Pharmacogenetics for Safe Codeine Use in Sickle Cell Disease

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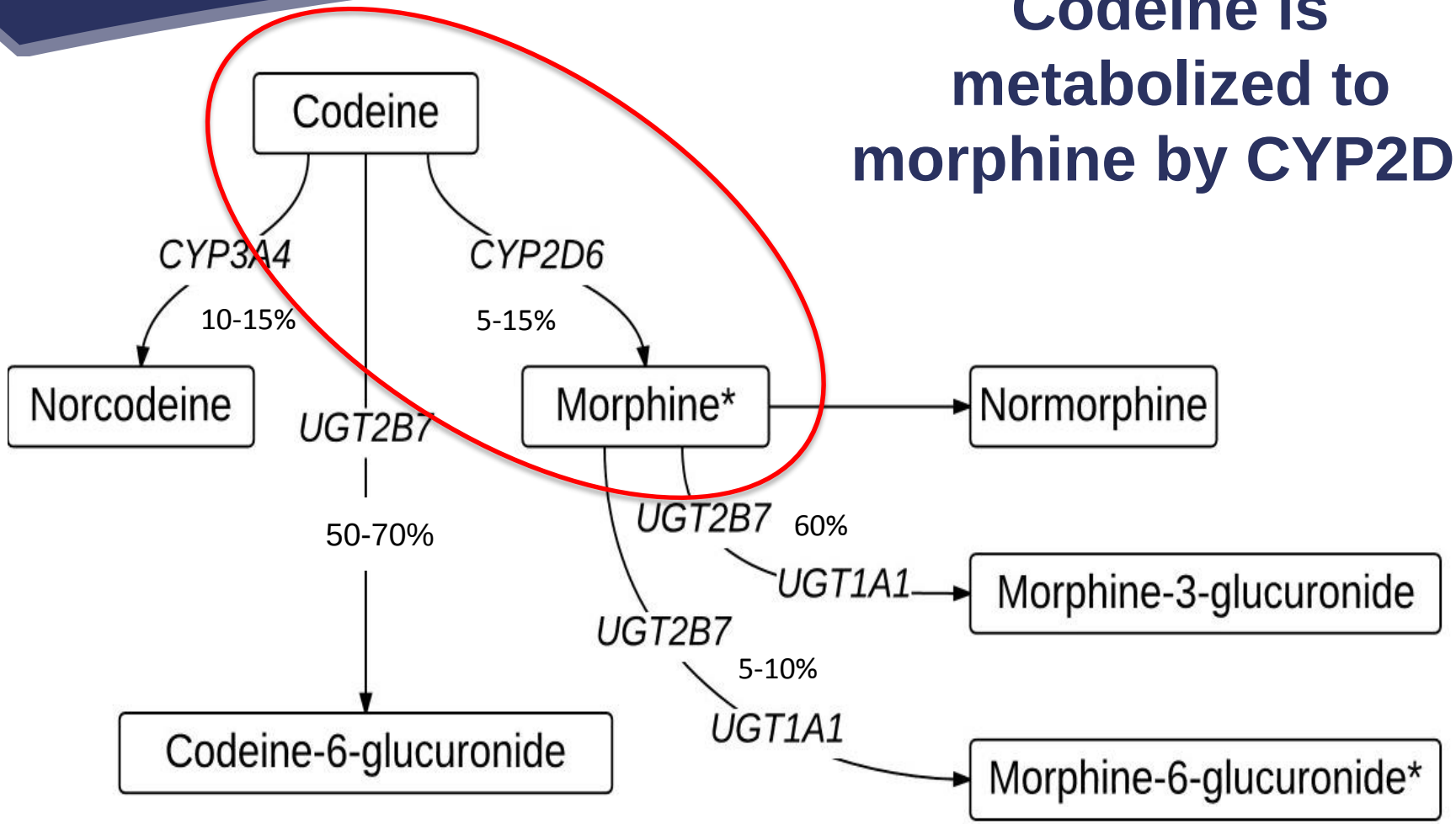
Gammal *et al*, *Pediatrics*, 2016 in press

Codeine is metabolized to morphine by CYP2D6



Asterisks (*) denote active metabolite

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

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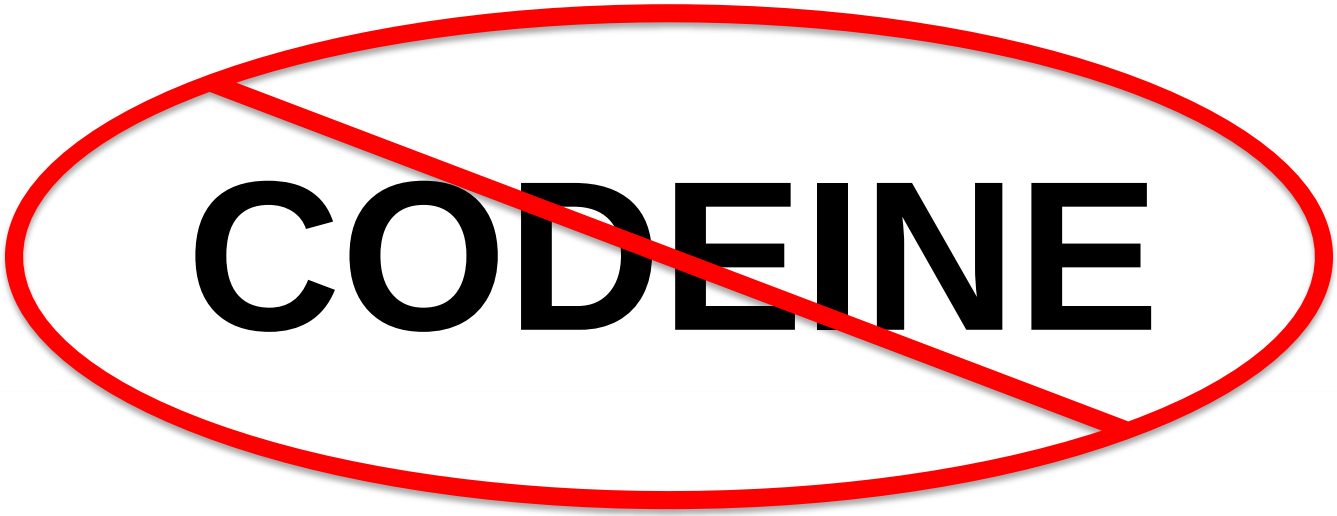
FDA, Codeine, and Children

- **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

Response

- Many pediatricians have stopped prescribing codeine and many pediatric hospitals have removed codeine from their formularies



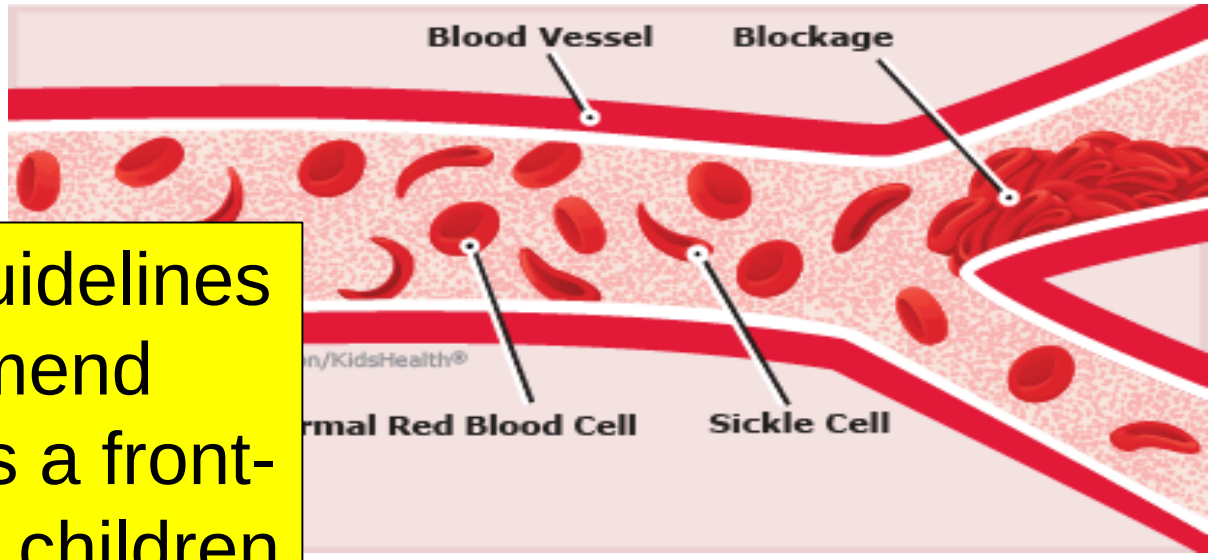
The Case for Codeine

- 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**)

Codeine Use in Sickle Cell Disease

- Patients with sickle cell disease experience recurrent and unexpected episodes of **vaso-occlusive pain crises** throughout their lives



http://discharge.seen.to/wp/sickle-cell-disease-vaso-occlusive-crisis/

National guidelines recommend **codeine** as a front-line drug in children

Manuscript Objectives

1. Describe the development and implementation of a **pharmacogenetics-based strategy** for codeine prescribing that accounts for CYP2D6 metabolizer status.
2. Report the **prescribing patterns** for a subset of our population, those with sickle cell disease, who most frequently require codeine-containing analgesics at our specialized pediatric institution.

Gammal *et al*, *Pediatrics*, 2016 in press

PG4KDS: Clinical Implementation of Pharmacogenetics at St. Jude

Primary Objective:

Migrate pharmacogenetic tests from the laboratory into routine patient care, to be available *preemptively*

Gammal *et al*, *Pediatrics*, 2016 in press

7 genes and 17 drugs have been integrated into the electronic health record

1. CYP2D6: codeine, oxycodone, tramadol, amitriptyline, fluoxetine, paroxetine, ondansetron
2. CYP2C19: clopidogrel, amitriptyline, voriconazole
3. CYP3A5: tacrolimus
4. DPYD: fluorouracil, capecitabine
5. SLCO1B1: simvastatin
6. TPMT: mercaptopurine, thioguanine, azathioprine
7. UGT1A1: atazanavir

Gammal *et al*, *Pediatrics*, 2016 in press

CYP2D6 Genotyping at St. Jude

- Mostly through PG4KDS
  - 97% of eligible St. Jude patients consent to protocol
- Single gene tests may also be ordered
  - Turn-around time: 5-7 days
- St. Jude hematologists often pre-emptively order *CYP2D6* genotypes for their patients with sickle cell disease

Gammal *et al*, *Pediatrics*, 2016 in press

CPIC™
Clinical Pharmacogenetics Implementation Consortium

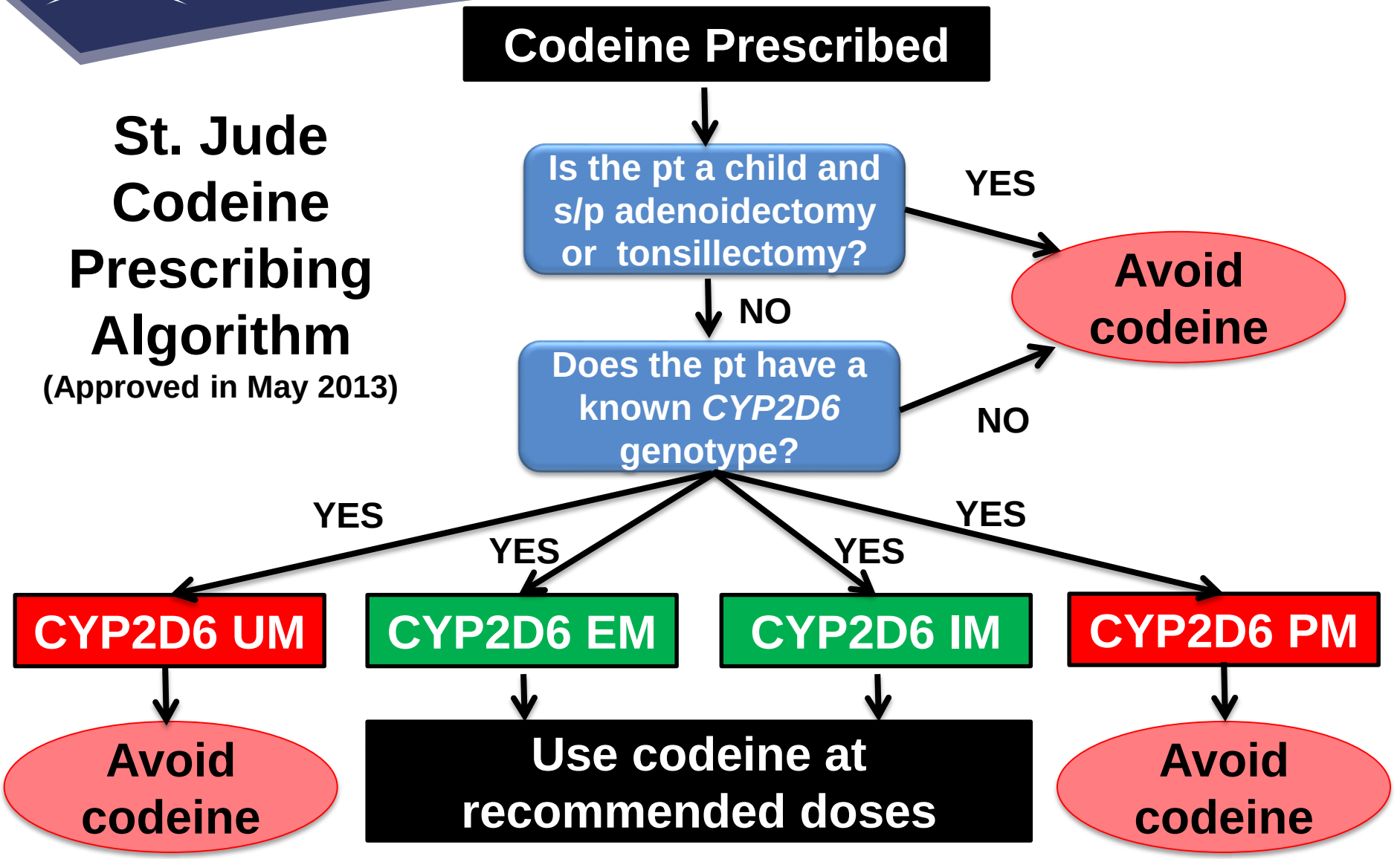
Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450 2D6 Genotype and Codeine Therapy: 2014 Update

KR Crews[1], A Gaedigk[2,3], HM Dunnenberger[1], JS Leeder[2,3], TE Klein[4], KE Caudle[1], CE Haidar[1], DD Shen[5,6], JT Callaghan[7,8], S Sadhasivam[9,10], CA Prows[11,12], ED Kharasch[13] and TC Skaar[7]

Clin Pharmacol Ther. 2014; 95(4): 376-82

St. Jude Codeine Prescribing Algorithm

(Approved in May 2013)



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Elements of a *CYP2D6* Consultation Note

PHARMACOGENETICS CONSULT FOR*
CYP2D6 GENOTYPE

Sample for CYP2D6 Genotype Obtained: 03/01/2016
PG4KDS CYP2D6 Genotype Result: (*5/*5)0N

Based on the genotype result this patient is predicted to be a poor metabolizer of CYP2D6 substrates. This patient may require either a dose adjustment of any drug metabolized by CYP2D6 or a therapeutic alternative.

A result of *5/*5 signifies that both CYP2D6 alleles are deleted in this patient. This patient may be at a high risk for an adverse or poor response to medications that are metabolized by CYP2D6. To avoid an untoward drug response, dose adjustments or alternative therapeutic agents may be necessary for medications metabolized by the CYP2D6 enzyme pathway. If codeine is prescribed to a poor metabolizer, suboptimal analgesia is very likely; therefore, a therapeutic alternative is recommended. The diplotype result yields a CYP2D6 activity score of 0. For more information about specific medications metabolized by CYP2D6, please go to www.stjude.org/pg4kds.

Jane Doe, PharmD, pager 1234

Phenotype Assignment

Diplotype Interpretation

Dosing Recommendation

Activity Score

Educational Link

Pharmacist Contact Information

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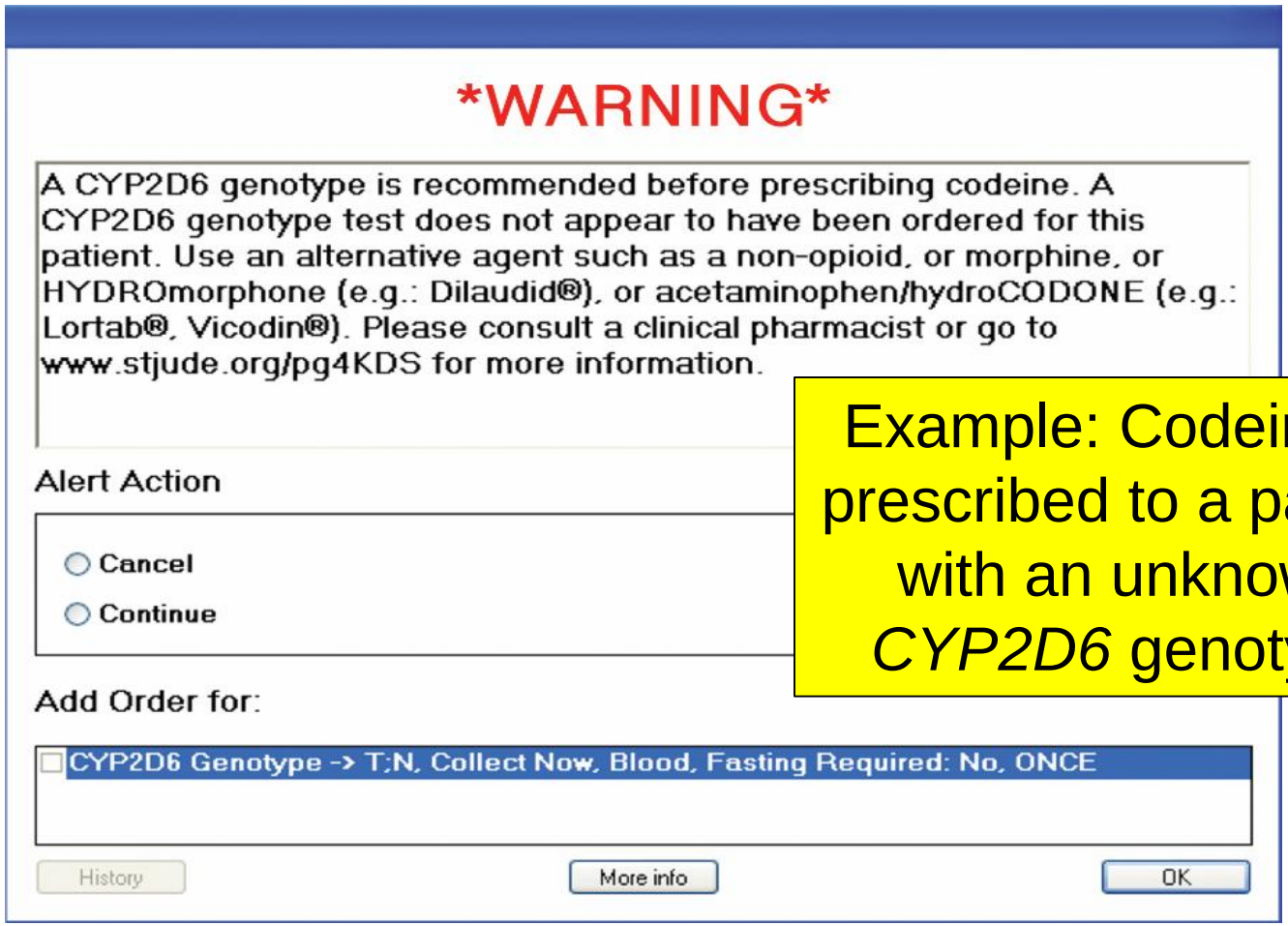
Pre-test alerts fire when no genotype is present in the EHR and a high-risk drug is prescribed



Example: Codeine is prescribed to a patient with an unknown *CYP2D6* genotype

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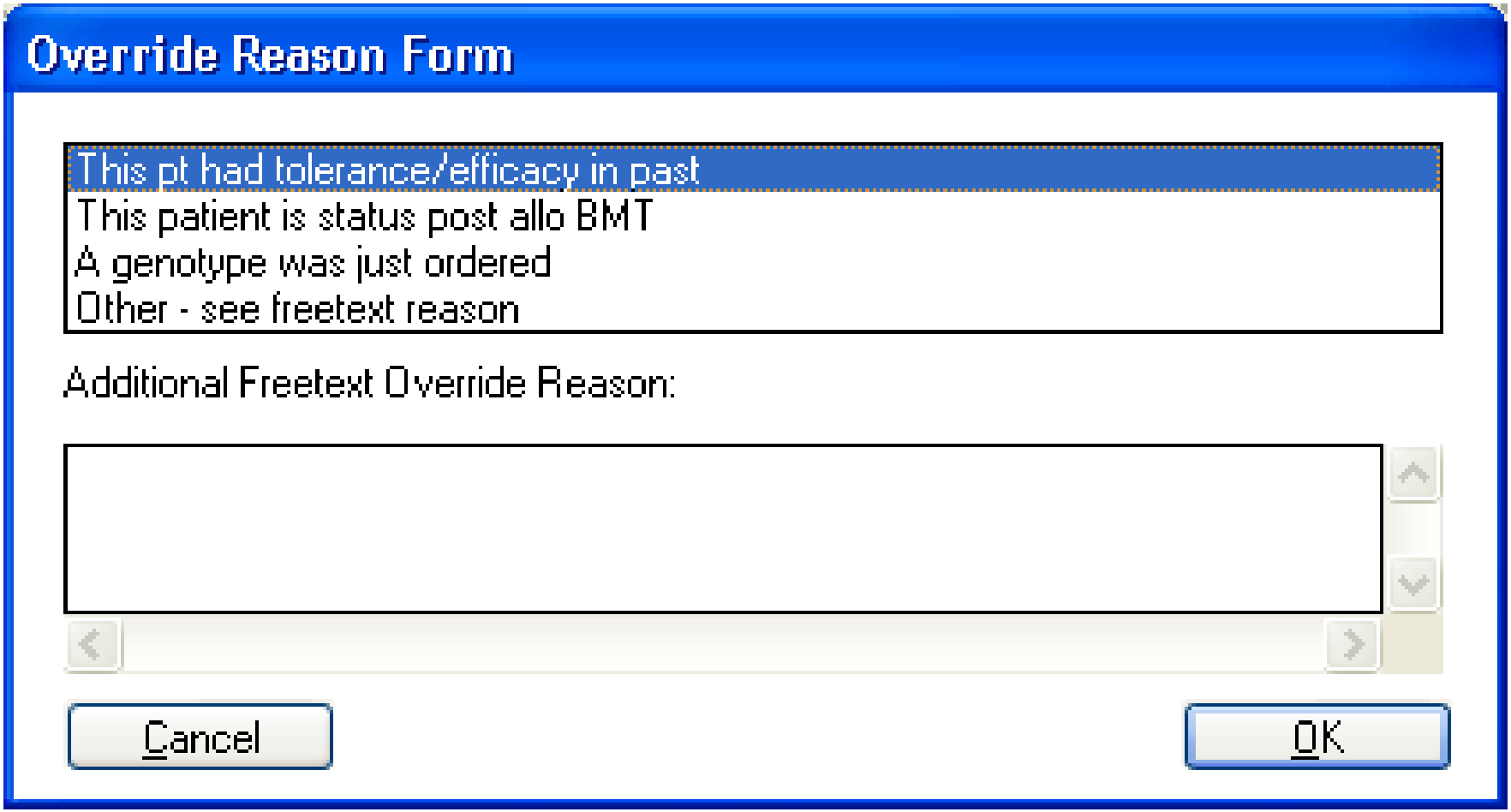
EHR = electronic health record

Prescribers may override alerts



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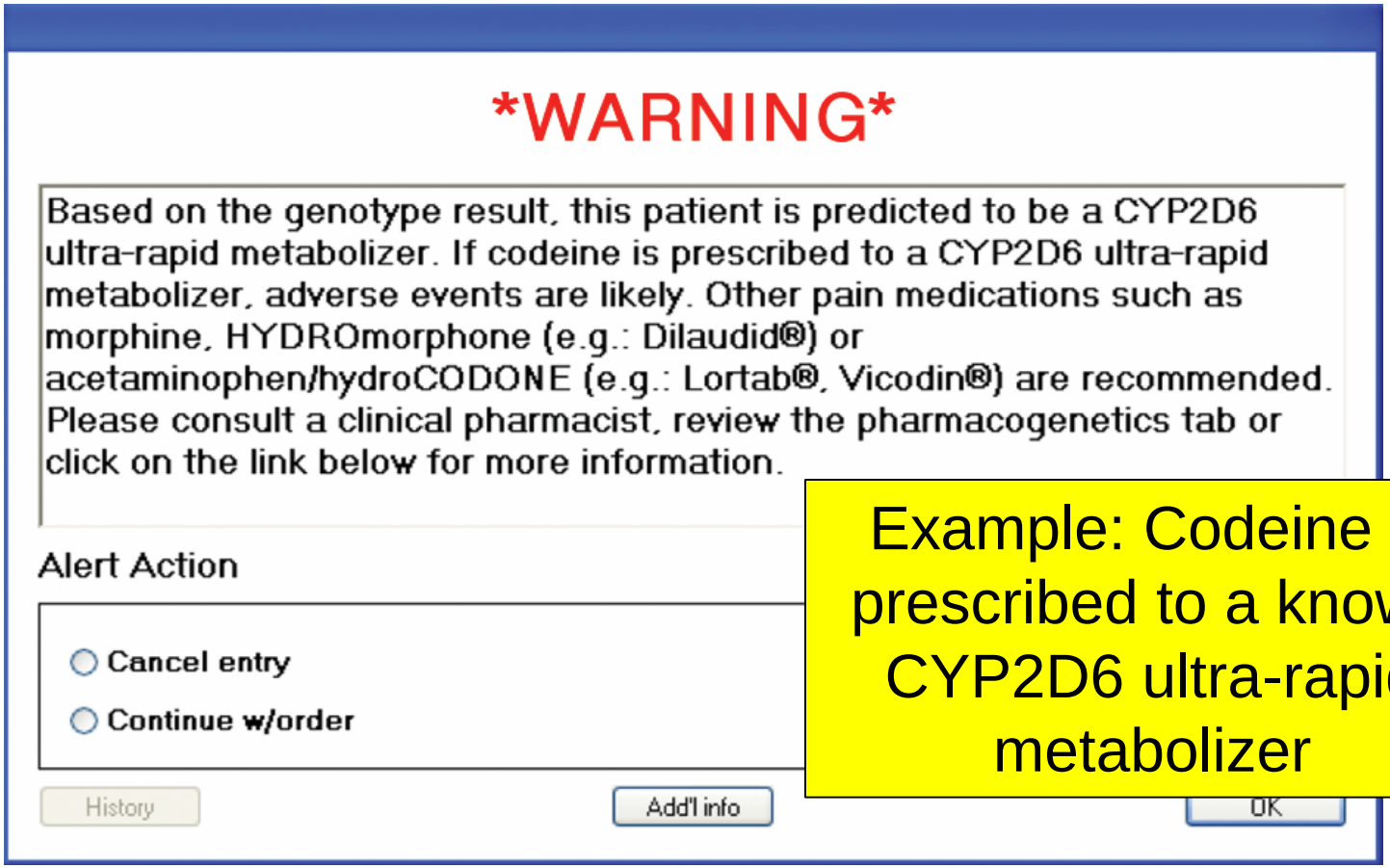
Post-test alerts fire when a high-risk genotype is present in the EHR and a high-risk drug is prescribed



Example: Codeine is prescribed to a known CYP2D6 ultra-rapid metabolizer

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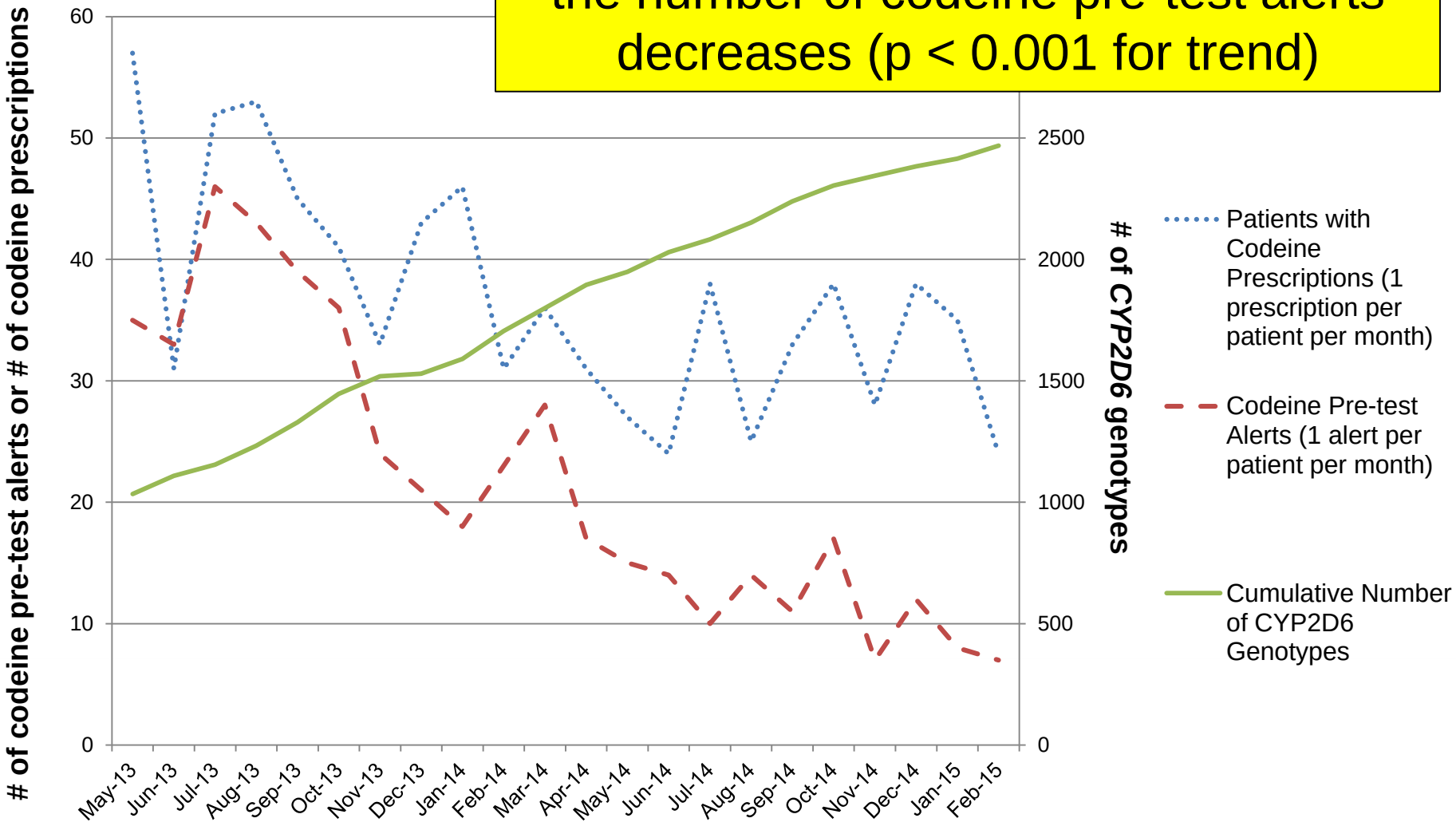
EHR = electronic health record

RESULTS

As the number of *CYP2D6*-genotyped patients increases ($p < 0.001$ for trend), the number of codeine pre-test alerts decreases ($p < 0.001$ for trend)



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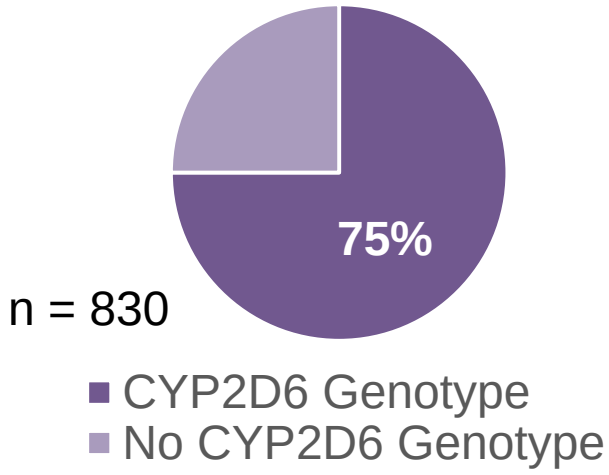
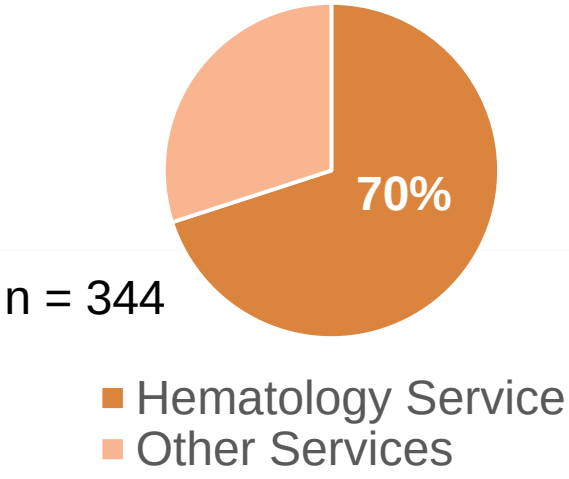
Patients with sickle cell disease (SCD)



- As of June 2015, 621 (75%) of the 830 active patients with SCD had a ***CYP2D6* genotype result** posted to the electronic health record



- Nearly 70% of patients (n = 233) for whom a *CYP2D6*/codeine **pre-test or post-test alert** have been presented to the prescriber are treated by the Hematology Service

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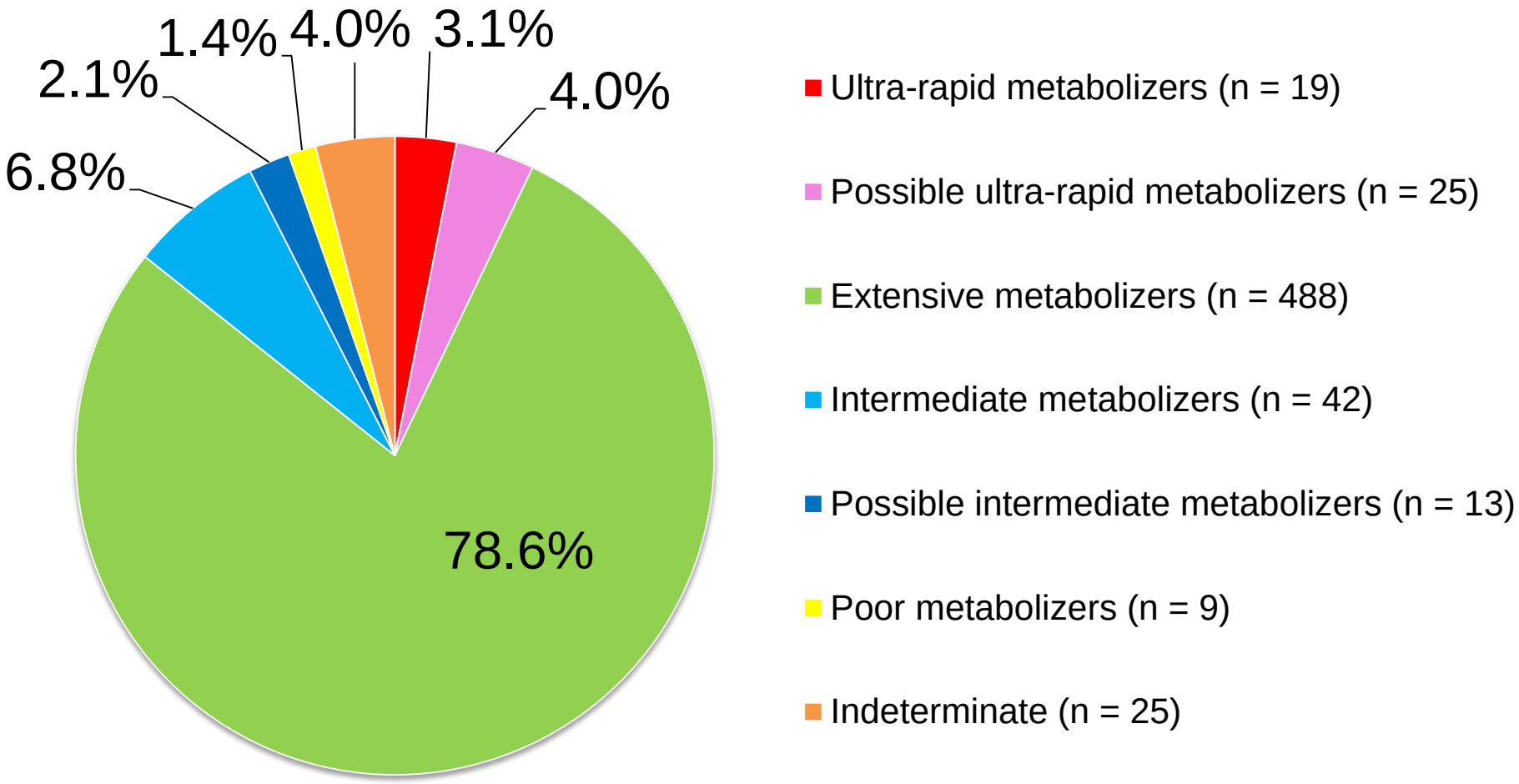
Distribution of *CYP2D6* phenotypes



n = 621 patients with sickle cell disease

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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 (%)
High-risk Phenotypes		
Ultra-rapid metabolizer	19	0
Possible ultra-rapid metabolizer	25	1[a] (4%)
Poor metabolizer	9	0
Non-high-risk Phenotypes		
Extensive metabolizer	488	161 (33%)
Intermediate metabolizer	42	8 (19%)
Possible intermediate metabolizer	13	4 (31%)
Unknown Risk		
Indeterminate	25	1[b] (4%)

[a]Patient had a documented history of tolerating codeine well in the past.

[b]Patient experienced adequate analgesia with codeine/acetaminophen plus ibuprofen, with no toxicity noted.

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Discussion Points

- Pharmacogenetic testing allows for the continued use of medications that may otherwise be deemed unsafe from a population perspective
  - Broadens and personalizes therapeutic options
- Application to other patient populations
  - Focus on high-risk, pharmacogenetically-relevant medications that are frequently used
- Implications for patient-provider relationship
  - *CYP2D6* genotyping may facilitate appropriate opioid prescribing and help reduce the mislabeling of patients as ‘drug-seekers’

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Limitations

- Cost of genotyping
- Lack of broad pharmacogenetic expertise
- Complexity of *CYP2D6* genotyping
- Future studies needed to show effect on clinical endpoints

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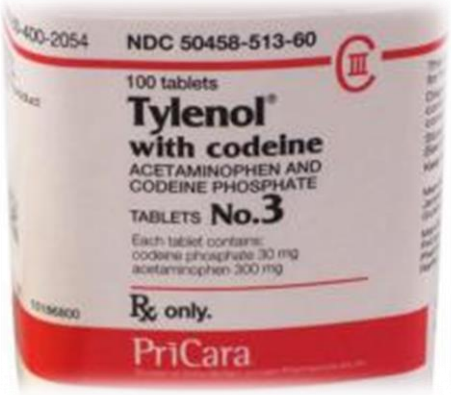
CONCLUSION

Pharmacogenetic testing was leveraged at our pediatric hospital to preserve the safe and effective use of codeine as an analgesic in our pediatric sickle cell disease population



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Acknowledgements

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