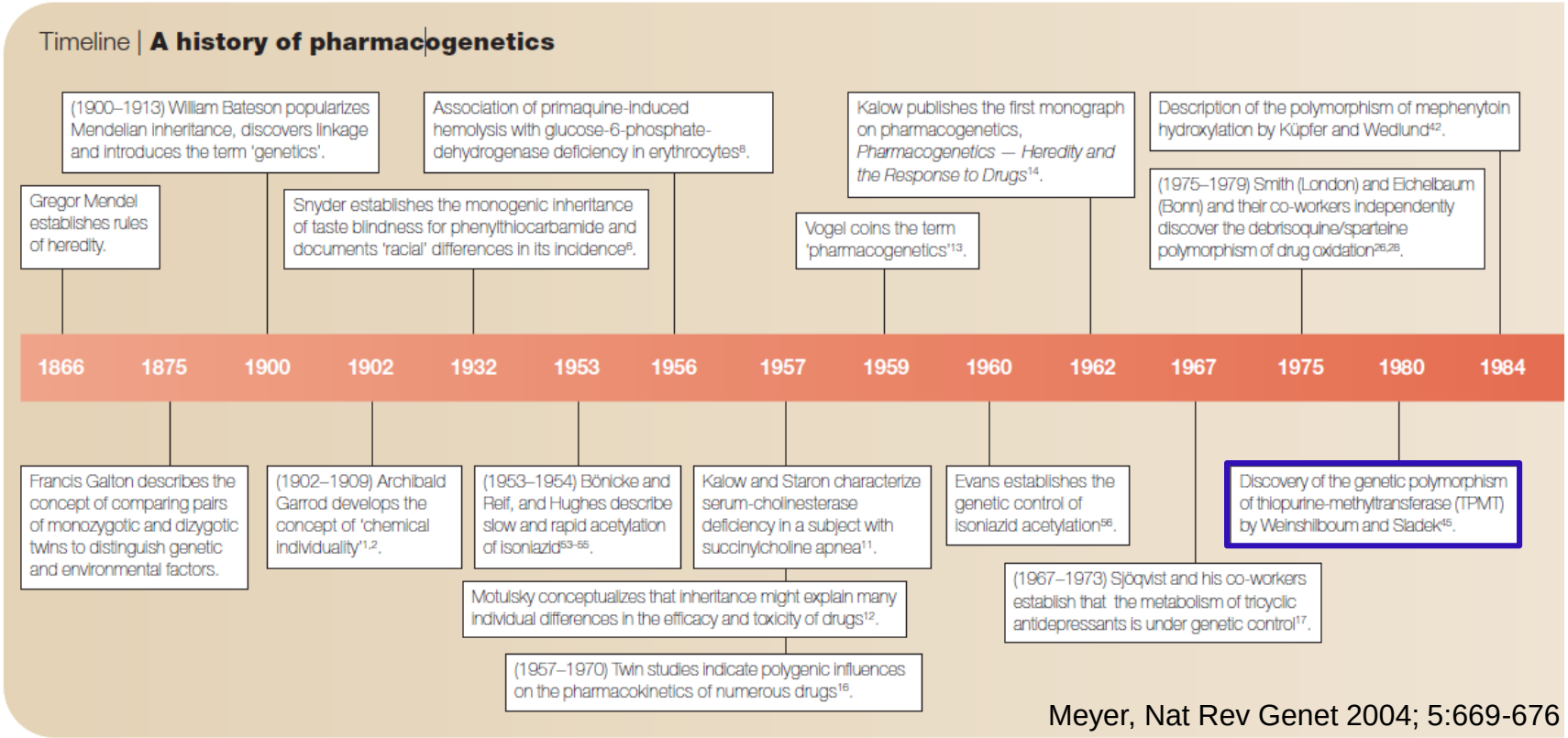
PGx problem, but developmental considerations may also be involved…

Malignant hyperthermia has not been observed in infants and children below the age of 3 years, but almost 25 per cent of all cases occurred prior to the fifth year of life and more than 30 per cent occurred during the first 10 years. Kalow and his associates have concluded that malignant hyperthermia is hereditary in a substantial number of cases but they cannot explain this apparent predisposition of young children (3 to 10 years of age) for the condition.

Early Days of Pediatrics PGx: Summary

- Increasing awareness of role for genetic factors contributing to variability in drug response, largely adverse drug reactions
  - Sulfonamides and G6PD deficiency
  - Speculation regarding risk of birth defects (Dan Nebert, 1981)
- Children may also be affected - same genes, same drugs, but …
- Observation that phenotypic traits/ADR risks may differ in children
  - Less risk of isoniazid peripheral neuropathy
  - Children at increased risk of drug-induced malignant hyperthermia
- No investigations of the genetic basis of a drug-related phenotype in children

Investigating Pharmacogenetics in Children:
1980s and Beyond



Meyer, Nat Rev Genet 2004; 5:669-676

Progress in Pediatric Pharmacogenetics: TPMT

- Weinshilboum and Sladek,1980: first “phenotyping” study conducted in children -- thiopurine *S*-methyl transferase (TPMT) polymorphism
- Study population included 115 children aged 13.0 ± 0.4 years
- Wide variation in RBC TPMT activity segregated as a monogenic trait consistent with autosomal codominant inheritance
- Lennard *et al*, 1983: Relationship between intracellular 6MP concentrations and neutropenia
- Lennard, Weinshilboum collaboration, 1987: Correlation of RBC TPMT activity and 6-TGN concentrations, and other observations …

Progress in Pediatric Pharmacogenetics: TPMT

Thiopurine pharmacogenetics in leukemia: Correlation of erythrocyte thiopurine methyltransferase activity and 6-thioguanine nucleotide concentrations

Thiopurine methyltransferase (TPMT) catalyzes the S-methylation of thiopurine drugs such as 6-mercaptopurine (6-MP) and azathioprine. Human erythrocyte (RBC) TPMT activity is controlled by a common genetic polymorphism. On a genetic basis approximately one in every 300 subjects lacks TPMT activity, and 11% of subjects have intermediate activities. 6-Thioguanine nucleotides (6-TGN) are major metabolites of 6-MP and azathioprine in humans. RBC 6-TGN concentrations are correlated directly with risk for the development of leukopenia in patients treated with thiopurine drugs. Our studies were performed to determine whether there was a relationship between genetically controlled levels of RBC TPMT activity and RBC concentrations of 6-TGN. We found a significant negative correlation between RBC TPMT activity and 6-TGN concentrations in blood samples from 40 children with acute lymphoblastic leukemia receiving long-term therapy with 6-MP ($r_s = -0.474$; $P < 0.005$). In addition, RBC TPMT activities were significantly higher in blood samples from these patients than in blood samples from adult control subjects ($P < 0.0001$) or children with acute lymphoblastic leukemia who were in remission but were not receiving drug therapy ($P < 0.0001$). Finally, three adult patients were studied who developed very high RBC 6-TGN concentrations and thiopurine-induced leukopenia. Two of the three patients had no detectable RBC TPMT activity—presumably on a genetic basis. These results indicate that low TPMT activity may be a risk factor for the occurrence of elevated 6-TGN concentrations and for the development of severe leukopenia in patients treated with thiopurine drugs. Measurement of RBC TPMT activity might make it possible to predict this risk factor for the development of thiopurine drug toxicity. (CLIN PHARMACOL THER 1987;41:18-25.)

Lynne Lennard, Ph.D., Jon A. Van Loon, B.A., John S. Lilleyman, M.B., and Richard M. Weinshilboum, M.D.* *Sheffield, United Kingdom, and Rochester, Minn.*

- Negative correlation between RBC TPMT activity and 6-TGN concentrations
- TPMT activity higher in children with ALL treated with 6MP than adult controls (ontogeny?)
- TPMT activity higher in children with ALL treated with 6MP than children with ALL in remission and not receiving drug (induction?)
- TPMT activity potential risk factor for development of severe leukopenia

Progress in Pediatric Pharmacogenetics: TPMT

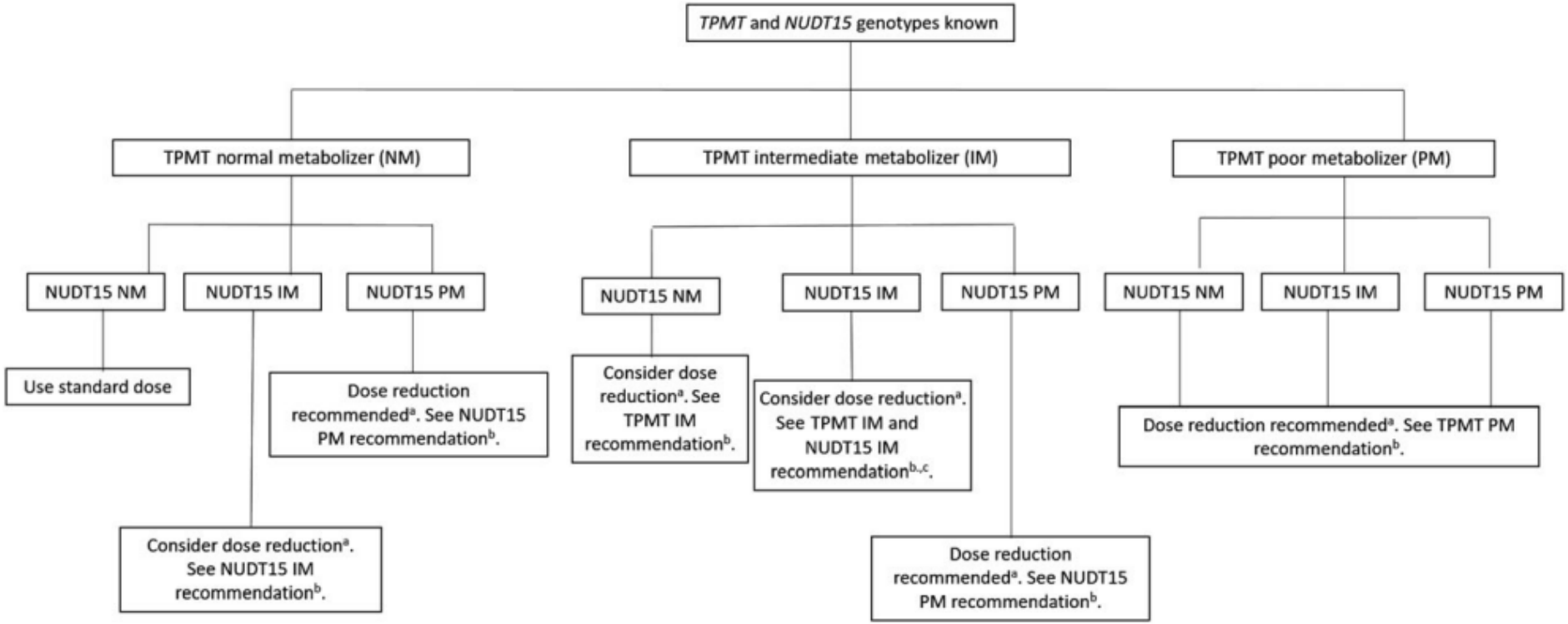
- McLeod *et al*, 1995: TPMT activity >50% higher in full term newborns relative to race-matched adults; distribution of activity consistent with demonstrated genetic polymorphism
- Krynetski *et al*, 1995: Identification of *TPMT*2* allele from cDNA
- Szumlanski *et al*, 1996: *TPMT* gene cloned and *TPMT*3A and *3B* alleles described
- Extensive literature in ALL and pediatric IBD in ‘80s, ‘90s and ‘00s
- CPIC guideline for TPMT and thiopurine dosing first published 2011
- NUDT15: 2014 (Crohn’s Disease; Korea), 2015 (ALL, St. Jude)

Progress in Pediatric Pharmacogenetics: TPMT

Clinical Pharmacogenetics Implementation Consortium Guideline for Thiopurine Dosing Based on *TPMT* and *NUDT*15 Genotypes: 2018 Update

Mary V. Relling[1], Matthias Schwab[2,3,4], Michelle Whirl-Carrillo[5], Guilherme Suarez-Kurtz[6], Ching-Hon Pui[7], Charles M. Stein[8], Ann M. Moyer[9], William E. Evans[1], Teri E. Klein[4], Federico Guillermo Antillon-Klussmann[10,11], Kelly E. Caudle[1], Motohiro Kato[12], Allen E.J. Yeoh[13,14], Kjeld Schmiegelow[15,16] and Jun J. Yang[1]

Progress in Pediatric Pharmacogenetics: TPMT



CLINICAL PHARMACOLOGY & THERAPEUTICS doi:10.1002/cpt.1304

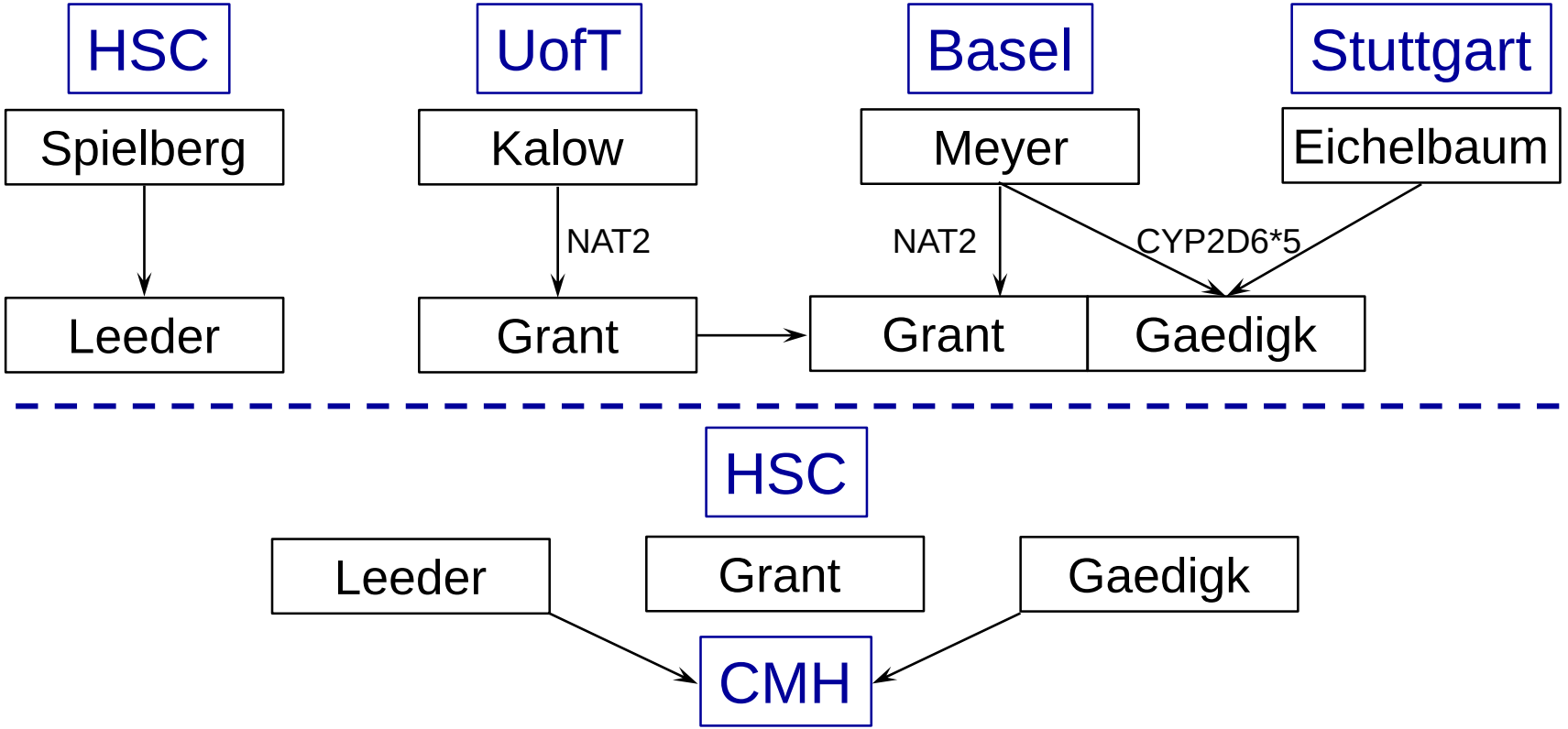
Circuitous Route to Pediatric Pharmacogenetics

PREDISPOSITION TO PHENYTOIN HEPATOTOXICITY ASSESSED IN VITRO

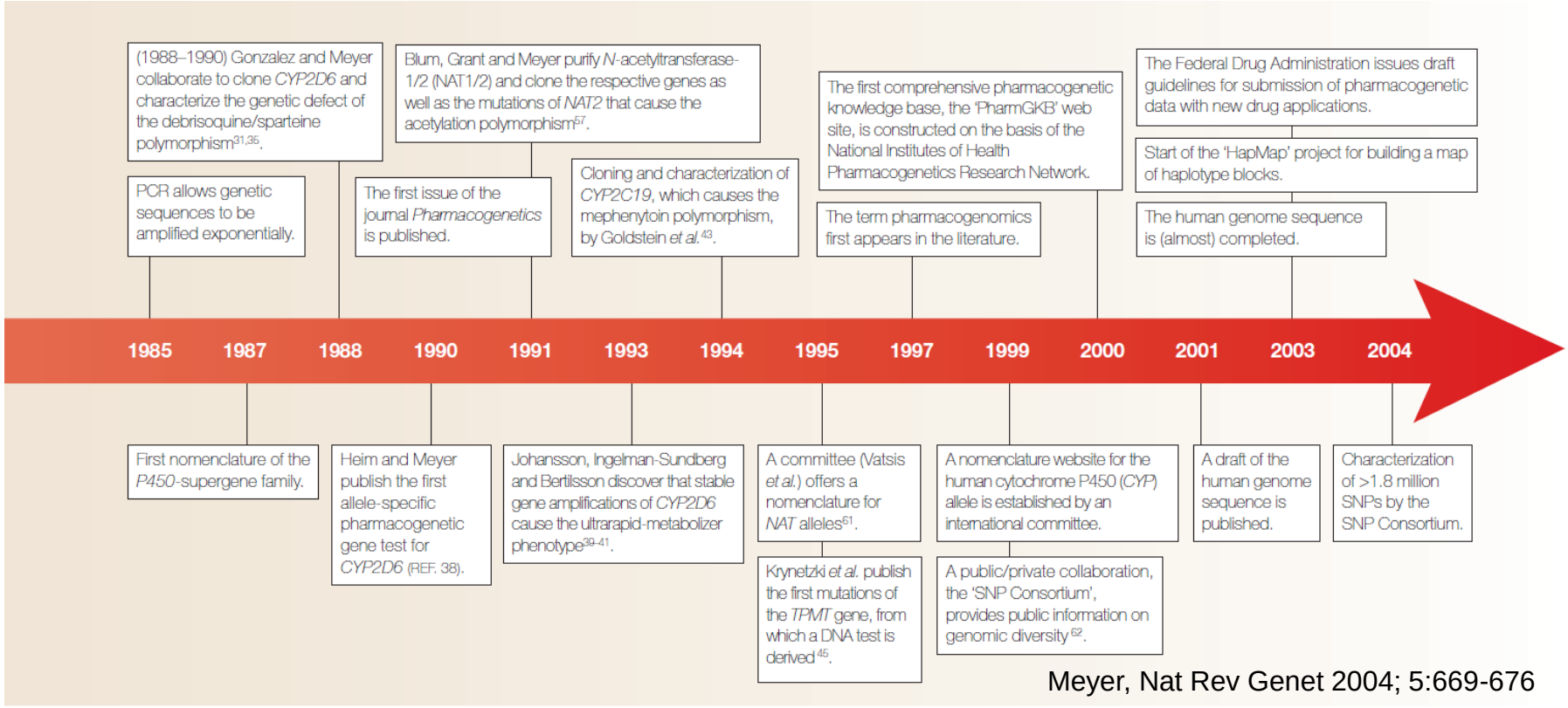
STEPHEN P. SPIELBERG, M.D., PH.D., GARY B. GORDON, M.D., PH.D, DAVID A. BLAKE, PH.D., DANIEL A. GOLDSTEIN, M.D., AND H. FRANKLIN HERLONG, M.D.

Abstract Arene oxide metabolites of phenytoin may be involved in the pathogenesis of drug-induced hepatotoxicity. We examined individual susceptibility to toxicity from such metabolites by exposing human lymphocytes to metabolites generated by a murine hepatic microsomal system. Cells from 17 controls showed no toxicity at concentrations of phenytoin from 31 to 125 μM. Cells from three patients with phenytoin hepatotoxicity manifested dose-dependent toxicity from the metabolites. Phenytoin alone was not toxic to cells. The patients' dose-response curves resembled the response of control cells in which epoxide hydrolase (a detoxification enzyme for arene oxides) was inhibited. Detoxification of non-arene oxide metabolites (e.g., of acetaminophen) was normal in patients' cells. Cells from parents of two patients had intermediate responses. Cells from a sibling of one patient showed no toxicity; a sibling of another patient had a response similar to that of the patient. A heritable defect in response to arene oxides thus may predispose some patients to phenytoin hepatotoxicity. (N Engl J Med. 1981; 305:722-7.)

Circuitous Route to Pediatric Pharmacogenetics



Investigating Pharmacogenetics in Children:
1990s and Beyond

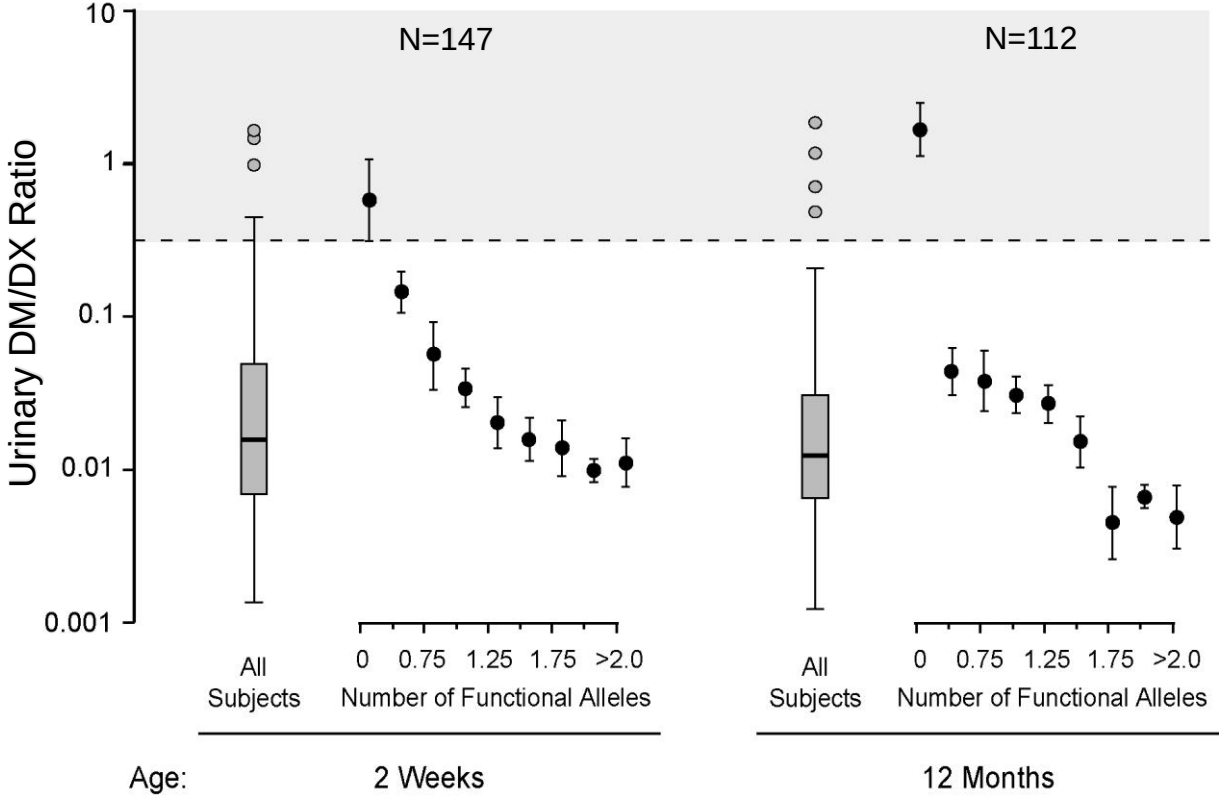


Meyer, Nat Rev Genet 2004; 5:669-676

Progress in Pediatric Pharmacogenetics: CYP2D6

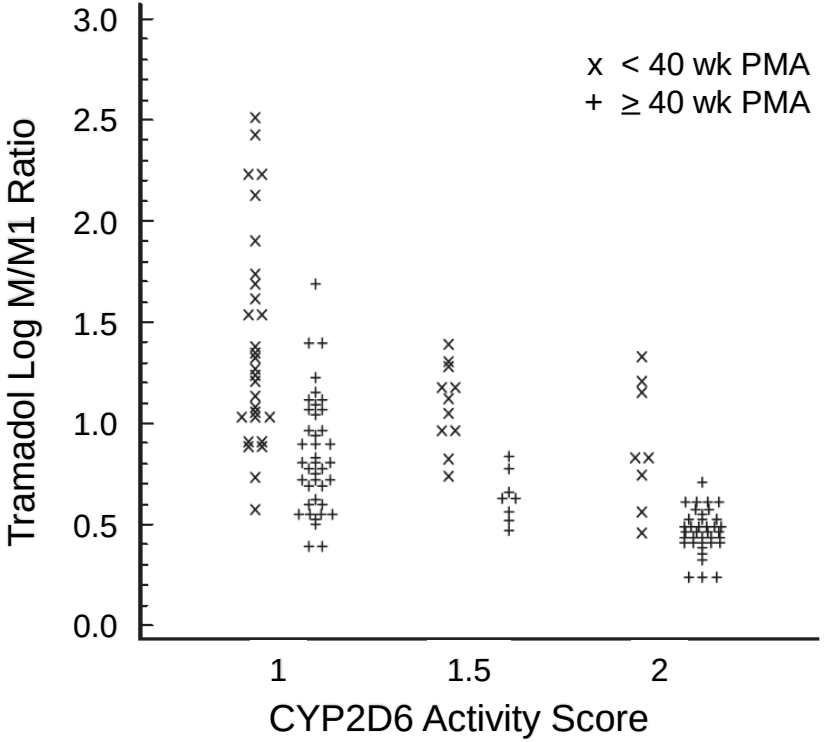
- Evans *et al*,1989: first CYP2D6 phenotyping study conducted in children (n=26, 3-21 y); dextromethorphan (DM) as the probe
- Jacqz-Aigrain *et al*, 1990: DM phenotyping in 13 children with autoimmune hepatitis *vs* 31 unaffected children
- Evans and Relling, 1991: CYP2D6 genotype-phenotype concordance assessed in 116 subjects with median age of ~10 years
- Treluyer *et al*, 1991: Early investigation of CYP2D6 ontogeny in fetal and newborn liver
- Blake *et al*, 2007: Longitudinal phenotyping study in first year of life

Progress in Pediatric Pharmacogenetics: CYP2D6



- Longitudinal DM phenotyping study in healthy term infants
- "Well-baby" visits at 2 weeks, 1 mo, 2 mo, 4 mo, 6 mo, and 12 months of age
- 0.3 mg/kg; overnight urine collection
- Analysis for DM and metabolites (DX, 3MM and 3HM) by HPLC
- Genotype concordant with phenotype at 2 wk

Progress in Pediatric Pharmacogenetics: CYP2D6



- In the very young critically ill, ontogeny and genetic variation are important, among other factors
- Genotyping may be of limited value in an acute neonatal setting due to the developmental changes in other factors, such as maturation of renal function
- PK studies in extreme genotypes (0 *vs* >2 functional alleles) are required to determine the magnitude of effect on dose-exposure-response relationships

Adapted from Allegaert *et al*., Pediatr Anesth 2011;21:266-73

Progress in Pediatric Pharmacogenetics: CYP2D6

Lancet 2006; 368: 704

Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother

Gideon Koren, James Cairns, David Chitayat, Andrea Gaedigk, Steven J Leeder

- FDA warning for nursing mothers issued Aug 17, 2007
- FDA reviewing reports of SADRs in tonsil- and adenoinectomy issued Aug 15, 2012
- Black box warning (contraindication) issued Feb 20, 2013
- CPIC guideline updated (CPT 2014; 95:376-82)
- Additional FDA updates for codeine and tramadol issued Apr 20, 2017 and Jan 11, 2018

ONTARIO EDITION » THURSDAY, AUGUST 21, 2008 — TORONTO, SUNNY, HIGH 25 LOW 17

THE GLOBE AND MAIL

CANADA'S NATIONAL NEWSPAPER

HEALTH » 'YOU CANNOT CONTINUE TO GIVE IT LIKE CANDIES'

Codeine can prove toxic for breastfed babies

Study highlights risk in mother's milk

BY LISA PRIEST

Nearly one-quarter of babies whose mothers took codeine while breastfeeding showed signs of central nervous system depression, according to a new study, suggesting the drug can transform mother's milk into a troubling brew.

Specifically, 17 of 72 babies became sedated or experienced abnormal breathing, including one who narrowly avoided a tragic reaction, according to Hospital for Sick Children researchers in collaboration with the University of Western Ontario.

"You cannot continue to give it [codeine] like candies," Gideon Koren, lead author of the study published in the journal Clinical Pharmacology & Therapeutics, said in a telephone interview. "... In some cases, this can be life-threatening."

Codeine is extremely prevalent: Dr. Koren estimated as many as 120,000 Canadian women a year receive the drug after childbirth. And although it has been known that some mothers carry multiple copies of a gene capable of converting the common pain reliever into strong concentrations of morphine, he said the study suggests the pharmacological phenomenon is broader than initially thought.

» SEE 'CODEINE' PAGE 5

Rani Jamieson, 36, was told to take codeine after the birth of her son, Tariq, in April, 2005. Though seemingly healthy, he died 12 days later and was found to have a toxic level of morphine in his blood. "This drug was killing him," Ms. Jamieson said. 'And we didn't know it.' CHARLA JONES/THE GLOBE AND MAIL

FOOD SAFETY » LISTERIA MONOCYTOGENES

Nationwide outbreak spurs massive meat recall

Maple Leaf plant shut after bacterial illness kills one and sickens at least 16 others

BY MATTHEW CAMPBELL TORONTO

One person is dead and at least 16 more have been sickened by a nationwide outbreak of listeria infection that may have originated in a Toronto meat-processing plant.

Maple Leaf Foods Inc. announced yesterday the recall of more than 20 meat products and temporarily shut down the Toronto factory where they were packaged. *Listeria monocytogenes*, a relatively common food-borne bacterium that can cause serious illness in pregnant women and the elderly, has been found in three tests of products in the past five days.

Products affected include sliced meats served by McDonald's and Mr. Sub restaurants, as well as lines supplied to grocery stores (under the Schneiders and Sure Slice brands) and many commercial kitchens including some serving hospitals or nursing homes.

The recall comes at a delicate time for Prime Minister Stephen Harper's government, which has already come under fire from the opposition over a leaked cabinet document that outlines plans to give the meat industry greater control of food inspection.

It was late July when a spike in illnesses caused by listeria came to the attention of public-health officials in Ontario, British Columbia, Saskatchewan and Quebec. They asked the Canadian Food Inspection Agency to "follow the food," said Garfield Balsom, an agency spokesman.

An investigation by agency inspectors, including one stationed permanently at the Toronto plant, led late last week to an identical strain of the bacterium in sealed Maple Leaf products produced there

Linda Smith, a spokeswoman for the Toronto-based meat and baked-goods producer, said the firm was first informe last Saturday that one of its products, Sure Slice brand roast beef, had tested positive for listeria, and began a recall of that line, as well as its Sure Slice corned beef, which was identified as problematic late

» SEE 'RECALL' PAGE 4

The symptoms

Listeriosis causes fever, chills, nausea, diarrhea, headache and aches and pains. The onset of illness after infection from the bacteria can be from 12 hours to three months. The median incubation period is estimated to be three weeks.

Progress in Pediatric Pharmacogenetics: CYP2D6

- Studies of CYP2D6 pharmacogenetics in pediatric patients few in number and generally uninformative; most common phenotype parent/metabolite ratios or clinically obtained trough concentrations
- General conclusions:

> 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]

Blázquez *et al.*, J Clin Psychopharmacol 2014;34: 318-326

- Few PK studies assessing influence of CYP2D6 genotype on drug clearance in pediatric age groups; atomoxetine, tramadol and risperidone exceptions

Progress in Pediatric Pharmacogenetics: CYP2D6

CPIC GUIDELINES

Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for *CYP2D6* and *CYP2C19* Genotypes and Dosing of Selective Serotonin Reuptake Inhibitors

JK Hicks[1], JR Bishop[2], K Sangkuhl[3], DJ Müller[4], Y Ji[5], SG Leckband[6], JS Leeder[7], RL Graham[8], DL Chiulli[9], A LLerena[10], TC Skaar[11], SA Scott[12], JC Stingl[13], TE Klein[3], KE Caudle[14] and A Gaedigk[7]

Progress in Pediatric Pharmacogenetics: CYP2D6

- Few pediatric pharmacogenetics studies/data
- Developmental changes in gene expression

Pediatrics. Data describing the relationship between *CYP2D6* or *CYP2C19* genotype and SSRI systemic exposure or steady-state plasma concentrations in pediatric patients are scarce (**Supplemental Data**). Because CYP2D6 activity is fully mature by early childhood,[32] it may be appropriate to extrapolate these recommendations to adolescents or possibly younger children with close monitoring. CYP2C19 activity may be increased in children relative to adults; therefore, these recommendations should be used with caution in children and accompanied by close monitoring. Ultimately, additional research and clinical trials in pediatric patients investigating the association between CYP2D6 or CYP2C19 and SSRI systemic exposure or treatment outcomes is needed.

Progress in Pediatric Pharmacogenetics: General

- Studies investigating the role of genetic variation as a factor contributing to variability in drug disposition and response have been reported in many areas:

ADHD	Autism	Asthma	BMT	CHD	CF
Epilepsy	HIV	IBD, PPIs	JIA	Kawasaki	Oncology
Neonatology	Pain	Transplant	Cisplatin	Morphine	Warfarin

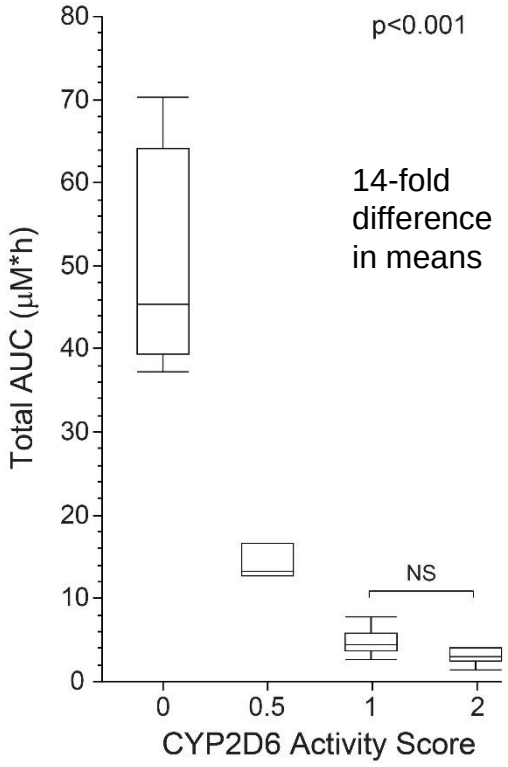
- Few studies have translated into clinically actionable, validated tests or models for routine application

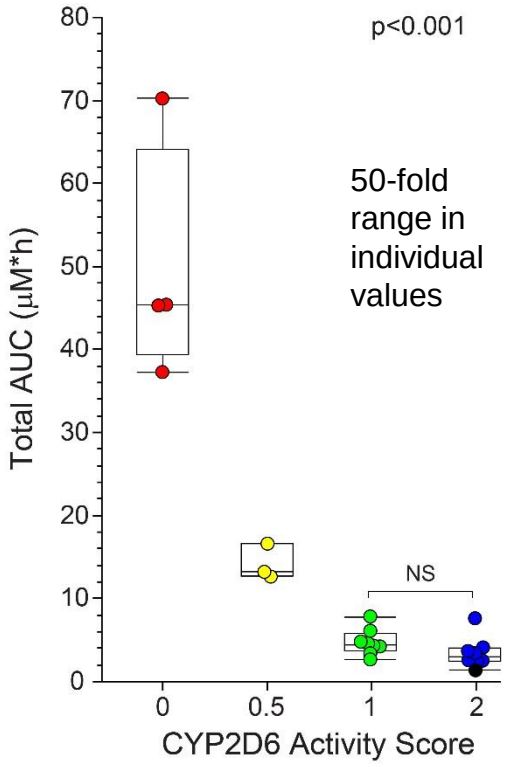
Pediatric Pharmacogenetics: Proposal for the Future

1. Genotype-stratified pharmacokinetic studies to establish population extremes and magnitude of pharmacogenetic effect on the dose→exposure relationship
2. Rich, intensive opportunistic sampling (aka “pragmatic pharmacology)
3. Prospective validation and model refinement
4. Exposure-controlled/escalation studies to investigate the exposure→ response relationship to establish therapeutically relevant exposure ranges, given knowledge of drug target expression and function
   - Biomarkers of drug effect

Proposal for the Future: 1. Genotype-Stratified PK Studies

- Previous participants in longitudinal DM study
- Primary diagnosis of ADHD
- Selected based on *CYP2D6* genotype
  - 2 or more functional alleles: EM2
  - 1 functional allele: EM1
  - 0 functional alleles: PM
  - 0.5 functional alleles: IM
- Single oral dosage unit closest to 0.5 mg/kg
- Serial plasma sampling

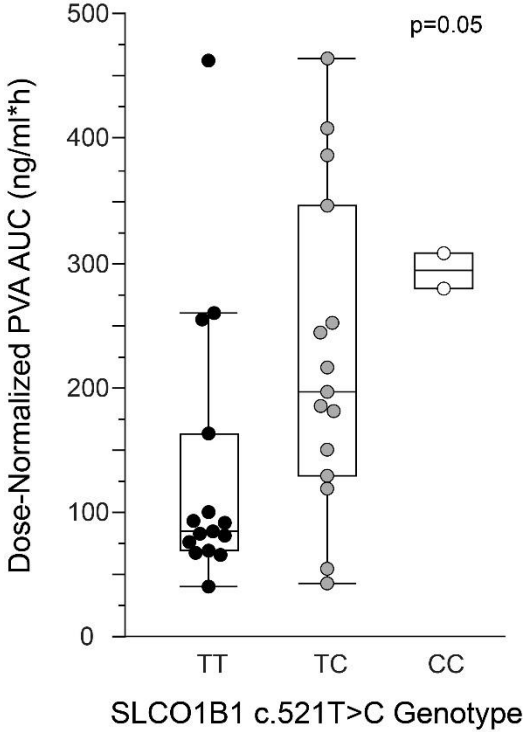




Brown *et al,* CPT 2016 (PMID: 26660002)

Genotype-Stratified Pravastatin Pharmacokinetics

- AAP recommendations for universal lipid screening
- Variability in response to statins (LDL reduction) in pediatric clinical trials
- Dose-exposure relationship subject to genetic variation (*SLCO1B1*)
- Only pediatric PGx study to date reported higher pravastatin exposure in *SLCO1B1* **521TT**



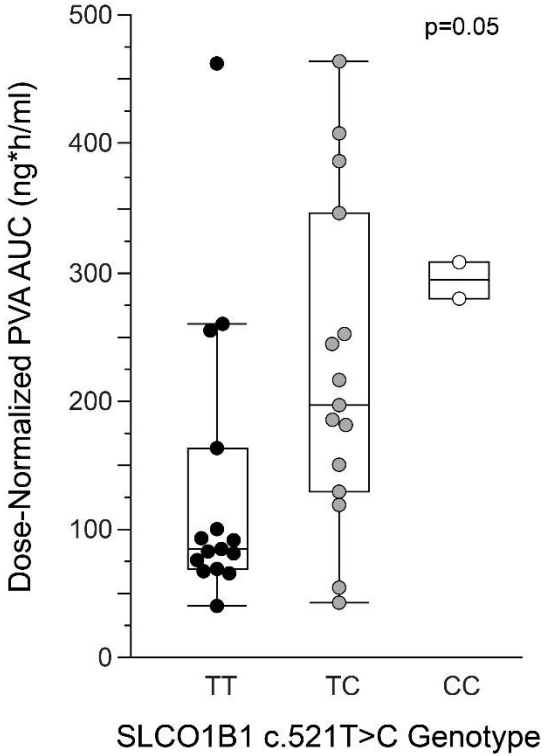
Adult genotype-phenotype relationship replicated

but …

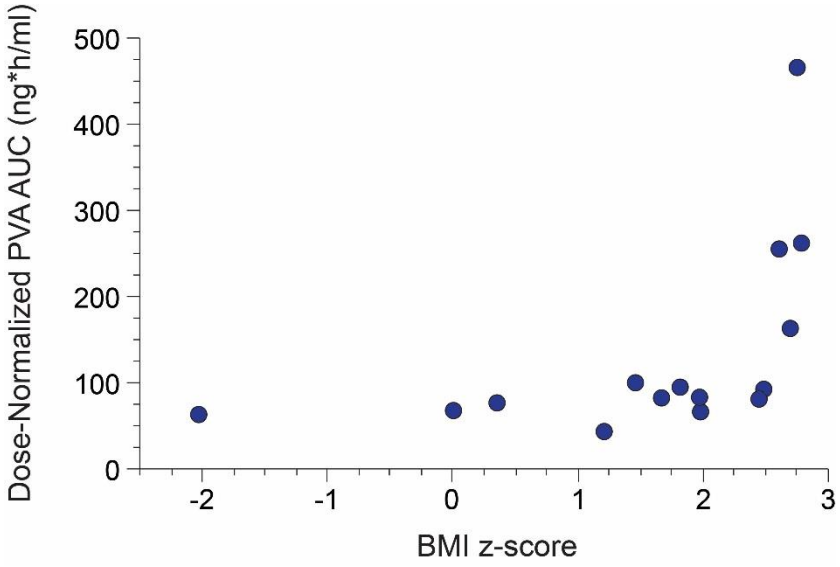
~11-fold inter-individual variability within the 521TT and 521TC groups

Wagner *et al,* CPT 2019 (PMID: 30549267)

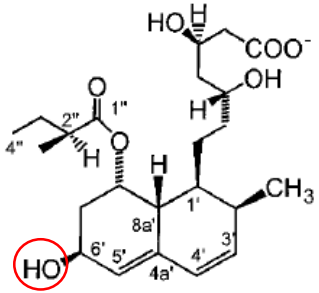
Sources of Variability: Demographic Factors



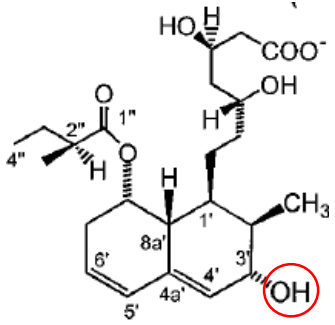
- In the 521 TT group, PVA AUC associated with weight (r^2=0.375, p13=0.015) and BMI (r^2=0.390, p=0.013)
- No association with any demographic variable in 521 TC



Sources of Variability: Conversion to 3α-PVA

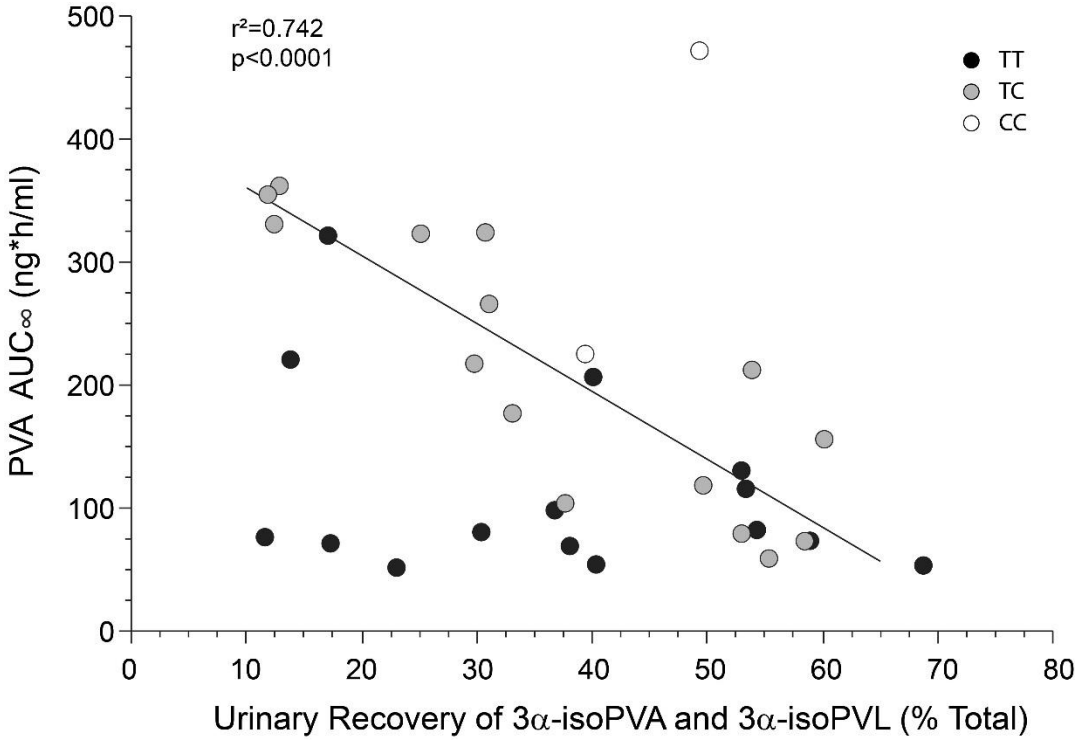


Pravastatin



3α-iso-Pravastatin

- Also an OATP1B1 substrate based on genotype-phenotype association
- PVA AUC decreases with increase in 3α-PVA formation for 521TC group (r^2=0.742, p<0.0001), but not 521TT



Wagner *et al,* CPT 2019 (PMID: 30549267)

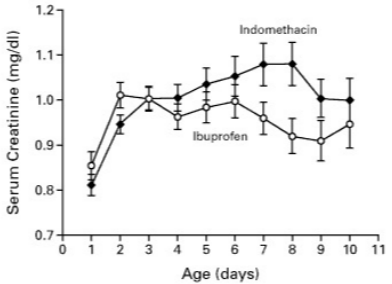
Proposal for the Future: 2. Rich Opportunistic Sampling
(aka “Pragmatic Pharmacology”)

PDA Outcomes are Unpredictable

Effective
Minimal Side Effects

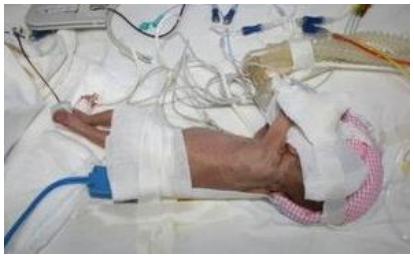
No further treatment

Effective
Acute Kidney Injury



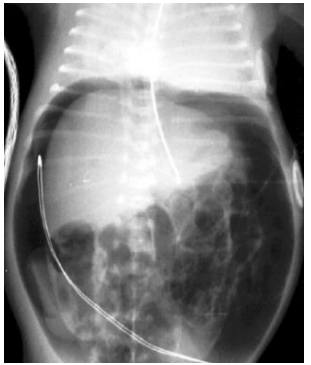
Renal function recovers

Not Effective
Minimal Side Effects



Heart Surgery
(25%)

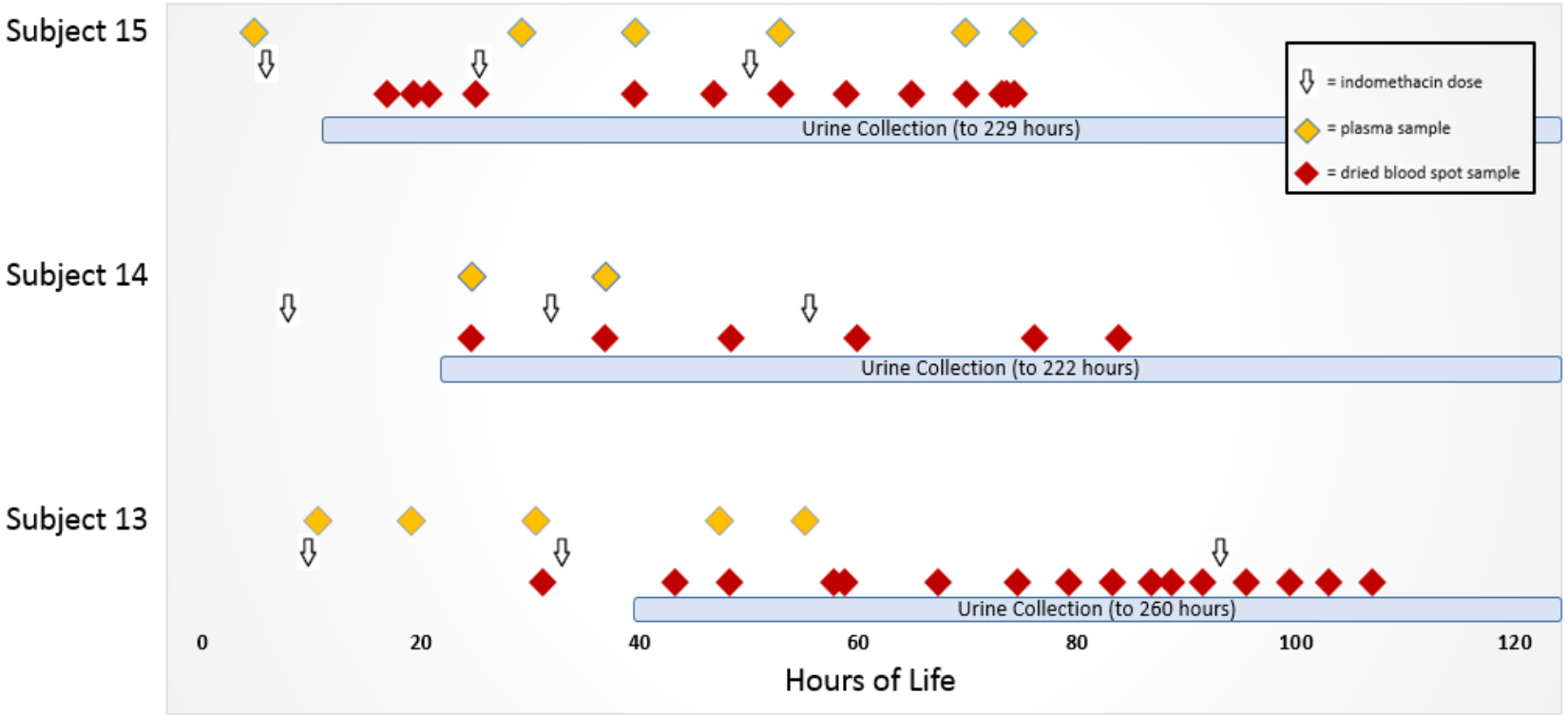
Not Effective
Intestinal Perforation



Bowel surgery
(and heart surgery later; 10%)

Courtesy of Tamorah Lewis, MD, PhD

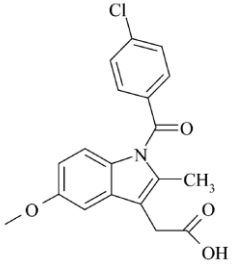
Indomethacin in PDA: Sample Collection Strategy



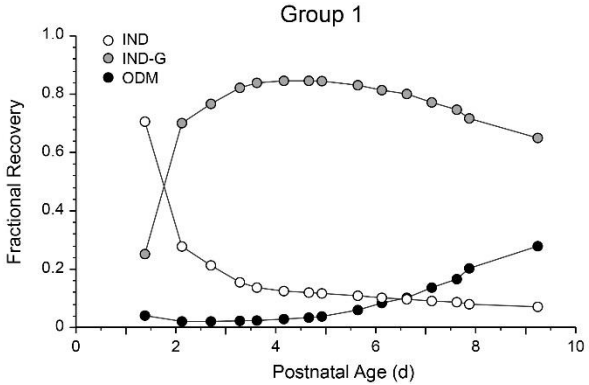
Courtesy of Tamorah Lewis, MD, PhD

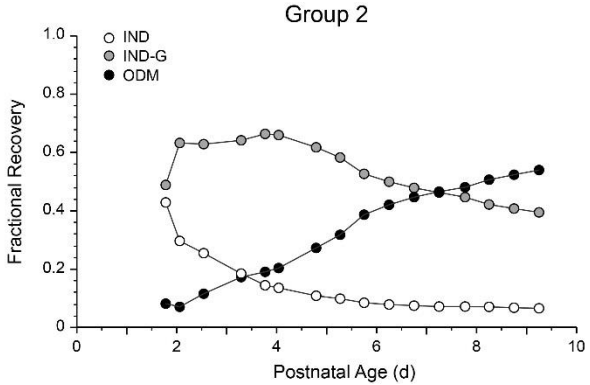
Distinct Patterns of Metabolite Formation and Excretion

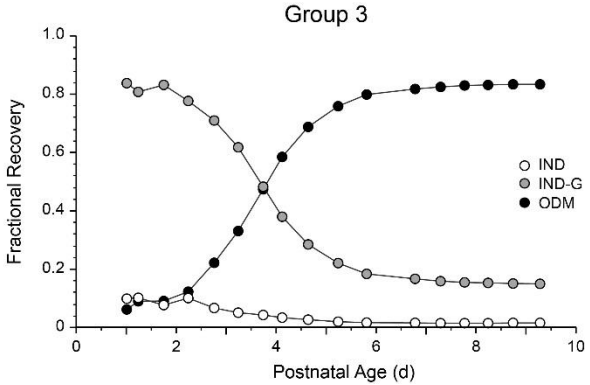
O-demethylation (ODM)



Acylglucuronidation (IND-G)







Lewis *et al,* Pediatr Res (PMID: 29967531)

Proposal for the Future: 3. Prospective Model Validation

JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY
Volume XX, Number XX, 2019

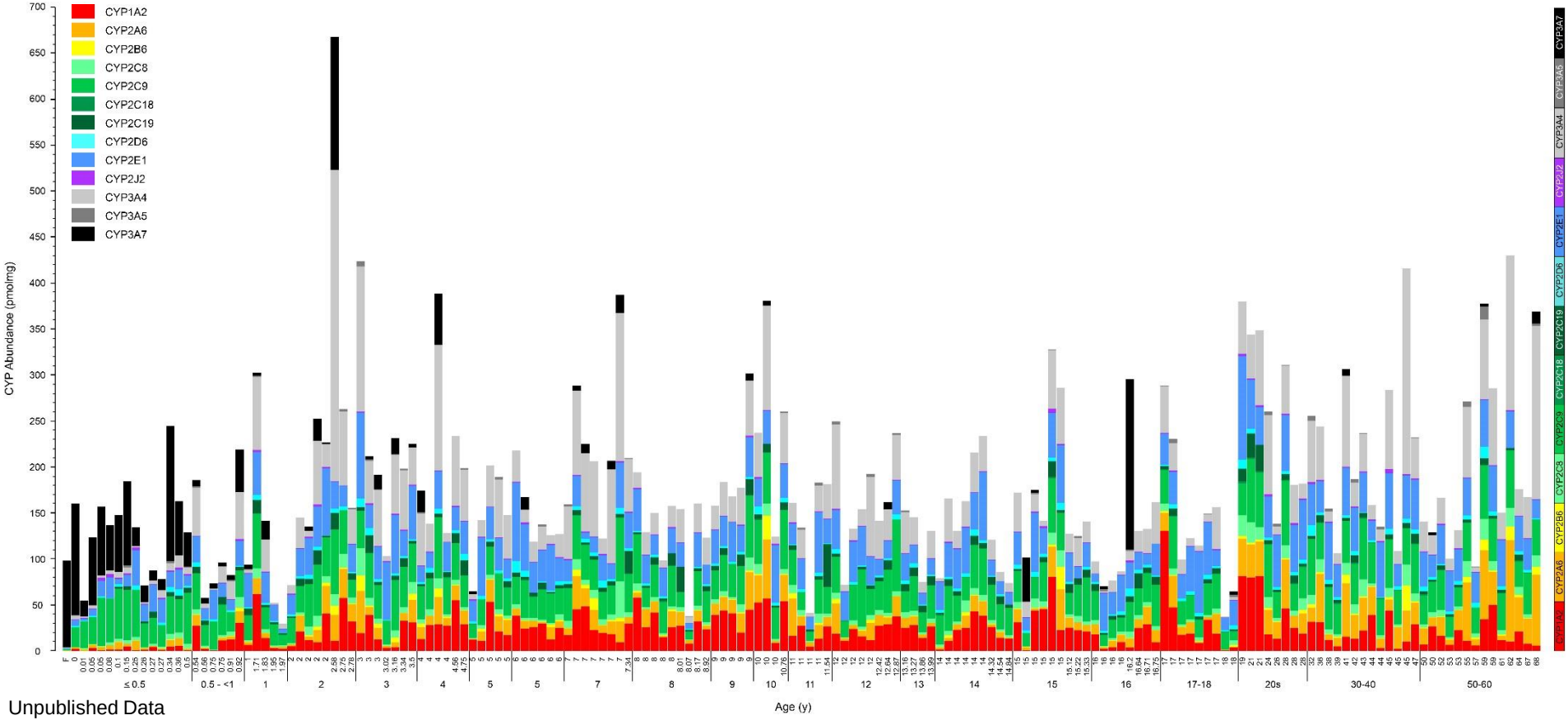
Pp. 1–8
DOI: 10.1089/cap.2018.0160

CYP2C19-Guided Escitalopram and Sertraline Dosing in Pediatric Patients: A Pharmacokinetic Modeling Study

Jeffrey R. Strawn, MD,[1,2] Ethan A. Poweleit,[3] and Laura B. Ramsey, PhD[3,4]

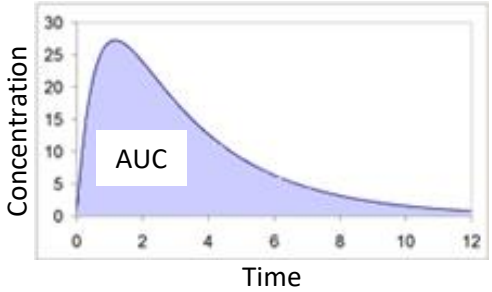
- Development of dosing models incorporating PGx is encouraging; clinical application requires prospective validation as the authors of this study acknowledge

Prospective Model Validation: Characterizing Individuals



Unpublished Data

Proposal for the Future: 4. Exposure-Controlled Dosing

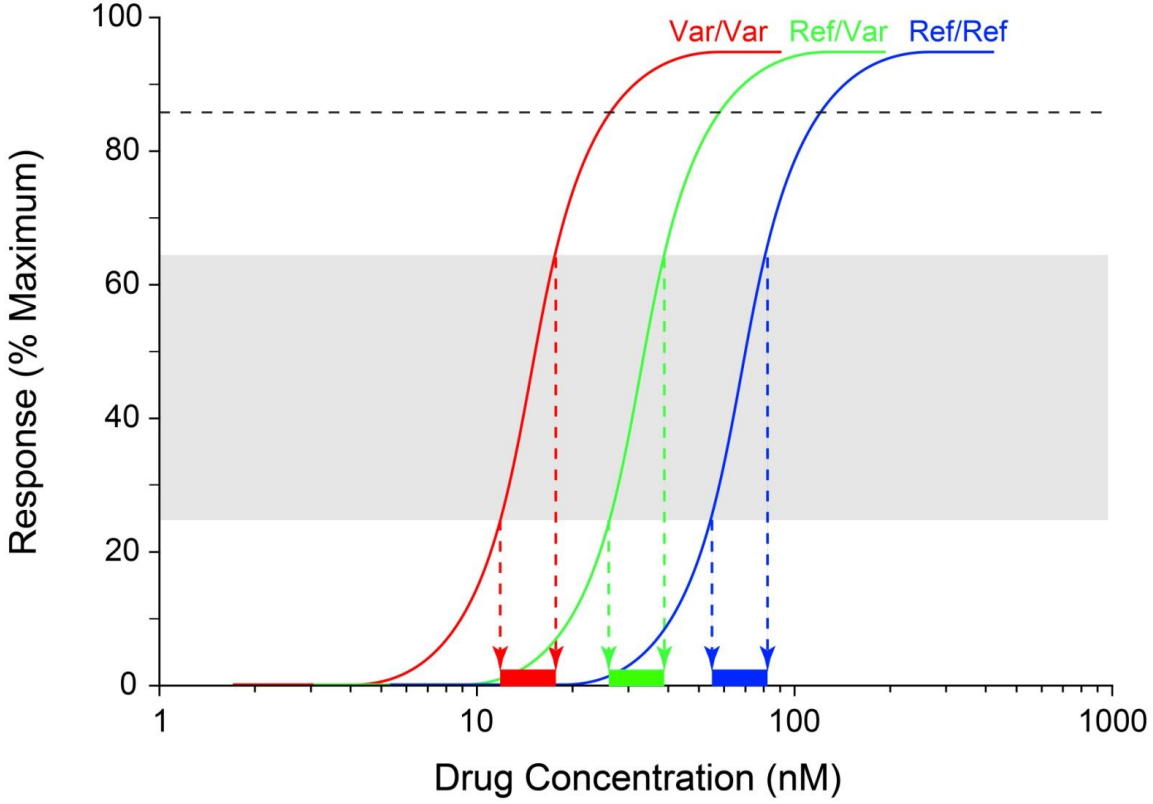


~~Dose~~ → ~~Exposure~~ → ~~Response~~

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?

Proposal for the Future: 4. Exposure-Controlled Dosing



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

What should the target exposure be?

Is it the same across drug target expression/function levels?

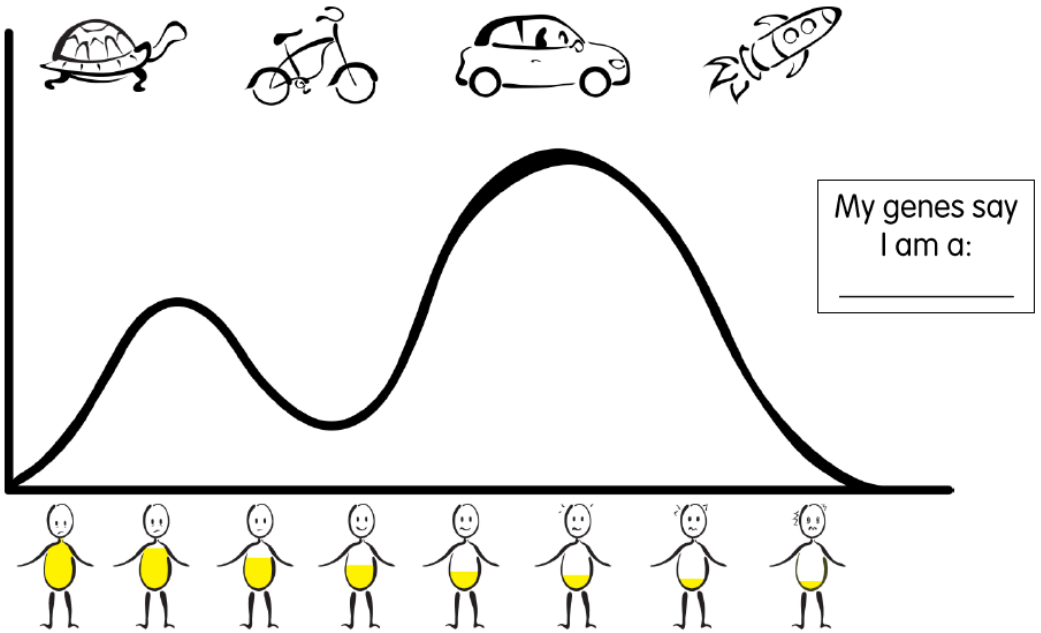
Accessible surrogate markers of drug response?

McLaughlin *et al,* CTS 2019 (PMID: 30516322)

Summary and Conclusions

- Origins of pediatric pharmacogenetics lightly linked to the development of pediatric clinical pharmacology as a discipline
- Some cases of demonstrable impact (TPMT+NUDT15 in ALL; regulatory changes for codeine), but few examples of widespread integration into clinical practice
- Genotype-stratified PK studies have the potential to efficiently capture magnitude of PGx effect, and to identify additional sources of variability
- Future studies should utilize all available sources of new data, especially the value of opportunistic sampling for PK and PD studies, including biomarkers predictive of drug disposition and response (metabolomics)
- Generating more models is not sufficient; require prospective validation

Engaging Patients and Families



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