Clinical Utility of Preemptive Pharmacogenetic Testing

December 16, 2015

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Agenda

- Background on pharmacogenetics
- Clinical Pharmacogenetics Implementation Consortium (CPIC)
- Using pharmacogenetics in practice

PATIENT CASE

- A **5.5-year-old** boy underwent ambulatory adenotonsillectomy and was discharged with a prescription for tramadol drops for postoperative pain.

- The same evening the patient received **1 oral dose of 20 mg of tramadol** when he complained of increasing pain. The next morning, the parents found him lethargic and brought him back to the hospital.

- At the ER he was **comatose, minimal respiratory effort, frequent episodes of apnea**. Arterial blood gazes were abnormal. His other vital functions were normal. He improved dramatically with noninvasive ventilation and intravenous naloxone normalizing consciousness, pupils and respiration within minutes. He was discharged the following day.

- Pharmacogenetic testing revealed that his genotype for **CYP2D6 was *2/*2 XN.** This genotype is consistent with an ultra-rapid metabolizer phenotype and an increased conversion of tramadol to a more active metabolite.

Orliaguet et al. Pediatrics 2015 Mar;135(3):e753-5

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PHARMACOGENETICS

- There is significant inter-patient variability in drug response
- Largely attributed to innate differences among individuals in their capacity to process and react to drugs.
- **Pharmacogenomics (PGx)**
- Identify genetic biomarkers affecting drug response and use them to make better drug therapy decisions.
- Pharmacogenetic knowledge uses principles from human genetics, pharmacokinetics and pharmacodynamics.

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DRUG RESPONSE

Pharmacokinetics

stomach

Liberation

Intestine

Absorption

Blood/organs

Distribution

Intestine & Liver

Metabolism

Urine/feces

Elimination

Pharmacodynamics

Targets (site of action)

Pharmacokinetics: capacity to process a drug
Pharmacodynamics: capacity to react to a drug

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PROTEINS IMPLICATED

- **Transporters**: absorption, distribution, elimination
- **Metabolizing enzymes**: metabolism
- **Receptors and Targets**: efficacy (and toxicity)

Variations in genes encoding these proteins may alter:

drug availability at the target - expected drug and metabolite plasma and tissue concentrations

drug affinity at the targets or receptors- target and receptor functions and desired or undesired drug effects

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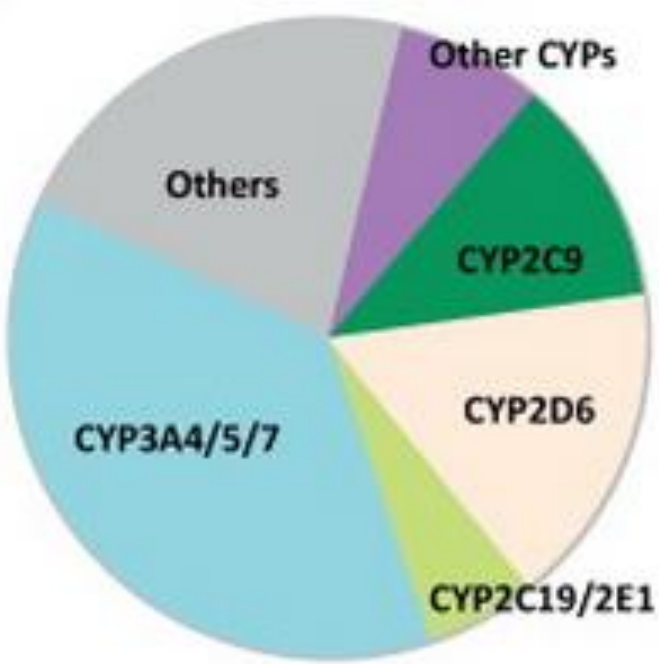
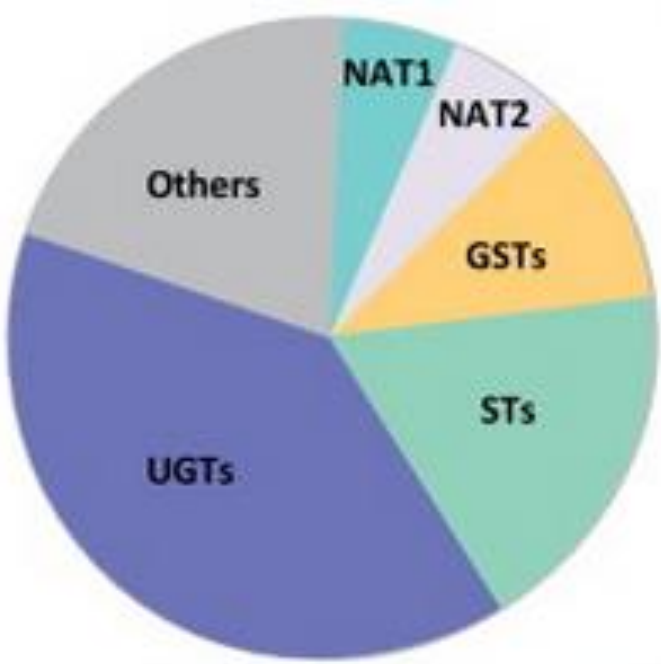
GENES FOR METABOLIZING ENZYMES

Genes encoding for Cytochrome P450 enzymes are highly polymorphic





Nomenclature Committee and Database: http://www.cypalleles.ki.se/

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CYP2D6 ENZYME

CYP2D6 is an enzyme that metabolizes many commonly prescribed medications:

- codeine, tramadol, oxycodone, hydrocodone
- amitriptyline, nortriptyline, desipramine, doxepin
- paroxetine, fluvoxamine
- halopperidol, risperidone
- metoprolol

Metabolism by CYP2D6 can either **ACTIVATE** or **INACTIVATE** a drug:

- codeine is a **prodrug** will be **activated** by to **morphine**

- risperidone, an **active drug**, will be inactivated by CYP2D6 to an inactive metabolite

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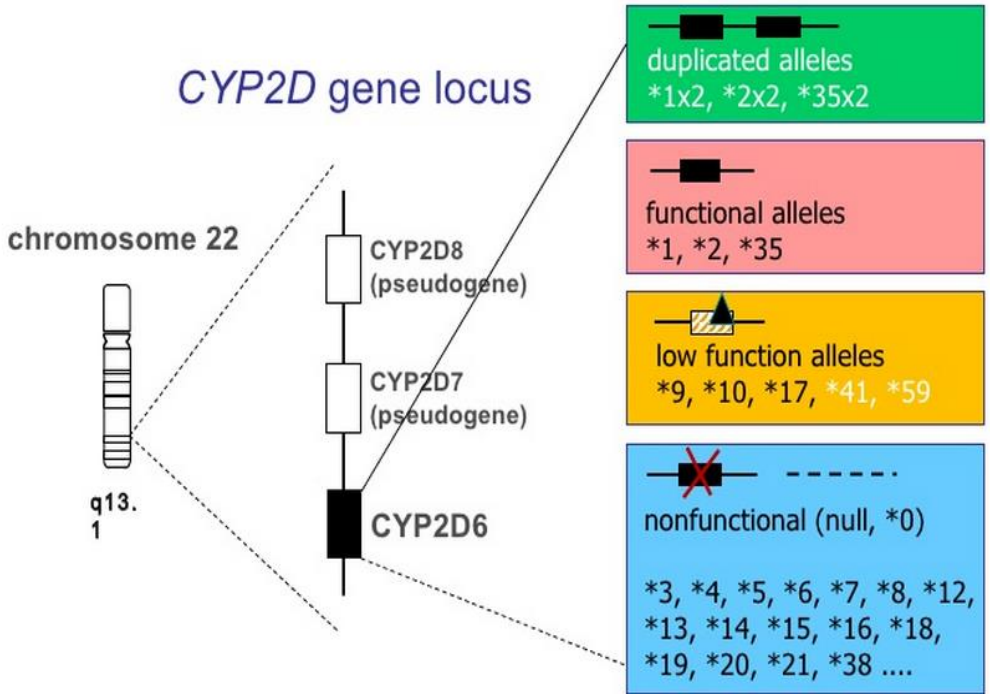
CYP2D6 GENETIC VARIATIONS

In a pharmacogenetic test, several type of genetic variants are interrogated to detect common alleles



> 140 alleles have been described

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CYP2D6 ALLELE FREQUENCY

Allele	Function	Caucasian	Africans	Mexican American	Asian
*1	Normal	22-32	29	55	32-53
*2	Normal	26	19	18	0-9
*3	Absent	1	5	0.2	-
*4	Absent	20	2-6	10	1
*5	Absent	2-3	4-6	1.7	6
*10	Reduced	1-2	2-6	2.8	38-70
*17	Reduced	0.3	16-35	0.2	0
*29	Reduced	0-1	7.5	0.2	-
*41	Reduced	8	2	5.5	0-2
*1XN	Increased	0.8	1.5-3	0.73	0
*2XN	Increased	1.27	1.5-4	2	0

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CYP2D6 GENOTYPE-PHENOTYPE

- Most patients have two copies of the CYP2D6 gene.
- Two sets of allele is called **genotype** (or diplotype) and will be used to assign the **phenotype**.
- For CYPs the phenotype is expressed as the **metabolizer status** (normal, intermediate, poor, rapid).
- Individuals with altered metabolism status (intermediate, poor, rapid) may require dose adjustments or alternative medication may be necessary.

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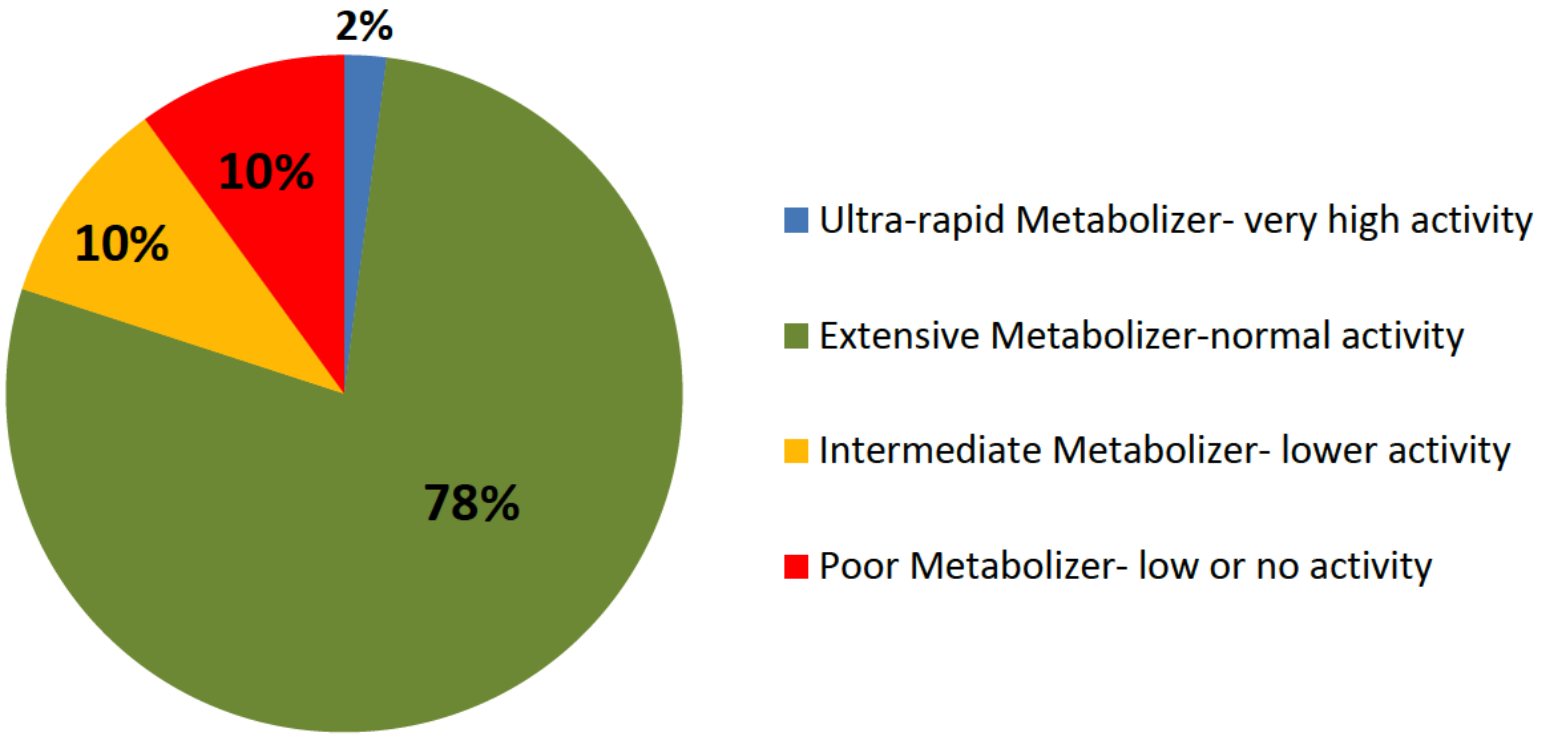
CYP2D6 PHENOTYPE FREQUENCY

Percentage of CYP2D6 Phenotype in General Population



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CYP2D6 GENE-BASED RECOMMEDATIONS

How can a doctor use the patient's genotype?

SUBSTRATES

1A2	2B6	2C8	2C9	2C19	2D6	2E1	3A4,5,7
amitriptyline caffeine[2] clomipramine clozapine cyclobenzaprine duloxetine estradiol fluvoxamine haloperidol imipramine N-DeMe mexiletine nabumetone naproxen olanzapine ondansetron phenacetin[1]→ acetaminophen→NAPQI propranolol riluzole ropivacaine tacrine[2] theophylline[2] tizanidine triamterene	artemisinin bupropion[1] cyclophosphamide efavirenz[1] ifosphamide ketamine meperidine methadone nevirapine propafol selegiline sorafenib	amodiaquine[2] cerivastatin paclitaxel repaglinide sorafenib torsemide	**NSAIDs:** diclofenac[1] ibuprofen lornoxicam meloxicam S-naproxen→Nor piroxicam suprofen **Oral Hypoglycemic Agents:** tolbutamide[1] glipizide **Angiotensin II Blockers:** losartan irbesartan **Sulfonylureas:** glyburide glibenclamide glipizide glimepiride	**PPIs:** esomeprazole lansoprazole omeprazole2 pantoprazole **Anti-epileptics:** diazepam→Nor phenytoin(O) S-mephenytoin[1] phenobarbitone amitriptyline carisoprodol citalopram chloramphenicol clomipramine clopidogrel cyclophosphamide hexobarbital imipramine N-DeME indomethacin labetalol R-mephobarbital	tamoxifen: **TAMOXIFEN GUIDE** **Beta Blockers:** carvedilol S-metoprolol propafenone timolol **Antidepressants:** amitriptyline clomipramine desipramine fluoxetine imipramine paroxetine venlafaxine **Antipsychotics:** haloperidol perphenazine risperidone→9-OH thioridazine zuclopenthixol	**Anesthetics:** enflurane halothane isoflurane methoxyflurane sevoflurane acetaminophen→NAPQI aniline2 benzene chlorzoxazone1 ethanol N,N-dimethylformamide theophylline→8-OH	**Macrolide antibiotics:** clarithromycin erythromycin[2] (not 3A5) NOT azithromycin telithromycin **Anti-arrhythmics:** quinidine→3-OH (not 3A5) **Benzodiazepines:** alprazolam diazepam→3OH midazolam[1] triazolam[2] **Immune Modulators:** cyclosporine tacrolimus (FK506) **HIV Antivirals:** indinavir

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USING CPIC GUIDELINES

>130 Members
Clinicians and Scientists
62 institutions
14 countries
12 Observers (NIH and FDA)

CPIC™
Clinical Pharmacogenetics Implementation Consortium

CPIC guidelines are designed to help clinicians understand HOW available genetic test results should be used to optimize drug therapy.

Key Assumptions

Pre-emptive genotyping will become more widespread.

Clinicians will be faced with having patients' genotypes available even if they did not order test with drug in mind.

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EVIDENCE BASED REVIEW PROCESS

CPIC prioritizes drug-gene pairs based upon community input and other criteria:

- FDA labeling recommends pharmacogenetic testing for the drug
- Evidence that CMS and/or third party payors reimburse for pharmacogenetic test
- Clinical trials demonstrating drug effects linked to functional pharmacogenetic loci
- Narrow therapeutic index drug (ratio between toxic dose and therapeutic dose)
- Professional organizations (ASCO, ASCPT, AHA…)

- The strength of the evidence is evaluated in each guideline

- CPIC has started with clinically **actionable genetic variants and drugs**

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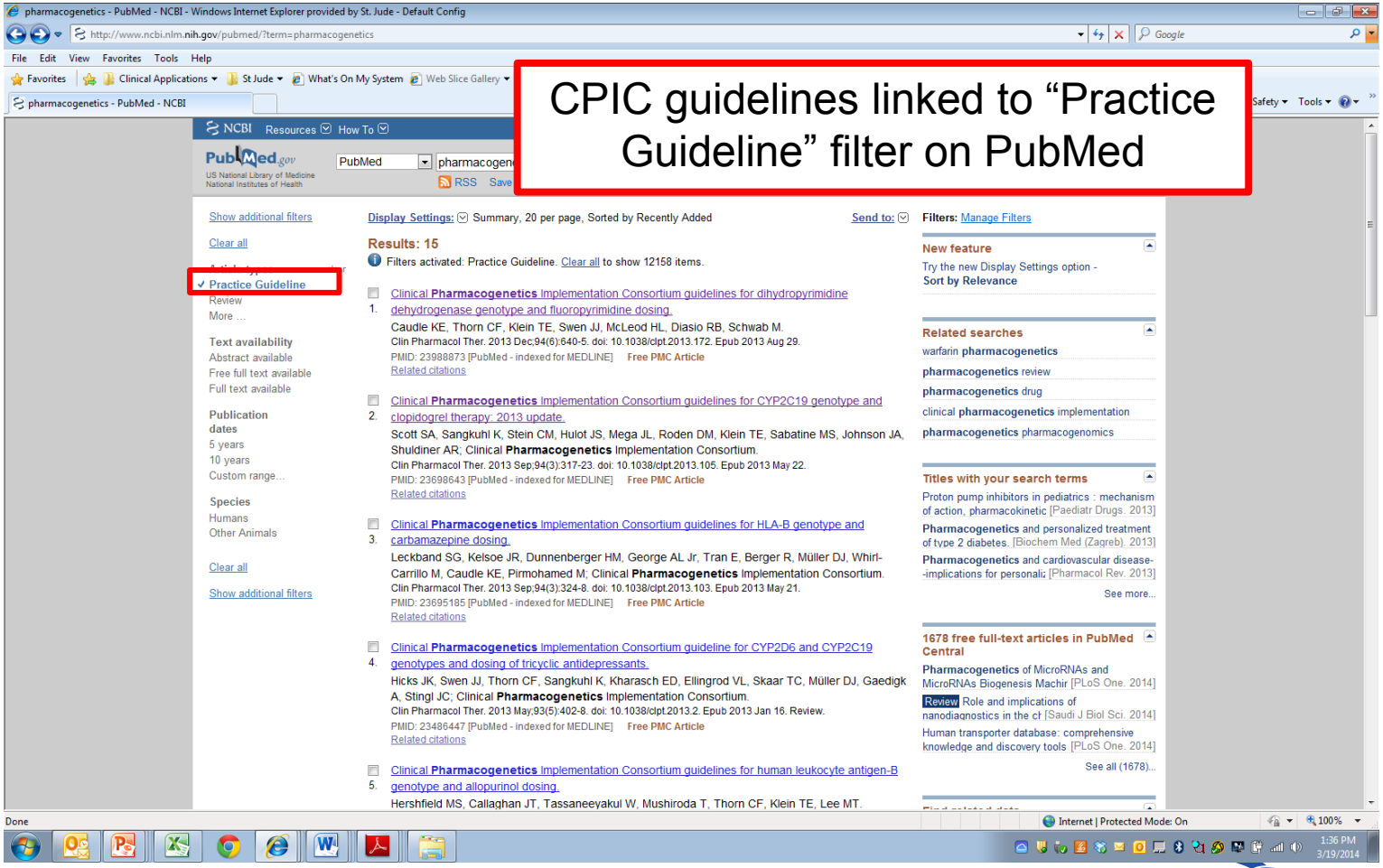
CPIC GUIDELINES AS PRACTICE GUIDELINES



CPIC guidelines linked to “Practice Guideline” filter on PubMed

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CPIC GUIDELINES

- ***TPMT***
  - thiopurines
- ***CYP2D6***
  - opioids, tricyclics, SSRIs
- ***CYP2C19***
  - tricyclics, clopidogrel, SSRIs
- ***VKORC1***
  - warfarin
- ***CYP2C9***
  - warfarin, phenytoin
- ***HLA-B***
  - allopurinol, carbamazepine, abacavir, phenytoin
- ***CFTR***
  - ivacaftor
- ***DPYD***
  - 5FU, capecitabine, tegafur
- ***G6PD***
  - rasburicase
- ***UGT1A1***
  - Irinotecan, atazanavir
- ***SLCO1B1***
  - simvastatin
- ***IFNL3 (IL28B)***
  - interferon
- ***CYP3A5***
  - tacrolimus

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INSTITUTIONS IMPLEMENTING PGX

INSTITUTION	DRUG	GENE
St. Jude Children's Research Hospital **PG4KDS**	Opioids, Ondansetron, SSRIs, Amitriptyline	CYP2D6
	Thiopurines	TPMT
	Fluorouracil, Capecitabine	DPYD
	Voriconazole, Clopidogrel, Amitripyline	CYP2C19
	Simvastatin	SLCO1B1
	Atazanavir	UGT1A1
Vanderbilt University Medical Center **PREDICT**	Clopidogrel	CYP2C19
	Tacrolimus	CYP3A5
	Simvastatin	SLCO1B1
	Warfarin	CYP2C9, VKORC1
UFHealth University of Florida Health	Clopidogrel	CYP2C19
Cleveland Clinic	Thiopurines	TPMT
	Carbamazepine, Phenyoin	HLAB*15:02
	Abacavir	HLA-B*5701

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CPIC GUIDELINES

DRUG	SPECIALTY	PHARMACOGENE	PROTEIN FUNCTION
Opioids	Pain management	CYP2D6	Metabolizing enzyme
SSRIS	Mental Health	CYP2D6 CYP2C19	Metabolizing enzyme
Tricyclics	Mental Health	CYP2D6 CYP2C19	Metabolizing enzyme
Tacrolimus	Immunosupression	CYP3A5	Metabolizing enzyme
Thiopurines	Oncology	TPMT	Metabolizing enzyme
Warfarin	Coagulation	CYP2C9 VKORC1	Metabolizing enzyme & Drug target
Simvastatin	Hyperlipidemias	SLCO1B1	Transporter
Phenytoin	Neurology	CYP2C9	Metabolizing enzyme

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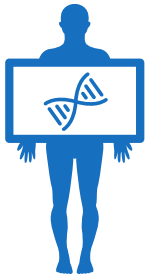
CYP2D6
GENE-BASED RECOMMEDATIONS

How can a doctor use the patient's genotype?



CPIC-Based Recommendations Available for:

- **Opioids**
- **Tricylics**
- **SSRIs**
- **(Ondansetron)**

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CYP2D6-OPIOIDS IN PRACTICE

Table 2 Codeine therapy recommendations based on cytochrome P450 2D6 (CYP2D6) phenotype

Phenotype	Implications for codeine metabolism	Recommendations for codeine therapy	Classification of recommendation for codeine therapy[a]	Considerations for alternative opioids
Ultrarapid metabolizer	Increased formation of morphine following codeine administration, leading to higher risk of toxicity	Avoid codeine use due to potential for toxicity.	Strong	Alternatives that are not affected by this CYP2D6 phenotype include morphine and nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity.[b,c]
Extensive metabolizer	Normal morphine formation	Use label-recommended age- or weight-specific dosing.	Strong	—
Intermediate metabolizer	Reduced morphine formation	Use label-recommended age- or weight-specific dosing. If no response, consider alternative analgesics such as morphine or a nonopioid.	Moderate	Monitor tramadol use for response.
Poor metabolizer	Greatly reduced morphine formation following codeine administration, leading to insufficient pain relief	Avoid codeine use due to lack of efficacy.	Strong	Alternatives that are not affected by this CYP2D6 phenotype include morphine and nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity; these agents should be avoided.[b,c]

[a]Rating scheme is described in **Supplementary Data** online. [b]There is substantial evidence for decreased efficacy of tramadol in poor metabolizers and a single case report

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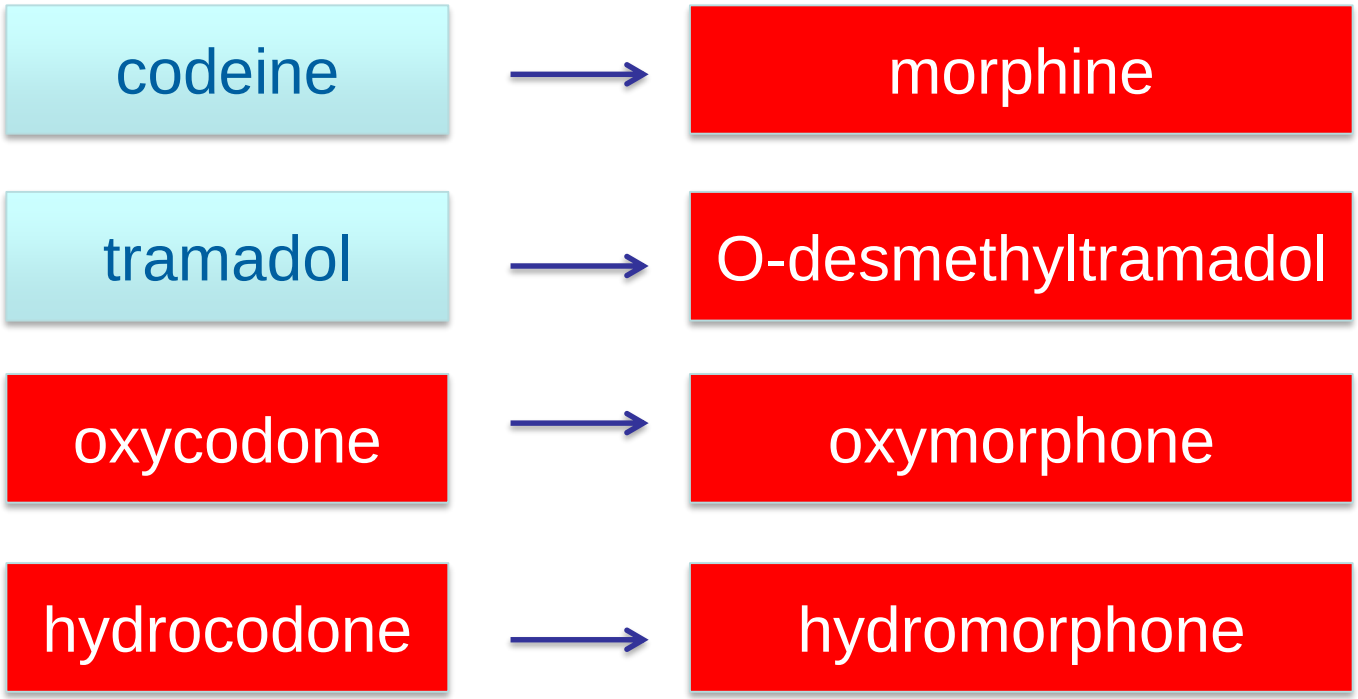
CYP2D6-OPIOIDS IN PRACTICE

CYP2D6 metabolizes opioids into more active metabolites



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CYP2D6-OPIOIDS IN PRACTICE

	Poor	Intermediate	Normal	Rapid
Codeine- prodrug	A	A	S	A
Tramadol - prodrug	A	A	S	A
Oxycodone Active drug + active metabolite	C	C	S	C
Hydrocodone Active drug + active metabolite	C	C	S	C
Morphine	S	S	S	S
Oxymorphone	S	S	S	S
Hydromorphone	S	S	S	S

A: Prescribe alternative medication

S: Prescribe according to standard recommendations

C: Caution (prescribe with monitoring or avoid)

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DRUG CATEGORIZATION

SUMMARY OF RESULTS

RED CATEGORY

Based upon the patient's results, the medication has potentially reduced efficacy or increased toxicity. Medication change or dose adjustment with increased monitoring is highly recommended with this drug.

YELLOW CATEGORY

Based upon the patient's results, the medication has potentially reduced efficacy or increased toxicity. Dose adjustment with increased monitoring may be needed with this drug.

GREEN CATEGORY

Based upon the patient's results, the medication can be prescribed according to standard regimens.

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CYP2D6 - OPIOIDS IN PRACTICE

YELLOW CATEGORY

Based upon the patient's results, the medication has potentially reduced efficacy or increased toxicity. Dose adjustment with increased monitoring may be needed with this drug.

Drug	Findings	What to Do - Dosing Regimens Suitable for Adult Patients
Clopidogrel (Plavix)	• Increased Response to Clopidogrel • Genotype: CYP2C19 *1/*17	Clopidogrel can be prescribed at standard label-recommended dosage. Individuals with the *17 allele may have an increased risk of bleeding while taking clopidogrel.
Codeine (Codeine; Fioricet with Codeine)	• Possible Non-Response to Codeine • Genotype: CYP2D6 *15/*17	Reduced morphine levels are anticipated, and the patient may or may not experience adequate pain relief with codeine. Codeine can be prescribed at standard label-recommended dosage and administration, with monitoring for symptoms of insufficient pain relief. Other opioids not metabolized by CYP2D6 may also be considered (i.e., morphine, oxymorphone, buprenorphine, fentanyl, methadone, and hydromorphone).
Desipramine (Norpramin)	• Moderate Sensitivity to Desipramine • Genotype: CYP2D6 *15/*17	Consider prescribing desipramine at 25% of recommended standard starting dose. Monitor plasma concentrations of desipramine and metabolites and titrate accordingly until a favorable response is achieved.

PGX REDUCES DRUG ADVERSE EVENTS

- A **5.5-year-old** boy underwent ambulatory adenotonsillectomy and was discharged with a prescription for tramadol drops for postoperative pain.
- The same evening the patient received 1 oral dose of 20 mg of **tramadol** when he complained of increasing pain. The next morning, the parents found him lethargic and brought him back to the hospital.
- At the ER he was **comatose, minimal respiratory effort, frequent episodes of apnea**. Arterial blood gazes were abnormal. His other vital functions were normal. He improved dramatically with noninvasive ventilation and intravenous naloxone normalizing consciousness, pupils and respiration within minutes. He was discharged the following day.
- Pharmacogenetic testing revealed that she his genotype for **CYP2D6 was *2/*2 XN.** This genotype is consistent with an ultra-rapid metabolizer phenotype.

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LIFETIME VALUE OF PHARMACOGENOMICS

Drug adverse event Burden

Infant	Child	Adolescent Young Adult	Adult	Elderly
Lactation	Pain	Contraception	**Polypharmacy**	
	Infections Transplantation Cancer	Psychiatry Addiction Transplantation Cancer	Cardiovascular Diabetes Gastroenterology Psychiatry Addiction Transplantation Cancer Autoimmune Diseases Surgery	Cardiovascular Diabetes Gatroenterology Psychiatry Neurology Surgery

LIFETIME VALUE OF PHARMACOGENOMICS

	Infant	Child	Adolescent Young Adult	Adult	Elderly
CYP2D6	Opioids	Opioids	ADHD drugs SSRIs	Opioids Beta-blockers Tricyclics SSRIs Antipsychotics	Opioids Beta-blockers Tricyclics SSRIs Antipsychotics
CYP2C19		Voriconazole	SSRIs	Clopidogrel Tricyclics SSRIs	Antidementia drugs Tricyclics SSRIs
CYP2C9		Phenytoin	Celecoxib Phenytoin	Celecoxib Phenytoin Warfarin Glipizide	Phenytoin Warfarin Glipizide
CYP3A5		Tacrolimus	Tacrolimus	Tacrolimus	
SLCO1B1				Statins	Statins
TPMT		Thiopurines		Thiopurines	
VKORC1		Warfarin		Warfarin	Warfarin

CONCLUSIONS

- Availability of robust, cost-effective and fast technologies for genome interrogation, allows preemptive pharmacogenetic testing
- Use of multiplexed pharmacogenetic testing offers the opportunity to doctors prevent adverse drug reactions and reduce healthcare costs along the continuum of care
- 18% of the most prescribed medications in the US have actionable genomics

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QUESTIONS

Thank you!

Contact
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