Personalized Care in Pediatric Medicine

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What is Pharmacogenomics?

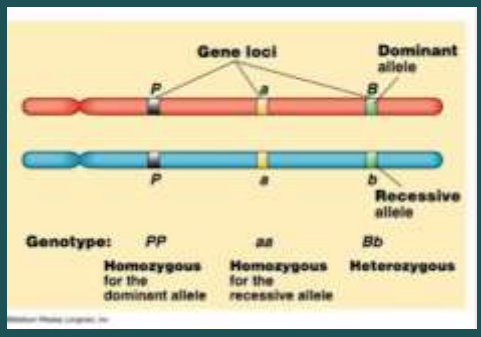
- Interchangeable with pharmacogenetics
  - Can be inferred as a single test result or the "bigger picture" as a science of pharmacogenomics
- Study of gene expression impact on both pharmacokinetic and pharmacodynamic processes
- One size does NOT fit all – era of personalized medicine

What is Pharmacogenomics?

- Goal: to reduce adverse drug reactions (ADEs)
- Companion testing
- Salvaging drugs with a profile high in toxicity
- Increased medication regimen adherence?

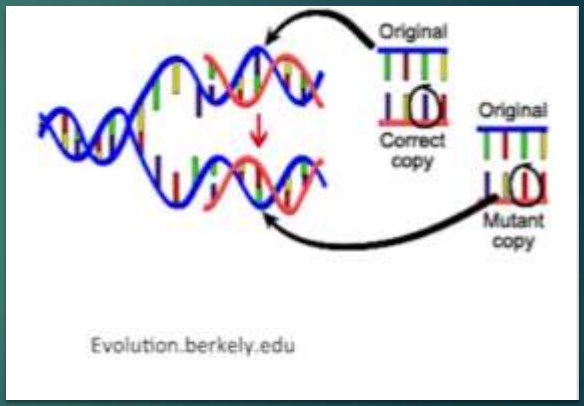
Allele Review

- Genes can be polymorphic between individuals with the same gene
- Differences are represented by variants or alleles
- If alleles are the same = homozygous
- If alleles are different = heterozygous



Mutation Review

- Can be single based substitutions, deletions, insertions
- "synonymous" – same enzyme coding
- "non-synonymous" – different enzyme coding
- Frame shifts move the entire codon down (or up)
- Induced mutations can occur such as by UV light

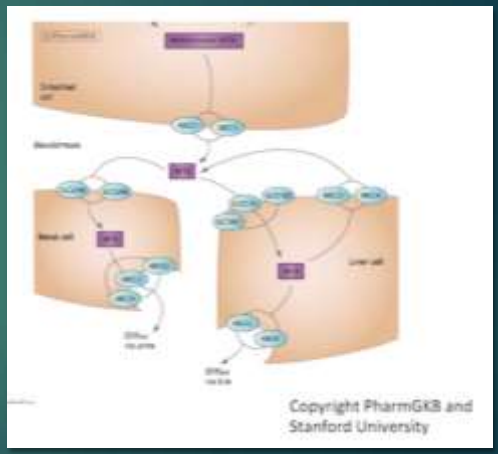


Phenotype and Genotype Review

- Phenotype refers to the expression of a genotype
- Can be visible ie: eye color, skin color, height
- Can be invisible: blood type, disease
- Health care team may need to provide phenotypes

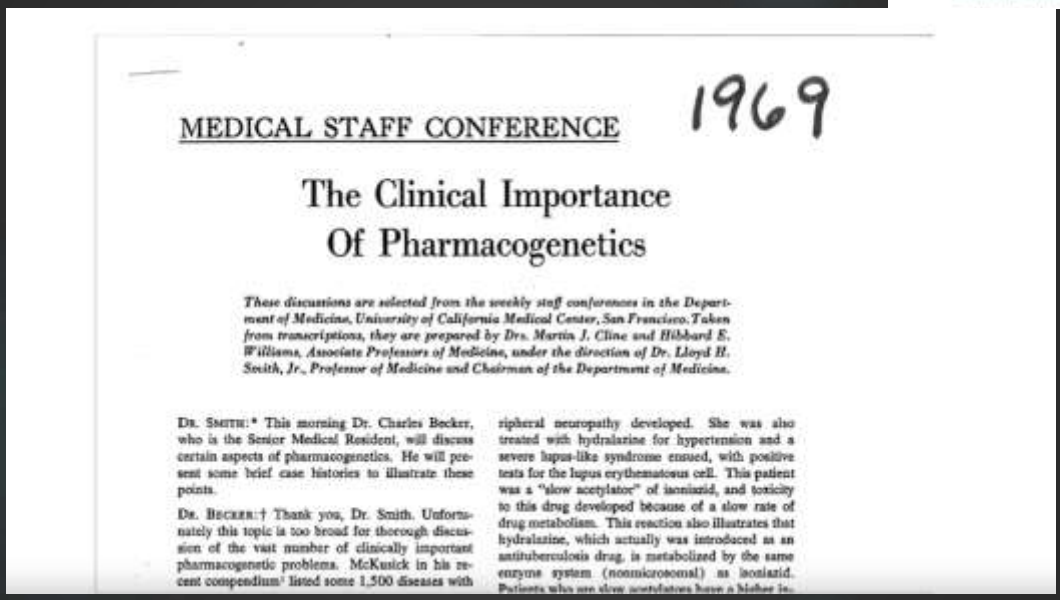
Basics of Pharmacogenomics

- Drug metabolism
  - CYP enzymes
- Drug transport
  - SLCO1B1, ABCG2
- Drug targets
  - VKORC1, ADRB1
- Other
  - Downstream effect of metabolites



Basics of Pharmacogenomics

- One more piece of information – use it like SCr or WBC
  - Only about 75% of heterozygotes show clinical manifestations
- Classifications include wild type (normal), heterozygotes (one variant) and homozygotes (two variants). Can be ultrarapid, rapid and poor metabolizers depending on gene expression
- **NOT** the only answer



MEDICAL STAFF CONFERENCE 1969

The Clinical Importance Of Pharmacogenetics

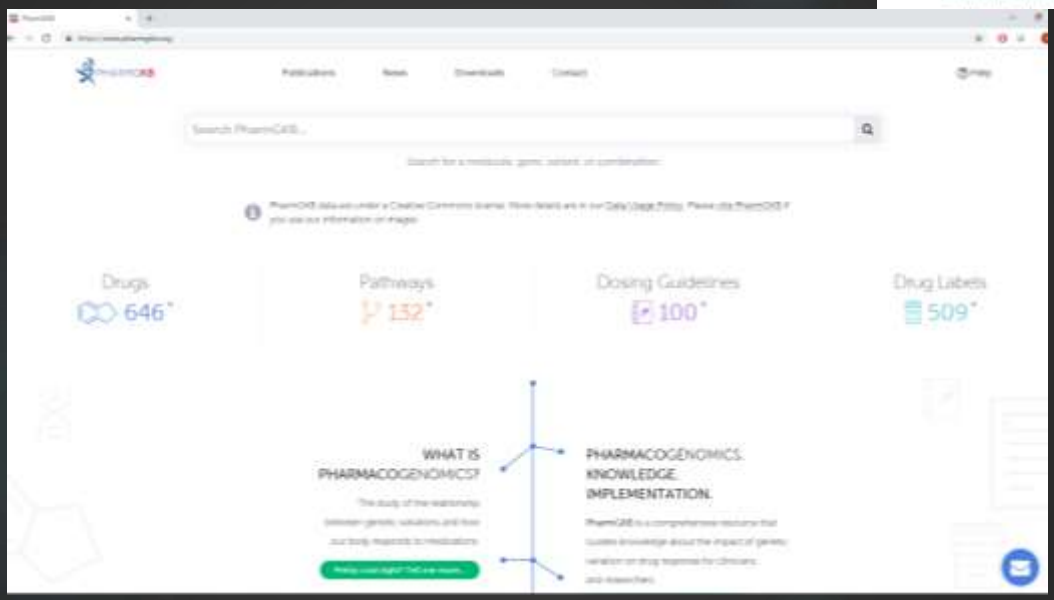
These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California Medical Center, San Francisco. Taken from transcriptions, they are prepared by Drs. Martin J. Cline and Hibbard E. Williams, Associate Professors of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine.

DR. SMITH:* This morning Dr. Charles Becker, who is the Senior Medical Resident, will discuss certain aspects of pharmacogenetics. He will present some brief case histories to illustrate these points.

DR. BECKER:† Thank you, Dr. Smith. Unfortunately this topic is too broad for thorough discussion of the vast number of clinically important pharmacogenetic problems. McKusick in his recent compendium[1] listed some 1,500 diseases with ripheral neuropathy developed. She was also treated with hydralazine for hypertension and a severe lupus-like syndrome ensued, with positive tests for the lupus erythematosus cell. This patient was a "slow acetylator" of isoniazid, and toxicity to this drug developed because of a slow rate of drug metabolism. This reaction also illustrates that hydralazine, which actually was introduced as an antituberculosis drug, is metabolized by the same enzyme system (nonmicrosomal) as isoniazid. Patients who are slow acetylators have a higher in-

Clinical Use of Pharmacogenomics

- Pre-emptive testing not currently in wide use
  - Primarily occurring at teaching/university hospitals, cancer centers
  - Requires investment in time and money as well as key policy development
- The FDA currently lists PGx biomarkers in 107 drug labels
  - Actionable pharmacogenetic data
    - Increase in ADE
    - Reduction in drug efficacy
  - Clinical Pharmacogenomics Implementation Consortium (CPIC) has published Level 1 evidence dosing guidelines.
    - Designed to provide safe dosing/drug use recommendations for drug/gene pairs for which there is sufficient evidence to support variance specific dosing
    - They do not address who should be tested, they only assume the test has been performed for some reason and the data is available
  - As the assays become more accurate and the cost decreases, testing will become embedded in the implementation of personalized medicine



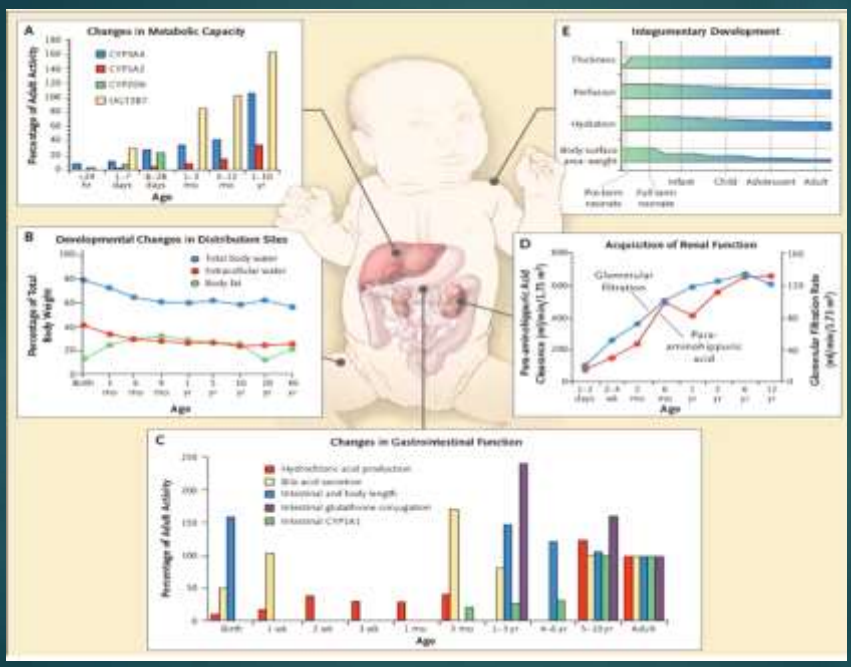
Pharmacogenomics Candidate

- Narrow therapeutic index
  - Toxicity and effective dose closely related
- Single gene mutation vs. multigenetic
- Published dosing guidelines
- Validated, reliable assay
- Many more…

Medication Consideration in Children

- 60% receive prescription medication annually
  - 25% have a chronic condition
    - Accounting for 70% of rx
- Children are at high risk for ADEs
- ADEs rank between 4-7 most common cause of death
- Healthcare costs of ADEs > 177 billion $
- As much as 60% of those ADEs associated with genetic variants in drug metabolizing enzymes

Becker ML and Leeder JS Pharmacogenomics 2010;11:1591-1602
Amur S et al Personalized Medicine 2010;7:633-642



Developmental Pharmacogenomics

- Ontogeny
  - The development or course of development especially of an individual organism
- Ontogeny of drug metabolizing enzymes (DME)
  - Impact of the organism's maturation on the disposition of a drug
  - Direct effect on systemic exposure

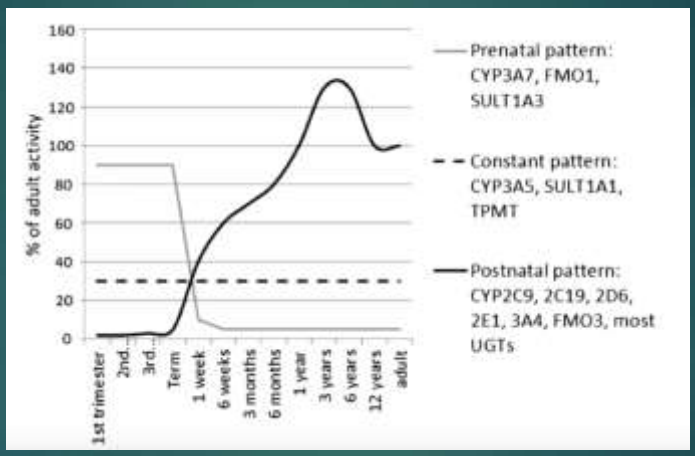
Merriam-Webster's collegiate dictionary, 1999

Example of Ontogeny With Respect to PGx

- Chloramphenicol
  - Grey baby syndrome
    - Grey appearance
    - Accompanied by multi organ failure
    - Increased toxic concentrations resulting in death
- UGT2B7
  - Immature at birth

De wildt SN et al Arch Dis Child 2014;99:1137-1142

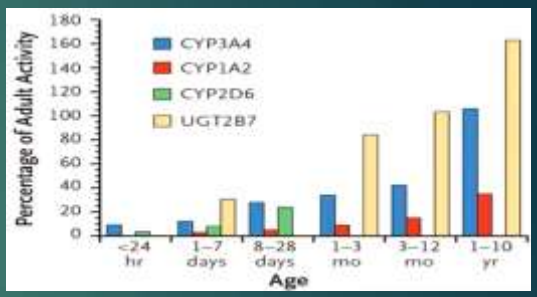
Patterns of DME with Maturation



De Wildt SN et al Arch Dis Child 2014;99:1137-1142;
Leeder JS et al J Clin Pharmacol 2010;50:1377-1378

Patterns of DME with Maturation

CYP ENZYME	BIRTH	POST – NATAL
CYP 1A2	NEGLIGIBLE	50% ADULT EXPRESSED AT 1 YEAR
CYP 2B6	NEGLIGIBLE	50% ADULT EXPRESSEION AT 16 MONTHS
CYP 2D6	NEGLIBIGLE	100% ADULT EXPRESSED AT 2 WEEKS
CYP 2C9	20% OF ADULT ACTIVITY	50% ADULT EXPRESSED AT 1 MONTH
CYP 2C19	30% OF ADULT ACTIVITY	100% ADULT ACTIVITY BY 12 MONTHS



Kearne CL et al NEJM 2003;349:1157-1167
Leeder JS et al J Clin Pharmacol 2010;50:1377-1387

Disease State

- Variable pharmacodynamic effects
- Prevalence in children vs adults
  - PPHN w/ sildenafil
- Pediatric diseases not observed in adult population
  - Kawasaki disease
- Variable presentation of diseases
  - HTN in adults vs. children

Pharmacist Assessment in Gene/Drug Pairing

- Is the treatment similar between the pediatric and the adult population?
- Based on the drug of interest what genes are important?
- Are the variations associated with specific consequences in vivo?
- What is the development profile for the gene of interest?

Leeder JS et al J Clinical Pharmacol 2010;50:1377-1387

CPIC Clinical Pharmacogenetics Implementation Consortium

- Ondansetron
  - "no data available on CYP2D6 genotype's effect on Ondasetron response in pediatric populations
  - "no reason to suspect CYP2D6 genetic variation will affect drug's metabolism differently in children…."
  - CYP2D6 activity depends strongly on developmental aspects
- SSRIs
  - "Data describing relationship between CYP2D6 and CYP2C19 genotype and SSRI exposure are scarce" – use caution and close monitoring

Bell GC et al Clin Pharmacol Ther 2017;102:21-218
Hicks JK et al Clin Pharmacol Ther 2015;98:127-134

FDA U.S. FOOD & DRUG ADMINISTRATION

- **Total → 65 with pediatric labeling including PGx**
  - 56 of them derived from adult trials
  - 9 derived from pediatric trials
  - 40 deemed "suitable" for pediatric patients
  - 16 unclear

When are Pharmacogenomic Tests Worth it?

- What is the number needed to treat?
- What is the ethnic variation?
- How much does the test cost to run? To interpret?
- Can insurance reimburse?
- What are the cost savings gained through the implementation of this type of pre-emptive testing?

Ethics of Pharmacogenomics in Children

- Incidental finding vs secondary findings
- American college of medical genetics and genomics
  - Published list of around two dozen VIP genes that will be required to be reported when exome and genome sequences are returned – initially discussed regardless of age
  - "this evaluation and reporting should be performed for all clinical germline exome and genome sequencing, including the 'normal' of tumor-normal subtractive analyzes in all subjects, irrespective of age, but excluding fetal samples."
  - "the working group also felt that the ethical concerns about providing children with genetic risk information about adult-onset diseases were outweighed by the potential benefit to the future health of the child and the child's parent of discovering an incidental finding where intervention might be possible"

Ethics of Pharmacogenomics in Children

- American Academy of Pediatrics (AAP)
  - Published "Disclosure of Incidental Findings From Next-Generation Sequencing in Pediatric Genomic Research"
  - Published "Ethical and Policy Issues in Genetic Testing and Screening of Children" advocating "predictive genetic testing for adult onset conditions generally should be deferred unless and intervention initiated in childhood may reduce morbidity or mortality"
  - "decisions about whether to offer genetic testing and screening should be driven by the best interest of the child"

What's Next?

- Add more drug/gene pair decision to support
- Alter prescriber to pre-emptive testing when appropriate
- Create new IT platform for handling pharmcogenomic results
- Move to clinical exome sequencing when appropriate
- Develop institutional policies on consenting, reporting of incidental findings in children

Thank You!

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