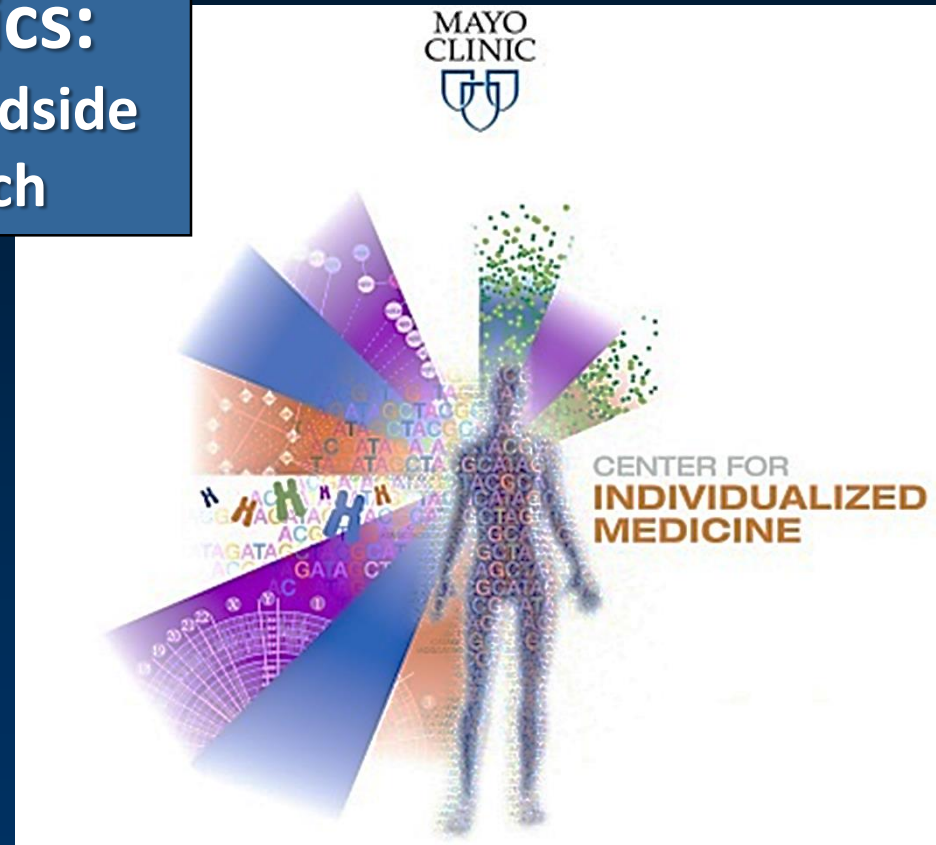


Pharmacogenomics: Implementation at the Bedside A Team Based Approach



Eric T. Matey, Pharm. D., RPh. BCACP
Center for Individualized Medicine
Mayo Clinic, Rochester MN

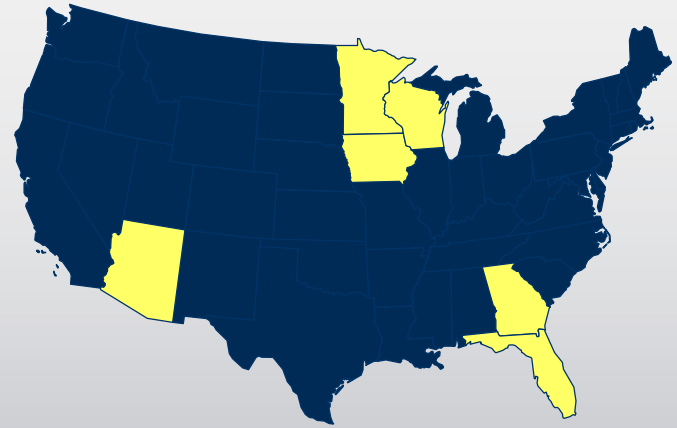
Objectives

- Describe implementation of bedside pharmacogenomics at the Mayo Clinic.
- Define modalities to provide prescribers pharmacogenomics information at the bedside.
- Briefly discuss current and future PGx state at Mayo Clinic.

After 150 years...

5 SCHOOLS

6 STATES



2,580 RESIDENTS & FELLOWS

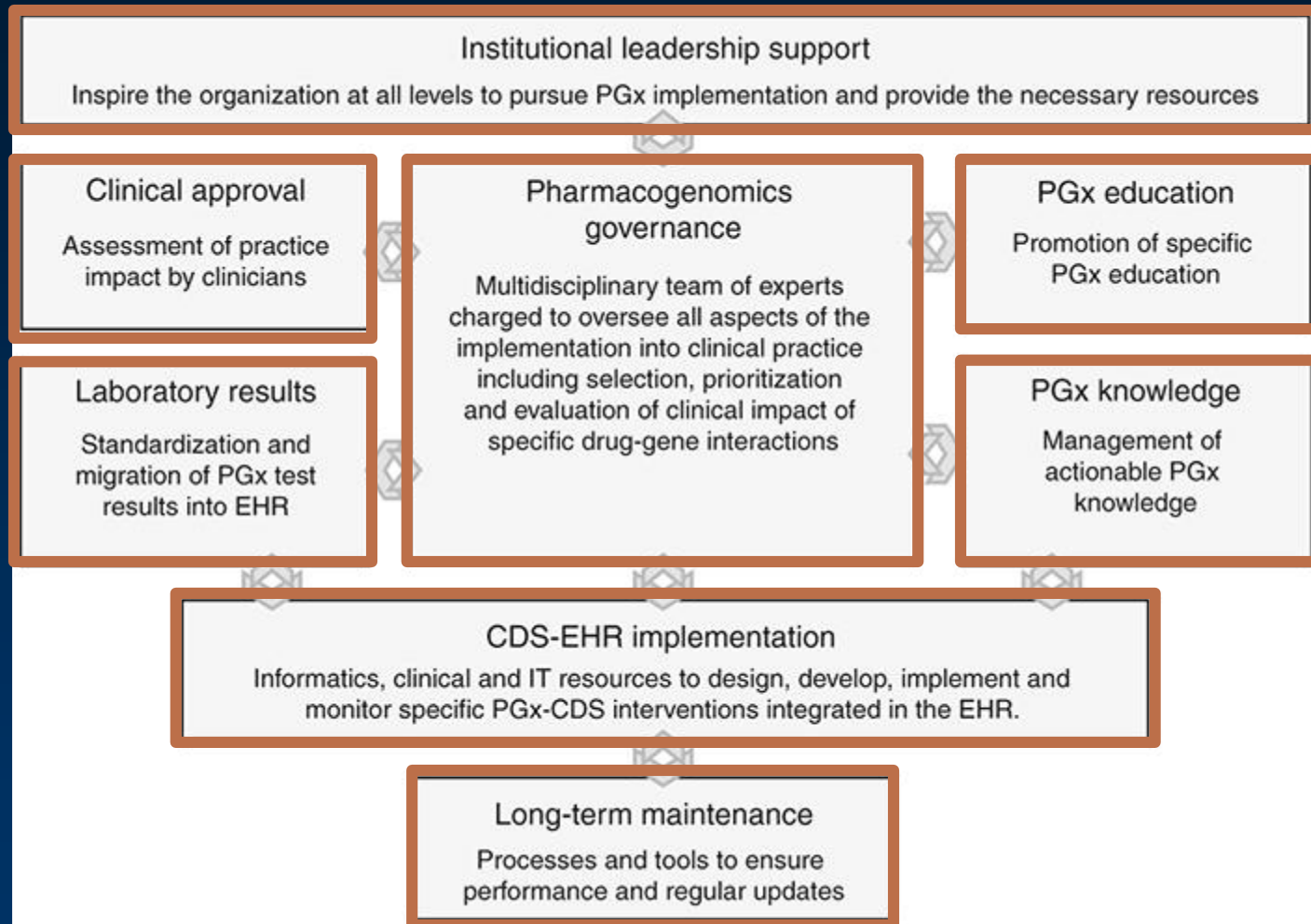
4,100 STAFF PHYSICIANS & SCIENTISTS

60,000 EMPLOYEES

1.3 million PATIENTS

from every state and 144 countries

Mayo's model for PGx Operations



How are results reported and interpreted?

For example CYP2D6 :

Ultra-rapid metabolizer. Greatly increased activity accelerating clearance or activation

Extensive (Normal) metabolizer. The norm.

Intermediate metabolizer. Heterozygotes for normal and reduced activity genes.

Poor metabolizer, absent or greatly reduced ability to clear or activate drugs.

Associated Phenotypes

Mayo Clinic for CYP 2D6

- **Ultra-rapid**
 - Extensive to Ultra-rapid
- **Extensive – (normal)**
 - Intermediate-Ultra-rapid
 - Intermediate to Extensive
- **Intermediate**
 - Poor to Intermediate
- **Poor**

Pro-drug
Activation



Not Activated

How are results reported and interpreted?

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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}

Electronic Order Support

Discern: (1 of 1)



Pharmacogenomics Alert: Cytochrome P450 Enzyme(s)

Metabolizer CYP2D6 Extensive to Ultra Rapid


Recommendation

Based on the medication order and the patient's CYP450 enzyme phenotype result: Metabolizer CYP2D6 Extensive to Ultra Rapid

Increased toxicity such as respiratory depression may occur, caution is advised with codeine and tramadol. See [AskMayoExpert \(codeine FAQ\)](#) for details.

Alert Action

- Cancel acetaminophen-codeine (acetaminophen-codeine, 300 mg-30 mg) order
- Proceed with acetaminophen-codeine (acetaminophen-codeine, 300 mg-30 mg) order



AskMayoExpert (AME)

AskMayoExpert



Sign in

Codeine and CYP2D6 (Pharmacogenomics)

Clinical Answers

Experts

Guidelines & Resources

Codeine and CYP2D6

Introduction

Overview

Testing Recommendations

Ordering Tests

Alternative Medication
Options

Medical Insurance Coverage

Introduction

Codeine is an opioid analgesic indicated for the relief of mild to moderately severe pain when the use of an opioid analgesic is appropriate. CYP2D6 is involved in the activation of codeine.

The CYP2D6 genotype has hundreds of known allelic variants. This can result in metabolic variations affecting the action of the drug from ineffective (poor metabolizers) to potentially toxic (ultra-rapid metabolizers).

Was this information helpful?

Yes

No

Search other sources

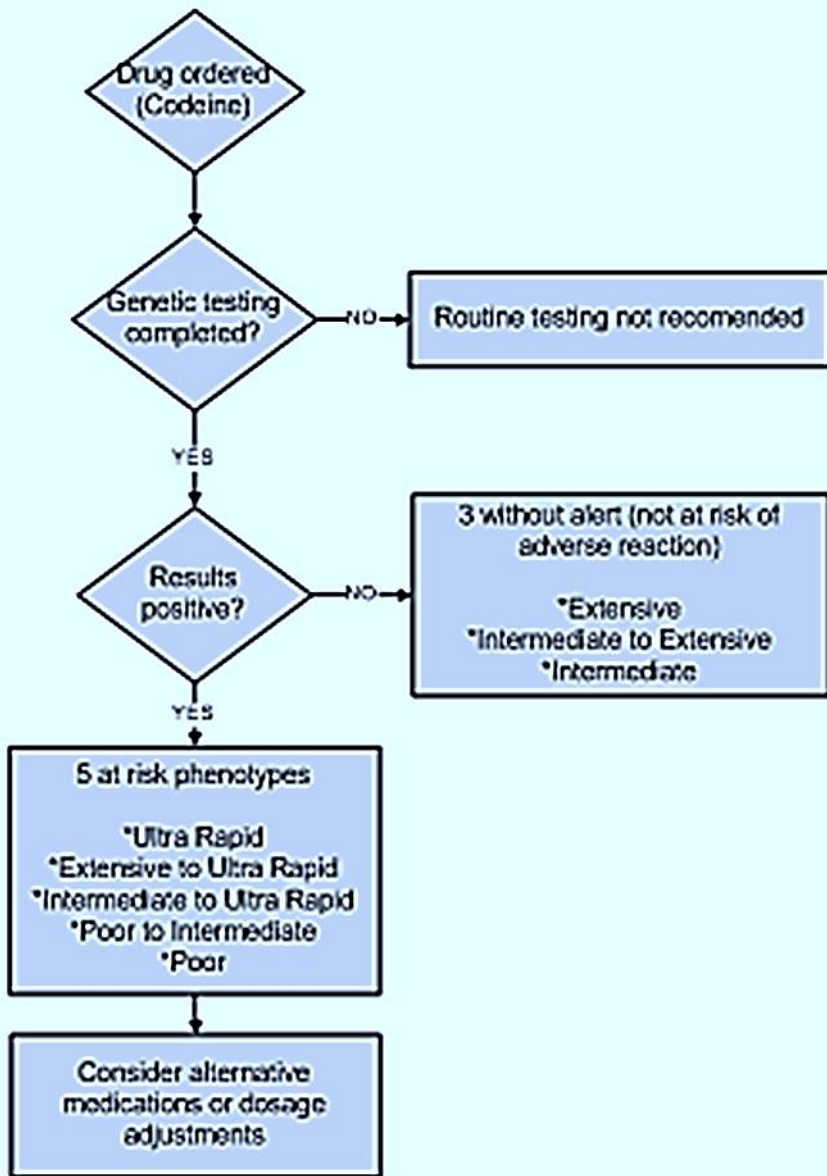
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Mayo library materials

Mayo authors library

AME Recommendations




CYP2D6 Test Result	Recommendations
Metabolizer CYP2D6 Ultra Rapid	Avoid codeine due to potential for toxicity. May consider avoiding tramadol
Metabolizer CYP2D6 Extensive to Ultra Rapid	Increased toxicity such as respiratory depression may occur; caution is advised with codeine and tramadol.
Metabolizer CYP2D6 Intermediate to Ultra Rapid	Reduced efficacy may occur if an intermediate metabolizer, or risk of toxicity may occur if an ultra rapid metabolizer. Caution is advised and an alternative medication other than codeine or tramadol might be considered.
Metabolizer CYP2D6 Poor to Intermediate	Efficacy may be reduced for codeine and tramadol. Other treatments should be considered
Metabolizer CYP2D6 Poor	Avoid codeine due to lack of efficacy. May consider avoiding tramadol

Allopurinol

- **Drug:** Allopurinol is indicated for the therapy of gout and conditions of elevated urinary uric acid levels.
- **Problem:** Risk of developing Stevens-Johnson syndrome or toxic epidermal necrolysis risk largest in Asian population.



Electronic Order Support

 MICS Decision Support System

 MICS Decision Support System

*Pharmacogenomics Alert: Allopurinol – HLA-B*5801*

Missing HLA-B*5801 Result

Recommendation

You are receiving this alert because this patient is of Asian ancestry and **does NOT have a documented HLA-B*5801 result**. If the patient has never been on allopurinol previously (i.e. initiation of therapy), please consider canceling or delaying the allopurinol order and order a *HLA-B*5801* test.

Please note: If this patient is currently taking allopurinol (i.e. continuation therapy), disregard this alert.

The presence of at least one *5801 allele is reported as positive on a genotyping test and significantly increases the patient's risk of severe cutaneous adverse reactions (SCAR). Patients at higher risk of allopurinol hypersensitivity syndrome include those of Han Chinese and Thai descent, as well as Korean patients with stage 3 or worse chronic kidney disease. The use of allopurinol in such patients is considered contraindicated due to increased risk of Stevens Johnson Syndrome/Toxic Epidermal Necrolysis.

For more information go to [AskMayoExpert \(Allopurinol\)](#) . If this alert is an error or you have questions ,send an email to micspgx@mayo.edu.

Alternatives

Allopurinol and HLA-B*5801 (Pharmacogenomics)

Clinical Answers

Experts

Guidelines & Resources

Allopurinol and HLA-B*5801

Introduction

Overview

Testing Recommendations

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Alerts With Interpretation

Alternative Medication
Options

Medical Insurance Coverage

Alternative Medication Options

Several alternative medications are available for allopurinol. Consider consulting rheumatology, nephrology, or oncology for each specialty's recommendation.

Tumor lysis syndrome:

- Rasburicase (Elitek) (Limited to use by hematology, oncology, or pediatrics services)

Gout:

- Probenecid
- Febuxostat (Uloric)
- Pegloticase (Krystexxa) (Limited to use by rheumatology)

Was this information helpful?

Yes

No

Current Drug Gene Pairs at Mayo

- Carbamazepine - HLA-B*15:02
- Abacavir - HLA-B*57:01
- Allopurinol - HLA-B*58:01
- Codeine - CYP2D6
- Tramadol - CYP2D6
- Tamoxifen - CYP2D6
- Fluoxetine, Paroxetine, Fluvoxamine - CYP2D6
- Venlafaxine - CYP2D6
- Clopidogrel - CYP2C19
- Citalopram, Escitalopram - CYP2C19
- Warfarin - CYP 2C9/VKORC1
- Thiopurine - TPMT
- Simvastatin - SLCO1B1

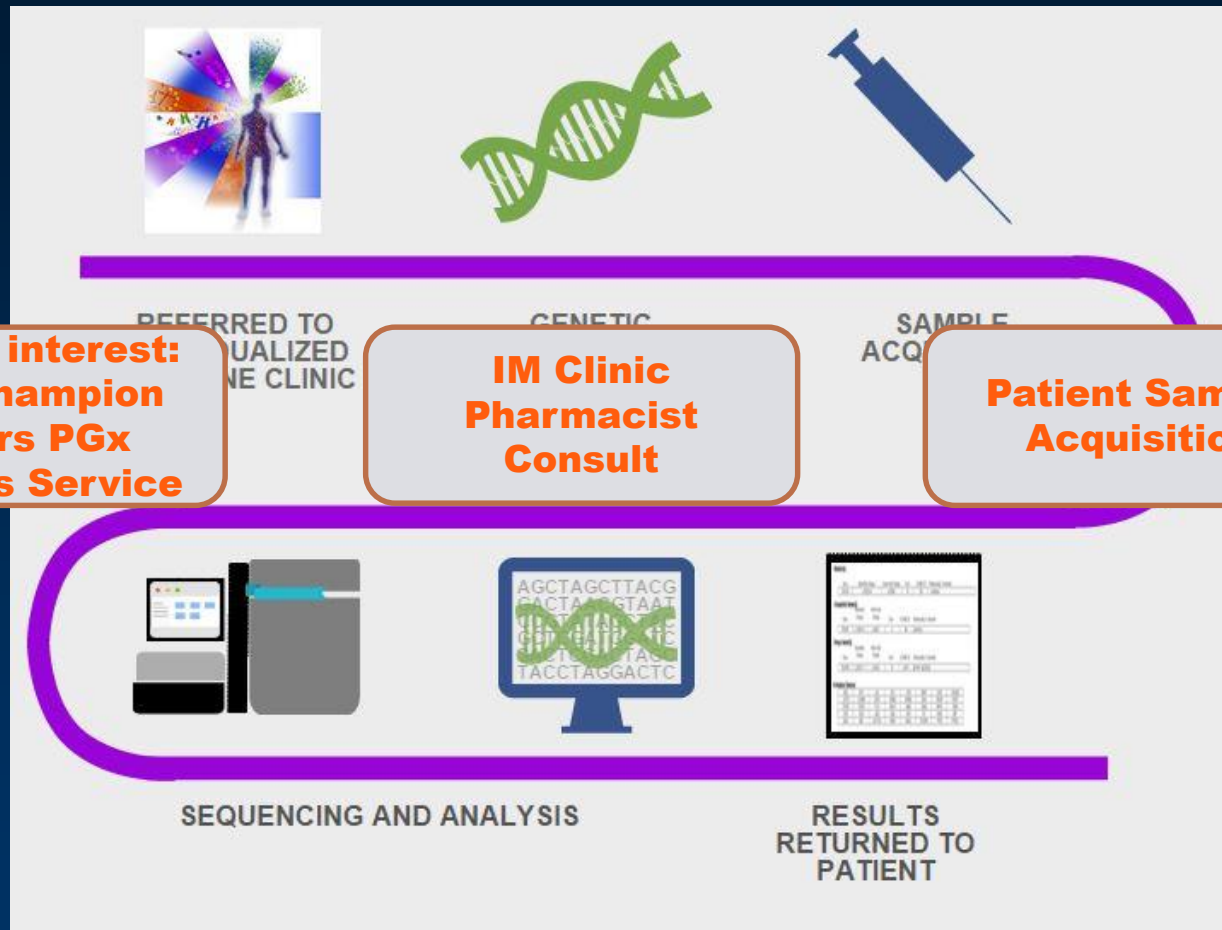
It takes a village



Building Blocks

- Institutional support
 - Center of Individualized Medicine
- Agreement with Practice
 - PGx Committee
 - Pharmacy and Therapeutics
- IT Infrastructure
 - Programming ability
- Education

Basic Flow- PGx Profile Service



**Patient interest:
CIM Champion
orders PGx
Express Service**

**IM Clinic
Pharmacist
Consult**

**Patient Sample
Acquisition**

**Mayo Lab Sequencing, Analysis and
Results: EMR Result and OneOme
Report in patient record**

**Results Returned to
Patient by Pharmacist**

Patient Case

Initial Presentation

- ▶ 18 year old female
- ▶ History of depression, suicide attempts and cutting
- ▶ Consumes 7 vodka shots 4x/week, smokes marijuana to sleep
 - ▶ Hx of medication intolerance

Medications:

- ▶ Current: multivitamin and Vitamin D3
- ▶ PMH: Escitalopram, sertraline, fluoxetine, bupropion, duloxetine

Side Effects:

- ▶ Worsened depression, dilation of eyes and tremors

Action:

- ▶ After medication reconciliation performed, 9-gene pharmacogenomics panel ordered



Patient case: Genetic Test Results

Gene (Metabolizing Enzyme)	Genotype	Phenotype
CYP2D6	*4/*9	Poor to Intermediate
SLCO1B1	*1/*5	Increased Risk
HLA-B*5801	Negative	Normal Risk
CYP1A2	Multiple Variations	Extensive
CYP2C9	*1/*1	Extensive
CYP2C19	*1/*2	Intermediate
VKORC1	-1639 GG	Normal Sensitivity
CYP3A4	*1/*1	Extensive
CYP3A5	*3/*3	Poor (Normal)

Patient Case: Drug-Gene Interactions

medication Hx	Metabolizing Enzyme	Phenotype
escitalopram	CYP2D6, CYP2C19	Poor to Intermediate, Intermediate
fluoxetine	CYP2D6	Poor to Intermediate
duloxetine	CYP2D6, CYP1A2	Poor to Intermediate, Extensive
sertraline	CYP2C19, many others	Intermediate
cefuroxime	none	n/a
cyclafem	CYP3A4, CYP1A2	Extensive, Extensive
bupropion	CYP2B6, CYP2D6	Not tested, poor to intermediate

Patient case: Recommendations

- ▶ **Desvenlafaxine 50 mg daily**
- ▶ Is active metabolite of venlafaxine (CYP2D6 substrate)

- ▶ **6 month follow-up:**

- ▶ Improvement in symptoms and no side effects
- ▶ Buspirone (CYP3A4 substrate) recommended for mood management



The Year of PGx: 2017

- **Expand PGx Panel Options**
- **Expand PGx Pharmacist team**
- **PGx Certification Program**

22 GENE PANEL COVERING MORE THAN 240 DRUGS

GENE	ALLELES	GENE	ALLELES
CYP1A2	1D, 1F, 1J, 1K, 1L, 1W	F5	1691G>A
CYP2B6	*3, *4, *5, *6, *18	OPRM1	118A>G
CYP2C19	*2, *3, *4, *4B, *10, *17, *18	COMT	322G>A (Val158Met)
CYP2C9	*2, *3, *4, *5, *6, *8, *11, *18	DRD2	939A>G, -241A>G,
CYP2D6	*2A, *2, *3, *4, *4N, *4M, *5, *6, *7, *9, *10, *11, *12, *13, *14, *15, *17, *18, *20, *21, *29, *31, *35, *36, *41, *42, *58, *63, *64, *68, *69, *70, *91, *109	HTR2C	-759C>T
CYP3A4	*1B, *22	HTR2A	IN2T>C, 1354C>T, 102T>C, -1438G>A
CYP3A5	*3, *6, *7	DPYD	*2A, *13, 97547947T>A
SLCO1B1	*5, *17	TPMT	*2, *3A, *3B, *3C, *4
UGT1A1	TA6, TA7	GRIK4	120663363T>C
VKORC1	-1639G>A	SLC6A4	La/Lg/S
F2	2021G>A		
IL28B	39248147C>T		

Future

- **In collaboration with Baylor use the PGRN-Seq Ver 3 panel and the Illumina HiSeq platform to sequence 76 pharmacogenes from 10,000 of Biobank patients who receive all of their healthcare at Mayo Rochester.**
- **Genotype results from a subset of the pharmacogenes will be prospectively placed into the EHR**
- **An interpretive report will be placed into the patient's medical record.**
- **With the specific genotypes loaded into the EHR for 10,000 patients, we can systematically evaluate the clinical and fiscal impact of pre-emptively firing the drug-gene pair CDS alerts already in the Mayo Clinic EHR.**

Thank you!



Questions?

