# Pharmacogenetics in Practice: Implementation and Outcomes

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# Learning Objectives

- Describe the evidence base and guidelines for use of genetic information to guide treatment decisions for commonly used medications
- Explain the rationale and process for integrating genotyping into clinical practice to guide prescribing decisions
- Evaluate data documenting the impact of genotype-guided therapy on clinical outcomes

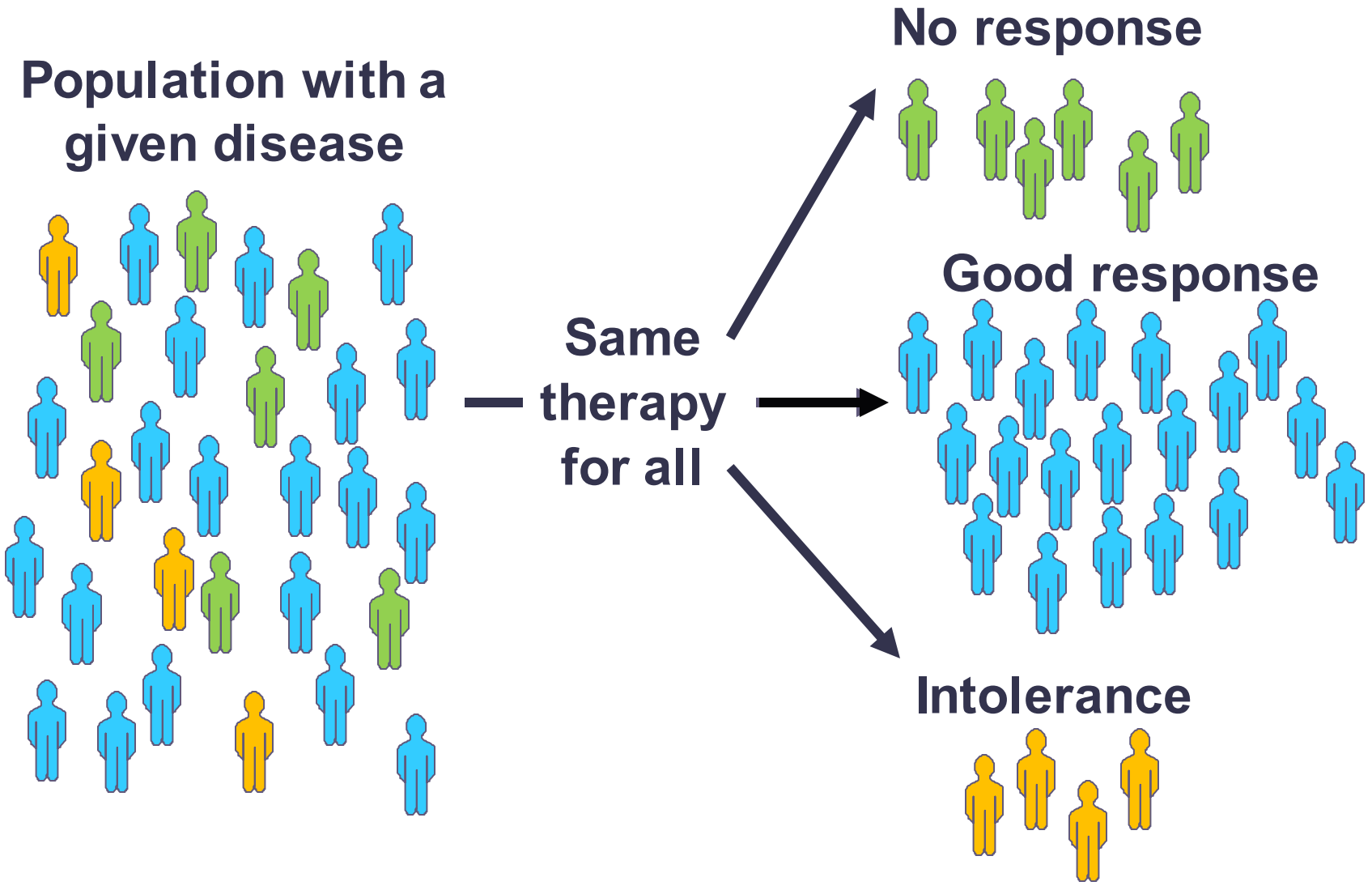
# Precision Medicine

Precision medicine is the future of medicine

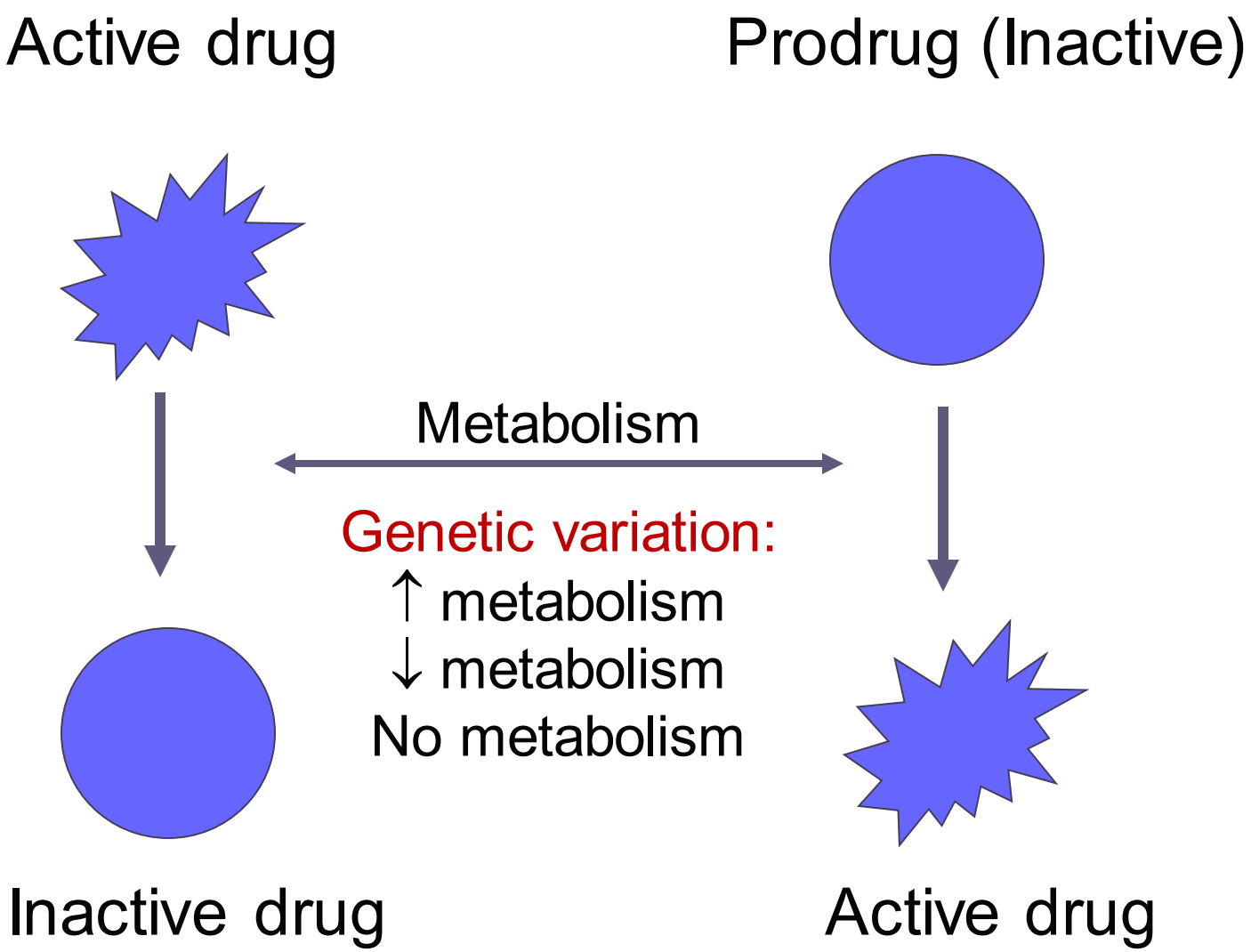
The concepts are not new, but the tools are much more robust and complex

Pharmacogenetics is among the most actionable elements of precision medicine at present

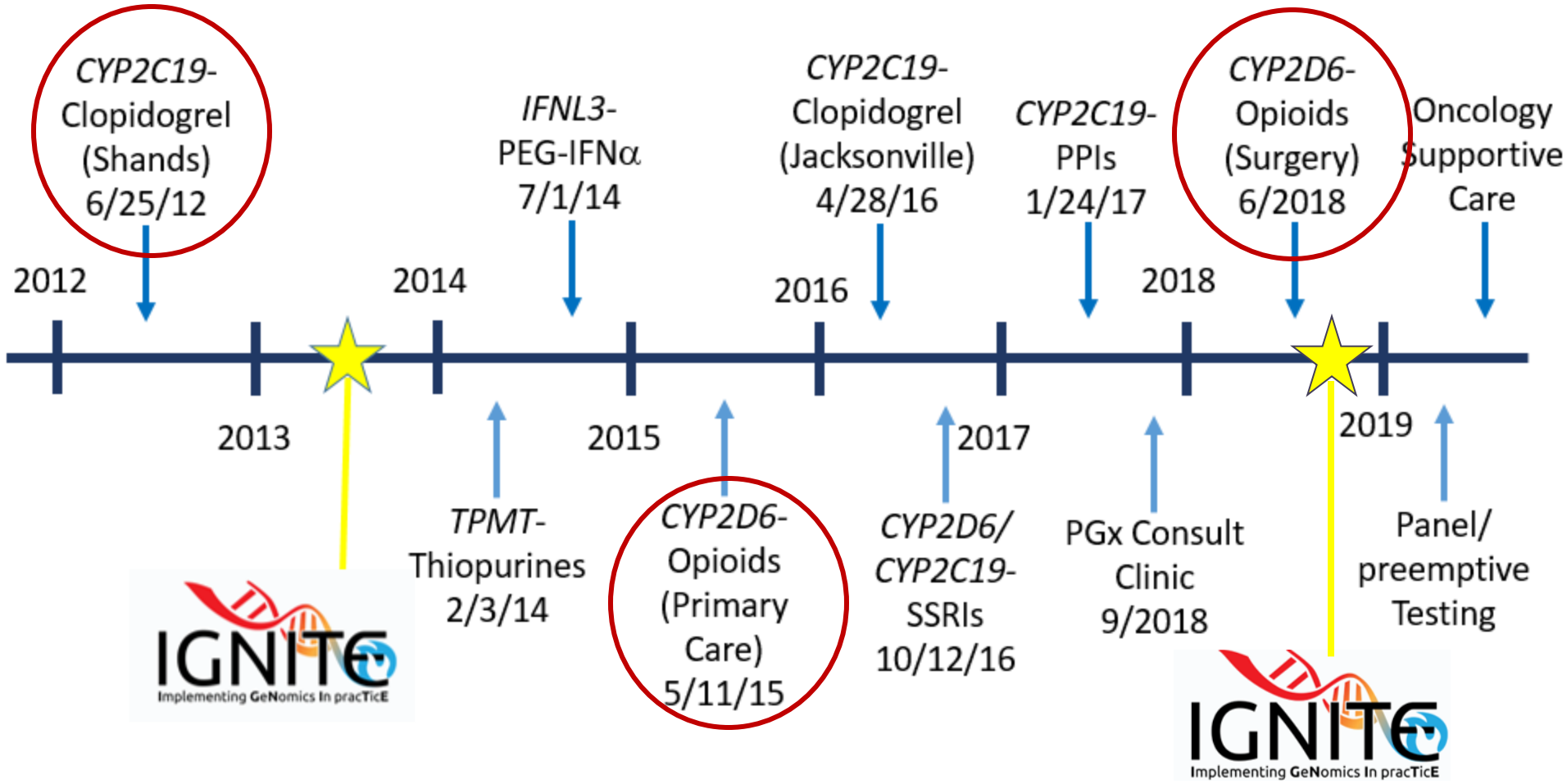
# Clinical Use of Pharmacogenetics



# Metabolism of Drugs



# UF Health
# Precision Medicine Program (PMP)




*Pharmacogenomics* 2017; PMID 28346068

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# *CYP2C19*-Clopidogrel

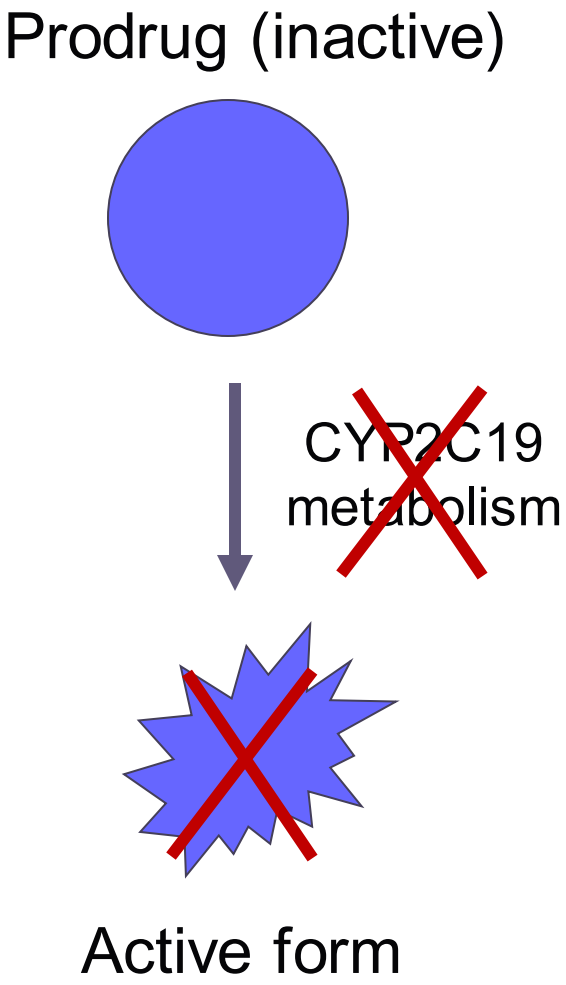
| | |
|---|---|
| Evidence that genotype influences drug response? | ✓ |
| Clinical Pharmacogenetics Implementation Guidelines? | ✓ |
| Alternative drug or dosing available? | ✓ |
| Reimbursed by many payers? | ✓ |

| | |
|---|---|
| Clinical trial data available on clinical utility? | ✗ |

cpicpgx.org
pharmgkb.org

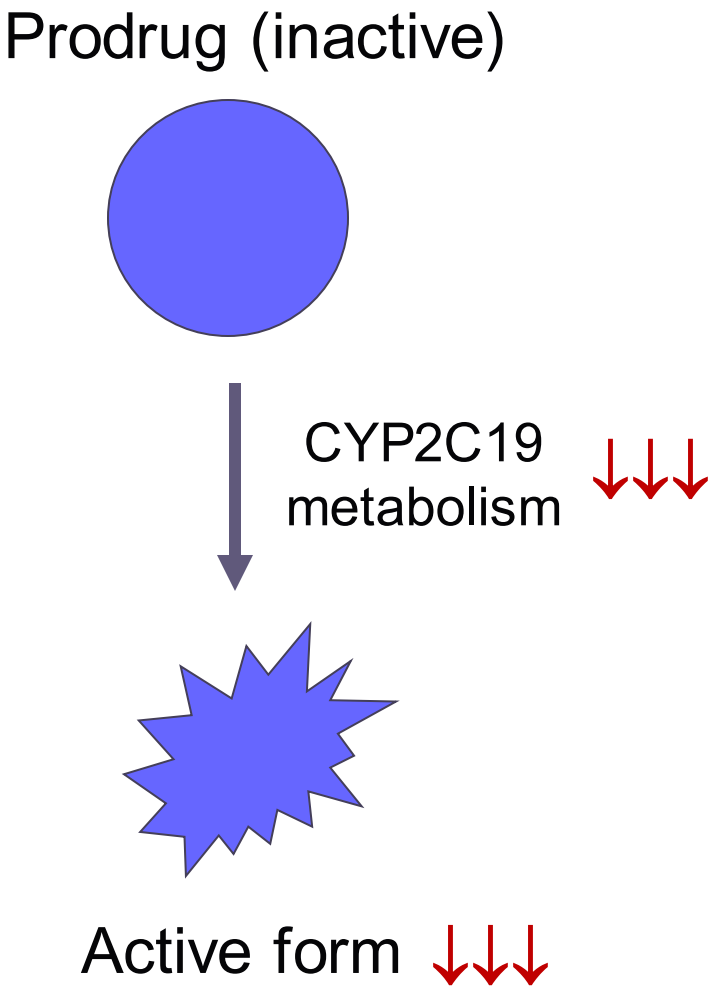
*Clin Pharmacol Ther* 2018; PMID 29280137

# Clopidogrel Metabolism




- Poor metabolizers (PMs)
  - 2-4%
  - 2 loss-of-function alleles: **2/*2, *2/*3, *3/*3*

# Clopidogrel Metabolism




- Poor metabolizers (PMs)
  - 2-4%
  - 2 loss-of-function alleles: **2/*2, *2/*3, *3/*3*
- Intermediate metabolizers (IMs)
  - 20-30%
  - 1 loss-of-function allele: **1/*2, *1/*3, *2/*17, *3/*17*

# Outcomes Based on RCT and Registry Post-Hoc Analyses

Meta-analysis of 9 trials and 9685 clopidogrel-treated high risk patients

| Outcome | PM/IM vs other |
|---|---|
| MACE* | HR 1.57 (1.13-2.16) |
| Stent Thrombosis | HR 2.81 (1.81-4.37) |

*Major adverse cardiovascular events (CV death, MI, or stroke)

*JAMA* 2010; PMID 20978260

# FDA-Approved Clopidogrel Label

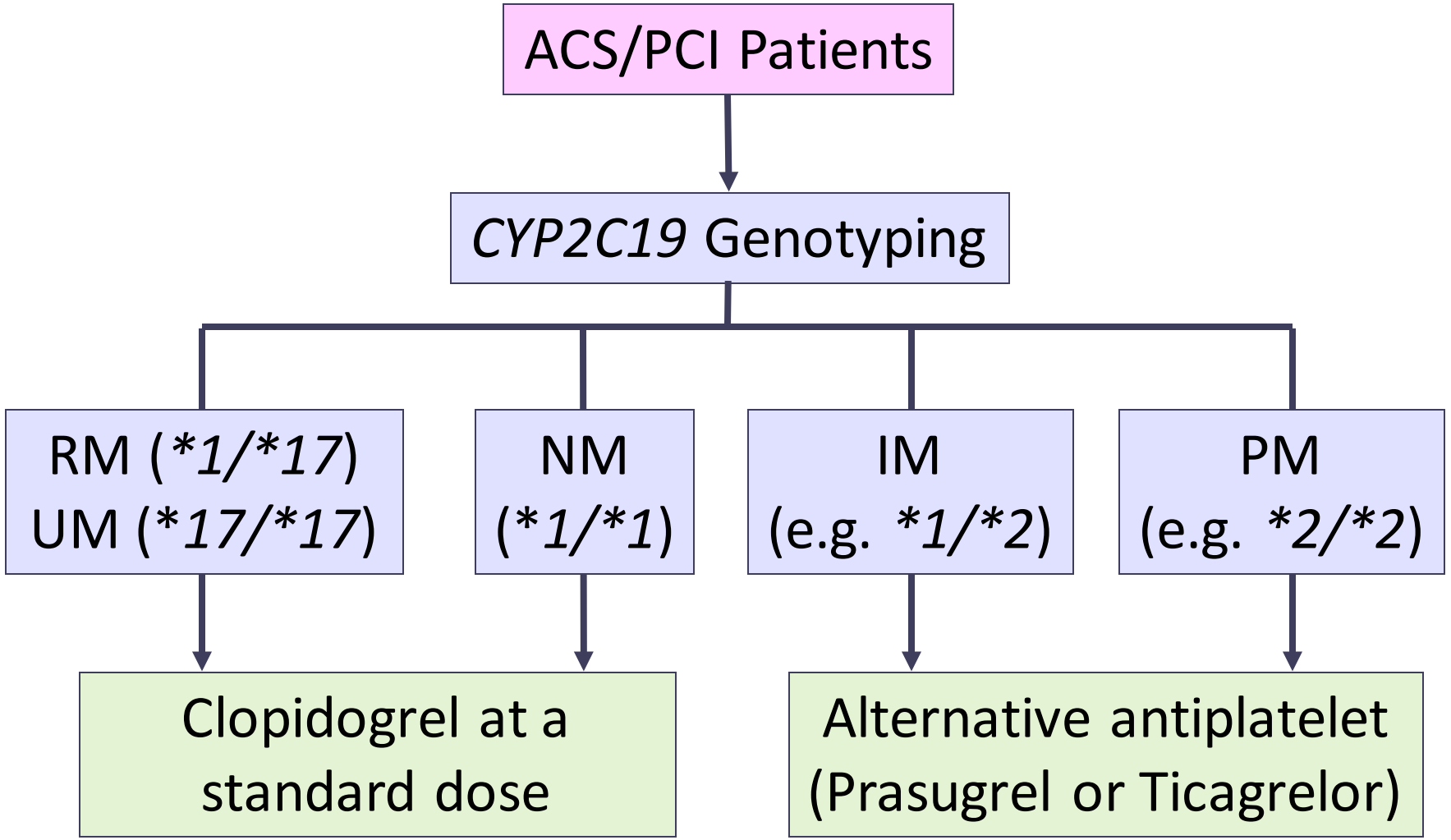
**WARNING: DIMINISHED ANTIPLATELET EFFECT IN PATIENTS WITH TWO LOSS-OF-FUNCTION ALLELES OF THE CYP2C19 GENE**

The effectiveness of clopidogrel bisulfate results from its antiplatelet activity, which is dependent on its conversion to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 *[see Warnings and Precautions (5.1), Clinical Pharmacology (12.3)]*. Clopidogrel bisulfate at recommended doses forms less of the active metabolite and so has a reduced effect on platelet activity in patients who are homozygous for nonfunctional alleles of the CYP2C19 gene, (termed "CYP2C19 poor metabolizers"). Tests are available to identify patients who are CYP2C19 poor metabolizers *[see Clinical Pharmacology (12.5)]*. Consider use of another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers.

CLOSE

# CPIC Guidelines for Clopidogrel

*Clin Pharmacol Ther* 2013;PMID 23698643.




CPIC: Clinical Pharmacogenetics Implementation Consortium

# *CYP2C19*-Clopidogrel Implementation at UF Health

- Implemented in June 2012 as part of routine clinical practice
  - Test added to standard order set
  - Run in UF Health Pathology Labs
  - *CYP2C19* genotype placed in the EHR
- Recommendations for alternative therapy provided for loss-of-function allele carriers

*Am J Med Genet C Semin Med Genet* 2014; PMID 24616371.

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# EHR Clinical Decision Support

Best Practice Advisory – Poor Metabolizer

**PROBLEM**

This patient's CYP2C19 genotype is associated with very impaired metabolic activation of the prodrug clopidogrel and elevated risk for stent thrombosis and other cardiovascular events after PCI.

**REASONS**

Reduced clopidogrel activation with this genotype results in significantly reduced platelet inhibition, increased residual platelet aggregation, and decreased clopidogrel efficacy

**RECOMMENDATIONS – MODIFY TREATMENT BY CHOOSING ONE OF THE FOLLOWING**

- Prasugrel 10 mg/day
- Ticagrelor 90 mg twice daily

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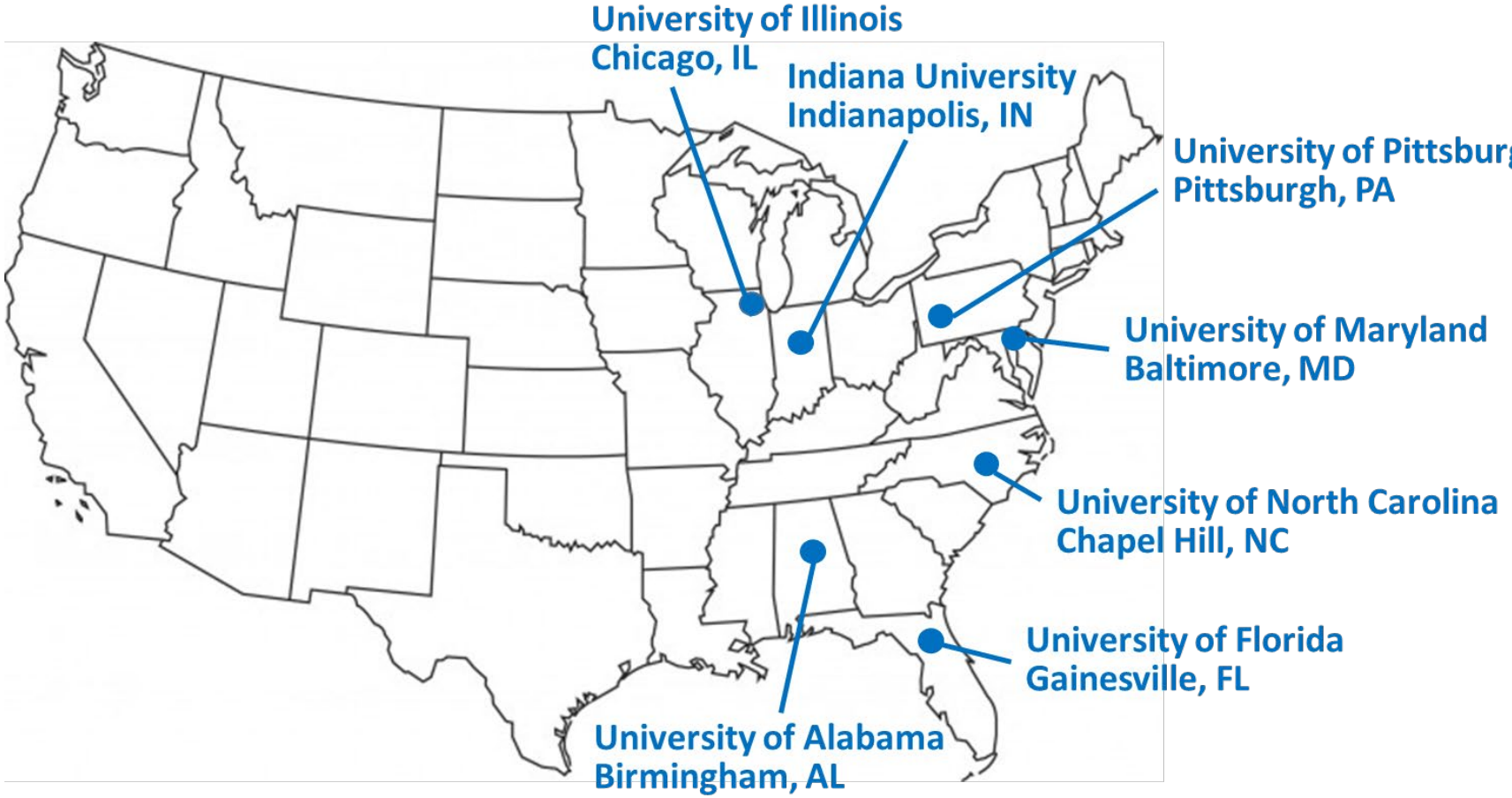
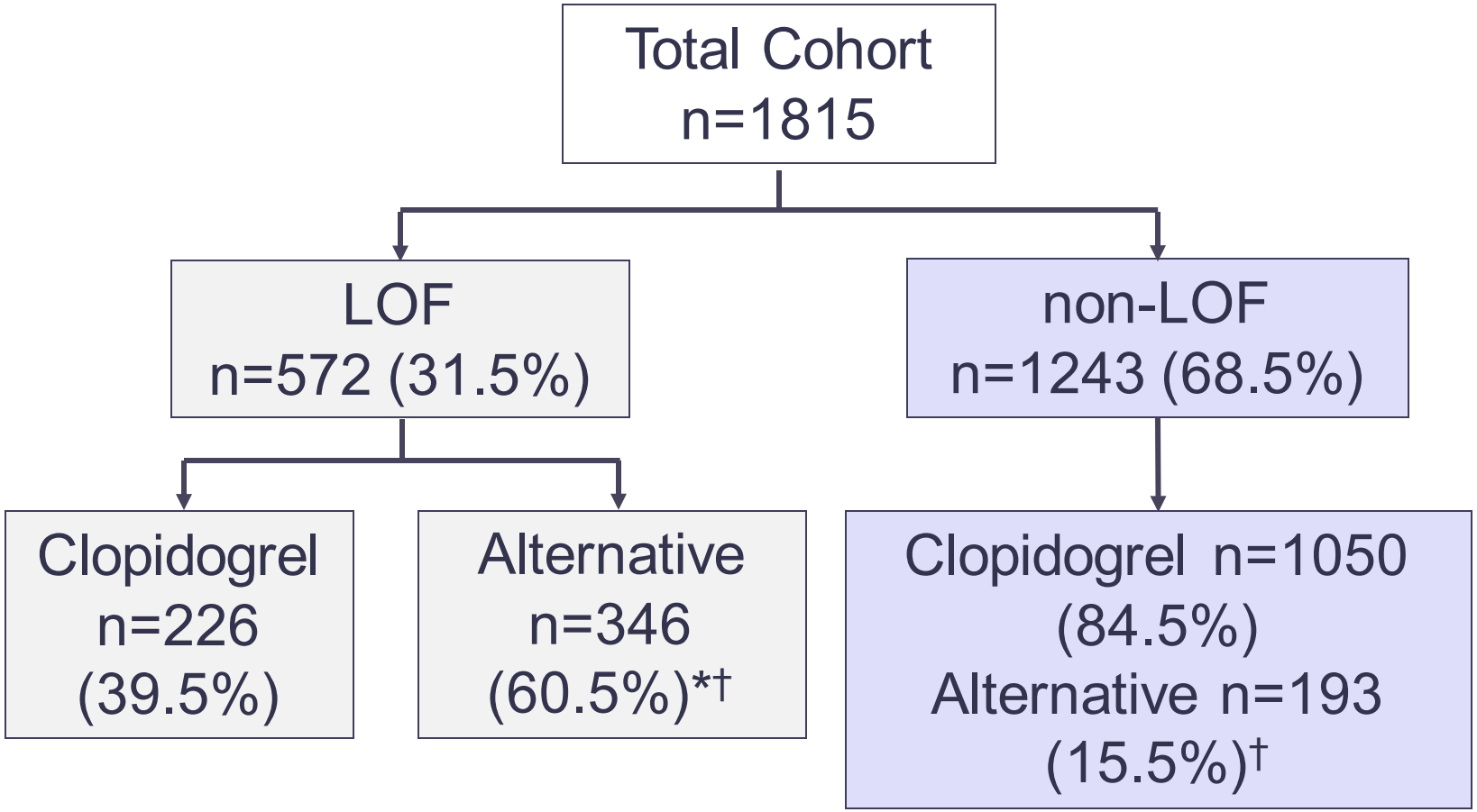
# Multisite Investigation of Outcomes with Implementation of *CYP2C19* Genotype-Guided Antiplatelet Therapy after PCI




*Clin Pharmacol Ther* 2018; PMID 29280137
*JACC Cardiovasc Interv* 2018; PMID 29102571

IGNITE
Implementing GeNomics In practicE

# Study Population by *CYP2C19* Group and Antiplatelet Therapy




*p<0.0001 for ALTERNATIVE between LOF and NON-LOF groups

†Prasugrel comprised >60% of ALTERNATIVE therapy

*JACC Cardiovasc Interv* 2018; PMID 29102571

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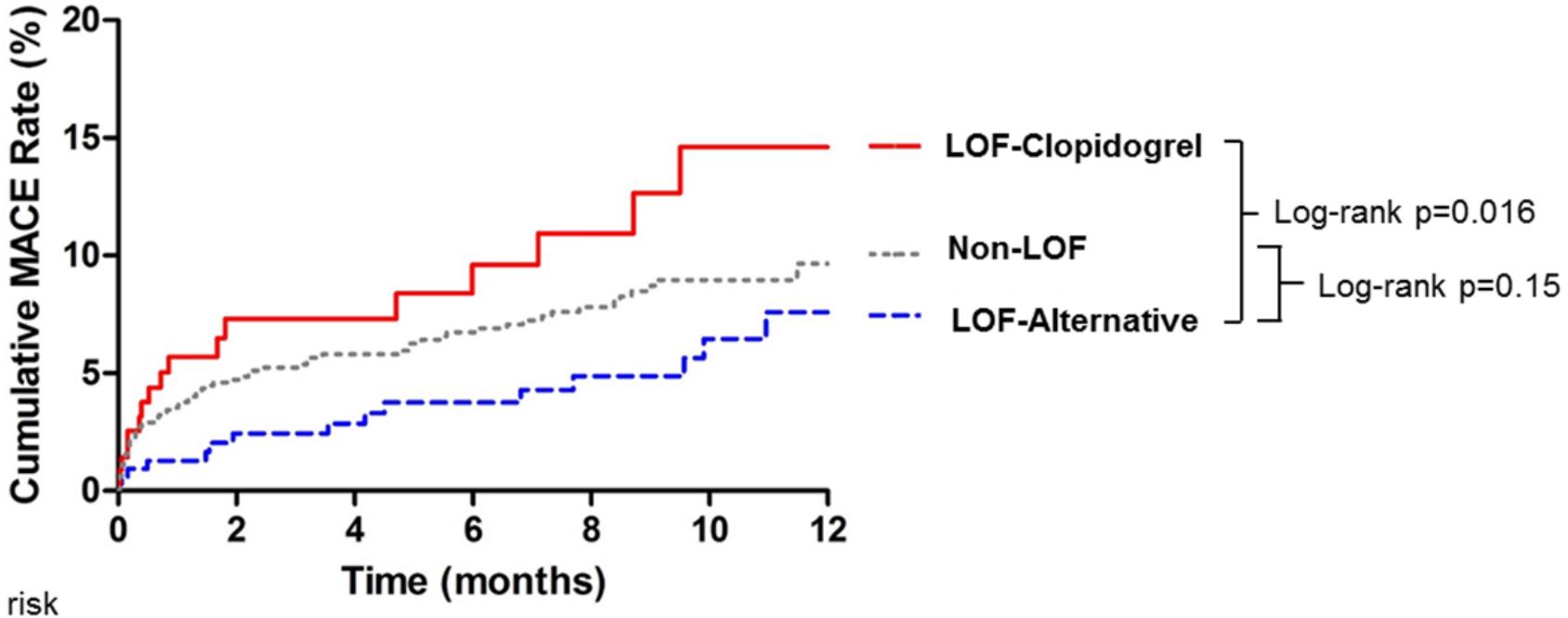
# Risk of Major Adverse Cardiovascular Events

## Death, MI, or ischemic stroke (MACE)




| No. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| LOF-Clopidogrel | 226 | 112 | 89 | 76 | 63 | 39 | 3 |
| Non-LOF | 1243 | 759 | 636 | 577 | 451 | 293 | 28 |
| LOF-Alternative | 346 | 245 | 221 | 195 | 161 | 112 | 9 |

**N=1815**

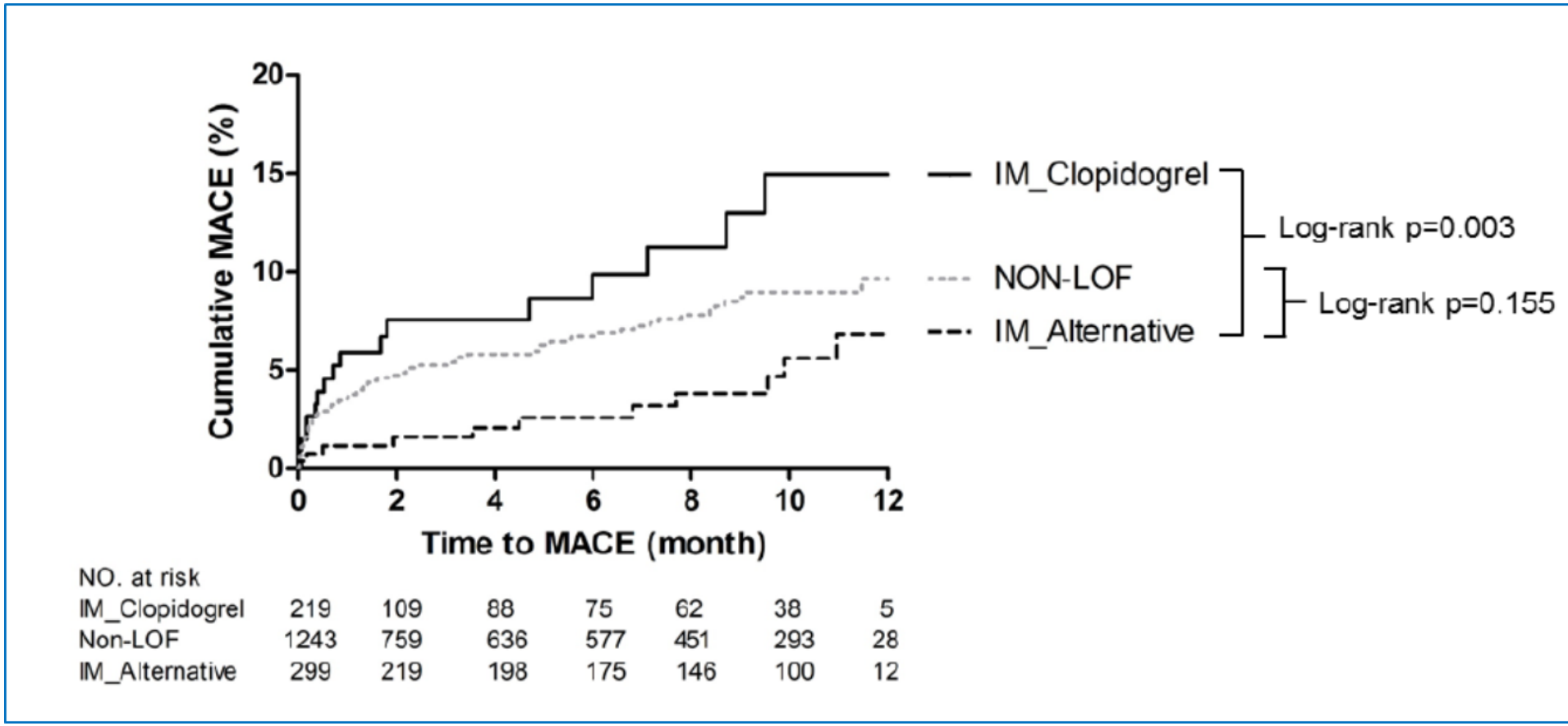
**LOF-Clop vs. LOF-Alt**
**Adjusted HR 2.26** (1.18-4.32), P=0.013

**Non-LOF vs. LOF-Alt**
**Adjusted HR 1.14** (0.69-1.88), P=0.600

*JACC Cardiovasc Interv* 2018; PMID 29102571

# Risk of Death, MI, or Ischemic Stroke (MACE)

## Risk driven by CYP2C19 intermediate metabolizers (IMs)

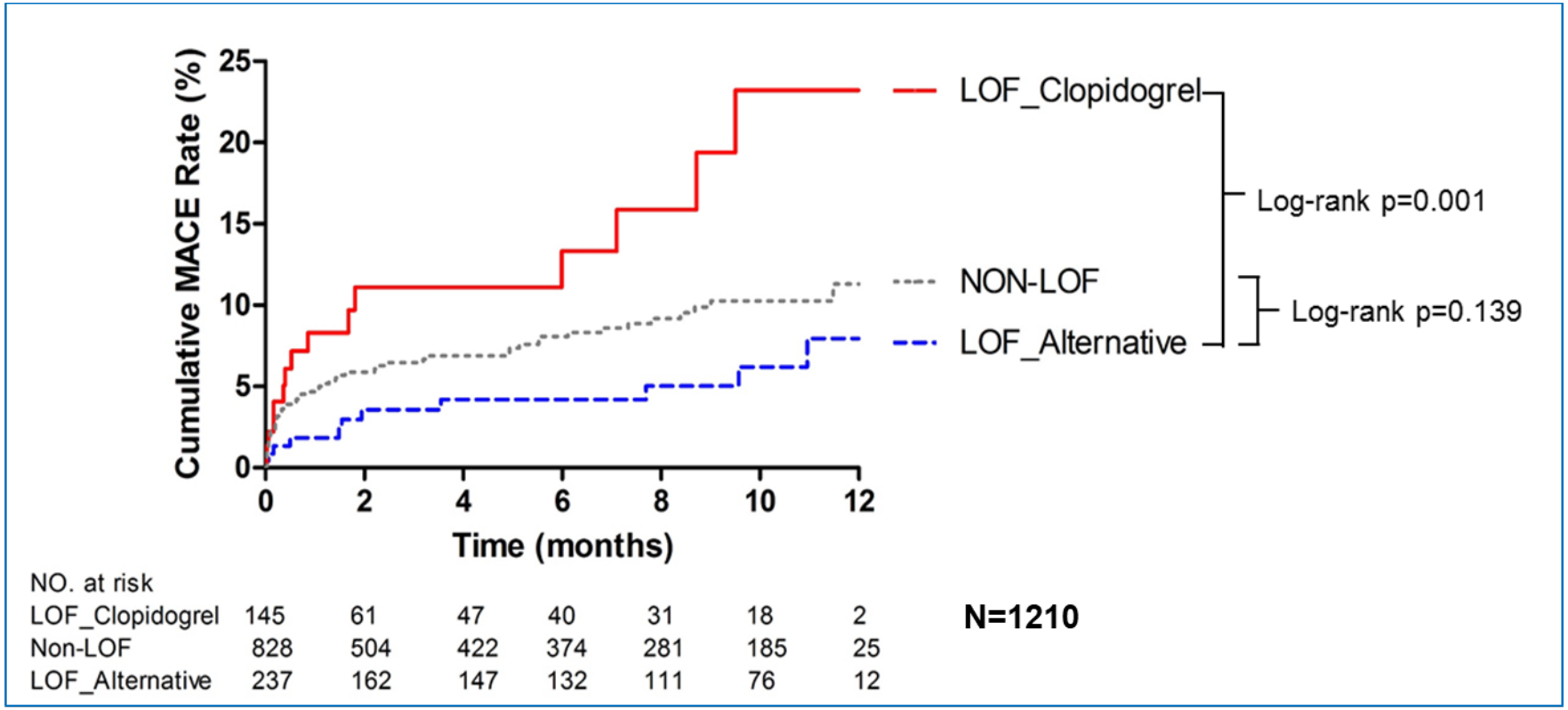



| NO. at risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| IM_Clopidogrel | 219 | 109 | 88 | 75 | 62 | 38 | 5 |
| Non-LOF | 1243 | 759 | 636 | 577 | 451 | 293 | 28 |
| IM_Alternative | 299 | 219 | 198 | 175 | 146 | 100 | 12 |

*JACC Cardiovasc Interv* 2018; PMID 29102571

# Risk of Death, MI, or Ischemic Stroke (MACE)

## Risk highest in those with ACS indication at index PCI




**LOF-Clop vs. LOF-Alt**
**Adjusted HR 2.87** (1.35-6.09)

**Non-LOF vs. LOF-Alt**
**Adjusted HR 1.26** (0.70-2.23)

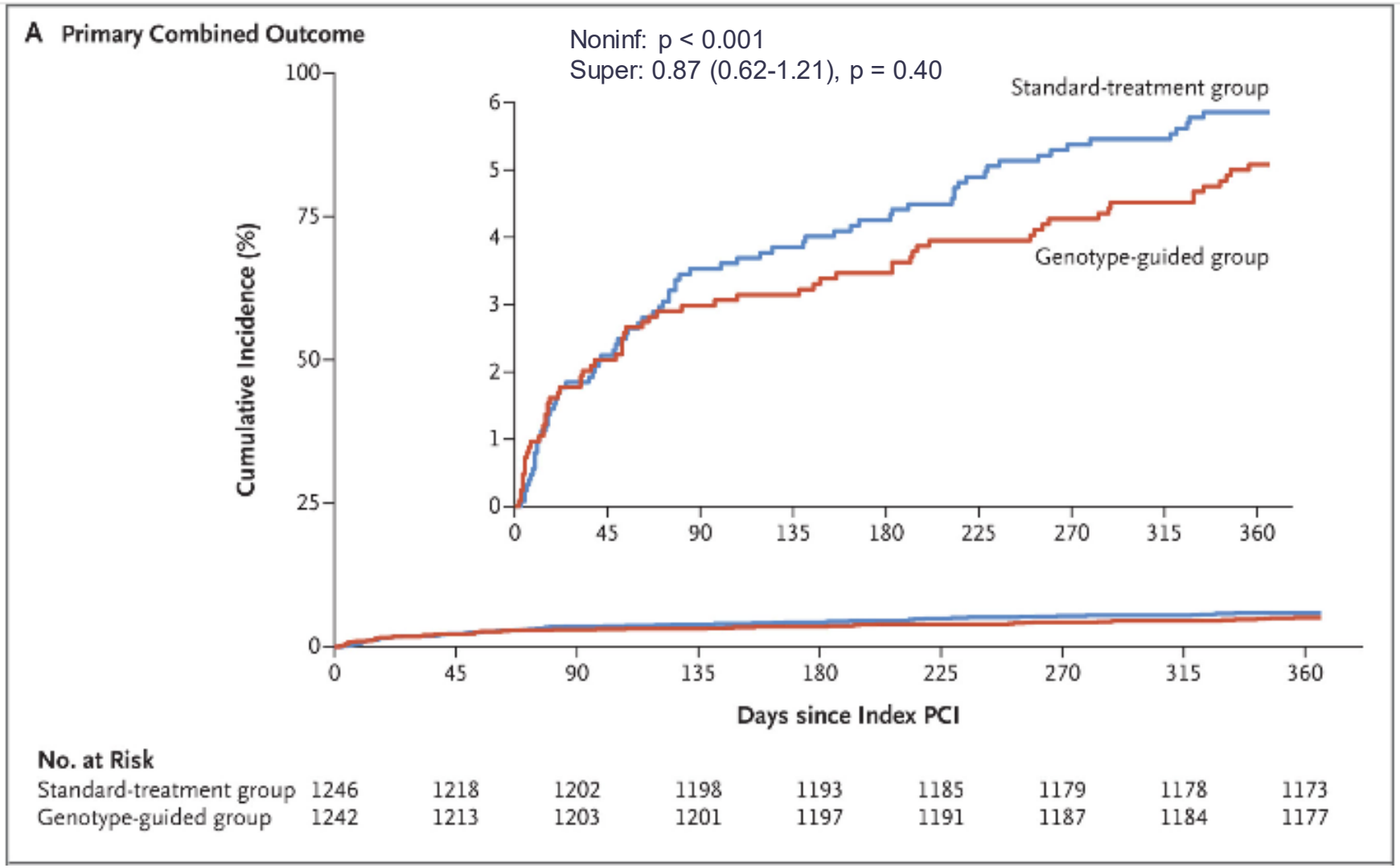
*JACC Cardiovasc Interv* 2018; PMID 29102571

# Summary: *CYP2C19* and clopidogrel

- Data across 7 institutions and over 1,800 patients suggest:
  - Clinical implementation of pharmacogenetic testing is feasible
  - Genotype-guided antiplatelet therapy reduces MACE in post PCI patients
- RCT confirmed that a *CYP2C19*-guided approach, including clopidogrel, is non-inferior to ticagrelor and prasugrel for clinical outcomes and superior for bleeding risk

# POPular Genetics: Genotype-guided $P2Y_{12}$ Inhibitors in Primary PCI

*NEJM 2019*; PMID 31479209



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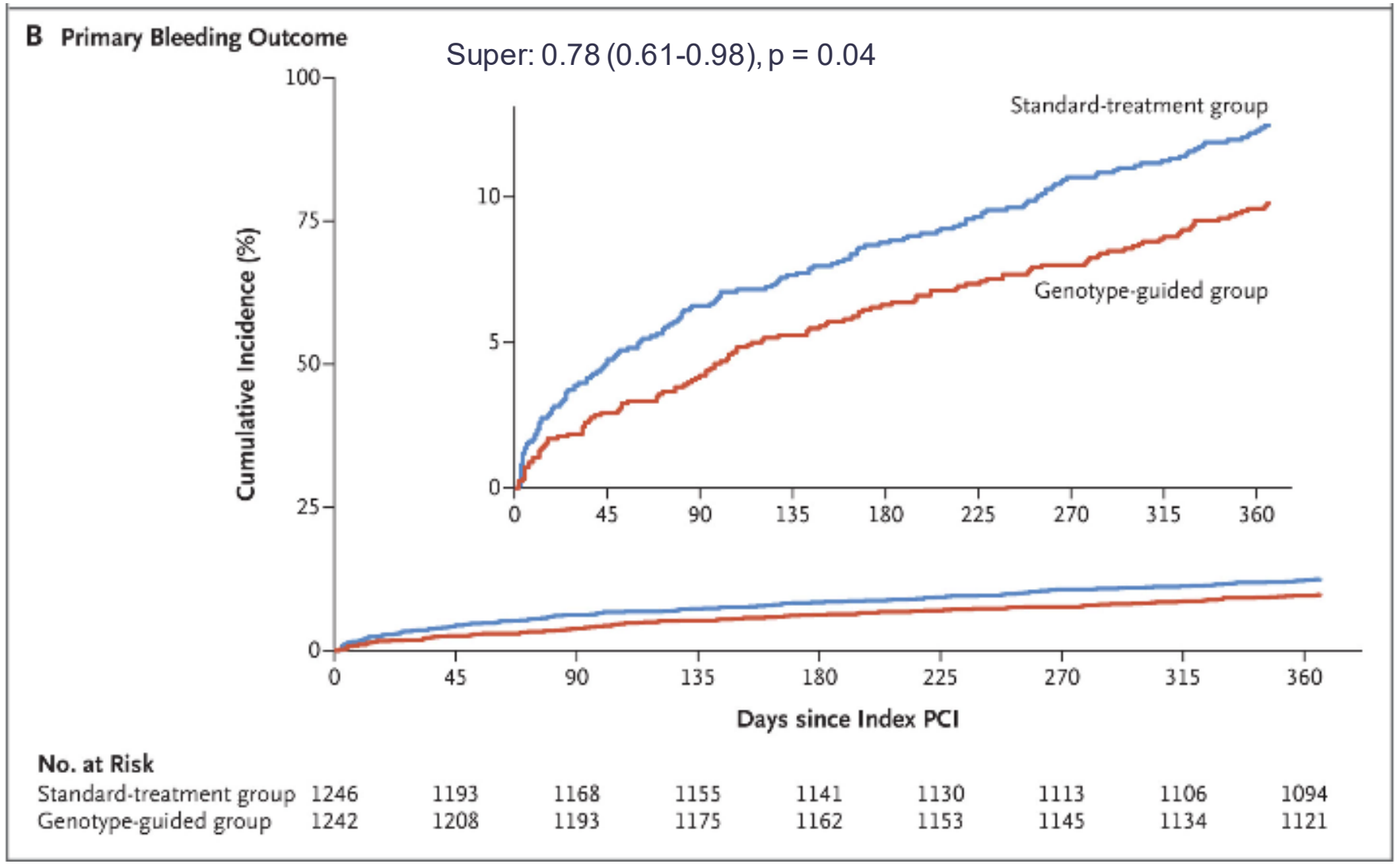
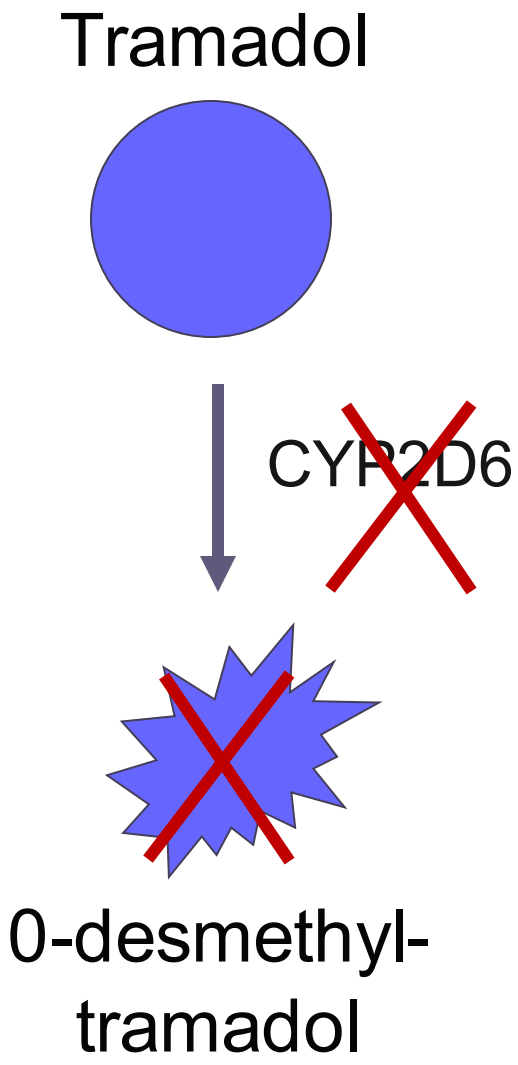


# *CYP2D6* Genotype and Opioid Metabolism

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  - 5-10%
  - 2 no-function alleles

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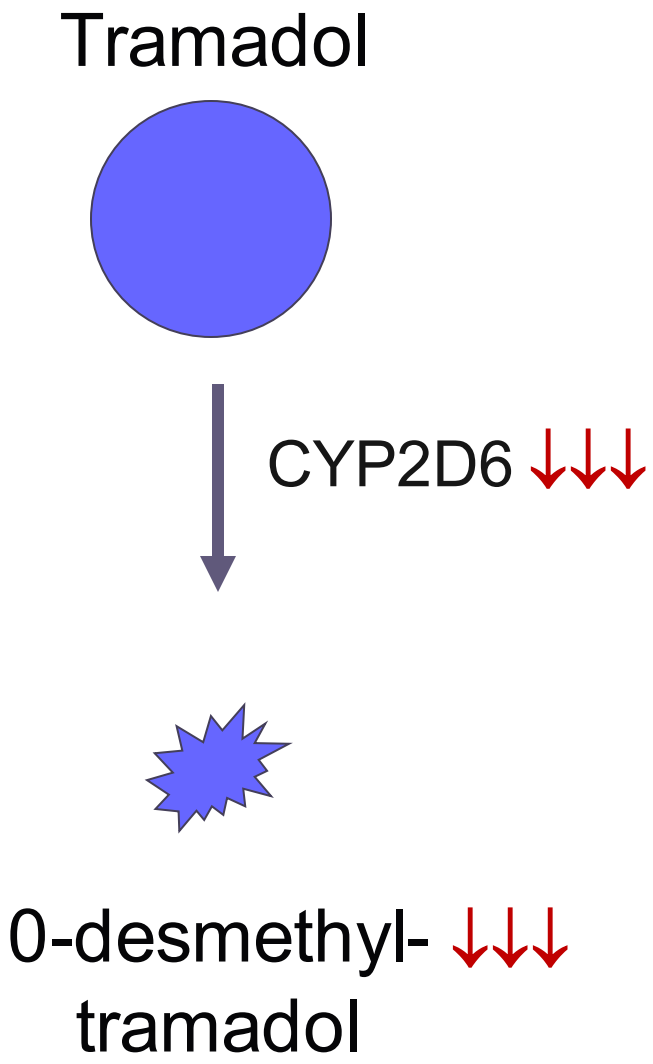


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- Intermediate metabolizers (IMs)
  - 2-11%
  - Reduced fxn + no fxn allele

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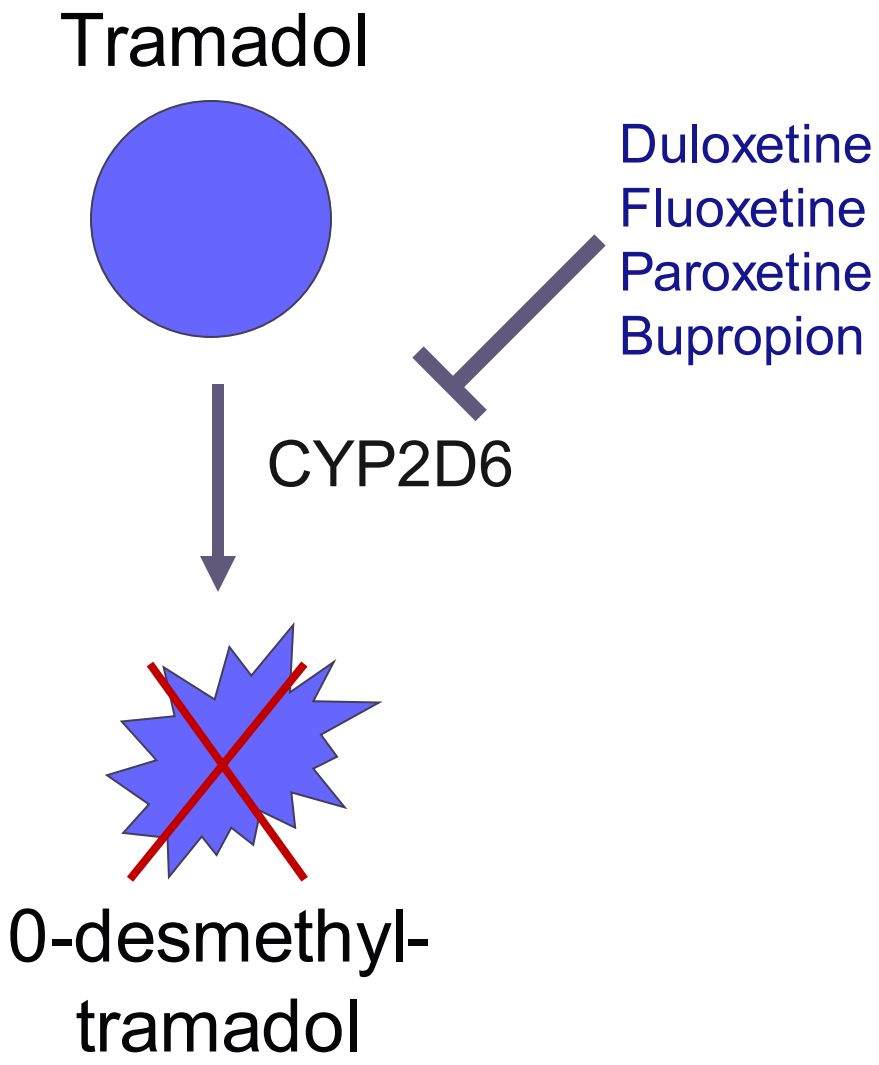
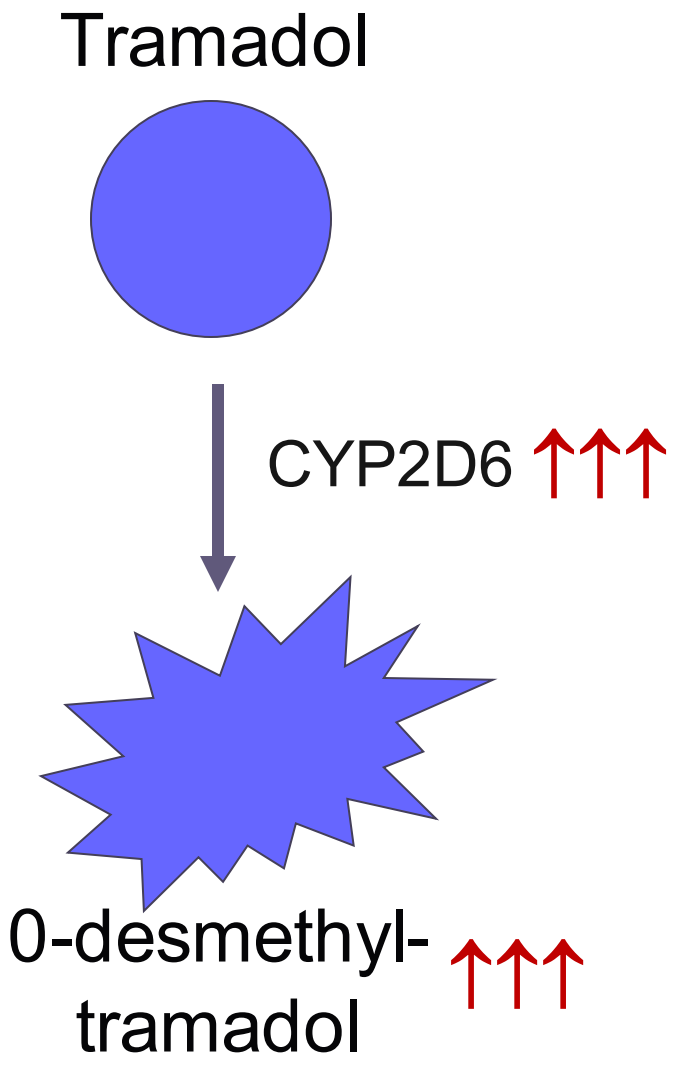



- Poor metabolizers (PMs)
  - 5-10%
  - 2 no function alleles
- Intermediate metabolizers (IMs)
  - 2-11%
  - Reduced fxn + no fxn allele
- Normal metabolizers (NMs)
  - 80-90%
  - Normal enzyme activity

# *CYP2D6* Genotype and Opioid Metabolism




- Poor metabolizers (PMs)
  - 5-10%
  - 2 no function alleles
- Intermediate metabolizers (IMs)
  - 2-11%
  - Reduced fxn + no fxn allele
- Normal metabolizers (NMs)
  - 80-90%
  - Normal enzyme activity
- Ultra-rapid metabolizers (UMs)
  - 1-2%
  - >2 fully functional *CYP2D6* alleles

Codeine → Morphine
Hydrocodone → Hydromorphone
Oxycodone → Oxymorphone

# Case Reports in CYP2D6 UMs

The NEW ENGLAND JOURNAL of MEDICINE

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CORRESPONDENCE

Codeine, Ultrarapid-Metabolism Genotype, and Postoperative Death

N Engl J Med 2009; 361:827-828 | August 20, 2009 | DOI: 10.1056/NEJMc0904266

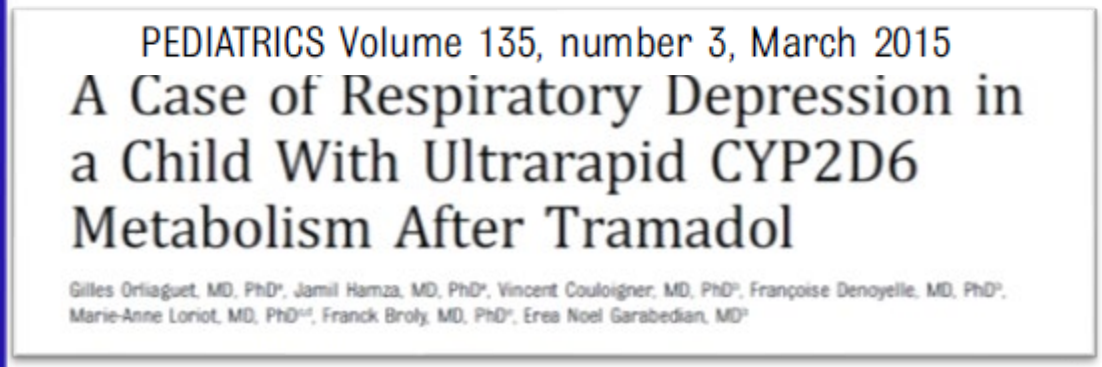
2 yo boy rx'd codeine/APAP s/p adenotonsillectomy died post-op day 2. Found to be a CYP2D6 UM and increased morphine concentrations.

THE LANCET

Volume 368, Issue 9636, 19–26 August 2006, Pages 704

Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother

Full-term breastfed male infant found dead on day 12, and blood concentrations of morphine were found to be in toxic range. Mother was taking codeine and had UM phenotype.



PEDIATRICS Volume 135, number 3, March 2015

A Case of Respiratory Depression in a Child With Ultrarapid CYP2D6 Metabolism After Tramadol

Gilles Orliaguet, MD, PhD[a], Jamil Hamza, MD, PhD[a], Vincent Couloigner, MD, PhD[b], Françoise Denoyelle, MD, PhD[b], Marie-Anne Loriot, MD, PhD[c,d], Franck Broly, MD, PhD[e], Erea Noel Garabedian, MD[b]

5 yo male rx'd tramadol s/p adenotonsillectomy developed severe respiratory depression. Recovered after naloxone. Had CYP2D6 UM phenotype and toxic O-desmethyltramadol concentrations.

Home | Food | Drugs | Medical Devices | Radiation-Emitting Products | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Tobacco Products

# Drugs

Home > Drugs > Drug Safety and Availability

**Ultra-Rapid Metabolism of Codeine and Other Risk Factors for Life-Threatening Respiratory Depression in Children**

Life-threatening respiratory depression and death have occurred in children who received codeine. Most of the reported cases occurred following tonsillectomy and/or adenoidectomy and many of the children had evidence of being ultra-rapid metabolizers of codeine due to a cytochrome P450 (CYP) 2D6 polymorphism (see WARNINGS, PRECAUTIONS; INFORMATION FOR PATIENTS/CAREGIVERS, NURSING MOTHERS). TYLENOL® with Codeine is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy (see CONTRAINDICATIONS). Avoid the use of TYLENOL® with Codeine tablets in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of codeine (see WARNINGS, PRECAUTIONS).

- Drug Safety and Avail
- Drug Alerts and Statem
- Medication Guides
- Drug Safety Communic
- Drug Shortages
- Postmarket Drug Safety Information for Patients Providers
- Information by Drug Cla
- Medication Errors
- Drug Safety Podcasts
- Safe Use Initiative
- Drug Recalls
- Drug Supply Chain Integrity
- Risk Evaluation and Mitigation Strategies (REMS)

equires cough dults 18

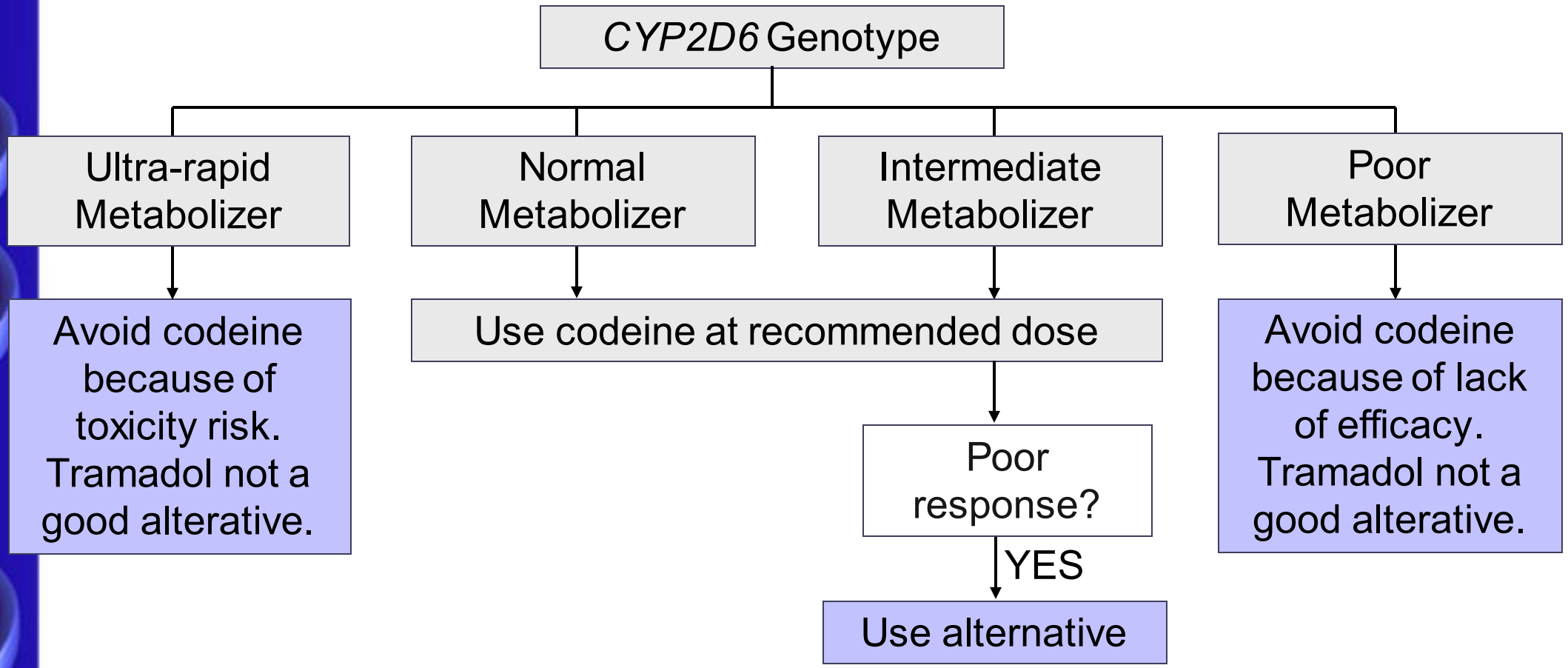
s use of prescrip- ommends against

## Safety Announcement

**[1-11-2018]** The U.S. Food and Drug Administration (FDA) is requiring safety labeling char cough and cold medicines containing codeine or hydrocodone to limit the use of these proc years and older because the risks of these medicines outweigh their benefits in children yo are also requiring the addition of safety information about the risks of misuse, abuse, addic death, and slowed or difficult breathing to the Boxed Warning, our most prominent warning for prescription cough and cold medicines containing codeine or hydrocodone.

We are taking this action after conducting an extensive review and convening a panel of ou of these determined the risks of slowed or difficult breathing, misuse, abuse, addiction, ove with these medicines outweigh their benefits in patients younger than 18.

# Clinical Pharmacogenetics Implementation Consortium (CPIC) Guidelines




*Clin Pharmacol Ther* 2014; PMID 24458010

# *CYP2D6* Genotyping at UF Health

- Implemented in May 2015 in response to request by primary care physicians
- Genotyping
  - Conducted in UF Health Pathology Laboratories
  - Validated for buccal cell samples

**Best Practice Advisory – Intermediate Metabolizer**

**PROBLEM:** This patient's CYP2D6 genotype is associated with decreased production of active form of tramadol. This patient may get **LITTLE TO NO PAIN RELIEF** with tramadol and other CYP2D6-mediated opioid analgesics such as codeine, hydrocodone, and oxycodone.

**RECOMMENDATIONS:**

(A) Consider a **non-opioid** analgesic

**OR**

(B) Consider an alternative opioid such as morphine, hydromorphone, or oxymorphone, which are not affected by CYP2D6 metabolism status

More information on tramadol and CYP2D6

For questions about this alert or the Precision Medicine Program, please send us an inbasket message to "P RX UF PMP MONITORING" or call us at (352) 273-6415.

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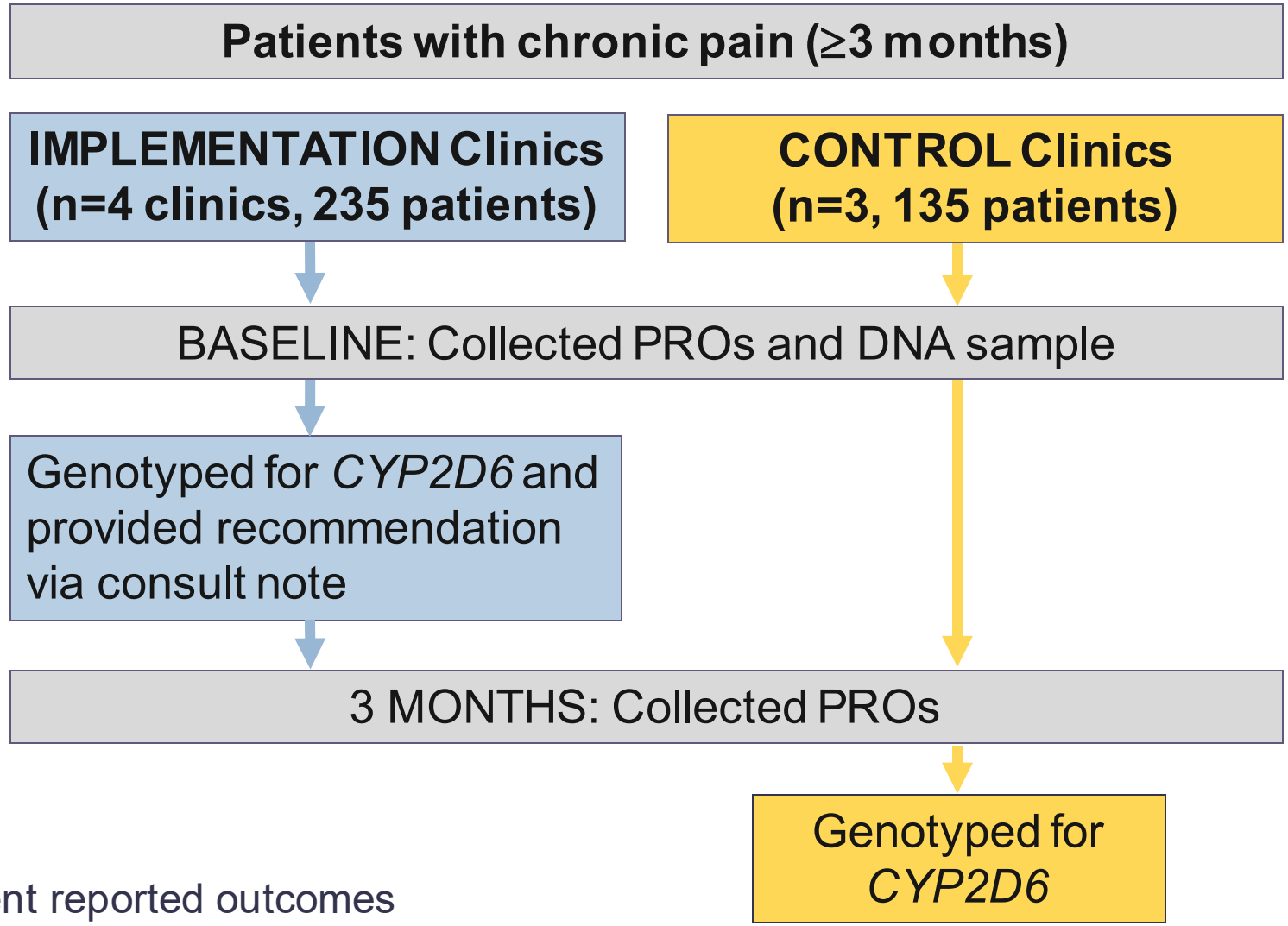
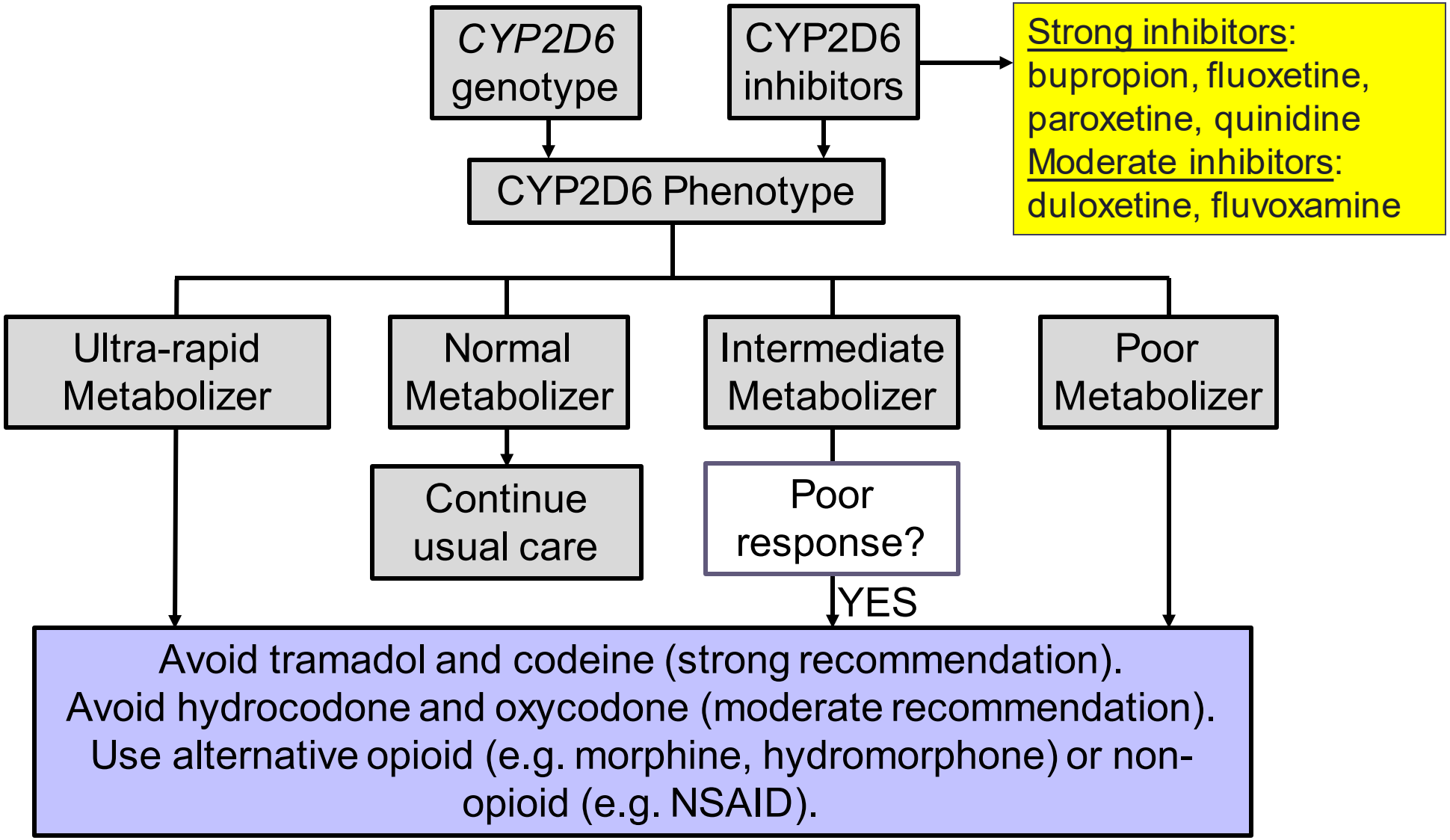
# Pragmatic Trial of CYP2D6-Guided Opioid Prescribing




PRO: Patient reported outcomes

# CYP2D6-Guided Recommendations



# Baseline Characteristics

- 370/375 completed baseline measures
  - Mean age was 59 years
  - 68% female, 71% white
  - Most common pain management indications were back pain and arthritis
  - Mean pain intensity was 6.55/10
  - 94% on an opioid at baseline
    - 45% on tramadol
    - 25% hydrocodone
    - 3% codeine

*Genet Med* 2019; PMID 30670877

# CYP2D6 Phenotype (n=343)

| Phenotype | Genotype only | Genotype + drug interactions* |
|---|---|---|
| PM | 5% | 19% |
| IM | 5% | 16% |
| NM | 86% | 61% |
| Other | 4% | 4% |

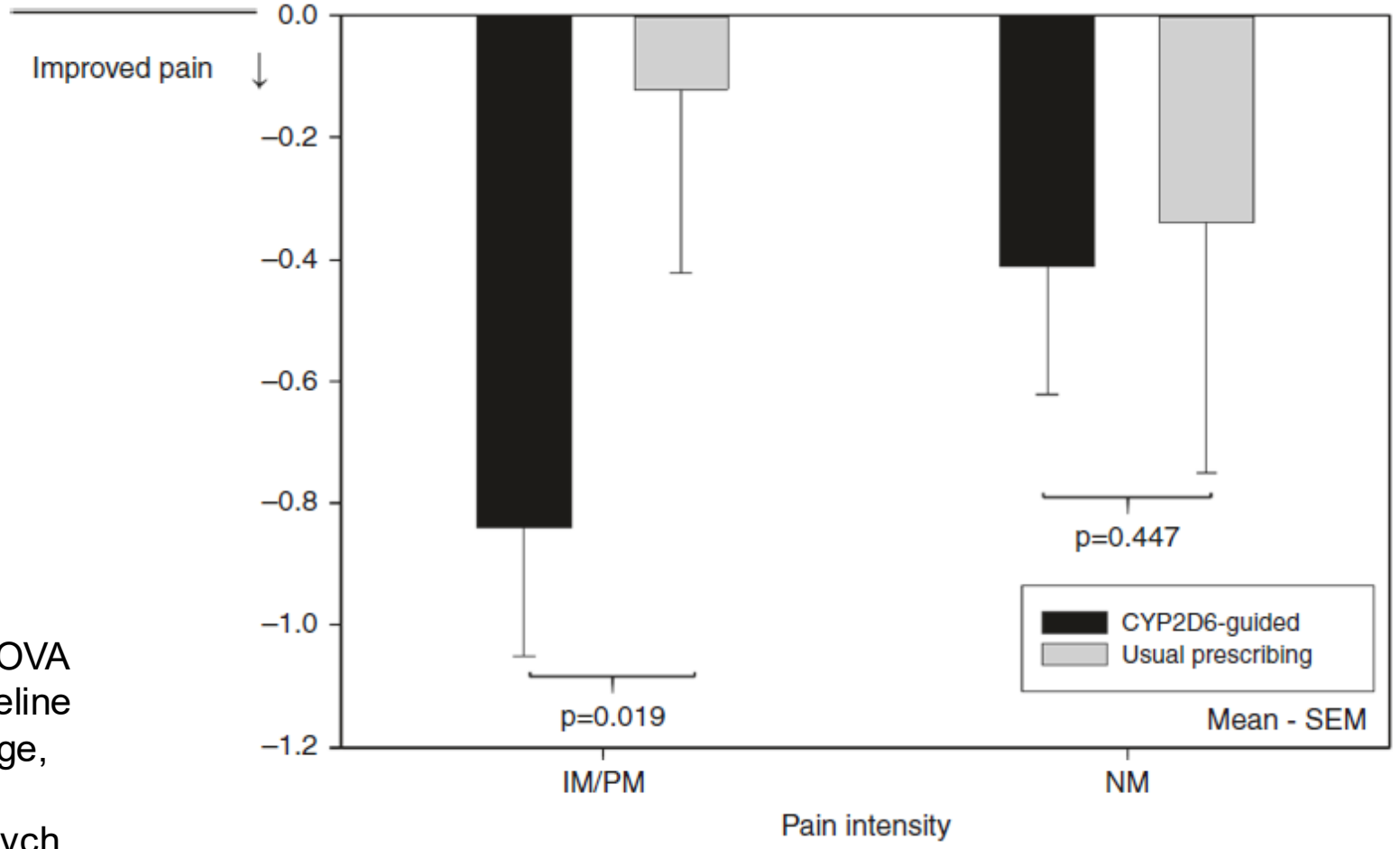
*Most common CYP2D6 inhibitors: duloxetine, bupropion, fluoxetine, paroxetine

Drug interactions "phenocoverted" 28% of NMs to IM/PMs

*Genet Med* 2019; PMID 30670877

# Change in Pain Intensity Composite

- Patients on tramadol, codeine, or hydrocodone at baseline




*p value by ANCOVA adjusted for baseline pain measure, age, sex, race, HTN, anxiety, other psych disorders

*Genet Med* 2019; PMID 30670877

# *CYP2D6* Genotype-Guided Pain Management in Patients Undergoing Arthroplasty Surgery

There is wide inter-individual variability in opioid analgesic response

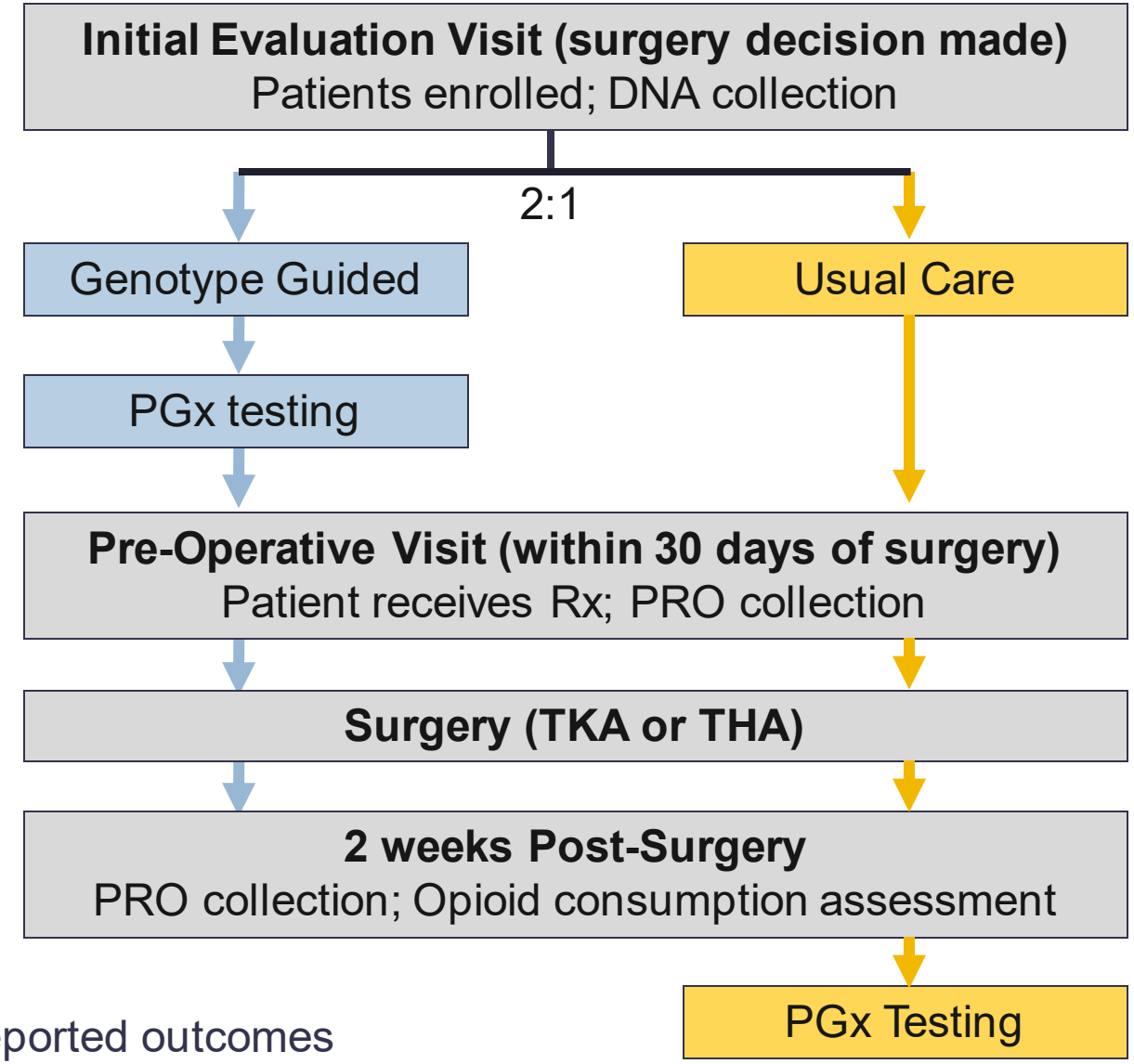
Opioid misuse is largely motivated by the pursuit of physical pain relief

Post-operative opioid prescribing represents a gateway to chronic opioid use

- Evidence of persistent opioid use in ~6% of opioid naïve individuals after an outpatient surgical procedure
- All together, there is a critical need to **improve pain control** and **optimize opioid prescribing**

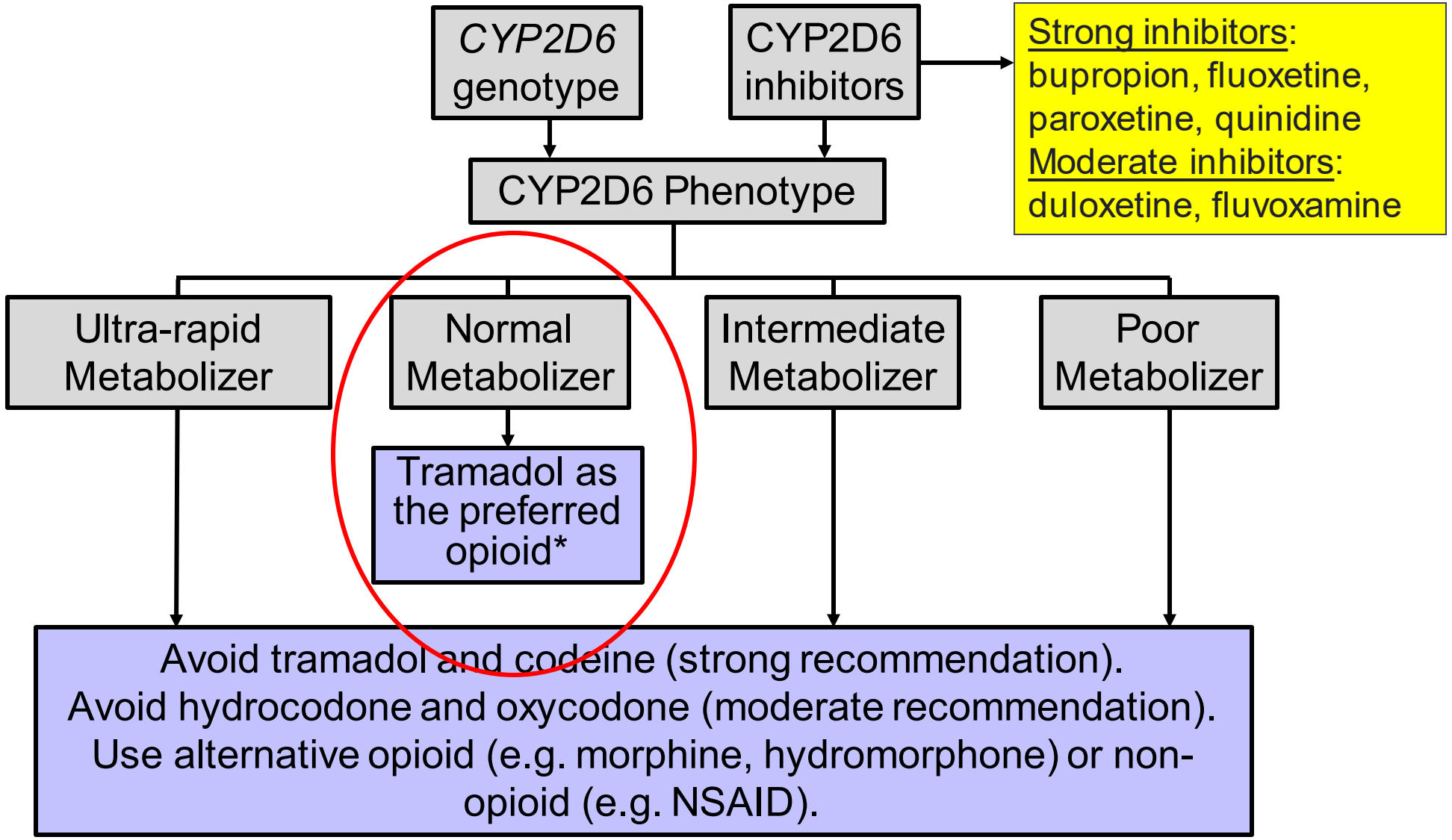
*Ann Intern Med*. 2017; PMID 28761945
*JAMA Surg*. 2017; PMID 28403427

# *CYP2D6* Genotype-Guided Pain Management in Patients Undergoing Arthroplasty Surgery




PRO: Patient reported outcomes

# CYP2D6-Guided Recommendations




*Evidence of lower addiction potential than C-II opioids (PMID 16716877, PMID 2029860)

# Preliminary Results

- 200/215 (93%) agreed to participate
- Percent with IM/PM phenotype
  - 11.2% based on genotype
  - 21.4% based on genotype + drug interactions
- Acceptance of recommendations among IM/PMs
  - 21% in guided group vs 100% in control group prescribed opioid metabolized by CYP2D6

# Summary and Next Steps

- Clinical implementation of pharmacogenetic testing is feasible
- Data suggest that CYP2D6 guided management of chronic pain improves pain control
- NHGRI-funded IGNITE Network to conduct multi-center pragmatic clinical trials
  - CYP2D6-guided management of chronic pain
  - CYP2D6-guided management of acute pain
  - CYP2D6/CYP2C19-guided antidepressant prescribing


https://gmkb.org/

# Lessons Learned

- Having a physician champion is key
- Prescribers will use genotype/phenotype data to guide treatment decisions
  - Genotype should be available during the patient encounter to optimize prescriber's ability to act on it
  - Clear guidance is needed through clinical decision support
  - Section of EHR with lifetime (e.g. genetic) results likely optimal
- Normal metabolism phenotype not actionable but informative
- Patients are enthusiastic to have pharmacogenetics data in their medical record
  - > 95% of control arm participants wanted pharmacogenetics reported after trial completed

*Genet Med* 2019. [Epub ahead of print]. PMID 30926959.

# UF Health Precision Medicine Program Team

Julie Johnson, PharmD; Kristin Wiisanen PharmD (Assoc Director); Amanda Elsey, MHA (Asst Director); Rhonda Cooper-DeHoff, PharmD; Petr Starostik, MD; Ben Duong, PharmD; Max Smith, PharmD; Meghan Arwood, PharmD (Michael Clare-Salzler, MD and David Nelson, MD not pictured)

- UF Investigators: Roger Fillingim, PhD; Siegfried Schmidt, MD, PhD; Hari Parvataneni, MD; Chancellor Gray, MD; David Anderson, MD; Yan Gong, PhD; Taimour Langaee, PhD; Cameron Thomas, PharmD
- IGNITE Investigators: Craig Lee, PharmD, PhD; Amber Beitelshees, PharmD, MS; Nita Limdi, PharmD, PhD; Phil Empey, PharmD, PhD; Julio Duarte, PharmD, PhD; Todd Skaar, PhD
- Funding: NIH/NCATS UF CTSA UL1 TR000064, IGNITE Network grant U01 HG007269 and substantial institutional support from UF and UF Health