

# Ontogeny and Application of Pharmacogenomics to Pediatrics

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*Pediatric Ontogeny: Ready for Incorporation into Modeling  
in Pediatric Drug Development?*

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# Outline

- Product Labeling
  - Considerations for including pharmacogenomic (PGx) information in labeling
  - Pediatric product labeling
- Application of PGx information in labeling to pediatric patients
  - Implications of ontogeny
- Case examples
  - Cisplatin
  - Codeine

# Disclaimer

- The views expressed in this talk represent my opinions and do not necessarily represent the views of FDA
- All specific drug development questions should be discussed with the relevant review division
- I have no financial relationships to disclose relating to this presentation



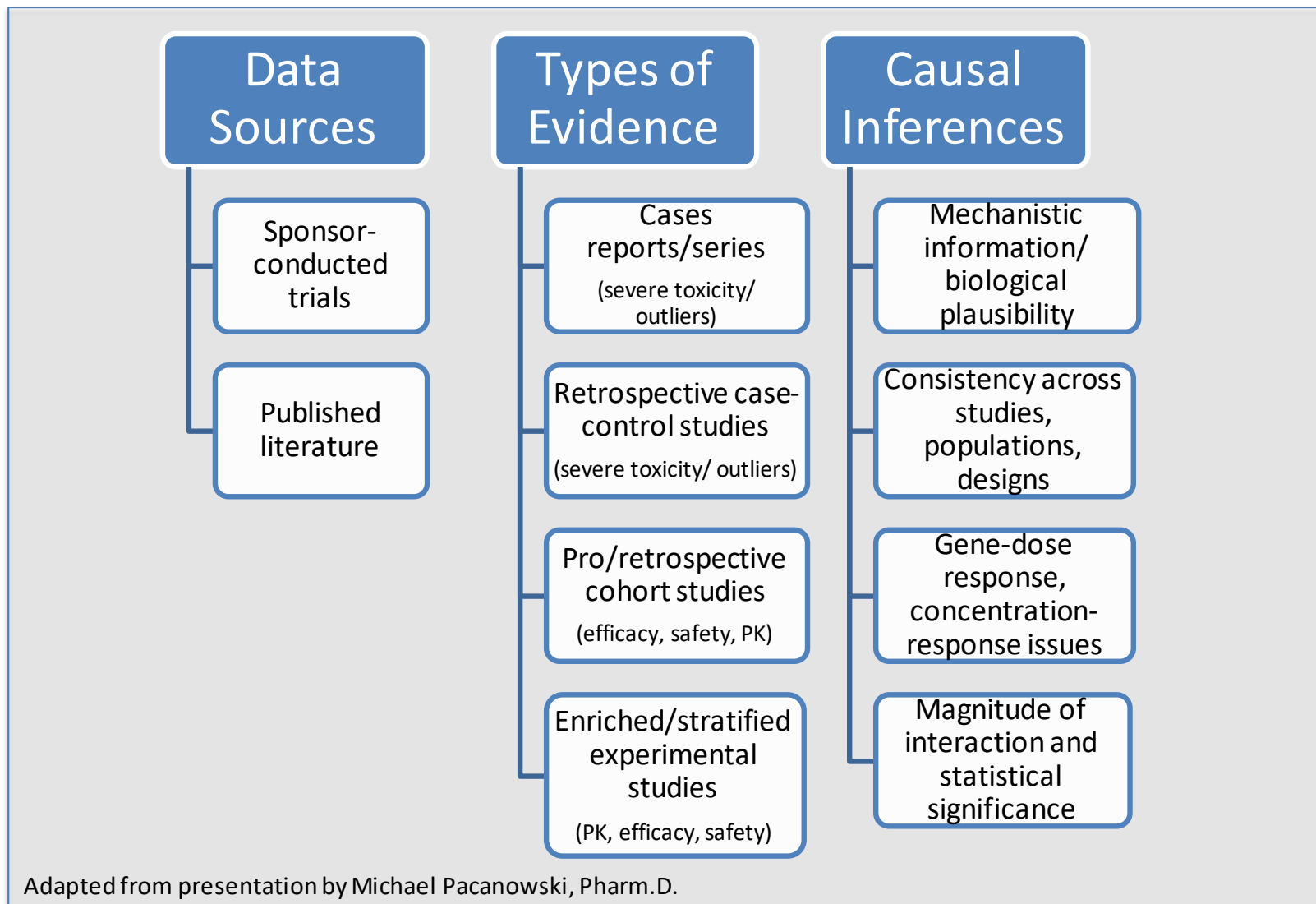
# Why Focus on Product Labeling?

- Contains a summary of the scientific information needed for safe and effective use of a product
- Provides health care providers the information they need to prescribe drug products appropriately
- Must be informative and accurate
  - Prior to incorporation, the information has been critically reviewed and vetted by the FDA
  - Updated when new information becomes available
  - Consensus must be reached amongst the FDA review team; and agreement with the application holder

# PGx Labeling Principles

- Labeling should include PGx information to:
  - Inform prescribers about the impact of genotype on phenotype
    - Should be clinically meaningful and inform prescribing decisions
  - Indicate whether a genomic test is available
    - If so, indicate whether testing should be considered, is recommended, or is necessary
- PGx information may include:
  - Data on allele frequencies
  - Description of functional effects of genomic variants
  - Description of the effect of genotype on PK/PD
  - Recommendations regarding dosing and patient selection based on genotype
- If applicable, a “Pharmacogenomics” subsection (12.5) should be included in the CLINICAL PHARMACOLOGY Section

# Considerations for Establishing the Clinical Validity of a Gene-Drug Interaction



# Experience with Labeling Gene-Drug Interactions

Data emerge mostly in post-marketing setting, often external to sponsor's clinical trials

Clinical events are usually severe and gene-drug interaction is highly replicated with significant increase in relative risk

Many gene-drug interactions are extensions of known clinical pharmacology (e.g., drug interactions)

Prospective validation trials are less common; totality of evidence must be considered (PK-PD-outcome)

# Considerations for Deciding to Update Product Labeling

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- ☒ Reliability of the data
  - ☒ Magnitude of the risk
  - ☒ Seriousness of the event
  - ☒ Plausibility of causality
- 
- ☒ Extent of patient exposure
  - ☒ Potential to prevent or mitigate the risk
  - ☒ Effect on clinical practice
  - ☒ Disproportionate impact on particular populations
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# Factors Guiding the Strengths of Prescribing Recommendations

## Points of Uncertainty

- Effectiveness of genotyping to optimize benefit/risk (utility)
- Quality of studies to establish validity (design, assay, statistics)
- Gaps in empirical evidence (e.g., inference from PK-outcome relationship vs. direct subgroup analysis of outcomes)
- Generalizability to diverse racial/ethnic populations

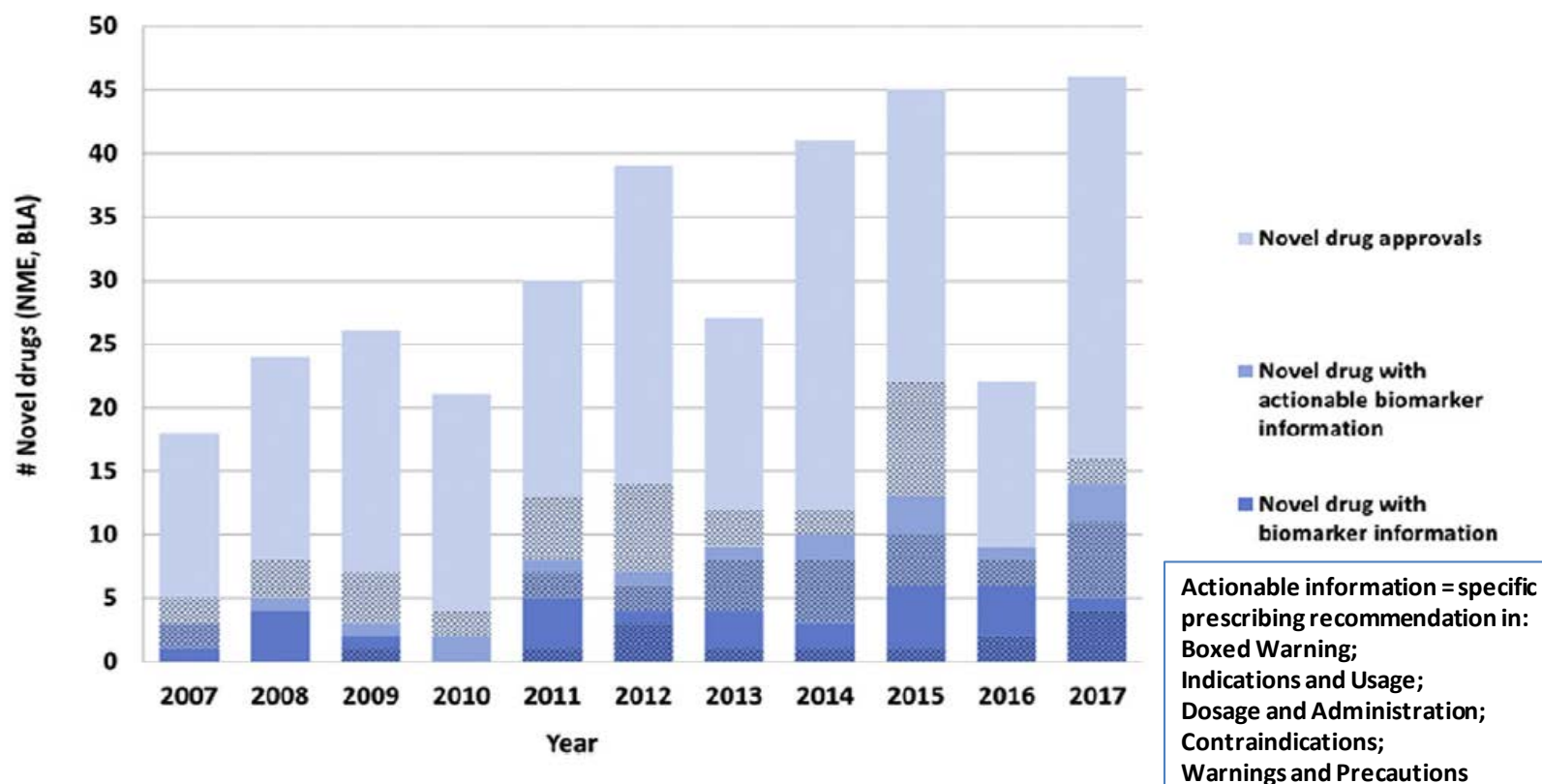
## Considerations

- Severity of the outcome
- Treatment context (benefit/risk of alternative treatments, clinical monitoring tools, dosage forms)
- Clinical performance attributes in the context of event rate
- Test accessibility and feasibility, likelihood of prescriber uptake

# Approaches to Incorporate Genetic Testing Recommendations

- Labeling is often silent on testing recommendations
  - Reference to '*known status*' and '*consider*' accommodates clinical judgment, uncertainty
  - Implicit that testing is essential when included in *Indications and Usage* or *Contraindications*
- When recommended, various approaches have been used
  - Test everyone (eliglustat, abacavir)
  - Test a targeted, at-risk subset (carbamazepine, valproic acid)
  - Test above a certain dose threshold (pimozide, tetrabenazine)
- Other considerations
  - Specific alleles are generally referenced
  - Population prevalence is not uniformly described

**FIGURE 1 Novel Drugs Approved (NME/BLA) Between 2007 and 2017 With Genomic and Other Selected Biomarker Information in Labeling**



# Questions to Ponder

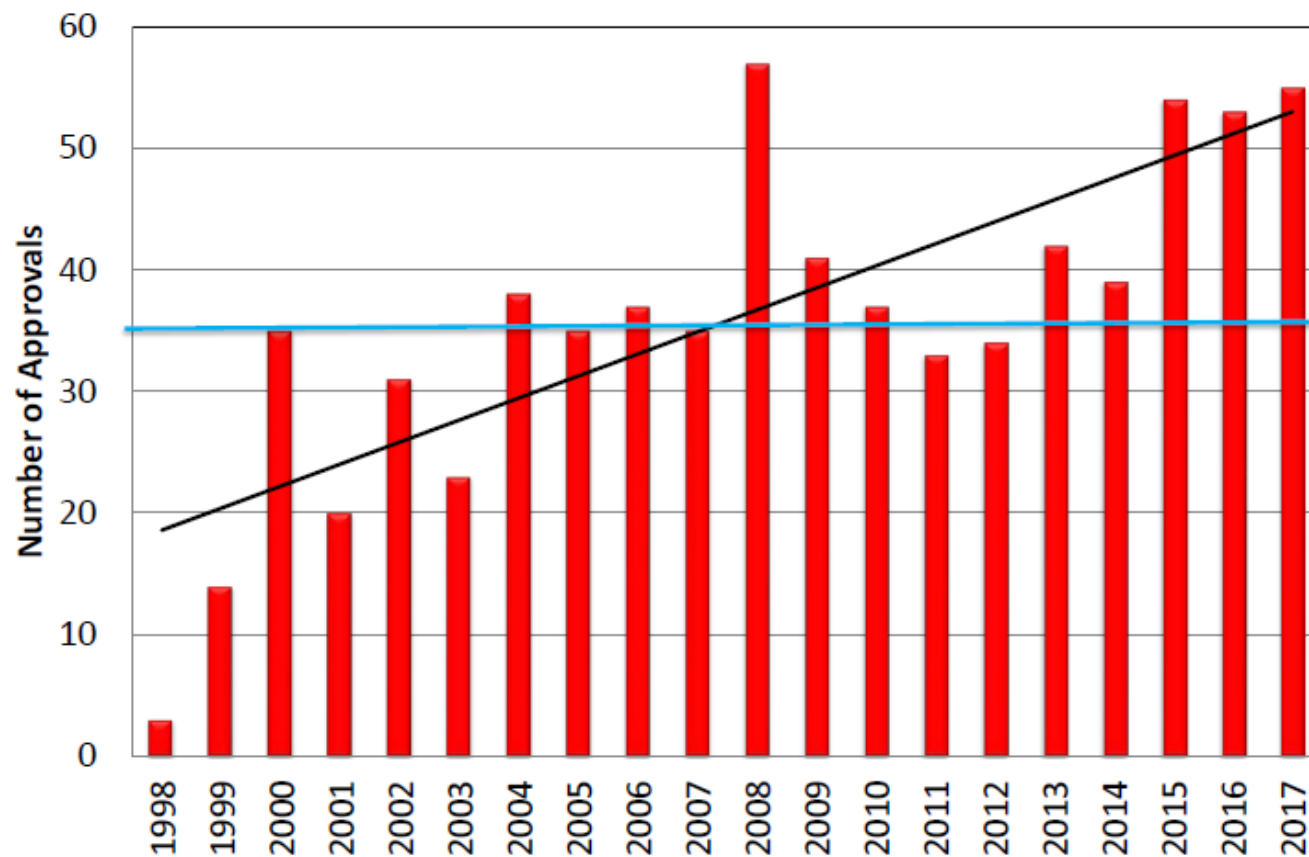
- What is the source of PGx information in labeling?
- How does the information apply to the care of pediatric patients?



# Why Focus on Pediatric Labeling?

- The Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA) have substantially increased the number of pediatric studies conducted and the amount of pediatric information in product labeling

## Pediatric Labeling Changes 1998 - 2017



# The Ultimate Goal

**783** drug labels updated (as of April 30, 2019)



**708** with new pediatric studies; **70** with no new pediatric studies



Information in product labeling that informs the safe and effective use of medications in the pediatric population

# PGx Information in Labeling: Application to Pediatric Patients?

Between 1945 - 2014

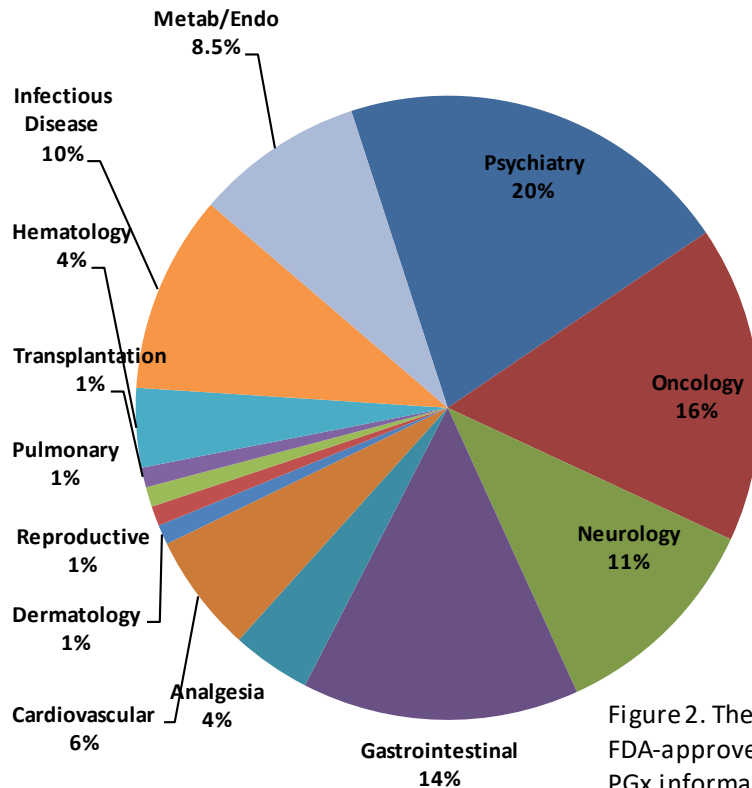


Figure 2. Therapeutic areas for the 65 FDA-approved drug labels containing PGx information for drugs that have been studied in pediatric PK, safety, and/or efficacy studies.

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



# PGx Information in Labeling: Application to Pediatric Patients?

- For 86% (56/65) of the drugs, the genetic biomarker data described in labeling was derived from adult studies
  - Of the 9 cases where PGx labeling was directly informed by pediatric studies, the majority involved diseases originating primarily in childhood
- For the purposes of this analysis, age greater than 2 years was used as a conservative cutpoint for when many metabolic enzymes have reached a level of activity that approximates adult levels
- 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
- Of those deemed unclear:
  - 11 cases involved children 2 years of age or younger and either a clear, conflicting, or unknown effect of ontogeny on the ADME-, 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

# Application to Pediatrics:

## Key Takeaways

- The majority of PGx information in drug labeling is derived from studies in adults
- Developmental differences in gene expression, drug response, and drug disposition 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

# Incorporation of Pediatric PGx in Labeling: Select Drug Safety Examples



- Cisplatin
- Codeine

# Differences in the Incidence of Pediatric & Adult Drug-Induced Hearing Loss

- Cisplatin – is a platinum based chemotherapeutic agent
  - FDA-approved since 1978 for the treatment of multiple adult cancers
  - Not approved for use in pediatrics
  - Critical and effective component of treatment regimens for many pediatric solid and CNS tumors
- Risk: drug-induced ototoxicity
  - Occurs in up to 10-25% of adults vs. 26-90% of children
  - High frequency, bilateral, sensorineural hearing loss
  - Progressive, irreversible
  - Negative impact on cognitive and social development
  - MOA unknown
  - **Younger age increases risk and severity** (Pediatric Ontogeny???)
- Source: published literature (retrospective candidate gene study and replication cohort)
  - Association identified between variants in the TPMT gene and cisplatin-induced ototoxicity in pediatric patients

# Differences in the Incidence of Pediatric & Adult Drug-Induced Hearing Loss



- Dec. 2011 – Cisplatin label updated
  - Informational only (regarding TPMT association and study description), stressed importance of aggressive monitoring for hearing loss, no testing recommendation
- Subsequent independent study published; failed to replicate gene-drug interaction findings (study design and study cohort were slightly different)
- Feb. 2015 – Cisplatin label updated
  - Informational only, mentions genetic factors may be associated with increased risk and lists TPMT as an example; study description removed

# CYP2D6 Polymorphism Alter Morphine Exposure and Response



- Codeine – an opioid analgesic
  - is a prodrug
  - must be metabolized into morphine for activity
  - CYP2D6 is the metabolizing enzyme in the liver
- Poor metabolizer (PM) phenotype
  - Reduced biotransformation to morphine
  - Poor analgesia
- Ultra-rapid metabolizer (UM) phenotype
  - Rapid and complete conversion to morphine
  - Higher than expected serum morphine levels
  - Possible toxicity
- Risk: respiratory depression; death
  - **Pediatric population at greater risk** (Pediatric Ontogeny???)
- Source: published literature (case series; PK studies)
  - Cases of respiratory depression or death in children with obstructive sleep apnea treated with codeine following tonsillectomy/adenoidectomy (CYP2D6 UMs)
  - Similar events in infants of breast-feeding mothers

# CYP2D6 Polymorphism Alter Morphine Exposure and Response

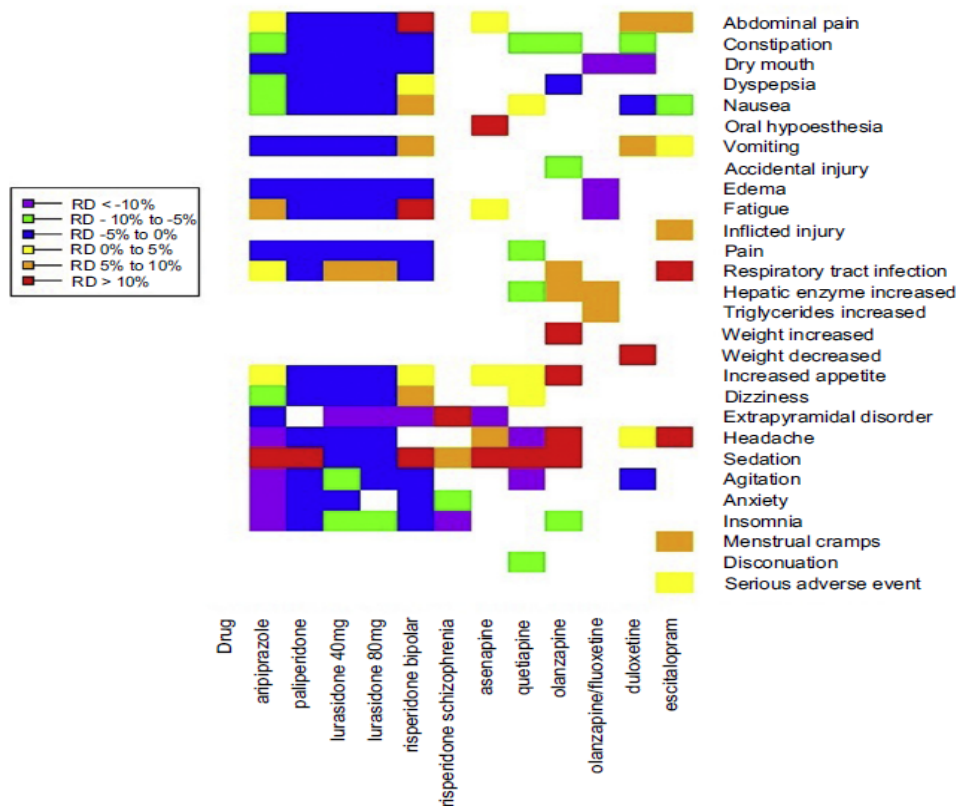


- Aug. 2012: FDA issued a safety alert regarding the use of codeine in children after tonsillectomy, adenoidectomy, or adenotonsillectomy
- Feb. 2013: FDA added a box warning to the label of codeine and codeine-containing preparations advising health care professionals to prescribe an alternative analgesic for postoperative pain control in children undergoing tonsillectomy and/or adenoidectomy and added a contraindication of use in this population
- Apr. 2017: FDA added a contraindication of use in children younger than 12 years to treat pain or cough; a new warning recommending against use in adolescents (12-18 years) who are obese or have sleep apnea or severe lung disease; and strengthened warnings recommending mothers not breastfeed if taking codeine
- Jan. 2018: FDA restricted use of prescription codeine pain and cough medicines in children less than 18 years of age

# Pediatrics and PGx Future is in Drug Safety:

Are differences in the incidence of adverse drug reactions (ADR) in pediatric patients a developmental/PGx related phenomenon?

Risk Difference (RD) = Risk in pediatric patients – Risk in adult patients



## Key Points

- 10 FDA-approved antipsychotic or antidepressant agents (2007 – 2017)
- 308 drug and ADR combinations
- 113 (36.7%) had significantly different incidence in pediatrics compared to adults
- 68 (60.2%) of these had a higher incidence in pediatrics than adults
- Sedation was higher in 6/10 drug and drug combinations (RD: 9.6% – 36.6%)

**PEDIATRIC ONTOGENY???**



# Summary

- PGx information is increasingly being incorporated in FDA-approved product labels and can facilitate tailored drug therapy for the individual patient by providing important information to prescribers;
- To date, the majority of PGx information in labeling has been derived from studies in adults;
- Previous recommendations of exercising caution when attempting to apply adult PGx guidelines to children below 2 years of age still holds true;
- Observed genotype-phenotype relationships in adults may not always be reflective of those in certain pediatric age groups;
- The quantitative data necessary for modeling certain PGx markers in pediatrics is still lacking and further research is needed; and
- Continued PGx/ontogeny research focused on drug safety and understanding the underlying mechanisms contributing to differences in ADRs between pediatrics and adults is warranted

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