

Pharmacogenomics in Pediatric Product Development and Labeling

Pediatric Advisory Committee

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Disclaimer

- *The views and opinions expressed in this presentation reflect those of the presenter and do not necessarily reflect the views and opinions of the U.S. Food and Drug Administration.*

Outline

- Introduction to Pharmacogenomics
- Regulatory Framework
- Pharmacogenomic Information in Labeling

Definition

- *Pharmacogenomics (PGx) – The study of variations of DNA and RNA characteristics as related to drug response*

Impact of Genetic Differences

Pharmacokinetics			
Absorption	Distribution	Metabolism	Elimination
Drug Target			
Intended Target	Unintended Target		
Efficacy/Safety			
Susceptibility/Prognosis	Immunologic/Idiosyncratic		

“Biomarker”

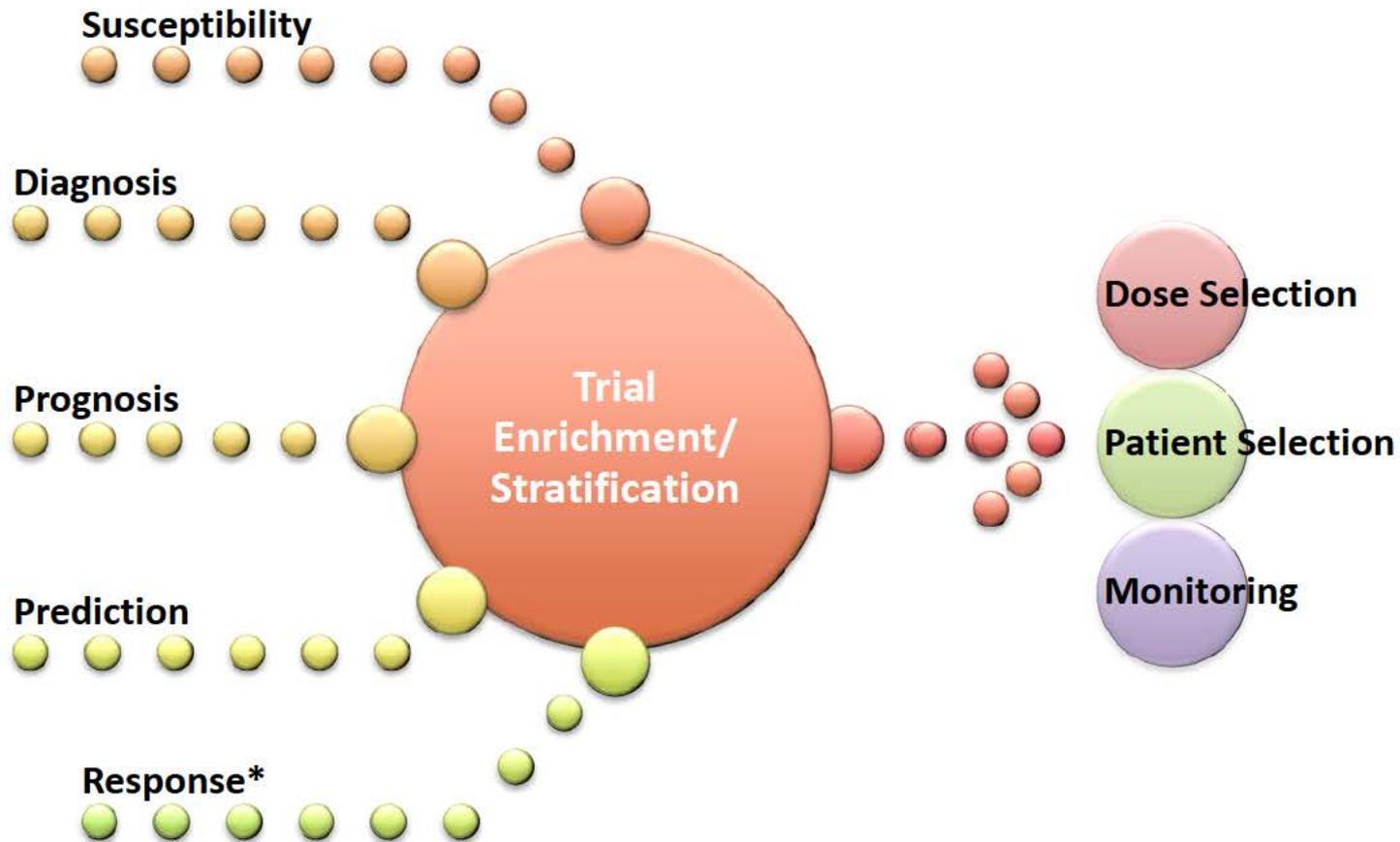
- A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions.
- Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers; in genomics it is a measurable DNA or RNA characteristic.
- A biomarker is not an assessment of how a patient feels, functions, or survives.
- Categories: diagnostic, monitoring, pharmacodynamic/response, predictive, prognostic, safety, susceptibility/risk



“Precision Medicines”*

- Drug or biologic intended for use with a genomic, proteomic, or other specific biomarker that identifies patients within a disease who are eligible for treatment, aids in determining the appropriate dose, or allows for monitoring response to individualize therapy
- Biomarkers may have diagnostic, prognostic, predictive, or other value; mechanistically related to the drug of interest in most cases

Biomarkers in Clinical Drug Development

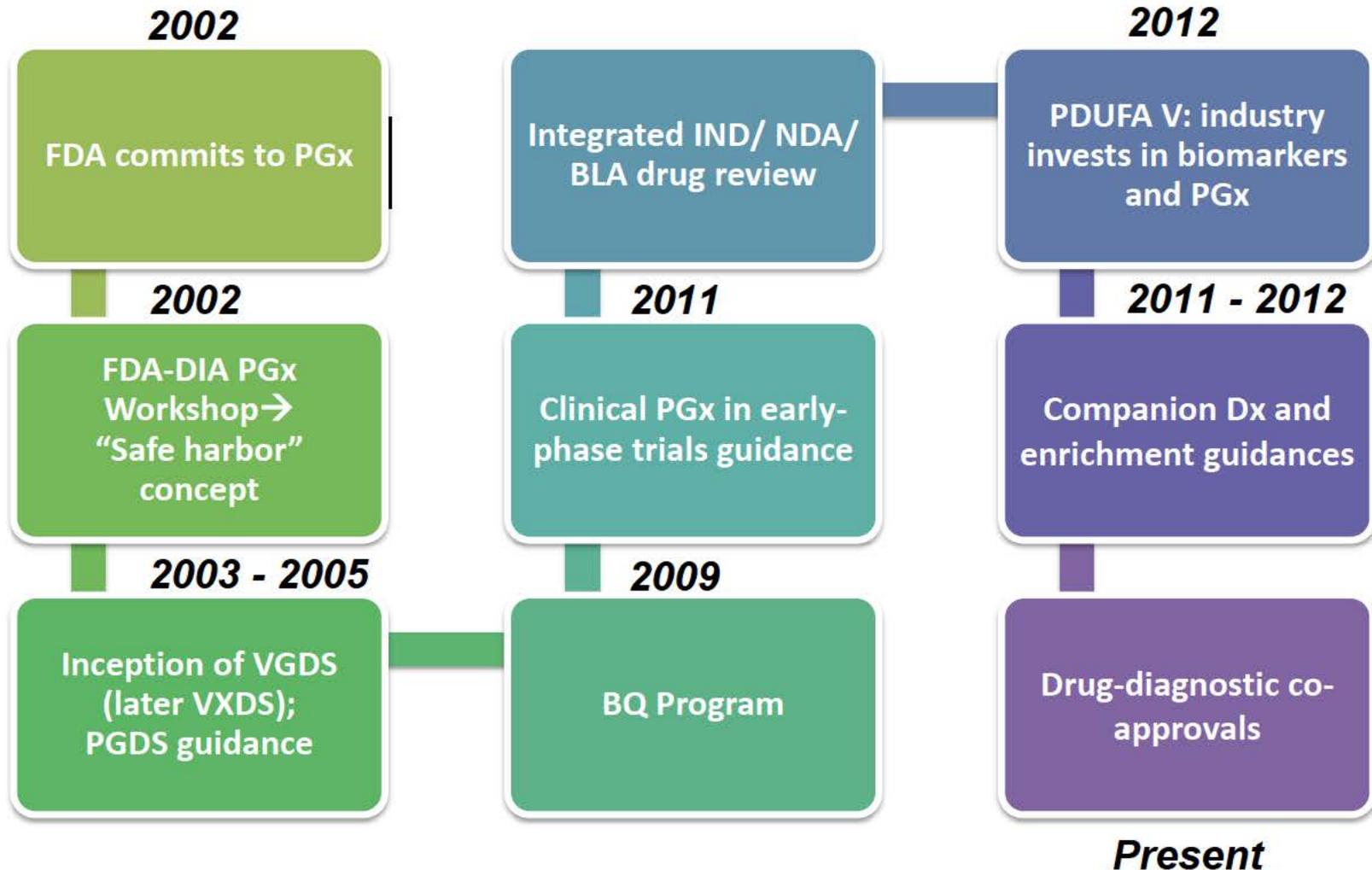


Pharmacogenomic Studies

- Uses for genomic data
 - Basis for evaluating PK/PD outliers, intersubject variability
 - Clinical trial enrichment
 - Analysis of subgroup effects
 - Estimating magnitude of potential drug-drug interactions
 - Investigating molecular/mechanistic basis for lack of efficacy, adverse drug effects
- Potential impact
 - Select patients for treatment based on risk/benefit profile
 - Modify dosing
 - Intensify adverse effect monitoring

Regulatory Framework

History of Genomics at FDA



Regulatory Guidance



Year	Guidance, Guideline or Other Regulatory Resource
2005	Pharmacogenomic Data Submissions
	Drug-Diagnostic Co-Development Concept Paper*
2007	Pharmacogenomic Data Submission - Companion Guidance*
	Pharmacogenomic Tests and Genetic Tests for Heritable Markers
2008	E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories
2010	E16 Genomic Biomarkers Related to Drug Response: Context, Structure, and Format of Qualification Submissions
	Qualification Process for Drug Development Tools
2012	Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products*
2013	Clinical Pharmacogenomics: Premarketing Evaluation in Early Phase Clinical Studies
	Rule: Orphan Subsets of a Common Disease
2014	Guidance on in vitro Companion Diagnostic Devices
2015	ICH E18 Genomic Sampling Methodologies (Step 3)*
2016	Use of Standards in FDA's Regulatory Oversight of Next Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Used for Diagnosing Germline Diseases*
	Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based In Vitro Diagnostics*
	Principles for Codevelopment of an In Vitro Companion Diagnostic Device with a Therapeutic Product*

Guidance: Clinical PGx in Early-Phase Studies

- Collection and storage of DNA from a large number of clinical trial participants (all arms, all phases) is a prerequisite for adequate genetic studies
- **If** known factors are likely to influence efficacy, safety, or dosing of investigational drug, comparator, or background, **then** collect DNA from all subjects; specify objective
- **If** concentrations or responses are highly variable or exhibit ethnic differences, or serious toxicities are observed, **then** collect DNA from as many subjects as possible for future use in exploratory studies

Guidance: Clinical Trial Enrichment

- Definition: prospective use of any patient characteristic to select a study population in which detection of a drug effect (if one is in fact present) is more likely than it would be in an unselected population.
 - Practical: Decrease noise (i.e., placebo responders)
 - Prognostic: Increase event rates
 - Predictive: Select responders
- Considerations
 - When should studies be restricted to test (+) patients?
 - What kind/amount of data needed in test (-)?
 - If data needed in test (-), pre- or post-approval?

PGx Information in Drug Labeling

Labeling Principles

- Labeling should include PGx information to:
 - Inform prescribers about the impact of genotype on phenotype
 - Indicate whether a genomic test is available
 - If so, indicate whether testing should be considered, is recommended, or is necessary

- If applicable, a “Pharmacogenomics” subsection (12.5) should be included in the CLINICAL PHARMACOLOGY Section

- PGx information may include:
 - Information on allele frequencies
 - Description of functional effects of genomic variants
 - Effect of genotype on PK/PD
 - Dosing and patient selection based on genotype

Biomarkers and Genetic Factors in Labeling

- Approximately 200 gene-drug pairs are described in labeling
 - Covers 163 drugs and 54 biomarkers*
 - *43% metabolism/transport*
 - *34% target/pathway*
 - *23% immunologic/other safety*
 - Roughly 50% are actionable**, otherwise descriptive of study design feature or presence/absence of gene-drug interaction

* Includes some products with multiple drugs and families of biomarkers resulting in a phenotype (e.g. urea cycle disorders)

** Management recommendations excluding “use with caution”

Developmental Pharmacogenomics

- Represents the dynamic change in gene expression that accompanies the maturation process (from embryonic life through adolescence)
- Confounded by:
 - the inherent variability in PK and PD as children grow
 - limited understanding of the genetic-basis of certain pediatric diseases
- Accurate prediction of the effect of complex interactions of polymorphic enzymes, transporters, and receptors is challenging

Pharmacogenomic Information in FDA-Approved Drug Labels: Application to Pediatric Patients

DJ Green¹, P Mummaneni², IW Kim³, JM Oh³, M Pacanowski² and GJ Burckart¹

Pharmacogenomic (PGx) information is increasingly being incorporated into US Food and Drug Administration-approved drug labels. We reviewed the data source (adults vs. pediatrics) of PGx information in approved drug labels and assessed the suitability of applying adult-derived PGx information and related prescribing recommendations to the care of pediatric patients. We identified 65 drugs with labels containing PGx information and that have also been evaluated in children and found that in the majority of cases (56/65, 86%), the PGx information described was derived from adult studies. The application of PGx information from adults to pediatrics was deemed suitable for 71.4% ($n = 40$) of the drugs and unclear for 28.6% ($n = 16$). An ontogeny effect, limited or conflicting data regarding ontogeny of the genetic biomarker, or a difference in the pathophysiology or progression of the adult vs. pediatric disease were the primary reasons for deeming direct application from adults to pediatrics unclear.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Pharmacogenomic information is increasingly being incorporated into FDA-approved drug labels in order to inform the safe and effective use of medications.

WHAT QUESTIONS DID THIS STUDY ADDRESS?

☑ What is the data source of pharmacogenomic information in FDA-approved drug labels? Is it always suitable to apply PGx information derived from adult populations to the pediatric

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

☑ This is the first systematic review to examine the source of pharmacogenomic information in drug labeling and the first to provide an assessment regarding the appropriateness of applying adult pharmacogenomic findings and labeling recommendations derived from the adult population to the care of pediatric patients.

HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY AND THERAPEUTICS

☑ This assessment highlights important factors to consider

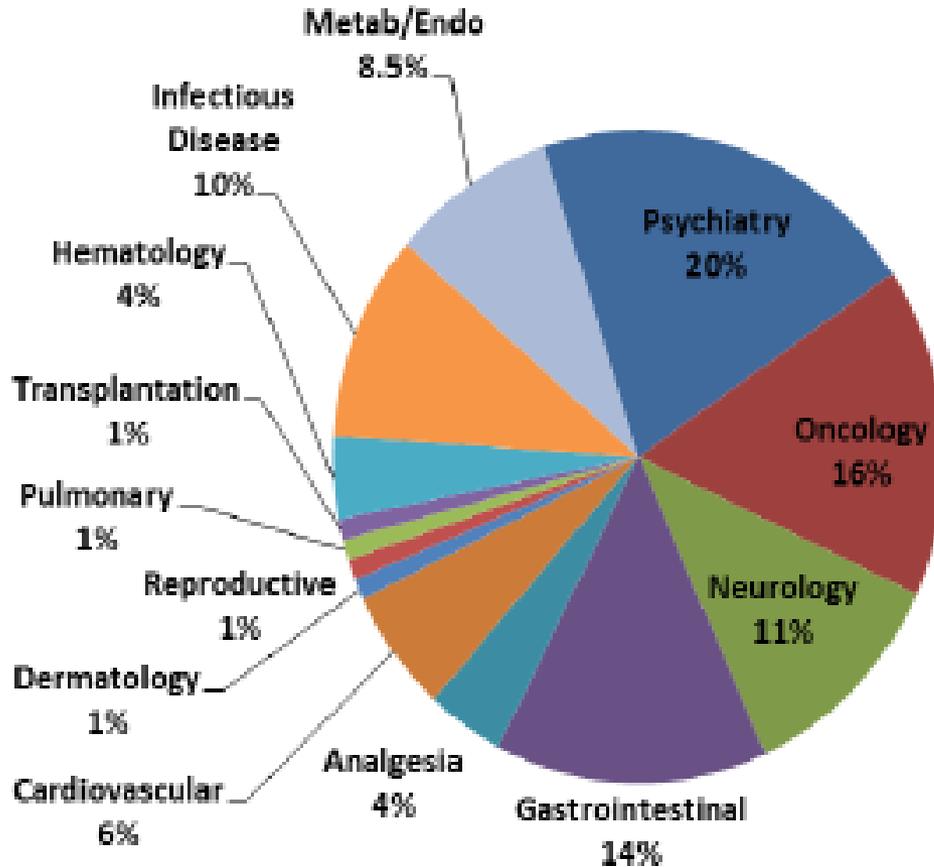
Objectives

- Survey FDA-approved drug labels for PGx data
- Determine the source (adults vs. pediatrics) of PGx data in FDA-approved drug labels
- Assess the suitability of applying adult-derived PGx-related findings and recommendations directly to the care of pediatric patients

Methods

- Searched Drugs@FDA; Daily Med; FDA Table of PGx Biomarkers
 - All labels 1945-2014
- Included only drugs which have been evaluated in pediatric PK, safety, and/or efficacy studies
- Categorized biomarkers as related to:
 - Safety and/or efficacy
 - Metabolic/transport, susceptibility, immunologic, or target/pathway
- Recorded actionable/recommended PGx-related prescribing statements

Results



65 drugs, 31 biomarkers

- 56% *metabolism/transport*
- 27% *target/pathway*
- 16% *susceptibility*
- 4% *immunologic*

- 68% *safety*
- 27% *efficacy*
- 6% *both*

28 “actionable”

- Otherwise, descriptive of study design feature or presence/absence of gene-drug interaction

Results

- For 56/65 drugs (86%), the genetic biomarker data described in labeling was derived from adult studies
 - Of the 9 cases when PGx labeling was directly informed by pediatric studies, the majority involved diseases that originate primarily in childhood

- The application of PGx information from adults to pediatrics was deemed
 - suitable for 71.4% (n=40) of drugs
 - unclear for 28.6% (n=16) of drugs
 - 11 cases involved children 2 years of age or younger* and either a clear, conflicting, or unknown effect of ontogeny on the absorption/distribution/metabolism/elimination-, susceptibility-, or immunologic-related genetic biomarker
 - 5 cases involved a target/pathway-related biomarker which was specific to the adult disease and which differed substantially from the pediatric disease studied

Summary

- PGx information is increasingly being incorporated in FDA-approved drug labels and can facilitate tailored drug therapy for the individual patient
- The majority of PGx information in drug labeling is derived from studies in adults
- Developmental differences in gene expression, drug response, and drug metabolizing capacity can result in an inability to universally assume similar genotype-phenotype relationships between adults and all pediatric age groups
- The application of adult-derived PGx information to pediatrics is particularly challenging when:
 - Attempting to apply findings to the youngest patients (e.g., neonates, infants)
 - There are differences between the adult and pediatric disease

