



# FDA's 2017 Warning for Codeine and Tramadol in Children

Kristine R. Crews, PharmD  
St. Jude Children's Research Hospital  
[Kristine.crews@stjude.org](mailto:Kristine.crews@stjude.org)

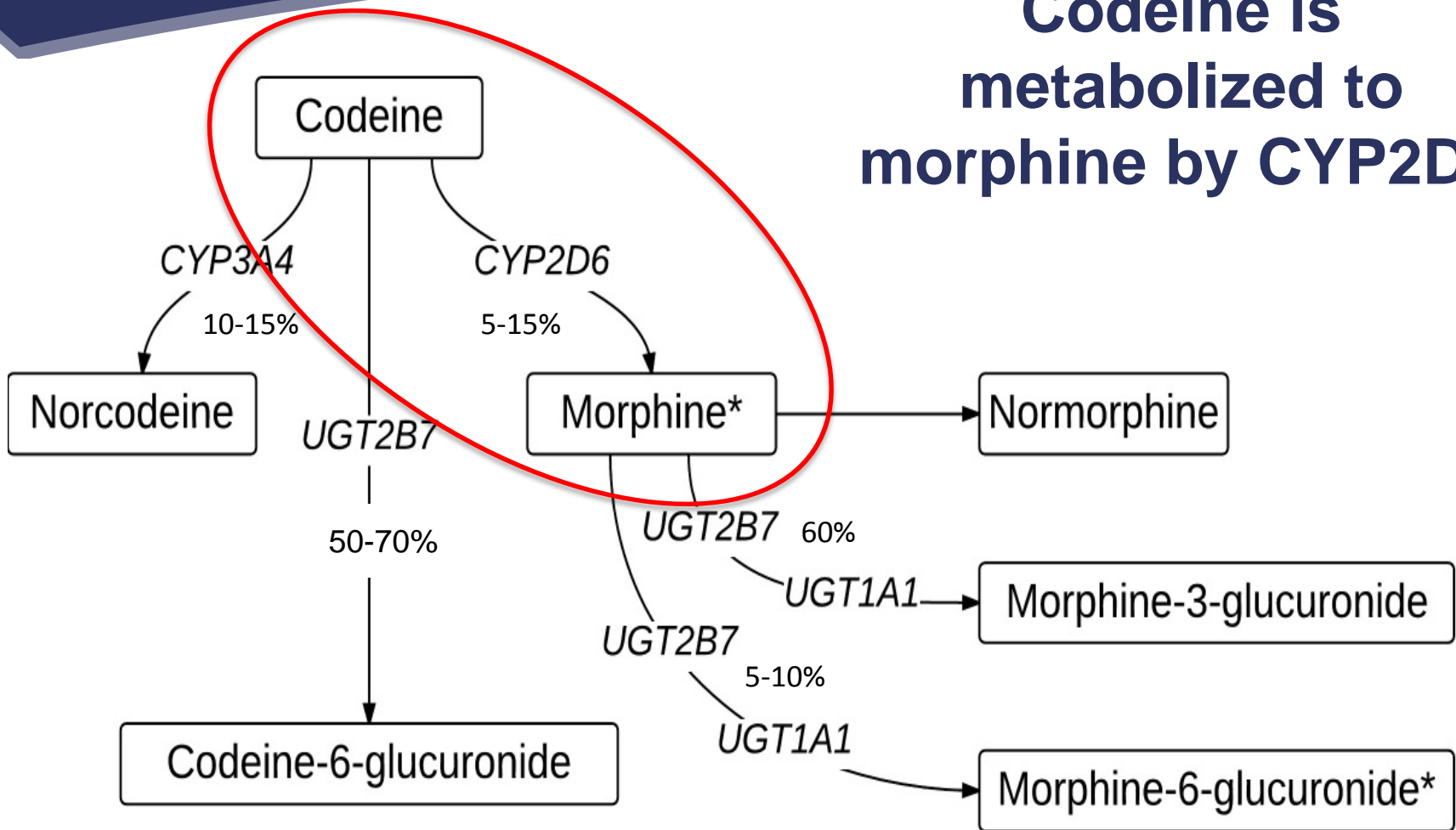


## April 20, 2017 FDA Drug Safety Advisory

- “The FDA has issued its strongest warning, called a **Contraindication**, to the drug labels of **codeine** and **tramadol** alerting that **codeine** should not be used to treat pain or cough and **tramadol** should not be used to treat pain in children younger than 12 years.
- A new **Contraindication** to the **tramadol** label warning against its use in children younger than 18 years to treat pain after surgery to remove the tonsils and/or adenoids.
- A new **Warning** to the drug labels of **codeine** and **tramadol** to recommend against their use in adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease, which may increase the risk of serious breathing problems.
- A strengthened **Warning** to mothers that breastfeeding is not recommended when taking **codeine** or **tramadol** medicines due to the risk of serious adverse reactions in breastfed infants. These can include excess sleepiness, difficulty breastfeeding, or serious breathing problems that could result in death.”



# Codeine is metabolized to morphine by CYP2D6



Asterisks (\*) denote active metabolite

**CYP2D6 UMs – Risk of toxicity**  
**CYP2D6 PMs – Lack of efficacy**



# 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 and/or adenoidectomy
- [2013](#) – FDA issues boxed warning on codeine-containing products regarding CYP2D6 UMs and contraindication against codeine use following tonsillectomy and/or adenoidectomy
- [2015](#) – FDA drug safety communication regarding codeine cough and cold medicines in children
- [2016](#) – AAP clinical report “Codeine: Time To Say ‘No’.”



# The Case for Codeine

- Used in children for many years
- Largely well-tolerated
- Relatively inexpensive
- Available in both liquid and tablet form
- Only Schedule III opioid analgesic as of 2014 (in combination with acetaminophen)
  - Verbal/facsimile rx
  - Refills

Particularly important for patients with chronic pain (e.g., **sickle cell disease**)

le uses a precision medicine approach to  
e prescribing (since 2013)

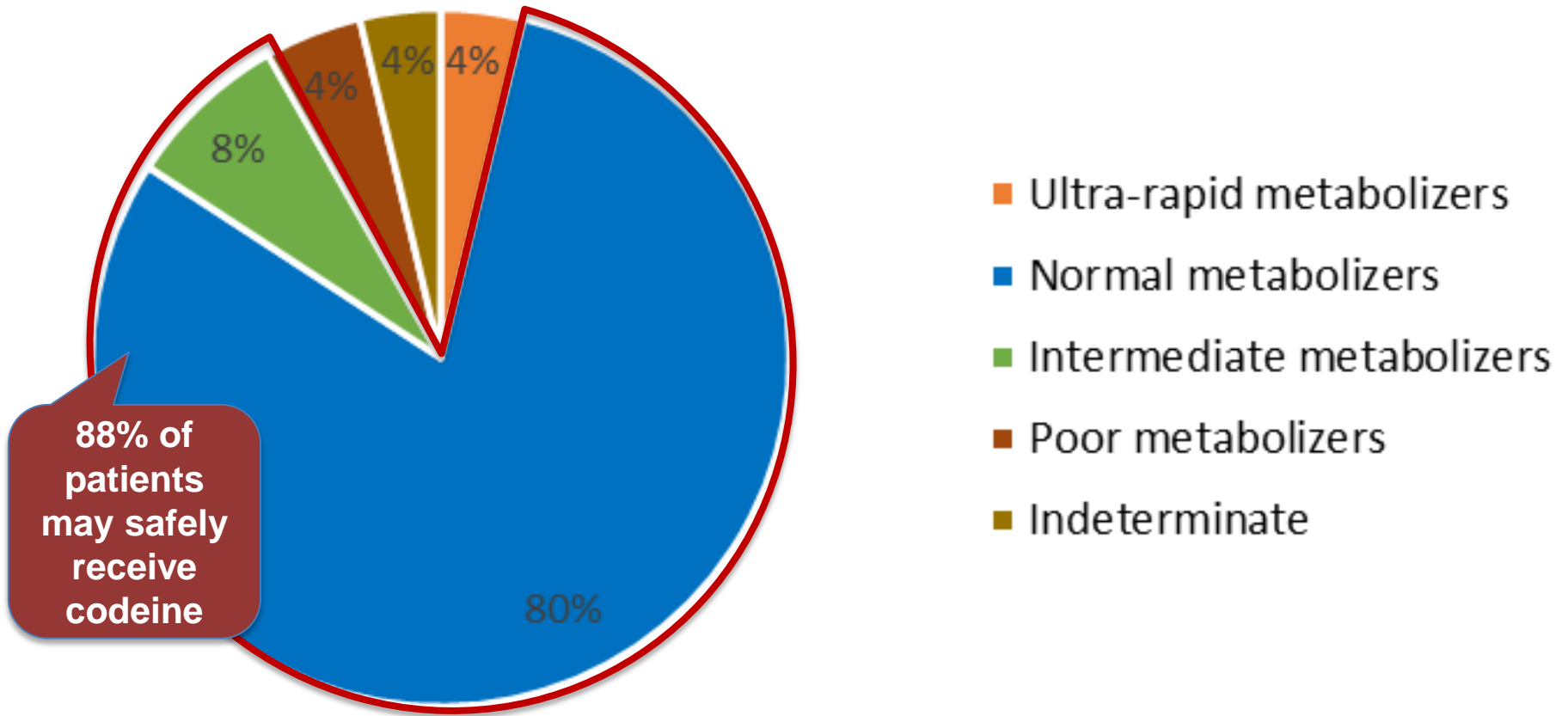


- St. Jude patients receive all medications from on-campus pharmacy
- Fully integrated EHR used for inpatient and outpatient areas



# Distribution of *CYP2D6* phenotypes at St. Jude

n=3639 children on PG4KDS

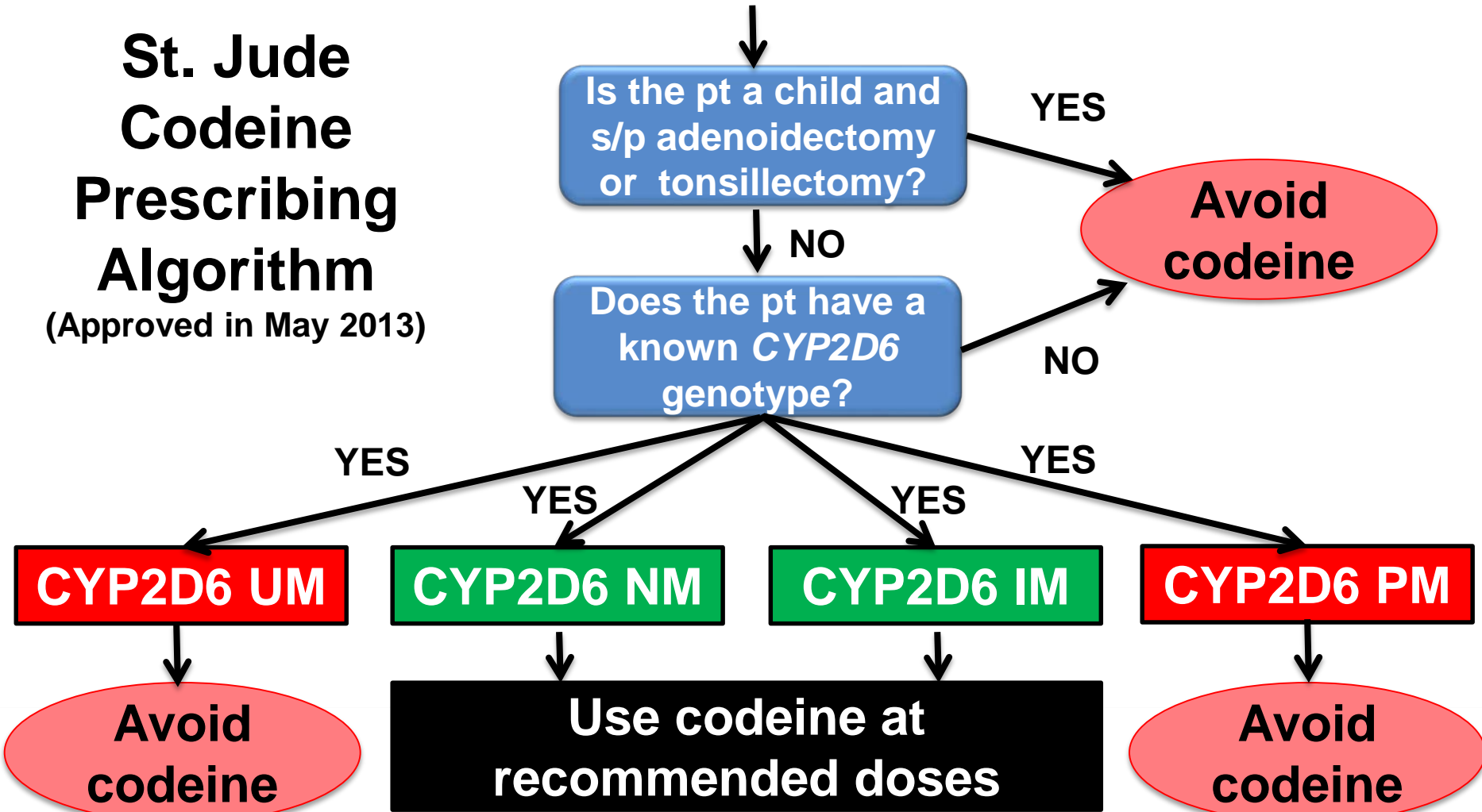




# Codeine Prescribed

## St. Jude Codeine Prescribing Algorithm

(Approved in May 2013)



Potential toxicity

Lack of efficacy



## Codeine prescribing patterns among genotyped patients with sickle cell disease (n = 621)

CYP2D6 phenotype	n	Number of patients for whom a codeine-containing analgesic was dispensed (%)
<b>High-risk Phenotypes</b>		
Ultra-rapid metabolizer	19	0
Possible ultra-rapid metabolizer	25	1 <sup>a</sup> (4%)
Poor metabolizer	9	0
<b>Non-high-risk Phenotypes</b>		
Extensive metabolizer	488	161 (33%)
Intermediate metabolizer	42	8 (19%)
Possible intermediate metabolizer	13	4 (31%)
<b>Unknown Risk</b>		
Indeterminate	25	1 <sup>b</sup> (4%)

<sup>a</sup>Patient had a documented history of tolerating codeine well in the past.

<sup>b</sup>Patient experienced adequate analgesia with codeine/acetaminophen plus ibuprofen, with no toxicity noted.



- A precision medicine approach has enabled our institution to safely and effectively administer codeine to the patients who are most likely to benefit and least likely to experience toxicity.
- St. Jude and other children's hospitals are pursuing local policies that would allow codeine in children < 12 years old in some circumstances.

# CPIC® Guideline for Codeine and CYP2D6

## Most recent guideline publication:

[Clinical Pharmacogenetics Implementation Consortium \(CPIC\) Guidelines for Cytochrome P450 2D6 \(CYP2D6\) Genotype and Codeine Therapy: 2014 Update \(April 2014\)](#) 

## Updates since publication:

**April 2017:** On April 20, the FDA updated a drug safety advisory for codeine and tramadol (full report [here](#)):

- The FDA has issued its strongest warning, called a Contraindication, to the drug labels of codeine and tramadol alerting that codeine should not be used to treat pain or cough and tramadol should not be used to treat pain in children younger than 12 years.
- A new Contraindication to the tramadol label warning against its use in children younger than 18 years to treat pain after surgery to remove the tonsils and/or adenoids.
- A new Warning to the drug labels of codeine and tramadol to recommend against their use in adolescents between 12 and 18 years who are obese or have conditions such as obstructive sleep apnea or severe lung disease, which may increase the risk of serious breathing problems.
- A strengthened Warning to mothers that breastfeeding is not recommended when taking codeine or tramadol medicines due to the risk of serious adverse reactions in breastfed infants. These can include excess sleepiness, difficulty breastfeeding, or serious breathing problems that could result in death.



## CPIC authors plan to mount a response to FDA

- One avenue to do this is through a submission of a Citizen's Petition under 21 CFR 10.30 → will trigger a response from FDA

The screenshot shows the homepage of regulations.gov. At the top, there is a navigation bar with links for Home, Help, Resources, and Feedback and Questions. Below this is a search bar with a magnifying glass icon and the word "Search", and two buttons labeled "Browse" and "Learn". The main content area features a "Participate Today!" section with text encouraging users to submit comments on proposed regulations. To the right, there is a "Are you new to the site?" section with a list of links for getting started. At the bottom, there is a search bar with the text "SEARCH for: Rules, Comments, Adjudications or Supporting Documents:" and a search box containing "FDA-2013-S-0610".

regulations.gov  
Your Voice In Federal Decision-Making

Home Help Resources Feedback and Questions

Search Browse Learn

**Participate Today!**

Submit your comments on proposed regulations and related documents published by the U.S. Federal government. You can also use this site to search and review original regulatory documents as well as comments submitted by others.

Help improve Federal regulations by **submitting your comments**.

SEARCH for: Rules, Comments, Adjudications or Supporting Documents:

FDA-2013-S-0610 Search

Advanced Search

**Are you new to the site?**

Click the links below to get started.

- > What can I find on this site?
- > How do I find a rule?
- > How do I submit a comment?
- > How do I find my comment?
- > Do my comments make a difference?

Newly Redesigned Comment

Site Enhancements

Unified Agenda Spring 2013



To contribute to the response to FDA:  
Please contact Kelly Caudle, PharmD, PhD  
CPIC Director

[Kelly.caudle@stjude.org](mailto:Kelly.caudle@stjude.org)