ashp® MIDYEAR 2018
Clinical Meeting & Exhibition

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.

Abbreviations

6-MP	6-mercaptopurine
ADHD	attention deficit hyperactivity disorder
AZA	azathioprine
BCPPS	Board Certified Pediatric Pharmacy Specialist
CFTR	cystic fibrosis transmembrane conductance regulator
CPIC	Clinical Pharmacogenetics Implementation Consortium
EHR	electronic health record
IM	intermediate metabolizer
MTM	medication therapy management
NM	normal metabolizer
NUDT15	nudix hydrolase 15
PGx	pharmacogenomics
PM	poor metabolizer
PPAG	Pediatric Pharmacy Advocacy Group
TDM	therapeutic drug monitoring
TG	thioguanine
TPMT	thiopurine methyltransferase
UM	ultra-rapid metabolizer

Genetics: Another Clinical Tool

WEIGHT

AGE

TDM

GENETICS

BCPPS Certification Requirements

- Knowledge of “pharmacogenomic considerations”

Pediatric Pharmacy Specialist Certification Content Outline. 2017. https://www.bpsweb.org/wp-content/uploads/Pediatric_ContentOutlineForPublication20171017.pdf (accessed 2018 Oct 17).

Question 1:

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

Kennedy MJ, et al. *J Pediatr Pharmacol Ther.* 2011; 16(2): 118-122.
American Society of Health-System Pharmacists. *Am J Health Syst Pharm.* 2015; 72(7): 579-581.
Brown JT, et al. *J Pediatr Pharmacol Ther.* [accepted for publication].

2011 PPAG Position Statement: Where Were We Then?

MJ Kennedy, H Phan, S Benavides, A Potts, S Sorensen

> **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.

Kennedy MJ, et al. *J Pediatr Pharmacol Ther.* 2011; 16(2): 118-122.

2018 PPAG Position Statement: Where Are We Now?

JT Brown, D Gregornik, MJ Kennedy

> 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.

Brown JT, et al. *J Pediatr Pharmacol Ther.* [accepted for publication].

2011 vs. 2018: Role of the Pharmacist

2011 PPAG POSITION STATEMENT	2018 PPAG POSITION STATEMENT
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.	PPAG endorses the involvement of pediatric pharmacists in pharmacogenomic testing and believes that pharmacists should be the healthcare professionals responsible for **ordering, interpreting, and applying** pharmacogenomic test results as they relate to pediatric pharmacotherapy.

Kennedy MJ, et al. *J Pediatr Pharmacol Ther.* 2011; 16(2): 118-122.
Brown JT, et al. *J Pediatr Pharmacol Ther.* [accepted for publication].

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

2011 PPAG POSITION STATEMENT	2018 PPAG POSITION STATEMENT
PPAG strongly encourages pharmacists to take responsibility for educating patients and their families about pharmacogenomic testing, especially in the community setting, where **genetic test kits are likely to be directly available** to patients or caregivers **in the near future**.	PPAG strongly encourages pharmacists to take responsibility for educating patients and their families about pharmacogenomic testing, especially in the community setting, where **direct-to-consumer genetic test kits are readily available** to patients and caregivers.

Kennedy MJ, et al. *J Pediatr Pharmacol Ther.* 2011; 16(2): 118-122.
Brown JT, et al. *J Pediatr Pharmacol Ther.* [accepted for publication].

2011 vs. 2018: Importance to Pediatric Pharmacotherapy

2011 PPAG POSITION STATEMENT	2018 PPAG POSITION STATEMENT
PPAG believes that pharmacogenomics is an emerging discipline that will become increasingly important in pediatric pharmacotherapy.	PPAG believes that pharmacogenomics is an emerging discipline that will become increasingly important in pediatric pharmacotherapy.

Kennedy MJ, et al. *J Pediatr Pharmacol Ther.* 2011; 16(2): 118-122.
Brown JT, et al. 2018. *J Pediatr Pharmacol Ther.* [accepted for publication].

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

CPIC™
Clinical Pharmacogenetics Implementation Consortium

Genes and Drugs with CPIC Guidelines (as of August 2018)

Did you know?
Each guideline has a pediatrics section.

Genes	Drugs
CFTR	ivacaftor
CYP2D6	codeine, SSRIs, TCAs, ondansetron, tamoxifen
CYP2C9	phenytoin, warfarin
CYP2C19	clopidogrel, SSRIs, TCAs, voriconazole
CYP3A5	tacrolimus
DPYD	capecitabine, 5-fluorouracil
G6PD	rasburicase
HLA-B	abacavir, allopurinol, carbamazepine, phenytoin
IFNL3	peginterferon alfa-based regimens
SLCO1B1	simvastatin
TPMT	azathioprine, mercaptopurine, thioguanine
UGT1A1	atazanavir
VKORC1	warfarin

https://cpicpgx.org/guidelines/.

Case Studies

Question 2:

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?

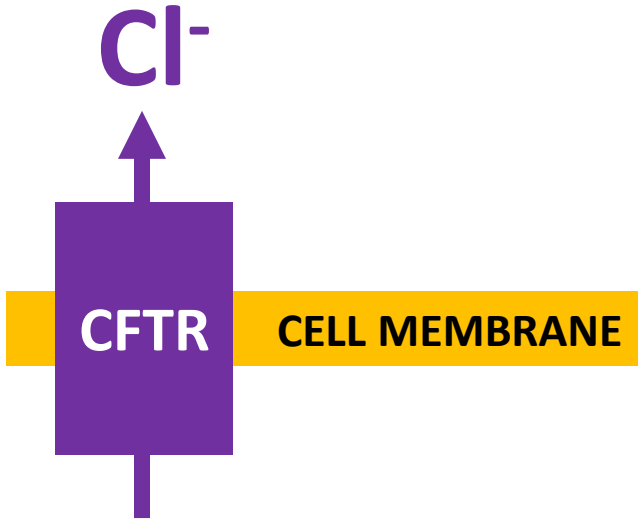
A. Ivacaftor
B. Lumacaftor/ivacaftor
C. Tezacaftor/ivacaftor + ivacaftor
D. AG is not a candidate for targeted therapy

Targeting the *Cause*, Not Just the Symptoms

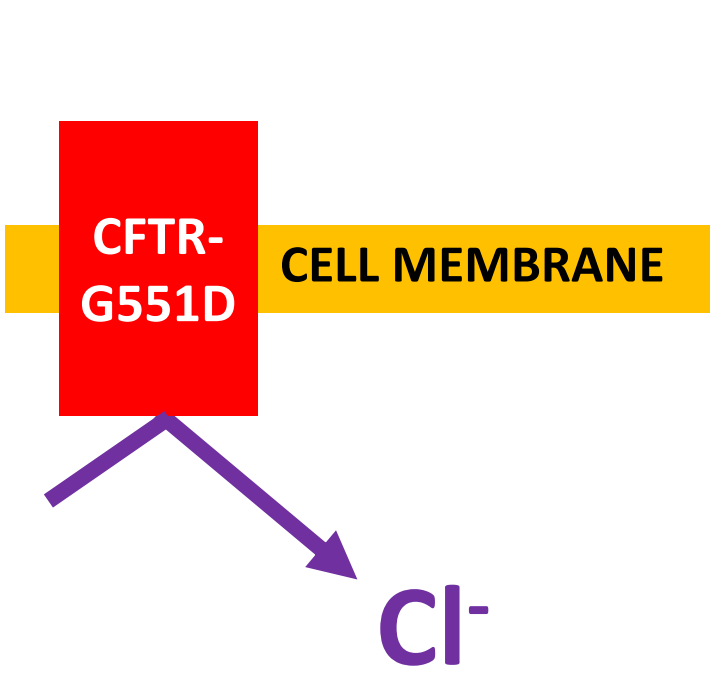
CFTR Modulators

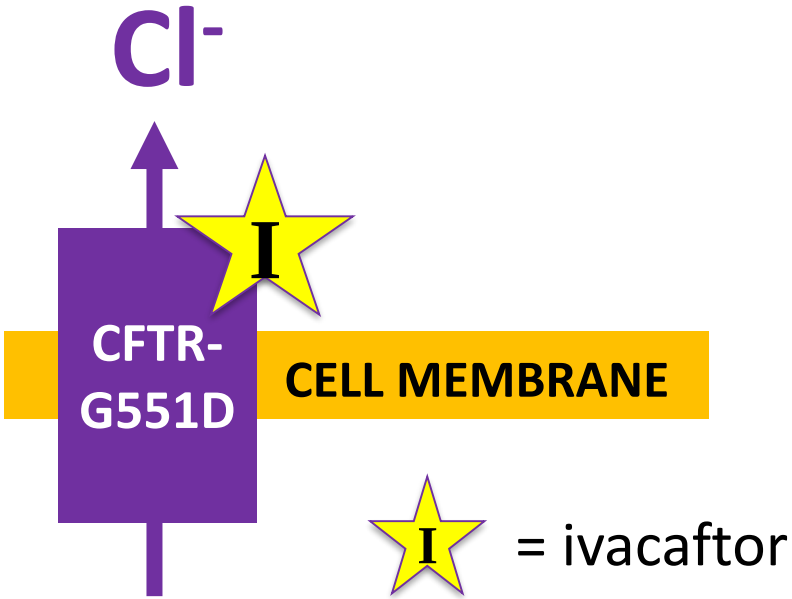
CFTR Potentiator
ivacaftor

CFTR Corrector
lumacaftor
tezacaftor



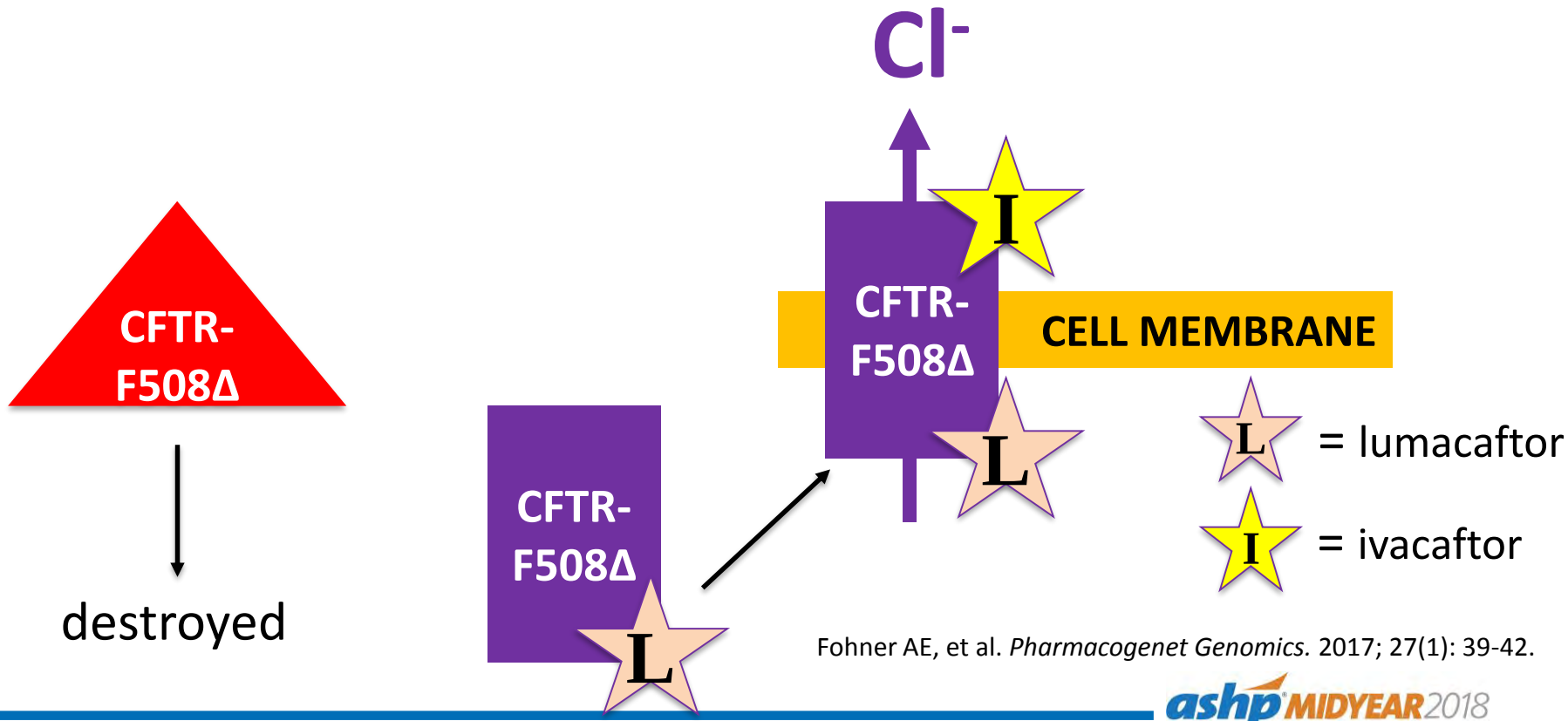
Ivacaftor Helps Keep the CFTR Channel Open





Fohner AE, et al. *Pharmacogenet Genomics.* 2017; 27(1): 39-42.

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



Fohner AE, et al. *Pharmacogenet Genomics.* 2017; 27(1): 39-42.

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

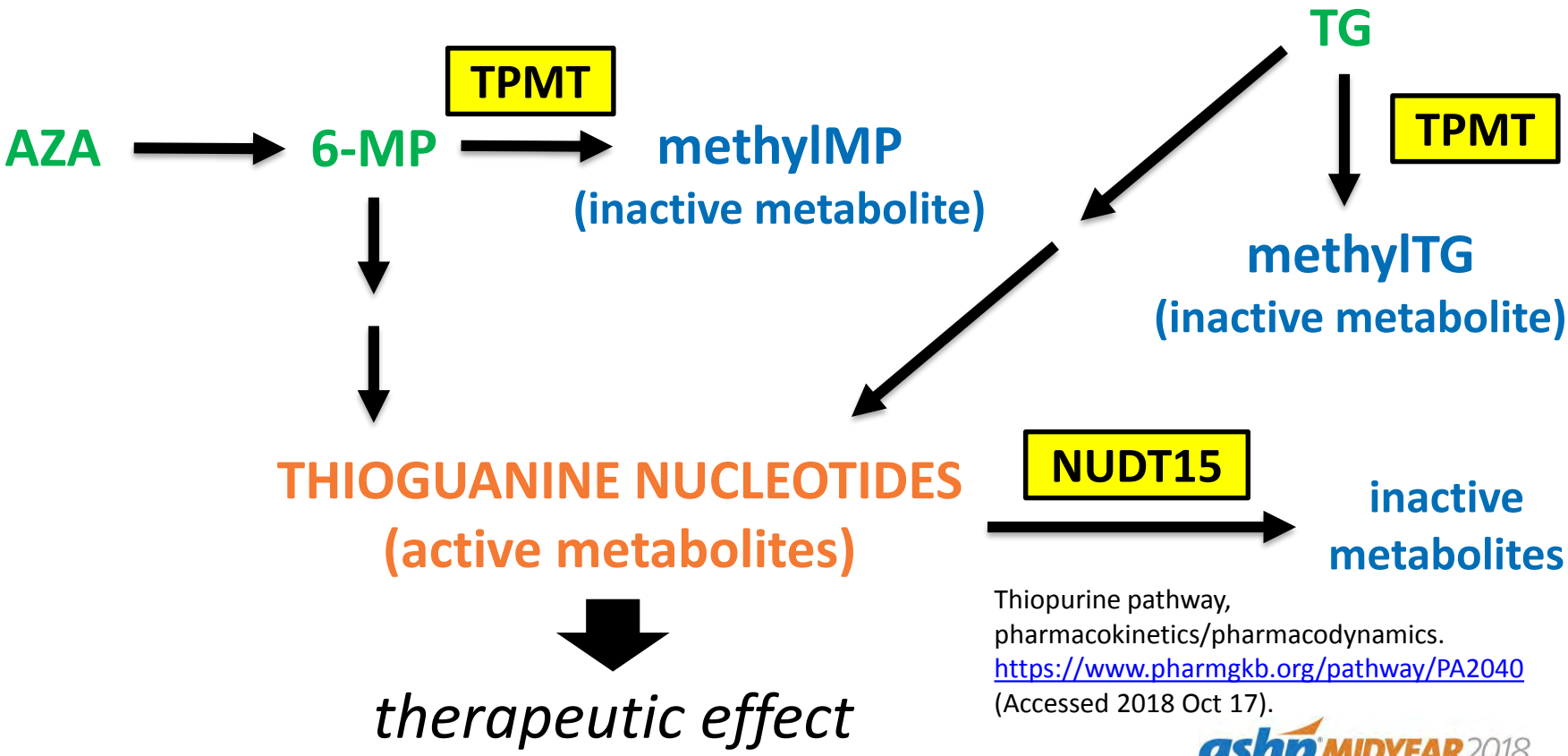
Kalydeco (ivacaftor) prescribing information. Boston, MA: Vertex Pharmaceuticals Inc; 2018 Aug.
Orkambi (lumacaftor/ivacaftor) prescribing information. Boston, MA: Vertex Pharmaceuticals Inc; 2018 Aug.
Symdeko (tezacaftor/ivacaftor and ivacaftor) prescribing information. Boston, MA: Vertex Pharmaceuticals Inc; 2018 Feb.

Question 3:

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?

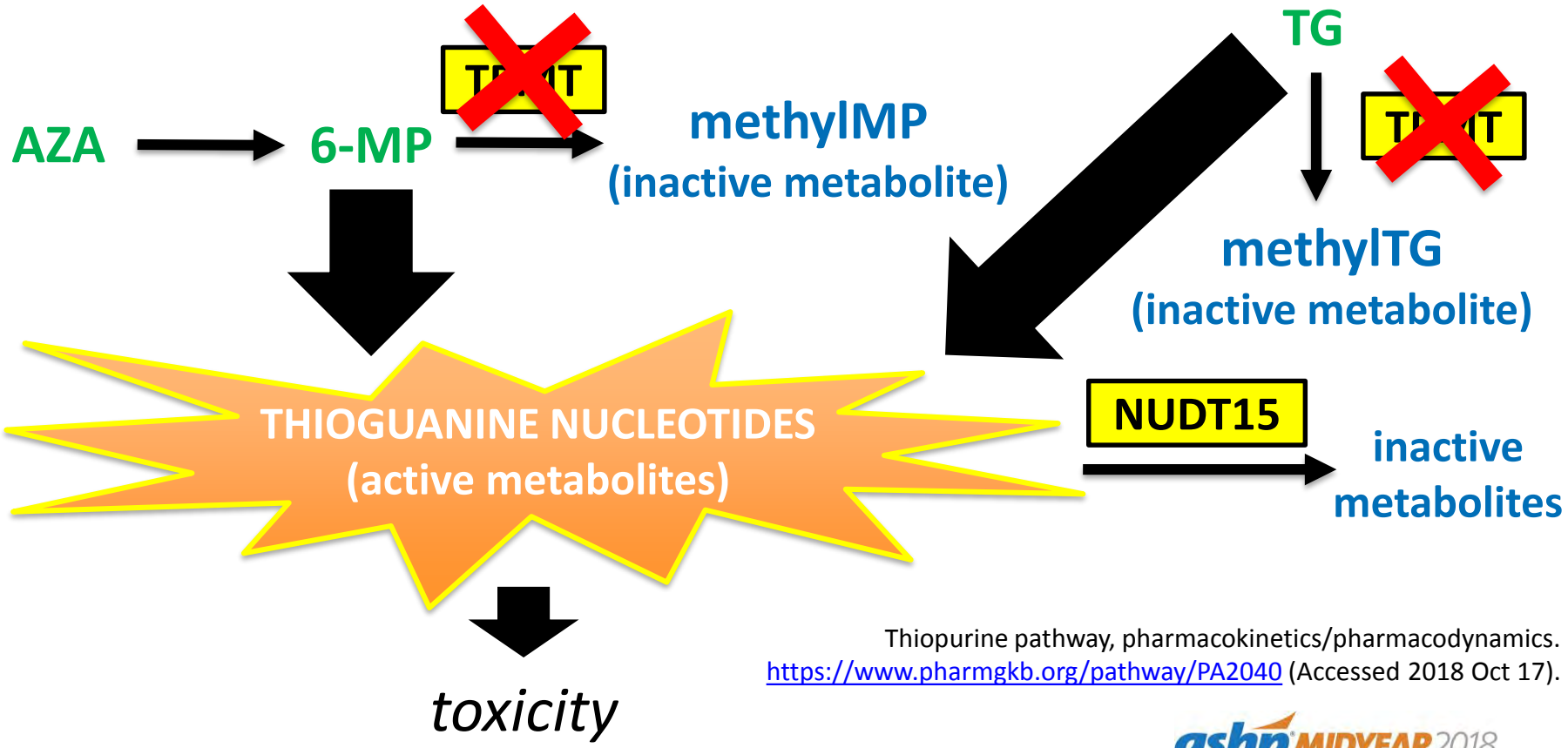
A. 4 mg/kg/day of azathioprine
B. 2 mg/kg/day of azathioprine (standard dose)
C. 1 mg/kg/day of azathioprine
D. Use alternative therapy

Thiopurine Metabolism



Thiopurine pathway, pharmacokinetics/pharmacodynamics. https://www.pharmgkb.org/pathway/PA2040 (Accessed 2018 Oct 17).

TPMT Deficiency



Thiopurine pathway, pharmacokinetics/pharmacodynamics. https://www.pharmgkb.org/pathway/PA2040 (Accessed 2018 Oct 17).

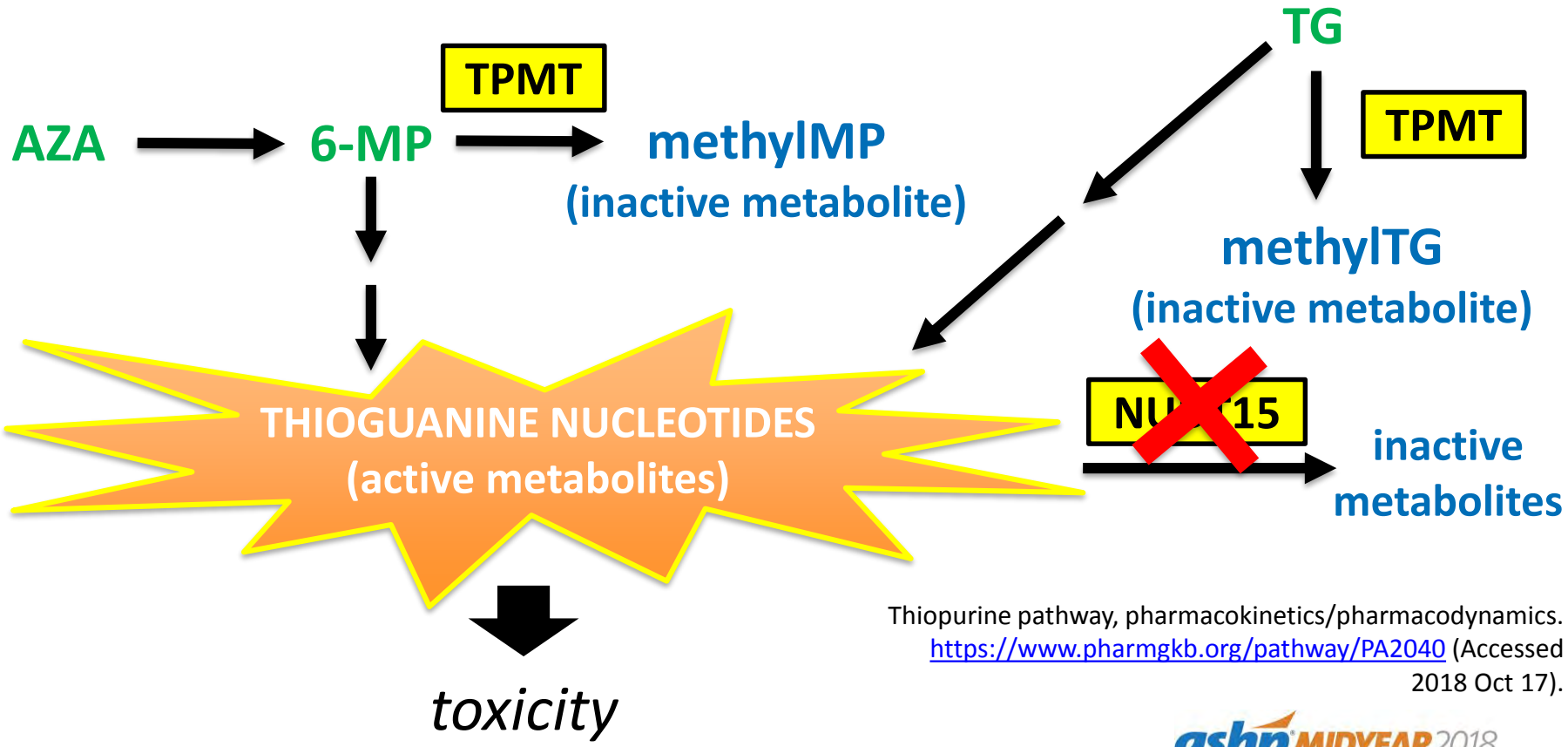
TPMT Phenotypes

ACTIONABLE

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

Relling MV, et al. *Clin Pharmacol Ther.* 2018. [in press].

NUDT15 Deficiency



Thiopurine pathway, pharmacokinetics/pharmacodynamics. https://www.pharmgkb.org/pathway/PA2040 (Accessed 2018 Oct 17).

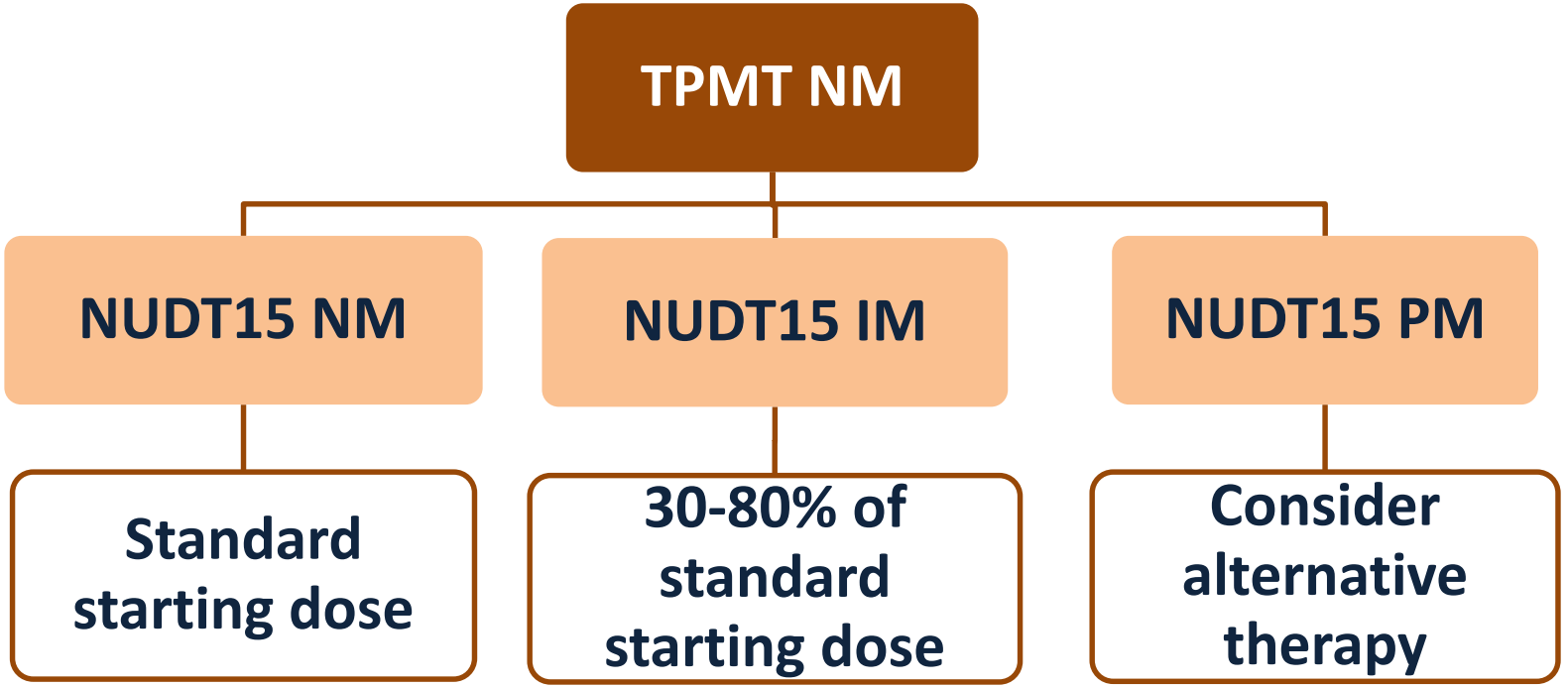
NUDT15 Phenotypes

ACTIONABLE

NUDT15 phenotype	Definition	Example diplotypes
Normal metabolizer (NM)	2 normal function alleles	*1/*1
Intermediate metabolizer (IM)	1 normal function allele + 1 no function allele OR 1 decreased function allele + 1 no function allele	*1/*2, *1/*3, *3/*4
Possible intermediate metabolizer	1 uncertain function allele + 1 no function allele	*2/*5, *3/*6
Poor metabolizer (PM)	2 no function alleles	*2/*2, *2/*3, *3/*3

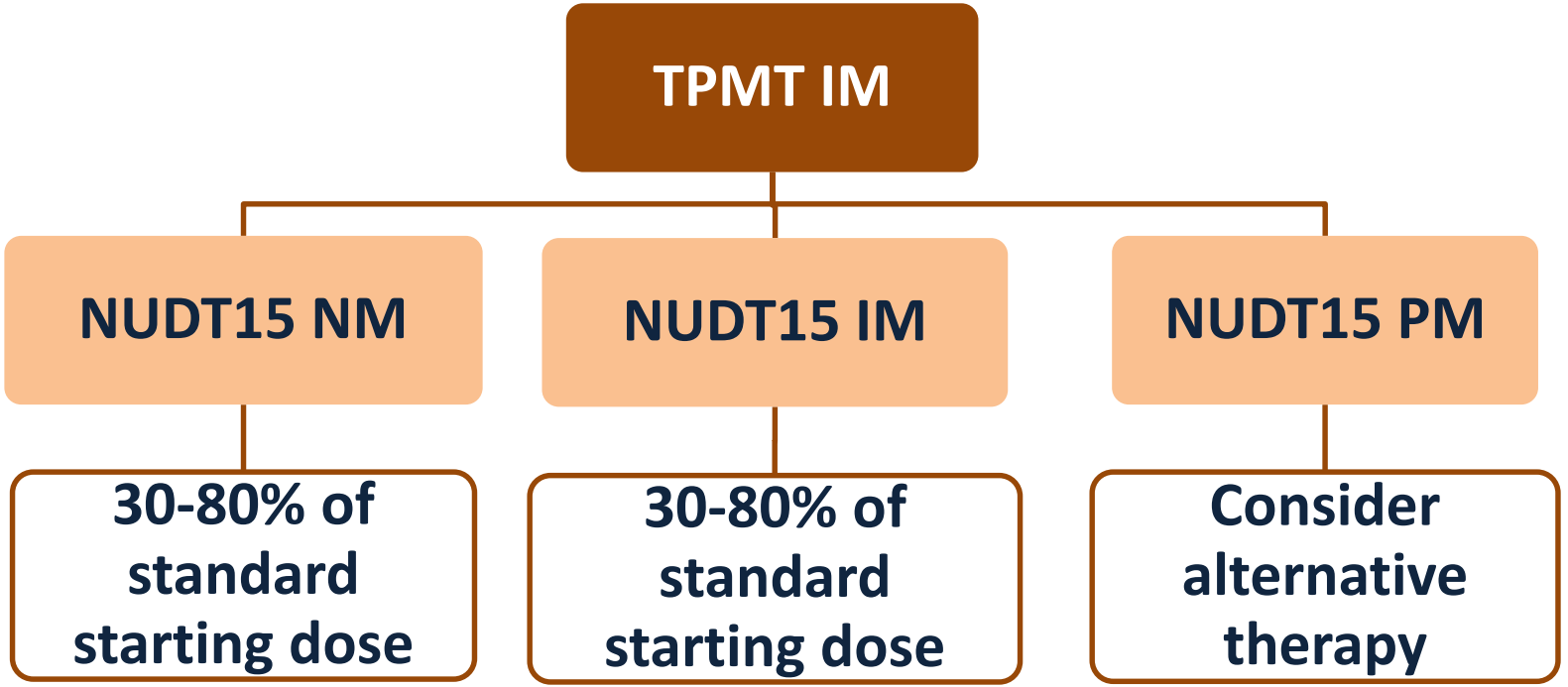
Relling MV, et al. *Clin Pharmacol Ther.* 2018. [in press].

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



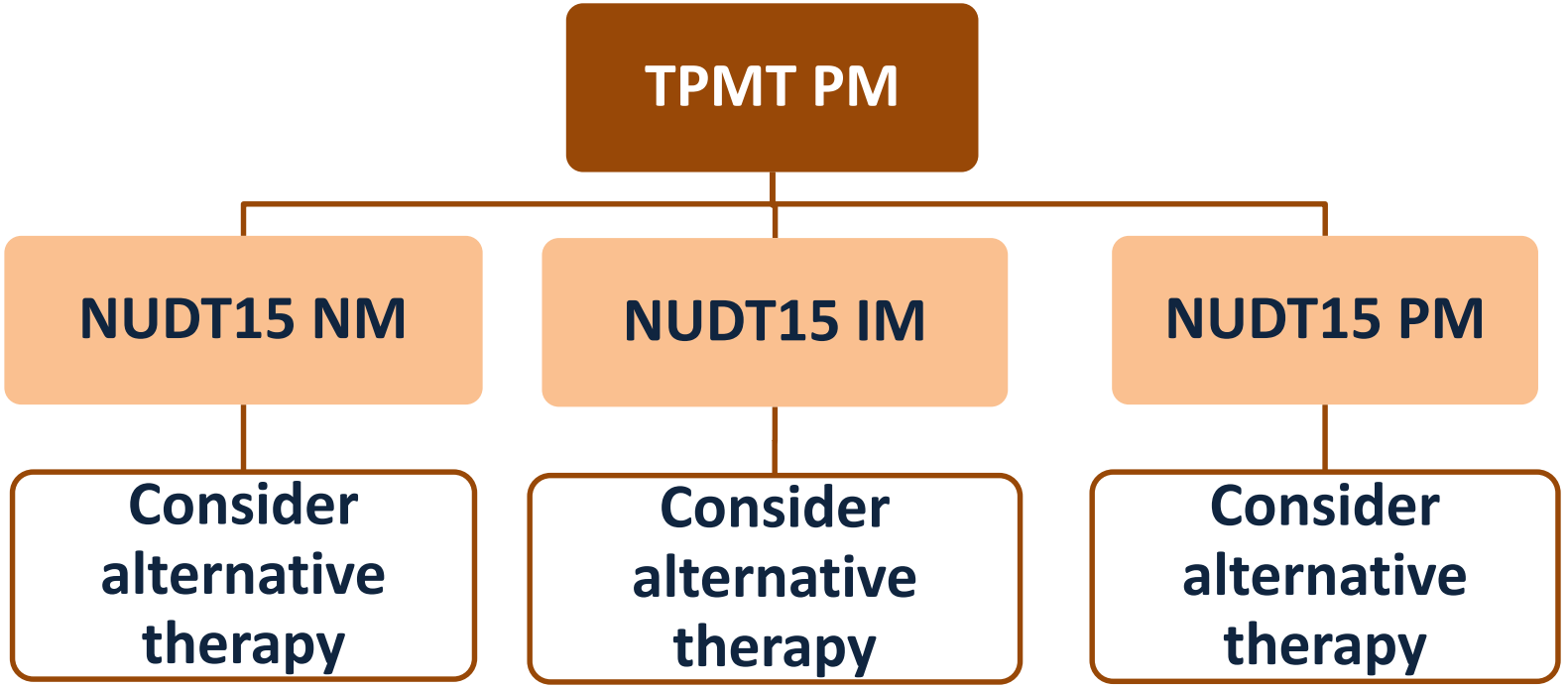
Relling MV, et al. *Clin Pharmacol Ther.* 2018. [in press].

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



Relling MV, et al. *Clin Pharmacol Ther.* 2018. [in press].

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



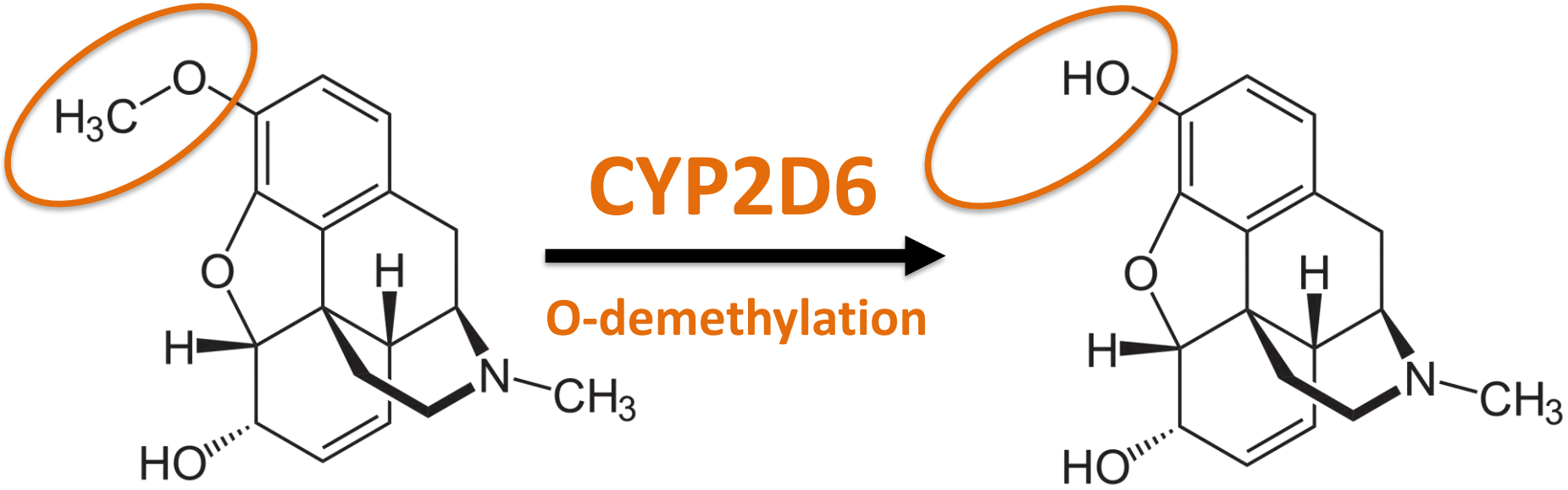
Relling MV, et al. *Clin Pharmacol Ther.* 2018. [in press].

Question 4:

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



codeine *morphine*

Image sources: https://en.wikipedia.org/wiki/Codeine; https://en.wikipedia.org/wiki/Morphine.

CYP2D6 Activity Dictates Morphine Production

UM	CODEINE	CYP2D6 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

IM

Use codeine at standard doses

PM

AVOID CODEINE (therapeutic failure)

Crews KR, et al. *Clin Pharmacol Ther.* 2014; 95(4): 376-82.

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

Use of codeine and tramadol products in breastfeeding women – questions and answers. https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm118113.htm. (Accessed 2018 Oct 17).
Safety review update of codeine use in children; New boxed warning and contraindication on use after tonsillectomy and/or adenoidectomy. https://www.fda.gov/downloads/Drugs/DrugSafety/UCM339116.pdf. (Accessed 2018 Oct 17).

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

FDA Drug Safety Communication. https://www.fda.gov/Drugs/DrugSafety/ucm549679.htm. (Accessed 2018 Oct 17).
FDA Drug Safety Communication. https://www.fda.gov/Drugs/DrugSafety/ucm590435.htm. (Accessed 2018 Oct 17).

What Do You Think?

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?

Question 5:

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!

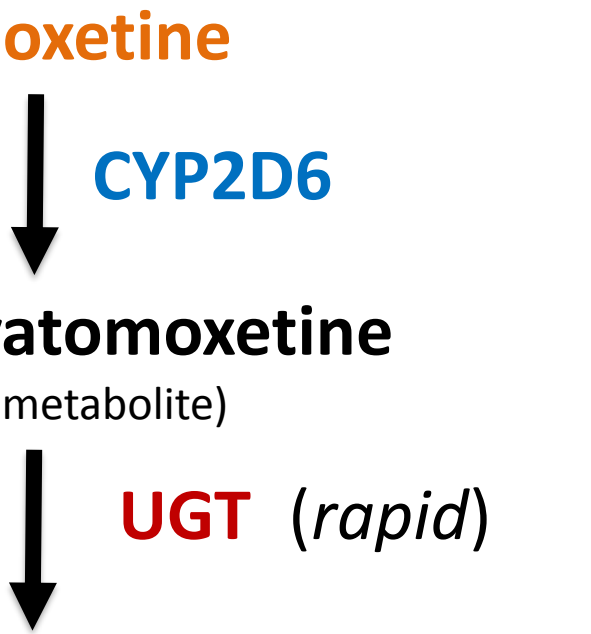
Just because a company offers testing for a particular gene ***DOES NOT*** *mean the gene has clinical utility!*

Question 6:

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?

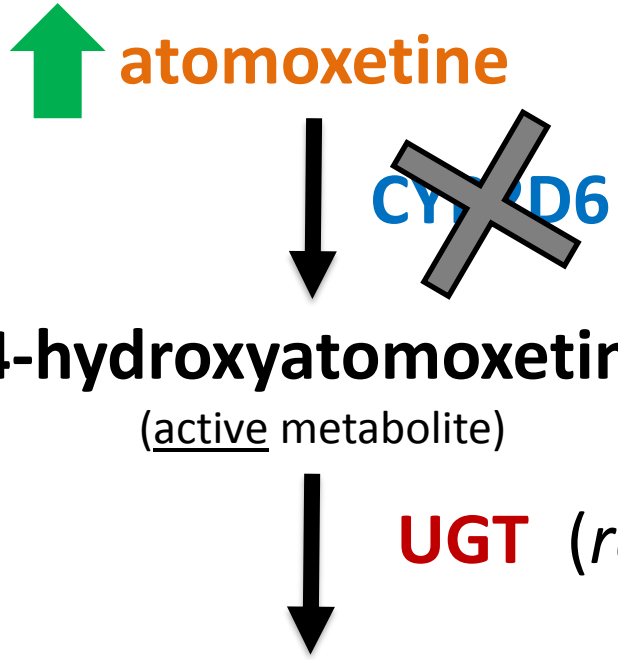
A. 0.5 mg/kg/day to start, then increase dose after a minimum of 3 days to a target dose of 1.2 mg/kg/day
B. 0.5 mg/kg/day to start, then increase to a target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated
C. 40 mg/day to start, then increase dose 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 Metabolism

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**.

Strattera (atomoxetine hydrochloride) prescribing information. Indianapolis, IN: Eli Lilly and Company; 2003.

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

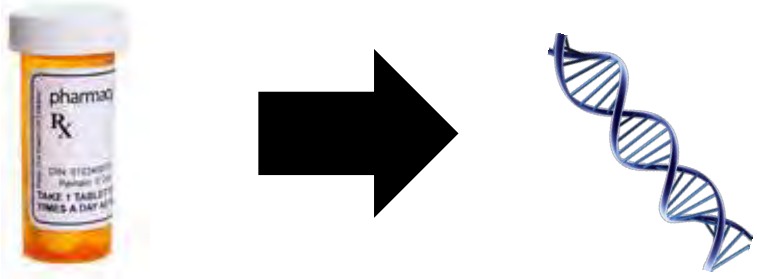
Question 7:

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

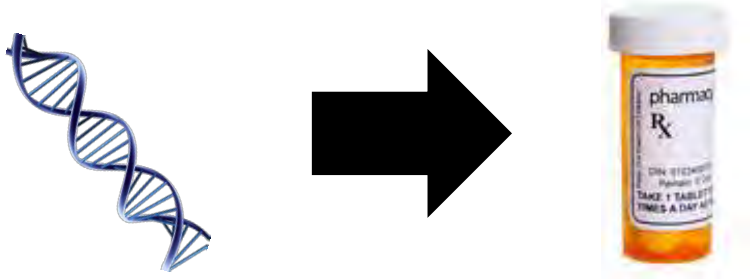
Reactive vs. Preemptive Genotyping

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.

Cincinnati Children's

Reactive Pharmacogenomic Testing

GENETIC PHARMACOLOGY SERVICE (2004-present)

- Genotyping
- Clinical interpretation
- Consultation
- Provider education
- Patient education

Certain psychiatric drugs → *CYP2D6*, *CYP2C19*

Certain opioids → *CYP2D6*

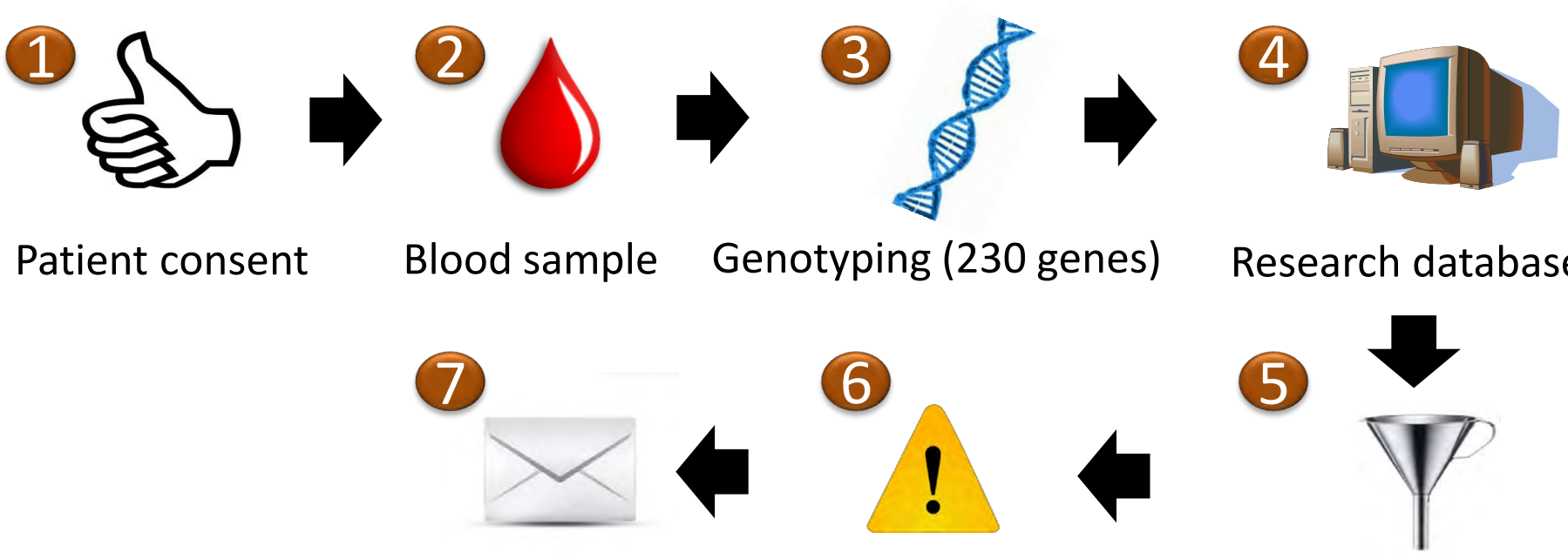
Thiopurines → *TPMT*

Warfarin → *CYP2C9*, *VKORC1*

Ramsey LB, et al. *Clin Pharmacol Ther.* 2018 Jul 29 [epub ahead of print].

St. Jude Children's Research Hospital

Preemptive Pharmacogenomic Testing

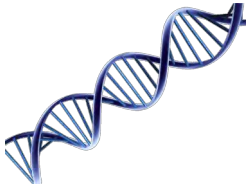


Hoffman JM, et al. *Am J Med Genet C Semin Med Genet.* 2014; 166C(1): 45-55.

Children's Minnesota

Pharmacogenomics Clinic

VISIT 1



PGx education + goals + expectations

Medication/family history + MTM

Decision for or against testing

14 days

VISIT 2

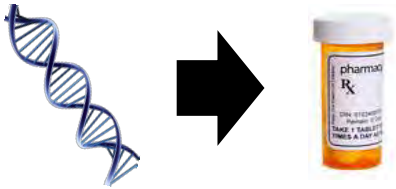
PGx education refresher

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

Weitzel KW, et al. *Pharm Res.* 2017; 34(8): 1551-1555.
MediMap Baby. https://www.inova.org/medimap/baby. (Accessed 2018 Oct 17).

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.