Optimizing Pediatric Pharmacotherapy Through the Use of Pharmacogenomics

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Disclosure

All planners, presenters, reviewers, and ASHP staff of this session report no financial relationships relevant to this activity.
Learning Objectives

• Analyze the role of the pediatric pharmacist in pharmacogenomics.
• Apply pharmacogenetic test results to the care of pediatric patients.
• Evaluate current pediatric pharmacy practice models that integrate pharmacogenomics.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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</thead>
<tbody>
<tr>
<td>6-MP</td>
<td>6-mercaptopurine</td>
</tr>
<tr>
<td>ADHD</td>
<td>attention deficit hyperactivity disorder</td>
</tr>
<tr>
<td>AZA</td>
<td>azathioprine</td>
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<tr>
<td>BCPPS</td>
<td>Board Certified Pediatric Pharmacy Specialist</td>
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<tr>
<td>CFTR</td>
<td>cystic fibrosis transmembrane conductance regulator</td>
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<tr>
<td>CPIC</td>
<td>Clinical Pharmacogenetics Implementation Consortium</td>
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<tr>
<td>EHR</td>
<td>electronic health record</td>
</tr>
<tr>
<td>IM</td>
<td>intermediate metabolizer</td>
</tr>
<tr>
<td>MTM</td>
<td>medication therapy management</td>
</tr>
<tr>
<td>NM</td>
<td>normal metabolizer</td>
</tr>
<tr>
<td>NUDT15</td>
<td>nudix hydrolase 15</td>
</tr>
<tr>
<td>PGx</td>
<td>pharmacogenomics</td>
</tr>
<tr>
<td>PM</td>
<td>poor metabolizer</td>
</tr>
<tr>
<td>PPAG</td>
<td>Pediatric Pharmacy Advocacy Group</td>
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<tr>
<td>TDM</td>
<td>therapeutic drug monitoring</td>
</tr>
<tr>
<td>TG</td>
<td>thioguanine</td>
</tr>
<tr>
<td>TPMT</td>
<td>thiopurine methyltransferase</td>
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<tr>
<td>UM</td>
<td>ultra-rapid metabolizer</td>
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</table>
Genetics: Another Clinical Tool

WEIGHT

AGE

TDM

GENETICS
BCPPS Certification Requirements

• Knowledge of “pharmacogenomic considerations”

Pediatric Pharmacy Specialist Certification Content Outline. 2017.
Which of the following best describes the role of the pediatric pharmacist in clinical pharmacogenomics?

A. Interpreting pharmacogenomic tests
B. Interpreting and applying pharmacogenomic tests
C. Ordering and interpreting pharmacogenomic tests
D. Ordering, interpreting, and applying pharmacogenomic tests
Defining the Role of the Pediatric Pharmacist in Pharmacogenomics

- **2011**  
  PPAG position statement on the role of the pediatric pharmacist in clinical pharmacogenomics

- **2015**  
  ASHP position statement on the role of the pharmacist in clinical pharmacogenomics

- **2018**  
  Updated PPAG position statement on the role of the pediatric pharmacist in clinical pharmacogenomics

The roles that pharmacists will ultimately play in clinical pharmacogenomics have yet to be defined. Our profession and practice specialty therefore have significant opportunities to advocate for and to establish the role of pediatric pharmacists in pharmacogenomics.

Opportunities for pharmacists exist in both inpatient and outpatient settings, such as pharmacist-managed clinical pharmacogenomics consultation services and educating patients and families about pharmacogenomic testing [...] successful implementation programs already exist at [children’s] hospitals.
PPAG endorses the involvement of pediatric pharmacists in pharmacogenomic testing and believes that pharmacists should be the healthcare professionals responsible for interpreting and applying pharmacogenomic test results as they relate to pediatric pharmacotherapy.


## 2011 vs. 2018: Availability of Direct-to-Consumer Genetic Tests

<table>
<thead>
<tr>
<th>2011 PPAG POSITION STATEMENT</th>
<th>2018 PPAG POSITION STATEMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPAG strongly encourages pharmacists to take responsibility for educating patients and their families about pharmacogenomic testing, especially in the community setting, where <strong>genetic test kits are likely to be directly available</strong> to patients or caregivers <strong>in the near future</strong>.</td>
<td>PPAG strongly encourages pharmacists to take responsibility for educating patients and their families about pharmacogenomic testing, especially in the community setting, where <strong>direct-to-consumer genetic test kits are readily available</strong> to patients and caregivers.</td>
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2011 vs. 2018: Importance to Pediatric Pharmacotherapy

<table>
<thead>
<tr>
<th>2011 PPAG POSITION STATEMENT</th>
<th>2018 PPAG POSITION STATEMENT</th>
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<tr>
<td>PPAG believes that pharmacogenomics is an emerging discipline that will become increasingly important in pediatric pharmacotherapy.</td>
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Challenges with Pediatric Pharmacogenomics

- Lack of data
- Limited pediatric-specific recommendations
- Extrapolation from adult data
- Impact of ontogeny
- Ethical issues
- Lifetime applicability of test results
<table>
<thead>
<tr>
<th>Genes</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>CFTR</em></td>
<td>ivacaftor</td>
</tr>
<tr>
<td><em>CYP2D6</em></td>
<td>codeine, SSRIs, TCAs, ondansetron, tamoxifen</td>
</tr>
<tr>
<td><em>CYP2C9</em></td>
<td>phenytoin, warfarin</td>
</tr>
<tr>
<td><em>CYP2C19</em></td>
<td>clopidogrel, SSRIs, TCAs, voriconazole</td>
</tr>
<tr>
<td><em>CYP3A5</em></td>
<td>tacrolimus</td>
</tr>
<tr>
<td><em>DPYD</em></td>
<td>capecitabine, 5-fluorouracil</td>
</tr>
<tr>
<td><em>G6PD</em></td>
<td>rasburicase</td>
</tr>
<tr>
<td><em>HLA-B</em></td>
<td>abacavir, allopurinol, carbamazepine, phenytoin</td>
</tr>
<tr>
<td><em>IFNL3</em></td>
<td>peginterferon alfa-based regimens</td>
</tr>
<tr>
<td><em>SLCO1B1</em></td>
<td>simvastatin</td>
</tr>
<tr>
<td><em>TPMT</em></td>
<td>azathioprine, mercaptopurine, thioguanine</td>
</tr>
<tr>
<td><em>UGT1A1</em></td>
<td>atazanavir</td>
</tr>
<tr>
<td><em>VKORC1</em></td>
<td>warfarin</td>
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</table>

**Did you know?**
Each guideline has a pediatrics section.

[https://cpicpgx.org/guidelines/](https://cpicpgx.org/guidelines/)
Case Studies
Case 1: AG is a 5-year-old female with cystic fibrosis who is homozygous for the F508del CFTR mutation. Which of the following targeted therapies would be most appropriate to initiate at this time?

A. Ivacaftor
B. Lumacaftor/ivacaftor
C. Tezacaftor/ivacaftor + ivacaftor
D. AG is not a candidate for targeted therapy
Targeting the *Cause*, Not Just the Symptoms

CFTR Modulators

- **CFTR Potentiator**: ivacaftor
- **CFTR Corrector**: lumacaftor, tezacaftor

Cell Membrane

$\text{Cl}^-$

CFTR

**CELL MEMBRANE**
Ivacaftor Helps Keep the CFTR Channel Open

Lumacaftor (and Tezacaftor) Promotes Proper Folding of the CFTR Protein

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Generic Name</th>
<th>Year Approved</th>
<th>Age (years)</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalydeco®</td>
<td>Ivacaftor</td>
<td>2012</td>
<td>≥ 2</td>
<td>≥ 1 of 33 gating (e.g., G551D) or residual function CFTR mutations</td>
</tr>
<tr>
<td>Orkambi®</td>
<td>Lumacaftor/ivacaftor</td>
<td>2015</td>
<td>≥ 2</td>
<td>Homozygous for F508del</td>
</tr>
<tr>
<td>Symdeko®</td>
<td>Tezacaftor/ivacaftor</td>
<td>2018</td>
<td>≥ 12</td>
<td>Homozygous for F508del OR ≥ 1 of 27 other CFTR mutations</td>
</tr>
</tbody>
</table>

Case 2: CB is a 15-year-old male with Crohn’s disease whose physician is considering prescribing azathioprine for maintenance of remission. If CB is a TPMT normal metabolizer and a NUDT15 intermediate metabolizer, which of the following is the most appropriate therapeutic recommendation?

A. 4 mg/kg/day of azathioprine  
B. 2 mg/kg/day of azathioprine (standard dose)  
C. 1 mg/kg/day of azathioprine  
D. Use alternative therapy
Thiopurine Metabolism

AZA → 6-MP → methylMP (inactive metabolite) → methylITG (inactive metabolite) → inactivemetabolites

THIOGUANINE NUCLEOTIDES (active metabolites) → therapeutic effect

TPMT Deficiency

AZA → 6-MP → methylMP (inactive metabolite)

THIOGUANINE NUCLEOTIDES (active metabolites) → toxicity

methylITG (inactive metabolite)

NUDT15 → inactive metabolites

## TPMT Phenotypes

<table>
<thead>
<tr>
<th>TPMT phenotype</th>
<th>Definition</th>
<th>Example diplotypes</th>
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<tr>
<td>Normal metabolizer (NM)</td>
<td>2 normal function alleles</td>
<td>*1/*1</td>
</tr>
<tr>
<td>Intermediate metabolizer (IM)</td>
<td>1 normal function allele + 1 no function allele</td>
<td>*1/*2, *1/*3A, *1/*3C</td>
</tr>
<tr>
<td>Possible intermediate metabolizer</td>
<td>1 uncertain function allele + 1 no function allele</td>
<td>*2/*8, *3A/*7</td>
</tr>
<tr>
<td>Poor metabolizer (PM)</td>
<td>2 no function alleles</td>
<td>*2/*2, *3A/*3C, *3C/*3C</td>
</tr>
</tbody>
</table>

NUDT15 Deficiency

AZA $\rightarrow$ 6-MP $\rightarrow$ methylMP (inactive metabolite)

THIOGUANINE NUCLEOTIDES (active metabolites)

Toxicity

# NUDT15 Phenotypes

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<td>Normal metabolizer (NM)</td>
<td>2 normal function alleles</td>
<td>*1/*1</td>
</tr>
<tr>
<td>Intermediate metabolizer (IM)</td>
<td>1 normal function allele + 1 no function allele OR</td>
<td>*1/*2, *1/*3, *3/*4</td>
</tr>
<tr>
<td></td>
<td>1 decreased function allele + 1 no function allele</td>
<td></td>
</tr>
<tr>
<td>Possible intermediate metabolizer</td>
<td>1 uncertain function allele + 1 no function allele</td>
<td>*2/*5, *3/*6</td>
</tr>
<tr>
<td>Poor metabolizer (PM)</td>
<td>2 no function alleles</td>
<td>*2/*2, *2/*3, *3/*3</td>
</tr>
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Genotype-guided Dosing of Azathioprine and 6-MP for Non-malignant Conditions

TPMT NM

- NUDT15 NM: Standard starting dose
- NUDT15 IM: 30-80% of standard starting dose
- NUDT15 PM: Consider alternative therapy

Genotype-guided Dosing of Azathioprine and 6-MP for Non-malignant Conditions

TPMT IM

- NUDT15 NM: 30-80% of standard starting dose
- NUDT15 IM: 30-80% of standard starting dose
- NUDT15 PM: Consider alternative therapy

Genotype-guided Dosing of Azathioprine and 6-MP for Non-malignant Conditions

TPMT PM

- NUDT15 NM: Consider alternative therapy
- NUDT15 IM: Consider alternative therapy
- NUDT15 PM: Consider alternative therapy

Case 3: SD is a 13-year-old female with sickle cell disease whose CYP2D6 genotype is *4/*4 (3N). Which of the following is the most appropriate recommendation for use of acetaminophen/codeine for the management of mild to moderate pain crises in SD?

A. Do not use it because it is contraindicated in patients < 18 years old
B. Do not use it because of the high probability of therapeutic failure
C. Do not use it because of the high probability of toxicity
D. It is appropriate to use at the standard starting dose
CYP2D6 Converts Codeine to Morphine

CYP2D6 Activity Dictates Morphine Production

- **UM**: CODEINE → CYP2D6 → CYP2D6 → MORPHINE!
- **NM**: CODEINE → CYP2D6 → CYP2D6 → MORPHINE
- **IM**: CODEINE → CYP2D6 → morphine
- **PM**: CODEINE →
Recommendations for Codeine Use Based on CYP2D6 Phenotype

- **UM**: AVOID CODEINE (toxicity)
- **NM**: Use codeine at standard doses
- **IM**: AVOID CODEINE (therapeutic failure)

FDA, Codeine, and Children

2007  FDA warning regarding codeine use by nursing mothers

2012  FDA drug safety communication regarding codeine use in children following tonsillectomy/adenoidectomy

2013  FDA boxed warning on codeine regarding CYP2D6 UMs and contraindication against codeine use following tonsillectomy/adenoidectomy


FDA, Codeine, and Children (Continued)

- **2015** FDA drug safety communication regarding codeine cough and cold medicines in children

- **2017** FDA contraindication on codeine use in all children < 12 years old and FDA warning on the use of codeine in adolescents ages 12-18 years who are at increased risk of respiratory depression

- **2018** FDA drug safety communication on restricting the use of codeine cough/cold products to patients ≥ 18 years

Would it be reasonable to prescribe acetaminophen/codeine to a pediatric patient < 12 years old who is known to be a CYP2D6 normal or intermediate metabolizer?
Case 4: DK is a 10-year-old male with ADHD. His mother asked DK’s physician to order pharmacogenomic testing before initiating therapy. You are given the results to review and interpret: CYP2D6 *1/*1(2N), COMT Val158Met homozygous, ADRA2A -1291 G>C heterozygous. Based on these results, which of the following is the best therapeutic recommendation?

A. Standard starting dose of mixed amphetamine salts
B. 50% of the starting dose of atomoxetine
C. Avoid methylphenidate
D. Avoid clonidine
Buyer Beware!

Just because a company offers testing for a particular gene DOES NOT mean the gene has clinical utility!
Case 5: EH is a 15-year-old male (75 kg) who is taking paroxetine 20 mg/day for depression. He has also been diagnosed with ADHD and after a trial of stimulant medication, his physician wants to try atomoxetine. His CYP2D6 test result is *1/*1(2N). Which of the following is the best atomoxetine therapeutic recommendation for EH?

A. 0.5 mg/kg/day to start, then increase dose after a minimum of 3 days to a target dose of 1.2 mg/kg/day

B. 0.5 mg/kg/day to start, then increase to a target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated

C. 40 mg/day to start, then increase dose after a minimum of 3 days to a target dose of 80 mg/day

D. 40 mg/day to start, then increase to a target dose of 80 mg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated
Atomoxetine Metabolism

Atomoxetine

\[ \text{CYP2D6} \]

4-hydroxyatomoxetine
(active metabolite)

\[ \text{UGT} \ (\text{rapid}) \]

4-hydroxyatomoxetine glucuronide
(inactive metabolite)
Atomoxetine Metabolism

4-hydroxyatomoxetine (active metabolite)

4-hydroxyatomoxetine glucuronide (inactive metabolite)

CYP2D6 PMs are at increased risk of supratherapeutic plasma levels and side effects!
Genotype-guided Dosing of Atomoxetine (≤ 70 kg)

Standard Dosing

0.5 mg/kg/day
Increase dose after a minimum of 3 days to a target total daily dose of 1.2 mg/kg/day.

CYP2D6 PM

0.5 mg/kg/day
Increase to usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.
Genotype-guided Dosing of Atomoxetine (> 70 kg)

**Standard Dosing**

- **40 mg/day**
- Increase dose after a minimum of 3 days to a target total daily dose of 80 mg/day.

**CYP2D6 PM**

- **40 mg/day**
- Increase to usual target dose of 80 mg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated.

Strattera (atomoxetine hydrochloride) prescribing information. Indianapolis, IN: Eli Lilly and Company; 2003.
Genetics is Just One Piece of the Puzzle!

- **Phenoconversion**: A phenomenon by which genotypic normal metabolizers are converted into phenotypic poor metabolizers of drugs, thereby modifying their clinical response to that of genotypic poor metabolizers.
- For atomoxetine, **use CYP2D6 poor metabolizer dosing schedule** for patients taking **strong CYP2D6 inhibitors** (e.g., paroxetine, fluoxetine).
Practice Model Examples

Cincinnati Children’s

St. Jude Children’s Research Hospital

Children’s Minnesota
You would like to establish a clinical pharmacogenomics service for pediatric patients. Which of the following is an essential component of your new service?

A. Obtaining formal written consent prior to testing
B. Genetic counselor involvement
C. Preemptive testing
D. Patient education
Reactive vs. Preemptive Genotyping

**REACTIVE**

Test is ordered as drug therapy is initiated or after drug therapy has begun. Need to wait for test results.

**PREEMPTIVE**

Test is ordered independent of medication use. Results already available to guide prescribing.
Reactive Pharmacogenomic Testing

GENETIC PHARMACOLOGY SERVICE (2004-present)
- Genotyping
- Clinical interpretation
- Consultation
- Provider education
- Patient education

Certain psychiatric drugs $\rightarrow$ CYP2D6, CYP2C19

Certain opioids $\rightarrow$ CYP2D6

Thiopurines $\rightarrow$ TPMT

Warfarin $\rightarrow$ CYP2C9, VKORC1

Preemptive Pharmacogenomic Testing

1. Patient consent
2. Blood sample
3. Genotyping (230 genes)
4. Research database
5. Select results in EHR
6. Clinical decision support
7. Patient education

Pharmacogenomics Clinic

**VISIT 1**

- PGx education + goals + expectations
- Medication/family history + MTM
- Decision for or against testing

14 days

**VISIT 2**

- PGx education refresher
- Interpretation of results
- Results added to EHR
Future Trends in Pediatric Pharmacogenomics

- More patients tested
- Reactive → preemptive testing
- PGx testing as part of newborn screening


Key Takeaways

1) **KEY TAKEWAY:** Pediatric pharmacists play an important role in ordering, interpreting, and applying pharmacogenomic test results for children, as well as providing pharmacogenomics education to patients, caregivers, and other healthcare providers.

2) **KEY TAKEWAY:** Refer to CPIC guidelines for gene-based prescribing recommendations, noting any pediatric-specific considerations.

3) **KEY TAKEWAY:** Integration of pharmacogenomic testing into pediatric pharmacy practice models is growing and is expected to become more widespread over time.